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2019 ANNUAL MEETING

Program

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**Best of ASCO® Baltimore Program Agenda**

**Friday, August 2, 2019**

7:00 AM-2:30 PM
**EXHIBITS OPEN**
Key Ballroom 8, 2nd Floor

7:00 AM-7:55 AM
**COMPLIMENTARY CONTINENTAL BREAKFAST**
Key Ballroom 8, 2nd Floor

7:55 AM-8:00 AM
**WELCOME AND CHAIR REMARKS**
Key Ballroom 4, 2nd Floor

- Tatiana M. Prowell, MD
  US Food and Drug Administration and Johns Hopkins Kimmel Comprehensive Cancer Center

8:00 AM-9:30 AM
**BREAST CANCER**
Key Ballroom 4, 2nd Floor

8:00 AM-8:35 AM
**Carey K. Anders, MD**
University of North Carolina

*Breast Cancer—Local/Regional/Adjuvant*

- **Abstract 503**: Impact of clinical risk category on prognosis and prediction of chemotherapy benefit in early breast cancer (EBC) by age and the 21-gene recurrence score (RS) in TAILORx. (*Joseph A. Sparano, MD*)
- **Abstract 504**: Benefit from letrozole as extended adjuvant therapy after sequential endocrine therapy: A randomized, phase III study of Gruppo Italiano Mammella (GIM). (*Lucia Del Mastro, MD*)
- **Abstract 508**: Patient-reported outcomes (PROs) in NRG oncology/NSABP B-39/RTOG 0413: A randomized phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) in stage 0, I, or II breast cancer. (*Patricia A. Ganz, MD, FASCO*)
- **Abstract 520**: Low-fat dietary pattern and long-term breast cancer incidence and mortality: The Women’s Health Initiative randomized clinical trial. (*Rowan T. Chlebowski, MD, PhD, FASCO*)

8:35 AM-9:10 AM
**Neelima Denduluri, MD**
The US Oncology Network

*Breast Cancer—Metastatic*

- **Abstract 1000**: SOPHIA primary analysis: A phase 3 (P3) study of margetuximab (M) + chemotherapy (C) versus trastuzumab (T) + C in patients (pts) with HER2+ metastatic (met) breast cancer (MBC) after prior anti-HER2 therapies (Tx). (*Hope S. Rugo, MD, FASCO*)
- **Abstract 1002**: Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Findings from the multinational, randomized, phase III NALA trial. (*Cristina Saura, MD, PhD*)
- **Abstract 1003**: IMpassion130: updated overall survival (OS) from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab (atezo) + nab-paclitaxel (nP) in previously untreated locally advanced or metastatic triple-negative breast cancer (mTNBC). (*Peter Schmid, MD, PhD, FCRP*)
- **Abstract LBA1008**: Phase III MONALEESA-7 trial of premenopausal patients with HR+/HER2− advanced breast cancer (ABC) treated with endocrine therapy ± ribociclib: Overall survival (OS) results. (*Sara A. Hurvitz, MD*)

9:10 AM-9:30 AM
**Panel Question and Answer**
GASTROINTESTINAL CANCERS
Key Ballroom 4, 2nd Floor

9:50 AM-11:00 AM
Matthew H. G. Katz, MD, FACS
The University of Texas MD Anderson Cancer Center
Gastrointestinal (Noncolorectal) Cancer

• Abstract LBA4: Olaparib as maintenance treatment following first-line platinum-based chemotherapy (PBC) in patients (pts) with a germline BRCA mutation and metastatic pancreatic cancer (mPC): Phase III POLO trial. (Hedy L. Kindler)
• Abstract 4000: APACT: phase III, multicenter, international, open-label, randomized trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P/G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma. (Margaret A. Tempero, MD, FASCO)
• Abstract 4003: ABC-06 | A randomised phase III, multi-centre, open-label study of Active Symptom Control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. (Angela Lamarca, MD, PhD)
• Abstract LBA4007: Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study. (Josep Tabernero, MD, PhD)
1:00 PM-1:35 PM
SARCOMA
Key Ballroom 4, 2nd Floor

1:00 PM-1:25 PM
Margaret von Mehren, MD
Fox Chase Cancer Center

- **Abstract LBA3**: ANNOUNCE: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS). *(William D. Tap, MD)*
- **Abstract 11001**: STRASS (EORTC 62092): A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma. *(Sylvie Bonvalot, MD, PhD)*
- **Abstract 11015**: Clinical activity of pembrolizumab (P) in undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated/pleomorphic liposarcoma (LPS): Final results of SARC028 expansion cohorts. *(Melissa Amber Burgess, MD)*

1:25 PM-1:35 PM
*Question and Answer*

1:35 PM-2:10 PM
CENTRAL NERVOUS SYSTEM TUMORS
Key Ballroom 4, 2nd Floor

1:35 PM-2:00 PM
Evanthia Galanis, MD
Mayo Clinic, Rochester

- **Abstract 2000**: Second interim and first molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q codeletion. *(Martin J. Van Den Bent, MD, PhD)*
- **Abstract 2001**: Randomized phase IIb clinical trial of continuation or non-continuation with six cycles of temozolomide after the first six cycles of standard first-line treatment in patients with glioblastoma: A Spanish research group in neuro-oncology (GEINO) trial. *(Carmen Balana, MD, PhD)*
- **Abstract 2002**: Updated predictive analysis of the WHO-defined molecular subgroups of low-grade gliomas within the high-risk treatment arms of NRG Oncology/RTOG 9802. *(Erica Hlavin Bell, PhD)*
- **Abstract 3005**: Single agent ONC201 in adult recurrent H3 K27M-mutant glioma. *(Isabel Arrillaga, MD, PhD)*

2:00 PM-2:10 PM
*Question and Answer*

2:10 PM-2:30 PM
BREAK
2:30 PM-4:30 PM
HEMATOLOGIC MALIGNANCIES
Key Ballroom 4, 2nd Floor

2:30 PM-3:00 PM
Naveen Pemmaraju, MD
The University of Texas MD Anderson Cancer Center
Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant

- Abstract 7000: Effect of gilteritinib on survival in patients with FLT3-mutated (FLT3mut+) relapsed/refractory (R/R) AML who have common AML co-mutations or a high FLT3-ITD allelic ratio. (Mark J. Levis, MD, PhD)
- Abstract 7002: Association of smoking with poor risk ELN 2017, cytogenetics/molecular profile, and survival outcomes in acute myeloid leukemia. (Mansour Al-Fayez)
- Abstract 7005: ENESTop 192-week results: Treatment-free remission (TFR) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) after stopping second-line (2L) nilotinib (NIL). (Timothy P. Hughes)
- Abstract 7006: End of phase I results of ZUMA-3, a phase 1/2 study of KTE-X19, anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in adult patients (pts) with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL). (Bijal D. Shah, MD)

3:00 PM-3:30 PM
Anthony R. Mato, MD, MD
Memorial Sloan Kettering Cancer Center
Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Lymphoma

- Abstract 6500: Effect of montelukast and rupatadine on rituximab infusion time, rate, severity of reactions, and cost of administration. (Rouslan Kotchetkov, MD, PhD)
- Abstract 7502: Effect of fixed-duration venetoclax plus obinutuzumab (VenG) on progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD–) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities. (Kirsten Fischer, MD)
- Abstract 7506: Umbralisib monotherapy demonstrates efficacy and safety in patients with relapsed/refractory marginal zone lymphoma: A multicenter, open label, registration directed phase II study. (Nathan Hale Fowler)
- Abstract 7507: Rituximab maintenance for patients with diffuse large B-cell lymphoma in first complete remission: Results from a randomized HOVON-Nordic Lymphoma Group phase III study. (Pieterenella J. Lugtenburg)
- Abstract 7510: Final analysis from RESONATE: Six-year follow-up in patients (pts) with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) on ibrutinib. (Paul M. Barr, MD)

3:30 PM-4:00 PM
Elizabeth O’Donnell, MD
Massachusetts General Hospital Cancer Center
Hematologic Malignancies—Plasma Cell Dyscrasia

- Abstract 8001: E3A06: Randomized phase III trial of lenalidomide versus observation alone in patients with asymptomatic high-risk smoldering multiple myeloma. (Sagar Lonial, MD)
- Abstract 8004: A phase III randomized, open label, multicenter study comparing isatuximab, pomalidomide, and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). (Paul G. Richardson, MD)
- Abstract 8005: Efficacy and safety of the randomized, open-label, non-inferiority, phase 3 study of subcutaneous (SC) versus intravenous (IV) daratumumab (DARA) administration in patients (pts) with relapsed or refractory multiple myeloma (RRMM): COLUMBA. (Maria-Victoria Mateos, PhD)
- Abstract 8007: Evaluation of AMG 420, an anti-BCMA bispecific T-cell engager (BiTE) immunotherapy, in R/R multiple myeloma (MM) patients: Updated results of a first-in-human (FIH) phase I dose escalation study. (Max Topp, MD)

4:00 PM-4:30 PM
Panel Question and Answer
Saturday, August 3, 2019

7:00 AM-2:30 PM
EXHIBITS OPEN
Key Ballroom 8, 2nd Floor

7:00 AM-8:00 AM
COMPLIMENTARY CONTINENTAL BREAKFAST
Key Ballroom 8, 2nd Floor

8:00 AM-9:30 AM
GENITOURINARY CANCERS
Key Ballroom 4, 2nd Floor

8:00 AM-8:35 AM
Richard J. Lee, MD, PhD
Massachusetts General Hospital Cancer Center
Genitourinary (Prostate) Cancer

- **Abstract LBA2**: Overall survival (OS) results of a phase III randomized trial of standard-of-care therapy with or without enzalutamide for metastatic hormone-sensitive prostate cancer (mHSPC): ENZAMET (ANZUP 1304), an ANZUP-led international cooperative group trial. (*Christopher Sweeney*)

- **Abstract 5006**: First results from TITAN: A phase III double-blind, randomized study of apalutamide (APA) versus placebo (PBO) in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) receiving androgen deprivation therapy (ADT). (*Kim N. Chi, MD, FRCPC*)

- **Abstract 5007**: Decreased fracture rate by mandating bone-protecting agents in the EORTC 1333/PEACE III trial comparing enzalutamide and Ra223 versus enzalutamide alone: An interim safety analysis. (*Bertrand F. Tombal, MD, PhD*)

- **Abstract 5008**: Alliance A031201: A phase III trial of enzalutamide (ENZ) versus enzalutamide, abiraterone, and prednisone (ENZ/AAP) for metastatic castration resistant prostate cancer (mCRPC). (*Michael J. Morris, MD*)

8:35 AM-9:10 AM
Trinity Bivalacqua, MD, PhD
Johns Hopkins Hospital
Genitourinary (Nonprostate) Cancer

- **Abstract 4500**: Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for metastatic renal cell carcinoma (mRCC): Outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of the phase 3 KEYNOTE-426 study. (*Brian I. Rini, MD, FACP*)

- **Abstract 4503**: CALGB 90601 (Alliance): Randomized, double-blind, placebo-controlled phase III trial comparing gemcitabine and cisplatin with bevacizumab or placebo in patients with metastatic urothelial carcinoma. (*Jonathan E. Rosenberg, MD*)

- **Abstract 4504**: Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients (pts) with metastatic urothelial cancer (mUC): HCRN GU14-182. (*Matt D. Galsky, MD, FASCO*)

- **Abstract LBA4505**: EV-201: Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors. (*Daniel Peter Petrylak, MD*)

9:10 AM-9:30 AM
Panel Question and Answer

9:30 AM-9:50 AM
BREAK
9:50 AM-10:35 AM
GYNECOLOGIC CANCER
Key Ballroom 4, 2nd Floor

9:50 AM-10:25 AM
Sarah M. Temkin, MD
Anne Arundel Medical Center

- **Abstract 5500:** A randomized phase 3 trial of paclitaxel (P) plus carboplatin (C) versus paclitaxel plus ifosfamide (I) in chemotherapy-naive patients with stage I-IV, persistent or recurrent carcinosarcoma of the uterus or ovary: An NRG oncology trial. *(Matthew A. Powell, MD)*

- **Abstract 5505:** Combination of niraparib and bevacizumab versus niraparib alone as treatment of recurrent platinum-sensitive ovarian cancer. A randomized controlled chemotherapy-free study—NSGO-AVANOVA2/ENGOT-OV24. *(Mansoor Raza Mirza, MD)*

- **Abstract 5506:** Olaparib monotherapy versus (vs) chemotherapy for germline BRCA-mutated (gBRCAm) platinum-sensitive relapsed ovarian cancer (PSR OC) patients (pts): Phase III SOLO3 trial. *(Richard T. Penson, MD, MRCP)*

- **Abstract 5508:** EWOC-1: A randomized trial to evaluate the feasibility of three different first-line chemotherapy regimens for vulnerable elderly women with ovarian cancer (OC): A GCIG-ENGOT-GINECO study. *(Claire Falandry)*

10:25 AM-10:35 AM
**Question and Answer**

10:35 AM-11:40 AM
SYMPTOMS AND SURVIVORSHIP, INCLUDING CLINICAL APPLICATIONS FOR IMMUNE CHECKPOINT INHIBITOR TOXICITIES
Key Ballroom 4, 2nd Floor

10:35 AM-11:10 AM
Cardinale B. Smith, MD, PhD
Icahn School of Medicine at Mount Sinai
Symptoms and Survivorship

- **Abstract 6509:** The impact of routine ESAS use on overall survival: Results of a population-based retrospective matched cohort analysis. *(Lisa Catherine Barbera, MD)*

- **Abstract 11503:** A randomized, double-blind, placebo-controlled phase III trial evaluating olanzapine 5 mg combined with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based chemotherapy: J-FORCE Study. *(Hironobu Hashimoto, BPharm)*

- **Abstract 11506:** Safety of pregnancy following breast cancer (BC) in patients (pts) carrying a BRCA mutation (mBRCA): Results of an international cohort study. *(Matteo Lambertini, MD)*

- **Abstract 11507:** Effects of exercise on cancer-related fatigue and muscular strength in patients with breast cancer. *(Po-Ju Lin, PhD, MPH, RD)*

- **Abstract 11514:** A randomized controlled trial of a novel artificial intelligence-based smartphone application to optimize the management of cancer-related pain. *(Mihir Kamdar, MD)*

11:10 AM-11:30 AM
Alexander N. Shoushtari, MD
Memorial Sloan Kettering Cancer Center
Recognizing, Understanding, and Overcoming Toxicities from Immune Checkpoint Inhibitors

11:30 AM-11:40 AM
**Panel Question and Answer**

11:40 AM-12:40 PM
COMPLIMENTARY BOXED LUNCH
Key Ballroom 8, 2nd Floor
12:40 PM-1:25 PM
**HEAD AND NECK CANCER**
Key Ballroom 4, 2nd Floor

12:40 PM-1:15 PM
**Eric J. Sherman, MD**
Memorial Sloan Kettering Cancer Center

- **Abstract 6000:** Protocol-specified final analysis of the phase 3 KEYNOTE-048 trial of pembrolizumab (pembro) as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). *(Danny Rischin)*
- **Abstract 6002:** TPEXèle randomized trial: TPEX versus Extreme regimen in 1st line recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). *(Joel Guigay, MD)*
- **Abstract 6003:** Gemcitabine and cisplatin (GP) induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT) versus CCRT alone in locoregionally advanced nasopharyngeal carcinoma (NPC): A phase 3, multicenter, randomized controlled trial. *(Jun Ma)*
- **Abstract 6015:** Primary analysis of Phase 2 results of cemiplimab, a human monoclonal anti-PD-1, in patients (pts) with locally advanced cutaneous squamous cell carcinoma (laCSCC). *(Michael Robert Migden, MD)*

1:15 PM-1:25 PM

**Question and Answer**

1:25 PM-2:10 PM
**MELANOMA/SKIN CANCERS**
Key Ballroom 4, 2nd Floor

1:25 PM- 2:00 PM
**Geoffrey T. Gibney, MD**
Georgetown-Lombardi Comprehensive Cancer Center

- **Abstract 2512:** Ipilimumab versus placebo after complete resection of stage III melanoma: Long-term follow-up results the EORTC 18071 double-blind phase 3 randomized trial. *(Alexander M. M. Eggermont, MD)*
- **Abstract 9500:** Phase 3 international trial of adjuvant whole brain radiotherapy (WBRt) or observation (Obs) following local treatment of 1-3 melanoma brain metastases (MBMs). *(Gerald Fogarty, MD)*
- **Abstract 9501:** Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204). *(Hussein Abdul-Hassan Tawbi, MD, PhD)*
- **Abstract 9503:** Pathological response and survival with neoadjuvant therapy in melanoma: A pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). *(Alexander M. Menzies, MBBS, FRACP, PhD)*
- **Abstract 9507:** Five-year analysis on the long-term effects of dabrafenib plus trametinib (D + T) in patients with BRAF V600–mutant unresectable or metastatic melanoma. *(Paul D. Nathan, MD)*

2:00 PM-2:10 PM

**Question and Answer**

2:10 PM-2:30 PM

**BREAK**
2:30 PM-4:00 PM
LUNG CANCER
Key Ballroom 4, 2nd Floor

2:30 PM-3:05 PM
Julie R. Brahmer, MD, FASCO
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University
Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Thoracic Cancers

- **Abstract 8502**: Initial reporting of NRG-LU001 (NCT02186847), randomized phase II trial of concurrent chemoradiotherapy (CRT) +/- metformin in locally advanced Non-Small Cell Lung Cancer (NSCLC). *(Theodoros Tsakiris)*
- **Abstract 8503**: Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3). *(David J. Kwiatkowski, MD, PhD)*
- **Abstract 8504**: Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study. *(Tina Cascone, MD, PhD)*
- **Abstract 8506**: Efficacy and safety profile of lurbinectedin in second-line SCLC patients: Results from a phase II single-agent trial. *(Luis G. Paz-Ares, MD, PhD)*

3:05 PM-3:40 PM
Benjamin P. Levy, MD
Johns Hopkins Sidney Kimmel Cancer Center
Lung Cancer—Non-Small Cell Metastatic

- **Abstract 9000**: RELAY: A multinational, double-blind, randomized Phase 3 study of erlotinib (ERL) in combination with ramucirumab (RAM) or placebo (PL) in previously untreated patients with epidermal growth factor receptor mutation-positive (EGFRm) metastatic non-small cell lung cancer (NSCLC). *(Kazuhiko Nakagawa, MD, PhD)*
- **Abstract 9001**: Phase III randomized trial comparing gefitinib to gefitinib with pemetrexed-carboplatin chemotherapy in patients with advanced untreated EGFR mutant non-small cell lung cancer (gef vs gef+C). *(Vanita Noronha)*
- **Abstract 9002**: ECOG-ACRIN 5508: Pemetrexed, bevacizumab or the combination as maintenance therapy for advanced non-squamous NSCLC. *(Suresh S. Ramalingam, MD)*
- **Abstract 9016**: Blood tumor mutational burden (bTMB) and tumor PD-L1 as predictive biomarkers of survival in MYSTIC: First-line durvalumab (D) ± tremelimumab (T) versus chemotherapy (CT) in metastatic (m) NSCLC. *(Naiyer A. Rizvi, MD)*

3:40 PM-4:00 PM
Panel Question and Answer
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Mayo Clinic, Rochester
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Developmental Immunotherapy and Tumor Immunobiology

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Developmental Therapeutics and Tumor Biology (Nonimmuno)
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Gastrointestinal Cancer-Colorectal

Vaibhav Sahai, MBBS, MS
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Gastrointestinal Cancer-Noncolorectal

Petros Grivas, MD, PhD
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Genitourinary Cancer-Nonprostate

Tanya B. Dorff, MD
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University of Virginia Health System
Gynecologic Cancer

Faye Johnson, MD, PhD
University of Texas MD Anderson Cancer Center
Head and Neck Cancer

Leslie Ellis, MD
Wake Forest University
Hematologic Malignancies-Leukemia, MDS, and Allotransplant

Tycel Phillips, MD
University of Michigan Health System Comprehensive Cancer Center
Hematologic Malignancies-Lymphoma and CLL

Brea Lipe, MD
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Hematologic Malignancies-Plasma Cell Dyscrasia
Alexander Chi, MD
West Virginia University
Lung Cancer–Non-small Cell Local-regional/Small Cell/Other

Gregory J. Riely, MD, PhD
Memorial Sloan Kettering Cancer Center
Lung Cancer–Non-small Cell Metastatic

Janice Mehnert, MD
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Melanoma/Skin Cancers

Rashmi Chugh, MD
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Onsite Meeting Information

Meeting Planning and Abstract Selection Process
The Best of ASCO Meetings are an educational initiative that condenses the most cutting-edge science and education from the ASCO Annual Meeting into a 2-day program. The program features science and education sessions that focus on the latest scientific findings in primary disease sites and practice-changing advances in cancer prevention and treatment.

The Best of ASCO Planning Committee met at the Annual Meeting Scientific Program Committee meeting to review and select abstracts for inclusion in the Best of ASCO program. All abstracts submitted to the Annual Meeting were eligible and considered. The abstracts chosen for presentation and discussion at the Best of ASCO Meetings are selected according to specific criteria and reflect the foremost research in oncology today. The research presented at the Best of ASCO Meetings focuses on those strategies that will most affect patient care.

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ASCO encourages attendees to visit the exhibits on Friday and Saturday from 7:00 AM to 2:30 PM. The exhibits offer you an opportunity to extend your learning about the most advanced therapies, products, and services in the treatment of cancer. Visit boa.asco.org to view a list of exhibiting companies.

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Breast Cancer—Local/Regional/Adjuvant
Impact of clinical risk category on prognosis and prediction of chemotherapy benefit in early breast cancer (EBC) by age and the 21-gene recurrence score (RS) in TAILORx.

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Background: TAILORx established that endocrine therapy (ET) alone is non-inferior to adjuvant chemotherapy (CT) plus ET in EBC and a 21-gene RS of 11-25, with some benefit if <50 years (y) with RS 16-25 (PMID: 29860917). We evaluated whether clinical risk (tumor size & histologic grade) provides additional prognostic information to RS, a secondary trial objective. Methods: Clinical risk by was assessed by Adjuvant! (version 8.0) using MINDACT criteria (PMID 27557300), defined as low clinical risk (LCR - tumor ≤3 cm and low grade, <2 cm and intermediate grade, or ≤1 cm and high grade) or high clinical risk (HCR -not meeting LCR criteria). Results: Of 9427 women with RS and clinical risk information, 70% were LCR and 30% HCR, with comparable distribution by age (<50 vs. ≥50). The RS was 26-100 in 9% of LCR and 27% of HCR patients, with similar distributions by age. Although LCR/HCR provided additional prognostic information in each RS category for iDFS, including RS 0-10 (9-year rates 86.7% vs. 75.7% LCR vs. HCR), 11-25 (85.4% vs. 78.9%), and 26-100 (82.0% vs. 70.4%), iDFS rates were similar irrespective of CT (no vs. yes) in the entire RS 11-25 cohort whether LCR (85.8% vs. 85.1%) or HCR (79.8% vs. 77.9%). DRFI rates were also similar irrespective of CT in the RS 11-25 cohort or > 50y group whether LCR (96.0% vs. 96.1% overall; 96.5% vs. 96.0% > 50y) or HCR (92.3% vs. 89.9% overall; 91.7% vs. 90.7% >50y). For women ≤50y, the absolute reduction in distant recurrence from CT with a RS of 16-20 (N=923) was -0.2% (standard error [SE]=±2.1%) for LCR vs. 6.5% (SE=±4.9%) for HCR (vs. 1.6% [SE±1.9%] overall), whereas for a RS 21-25 (N=492) it was 6.4% (SE±4.9%) for LCR vs. 8.6% (SE±6.2%) for HCR (vs. 6.5% [SE±3.7%] overall). Conclusions: Clinical risk stratification provides additional prognostic information to the 21-gene RS, but not prediction of CT benefit in the overall TAILORx population or those > 50y, and facilitates more refined estimates of absolute CT benefit for women ≤50y with a RS 16-25. (Funded by National Cancer Institute, Komen Foundation, Breast Cancer Research Foundation). Clinical trial information: NCT00310180.
Benefit from letrozole as extended adjuvant therapy after sequential endocrine therapy: A randomized, phase III study of Gruppo Italiano Mammella (GIM).

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Background: The effect of extended adjuvant endocrine therapy (ET) with aromatase inhibitors (AI) after sequential ET with tamoxifen (Tam) followed by AI for 5 years is still controversial. We conduct a clinical trial to assess different durations of ET of letrozole after tam. Methods: The GIM4 LEAD (Gruppo Italiano Mammella 4- Letrozole adjuvant therapy duration study, ClinicalTrials.gov:NCT01064635) was a prospective, randomized, Italian multicentric trial. Post-menopausal patients (pts) with hormone receptor positive early breast cancer free of recurrence after 2-3 years of adjuvant tam, were randomized in a 1:1 ratio to receive 3-2 years (short arm, S) or 5 years (long arm, L) of letrozole. The primary study end point was disease-free survival (DFS). Results: Between August 2005 and May 2010, 2056 pts were randomly assigned to receive 3-2 years (n=1030) or 5 years (n=1026) of letrozole. Main patients characteristics in the S and L arms were, respectively: median age 60 vs 61 years, node negative 56 vs 56%, (neo)adjuvant chemotherapy 53.4 vs 54.1%. The median follow-up was 10 years (IQR range: 8.6-11.4). The 8-year DFS was 80% (95% CI:77.3-82.7) and 85% (95% CI:82.9-87.6) in the S and L arm, respectively (hazard ratio, HR 0.82; 95% CI:0.68-0.98; p=0.031). This effect did not change in a multivariate Cox model that included nodal status, grading and age. No evidence of interaction between random assignment and nodal status, age and grading was observed. Among 1960 pts evaluable for toxicity, osteoporosis was diagnosed in 47 (4.8%) in S arm and 81 (8.3%) pts in L arm (chi-square=9.88; p=0.002). Bone fractures occurred in 5 (0.5%) and 9 (0.9%) pts in S and L arm, respectively (p=0.29, Fisher exact test). Conclusions: After 2-3 years of adjuvant tam, extended treatment with 5 years of letrozole resulted in significant improvement in DFS compared to the standard duration of 2-3 years of letrozole. Clinical trial information: NCT01064635.
Patient-reported outcomes (PROs) in NRG oncology/NSABP B-39/RTOG 0413: A randomized phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) in stage 0, I, or II breast cancer.

Patricia A. Ganz, Reena S. Cecchini, Julia R. White, Frank Vicini, Thomas B. Julian, Douglas W Arthur, Rachel Rabinoевич, Robert R. Kuske, David S. Parda, Michael Scheier, Kathryn A. Winter, Soonmyung Paik, Henry Mark Kuerer, Laura Vallow, Lori J. Pierce, Eleftherios P. Mamounas, Joseph P. Costantino, Beryl McCormick, Walter John Curran, Jr., Norman Wolmark; NRG Oncology, and The UCLA Jonsson Comprehensive Cancer Center at UCLA, Los Angeles, CA; NRG Oncology and Biostatistical Center, Pittsburgh, PA; NRG Oncology, and The Ohio State University Comprehensive Cancer Center, Columbus, OH; NRG Oncology, and 21st Century Oncology, Pontiac, MI; NRG Oncology, and The Allegheny Health Network Cancer Institute, Pittsburgh, PA; NRG Oncology/Virginia Commonwealth University, Richmond, VA; NRG Oncology/University of Colorado School of Medicine, Aurora, CO; NRG Oncology, and Arizona Breast Cancer Specialists, Scottsdale, AZ; Allegheny Health Network Cancer Institute, Pittsburgh, PA; Carnegie Mellon University, Pittsburgh, PA; NRG Oncology SDMC - American College of Radiology, Philadelphia, PA; NRG Oncology, and Yonsei University College of Medicine, Seoul, South Korea; NRG Oncology/The University of Texas MD Anderson Cancer Center, Houston, TX; NRG Oncology/Mayo Clinic, Jacksonville, FL; NRG Oncology/University of Michigan Health System, Ann Arbor, MI; NRG Oncology, and Orlando Health UF Cancer Center, Orlando, FL; NSABP Foundation and The University of Pittsburgh, Pittsburgh, PA; NRG Oncology, and Memorial Sloan Kettering Cancer Center, New York, NY; NRG Oncology, and the Winship Cancer Institute, Atlanta, GA

Background: PBI is an alternative to WBI, with potentially greater therapy (tx) compliance, and better integration with chemotherapy (CTX). NSABP B-39/RTOG 0413 clinical outcome results from 2018 did not show equivalence of PBI to WBI in local tumor control; PBI was statistically inferior, but with clinically small differences. PBI may be an acceptable alternative to WBI for some women. Understanding cosmesis and quality of life (QOL) treatment outcomes is important. Methods: B-39/0413 included a prospective QOL substudy with PRO evaluation of breast cancer treatment outcomes (cosmesis, function, pain) and fatigue using BCTOS and SF-36 vitality scales. Secondary QOL parameters included treatment related symptoms, perceived convenience of care, and the BPI pain scale. The study sample was stratified by CTX or not, as CTX is given before WBI but after PBI. PRO assessments occurred before randomization, the last day of adjuvant tx [CTX or radiation], 4 wks later, and 6, 12, 24, and 36 mo later. Primary aims included comparisons of change in fatigue from baseline to end of tx and equivalency of change in cosmesis from baseline to 36 mo for PBI v WBI. Separate analyses were done for CTX and non-CTX pts, controlling for axillary dissection. Each comparison used α=0.0125. Planned sample size was 964. Results: From 3-23-05 to 5-27-09, 975 pts were enrolled in the PRO study; 950 had follow-up data. 504 did not receive CTX and 446 received CTX. In non-CTX pts, PBI had less fatigue (p=0.011) and did not meet criteria for cosmesis equivalence (97.5% CI, -0.02 to 0.22; Δ=0.20). In CTX pts, PBI had worse fatigue (p=0.011) and equivalent cosmesis to WBI (97.5% CI, -0.09 to 0.21; Δ=0.24). In both groups, PBI pts reported less pain at end of tx. In non-CTX pts, PBI had more pain at 36 mo but in CTX pts, there was no difference. Convenience of care and treatment related symptom outcomes will be presented. Conclusions: In non-CTX pts, PBI is more convenient with less fatigue and slightly poorer cosmesis at 36 mo. Cosmesis was equivalent at 36 mo in CTX pts. Support: U10CA180868, -180822, UG1CA189867. Clinical trial information: NCT00103181.
Low-fat dietary pattern and long-term breast cancer incidence and mortality: The Women’s Health Initiative randomized clinical trial.

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Background: Observational studies of dietary fat intake and breast cancer have inconsistent findings. To address this issue, the Women’s Health Initiative (WHI) Dietary Modification (DM) clinical trial assessed a low-fat dietary pattern influence on breast cancer incidence and outcome. Methods: The WHI DM trial is a randomized, controlled clinical trial conducted at 40 US centers, where 48,835 postmenopausal women, aged 50-79 years, with no previous breast cancer and dietary fat intake ≥32% of total energy, were randomly assigned, from 1993-1998, to a usual diet comparison group (60%) or dietary intervention group (40%) with goals to reduce fat intake to 20% of energy and increase vegetables, fruit, and grain intake. This study is registered as: NCT00000611. Results: The dietary intervention significantly reduced fat intake; increased fruit, vegetable and grain intake with modest weight loss (3%) (all P < 0.001). During 8.5 years of dietary intervention, there were 8% fewer breast cancers and deaths from breast cancer were somewhat lower in the intervention group but the rates were not significantly different. However, deaths after breast cancer (breast cancer followed by death from any cause) were significantly reduced in the intervention group, both during intervention (hazard ratio [HR] 0·65 95% confidence interval [CI] 0·45-0·95) and through 16.1 year (median) cumulative follow-up. Now, after long-term, cumulative 19.6 year (median) follow-up, with 3,374 incident breast cancers, the significant reduction in deaths after breast cancer continued (with 1,011 deaths, HR 0·85 95% CI 0·74-0·96) and a significant reduction in deaths from breast cancer (breast cancer followed by death attributed to the breast cancer) emerged (with 383 deaths, HR 0·79 95% CI 0·64-0·97). Conclusions: Adoption of a low-fat dietary pattern associated with increased vegetable, fruit, and grain intake, demonstrably achievable by many, significantly reduced the risk of death from breast cancer in postmenopausal women. To our review, these findings provide the first randomized clinical trial evidence that a dietary change can reduce a postmenopausal woman’s risk of dying from breast cancer. Clinical trial information: NCT00000611.
Breast Cancer—Metastatic
Background: Pretreated HER2+ MBC lacks a defined standard of care, although T is commonly used. M has similar HER2 binding and antiproliferative effects as T. By contrast, M’s Fc region is engineered to increase affinity for both alleles of the activating Fc receptor (FcR), CD16A, and decrease affinity for the inhibitory FcR, CD32B. The low affinity CD16A-158F allele (~85% of population) has been associated with diminished clinical response to T. In a Phase 1 trial, M demonstrated acceptable safety, anti-tumor activity, and evidence of HER2-specific antibody and T-cell responses. Methods: SOPHIA (NCT02492711), a randomized, open-label P3 trial, enrolled pts with HER2+ MBC after pertuzumab and 1–3 lines of prior Tx for MBC. Pts were randomized 1:1 to M (15 mg/kg IV q3w + C) or T (6 [8 for loading dose] mg/kg IV q3w + C), stratified by met sites (≥2, > 2), lines of Tx for met disease (≥2, > 2), and C choice (standard dose capecitabine, eribulin, gemcitabine, or vinorelbine). Primary endpoints are central blinded PFS and OS, assessed sequentially using the stratified log-rank test. Objective response rate (ORR) was a secondary endpoint. 257 PFS events were required to provide 90% power to show PFS superiority at 2-sided α = 0.05. Results: Intent-to-treat analysis (536 pts: M 266; T 270) occurred after 265 PFS events. M prolonged PFS over T (median 5.8 vs 4.9 mo, hazard ratio [HR], 0.76; 95% CI, 0.59–0.98; P= 0.033). Treatment effects were more pronounced in pts with CD16A genotypes containing a 158F allele (median PFS 6.9 vs 5.1 mo, HR, 0.68; 95% CI, 0.52–0.90; P= 0.005). In 524 pts with baseline measurable disease (M 262; T 262), ORR was higher with M (22% vs 16%; 95% CI, 17.3-27.7%) vs T (16%; 95% CI 11.8-21.0%). Safety profiles were comparable in 529 pts who received study therapy. Grade ≥3 AEs and serious AEs occurred in 138 (52%) and 39 (15%) vs 128 (48%) and 46 (17%) pts on M vs T, respectively. PFS data cutoff: 10/10/18. Conclusions: In combination with chemotherapy in pretreated HER2+ MBC, M improves PFS over T with comparable safety. CD16A genotyping suggests a differential benefit in patients with a 158F allele. OS data are maturing. Clinical trial information: NCT02492711.
Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Findings from the multinational, randomized, phase III NALA trial.

Cristina Saura, Mafalda Oliveira, Yin-Hsun Feng, Ming-Shen Dai, Sara A. Hurvitz, Sung-Bae Kim, Beverly Moxoy, Suzette Delalogen, William John Gradishar, Norikazu Masuda, Marketa Palacova, Maureen E. Trudeau, Johanna Mattson, Yoon Sim Yap, Richard Bryce, Bin Yao, Judith D. Bebchuk, Kianna Keyvanjani, Adam Brufksy, NALA Investigators; Vall d’Hebron University Hospital, Barcelona, Spain; Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; Chi Mei Medical Centre, Tainan, Taiwan; Tri-Service General Hospital, Taipei, Taiwan; UCLA Hematology / Oncology Clinical Research Unit, Santa Monica, CA; University of Ulsan College of Medicine, Seoul, South Korea; Massachusetts General Hospital Cancer Center, Boston, MA; Institut Gustave Roussy, Villejuif, France; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; NHO Osaka National Hospital, Osaka, Japan; Masaryk Memorial Cancer Institute, Brno, Czech Republic; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; National Cancer Centre Singapore, Singapore, Singapore; Puma Biotechnology Inc, Los Angeles, CA; Magee-Womens Hospital of UPMC, Pittsburgh, PA

Background: NALA (ClinicalTrials.gov NCT01808573) is a multinational, randomized, open-label, phase III trial of neratinib (an irreversible pan-HER tyrosine kinase inhibitor [TKI]) + capecitabine (N+C) vs lapatinib (a reversible dual TKI) + capecitabine (L+C) in patients with stage IV HER2+ metastatic breast cancer (MBC) who had received ≥ 2 prior HER2-directed regimens for MBC. Methods: Patients were randomized 1:1 to N (240 mg qd po) + C (750 mg/m² bid po) or L (1250 mg qd po) + C (1000 mg/m² bid po). Primary endpoints were centrally assessed progression-free survival (PFS) and overall survival (OS). Secondary endpoints were investigator-assessed PFS; objective response rate (ORR); duration of response (DoR); clinical benefit rate (CBR); time to intervention for symptomatic metastatic central nervous system (CNS) disease; safety; and patient-reported health outcomes. Results: 621 patients were randomized (307 to N+C; 314 to L+C). The risk of disease progression or death was reduced by 24% with N+C vs L+C (HR = 0.76; 95% CI 0.63–0.93; p = 0.006); 6- and 12-month PFS rates were 47.2% vs 37.8% and 28.8% vs 14.8% for N+C vs L+C, respectively. OS rates at 6 and 12 months were 90.2% vs 87.5% and 72.5% vs 66.7% for N+C vs L+C, respectively (HR = 0.88; 95% CI 0.72–1.07; p = 0.2086). ORR in patients with measurable disease at screening was improved with N+C vs L+C (32.8% vs 26.7%; p = 0.1201), as was CBR (44.5% vs 35.6%; p = 0.0328) and DoR (HR = 0.50; 95% CI 0.33–0.74; p = 0.0004). Time to intervention for symptomatic CNS disease (overall cumulative incidence 22.8% vs 29.2%; p = 0.043) was delayed with N+C vs L+C. Treatment-emergent adverse events (TEAEs) were similar between arms, but there was a higher rate of grade 3 diarrhea with N+C vs L+C (24.4% vs 12.5%). TEAEs leading to neratinib/lapatinib discontinuation were lower with neratinib (10.9%) than with lapatinib (14.5%). Conclusions: N+C significantly improved PFS with a trend towards improved OS vs L+C, N+C also resulted in a delayed time to intervention for symptomatic CNS disease. Tolerability was similar between the two arms, with no new safety signals observed. Clinical trial information: NCT01808573.
IMpassion130: updated overall survival (OS) from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab (atezo) + nab-paclitaxel (nP) in previously untreated locally advanced or metastatic triple-negative breast cancer (mTNBC).

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Background: IMpassion130 evaluated atezo (anti–PD-L1) + nP vs placebo + nP in 1L mTNBC. The primary PFS analysis found that atezo + nP significantly improved PFS in intent-to-treat (ITT) and PD-L1+ pts vs placebo + nP, with efficacy driven by the PD-L1+ population. At that time, the 1st interim OS analysis was conducted (Schmid, NEJM 2018). Here we report the 2nd interim OS analysis. Methods: Eligible pts had histologically documented locally advanced or mTNBC, ECOG PS 0-1 and tumor tissue for PD-L1 testing. Pts were randomized 1:1 to IV atezo 840 mg or placebo on d1 and d15 + nP 100 mg/m² on d1, d8 and d15 of each 28-d cycle until progression (stratification factors: prior taxanes, liver metastases, PD-L1 on tumor-infiltrating immune cells [IC]). RECIST 1.1 PFS (in ITT and PD-L1+ pts) and OS (tested in ITT and, if significant, PD-L1+ pts) were co-primary endpoints. Results: OS data are shown (Table). As of data cutoff (Jan 2, 2019), 9% of pts in the atezo + nP arm and 3% in the placebo + nP arm were still on treatment. Statistical significance was not demonstrated in ITT pts, but a 7.0-month improvement in median OS was observed in PD-L1+ pts with atezo + nP (25.0 mo) vs placebo + nP (18.0 mo; HR, 0.71 [95% CI: 0.54, 0.93]). A 4.5-mo safety update (Schneeweiss, ASCO 2019, submitted) showed that atezo + nP remained tolerable. Conclusions: The 2nd IMpassion130 interim OS analysis was consistent with the 1st analysis, confirming clinically meaningful OS benefit with atezo + nP in previously untreated PD-L1+ mTNBC. Clinical trial information: NCT02425891.

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<tr>
<th>Atezo + nP</th>
<th>Placebo + nP</th>
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<tr>
<td>ITT population, events/pts, n/n (%)</td>
<td>255/451 (57%)</td>
</tr>
<tr>
<td>HR (95% CI); log-rank P</td>
<td>0.86 (0.72, 1.02); 0.078*</td>
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<tr>
<td>Median OS (95% CI), mo</td>
<td>21.0 (19.0, 22.6)</td>
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<tr>
<td>2-year OS (95% CI), %</td>
<td>42 (37, 47)</td>
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<tr>
<td>Median follow-up duration, mo</td>
<td>18.5</td>
</tr>
<tr>
<td>PD-L1+ population, events/pts, n/n (%)</td>
<td>94/185 (51%)</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.71 (0.54, 0.93)</td>
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<tr>
<td>Median OS (95% CI), mo</td>
<td>25.0 (19.6, 30.7)</td>
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<tr>
<td>2-year OS (95% CI), %</td>
<td>51 (43, 59)</td>
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HRs estimated per stratified Cox model. * Not significant. † PD-L1 on IC ≥ 1% (VENTANA SP142 IHC assay).
Phase III MONALEESA-7 trial of premenopausal patients with HR+/HER2− advanced breast cancer (ABC) treated with endocrine therapy ± ribociclib: Overall survival (OS) results.

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Background: The phase III MONALEESA-7 study (NCT02278120) is the first dedicated trial of endocrine therapy (ET) ± a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in premenopausal patients (pts) with hormone receptor–positive (HR+)/HER2− ABC. The study met its primary endpoint of significantly longer progression-free survival (PFS) with ribociclib (RIB; a CDK4/6 inhibitor) + ET vs placebo (PBO) + ET (median, 23.8 vs 13.0 mo; HR, 0.55; P < 0.0001; Tripathy D, et al. Lancet Oncol. 2018). Methods: Premenopausal pts (N=672) with HR+/HER2− ABC were treated with RIB or PBO + goserelin and either a nonsteroidal aromatase inhibitor (NSAI; letrozole or anastrozole) or tamoxifen. This is the 2nd of 3 protocol-specified OS analyses (scheduled to occur after >189 deaths [75% of the planned total events]). OS was evaluated by Kaplan-Meier methods, and statistical comparison was made by 1-sided stratified log-rank test, with a protocol-defined Lan-DeMets (O’Brien-Fleming) stopping boundary of p < 0.01018 for superior efficacy. Results: The data cutoff for this prespecified interim analysis was Nov 30, 2018, and the median follow-up was 34.6 mo (min, 28.0 mo). At cutoff, 173 pts were continuing study treatment (RIB, n=116; PBO, n=57), and OS was evaluated after 192 deaths (RIB, n=83; PBO, n=109). RIB + ET demonstrated a significantly longer OS than PBO + ET (median, not reached vs 40.9 mo [95% CI, 37.80 mo–not evaluable]; HR, 0.712 [95% CI, 0.54–0.95]; p = 0.00973). The result crossed the prespecified stopping boundary for superior efficacy. Estimated OS rates with RIB + ET vs PBO + ET at 42 mo were 70.2% vs 64.6%, respectively. In pts who received an NSAI (n=495), RIB + ET demonstrated a consistent OS improvement vs PBO + ET (HR, 0.699 [95% CI, 0.50–0.98]). Posttreatment therapy use was balanced between treatment arms (RIB, 68.9%; PBO, 73.2%). Conclusions: RIB + ET demonstrated a clinically and statistically significant longer OS than ET alone in premenopausal pts with HR+/HER2− ABC. This is the first time that a CDK4/6 inhibitor or any targeted agent + ET has demonstrated significantly longer OS vs ET alone as initial endocrine-based therapy. Clinical trial information: NCT02278120.
Gastrointestinal (Colorectal) Cancer
Prospective pooled analysis of four randomized trials investigating duration of adjuvant (adj) oxaliplatin-based therapy (3 vs 6 months (m)) for patients (pts) with high-risk stage II colorectal cancer (CC).

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Background: 6m of oxaliplatin-based treatment is an option as adj chemotherapy for patients with high-risk stage II CC (T4, inadequate nodal harvest, poorly differentiated, obstruction, perforation or vascular/perineural invasion). The IDEA collaboration showed shorter treatment duration to be appropriate for most pts with stage III colon cancer. The results of the 4 IDEA studies with stage II pts are presented here. Methods: A prospective, pre-planned pooled analysis of high-risk stage II patients from 4 concurrently conducted randomized phase III trials (SCOT, TOSCA, ACHIEVE-2, HORG) was performed to evaluate non-inferiority (NI) of 3m compared with 6m (ref) of adj FOLFOX/CAPOX (regimen preselected, not randomized). The primary endpoint was disease-free survival (DFS), NI was to be declared if the 2-sided 80% confidence interval (CI) for DFS hazard ratio (HR 3m v 6m) estimated by a stratified Cox model was below 1.2. 542 DFS events were required to provide 80% power to declare NI. NI was also examined within regimen, T4 (Yes v No) and inadequate nodal harvest (Yes v No) as pre-planned subgroups. Results: The primary analysis included 3273 randomised pts of which 1254 had FOLFOX and 2019 had CAPOX. There were 552 events and the median follow-up was 60.2 m. There was significantly less grade 3-5 toxicity with 3m treatment (p < .0001). The 5-year DFS rate was 80.7% and 84.0% for 3m and 6m treatment with an estimated DFS HR of 1.18 (80% CI: 1.05-1.31, p for NI = 0.404). For CAPOX the estimated HR was 1.02 (80% CI: 0.88-1.17, p for NI = 0.087) and for FOLFOX the estimated HR was 1.42 (80% CI: 1.19-1.70, p for NI = 0.894). The test for interaction between duration and regimen was not statistically significant (p = .174 adjusted for multiple testing) but was stronger than that for the other subgroups examined. Conclusions: In the overall population non-inferiority for 3m adj treatment in pts with high-risk stage II CC was not shown. As with the stage III population the choice of adj regimen appears important (although this did not reach statistical significance) with a small difference in DFS between 3 and 6 m treatment if CAPOX is used. Clinical trial information: ISRCTN59757862.
FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer.

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Background: NAC is well established in many solid tumours but has not undergone large-scale evaluation in colon cancer. Methods: Pts had operable, non-obstructed colon cancer; CT-predicted stage T3-4, N0-2, M0, and were fit for FOLFOX and surgery. They were randomised 2:1 to the novel sequence (6 wk FOLFOX NAC, then surgery, then 18 wk FOLFOX) or control (surgery then 24 wk FOLFOX). RAS-wt pts allocated to the novel arm could optionally be sub-randomized 1:1 to ± panitumumab (pan) during the NAC phase. Two "dealer's choices" allowed total chemo duration 12 wk instead of 24 (in older/low-risk pts) and OxCap in place of FOLFOX (except in pts randomized ± pan). Primary endpoint is freedom from recurrent or persistent disease after 2 yrs, by ITT. Secondary endpoints include safety, histological stage, completeness of resection, OS. Results: 1052 pts were randomised, Jun 2008-Dec 2016, at 85 centres in UK, Denmark and Sweden. Conclusions: NAC was well tolerated and safe, with no increase in perioperative morbidity and a trend toward fewer serious postoperative complications. Evidence of histological regression was seen in 59% pts after NAC, including some pCRs. This resulted in marked histological downstaging and a halving of the rate of incomplete resections. We observed an improvement in 2-yr failure rate (HR=0.77), but this fell short of statistical significance (p=0.11). NAC for colon cancer improves surgical outcomes and can now be considered as a treatment option; longer follow-up and further trials are required to confirm the long-term benefits, refine its use and optimise case selection. Clinical trial information: 87163246.
NRG-GI002: A phase II clinical trial platform using total neoadjuvant therapy (TNT) in locally advanced rectal cancer (LARC)—First experimental arm (EA) initial results.

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Background: This NCTN multi-arm randomized phase II modular clinical trial platform utilizes TNT with parallel EAs in LARC. EAs are not intended for direct comparison, but rather to test a variety of hypotheses in a consistent high-risk pt population with correlative biomarkers. Primary endpoint (EP) and available secondary EPs from the first EA using veliparib (a PARPi) are reported. NCT02921256. Methods: Stage II/III pts with LARC (with any ONE of the following: distal location [cT3-4 ≤5cm from anal verge, any N]; bulky [any cT4 or tumor within 3mm of mesorectal fascia]; high risk for metastatic disease [cN2]; or not a sphincter-sparing surgery [SSS] candidate) were randomized to neoadjuvant FOLFOX (x 4mo) → chemoRT (cape with 50.4Gy +/- veliparib 400mg PO BID) → surgery 8-12 wks later. Primary EP: 4-point reduction in Neoadjuvant Rectal Cancer (NAR) score with a one-sided α = 0.10 and 80% power. NAR compared by linear model controlling for stratification and possibly other factors. Secondary EPs: OS, DFS, toxicity, pCR, cCR, therapy completion, negative surgical margins, and SSS. Binary EPs compared by Fisher’s exact test. Reported p-values are two-sided. Results: From 10/2016 - 2/2018, 178 pts were randomized (88 control, 90 veliparib). Baseline characteristics were balanced except for candidate for SSS at entry (39% control, 61% veliparib). 140 pts were evaluable for NAR (72 control, 68 veliparib). Mean NAR was 12.6 control (95% CI: 9.8–15.3) vs 13.7 for veliparib (CI: 10.2–17.2). Controlling for stratification (p = 0.69) or stratification and candidate for SSS (p = 0.78), NAR difference was not significant. pCR = 21.6% vs 33.8% (p = 0.14); cCR = 28.2% vs 33.3% (p = 0.60); and SSS = 52.5% vs 59.3% (p = 0.43). Most common grade 3/4 AEs were diarrhea and cytopenias. The EA had two deaths (cardiac arrest [FOLFOX]; enterocolitis [chemoRT]). Conclusions: Veliparib added to chemoRT as part of TNT was safe and without unexpected short-term toxicities but failed to improve the NAR score. Support: U10CA180868, -180822; UG1-189867; U24-196067; AbbVie. Clinical trial information: NCT02921256.
Updated results of TRIBE2, a phase III, randomized strategy study by GONO in the first- and second-line treatment of unresectable mCRC.

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Background: In the phase III TRIBE study FOLFOXIRI/bev significantly improved Response Rate (RR), PFS and OS when compared with FOLFIRI/bev as initial treatment of mCRC. However, the actual advantage by the triplet could be lower when compared with a pre-planned sequential strategy of doublets (FOLFOX, FOLFIRI). TRIBE2 (NCT02339116) is a phase III trial in which unresectable mCRC pts were randomized 1:1 to FOLFOX/bev followed by FOLFIRI/bev after PD (arm A) or FOLFOXIRI/bev followed by the reintroduction of the same regimen after PD (arm B). A pre-planned interim analysis showed a significant advantage for arm B in terms of PFS2, primary endpoint of the study, defined as the time from randomization to PD on any treatment given after first PD or death (PD2).

Methods: The study had 80% power to detect a HR for PFS2 of 0.77 in favor of arm B with an overall 2-sided-α error of 0.05 (0.0131 and 0.0455 for the interim and final analyses, planned at 303 and 466 PFS2 events, respectively). Secondary endpoints included RR, 1st-PFS, i.e. the time from randomization to the first evidence of PD or death (PD1), 2nd-PFS, i.e. the time from PD1 to PD2, and OS. Results: From February 2015 to May 2017, 679 pts (arm A/B: 340/339) were enrolled in 58 Italian sites. Main pts’ characteristics were (arm A/B): right side 38%/38%, synchronous mets 89%/89%, RAS mutant 65%/63%, BRAF mutant 10%/10%. At a median follow up of 30.6 mos, 514 (arm A/B: 272/242) PD2, 594 (arm A/B: 303/291) PD1 and 408 (arm A/B: 217/191) OS events were collected. A significant advantage by upfront FOLFOXIRI/bev was confirmed in terms of PFS2 (19.1 vs 16.4 mos, HR 0.74, 95%CI 0.62-0.88, p=0.001), RR (62% vs 50%, OR 1.61, 95%CI 1.19-2.18, p=0.002) and 1st-PFS (12.0 vs 9.8 mos, HR 0.75, 95%CI 0.63-0.88, p<0.001). A significant OS benefit for pts in arm B was also observed (27.6 vs 22.6 mos, HR 0.81, 95%CI: 0.67-0.98, p=0.033). Out of 594 pts with a PD1 event, 470 (79%, arm A/B: 251/219) received a treatment after PD. In the per-protocol analysis (N=323), pts in arm B showed significantly longer 2nd-PFS (6.5 vs 5.8 mos, HR 0.76, 95%CI 0.59-0.97, p=0.024). Conclusion: Upfront FOLFOXIRI/bev followed by the pre-planned reintroduction of the same agents after PD provided a statistically significant and clinically relevant PFS2 and OS benefit when compared with the pre-planned sequential administration of FOLFOX/bev and FOLFIRI/bev in unresectable mCRC patients. A median OS of 27.6 mos was reached despite the high percentage of pts with poor prognostic features (RAS and BRAF mutations, right side, synchronous mets). Clinical trial information: NCT02339116.
Gastrointestinal (Noncolorectal) Cancer
Olaparib as maintenance treatment following first-line platinum-based chemotherapy (PBC) in patients (pts) with a germline BRCA mutation and metastatic pancreatic cancer (mPC): Phase III POLO trial.

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Background: Pancreatic cancer (PC) pts with a germline BRCA1 and/or BRCA2 mutation (gBRCAm) have shown response to the PARP inhibitor olaparib (Kaufman 2015). POLO is the first phase III trial to evaluate efficacy of maintenance treatment with a PARP inhibitor in PC. Methods: POLO is an international, randomized, double-blind, placebo-controlled trial of pts with a gBRCAm and pancreatic adenocarcinoma who had received ≥16 weeks of first-line PBC for metastatic disease without progression. Pts were randomized 3:2 to maintenance olaparib (O) tablets (300 mg bid) or placebo (P). Treatment began 4–8 weeks after last PBC dose, continuing until investigator-assessed progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) by blinded independent central review (modified RECIST 1.1). Results: We screened 3315 pts, identified 247 with a gBRCAm, randomized 154 (O 92, P 62), and treated 151 (O 90, P 61). Pt characteristics (O/P): age, median (range) 57 (37–84)/57 (36–75); male, 58%/50%; ECOG performance status 0, 71%/61%. With 104 events, PFS was significantly improved with O vs. P (hazard ratio [HR] 0.53; 95% CI 0.35, 0.82; p = 0.0038; median PFS was 7.4 vs. 3.8 months [mo], respectively) and consistent irrespective of response to prior PBC (complete/partial HR 0.62; stable disease HR 0.50). From 6 mo, the % of pts progression-free in the O arm was more than twice that in the P arm (Table). At the interim overall survival analysis (46% maturity), HR was 0.91 (95% CI 0.56, 1.46; p = 0.68). Grade ≥3 adverse events (AE) occurred in 40% of O- and 23% of P-treated pts; 5.5% and 1.7% of pts, respectively, discontinued treatment due to an AE. Conclusions: Maintenance olaparib provided a statistically significant and clinically meaningful improvement in PFS in mPC pts with a gBRCAm who had not progressed on PBC. Safety was consistent with the known profile for olaparib. POLO is the first phase III trial to validate a biomarker-driven treatment in PC. Clinical trial information: NCT02184195.

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*Kaplan-Meier method
**Background:** In metastatic pancreatic cancer (PC), nab-P/G demonstrated significantly longer overall survival (OS) vs G. APACT assessed efficacy & safety of nab-P/G vs G in surgically resected PC.

**Methods:** Treatment (tx)-naive patients (pts) with histologically confirmed PC, macroscopic complete resection, ECOG PS 0/1, & CA19-9 < 100 U/mL were eligible. Stratification factors: resection status (R0/R1), lymph node status (LN+/−), & geographic region. Tx was initiated ≥ 12 wks postsurgery. Pts received nab-P 125 mg/m² + G 1000 mg/m² or G 1000 mg/m² on days 1, 8, 15 of six 28-day cycles. Primary endpoint was disease-free survival (DFS) by independent reviewer (IR); IRs received baseline clinical data & scans. Secondary endpoints were OS & safety.

438 DFS events were needed for 90% power to detect an HR for disease recurrence or death of 0.73 with nab-P/G vs G at a 2-sided significance level of 0.05.

**Results:** 866 pts were randomized. Median age was 64 y (range, 34 - 86); most pts had ECOG PS 0 (60%), LN+ (72%), & R0 (76%). 69% of pts completed 6 tx cycles (nab-P/G, 66%; G, 71%). Median follow up for OS was 38.5 mo. Median IR-assessed DFS (439 events) was 19.4 mo (nab-P/G) vs 18.8 mo (G) (HR, 0.88; 95% CI, 0.729 - 1.063; stratified log-rank P = 0.1824). Investigator-assessed DFS (571 events) was 16.6 mo (nab-P/G) vs 13.7 mo (G) (HR, 0.82; 95% CI, 0.694 - 0.965; nominal P = 0.0168). Interim OS (427 events) was 40.5 mo (nab-P/G) vs 36.2 mo (G) (HR, 0.82; 95% CI, 0.680 - 0.996; nominal P = 0.045). Grade ≥ 3 TEAEs were reported in 86% vs 68% of pts with nab-P/G vs G. The most common grade ≥ 3 hematologic & nonhematologic TEAEs with nab-P/G vs G were neutropenia (49% vs 43%) & fatigue (10% vs 3%). TEAEs led to death in 2 pts in each arm.

**Conclusions:** IR DFS with nab-P/G was not significantly longer vs G; median DFS with G was longer than historical data. DFS by investigator (sensitivity analysis) and interim OS were improved with nab-P/G vs G (HR 0.82 for both). Adjuvant nab-P/G may be an option for pts who are ineligible for FOLFIRINOX. Additional OS follow-up may better support nab-P/G as an option in the adjuvant setting. Clinical trial information: NCT01964430.

**Background:** Level A evidence supports use of CisGem as first-line chemotherapy for ABC; no robust evidence is available for second-line chemotherapy. **Methods:** Pts diagnosed with ABC with disease progression after prior CisGem were randomised (1:1) to either ASC+mFOLFOX or ASC. Randomisation was stratified by serum albumin levels (≤35 vs >35 g/L), platinum sensitivity (determined from first-line CisGem) and disease extent (locally advanced vs metastatic). Pts with ECOG PS0-1, adequate haematological, renal and liver function, and adequate biliary drainage were eligible. Primary end-point was overall survival (OS) (multivariable Cox regression adjusted for stratification factors); sample size: 162 pts delivering 148 events were required (80% power; 5% two-sided alpha) for a hypothesised hazard ratio (HR) of 0.63. Assumed median survival for ASC was 4 months. **Results:** 162 pts (81 in each arm) were randomised (27 March ‘14 - 04 Jan ‘18); median age 65 yrs (range 26-84); sex: 80 (49%) male, 82 (51%) female; primary site: intrahepatic 72 (44%), extrahepatic 45 (28%), gallbladder 34 (21%) and ampullary 11 (7%). Baseline characteristics were balanced between arms except platinum sensitivity (ASC+mFOLFOX 27 pts (33%); ASC 34 pts (42%)). After 150 OS events, the adjusted HR was 0.69 (95% CI 0.50-0.97; p = 0.031; ASC+mFOLFOX vs ASC). Median OS (months (m)), 6m and 12m OS-rate (%) were 6.2m, 50.6% and 25.9% for the ASC+mFOLFOX and 5.3m, 35.5%, 11.4% for the ASC arm, respectively. Grade 3/4 toxicities were reported in 48 (59%) and 32 (39%) pts in the ASC+mFOLFOX and ASC arm, respectively; these were balanced between arms except for fatigue and neutropenia (more frequent in ASC+mFOLFOX arm); data cleaning is ongoing. No chemotherapy-related deaths were reported. **Conclusion:** Survival with ASC was greater than assumed; ASC+mFOLFOX improved OS after progression to CisGem with a clinically meaningful increase in 6m and 12m OS rate. ASC+mFOLFOX should become standard of care in second-line for ABC. Clinical trial information: NCT01926236.
Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study.

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**Background:** KEYNOTE062 (NCT02494583) was a randomized, active controlled study of 1L P or P+C vs C in pts with PD-L1 combined positive score ≥1 (CPS ≥1), HER2-negative, advanced GC.

**Methods:** Eligible pts were randomized 1:1:1 to P 200 mg Q3W for up to 2 y, P+C (cisplatin 80 mg/m² + 5-FU 800 mg/m²/d on d1-d5 Q3W [or capecitabine 1000 mg/m² BID on d1-d14 Q3W per local guideline]) or placebo Q3W + C. Randomization was stratified by region, disease status, and fluoropyrimidine treatment. Primary endpoints were OS in CPS ≥1 and CPS ≥10 for P+C vs C and P vs C and PFS (RECIST v1.1; central review) in CPS ≥1 for P+C vs C. ORR (RECIST v1.1; central review) in CPS ≥1 for P+C vs C was the secondary endpoint. Final analysis cutoff date was 26 Mar 2019.

**Results:** 763 pts (281 with CPS ≥10) were randomized to P+C (257), P (256), or C (250) (Table). Median follow-up was 11.3 mo. P was noninferior to C for OS in CPS ≥1 per prespecified margins. P vs C prolonged OS in CPS ≥10 (median 17.4 vs 10.8 mo; HR 0.69; 95% CI 0.49-0.97) but wasn’t tested per analysis plan. P+C vs C was not superior for OS in CPS ≥1 or CPS ≥10, with a favorable trend for P+C. P+C did not significantly prolong PFS in CPS ≥1. ORR was higher for P+C vs C. Grade 3-5 drug-related AE rates were 17% (P), 73% (P+C), and 69% (C).

**Conclusions:** As 1L therapy for advanced GC, P was noninferior to C for OS in CPS ≥1 with clinically meaningful improvement for OS in CPS ≥10. P+C did not show superior OS and PFS in CPS ≥1 and OS in CPS ≥10. The safety profile was more favorable for P vs C. Clinical trial information: NCT02494583.

<table>
<thead>
<tr>
<th>CPS ≥1</th>
<th>Median, mo (95% CI)</th>
<th>P+C N=257</th>
<th>C N=250</th>
<th>P N=256</th>
<th>C N=250</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS*</td>
<td>12.5 (10.8-13.9)/10.6 (7.7-13.8)/11.1 (9.2-12.8)</td>
<td>11.1 (9.2-12.8)</td>
<td>0.85 (0.70, 1.03)</td>
<td>0.91 (0.74-1.10)</td>
<td>P=0.046</td>
</tr>
<tr>
<td>HR (95% CI)/</td>
<td>99.2% CI</td>
<td>0.85 (0.70, 1.03)</td>
<td>0.91 (0.74-1.10)</td>
<td>P=0.046</td>
<td></td>
</tr>
<tr>
<td>PFS*</td>
<td>6.9 (5.7-7.3)/6.4</td>
<td>2.0 (1.5-2.8)/6.4</td>
<td>P=0.039</td>
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</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.84 (0.70-1.02)</td>
<td>1.66 (1.37-2.01)</td>
<td>P=0.039</td>
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<td></td>
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<tr>
<td>ORR, % (95% CI)</td>
<td>48.6 (42.4-54.9)/14.5 (10.4-19.4)</td>
<td>36.8 (30.8-43.1)/36.8 (30.8-43.1)</td>
<td>P=0.039</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPS ≥10</td>
<td>Median, mo (95% CI)</td>
<td>P+C N=90</td>
<td>C N=90</td>
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<td></td>
</tr>
<tr>
<td>OS*</td>
<td>12.3 (9.5-14.8)/10.8 (8.5-13.8)</td>
<td>10.8 (8.5-13.8)</td>
<td>P=0.058</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.85 (0.62-1.17)</td>
<td>0.69 (0.49-0.97)</td>
<td>P=0.058</td>
<td></td>
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<tr>
<td>PFS*</td>
<td>5.7 (5.5-8.2)/6.1</td>
<td>2.9 (1.6-5.4)/6.1</td>
<td>P=0.058</td>
<td></td>
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<tr>
<td>ORR, % (95% CI)</td>
<td>52.5 (42.2-62.7)/25.0 (16.6-35.1)</td>
<td>36.7 (26.8-47.5)</td>
<td>P=0.058</td>
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</table>
Sarcoma
LBA3  Plenary Session, Sun, 1:00 PM-4:00 PM

ANNOUNCE: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS).

William D. Tap, Andrew J. Wagner, Zsuzsanna Papai, Kristen N. Ganjoo, Chueh-Chuan Yen, Patrick Schoffski, Albiruni Ryan Abdul Razak, Javier Martin Broto, Alexander I. Spira, Akira Kawai, Anders Krarup-Hansen, Axel Le Cesne, Brian Van Tine, Yoichi Naito, Se Hoon Park, Victoria Soldatenkova, Gary Mo, Ashwin Shahir, Jennifer Wright, Robin Lewis Jones; Memorial Sloan Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Allami Egeszsegugyi Kozpont (State Health Center), Budapest, Hungary; Stanford Cancer Institute, Stanford, CA; Taipei Veterans General Hospital, Taipei, Taiwan; Leuven Cancer Institute, University Hospitals Leuven, Belgium; Princess Margaret Hospital, Toronto, ON, Canada; Virgen del Rocio University Hospital, Institute of Biomedicine Research (IBIS)/CSIC/Universidad de Sevilla, Seville, Spain; Virginia Cancer Specialists, Fairfax, VA; National Cancer Center Hospital, Tokyo, Japan; University Hospital Copenhagen, Denmark; Gustave Roussy Cancer Campus, Villejuif, France; Washington University in Saint Louis, MO; National Cancer Center Hospital East, Kashiwa, Japan; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; European Statistics, Oncology, Lilly Deutschland GmbH, Bad Homburg, Germany; Eli Lilly and Company, Indianapolis, IN; Eli Lilly and Company, Erl Wood, United Kingdom; University of Utah, Salt Lake City, UT; Royal Marsden Hospital, The Institute of Cancer Research, London, United Kingdom

Background: Dox is standard therapy in STS. In a Ph 2 trial, olaratumab (a human IgG1 antibody targeting PDGFRα) + dox improved overall survival (OS) and progression-free survival (PFS) vs dox. ANNOUNCE aimed to confirm the OS benefit in advanced STS. Methods: Adult pts with unresectable locally advanced or metastatic STS, anthracycline-naive, and ECOG PS 0-1 were eligible. Pts were randomized 1:1 to olaratumab (20mg/kg Cycle 1, 15mg/kg subsequent cycles) or PBO on Days 1 and 8 of each 21-day cycle combined with dox (75mg/m²) on Day 1 for up to 8 cycles. After 8 cycles, pts with disease control continued olaratumab or PBO until progression or toxicity. Randomization was stratified by histology, prior systemic therapy, ECOG PS, and geographic region. Dexrazoxane use was allowed to mitigate dox-related cardiotoxicity. Primary endpoints were OS in the intent-to-treat (ITT) population and/or leiomyosarcoma (LMS) subset of the ITT population; the study was designed to be positive if either primary endpoint was met. Secondary endpoints included PFS, response/disease control rates, safety, and pharmacokinetics. Results: 509 pts were randomized: 258 in the investigational and 251 in the control arm. Baseline pt characteristics were well balanced. Dexrazoxane was received by 63.0% vs 65.1% of pts (investigational vs control arm, respectively, for all data). In the ITT population, median OS was 20.4 vs 19.8 months (m) (HR=1.05, 95% CI: 0.84-1.30; p = 0.69) and was 21.6 vs 21.9 m in LMS pts (HR=0.95, 95% CI: 0.69-1.31; p = 0.76). Median PFS was lower in the investigational arm in the ITT population (5.4 vs 6.8 m; HR=1.23, 95% CI: 1.01-1.50; p = 0.04) and in LMS pts (4.3 vs 6.9 m, HR=1.22, 95% CI: 0.92-1.63; p = 0.17). Median dox exposure was 6 vs 7 cycles. Safety was similar between arms. Olaratumab serum concentrations reached levels expected from prior trials. Additional subgroup/biomarker results will be presented. Conclusions: ANNOUNCE did not confirm that olaratumab + dox, followed by olaratumab monotherapy, improves OS over dox in pts with advanced STS. Further analyses are warranted to explore the inconsistent outcomes between the Ph 3 and Ph 2 studies. Clinical trial information: NCT02451943.
Background: The predominant pattern of failure of retroperitoneal sarcoma (RPS), frequently associated with subsequent death, is locoregional recurrence. Unlike in limbs, the efficacy of radiotherapy (RT) combined with surgery is not established. Methods: STRASS is a randomized, multicentre, international trial. Eligible patients had histologically-proven localized primary RPS, operable and suitable for radiotherapy. Patients were randomized 1:1 to preoperative RT (3D-CRT or IMRT) 50.4 Gy followed by surgery (RT/S group) or surgery alone (S group), stratified by hospital and performance status (0-1 vs 2). Primary endpoint is abdominal recurrence-free survival (ARFS; local relapse after complete resection, peritoneal sarcomatosis, R2 surgery, progressive disease during RT or unresectable disease). IDMC recommended a sensitivity analysis in which local progression on RT is not regarded as an event for patients who subsequently achieve complete surgical resection. Secondary endpoints were recurrence-free survival, overall survival, acute toxicity profile of RT, perioperative and late complications, and QoL. The study was designed to provide 90% power to show an increase of 20% in the 5-year ARFS rate, from 50% to 70% (corresponding to a HR of 0.52) at 2-sided 5% significance level.

Results: 266 patients from Europe, USA and Canada were randomized between January 2012 and April 2017; 198 patients (74.5 %) had liposarcoma (LPS). Eighteen patients were designated ineligible. Overall rate of re-operation for any complication was 10.1%: 13 (10.9%) and 12 (9.4%) patients in RT/S versus S groups. 19 pts (14%) progressed during RT, 4 of whom did not undergo surgery. 3-year ARFS was 60.4% (95% Confidence interval (CI) 51.4-68.2%) and 58.7% (49.5-66.7%) (HR = 1.01, 95%CI 0.71-1.44, p=0.954) in RT/S versus S groups. In the sensitivity analysis, 3-year ARFS was 66.0% (57.1-73.5%) and 58.7% (49.5-66.7%) in RT/S versus S groups (HR = 0.84, 95% CI 0.58-1.21, p=0.340). In the LPS subgroup, 3-year ARFS (sensitivity analysis) was 71.6% (61.3-79.6%) and 60.4% (49.8-69.5%) in RT/S versus S groups (HR = 0.64, 95% CI 0.40-1.01, p =0.049). Conclusion: STRASS failed to demonstrate a benefit of pre-operative RT for RPS. In the exploratory analysis, preoperative RT may benefit the LPS subgroup. Funding Source: EORTC and EUROSARC FP7 278472. Clinical trial information: EORTC 62092.
Clinical activity of pembrolizumab (P) in undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated/pleomorphic liposarcoma (LPS): Final results of SARC028 expansion cohorts.

Melissa Amber Burgess, Vanessa Bolejack, Scott Schuetze, Brian Andrew Van Tine, Steven Attia, Richard F. Riedel, James S Hu, Lara Emily Davis, Scott H. Okuno, Dennis A. Priebat, Sujana Movva, Damon R. Reed, Sandra P. D’Angelo, Alexander J. Lazar, Emily Zhi-Yun Keung, Denise K. Reinke, Laurence H. Baker, Robert G. Maki, Shreyaskumar Patel, Hussein Abdul-Hassan Tawbi; University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA; Cancer Research and Biostatistics, Seattle, WA; University of Michigan, Ann Arbor, MI; Washington University in St. Louis, St. Louis, MO; Mayo Clinic, Jacksonville, FL; Duke University Medical Center, Durham, NC; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Oregon Health & Science University, Portland, OR; Mayo Clinic, Rochester, MN; Washington Hospital Center, Washington, DC; Fox Chase Cancer Center, Philadelphia, PA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Memorial Sloan-Kettering Cancer Center, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; Brigham and Womens Hosp, Brookline, MA; SARC, Ann Arbor, MI; Northwell Cancer Institute and Cold Spring Harbor Laboratory, New Hyde Park, NY

Background: Immune checkpoint inhibitors have demonstrated activity in multiple tumor types but their activity in soft tissue sarcomas remains limited. In the multicenter phase II study, SARC028, the anti-PD-1 antibody, P demonstrated objective responses that were largely restricted to UPS and LPS subtypes. We now report outcomes from 2 expansion cohorts of SARC028 in advanced UPS and LPS.

Methods: To further confirm the clinical activity of P in UPS and LPS, we enrolled an additional 30 pts in each of 2 expansion cohorts for a total of 40 UPS and 40 LPS pts. Primary endpoint was investigator-assessed response by RECIST v1.1. Secondary endpoints were safety, progression-free survival (PFS), 12-week PFS rate, and overall survival (OS). An ORR of 25% was considered clinically meaningful and < 10% was considered to show lack of efficacy. P was to be considered a success if 8 or more of 40 enrolled patients had a PR or better (1-sided α = 0.042, 82% power). Pts age ≥18 with advanced, refractory UPS or LPS received 200 mg of P IV every 3 weeks until progression or unacceptable toxicity.

Results: Preliminary results from the first 10 pts in each of the UPS and LPS cohorts have been reported. We now present summary data after enrolling an additional 30 pts in each cohort. The ORR in the UPS cohort was 23% (9/40), with an additional 5/30 PRs observed in the expansion cohort (total 2 CRs, 7 PRs). In the LPS cohort, the ORR was 10% (4/39 evaluate pts), with an additional 2/30 PRs observed (total 4 PRs). Median PFS for the UPS group was 3 months [95% CI: 2, 5] and 2 months [95% CI: 2, 4] for the LPS group. 12-week PFS rate was 50% in UPS [95% CI: 35, 65] and 44% in LPS [95% CI: 28, 60]. The UPS group had a median OS of 12 months [95% CI: 7, 34] and 13 months [95% CI: 8, NR] for the LPS group. P was well tolerated with no unexpected toxicities.

Conclusions: The UPS cohort achieved its primary endpoint, however the activity of P in UPS deserves further evaluation in a randomized study. The activity of P was not confirmed in the LPS cohort. Ongoing biomarker analyses may direct better patient selection and guide future combination strategies. Clinical trial information: NCT02301039.
Central Nervous System Tumors
Second interim and first molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q codeletion.

Martin J. Van Den Bent, Sara Erridge, Michael A. Vogelbaum, Anna K. Nowak, Marc Sanson, Alba Ariela Brandes, Wolfgang Wick, Paul M. Clement, Jean-Francois Baurain, Warren P. Mason, Helen Wheeler, Michael Weller, Kenneth D. Aldape, Mircea Tesileanu, Vassilis Golfinopoulos, Thierry Gorlia, Brigitte G. Baumert, Pim French; Erasmus MC Cancer Centre, Rotterdam, Netherlands; Edinburgh Cancer Research UK Centre, Edinburgh, United Kingdom; Cleveland Clinic, Cleveland, OH; Sir Charles Gairdner Hospital, Perth, WA, Australia; Universite Pierre Et Marie Curie-Paris 6, Centre de Recherche de L’institut Du Cerveau et de la Moelle Épinière (CRICM), Neurologie 2, Paris, France; AUSL-IRCCS Institute of Neurological Sciences, Bologna, Italy; National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), Heidelberg, Germany; Department of Oncology, KU Leuven, Leuven Cancer Institute, Leuven, Belgium; Department of Medical Oncology, Institut Roi Albert II, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Bruxelles, Belgium; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Royal North Shore Hospital, Department of Oncology, St Leonards, Australia; Laboratory of Molecular Neuro-Oncology, Department of Neurology, and Neuroscience Centre Zurich, University Hospital and University of Zurich, Zurich, Switzerland; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, VU University Medical Center, Amsterdam, Netherlands; Department of Neuropathology, Erasmus Medical Center – Cancer Institute, Rotterdam, Netherlands; Erasmus MC Cancer Institute, Rotterdam, Netherlands; EORTC Headquarters, Brussels, Belgium; Dept Radiation-Oncology, University Hospital Bonn, Germany; Bonn, Germany; Erasmus MC, Rotterdam, Netherlands

Background: The 1st interim analysis of the CATNON trial showed benefit from adjuvant (adj) temozolomide (TMZ) on overall survival (OS) but remained inconclusive about concurrent (conc) TMZ. A 2nd interim analysis was planned after 356 events. Methods: The 2x2 factorial design phase III CATNON trial randomized 751 adult patients with newly diagnosed non-codeleted anaplastic glioma to either 59.4 Gy radiotherapy (RT) alone; the same RT with concTMZ; the same RT and 12 cycles of adjTMZ or the same RT with both concTMZ and adjTMZ (doi: 10.1016/S0140-6736(17)31442-3). MGMT promoter methylation (MGMTmethyl) status was re-assessed with the Infinium Methylation EPIC Beadchip using the MGMT_STP27 model. Isocitrate dehydrogenase 1 and 2 (IDH) mutation (mt) status was assessed with glioma targeted Agilent SureSelect baits sequence using an Illumina HiSeq2500 Rapid PE100. Results: With a median follow-up of 56 months and 356 events, the hazard ratio (HR) for OS adjusted for stratification factors after concTMZ was 0.968 (99.1% CI 0.73, 1.28). 5-year OS was 50.2% with and 52.7% without concTMZ (95% CI [44.4, 55.7] and [46.9, 58.1]). An IDHmt was found in 335 of 480 assessed cases (70%). Median OS was 19 mo (95% CI 16.3, 22.3) in IDHwt tumors and 116 mo (95% CI 82.0, 116.6) in IDHmt tumors. HR for OS after concTMZ in patients with known IDH status. Clinical trial information: NCT00626990. IDHmt was predictive of benefit from adjTMZ (IDHmt HR: 0.41, 95% CI 0.27, 0.64; IDHwt: HR 1.05, 95% CI 0.73, 1.52; interaction test p = 0.001). In IDHmt patients that received adjTMZ, the HR for OS after concTMZ was 0.71 (95% CI 0.35, 1.42, p=0.32). MGMTmeth was found in 288 of 410 assessed cases (70%), interaction test for concTMZ (p = 0.092) and adjTMZ (p = 0.166) did not reach statistical significance. Conclusions: In the entire study cohort, concTMZ did not increase OS. However, in IDHmt tumors a trend towards benefit of concTMZ is present. AdjTMZ increased OS in IDHmt but not in IDHwt tumors. The ongoing molecular analyses and further follow-up will allow full assessment of efficacy in the molecular subgroups.

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>events</th>
<th>HR [95% CI]</th>
<th>interaction test</th>
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<tbody>
<tr>
<td>IDH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wt</td>
<td>145</td>
<td>120</td>
<td>1.27 [0.89, 1.82]</td>
<td>p = 0.19</td>
</tr>
<tr>
<td>mt</td>
<td>335</td>
<td>92</td>
<td>0.67 [0.44, 1.03]</td>
<td>p = 0.06</td>
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</table>

Randomized phase IIb clinical trial of continuation or non-continuation with six cycles of temozolomide after the first six cycles of standard first-line treatment in patients with glioblastoma: A Spanish research group in neuro-oncology (GEINO) trial.

Carmen Balana, Carlos Mesia Barroso, Sonia Del Barco Berron, Estela Pineda Losada, Jose Munoz-Langa, Anna Estival, Ramon De Las Penas, Jose Fuster, Miguel J. Gil Gil, L Miguel Navarro, Miriam Alonso, Ana Herrero, Maria Angeles Vaz Salgado, Sergi Peralta, Clara Olier, Pedro Perez-Segura, Marta Covela Ria, Cristina Carrato, Carolina Sanz, Juan Manuel Sepulveda-Sanchez; Institut Catala Oncologia Badalona, Hospital Germans Trias I Pujol, Badalona/Barcelona, Spain; Institut Catala d’Oncologia Hospital Duran i Reynals, Barcelona, Spain; Institut Catala d’Oncologia, Hospital Universitari Josep Trueta, Girona, Spain; Medical Oncology, Hospital Clinic de Barcelona, Barcelona, Spain; Hospital Universitario La Fe, Valencia, Spain; Medical Oncology Department. Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Barcelona, Spain; Oncology Service. Hospital Provincial de Castellon, Castellon, Spain; Hospital Son Espases, Palma De Mallorca, Spain; Breast Cancer Unit & Medical Oncology Department, Institut Catala d’Oncologia, IDIBELL, Barcelona, Spain; Department of Medical Oncology, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain; Instituto de Biomedicina de Sevilla, IBIIS/Hospital Universitario Virgen del Rocio/CSIC/Universidad de Sevilla, Seville, Spain; Hospital Miguel Servet, Zaragoza, Spain; Medical Oncology Department, Ramon y Cajal University Hospital, Madrid, Spain; Hospital Sant Joan de Reus, Reus/Tarragona, Spain; H Universitario Fundacion Alcorcon, Alcorcon, Spain; Medical Oncology Department, Hospital Universitario Clinico San Carlos, Madrid, Spain; Hospital Universitario Lucas Augusti, Lugo, Spain; Hospital Germans Trias i Pujol, Barcelona, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain

Background: The GEINO-14-01 trial (NCT02209948) investigated the role of extending temozolomide (TMZ) for 6 cycles after the standard 6 cycles to improve 6m-PFS, SLP and OS in newly diagnosed glioblastoma (GBM) patients (p). Methods: Between 08/2014 and 11/2018, 166 p were screened and 159 randomized to extend (80p) or not (79p) TMZ treatment for 6 cycles after proving stable disease in the MRI performed before inclusion. Centralized review of histology and determination of MGMT status, if not previously available, were performed before randomizing patients. Two criteria of stratification were used: MGMT status and presence/absence of residual disease on the basal MRI (defined as a residual enhancement larger than 1cm in one). The primary endpoint was differences in 6mPFS, secondary endpoints were differences in PFS, OS, toxicity, between arms and per stratification factors. Results: Median age was 60.3 (range 29-83), 97p (61%) were methylated, basal MRI showed residual disease in 57p (35.8%). After a median follow up of 14.0 months, with 121 p(76.1%) already progressed and 81p (50.9%) already dead, median PFS is presented. Median (m) PFS is 8.0 months (95%CI: 5.7-10.2). There is no difference in mPFS between arms (adjusted HR = 0.98, 95% CI: 0.82-1.18, P = 0.907). Methylated tumors had longer mPFS (HR=0.57, 95% CI: 0.39-0.83, P=0.004) irrespectively to the study treatment. Conclusions: There is not apparent benefit of continuing TMZ treatment for more than 6 cycles. Data will be actualized for the congress. Supported by a Grant of the ISCIII: PI13/01751. Clinical trial information: NCT02209948.
Updated predictive analysis of the WHO-defined molecular subgroups of low-grade gliomas within the high-risk treatment arms of NRG Oncology/RTOG 9802.

Erica Hlavin Bell, Minhee Won, Jessica L. Fleming, Aline P. Becker, Joseph P. McElroy, Edward G. Shaw, Minesh P. Mehta, David G. Brachman, Stanley Z. Gertler, Albert D. Murtha, Christopher J. Schultz, David B. Johnson, Nadia N. Laack, Grant Kirton Hunter, Ian R. Crocker, Arnab Chakravarti; The Ohio State University, Columbus, OH; NRG Oncology Statistics and Data Management Center, Philadelphia, PA; Wake Forest School of Medicine, Winston-Salem, NC; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Saint Joseph’s Hospital and Medical Center, Phoenix, AZ; Ottawa Hospital and Cancer Center, Ottawa, ON, Canada; Cross Cancer Institute, Edmonton, AB, Canada; Medical College of Wisconsin, Milwaukee, WI; St. Francis Reg West Med Ctr, Lagrange, WY; Mayo Clinic, Rochester, MN; Intermountain Healthcare, Murray, UT; Emory University Hospital/Winship Cancer Institute, Atlanta, GA

Background: This study sought to update the predictive significance of the three WHO-defined molecular glioma subgroups (IDHwt, IDHmt/non-codel, and IDHmt/codel) in the subset of specimens available for analysis in NRG Oncology/RTOG 9802, a phase III trial of high-risk low-grade gliomas (LGGs) treated with radiation (RT) with and without PCV after biopsy/surgical resection. Notably, this is the first phase III study to evaluate the predictive value of the WHO subgroups in LGGs using prospectively-collected, well-annotated long-term overall survival data, in a post-hoc analysis.

Methods: IDH1/2 mutation status was determined by immunohistochemistry and/or next-generation sequencing. 1p/19q status was determined by Oncoscan and/or 450K methylation data. Treatment effects on overall survival (OS) and progression-free survival (PFS) by marker status were determined by the Cox proportional hazard model and tested using the log-rank test in a secondary and exploratory analysis.

Results: Of all the randomized eligible high-risk G2 patients (N = 251) in NRG Oncology/RTOG 9802, 106 (42%) patients had tissue available with sufficient quality DNA for profiling. Of these, 80 (75%) were IDHmut; 43 (41%) were IDHmut/non-co-deleted, 37 (35%) were IDHmut/co-deleted, and 26 (24%) were IDHwt. Upon univariate analyses, no significant difference in either PFS or OS was observed with the addition of PCV in the IDHwt subgroup. Both the IDHmut/non-co-deleted and IDHmut/co-deleted subgroups were significantly correlated with longer PFS (HR = 0.32; p = 0.003; HR = 0.13; p < 0.001) and OS (HR = 0.38; p = 0.013; HR = 0.21; p = 0.029) in the RT plus PCV arm, respectively.

Conclusions: Our analyses suggest that both IDHmut/non-co-deleted and IDHmut/co-deleted subgroups received benefit from treatment with PCV although sample size is limited and analyses are post-hoc. Our results also support the notion that IDHwt high-risk LGG patients do not benefit from the addition of PCV to RT. Funding: U10CA180868, U10CA180822, and U24CA196067. Also, R01CA108633, R01CA169368, RC2CA148190, U10CA180850-01, BTFC, OSU-CCC (all to AC). Clinical trial information: NCT00003375.
Single agent ONC201 in adult recurrent H3 K27M-mutant glioma.

Isabel Arrillaga, Sylvia Kurz, Ashley Sumrall, Nicholas A. Butowski, Rebecca A. Harrison, John Frederick De Groot, Nicole A. Shonka, Frank S. Lieberman, Yazmin Odia, Rohinton Tarapore, Krystal Merdinger, Joshua E. Allen, Wolfgang Oster, Minesh P. Mehta, Timothy Francis Cloughesy, Andrew S. Chi, Andrew B. Lassman, Tracy Batchelor, Patrick Y. Wen; Massachusetts General Hospital, Boston, MA; NYU Langone Medical Center and School of Medicine, New York, NY; Levine Cancer Institute, Charlotte, NC; University of California, San Francisco, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Nebraska Medical Center, Omaha, NE; University of Pittsburgh Medical Center, Pittsburgh, PA; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Oncoceutics, Philadelphia, PA; University of California Los Angeles, Los Angeles, CA; Columbia University Irving Medical Center, New York, NY; Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA

Background: H3 K27M-mutant glioma is associated with a poor prognosis and there is no effective therapy following radiation. We report the clinical experience with single agent ONC201, the first small molecule DRD2 antagonist in oncology, in adults with recurrent H3 K27M-mutant glioma. Methods: Twenty-nine adult patients with recurrent H3 K27M-mutant glioma have been treated with single agent ONC201 as of January 20, 2019: 19 patients on NCT03295396; 8 patients on NCT02525692; 2 patients on compassionate use protocols under the Sponsor's IND. Median age was 57 years old (range: 17-74), median prior lines of therapy was 2 (range: 1-4) and all patients received prior radiation (median 8.5 months from radiation completion to ONC201 initiation). ONC201 was orally administered at 625 mg weekly, except for one patient dosed once every 3 weeks.

Results: As of February 5, 2019, 13 of 29 patients remain on-trial within median follow up of 6.5 months (range: 0.6-33.6), 8 patients are alive but off-trial with median follow up of 2.4 months (range: 0.2-9), and 8 patients have expired. Nine of 29 patients (31%) remain progression-free on ONC201 with a median follow up of 6.5 months (range 0.6-33.6). No dose-limiting toxicities or treatment discontinuations due to toxicity occurred. Three patients have experienced durable partial responses by RANO (4.3-28.5 months). In addition, one patient experienced complete regression that continues for 14 months of all 1 cm tumor lesions that are not measurable by RANO. Furthermore, 10 patients had a best response of stable disease by RANO, 12 patients experienced progressive disease, and 3 patients are not yet evaluable. Among the patients with a best response of stable disease by RANO, one patient had > 50% tumor regression in the basal ganglia that did not qualify as a partial response by RANO due to a new lesion on a confirmatory scan. Another patient with stable disease by RANO has had 37% tumor regression so far in the brainstem and remains on-treatment for 6 months. All tumor regressions remain durable to date and some were associated with improvements in disease-associated neurological symptoms.

Conclusions: Single agent ONC201 is well tolerated and clinically active in adult recurrent H3 K27M-mutant glioma patients. Clinical trial information: NCT03295396; NCT02525692.
Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant
Effect of gilteritinib on survival in patients with \( \text{FLT3}^{\text{mut+}} \) relapsed/refractory (R/R) AML who have common AML co-mutations or a high \( \text{FLT3} \)-ITD allelic ratio.

Mark J. Levis, Alexander E. Perl, Giovanni Martinelli, Jorge E. Cortes, Andreas Neubauer, Elin Berman, Pau Montesinos, Maria R. Baer, Richard A. Larson, Wen-Chien Chou, Hisayuki Yokoyama, Christian Recher, Sung-Soo Yoon, Jason E Hill, Matt Rosales, Charles Liu, Erkut Bahceci; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; The University of Texas MD Anderson Cancer Center, Houston, TX; Univeristätsklinikum Giessen und Marburg GmbH, Marburg, Germany; Memorial Sloan Kettering Cancer Center, New York, NY; Hospital Universitari i Politècnic La Fe, Valencia & CIBERONC, Instituto Carlos III, Madrid, Spain; University of Maryland Greenebaum Comprehensive Cancer Center (UMGCC), Baltimore, MD; The University of Chicago, Chicago, IL; National Taiwan University, Taipei City, Taiwan; Sendai Medical Center, National Hospital Organization, Sendai, Japan; Institut Universitaire du Cancer Toulouse–Oncopole, Cedex, France; Seoul National University, Seoul, South Korea; Astellas Pharma US, Inc., Northbrook, IL

Background: The FLT3 inhibitor, gilteritinib, showed superior response and overall survival (OS) compared with salvage chemotherapy (SC) in patients (pts) with \( \text{FLT3}^{\text{mut+}} \) R/R AML in the phase 3 ADMIRAL study. We analyzed the impact of baseline co-mutations and \( \text{FLT3} \)-ITD allelic ratio (AR) on response and OS. 

Methods: A total of 37 recurrently mutated genes in AML (Archer Core Myeloid Panel) were analyzed by next-generation sequencing; the cutoff for co-mutation positivity (co-mut+) was $\geq 0.027$. Baseline \( \text{FLT3} \)-ITD AR (\( \text{FLT3} \)-ITD to \( \text{FLT3} \) wild-type DNA) was measured by the LeukoStrat CDx \( \text{FLT3} \) Mutation Assay. The median \( \text{FLT3} \)-ITD AR value of 0.77 was used to define high ($\geq 0.77$) vs low ($<0.77$) \( \text{FLT3} \)-ITD AR. 

Results: Analysis of 361 \( \text{FLT3}^{\text{mut+}} \) pts identified four major co-mutation cohorts, each with $\geq 10\%$ of pts: \( NPM1 \) (n=173; 47.9%), \( DNMT3A \) (n=115; 31.9%), \( DNMT3A/NPM1 \) (n=86; 23.8%), and \( WT1 \) (n=65; 18.0%). In addition, seven pts (1.9%) had all three co-mutations (ie, \( NPM1 \), \( DNMT3A \), and \( WT1 \)). The gilteritinib arm had superior response rates and OS across all four major co-mutation cohorts, with the greatest survival benefit in pts with \( DNMT3A/NPM1 \) co-mut+ (Table). In \( \text{FLT3} \)-ITD AR analyses (n=335), gilteritinib conferred longer OS than SC in pts with a high or low \( \text{FLT3} \)-ITD AR (gilteritinib: high \( \text{FLT3} \)-ITD AR, 7.1 mos vs low \( \text{FLT3} \)-ITD AR, 10.6 mos; SC: high \( \text{FLT3} \)-ITD AR, 4.3 mos vs low \( \text{FLT3} \)-ITD AR, 6.9 mos). In both arms, OS was longer in the low \( \text{FLT3} \)-ITD AR cohort than the high \( \text{FLT3} \)-ITD AR cohort but the difference in the gilteritinib arm was not statistically significant (gilteritinib: HR=1.341, \( P=0.0712 \); SC: HR=2.01, \( P=0.0021 \)).

Conclusions: The ADMIRAL trial shows that the clinical benefit of gilteritinib in \( \text{FLT3}^{\text{mut+}} \) R/R AML is maintained regardless of \( NPM1 \), \( DNMT3A \), \( DNMT3A/NPM1 \), or \( WT1 \) co-mut+ or high \( \text{FLT3} \)-ITD AR. Clinical trial information: NCT02421939.

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<th>Patients</th>
<th>CR/CRh (%)</th>
<th>Median OS (mos)</th>
<th>HR</th>
<th>P-Value</th>
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<tr>
<td>ITT population (n=371)</td>
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<tr>
<td>Gilteritinib</td>
<td>34.0</td>
<td>15.3</td>
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<td>SC</td>
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<tr>
<td>Co-mut+ cohorts</td>
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<tr>
<td>( NPM1 ) (n=173)</td>
<td>32.2</td>
<td>12.1</td>
<td>8.3</td>
<td>5.1</td>
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<tr>
<td>( DNMT3A ) (n=115)</td>
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<td>12.5</td>
<td>9.1</td>
<td>5.5</td>
</tr>
<tr>
<td>( DNMT3A/NPM1 ) (n=86)</td>
<td>40.0</td>
<td>9.7</td>
<td>10.8</td>
<td>5.0</td>
</tr>
<tr>
<td>( WT1 ) (n=65)</td>
<td>35.6</td>
<td>5.0</td>
<td>9.1</td>
<td>3.4</td>
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</tbody>
</table>

Association of smoking with poor risk ELN 2017, cytogenetics/molecular profile, and survival outcomes in acute myeloid leukemia.

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Background: Smoking increases the relative risk of AML by 40% and 25% in active and former smokers, respectively, compared with non-smokers (Fircanis et al., 2014). While the relationship of smoking with AML development is recognized, whether smoking impacts underlying AML biology and clinical outcome remains ill-defined. Methods: Newly diagnosed, treatment naive AML pts seen at MDACC between 2012 and 2017 with available smoking history were evaluated, along with baseline parameters, co-occurring mutations, cytogenetics and clinical outcome. Results: We identified 858 pts [486 (57%) male; median age 67 yrs (14-97)], representing 535 (62%) treatment naive and 323 (38%) salvage pts. Smoking status was recorded as smokers (active = 39 pt, former = 380 pt), versus never smoker (439 pt). In tx naive group, smoking is associated with lower remission rates (OR 0.63, 95% CI 0.43-0.94, p = 0.02) and inferior OS (HR = 1.6, 95% CI 1.27-2.02, p < 0.001). Smoking status was not significant in multivariate analysis including AML biologic characteristics and ELN 2017 risk stratification. Therefore we postulated that worse OS may be driven by smoking associated AML biology rather than smoking associated comorbidities. Indeed, in univariate analysis smoking was associated with poor ELN risk (p = 0.015), complex karyotype (p = 0.0002), and TP53 mutation (p = 0.0235) while negatively associated with NPM1 (p = 0.018), FLT3-ITD (p = 0.032) and GATA2 (p = 0.0497). Age was a significant cofounder between smokers vs non-smoker ( < 0.0001). After controlling for age, significance was retained for ELN risk, complex karyotype and GATA2 at p = 0.0454, p = 0.0006, p = 0.048 respectively, while significance was lost for NPM1 (p = 0.079), FLT3-ITD (p = 0.1) and TP53 (p = 0.084). Analysis of young pts (< 60 yr), smoking is positively associated with complex karyotype (p = 0.0042) and TP53 (p = 0.0289), and negatively associated with RUNX1 (p = 0.0143) and IDH2 (p = 0.0357). Conclusions: We report the largest analysis of smoking status and impact on molecular, cytogenetics, and AML clinical outcomes. Smoking history is associated with poorer risk molecular and cytogenetics, lower response rate and shorter survival in treatment naive patients.
ENESTop 192-week results: Treatment-free remission (TFR) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) after stopping second-line (2L) nilotinib (NIL).

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Background: In the ENESTop study (NCT01698905) of TFR in pts with CML-CP who achieved a sustained deep molecular response (MR) with 2L NIL, 57.9% remained in TFR 48 wks after stopping NIL (primary endpoint). Analyses at 144 wks showed durability of TFR. Data from longer follow-up (192 wks) evaluating the maintenance of TFR are reported. Methods: Pts treated with ≥2 y NIL after ≥4 wks imatinib (≥3 y total) and achieving MR4.5 (BCR-ABL1 IS ≤0.0032%) on NIL were eligible. After a 1 y consolidation, pts with no confirmed loss of MR4.5 could attempt TFR. NIL was resumed upon loss of major MR (BCR-ABL1 IS ≥0.1%) or confirmed loss of MR4 (BCR-ABL1 IS ≤0.01%). At the data cut-off (Sep 24 2018), all pts had completed ≥192 wks of TFR, resumed NIL, or discontinued the study. Results: By the data cut-off, of 126 pts entering TFR, 56 were ongoing, 59 had resumed NIL, and 11 had discontinued. TFR rate at 192 wks was 46.0% (58/126; 95% CI, 37.1–55.1%); all but 1 of the 58 pts were in MR4.5. Only 1/61 pts in TFR at 144 wks lost response by 192 wks (confirmed loss of MR4); another 2 pts discontinued due to serious AE (polycythemia vera) and pt/guardian decision, respectively. Of 59 pts who resumed NIL, 56 (94.9%) and 55 (93.2%) regained MR4 and MR4.5 respectively. 40/56 pts (71.4%) who regained MR4 had stable MR4 at 96 wks (12 discontinued < 96 wks, and 4 remained on study with < 96 wks, after regaining MR4); 37/55 pts (67.3%) who regained MR4.5 had stable MR4.5 at 96 wks (12 discontinued < 96 wks, and 6 remained on study with < 96 wks, after regaining MR4.5). There were no disease progressions, deaths due to CML, or new deaths since the 144-wk analysis. The 192 wk treatment-free survival rate was 50.3% (95% CI, 41.2–58.7%). Of 62 pts who remained in TFR for > 144 wks, 13.3%, 53.2%, 21.0%, 14.5% and 3.2% had musculoskeletal pain AEs during consolidation and each subsequent 48 wk period of TFR. Among 59 pts who resumed NIL, most common AEs were hypertension (20.3%) and arthralgia (13.6%); the majority of AEs were grade 1/2. Conclusions: Results demonstrate long-term durability and safety of TFR following 2L NIL, with no disease progressions or CML-related deaths, and musculoskeletal pain AEs were transient. Clinical trial information: NCT01698905.
End of phase I results of ZUMA-3, a phase 1/2 study of KTE-X19, anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in adult patients (pts) with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL).

Bijal D. Shah, Michael Russell Bishop, Olalekan O. Oluwole, Aaron Logan, Maria R. Baer, William Bruce Donnellan, Kristen Marie Carr-O’Dwyer, Houston Holmes, Martha Lucia Arellano, Armin Ghobadi, John M. Pagel, Yi Lin, Ryan Daniel Cassaday, Jae Hong Park, Armen Mardiros, Tong Shen, Lovely Goyal, Remus Vezan, Rajul K. Jain, William G. Wierda; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; University of Chicago Medical Center, Chicago, IL; Vanderbilt-Ingram Cancer Center, Nashville, TN; Helen Diller Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; University of Maryland Greenebaum Comprehensive Cancer Center (UMGCC), Baltimore, MD; Sarah Cannon Research Institute, Nashville, TN; University of Rochester Medical Center, Rochester, NY; Texas Oncology–Baylor Charles A. Sammons Cancer Center, Dallas, TX; Winship Cancer Institute, Atlanta, GA; Washington University School of Medicine and Siteman Cancer Center, Saint Louis, MO; Swedish Cancer Institute, Seattle, WA; Mayo Clinic, Rochester, MN; University of Washington School of Medicine and Fred Hutchinson Cancer Research Center, Seattle, WA; Memorial Sloan-Kettering Cancer Center, New York, NY; Kite, a Gilead Company, Santa Monica, CA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: KTE-X19 is an autologous anti-CD19 CAR T cell therapy under investigation for adult R/R ALL. In an interim analysis of Phase 1 of ZUMA-3, we reported manageable safety and encouraging efficacy of KTE-X19; 72% of pts achieved a complete remission (CR) or CR with incomplete bone marrow (BM) recovery (CRi; Wierda et al, ASH 2018. #897). Here, we present end of Phase 1 results. Methods: Adults with R/R B cell ALL, $>5\%$ BM blasts, and ECOG 0-1 received 2, 1, or $0.5 \times 10^6$ KTE-X19 cells/kg after conditioning chemotherapy. Revised adverse event management (rAE mgmt) was implemented for additional pts in a $1 \times 10^6$ dose cohort: corticosteroids were given earlier at onset of Grade $\geq 2$ neurologic events (NEs) and tocilizumab was used only for active toxicity. The primary endpoint was the dose-limiting toxicity (DLT) rate. Key additional endpoints were KTE-X19 levels, incidence of AEs, minimal residual disease (MRD), and CR/CRi rate. Results: As of 9/27/18, 45 pts had received KTE-X19 (median follow-up [f/u], 16 mo). The median age was 46 y (range, 18–77); 30 pts (66%) had $\geq 3$ prior therapies and the median pre-conditioning BM blasts was 70% (range, 0–97). Six, 23, and 16 pts received 2, 1, and $0.5 \times 10^6$ cells/kg, respectively. There were no DLTs in the DLT-evaluable pts. The most common Grade $\geq 3$ AEs were hypotension (38%), pyrexia (38%) and thrombocytopenia (31%). There were 2 previously reported KTE-X19–related Grade 5 AEs of cerebral infarction and multiorgan failure, both in the context of CRS. Grade $\geq 3$ CRS and NEs occurred in 13 (29%) and 17 (38%) pts, respectively. Of 41 pts with $\geq 2$ mo of f/u, 68% had CR/CRi, and 73% had undetectable MRD. Of 19 pts with $\geq 2$ mo of f/u treated with $1 \times 10^6$ cells/kg, 16 (84%) had a CR/CRi and the median event-free survival was 15 mo. In 9 pts treated with $1 \times 10^6$ cells/kg and rAE mgmt, 2 (22%) had Grade 3 CRS and 1 (11%) had Grade 3 NE with no Grade 4/5 events. Conclusions: KTE-X19 dosing and safety mgmt have been successfully refined by testing 3 cell doses and evaluating a new AE mgmt guideline with altered corticosteroids/tocilizumab use for NE/CRS. Pivotal Phase 2 is ongoing at the $1 \times 10^6$ dose with rAE mgmt. Clinical trial information: NCT02614066.
Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia
Effect of montelukast and rupatadine on rituximab infusion time, rate, severity of reactions, and cost of administration.

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Background: Rituximab is associated with frequent infusion reactions which carry significant burden to patients and health care practitioners. Standard pre-medications (SP) do not prevent reactions sufficiently. Rupatidine (R) and Montelukast (M) are used for symptomatic treatment of urticaria and allergic rhinitis. We assessed addition of R, M and their combination on Rituximab infusion, rate, severity of reactions and cost of administration. Methods: Adult patients with lymphoproliferative disorders treated at our cancer center between Jan 2018 to Jan 2019 were evaluated with Rituximab-containing regimens. Since the majority of reactions occur during the first infusion, our study was limited to the initial Rituximab treatment. Patients received either SP with diphenhydramine/acetaminophen and additional R, M or R+M combination. Comparative analysis of infusion time/rate, severity of infusion reactions, number of rescue medications and cost of Rituximab infusions among groups was performed using one-way ANOVA with Tukey post-hoc or chi-square. The study was approved by our institutional IRB. Results: Patients received either: 1) SP; 2) SP + Rupatadine (R) 10 mg; 3) SP + Montelukast (M) 10 mg; or 4) both (SP+R+M). Patient demographics are shown in the table. Compared to SP, the R, M and R+M groups had greater improvement in Rituximab delivery. Mean infusion time was 306 [range 235-441] min. in SP, 254 [105-390] in M, 265 [193-350] in R and 248 [196-342] in R+M groups, (p=0.0001). Infusion reactions occurred in 92% in SP vs. 38, 45, 33% in M, R and R+M groups (p=0.0001). Median reaction grade was 2 in SP, 1 (M), 0 (R and R+M). Median number of rescue medications was 3 [0-10] in SP vs 0 [0-7] in M, R and R+M groups. Cost of rescue medications (US$) was 38 [0-63] (SP), 11 [0-50] (M), 17 [0-63] (R), 12 [0-58] (R+M) groups (p<0.0001). Mean nursing cost (US$) per patient infusion was calculated as 269 [207-388] in SP vs 222 [92-343] (M), 233 [170-308] (R), 218 [174-301] (R+M) group. Conclusions: Addition of R, M and particularly R+M significantly improved Rituximab delivery, lowered the rate and severity of infusion reactions, and lowered the cost of Rituximab administration.

Overall Survival: Age and Toxicity.

<table>
<thead>
<tr>
<th></th>
<th>SP</th>
<th>M</th>
<th>R</th>
<th>M+R</th>
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<tr>
<td>N (pts)</td>
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<td>21</td>
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<td>Mean age</td>
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<tr>
<td>Male (%)</td>
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<td>Hx of allergy (%)</td>
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<td>Disease (%)</td>
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<td>Mean Rituximab dose (mg):</td>
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Effect of fixed-duration venetoclax plus obinutuzumab (VenG) on progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD–) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities.

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Background: The multinational, open-label, phase 3 CLL14 trial compared fixed-duration targeted VenG treatment with chlorambucil-obinutuzumab (ClbG) in previously untreated pts with CLL and comorbidities. Here we present endpoint analyses with particular emphasis on MRD– and PFS. Methods: Pts with a CIRS score >6 and/or an estimated creatinine clearance <70 mL/min were randomized 1:1 to receive equal duration treatment with 12 cycles (C) of standard Clb or Ven 400 mg daily in combination with G for first 6 C. Primary endpoint was PFS. MRD– in peripheral blood (PB) or bone marrow (BM) 3 months (mo) after treatment completion was a key secondary endpoint. MRD was analyzed serially from C4 every 3 mo by an allele-specific oligonucleotide polymerase chain reaction assay (ASO-PCR; cut-off, 10–4) and by next generation sequencing (NGS; cut-offs, 10–4, 10–5, 10–6). Results: 432 pts were enrolled; 216 in each treatment group (intent-to-treat population). After 29 mo median follow-up, superior PFS was observed with VenG vs ClbG (HR 0.35; 95% CI 0.23–0.53; P=0.0001). MRD– by ASO-PCR was significantly higher with VenG vs ClbG in both PB (76% vs 35% [P<0.0001]) and BM (57% vs 17% [P<0.0001]) 3 mo after treatment completion. Overall, 75% of VenG MRD-negative pts in PB were also MRD-negative in BM vs 49% in the ClbG group. Landmark analysis for this timepoint by PB MRD status showed that MRD– was associated with longer PFS. Higher MRD– rates were achieved early and were more sustainable with VenG: 81% (VenG) vs 27% (ClbG) of pts were MRD-negative 12 mo after treatment completion; HR for MRD conversion 0.19; 95% CI 0.12–0.30 (median time off-treatment: 19 mo). MRD+ rates by NGS confirmed these results; 78% (VenG) vs 34% (ClbG) of pts had MRD+ at <10–4, 31% vs 4% at <10–6, and 35% vs 15% at ≥10–6–<10–5, respectively. Conclusions: Fixed-duration VenG induced deep (<10–6 in 1/3 of pts), high, and long lasting MRD– rates (with a low rate of conversion to MRD+ status 1 year after treatment) in previously untreated pts with CLL and comorbidities, translating into improved PFS. Clinical trial information: NCT02242942.
Umbralisib monotherapy demonstrates efficacy and safety in patients with relapsed/refractory marginal zone lymphoma: A multicenter, open label, registration directed phase II study.

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Background: Rituximab (RTX) alone or with chemo has substantially improved outcomes for patients (pts) with marginal zone lymphoma (MZL), but relapse is common and not all pts are candidates for or respond to current salvage therapies. Umbralisib is a novel, next-gen PI3Kδ inhibitor with unique inhibition of casein kinase-1ε (CK1ε) and a differentiated tolerability profile compared to earlier PI3Kδ inhibitors (Burris et al, 2018). This registration-directed study evaluates the efficacy and safety of umbralisib in pts with rel/ref (R/R) MZL. Methods: Pts had histologically confirmed MZL, ECOG PS ≤2, and ≥1 prior therapy including ≥1 anti-CD20 mAb-containing regimen. Pts received umbralisib 800 mg orally once daily until PD or unacceptable toxicity. The primary endpoint was overall response (ORR) as assessed by independent review (IRC) per 2007 IWG criteria. ORR by investigator assessment is reported here, and ORR by IRC is forthcoming. Secondary endpoints included duration of response (DOR), PFS, and safety. Results: 69 pts were enrolled; we report on the first 38 who are eligible for at least 6 months (mos) of follow-up as of the data cutoff. Among the 38 pts: extranodal (n = 23), nodal (n = 8), and splenic (n = 7). Median age was 67 years (range, 34-81). Median # of prior systemic therapies was 2 (range, 1-5). Seven pts (18%) had monotherapy RTX only, and 26 (68%) had at least one anti-CD20 mAb-containing chemioimmunotherapy. Median follow-up was 9.6 mos. ORR was 55% (4 CRs and 17 PRs). Eleven pts (29%) had stable disease (SD) of which 6 of these SD pts remain on study ranging from 7-12+ mos. The clinical benefit rate (CR+PR+SD) was 84%, and 91% of pts with at least 1 post-baseline assessment experienced tumor reductions. Median time to initial response was 2.7 mos, while median DOR was not reached (95% CI: 8.4-NR). The 12-month PFS was 71%. The most common adverse events (AE) of any grade included: diarrhea (45%), nausea (29%), fatigue (26%), headache (26%), cough (24%), and decreased appetite (21%). The most common Grade 3/4 events were neutropenia (8%), febrile neutropenia (5%), and diarrhea (5%). As of the cutoff date 58% continue treatment. Conclusions: PI3Kδ inhibition with single-agent umbralisib is active and well tolerated in pts with R/R MZL, achieving durable responses with chemotherapy-free therapy. Clinical trial information: NCT02793583.

Rituximab maintenance for patients with diffuse large B-cell lymphoma in first complete remission: Results from a randomized HOVON-Nordic Lymphoma Group phase III study.

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Background: This randomized phase III trial assessed whether intensification of rituximab (R) during the first 4 cycles of R-CHOP can improve outcome of diffuse large B-cell lymphoma (DLBCL) patients compared with standard R-CHOP. Patients in complete remission (CR) after induction treatment were randomized between rituximab maintenance and observation. Intensification of rituximab was not more effective than standard R-CHOP, showing same CR-rates and progression free survival after induction (ASCO 2016 # 7504). Here, we report the results of the second randomization for rituximab maintenance therapy. Methods: Patients in CR after R-CHOP were randomized between 24 months of rituximab maintenance 375 mg/m² intravenous every 8 weeks (n = 199) or observation (n = 199). CT scans were performed at 6, 12, 18 and 24 months in both arms. The primary endpoint was disease free survival (DFS) from maintenance randomization. Secondary endpoints were overall survival (OS) and adverse events (AEs). Results: Median age was 65 years (range 31-80), 48% were 66 years or older and 49% were male. The majority of patients (54%) had a high-intermediate or high aa-IPI score. After a median follow-up of 79.9 months (maximum 125.7 months), the 5-year DFS rate was 79% for rituximab maintenance versus 74% for observation. This difference was not statistically significant, with a hazard ratio of 0.83 (95% confidence interval 0.57-1.19, \( p = 0.31 \), adjusted for age and aa-IPI). The secondary endpoint OS was also not significantly different (85% versus 83% at 5 years). No clinical subgroup benefited from rituximab maintenance. Toxicity was mild. Among patients who received rituximab maintenance CTCAE grade 3 and 4 AEs were reported in 17% and 6% of patients, respectively. Infection was the most frequent AE, a grade 3 infection occurred in 6% of patients. Neutropenia was seen in 1% (grade 3) and 3% (grade 4) of patients. Conclusions: Rituximab maintenance therapy provides no additional benefit for DLBCL patients in first CR after R-CHOP. Clinical trial information: www.trialregister.nl NTR1014.
Final analysis from RESONATE: Six-year follow-up in patients (pts) with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) on ibritinib.

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Background: Ibrutinib (ibr), a first-in-class, once-daily Bruton’s tyrosine kinase inhibitor, has redefined treatment paradigms for CLL/SLL. We report final analysis with up to 6 years of follow-up on ibr from the phase 3 RESONATE study of single-agent ibr vs ofatumumab (ofa) in pts with relapsed/refractory (R/R) CLL/SLL. **Methods:** Pts were randomized to receive oral ibr 420 mg daily until PD or intravenous ofa for up to 24 weeks. Long-term efficacy endpoints were investigator-assessed. **Results:** Among 391 pts randomized to receive ibr (n=195) or ofa (n=196), 86% and 79%, respectively, were in the genomic high-risk population (del(17p), del(11q), TP53 mutation, and/or unmutated IGHV). At final analysis, median follow-up was 64 mo (range, 0.3-72) on ibr. Of pts randomized to ofa, 68% crossed over to receive ibr. Significant sustained PFS benefit was observed with ibr vs ofa, with median PFS 44.1 vs 8.1 mo (HR 0.15; 95% CI 0.11-0.20; P < 0.0001) and was consistent across baseline subgroups. Median PFS in genomic high-risk population was 44.1 vs 8.0 mo on ibr vs ofa (HR 0.64; 95% CI 0.42-0.98). ORR with ibr was 88% (CR/CRi in 11%). Initial ibr treatment conferred better OS than ofa when censored for crossover (HR 0.64; 95% CI 0.42-0.98). Median duration of ibr was 41 mo (range 0.2-71); 41% of pts received ibr >4 yrs. AE profile with ibr remained consistent with prior reports. Cumulatively during long-term ibr therapy, all-grade (grade $\geq$3) hypertension and atrial fibrillation occurred in 21% (9%) and 12% (6%) of pts, respectively; major hemorrhage occurred in 10%. Most common reasons for ibr discontinuation (DC) prior to study closure were PD (37%) and AEs (16%); DC due to AEs occurred in 6%, 3%, 4%, 4%, 6% and 4% of pts during yrs 0-1, 1-2, 2-3, 3-4, 4-5 and 5-6, respectively. **Conclusions:** With up to 6 years of follow-up, extended ibr treatment showed sustained efficacy in pts with R/R CLL, including in pts with high-risk genomic features. Safety remained acceptable with low rates of DC due to AEs, and with no new safety signals over long-term therapy. These results establish long-term benefit and tolerability for continuous ibr treatment in pts with R/R CLL. Clinical trial information: NCT01578707.
Hematologic Malignancies—Plasma Cell Dyscrasia
E3A06: Randomized phase III trial of lenalidomide versus observation alone in patients with asymptomatic high-risk smoldering multiple myeloma.

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Background: Smoldering multiple myeloma (SMM) is a precursor to myeloma, wherein current standard of care is observation (obs). Data from a randomized Spanish trial (Mateos et al, NEJM 2015) suggest that lenalidomide(len)/dexamethasone improves time to developing myeloma (TTP) and overall survival (OS) for patients (pts) with high risk (HR) SMM over obs. However, pts were not screened with advanced imaging techniques, used a HR definition that is not routinely available, and combination therapy limited the ability to isolate the effect of len, and thus has not become standard of care. Methods: E3A06 is a randomized phase III intergroup trial, testing the effect of single agent len compared with obs for pts with intermediate or high risk SMM. In an initial phase II run in all pts received len to demonstrate safety. Eligibility required ≥10% PCs and abnormal serum FLC ratio (<0.26 or >1.65). The primary endpoint was progression free survival (PFS) estimated by the Kaplan-Meier method and compared using the one-sided stratified log-rank test. Results: PII enrolled 44 pts and PIII randomized 182 pts to either len (n=90) or obs (n=92) (stratified on time since SMM diagnosis ≤1y vs >1y). Baseline characteristics were similar between the arms. 80% (PII) and 51% (PIII) are off len, primarily due to adverse events (AE) or pt withdrawal. Among the len treated pts, G3/4 non-hematologic AE occurred in 28% of PIII pts with fatigue being most common (n=5). G4 hematologic AE rate was 5.7%, primarily neutropenia (n=4). 3-year cumulative incidence of invasive SPMs was 5.2% (len) and 3.5% (obs). Overall response rate was 47.7% for the phase II study, and in phase III, 48.9% for the len arm, and 0% for the obs arm. Median follow up was 71 months (PII), and 28 months (PIII). 3-year PFS was 87% for the PII cohort. One, 2 and 3-year PFS was 98%, 93%, and 91% for len, and 89%, 76%, and 66% for the obs arm (HR 0.28, p=0.0005) favoring the len arm. No difference in QOL score was noted between arms. Conclusions: Overall, this trial represents the largest randomized trial in SMM to date. In conjunction with the Spanish data, this trial may support a change in clinical practice. Clinical trial information: NCT01169337.

| Phase 2 PFS | 1 yr | 0.98 |
| 2 yr | 0.87 |
| 3 yr | 0.78 |

| Phase 3 PFS | Len | 0.98 |
| Obs | 0.89 |

| 2 yr | 0.93 | 0.76 |
| 3 yr | 0.91 | 0.66 |
A phase III randomized, open label, multicenter study comparing isatuximab, pomalidomide, and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM).

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Background: The primary objective of this phase 3 trial was to demonstrate progression free survival (PFS) improvement of isatuximab (Isa), a novel anti-CD38 monoclonal antibody, combined with pomalidomide (P)/dexamethasone (d) versus (vs) Pd. Methods: Patients (pts) with RRMM who received ≥2 prior lines, including lenalidomide (len) and a proteasome inhibitor (PI), refractory to last therapy were enrolled. IsaPd arm received Isa 10 mg/kg IV weekly for first 4 weeks (wks), then every 2 wks. Both arms received approved schedules of pom and dex (4mg PO days 1-21; 40mg [20mg if >75 yrs] PO or IV weekly) every 28 days until progression or unacceptable toxicity. Results: 307 pts (154 IsaPd, 153 Pd) were randomized and analyzed (ITT). Patient characteristics were well balanced across arms. Median age: 67 (36-86) yrs; median prior lines of therapy: 3 (2-11); estimated GFR, 60ml/min in 33.9% pts; 92.5% refractory to len, 75.9% to PI; and 19.5% pts had high-risk cytogenetics. At median follow-up of 11.6 months (mos), median PFS was 11.5 mos IsaPd vs 6.5 mos Pd; HR 0.596 (95% CI 0.44-0.81), P=0.001. PFS benefit was consistent across all major subgroups. ORR (≥PR) was 60.4% IsaPd vs 35.3% Pd, P<0.0001. VGPR rate or better was 31.8% IsaPd vs 8.5% Pd, and MRD negativity (NGS, 10⁻⁵) was seen in 5.2% IsaPd pts vs 0% Pd. At analysis date, overall survival (OS) was immature (99 events) but a trend to OS improvement in IsaPd (vs Pd) was observed (HR 0.687; 95% CI 0.461-1.023). Median treatment duration was 41 wks IsaPd vs 24 wks Pd; median Isa infusion (inf.) duration was 3.3h at 1st inf. and 2.8h at subsequent inf. Grade ≥3 AEs were observed in 86.8% IsaPd vs 70.5% Pd; 7.2% IsaPd and 12.8% Pd pts discontinued due to AEs; 7.9% IsaPd and 9.4% Pd pts died due to AEs. Inf. reactions were reported in 38.2% (2.6% grade 3-4) IsaPd. Grade ≥3 infections were seen in 42.8% IsaPd and 30.2% Pd, grade ≥3 neutropenia in 84.9% (febrile 11.8%) IsaPd and 70.1% (febrile 2.0%) Pd. Conclusions: IsaPd significantly improved PFS and ORR vs Pd, with a manageable safety profile. IsaPd is an important new treatment option for the management of RRMM. Clinical trial information: NCT02990338.
Efficacy and safety of the randomized, open-label, non-inferiority, phase 3 study of subcutaneous (SC) versus intravenous (IV) daratumumab (DARA) administration in patients (pts) with relapsed or refractory multiple myeloma (RRMM): COLUMBA.

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Background: In a phase 1b trial, a SC formulation of DARA with recombinant human hyaluronidase PH20 (rHuPH20; ENHANZE drug delivery technology, Halozyme, Inc.) had adequate PK, low rates of infusion-related reactions (IRRs) and similar efficacy to DARA IV. This phase 3 study compared the efficacy, PK, and safety of DARA SC vs IV in pts with RRMM. Methods: DARA SC (1,800 mg DARA + rHuPH20 [2,000 U/mL]) and DARA IV (16 mg/kg IV) were given weekly for C1-2 (28-day cycles), every 2 weeks for C3-6, and every 4 weeks thereafter. DARA SC (15 mL) was given over 3-5 mins at alternating left/right abdominal sites. Pts (≥18 years) must have received ≥3 prior lines of therapy (LOT), including a PI and an IMiD, or were double refractory. Co-primary endpoints were ORR (analyzed by Farrington-Manning test, with non-inferiority = 60% retention of ORR) and pre-dose C3D1 DARA C trough (non-inferiority = lower bound of 90% CI for the ratio of the geometric means [GM] ≥80%). Results: 522 pts were randomized (n=263 SC; n=259 IV). Median age was 67 yrs. Median baseline body weight was 73 kg. Pts received a median of 4 LOT and 100% had received both PI and IMiD; 17% had high cytogenetic risk at baseline. Median follow-up was 7.5 mos. ORR was 41% for DARA SC and 37% for DARA IV. DARA SC retained at least 89% of the benefit of DARA IV (97.5% confidence). The ratio of GM of C trough for DARA SC over DARA IV was 108% (90% CI, 96%-122%). A significantly lower rate of IRRs was observed with DARA SC vs DARA IV (12.7% vs 34.5%; P, 0.0001). Median duration of injection was 5 mins for DARA SC and median duration of infusion was 421/255/205 mins for the first/second/subsequent DARA IV infusions. Median PFS was 5.6 mos DARA SC vs 6.1 mos DARA IV (HR, 0.99; 95% CI, 0.78-1.26). Most common TEAEs (≥15%) were anemia, neutropenia, thrombocytopenia, and diarrhea. Primary reasons for treatment discontinuation included progressive disease (43% SC vs 44% IV) and AEs (7% SC vs 8% IV). Conclusions: Efficacy and PK co-primary endpoints were met, demonstrating non-inferiority of DARA SC to IV. DARA SC significantly decreased IRR rate and administration time, with a comparable safety profile to DARA IV. Clinical trial information: NCT03277105.
Evaluation of AMG 420, an anti-BCMA bispecific T-cell engager (BiTE) immunotherapy, in R/R multiple myeloma (MM) patients: Updated results of a first-in-human (FIH) phase I dose escalation study.

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Background: Objectives of this study included assessing safety and activity of AMG 420/BI 836909, which binds BCMA (B-Cell Maturation Antigen) on MM cells and CD3 on T cells, in relapsed and/or refractory (R/R) MM. Methods: In this FIH study, 6-week cycles of AMG 420 were given for ≤5 cycles or until disease progression (PD), toxicity, or consent withdrawal; 5 more cycles could be given for benefit. Eligible patients had progression after ≥2 lines (incl PI and IMiD). Excluded were PC leukemia, extramedullary relapse, CNS involvement, or prior allo-SCT. MRD was defined as <1 tumor cell / 10^4 bone marrow cells per flow cytometry. Results: As of Dec 10, 2018, 42 patients received AMG 420 (0.2-800 µg/d). Patients D/C for PD (n=24), adverse events (AE, n=7, incl 3 DLTs), death (4), completed 10 cycles (2), and consent (1). Median age was 65 y, median MM duration 5.2 y, and median # prior therapies 4. Patients were treated for a mean (SD) of 2.5 (2.6) cycles. There were 2 deaths from AEs (acute respiratory distress from flu / aspergillosis; fulminant hepatitis related to adenovirus infection); neither treatment related. Of those with serious AEs (SAEs, n=21, 50%), 18 required hospitalization. SAEs occurring in >1 patient were infections (n=12) and polyneuropathy (PN, n=2). Treatment-related SAEs included 2 grade 3 PNs and 1 edema. Grade 2-3 CRS was seen in 3 patients. No anti-AMG 420 Ab were detected. In this study, 800 µg/d was determined to not be tolerable as 2/3 patients had DLTs, 1 case of grade 3 CRS and 1 case of grade 3 PN; both required hospitalization and subsequently resolved. At 400 µg/d, there were 5 minimal residual disease (MRD)-negative sCRs, 1 VGPR, and 1 PR, for a response rate of 7/10 (70%); at Dec data cut, responses lasted for 5.6-10.4 months with 4 patients ongoing on treatment. As of Feb 2019, some responses lasted >1 year. Overall, there were 13/42 responders (6 sCRs, 3 CRs, 2 VGPRs, 2 PRs). Median time to any response was 1 month. Conclusions: In this FIH study of AMG 420, a BiTE vs BCMA, in R/R MM, there was a 70% response rate (7/10) with 5 out of 7 responders achieving a sCR at 400 µg/d, a recommended dose for further investigation. Clinical trial information: NCT02514239.
Genitourinary (Prostate) Cancer
Overall survival (OS) results of a phase III randomized trial of standard-of-care therapy with or without enzalutamide for metastatic hormone-sensitive prostate cancer (mHSPC): ENZAMET (ANZUP 1304), an ANZUP-led international cooperative group trial.

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Background: Testosterone suppression (TS) is the backbone of treatment for mHSPC. OS is improved by the addition of early docetaxel (DOC) or abiraterone to TS. ENZAMET assessed the effects of enzalutamide (ENZA), a potent androgen receptor (AR) inhibitor, versus a nonsteroidal anti-androgen (NSAA: bicalutamide, nilutamide, or flutamide) in addition to SOC (TS with or without DOC) in mHSPC. Methods: Men with mHSPC were randomly assigned 1:1 to receive TS plus either ENZA or NSAA. Randomization was stratified by: volume of disease (high vs low, according to CHAARTED); planned early DOC; planned anti-resorptive therapy, comorbidity score (ACE-27), and study site. The primary endpoint was overall survival. Accrual of 1100 men provided 80% power to detect a 25% reduction in the hazard of death (HR 0.75) with up to 4 interim analyses (IA), the first planned to occur after 235 deaths (50% of total information with a critical p-value threshold <0.0031 by the Lan-DeMets alpha-spending approach with O’Brien-Fleming type shape). Subgroup analyses to assess possible modulation of the treatment effect were specified a priori and included planned early docetaxel (yes vs no) and volume of disease (high vs low). Results: We randomly assigned 1125 patients from 31MAR14 to 24MAR17. The treatment groups were well balanced for all important baseline factors. Criteria for early reporting were met at the first IA (28FEB2019) after a median follow-up of 33 months. Overall survival was prolonged by ENZA (see below). At 3 years, 36% NSAA vs 64% ENZA were still on their assigned study treatment. Serious adverse events (regardless of attribution) within 30 days of study treatment occurred in 42% ENZA vs 34% NSAA, commensurate with the different durations of study treatment. Conclusions: ENZA significantly improved OS when added to SOC in mHSPC. The benefits appeared lower in those planned to receive early DOC. Results of analyses with updated follow-up triggered by this IA will be presented. Clinical trial information: NCT02446405.
First results from TITAN: A phase III double-blind, randomized study of apalutamide (APA) versus placebo (PBO) in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) receiving androgen deprivation therapy (ADT).

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Background: TITAN was designed to determine whether APA, a selective next-generation androgen receptor inhibitor, plus ADT improves radiographic progression-free survival (rPFS) and overall survival (OS) compared with PBO plus ADT in pts with mCSPC. Methods: In this randomized, double-blind phase 3 study, pts with mCSPC regardless of extent of disease were randomized (1:1) to APA (240 mg/d) or PBO, added to ADT, in 28-day cycles. Pts with prior treatment (tx) for localized disease or prior docetaxel for mCSPC were allowed. All pts received continuous ADT. Dual primary end points were rPFS and OS. Secondary end points were time to a) initiation of cytotoxic chemotherapy, b) pain progression, c) chronic opioid use, d) skeletal-related event. Time-to-event end points were estimated by Kaplan-Meier and Cox proportional hazards methods. This first planned OS interim analysis took place after ~50% of expected events. Results: 525 pts were randomized to APA and 527 to PBO. Median age was 68 y; 8% had prior tx for localized disease; 63% and 37% had high- or low-volume disease, respectively. At median 22.6 mo follow-up, 66% APA and 46% PBO pts remained on tx. APA significantly improved rPFS (HR, 0.48; 95% CI, 0.39-0.60; p < 0.0001), with a 52% reduction in risk of death or radiographic progression; benefit was observed across all subgroups analyzed. Median rPFS was not reached in the APA group and 22.1 mos in the PBO group. APA also significantly improved OS (HR, 0.67; 95% CI, 0.51-0.89; p = 0.0053), with a 33% reduction in risk of death. Median OS was not reached in the APA or PBO group. Time to initiation of cytotoxic chemotherapy was significantly improved with APA (HR, 0.39; 95% CI, 0.27-0.56; p < 0.0001). Based on these results, the independent data monitoring committee recommended unblinding to allow crossover of PBO pts to receive APA. Rates of grade 3/4 adverse events (AEs) (42% APA, 41% PBO) were similar, and discontinuations due to AEs (8% APA, 5% PBO) were low. Conclusions: In the TITAN study in pts with mCSPC, including pts with high- and low-volume disease and prior docetaxel, addition of APA to ADT significantly improved rPFS and OS, and the safety profile was tolerable. These results support the addition of APA to ADT for tx of pts with mCSPC.

Clinical trial information: NCT02489318.
Decreased fracture rate by mandating bone-protecting agents in the EORTC 1333/PEACE III trial comparing enzalutamide and Ra223 versus enzalutamide alone: An interim safety analysis.

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Background: Skeletal fractures, pathological or not, are a frequent and underestimated side-effect of systemic treatment of metastatic castration resistant prostate cancer (mCRPC). The ERA223 trial (NCT02043678) was recently unblinded following the report of a significant increase in the fracture rates when abiraterone is combined with Ra223. Hence, FDA and EMA advised against this combination. The question whether mandated use of bone protecting agents (BPA), zoledronic acid or denosumab, would have mitigated the fracture risk and whether this risk also exists in the enzalutamide/Ra223 combination is presently unknown. Methods: The phase III EORTC-1333-GUCG/PEACEIII (NCT02194842) trial compares enzalutamide vs. a combination of Ra223 and enzalutamide in asymptomatic or mildly symptomatic mCRPC patients (https://www.eortc.org/research_field/clinical-detail/1333/). After the unblinding of ERA223, the trial was amended (v4.0, April 19, 2018) to mandate that all patients must start a BPA. We report the fracture rate in the safety population of 146 treated patients as of 28/01/2019. Results: Overall, 54.2% of the patients in the enza/Ra223 arm and 51.4% of the enza arm did not receive BPA; 18.0% in the enza/Ra223 arm and 27.0% in the enza arm did not use BPA at randomization, but started during protocol treatment according to the v4.0 amendment. 27.8% and 21.6% respectively, received BPA as of randomization. In total, 45.8% of enza/Ra223 patients and 48.6% of enza only patients receive bone protection on treatment. The fracture rate is reported in the table. Conclusions: There is a 13% risk of fracture with enzalutamide in asymptomatic mCRPC, in line with previous reports. This risk is significantly increased to 33% when Ra223 is added to enzalutamide. Strikingly, the risk is almost abolished by mandatory continuous administration of BPA starting at least 6 weeks before the first injection of Ra223, thus emphasizing the importance of treating mCRPC patients with BPA. Clinical trial information: NCT02194842.

<table>
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<th>Bone fracture</th>
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<th>Enza With BPA n=36</th>
<th>Enza/Ra223 Without BPA n=39</th>
<th>Enza Without BPA n=38*</th>
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<td>-</td>
<td>19-50%</td>
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(*)BPA started after fracture in 1 patient
Alliance A031201: A phase III trial of enzalutamide (ENZ) versus enzalutamide, abiraterone, and prednisone (ENZ/AAP) for metastatic castration resistant prostate cancer (mCRPC).

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Background: Androgen receptor (AR) signaling is an important growth mechanism in mCRPC, providing the rationale for treatment with AR axis inhibitors such as ENZ and AAP. Targeting AR with anti-androgens such as ENZ can result in compensatory autocrine and paracrine androgenic stimulation. Therefore, using ENZ with the androgen biosynthesis inhibitor AAP to dampen these resistance mechanisms could improve clinical outcomes relative to ENZ alone.

Methods: Men with progressive mCRPC by Prostate Cancer Working Group 2 criteria were eligible. Prior treatment with taxanes for mCRPC and any prior treatment with ENZ or AAP was exclusionary. Patients (pts) were randomized 1:1 to ENZ or ENZ/AAP at standard FDA-approved doses. Randomization was stratified by prior chemotherapy and Halabi prognostic three risk groups. Castrating therapy was maintained. The primary endpoint was overall survival (OS) defined as the date of randomization from date of death or last follow-up. The log-rank test had 90% power to detect a hazard ratio for OS of 0.77 with a one-sided type I error rate of 0.025. Secondary endpoints included radiographic progression free survival (rPFS) and on-treatment PSA declines. Exploratory endpoints included imaging changes, and changes in serum biomarkers such as androgens, angiokines, and circulating microRNA and RNA. The primary analysis was based on the stratified log-rank test adjusting on the stratification factors.

Results: Between January 2014 and August 2016, 1311 men were randomized: 657 to ENZ and 654 to ENZ/AAP. Groups were well balanced between arms, including stratification variables. 15.6% of pts were high risk, 35.3% intermediate, and 48.1% low. Median OS was 33.6 mo (95% CI 30.5-36.4) and 32.7 mo (29.9-35.4) respectively, two-sided p = 0.53. Fifty percent PSA decline rate was 80% vs. 76.5%. Grade 3-5 adverse events (AE) (all attributions) were 55.6% and 68.8% respectively. Treatment discontinuation due to AEs occurred in 5% and 12%, pt withdrawal in 5% and 13%, and progression or death in 57% and 48% of pts respectively. Conclusions: Addition of abiraterone acetate to enzalutamide did not prolong survival in men with mCRPC. The combination resulted in more AEs than enzalutamide alone. Support: U10CA180821, U10CA180882, U24CA196171; https://acknowledgments.alliancefound.org. Clinical trial information: NCT01949337.
Genitourinary (Nonprostate) Cancer
Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for metastatic renal cell carcinoma (mRCC): Outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of the phase 3 KEYNOTE-426 study.

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Background: In KEYNOTE-426, pembro + axi significantly improved OS (HR 0.53, P < .0001), PFS (HR 0.69, P = .0001), and ORR (59.3% vs 35.7%, P < .0001) vs sunitinib and had manageable toxicity as first-line therapy for mRCC (NCT02853331). The pembro + axi benefit was observed across all IMDC risk groups and regardless of PD-L1 expression. We present data for the combined intermediate/poor risk group and for patients (pts) with sarcomatoid features. Methods: 861 eligible pts with clear-cell mRCC, no prior systemic therapy for mRCC, and KPS $\geq 70$ were randomized 1:1 to pembro 200 mg IV Q3W for a maximum of 35 cycles plus axi 5 mg orally BID (N = 432) or sunitinib 50 mg orally QD (4-wk on/2-wk off) (N = 429). Primary endpoints were OS and PFS (RECIST v1.1 by blinded, independent central review [BICR]). ORR (RECIST v1.1 by BICR) was the key secondary endpoint. The intermediate/poor risk group was prespecified; the sarcomatoid group was exploratory. HRs and their 95% CIs were calculated with a Cox proportional hazards model. None of the analyses were multiplicity-controlled. Results: 592 (68.8%) of all randomized pts were of IMDC intermediate/poor risk — 294 in the pembro + axi arm, 298 in the sunitinib arm. Pembro + axi improved OS (HR 0.52, 95% CI 0.37-0.74; 12-mo rate 87.3% vs 71.3%), PFS (HR 0.67, 95% CI 0.53-0.85; median 12.6 vs 8.2 mo), and ORR (59.3% vs 35.7%) vs sunitinib in pts with intermediate/poor risk; CR rates were 4.8% (95% CI 2.6-7.9) vs 0.7% (0.1-2.4). Of the 578 pts with known status, 105 (18.2%) had sarcomatoid features — 51 in the pembro + axi arm, 54 in the sunitinib arm. Pembro + axi improved OS (HR 0.58, 95% CI 0.21-1.59; 12-mo rate 85.7% vs 79.5%), PFS (HR 0.54, 95% CI 0.29-1.00; median not reached vs 8.4 mo), and ORR (58.8% [95% CI 44.2-72.4] vs 31.5% [19.5-45.6]) vs sunitinib in pts with sarcomatoid features; CR rates were 11.8% (95% CI 4.4-23.9) vs 0% (0.0-6.6). Conclusions: Pembrolizumab plus axitinib provides benefit in the combined population of pts with IMDC intermediate or poor risk and in pts whose tumors had sarcomatoid features. The observed benefits were consistent with those seen in the total population. Clinical trial information: NCT02853331.
CALGB 90601 (Alliance): Randomized, double-blind, placebo-controlled phase III trial comparing gemcitabine and cisplatin with bevacizumab or placebo in patients with metastatic urothelial carcinoma.

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Background: The combination of gemcitabine (G) and cisplatin (C) is a standard therapy for metastatic urothelial carcinoma (mUC). Based on data that angiogenesis plays a role in UC growth and progression, a randomized placebo-controlled trial was performed. Methods: Patients mUC, no prior chemotherapy for metastatic disease and >12 months from prior (neo)adjuvant chemotherapy and ECOG PS 0-1 were randomized 1:1 to G 1000 mg/m² IV days 1 and 8 and C IV 70 mg/m² day 1 with bevacizumab (GCB) 15 mg/kg IV or placebo (GCP) day 1 every 21 days. Randomization was stratified by the presence of visceral metastases and prior chemotherapy. The primary endpoint was overall survival (OS) defined as the time from randomization to death or last follow-up (FU). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and grade 3 toxicity. With 445 deaths, the log-rank test had an 87% power to detect a hazard ratio (HR) of 0.74 with a 2-sided α=0.05. The primary analysis was based on the stratified log-rank test adjusting on stratification factors. Alliance Data Safety and Monitoring Board approved the final OS analysis be performed at 420 events due to lower than expected event rates. Results: 506 patients were randomly assigned (252 GCB, 254 GCP) stratified by the presence of visceral disease and prior chemotherapy for UC. The median FU for patients still alive was 46.2 months. Median OS was 14.5 months for patients treated with GCB and 14.3 months for patients treated with GCP with a HR of 0.87 (95%CI 0.72-1.06; 2-sided Wald p=0.17). The HR for PFS was 0.77 (95%CI 0.63-0.93) in favor of GCB (p=0.0074). Grade 3 or greater adverse event rate was 83.5% with GCB compared to 80.7% with GCP. Conclusions: The addition of bevacizumab to GC chemotherapy did not result in improved OS (primary endpoint) in patients with mUC but there was a PFS improvement. The observed median OS of about 14 months is consistent with prior phase III trials of cisplatin-based chemotherapy. Support: U10CA180821, U10CA180882, U10CA180820, U10CA180853, U10CA180888, Genentech https://acknowledgments.alliancefound.org. Clinical trial information: NCT00942331.
Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients (pts) with metastatic urothelial cancer (mUC): HCRN GU14-182.

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Background: Platinum-based chemotherapy for 1st-line treatment of pts with metastatic urothelial cancer (mUC) is typically administered for a fixed duration followed by observation until recurrence. PD-1 blockade with pembrolizumab improves survival of pts with mUC progressing despite platinum-based chemotherapy. We explored the potential benefit of earlier use of PD-1 blockade using a "switch maintenance" approach. Methods: Pts with mUC achieving at least stable disease after up to 8 cycles of 1st-line platinum-based chemotherapy were enrolled. Pts were randomized 1:1 to pembrolizumab 200 mg IV q3 weeks versus placebo for up to 24 months; pts progressing on placebo could cross over to pembrolizumab. Randomization was stratified based on pre-chemotherapy visceral metastases (Y/N) and response to 1st-line chemotherapy (CR/PR vs. SD). The primary objective was to determine the progression-free survival (PFS) as per irRECIST among pts treated with pembrolizumab versus placebo. Results: Between 12/2015 and 11/2018, 107 pts were randomized to placebo (n=52) versus pembrolizumab (n=55). The baseline pt characteristics are shown in the Table. Pts randomized to placebo and pembrolizumab received a median of 6 and 8 cycles, respectively. Excluding patients with baseline CRs, the objective response rate was 12% (5/42) on placebo and 22% (10/46) on pembrolizumab. Grade 3-4 treatment emergent adverse events occurred in 48% of pts on placebo and 56% on pembrolizumab. At a median follow-up of 14.7 months, 41 pts have died and 26/52 pts randomized to placebo have crossed over to pembrolizumab. PFS was significantly longer in patients randomized to pembrolizumab vs. placebo (Maximum Efficiency Robust Test p=0.036; log-rank p = 0.038). The 18-month restricted mean progression-free survival time was 5.6 months with placebo and 8.2 months with pembrolizumab (p=0.023). Conclusions: Switch maintenance pembrolizumab may "deepen" responses achieved with 1st-line chemotherapy. Switch maintenance pembrolizumab prolongs PFS in pts with mUC completing 1st-line platinum-based chemotherapy. Clinical trial information: NCT02500121.
EV-201: Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors.

Background: Locally advanced or metastatic urothelial cancer (la/mUC) remains a lethal disease with limited treatment options for patients (pts) who progress on or after platinum and/or checkpoint inhibitor (CPI). Enfortumab vedotin (EV) is an antibody-drug conjugate targeting Nectin-4, which is highly expressed in UC. EV-201 is a pivotal, single-arm, two-cohort study of EV in la/mUC patients with prior CPI and platinum-containing chemotherapy (Cohort 1) or a CPI and no prior chemotherapy (Cohort 2). Here, we present preliminary data from Cohort 1.

Methods: Pts in this open-label, multicenter study received 1.25 mg/kg EV on Days 1, 8, and 15 of each 28-day cycle. The primary endpoint was confirmed ORR per RECIST 1.1 by blinded independent central review. Secondary endpoints are duration of response, PFS, OS, safety/tolerability.

Results: Between Oct 2017 and Jul 2018, EV-201 enrolled 128 pts in Cohort 1 (la/mUC pts previously treated with platinum and a CPI), 125 of whom were treated with EV (70% male; median age 69 y [range 40–84 y]; 34% upper tract; a median of 2 prior systemic therapies). As of 03 Jan 2019, the confirmed ORR was 42% (95% CI: 33.6%–51.6%), with 9% CR. The ORR in CPI non-responders was 38% (95% CI: 27.3%–49.2%), and 36% (95% CI: 22.9%–50.8%) in pts with liver metastases (LM). Most common treatment-related AEs, as determined by investigators, included fatigue (50%), alopecia (48%), and decreased appetite (41%). Treatment-related AEs of interest include any rash (48% all grade, 11% G3) and any peripheral neuropathy (50% all grade, 3% ≥ G3). One death was reported as treatment related by the investigator (interstitial lung disease), but was confounded by a suspected pulmonary infection.

Conclusions: Preliminary results from this EV pivotal study demonstrated a clinically meaningful ORR, consistent with the phase 1 trial, in la/mUC pts with prior platinum and CPI, including LM pts, where there is a high unmet need. EV was well tolerated with a manageable safety profile in these pts. Updated data, including duration of response, PFS, and OS will be presented. Clinical trial information: NCT03219333.
Gynecologic Cancer
A randomized phase 3 trial of paclitaxel (P) plus carboplatin (C) versus paclitaxel plus ifosfamide (I) in chemotherapy-naive patients with stage I-IV, persistent or recurrent carcinosarcoma of the uterus or ovary: An NRG Oncology trial.

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Background: Gynecologic carcinosarcomas (CS) are rare yet aggressive epithelial malignancies for which optimal therapy is debated. PI was shown to be superior to I. PC demonstrated compelling phase 2 activity with improved safety and convenience. Methods: Main inclusion: ≥18 y; chemotherapy naïve stage I-IVB or recurrent uterine (U) or ovarian (O) CS. Treatment randomised 1:1 to PC (P 175mg/m2 with C: AUC 6 or 5 if prior RT on D1) or PI (P: 135 mg/m2; I 1.6 g/m2 D1-3; G-CSF support with dose escalation & de-escalation based on nadir counts) q21days for 6-10 cycles. Quality of life (QOL) (FACT-En TOI) and neurotoxicity (FACT/GOG-Ntx subscale) administered at 4 timepoints. A stratified log-rank test compared primary endpoint of overall survival (OS) from entry between treatment groups for non-inferiority (NI) of PC to PI. With 264 events, power was 80% for a null hazard ratio of 1.2 against a 13% greater death rate on PI when type I error is limited to 5% for a one-tail test. NCT00954174. Results: 637 pts accrued with a median follow-up of 61 months. The primary (U, n = 536) and secondary (O, n = 101) cohorts are analyzed separately and included 449 and 90 pts eligible pts, respectively. For the U cohort:PC and PI were randomly assigned to 228 and 221 eligible pts. Stage distribution: I (40%), II (6%), III (31%), IV (15%) and recurrent (8%). The study met its primary objective withPC not inferior to PI (intention-to-treat analysis; Median OS 37 vs. 29 mo, HR = 0.87; 90% CI = 0.70 to 1.075; p < 0.01 for NI, p > 0.1 for superiority (S)). PFS (median on PC 16mo vs PI 12mo; HR = 0.73; p = < 0.01 for NI, p < 0.01 for S). Toxicity (grade 1/2/3/4/5: PC 1/8/40/48/2%; PI 1/32/39/25/1%). Most of increase toxicity for PC was hematologic with G-CSF rarely used (N = 6). Confusion and genitourinary hemorrhage were significantly worse with PI. Both groups had decline in QOL and neurotoxicity scores. Similar trends were noted for the O cohort (OS: PC 30mo vs PI 25mo; and PFS: 15 mo vs 10 respectively). Conclusions: PC was not inferior to PI for OS with longer PFS and similar QOL and neurotoxicity. These results establish a new standard regimen for women with CS. Clinical trial information: NCT00954174.

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Background: Standard treatment of platinum-sensitive recurrent ovarian cancer (PSROC) is platinum based combination chemotherapy ± bevacizumab. However, this treatment modality is hardly curative, and is associated with significant toxicity. Both bevacizumab (BEV) and PARP inhibitors (PARPi) have demonstrated efficacy in PSROC. There is preclinical evidence of enhanced activity of the combination. This is the proof-of-concept randomized trial of PARPi-BEV combination against PARPi monotherapy as treatment in PSROC, regardless of number of previous lines of therapies. Methods: In this randomized, open-label, phase 2 study, women with measurable/evaluatable, high-grade serous or endometrioid PSROC were randomized to niraparib 300mg once daily or the combination of niraparib 300mg once daily and BEV 15mg/kg IV every 3 weeks until disease progression (1:1 randomization). The primary endpoint was progression-free survival (PFS). Stratification was according to homologous recombination-deficiency (HRD) status (MyChoice HRD) and chemotherapy-free-interval (CFI)(6-12months (mo) vs. >12mo). First-line maintenance bevacizumab was permitted. Results: Of 97 enrolled patients, 48 were randomized to niraparib monotherapy and 49 to the chemotherapy-free combination. The combined treatment significantly improved PFS compared to niraparib alone: median 11.9 vs. 5.5 mo; hazard ratio (HR) adjusted for stratification factors 0.35; 95% confidence interval (CI),[0.21 to 0.57]; P<0.001. Pre-planned exploratory subgroup analyses: patients with HRD-positive tumors (n=54) HR 0.36 (CI, 0.18-0.69); HRD-negative disease (n=43) HR, 0.47 (CI, 0.24-0.95); gBRCAmut patients (n=34) HR 0.53 (CI, 0.23-1.21); non-gBRCAmut patients (n=63) HR 0.33; CI, 0.18-0.61); CFI of 6 to 12 mo (n=38) HR, 0.29 (CI, 0.14 to 0.62); CFI of ≥12 mo (n=59) HR, 0.42; (CI, 0.22 to 0.80). There was no difference in treatment-emergent grade 3-4 adverse events except for the rate of hypertension (26.5% vs. 0%) and neutropenia (12.2% vs. 2.1%). Patient-reported outcomes measured using EORTC QLQ-C30 and OV28 were similar for both treatment arms. Conclusions: Both niraparib alone and the combination had meaningful activity in PSROC. Compared to niraparib alone, the chemotherapy-free regimen of niraparib and BEV significantly improved PFS in women with PSROC, regardless of HRD status and duration of CFI. Clinical trial information: NCT02354131.
Olaparib monotherapy versus (vs) chemotherapy for germline BRCA-mutated (gBRCAm) platinum-sensitive relapsed ovarian cancer (PSR OC) patients (pts): Phase III SOLO3 trial.

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Background: Data from a randomized Phase II trial (NCT00628251) of olaparib (capsules, 200 or 400 mg bid, n=32 per arm) vs pegylated liposomal doxorubicin (PLD, n=33) in gBRCAm OC pts with recurrence ≤12 months after prior platinum therapy indicated efficacy for olaparib (Kaye et al. JCO 2012). However, the efficacy of PLD was higher than previously reported in this setting. We led a confirmatory Phase III, open-label study of olaparib vs non-platinum chemotherapy in gBRCAm PSR OC pts (NCT02282020). Methods: Pts were randomized (2:1) to olaparib tablets (300 mg bid) or chemotherapy treatment of physician’s choice (TPC) (paclitaxel [P; 80 mg/m² on day 1 (D1), D8, D15, D22 every 4 weeks (q4w)], topotecan [T; 4 mg/m² D1, D8, D15 q4w], gemcitabine [G; 1000 mg/m² D1, D8, D15 q4w]) or PLD (50 mg/m² D1 q4w) until progression, stratified by: TPC, prior lines of chemotherapy (2–3 vs ≥4) and platinum-free interval (6–12 vs >12 months). Primary endpoint: ORR (blinded independent central review [BICR]). Secondary endpoints included PFS and safety. Results: 266 gBRCAm PSR OC pts were randomized (olaparib, n=178; TPC, n=88 [PLD, n=47; P, n=20; G, n=13; T, n=8]); 12 in the TPC arm withdrew before receiving study treatment. 223 pts (84%) had baseline BICR measurable disease (olaparib, n=151; TPC, n=72). ORR was 72% with olaparib vs 51% with TPC (OR 2.53, 95% CI 1.40–4.58; P=0.002). HR for PFS by BICR was 0.62 (95% CI 0.43–0.91; P=0.013; median 13.4 vs 9.2 months [olaparib vs TPC]) and by investigator assessment was 0.49 (95% CI 0.35–0.70; P<0.001; median 13.2 vs 8.5 months, respectively). Most common adverse events (AEs) with olaparib were nausea (65% vs 34% [TPC]) and anemia (50% vs 25%) and with TPC were palmar-plantar erythrodysesthesia (PPE; 36% vs 1% [olaparib]) and nausea. Most common grade ≥3 AEs in either arm were anemia (21% [olaparib] vs 0 [TPC]), PPE (0 vs 12%) and neutropenia (6% vs 11%). For olaparib vs TPC, serious AEs were reported by 24% vs 18% and AEs led to treatment discontinuation in 7% vs 20%. Conclusions: Pts with gBRCAm PSR OC receiving olaparib monotherapy had a significant, clinically relevant improvement in ORR and PFS vs TPC, with no new safety signals. Clinical trial information: NCT02282020.
EWOC-1: A randomized trial to evaluate the feasibility of three different first-line chemotherapy regimens for vulnerable elderly women with ovarian cancer (OC): A GCIG-ENGOT-GINECO study.

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Background: The Geriatric Vulnerability Score (GVS) combining albumin, lymphocyte count, ADL, IADL and HADS scores has been reported (Falandry C Ann Oncol 2013) to identify vulnerable elderly OC patients (pts) as those with a GVS $\geq$3. For such pts, Carboplatin (Cb) monotherapy or weekly Cb plus paclitaxel (Pa) are often proposed as an alternative to Cb-Pa given every 3 weeks. Methods: Pts $\geq$70 yrs with first line FIGO stage III/IV epithelial OC were screened for GVS. Those with GVS $\geq$3 were randomized to receive either arm A: Cb AUC5-6 + Pa 175mg/m², d1q3week or arm B: Cb AUC5-6 d1q3week or arm C: weekly Cb AUC2 + Pa 60mg/m² d1-d8-d15 q4week. Primary endpoint is treatment feasibility defined as the ability to complete 6 chemotherapy courses without disease progression, early treatment stopping due to unacceptable toxicity or death. Inclusion of 240 pts was planned. Results: Among 444 screened pts, 120 were randomized from 12/2013 to 04/2017 (arm A = B = C = 40). Pts characteristics were well balanced between arms A-B-C respectively: median age (79-82-80 yrs), FIGO stage IV (32-37-27%), primary surgery (65-72-70%), absence of macroscopic residuals (CC-0) (7-5-7%), ECOG $\geq$2 (50-50-47%). Feasibility per protocol for arms A-B-C is 65%, 47% and 60% (p = 0.15). Main reasons for treatment arrest are treatment toxicity (A:20%; B:15%; C:22.5%; p = 0.771) and disease progression (A: 7.5%; B:30%; C:2%; p = 0.004). Median PFS for arm A-B-C are 12.5 mos (95%CI 10.3-15.3), 4.8 (3.8-15.3) and 8.3 (6.6-15.3), respectively (p < 0.001) and median OS for arm A-B-C is not reached (NR) (21, NR), 7.4 (5.3-NR) and 17.3 (10.8-NR), respectively (p = 0.001). At the pre-planned intermediate analysis, the IDMC recommended to prematurely close the study as survival in arm B was found significantly worse and the number of potential pts required to find a significant difference between both Cb-Pa regimens (arms A&C) was out of reach. Conclusions: Compared to 3-weekly and weekly Cb-Pa regimens, Cb single agent was reported to be less active with significant worse survival outcome in vulnerable elderly pts. In this population Cb-Pa combination remains a standard. Clinical trial information: NCT02001272.
Symptoms and Survivorship
The impact of routine ESAS use on overall survival: Results of a population-based retrospective matched cohort analysis.

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Background: The study objective was to examine the impact of routine Edmonton Symptom Assessment System (ESAS) use on overall survival among adult cancer patients. We hypothesized that patients exposed to ESAS would have better overall survival rates than those who didn’t have ESAS. Methods: The effect of ESAS screening on survival was evaluated in a retrospective matched cohort study. The cohort included all Ontario patients aged 18 or older who were diagnosed with cancer between 2007 and 2015. Patients completing at least one ESAS assessment during the study were considered exposed. The index date was the day of their first ESAS assessment. Follow up time for each patient was segmented into one of three phases: initial, continuing, or palliative care. Exposed and unexposed patients were matched 1:1 using hard (birth year $\pm$ 2 years, cancer diagnosis date $\pm$ 1 year, cancer type and sex) and propensity-score matching (14 measures including cancer stage, treatments received, and comorbidity). Matched patients were followed until death or the end of study at Dec 31, 2015. Kaplan-Meier curves and multivariable Cox regression were used to evaluate the impact of ESAS on survival. Results: There were 128,893 pairs well matched on all baseline characteristics (standardized difference $< 0.1$). The probability of survival within the first 5 years was higher among those exposed to ESAS compared to those who were not (73.8% vs. 72.0%, P-value $< 0.0001$). In the multivariable Cox regression model, ESAS assessment was significantly associated with a decreased mortality risk (HR: 0.49, 95% CI: 0.48-0.49) and this protective effect was seen across all phases. Conclusions: ESAS exposure is associated with improved survival in cancer patients, in all phases of care. To the extent possible, extensive matching methods have mitigated biases inherent to observational data. This provides real world evidence of the impact of routine symptom assessment in cancer care.
A randomized, double-blind, placebo-controlled phase III trial evaluating olanzapine 5 mg combined with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based chemotherapy: J-FORCE Study.

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Background: Olanzapine (OLZ) 10 mg added to standard antiemetic therapy including aprepitant (APR), palonosetron (PALO), and dexamethasone (DEX) has been recommended for the prevention of chemotherapy-induced nausea and vomiting (CINV) caused by highly emetogenic chemotherapy (HEC). Guidelines suggest that a dose of 5 mg should be taken into consideration in patients at risk of sedation. OLZ 5 mg showed an equivalent activity and favorable toxicity to somnolence in several phase II studies. We conducted a randomized, double-blind, placebo-controlled phase III trial to evaluate OLZ 5 mg in addition to standard antiemetic therapy for the prevention of CINV in patients receiving cisplatin-based chemotherapy. Methods: Patients receiving cisplatin (≥ 50 mg/m²) were randomly assigned to either OLZ 5 mg or placebo on days 1–4, combined with APR, PALO and DEX. The primary endpoint was complete response (CR), defined as no vomiting and no rescue medications in the delayed phase (24–120 h). A total of 690 patients were required to detect a 10% increase in CR from 65% in the placebo to 75% in the OLZ, with a one-sided alpha of 2.5% and a power of 80%. Results: A total of 710 patients were enrolled (OLZ 356 and placebo 354). CR in the delayed phase was 79.1% (95% CI: 74.9–83.3) in the OLZ 5 mg and 65.8% (95% CI: 60.9–70.8) in the placebo (p < 0.001). Other efficacy results are summarized in Table. The most common treatment-related adverse events was somnolence (43.1% for OLZ vs. 33.0% for placebo). Conclusions: OLZ 5 mg combined with APR, PALO and DEX can be considered a new standard antiemetic therapy in patients receiving cisplatin-based chemotherapy. Clinical trial information: UMIN000024676.

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*TC (total control): no vomiting, nausea and rescue medications.
Safety of pregnancy following breast cancer (BC) in patients (pts) carrying a BRCA mutation (mBRCA): Results of an international cohort study.

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Background: Very limited data are available on the safety of pregnancy and reproductive outcomes in mBRCA pts with prior BC history. We report the results of the largest study to date addressing these questions. Methods: This international, multicenter, hospital-based, retrospective cohort study included consecutive pts with invasive early BC (stage I-III) diagnosed between Jan-2000 and Dec-2012 at the age of ≤40 years and carrying a deleterious germline mBRCA. Primary endpoints were pregnancy rate and disease-free survival (DFS); overall survival (OS) and pregnancy outcomes were secondary endpoints. To account for guarantee-time bias, we performed two survival analyses: 1) Case-control approach matching pregnant and non-pregnant (1:3) pts for classic prognostic factors (each non-pregnant control had a disease-free interval than the time elapsing between BC diagnosis and date of pregnancy of the matched pregnant case); 2) Extended Cox model with time-varying covariates including all pts. Results: 1,252 mBRCA BC pts (811 mBRCA1, 430 mBRCA2, 11 mBRCA1&2) were included from 30 centers worldwide, of whom 195 pts had a pregnancy (pregnancy rate = 16% [95% CI 14-18%]) after a median 4.5 years (range 3.1-6.7 years) following BC diagnosis. Pregnant pts were younger and had more ER-negative tumors (all p < 0.01). 16 (8.2%) and 20 (10.3%) pts had an induced and spontaneous abortion, respectively. Among the 150 (76.9%) pts who conceived (n = 170 babies), pregnancy complications and congenital anomalies were described in 13 (11.6%) and 2 (1.8%) cases, respectively. Median follow-up was 8.3 years (range 8.1-8.7 years). In the case-control analysis, pregnant pts had better DFS (HR 0.71; 95% CI 0.51-0.99; p = 0.045), with no difference in OS (HR 0.86; 95% CI 0.44-1.67; p = 0.65). Subgroup analysis suggested that the superior outcome was restricted to mBRCA1 pregnant pts (p-interaction < 0.01). Similar results were obtained in the second supportive analysis. Conclusions: Pregnancy following BC is safe in mBRCA pts, particularly mBRCA1, with no detrimental impact on maternal prognosis or fetal outcomes. These findings are of paramount importance for fertility counseling in young mBRCA BC pts.

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Background: Cancer-related fatigue (CRF) is a persistent daily lack of energy commonly experienced by breast cancer (BC) patients. Due to CRF, BC patients have difficulties carrying out daily activities, become less active and consequently reduce muscular strength. Exercise can improve muscular strength and increase energy level; therefore it may alleviate CRF. This phase II RCT assessed the effects of exercise on CRF and muscular strength in BC patients. Methods: Ninety BC patients (55.5±9.6 years, 79% white, 48% and 46% under radiation or hormone therapy) were randomized into two arms: a 6-week Exercise for Cancer Patients (EXCAP) program or standard care (Control). EXCAP is a home-based, personalized, progressive exercise program combining aerobic walking and resistance band training. The Brief Fatigue Inventory was used to assess CRF and CRF interference with daily activities and a 7-10 repetition maximum chest press and leg extension strength test was used to assess upper- and lower-body strength at pre- and post-intervention. T-tests and ANCOVA with pre-intervention as the covariate were used to analyze within- and between-group changes, respectively. Results: Participants in the EXCAP group decreased CRF (-0.9±0.3, p = 0.01) and CRF interference with daily activities (-1.1±0.3, p < 0.01) from pre- to post-intervention while participants in the Control group did not. The mean improvement (from pre- to post-intervention) in CRF and CRF interference of daily activities for the EXCAP group were significantly higher than the change in the Control group (both p < 0.01). Participants in the EXCAP group increased upper- (3.9±1.4, p < 0.01) and lower-body strength (6.4±1.3, p < 0.01) from pre- to post-intervention, while participants in the Control group did not. The mean increase (from pre- to post-intervention) in lower-body strength for the EXCAP group was significantly higher than the change in the Control group (p = 0.01). Conclusions: Exercise combining aerobic walking and resistance band training reduces CRF and CRF interference with daily activities and improves muscular strength in BC patients. Results from this study provide further evidence of the benefits of exercise for supportive cancer care. Clinical trial information: NCT00851812.
A randomized controlled trial of a novel artificial intelligence-based smartphone application to optimize the management of cancer-related pain.

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Background: Cancer pain is a significant problem that impairs patient quality of life and increases healthcare utilization. ePAL is a smartphone application that utilizes patient-reported outcomes (PROs) and artificial intelligence (AI) to optimize cancer pain management. This randomized controlled trial examined the impact of ePAL on cancer pain severity, attitudes toward cancer treatment, and healthcare utilization. Methods: Patients with pain from metastatic solid tumors (n = 112) undergoing treatment in a palliative care clinic were randomized to either a control group (n = 56) that received usual care or an intervention group (n = 56) that received ePAL in addition to usual care for 8 weeks. Measures of pain severity (Brief Pain Inventory), attitudes towards cancer treatment (Barriers Questionnaire II) and anxiety (General Anxiety Disorder-7) were assessed. We used repeated measures mixed modeling to assess change in outcome measures over time. We also conducted a chart review to identify pain-related hospital admissions and emergency department (ED) visits and compared risk between study groups. Results: Pain severity (BPI) and negative attitudes toward cancer treatment (BQ-II) decreased significantly for those assigned to ePAL compared to controls (β = -0.09, p = 0.034 and β = -0.037, p = 0.042, respectively). Patients assigned to ePAL reported higher anxiety scores compared to controls (β = 0.21, p = 0.015). Patients assigned to ePAL had significantly fewer pain-related hospital admissions (n = 4 vs. n = 20, per patient risk ratio 0.31, p = 0.018) and fewer pain-related admissions through the ED (n = 2 vs. n = 14, per patient risk ratio 0.18, p = 0.008) compared to control group. Conclusions: To our knowledge, this is the first mobile app to utilize patient reported outcomes and artificial intelligence to significantly decrease pain scores and pain-related hospitalizations in patients with cancer-related pain. Future directions include examining the efficacy of ePAL in settings with limited access to palliative care.
Head and Neck Cancer
Protocol-specified final analysis of the phase 3 KEYNOTE-048 trial of pembrolizumab (pembro) as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC).

Danny Rischin, Kevin J. Harrington, Richard Greil, Denis Soulieres, Makoto Tahara, Gilberto de Castro, Amanda Psyri, Neus Baste, Prakash C. Neupane, Ase Bratland, Thorsten Fuereeder, Brett Gordon Maxwell Hughes, Ricard Mesia, Nuttapong Ngamphaiboon, Tamara Rordorf, Wan Zamaniah Wan Ishak, Yayan Zhang, Fan Jin, Burak Gumuscu, Barbara Burtness; Peter MacCallum Cancer Centre, Melbourne, Australia; The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London, United Kingdom; Paracelsus Medical University, Salzburg Cancer Research Institute, and Cancer Cluster Salzburg, Salzburg, Austria; Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada; National Cancer Center Hospital East, Kashiwa, Japan; Instituto do Cancer do Estado de São Paulo, São Paulo, Brazil; National Kapodistrian University of Athens Medical School, Attikon University Hospital, Athens, Greece; Vall d’Hebron University Hospital, Barcelona, Spain; University of Kansas Medical Center, Westwood, KS; Oslo University Hospital, Oslo, Norway; Medical University of Vienna, Vienna, Austria; Royal Brisbane and Women’s Hospital, Herston and University of Queensland, Queensland, Australia; Catalan Institute of Oncology, Hospitalitat de Llobregat, Barcelona, Spain; Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; University Hospital, Zurich, Switzerland; University Malaya, Kuala Lumpur, Malaysia; Merck & Co., Inc., Kenilworth, NJ; Yale University School of Medicine and Yale Cancer Center, New Haven, CT

Background: KEYNOTE-048 is a phase 3 study of P or P + chemo (C) vs EXTREME (E) as 1L therapy for R/M HNSCC (NCT02358031). At the second interim analysis (IA2), P significantly improved OS in the PD-L1 combined positive score (CPS) ≥20 and ≥1 populations and had noninferior OS in the total population with comparable safety. We present the protocol-specified final results. Methods: 882 pts with locally incurable R/M HNSCC and no prior systemic therapy in the R/M setting who provided a tumor sample for PD-L1 testing were randomized to P 200 mg Q3W for 24 mo (n = 301), P for 24 mo + 6 cycles of C (cisplatin 100 mg/m² or carboplatin AUC 5 Q3W + 5-FU 1000 mg/m²/d for 4 d Q3W) (n = 281), or E (cetuximab 400 mg/m² loading/250 mg/m² QW + 6 cycles of chemo) (n = 300). OS superiority was tested sequentially for P+C vs E in the CPS ≥20 population, then the CPS ≥1 population, and for P vs E in the total population (superiority thresholds: one-sided P = .0023, .0026, and .0059, respectively). Data cutoff was 25 Feb 2019 (~25 mo after last pt randomized). Results: P+C significantly improved OS vs E in the CPS ≥20 (HR 0.60, 95% CI 0.45-0.82, P = .0004; median 14.7 vs 11.0 mo) and CPS ≥1 (HR 0.65, 95% CI 0.53-0.80, P < .0001; median 13.6 vs 10.4 mo) populations. HR (95% CI) for PFS was 0.76 (0.58-1.01) for CPS ≥20 and 0.84 (0.69-1.02) for CPS ≥1. ORR (P+C vs E) was 42.9% vs 38.2% for CPS ≥20 and 36.4% vs 35.7% for CPS ≥1; median DOR was 7.1 vs 4.2 mo and 6.7 vs 4.3 mo, respectively. P did not significantly improve OS vs E in the total population (HR 0.83, 95% CI 0.70-0.99, P = .0199; median 11.5 vs 10.7 mo). HR (95% CI) for PFS was 1.29 (1.09-1.53). ORR (P vs E) was 16.9% vs 36.0%; median DOR was 22.6 vs 4.5 mo. All-cause gr 3-5 AE rates were 54.7% for P, 85.1% for P+C, and 83.3% for E. Conclusion: Overall, KEYNOTE-048 showed that compared with E, P+C had superior OS in the PD-L1 CPS ≥20, CPS ≥1, and total populations with comparable safety and P had superior OS in the CPS ≥20 and ≥1 populations, noninferior OS in the total population, and favorable safety. These results support pembrolizumab and pembrolizumab + platinum + 5-FU as new 1L standards of care for R/M HNSCC. Clinical trial information: NCT02358031.
TPExtreme randomized trial: TPEx versus Extreme regimen in 1st line recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC).

Joel Guigay, Jerome Fayette, Ricard Mesia, Cedrik Lafond, Esma Saada-Bouzid, Lionnel Geoffrois, Laurent Martin, Didier Cupissol, Olivier Capitain, Helene Castanie, Damien Vansteene, Philippe Schafhausen, Catherine Dubos Arvis, Caroline Even, Christian Sire, Melissa Delhommeau, Cecile Michel, Jean Bourhis, Ulrich Keilholz, Anne Auperin, GORTEC - AI0 Studien gGmbH - TTCC - H&N Unicancer; Department of Medical Oncology, Antoine Lacassagne Comprehensive Cancer Centre, FHU OncoAge, Université Côte d’Azur, Nice, France; Centre Léon Bérard, Medical Oncology, Lyon, France; Catalan Institute of Oncology, IDIBELL, Barcelona, Spain; Clinique Victor Hugo, Le Mans, France; Centre Antoine Lacassagne, Université Côte d’Azur, Nice, France; Institut de Cancérologie de Lorraine, Vandoeuvre-Lés-Nancy, France; Clinique des Ormeaux, Le Havre, France; Institut du Cancer de Montpellier, Montpellier, France; Institut de Cancérologie de l’Ouest, Site Paul Papin, Angers, France; Hôpital Privé du Confluent S.A.S, Nantes, France; Institut de Cancérologie de l’Ouest–René Gauducheau, Nantes, France; Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; Centre François Baclesse, Oncology, Caen, France; Gustave Roussy, Villejuif, France; Groupe Hospitalier Bretagne Sud-Radiothérapie-Oncologie, Lorient, France; GORTEC, Tours, France; Charité Comprehensive Cancer Center, Berlin, Germany

Background: After promising results from the GORTEC TPEx phase II trial, the role of taxane instead of 5FU in 1st-line R/M HNSCC chemotherapy (CT) remained to be confirmed by comparing TPEx to the reference EXTREME regimen. Methods: Randomized (1:1), open-label trial. Main inclusion criteria were R/M HNSCC not suitable for locoregional treatment, age 18-70 years, PS <2, creatinine clearance >60ml/min, prior cisplatin <300 mg/m². Reference EXTREME regimen (arm A: 6 cycles every 3 weeks (Q3W) of 5FU–cisplatin-cetuximab (cetux) followed by weekly cetux maintenance) was compared to TPEx regimen (arm B: 4 cycles Q3W of docetaxel 75mg/m²–cisplatin 75mg/m²– cetux 250mg/m² with mandatory G-CSF support followed by every 2W cetux 500mg/m² maintenance). The primary endpoint was Overall Survival (OS). To detect a hazard ratio (HR) of 0.72 (median OS increase from 10.1 to 14.0 months (mo) with 88% power, 2-sided significance level of 0.05, 374 deaths were required. 540 patients (pts) were planned to enroll. Results: 539 pts were enrolled in 37 mo. Median age was 60 years, 93% were smokers, 40% had oropharyngeal tumor (p16 or HPV DNA was done in 85%, positive in 28%). In arm A, 44% of pts received all CT cycles vs 72% in arm B. Delays in administration were more frequent in arm A (27% vs 10%). Cisplatin was more frequently switched to carboplatin in arm A (34% vs 9%). Toxicity was lower in arm B: 34% pts had grade ≥4 adverse events during CT in arm B vs 50% in arm A (p<0.001). Less pts in arm A started maintenance than in arm B (53% vs 73%). At time of analysis, the median follow-up duration was 30 mo and 406 pts had died. OS was not significantly different between arms: HR=0.87 (95%CI: 0.71-1.05), p=0.15. Median OS was 13.4 mo in arm A vs 14.5 in arm B. 2-year OS rate was 21.0% in arm A vs 28.6% in arm B. Conclusions: This large randomized trial confirmed the encouraging survival results of the TPEx regimen observed in the first phase II. OS in both arms was higher than observed in previous randomized CT or immunotherapy combination trials. Despite lack of significant OS increase, taxane based TPEx regimen appears to be a new option in 1st line R/M HNSCC, with a shorter time on CT and significantly lower toxicity than the EXTREME regimen. Clinical trial information: NCT02268695.
Gemcitabine and cisplatin (GP) induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT) versus CCRT alone in locoregionally advanced nasopharyngeal carcinoma (NPC): A phase 3, multicenter, randomized controlled trial.

Jun Ma, Yuan Zhang, Ying Sun, Fangyun Xie, Weihan Hu, Guoqing Hu, Ning Zhang, Kun-Yu Yang, Xiaodong Zhu, Fengjin Zhi-Bin Cheng, Mei Shi, Fei Han, Ye Tian, Yan Sun, Hao-Yuan Mo, Jin-Gao Li; Sun Yat-sen University Cancer Center, Guangzhou, China; Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China; The First People’s Hospital of Foshan, Foshan, China; Union Hospital, Huazhong University of Science and Technology, Wuhan, China; Cancer Hospital of Guangxi Medical University, Nanning, China; Guizhou Cancer Hospital, Guiyang, China; The Fifth Affiliated Hospital of Sun Yat-Sen University, Zhuhai, China; Xijing Hospital, Xi’an, China; Second Affiliated Hospital of Soochow University, Suzhou, China; Beijing Cancer Hospital, Beijing, China; Jiangxi Cancer Hospital, Nanchang, China

Background: GP regimen has been established as the standard first-line treatment option for patients with recurrent/metastatic NPC. However, its efficacy in locoregionally advanced disease remains unclear. Methods: Patients with previously untreated, non-metastatic stage III-IVB (except T3-4N0M0, AJCC 7th) NPC, aged 18–64 years without severe comorbidities were eligible. They were randomly assigned (1:1) to receive GP IC (gemcitabine 1 g/m² on days 1 & 8, cisplatin 80 mg/m² on day 1, q3w for 3 cycles) plus CCRT (cisplatin 100 mg/m², q3w for 3 cycles, concurrently with intensity-modulated radiotherapy) or CCRT alone. The primary endpoint was failure-free survival (FFS). The calculated sample size was 238 per group, with an 80% power (two-sided α 0.05) to detect a treatment failure hazard ratio (HR) of 0.52. Results: From Dec 2013 to Sep 2016, 480 patients from 12 centers were randomly assigned to IC+CCRT (n = 242) or CCRT alone (n = 238) group. Baseline characteristics were well balanced. After a median follow-up of 39 months, 3-year FFS was 85.8% in the IC+CCRT group and 77.2% in the CCRT alone group (intention-to-treat population; HR 0.53, 95% confidence interval 0.34–0.81; P = 0.003). In GP+CCRT group, 239 patients started GP IC and 231 (96.7%) completed all three cycles. The most common grade 3 adverse events (AE) in IC+CCRT and CCRT group were mucositis (28.9% vs. 32.1%), neutropenia (28.0% vs. 10.5%) and leukopenia (26.4% vs. 20.3%). Conclusions: Adding GP IC to CCRT significantly improved FFS in locoregionally advanced NPC and is well tolerated with favorable toxicity profile. Clinical trial information: NCT01872962.

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<thead>
<tr>
<th></th>
<th>IC+CCRT (%)</th>
<th>CCRT (%)</th>
<th>P value</th>
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<tr>
<td>Intention-to-treat population</td>
<td>n = 242</td>
<td>n = 238</td>
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<tr>
<td>3-y failure-free survival</td>
<td>85.8</td>
<td>77.2</td>
<td>0.003</td>
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<tr>
<td>3-y overall survival</td>
<td>94.9</td>
<td>90.7</td>
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<tr>
<td>3-y distant metastasis-free survival</td>
<td>91.6</td>
<td>89.9</td>
<td>0.03</td>
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<tr>
<td>3-y locoregional failure-free survival</td>
<td>92.5</td>
<td>92.1</td>
<td>0.75</td>
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<tr>
<td>Safety population</td>
<td>n = 239</td>
<td>n = 237</td>
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<tr>
<td>Completed radiotherapy</td>
<td>100.0</td>
<td>99.2</td>
<td>0.25</td>
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<tr>
<td>Received concurrent cisplatin ≥ 200 mg/m²</td>
<td>80.6</td>
<td>95.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ grade 3 AEs during IC</td>
<td>38.9</td>
<td>55.3</td>
<td>0.03</td>
</tr>
<tr>
<td>≥ grade 3 AEs during CCRT</td>
<td>65.3</td>
<td>55.3</td>
<td>0.03</td>
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Primary analysis of phase 2 results of cemiplimab, a human monoclonal anti-PD-1, in patients (pts) with locally advanced cutaneous squamous cell carcinoma (laCSCC).

Michael Robert Migden, Nikhil I. Khushalani, Anne Lynn S. Chang, Danny Rischin, Chrysalyne D. Schmults, Leonel Fernando Hernandez-Aya, Friedegund Elke Meier, Dirk Schadendorf, Alexander David Guminski, Axel Hauschild, Deborah J.L. Wong, Gregory A. Daniels, Carola Berking, Vladimir Jankovic, Elizabeth Stanevitch, Jocelyn Booth, Siyu Li, Israel Lowy, Matthew G. Fury, Karl D. Lewis; Departments of Dermatology and Head and Neck Surgery, University of Texas, MD Anderson Cancer Center, Houston, TX; Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL; Stanford University Medical Center, Stanford, CA; Peter MacCallum Cancer Centre, Melbourne, Australia; Department of Dermatology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO; Department of Dermatology, University Hospital Dresden, Dresden, Germany; Department of Dermatology, University Hospital Essen, Essen, Germany; Department of Medical Oncology, Royal North Shore Hospital, St Leonards, Australia; Universitats-Hautklinik Kiel, Kiel, Germany; UCLA Department of Medicine, Los Angeles, CA; University of California, San Diego, La Jolla, CA; Department of Dermatology and Allergy, University Hospital of Munich (LMU), Munich, Germany; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ; University of Colorado Denver, School of Medicine, Aurora, CO

Background: Cemiplimab (REGN2810) produced substantial antitumor activity with durable responses in Phase 1 CSCC expansion cohorts and Phase 2 metastatic (m) CSCC cohort. We now present the primary analysis of the Phase 2 laCSCC cohort (NCT02760498; data cutoff date: Oct 10, 2018). Methods: Pts with laCSCC received cemiplimab 3 mg/kg IV every 2 weeks (Q2W). Tumor measurements were performed Q8W. The primary objective was to evaluate objective response rate (ORR; complete response [CR] + partial response [PR]) according to independent central review (per RECIST 1.1 for scans; modified WHO criteria for photos). Results: 78 pts were enrolled (59 M/ 19 F; median age: 74 years; ECOG PS: 0 in 38 pts, 1 in 40 pts; primary CSCC site: head/neck in 79.5%; prior systemic therapy: 15.4%; prior radiotherapy: 55.1%). Median duration of follow-up was 9.3 months (range: 0.8–27.9). ORR by central review was 43.6% (95% CI: 32.4–55.3; 10 CRs and 24 PRs); investigator-assessed (INV) ORR was 52.6% (95% CI: 40.9–64.0; 13 CRs and 28 PRs). Median duration of response (DOR) has not been reached. The longest DOR at data cut-off was 24.2 months and was still ongoing. Durable disease control rate (stable disease or response for ≥16 weeks) was 62.8% (95% CI: 51.1–73.5). Median observed time to response was 1.9 months (range: 1.8–8.8). Median progression-free and overall survival have not been reached. Tumor PD-L1 status is available for 48/78 pts, tumor mutational burden analysis (from targeted exome panel) is ongoing for 40/78 pts; response correlation analyses are planned. The most common treatment-emergent adverse events (AEs; all grades, Grade ≥3) were fatigue (42.3%, 1.3%), diarrhea and pruritus (both 26.9%, 0%), and nausea (21.8%, 0%). INV grade ≥3 immune-related AEs occurred in 10.3% of pts. One pt died due to an unknown cause that was assessed as treatment-related. Conclusions: Cemiplimab 3 mg/kg Q2W showed substantial antitumor activity, durable responses, and acceptable safety profile in pts with laCSCC. These data strongly support the recent FDA approval of cemiplimab-rwlc for pts with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation. Clinical trial information: NCT02760498.
Melanoma/Skin Cancers
Ipilimumab versus placebo after complete resection of stage III melanoma: Long-term follow-up results the EORTC 18071 double-blind phase 3 randomized trial.

Alexander M. M. Eggermont, Vanna Chiarion-Sileni, Jean Jacques Grob, Reinhard Dummer, Jedd D. Wolchok, Henrik Schmidt, Omid Hamid, Caroline Robert, Paolo Antonio Ascierto, Jon M. Richards, Celeste Lebbe, Virginia Ferraresi, Michael Smylie, Jeffrey S. Weber, Michele Maio, Fareeda Hosein, Veerle de Pril, Michal Kicinski, Stefan Suciu, Alessandro Testori; Gustave Roussy Cancer Centre and University Paris-Saclay, Paris, France; Veneto Oncology Research Institute, Padua, Italy; AIX-Marseille University, Marseille, France; Department of Dermatology, University Hospital Zürich Skin Cancer Center, Zürich, Switzerland; Memorial Sloan Kettering Cancer Center, New York, NY; Aarhus University Hospital, Aarhus, Denmark; The Angeles Clinic and Research Institute, Los Angeles, CA; Paris-Sud University, Gustave Roussy, Villejuif Cedex, France; Istituto Nazionale dei Tumori IRCCS Fondazione, Naples, Italy; Oncology Specialists, SC, Park Ridge, IL; APHP Dermatology and CIC, U976, Université de Paris, Hôpital Saint-Louis, Paris, France; Regina Elena National Cancer Institute, Rome, Italy; Cross Cancer Institute, Edmonton, AB, Canada; Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY; Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; Bristol-Myers Squibb, Lawrenceville, NJ; Bristol-Myers Squibb, Braine-L’alleud, Belgium; EORTC Headquarters, Brussels, Belgium; Formerly at European Institute of Oncology, Milan, Italy

Background: Since 2015, ipilimumab (Ipi) is an approved treatment for stage III melanoma based on a significantly (P=0.0013) prolonged recurrence-free survival (RFS) (Eggermont et al, Lancet Oncology, 2015). At a median follow-up of 5.3 years, RFS (HR=0.76) and distant metastasis-free survival (DMFS) (HR=0.76), assessed by an IRC, and overall survival (OS) (HR=0.72) were prolonged in the Ipi group as compared to the placebo (Pbo) group (Eggermont et al, NEJM, 2016), despite a 53.3% (Ipi) vs 4.6% (Pbo) treatment discontinuation rate due to adverse events. Methods: In this randomized double-blind trial, eligible patients (pts) included those ≥18 yrs of age who underwent complete resection of stage III cutaneous melanoma (excluding lymph node metastasis ≤1 mm or in-transit metastasis). 951 pts were randomized (stratified by stage and region) 1:1 to Ipi 10 mg/kg (n=475) or placebo (Pbo, n=476) q3w for 4 doses, then every 3 mos for up to 3 yrs until completion, disease recurrence, or unacceptable toxicity. Here, we report the comparison between the Ipi and Pbo groups regarding the long-term efficacy outcomes using the local investigator assessments. Results: Overall, 20%/44%/36% of pts had AJCC-7 stage IIIA/IIIB/IIIC, 42% ulcerated primary, and 58% macroscopic lymph node involvement. Median follow-up was 6.9 yrs. The RFS, DMFS and OS benefit observed in the Ipi group was long-lasting (almost 10% difference at 7 years) and consistent across subgroups: no significant predictive factors could be detected. Conclusions: In this phase III trial, Ipi, administered at 10 mg/kg, as adjuvant therapy provided, at a 6.9 yr median follow-up, a sustained improvement in the RFS, DMFS, and OS long-term results in patients with high-risk stage III melanoma. Clinical trial information: NCT00636168.

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<thead>
<tr>
<th></th>
<th>Ipi</th>
<th>Pbo</th>
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<tr>
<td>5-year rate</td>
<td>43.9%</td>
<td>30.5%</td>
</tr>
<tr>
<td>7-year rate</td>
<td>33.2%</td>
<td>30.9%</td>
</tr>
<tr>
<td>Median (yrs)</td>
<td>2.2 (IQR: 1.2-2.8)</td>
<td>1.5 (IQR: 1.2-2.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.75 (0.60-0.94)</td>
<td>0.76 (0.64-0.90)</td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>0.0004</td>
<td>0.0018</td>
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HR: Hazard Ratio provided by the Cox model; CI: Confidence intervals; NR: not reached; stratified by stage provided at randomization.

Phase 3 international trial of adjuvant whole brain radiotherapy (WBRT) or observation (Obs) following local treatment of 1-3 melanoma brain metastases (MBMs).

Gerald Fogarty, Kari Dolven-Jacobsen, Rachael L. Morton, George Hruby, Anna K. Nowak, Janette L. Vardy, Katharine J. Drummond, Haryana M. Dhillon, Catherine Mandel, Richard A. Scolyer, Brindha Shivalingham, Mark R. Middleton, Bryan H. Burmeister, Serigne Lo, Claudia H. Reisse, Elizabeth J. Paton, Victoria Steel, Narelle C. Williams, John F. Thompson, Angela M. Hong; Melanoma Institute Australia, The University of Sydney, Mater Hospital, Genesis Care, Australia and New Zealand Melanoma Trials Group, University of Notre Dame, University of Technology, Sydney, NSW, Australia; Oslo University Hospital, The Radium Hospital, Oslo, Norway; Melanoma Institute Australia, NIMRCC Clinical Trials Centre, The University of Sydney, Sydney, NSW, Australia; Sydney Medical School, The University of Sydney, Royal North Shore Hospital, Sydney, NSW, Australia; Medical School, University of Western Australia, Perth, Australia; Sydney Medical School, The University of Sydney, Sydney, NSW, Australia; Department of Neurosurgery, Royal Melbourne Hospital, Department of Surgery, University of Melbourne, Parkville, VIC, Australia; University of Sydney, Sydney Medical School, Sydney, NSW, Australia; Royal Prince Alfred Hospital, Sydney, NSW, Australia; Royal Prince Alfred Hospital, Sydney, NSW, Australia; University of Oxford, Oxford, United Kingdom; Genesis Care, Fraser Coast, Hervey Bay, QLD, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Royal Prince Alfred Hospital, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; University of Western Australia, Perth, Australia; Sydney Medical School, The University of Sydney, Sydney, NSW, Australia; Department of Neurosurgery, Royal Melbourne Hospital, Department of Surgery, University of Melbourne, Parkville, VIC, Australia; University of Sydney, Sydney Medical School, Sydney, NSW, Australia; Royal Prince Alfred Hospital, Sydney, NSW, Australia; University of Oxford, Oxford, United Kingdom; Genesis Care, Fraser Coast, Hervey Bay, QLD, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Oslo University Hospital, Oslo, Norway; Australia and New Zealand Melanoma Trials Group, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, Department of Melanoma and Surgical Oncology at Royal Prince Alfred Hospital, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Mater Hospital, Genesis Care, Sydney, NSW, Australia

Background: The role of adjuvant WBRT in MBMs is controversial. This trial compares WBRT with Obs after local treatment of 1-3 MBMs. Methods: The primary endpoint is distant intracranial failure (DIF) within 12 months of randomization. The a priori neurocognitive function (NCF) endpoint is Hopkins Verbal Learning Test-Revised (HVLT-R) delayed recall at 4 months. Secondary endpoints include local failure (LF), overall survival (OS) and global quality of life (QoL). Analyses were conducted on intention-to-treat basis with nominal two-sided significance level 5%. Drug therapy was allowed. Effective drugs became available during trial and their impact was analysed. Results: Of 586 eligible patients (pts), 215 consented from 31 sites in 3 countries (Australia, UK and Norway) between 2009 and 2017. Eight (0.04%) who withdrew or had no data collected were excluded. 107 randomized to Obs and 100 to WBRT. Mean age 62 years, 67% males, 61% with single MBM of mean size 2cm, 67% had extracranial disease at randomization. The two arms were well matched. NCF was completed by English speakers; 50 WBRT and 70 Obs at baseline, declining to 26 and 35 respectively at 4 months. Within 12 months, 54 (50.5%) Obs had DIF compared with 42 (42.0%) WBRT pts (OR 0.71; 95%CI 0.41-1.23; p = 0.222). There was no difference in LF (p = 0.100) or OS (log-rank p = 0.861). 53% (Obs) and 59% (WBRT) pts were alive at 12 months. There was no significant between-group difference in mean intervention effect on global QoL (p = 0.083). Pts who received T-cell checkpoint inhibitors and/mitogen-activated protein kinase (MAPK) pathway inhibitors and WBRT before or within 12 months of randomization had DIF rate 29% compared with Obs and no systemic therapy had 44%, but was not significant (p = 0.228). Obs had greater relative improvement from baseline in HVLT-R at every timepoint. At 4 months, Obs had 20.9% improvement from baseline in HVLT-R-delayed recall compared to 2.7% decline in WBRT; overall adjusted average intervention effect 23.6% (95%CI 9.0, 38.2; p = 0.0018). There was no difference in time to cognitive failure or in proportions with global cognitive impairment. Conclusion: This level one evidence shows WBRT does not improve outcomes in MBMs. This practice-changing trial justifies the recent move away from WBRT that occurred during the course of the trial. Clinical trial information: NCT01503827.
Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204).

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Background: We previously reported efficacy and safety of NIVO+IPI in patients (pts) with untreated, asymptomatic, melanoma brain metastases (MBM) from the CheckMate 204 study. Here, we provide the first report of NIVO+IPI in pts with symptomatic MBM, and report updated data in pts with asymptomatic MBM. Methods: In this phase II trial, pts with ≥1 measurable, nonirradiated MBM 0.5–3.0 cm were enrolled into two cohorts: (1) those with no neurologic symptoms or steroid Rx (asymptomatic; cohort A); and (2) those with neurologic symptoms, whether or not they were receiving steroid Rx (symptomatic; cohort B). In both cohorts, pts received NIVO 1 mg/kg + IPI 3 mg/kg Q3W × 4, then NIVO 3 mg/kg Q2W until progression or toxicity. The primary endpoint was intracranial clinical benefit rate (CBR; proportion of pts with complete response [CR] + partial response [PR] + stable disease [SD] ≥6 mo). As of the clinical cutoff date on May 1, 2018, all treated pts (101 in cohort A and 18 in cohort B) had been followed for ~6 mo or longer. Results: In this updated analysis of cohort A (median follow-up of 20.6 mo), the CBR was 58.4% (Table). In cohort B, pts received a median of 1 NIVO+IPI dose and 2 of 18 pts (11%) received all 4 doses. At a median follow-up of 5.2 months in cohort B, intracranial objective response rate was 16.7% and the CBR was 22.2%. Grade 3/4 adverse events occurred in 54.5% of pts in cohort A and in 55.6% of pts in cohort B (6.9% and 16.7% in the nervous system, respectively), with one death related to treatment in cohort A (immune-related myocarditis). Conclusions: In pts with asymptomatic MBM, our updated results show a high rate of durable intracranial responses, further supporting NIVO+IPI as a first-line treatment in this population. Intracranial antitumor activity was observed with NIVO+IPI in pts with symptomatic MBM, but further study is needed to understand the biologic mechanisms of resistance to immunotherapy and to improve treatments in this challenging population. Clinical trial information: NCT02320058.

<table>
<thead>
<tr>
<th>Intracranial response</th>
<th>Asymptomatic (Cohort A; n = 101)</th>
<th>Symptomatic (Cohort B; n = 18)</th>
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<tr>
<td>Best overall response, n (%)</td>
<td>CR: 29 (29)</td>
<td>2 (11)</td>
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<tr>
<td></td>
<td>PR: 26 (26)</td>
<td>1 (5.6)</td>
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<td></td>
<td>SD: 4 (4)</td>
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<td>CBR, % (95% CI)</td>
<td>58.4 (48.2-68.1)</td>
<td>22.2 (6.4-47.6)</td>
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</table>
Pathological response and survival with neoadjuvant therapy in melanoma: A pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC).

Alexander M. Menzies, Elisa A. Rozeman, Rodabe Navroze Amaria, Alexander Chan Chi Huang, Richard A. Scolyer, Michael T. Tetzlaff, Bart A. Van De Wiel, Serigne Lo, Ahmad A. Tarhini, Hussein Abdul-Hassan Tawbi, Elizabeth M. Burton, Giorgos Karakousis, Paolo Antonio Ascierto, Andrew Spillane, Michael A. Davies, Alexander Christopher Jonathan Van Akkooi, Tara C. Mitchell, Georgina V. Long, Jennifer Ann Wargo, Christian U. Blank, International Neoadjuvant Melanoma Consortium (INMC); Melanoma Institute Australia, University of Sydney, Royal North Shore Hospital, Sydney, Australia; Netherlands Cancer Institute, Amsterdam, Netherlands; The University of Texas - MD Anderson Cancer Center, Houston, TX; Univ of Pennsylvania, Bryn Mawr, PA; The University of Sydney, Melanoma Institute Australia and Royal Prince Alfred Hospital, Sydney, NSW, Australia; The University of Texas MD Anderson Cancer Center, Houston, TX; Melanoma Institute Australia, University of Sydney, Sydney, NSW, Australia; Case Comprehensive Cancer Center/Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Istituto Nazionale dei Tumori IRCCS Fondazione, Naples, Italy; Melanoma Institute Australia, Sydney, Australia; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia

Background: Pathological complete response (pCR) to neoadjuvant systemic therapy (NST) correlates with survival, and is recognized as a path to regulatory approval in several cancers. Recent trials have reported that neoadjuvant immunotherapy (IT) and targeted therapy (TT) regimens achieve high pCR rates and impressive recurrence-free survival in stage III melanoma, however, the relationship between pCR, relapse-free (RFS) and overall survival (OS) in larger datasets of melanoma patients (pts) remains unknown. Methods: We pooled data from 6 modern NST clinical trials of anti-PD-1 based immunotherapy or BRAF/MEK targeted therapy conducted across institutions participating in the INMC. Pts with RECIST measurable, surgically resectable clinical stage III melanoma who underwent surgery were included. NST regimens included nivolumab (as monotherapy or in combination with ipilimumab), pembrolizumab or dabrafenib+trametinib. Baseline disease characteristics, treatment regimen, pCR and RFS were examined. Results: 184 pts with clinical stage III melanoma (AJCCv7: 100 IIIB, 84 IIIC) completed NST (133 IT, 51 TT) and underwent surgery. Median age was 57y (range 18-87). A pCR was observed in 41% of patients; 51 (38%) with IT and 24 (47%) with TT. Median follow-up post-surgery is 13 mo (95% CI 12-16); 10 mo with IT and 22 mo with TT. 44 (24%) pts have recurred (17 loco-regional, 21 distant, 6 both sites at first recurrence), 18 (14%) after IT and 26 (51%) after TT. 12-month RFS was improved with IT vs TT (83% vs 65%, p < 0.001). For those with pCR, 7% have recurred, 0/51 (0%) after IT, 7/17 (41%) after TT. For those without pCR, 34% have recurred, 18/82 (22%) after IT and 19/27 (70%) after TT. 12-month RFS was improved in those with pCR vs without pCR (95% vs 62%, p < 0.001), including in those with IT (100% vs 72%, p < 0.001) and TT (88% vs 43%, p < 0.001). 16 (9%) patients have died including two who had a pCR, both from TT. Conclusions: Neoadjuvant IT and TT are active regimens in resectable clinical stage III melanoma patients and are associated with high pCR rate. The ability to achieve pCR correlates with improved RFS and remarkably no patient with pCR from immunotherapy has recurred to date.
Five-year analysis on the long-term effects of dabrafenib plus trametinib (D + T) in patients with BRAF V600-mutant unresectable or metastatic melanoma.

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Background: First-line treatment with D+T demonstrated prolonged progression-free survival (PFS) and overall survival (OS) in patients with BRAF V600-mutant unresectable or metastatic melanoma. With 5 years of follow-up, we report survival and describe characteristics of patients in the phase 3 COMBI-d and COMBI-v trials with long-term benefit. Methods: Pooled 5-year landmark data for patients treated with D+T in the phase 3 COMBI-d (NCT01584648) and COMBI-v (NCT01597908) trials were analyzed. The trials enrolled patients with previously untreated BRAF V600E/K-mutant unresectable or metastatic melanoma. Patients received D 150 mg twice daily plus T 2 mg once daily vs either D + placebo (COMBI-d) or vemurafenib (COMBI-v). The primary endpoints were PFS in COMBI-d and OS in COMBI-v. Results: The pooled population included 563 patients who received D+T (COMBI-d, n = 211; COMBI-v, n = 352). Four- and 5-year PFS and OS rates were similar, suggesting a stabilization (4- and 5-year PFS, 21% [95% CI, 17%-24%] and 19% [95% CI, 15%-22%, respectively]; 4- and 5-year OS, 37% [95% CI, 33%-42%] and 34% [95% CI, 30%-38%], respectively). In patients with normal baseline lactate dehydrogenase (LDH) levels the 5-year PFS rate was 25% vs 8% in patients with elevated baseline LDH levels. Similarly, the 5-year OS rate was considerably higher in patients with normal baseline LDH levels vs those with elevated LDH levels at baseline (43% vs 16%). Among patients with normal baseline LDH levels and < 3 organ sites with metastases, the 5-year PFS and OS rates were 31% and 55%, respectively. In addition, exploratory analyses will be performed to characterize subgroup(s) of patients most likely to experience long-term benefit. Of 299 patients who received subsequent anticancer therapy following treatment with D+T, 151 (51%) received an anti-CTLA-4 therapy and 102 (34%) received an anti-PD-1 therapy. The safety profile of D+T was as previously reported, and no new safety signals were observed. No treatment-related deaths were reported. Conclusions: First-line treatment with D+T leads to durable long-term benefit in many patients with BRAF V600-mutant unresectable or metastatic melanoma. Clinical trial information: NCT01584648; NCT01597908.
Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Thoracic Cancers
Initial reporting of NRG-LU001 (NCT02186847), randomized phase II trial of concurrent chemoradiotherapy (CRT) +/- metformin in locally advanced Non-Small Cell Lung Cancer (NSCLC).

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Background: Metformin, a diabetes agent that inhibits mitochondria complex I, enhances radiotherapy and chemotherapy responses in pre-clinical models of NSCLC. NRG-LU001 examined whether metformin can improve outcomes of curative CRT in locally advanced (LA)-NSCLC. Methods: The primary endpoint of this trial was 1-year progression free survival (PFS). Unresected, non-diabetic, stage IIIA/B NSCLC patients were randomized (1:1) to either carboplatin-paclitaxel chemotherapy concurrent with chest RT (60Gy), followed by consolidation carboplatin-paclitaxel chemotherapy (Control Arm) or the same and oral metformin (2000mg daily) during cytotoxic therapy (Experimental Arm). PFS and overall survival (OS) were estimated with the Kaplan-Meier method; time to local-regional progression (TTLRP), time to distant metastasis (TTDM) were estimated using the cumulative incidence method. Adverse events (AEs) were graded with CTCAE v.4.0. Results: Between Aug.2014 and Dec.2016, 170 patients were accrued. Analysis was planned at 102 PFS events (Feb. 2019). There was no significant difference in rates or grade of toxicity between the two arms. 1- and 2-year PFS was 60.4% (95% CI: 48.5, 70.4) and 40.1% (95% CI: 29.0, 51.0) in Control vs 51.3% (95% CI: 39.8, 61.7) and 34.5% (95% CI: 24.2, 45.1) in the Metformin arm (multivariable Cox proportional HR=1.20 (95% CI: 0.81, 1.78), p=0.36). OS at 2 years was 65.4% (95% CI: 53.5, 75.0) for Control vs 64.9% (95% CI: 51.3, 74.5) for the Metformin arm (HR=1.03 (95% CI: 0.64, 1.68)), while deaths due to disease were 90% vs 71%, respectively. No significant differences were found for TTLRP or TTDM. Conclusions: NRG-LU001 center reported outcomes show that oral daily metformin was well-tolerated in combination with CRT treatment for LA-NSCLC. However, metformin did not improve PFS and OS and did not alter the rates of local-regional failure or distant metastasis. Acknowledgements: TT and HS are Co-Principal Investigators. This project was supported by National Cancer Institute (NCI) grants: U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG SDMC), UG1CA189867 (NCGRP), U24CA180803 (IROC). Clinical trial information: NCT02186847.
Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3).

David J. Kwiatkowski, Valerie W. Rusch, Jamie E. Chaft, Bruce E. Johnson, Alan Nicholas, Ignacio Ivan Wistuba, Robert Merritt, Jay M. Lee, Paul A. Bunn, Yan Tang, See-Chun Phan, Saitama Naheed Waqar, Alexander Patterson, Eric B. Haura, Eric M. Toloza, Karen L. Reckamp, Dan Raz, Katja Schulze, Ann Johnson, David Paul Carbone; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Thoracic Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; Genentech, Inc., South San Francisco, CA; Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; The Ohio State University Comprehensive Cancer Center, James Cancer Hospital, Solove Research Institute, Columbus, OH; David Geffen School of Medicine at UCLA, Los Angeles, CA; University of Colorado Denver, Aurora, CO; Brigham and Women’s Hospital, Boston, MA; Genentech, Inc., San Francisco, CA; Washington University School of Medicine, St. Louis, MO; Department of Thoracic Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL; Moffitt Cancer Center, Tampa, FL; City of Hope Comprehensive Cancer Center, Duarte, CA; The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Small pilot studies (e.g., *N Engl J Med*. 2018;378:1976) have shown that preoperative immune checkpoint inhibitor therapy may be of benefit in early-stage NSCLC. This large multicenter trial assesses the benefit of neoadjuvant treatment with atezolizumab (atezo; NCT02927301).

Methods: Patients (pts) with stages IB to selected IIIB resectable NSCLC receive 2 cycles of atezo 1200 mg (days 1, 22) then undergo resection (day 40 ± 10). Primary tumor +/- node biopsies and blood samples are obtained before atezo and at surgery for biomarker studies. The primary endpoint is major pathological response (MPR), defined as ≤ 10% viable tumor cells in the resection specimen. Secondary endpoints include safety and correlation of response with PD-L1 expression, tumor mutation burden (TMB) and gene expression signatures.

Results: For this interim efficacy analysis (5 Sep 2018 data cut), we report on the first 101 of 180 planned pts: 47 males, median age, 64 y; all ECOG PS 0-1; 23 current and 68 former smokers; 66 non-squamous NSCLC; clinical stages IB/IIA/IIB/IIIA/IIIB n = 11/16/28/39/7. There were 2 treatment-unrelated Gr 5 AEs (cardiac death post surgical resection; death due to disease progression), 29 Gr 3-4 AEs (6 [6%] treatment related). 90 pts had surgery. Excluding 8 pts who had driver mutations (7 EGFR, 1 ALK, no MPR), MPR rate was 15/82 (18%, 95% CI 11%-28%), 4 pts had pathological complete response (pCR). By RECIST, 6/82 pts had PR, 72 had SD and 4 had PD. Two of 26 (8%) PD-L1− (TC0 and IC0, clone SP142) and 10 of 35 (29%) PD-L1+ had MPR (P= 0.055). Five of 44 (11%) TPS < 50 (PD-L1 clone 22C3) and 7 of 20 (35%) TPS > 50 had MPR (P= 0.040). Exome sequencing data was available for 47/101 pts. Median TMB was 10.4 (range, 1.5-46.5) mutations per Mb and was not different in those with MPR compared with those without MPR. Further analysis of TMB, mutation signatures, and gene expression profiling is ongoing. Conclusions: Atezo in the neoadjuvant setting was well tolerated, and pCR and MPR rates are encouraging in this large multicenter trial. Efficacy interim analysis passed its futility boundary, and study enrollment continues. Safety, efficacy results and ongoing correlative analyses will be presented. Clinical trial information: NCT02927301.

Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study.

Tina Cascone, William Nassib William, Annikka Weissferdt, Heather Y. Lin, Cheuk Hong Leung, Brett W. Carter, Frank V. Fossella, Frank Mott, Vassiliki Papadimitrakopoulou, George R. Blumenschein, Jr., Xiuning Le, Lorenzo Federico, Edwin Roger Parra Cuentas, Chantale Bernatchez, Ignacio Ivan Wistuba, Ara A. Vaporiyan, Don Lynn Gibbons, Stephen Swisher, John Heymach, Boris Sepes, NEOSTAR Study Group; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic and Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic and Head and Neck Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Neoadjuvant immune checkpoint inhibitors (ICIs) induce major pathologic response (MPR) rates of 20 to 45% in resected NSCLCs. We report the results of NEOSTAR - a phase 2 trial of neoadjuvant N or NI for NSCLCs. Methods: Pts with stage I-IIIA (single N2) resectable NSCLC (AJCC 7th), PS 0-1, were randomized to N (3 mg/kg IV, D1, 15, 29) or N plus I (1 mg/kg IV, D1) followed by surgery (n = 44). Primary endpoint: MPR (≥10% viable tumor), hypothesized to be higher than MPR to induction chemotherapy historical controls. Tumor immune infiltrates and pre- & post-ICI tumor PD-L1 % were assessed by flow cytometry & IHC. Wilcoxon ranked sum test & Fisher's exact test were used for comparisons. Results: 44 pts were randomized, 23 N, 21 NI: mean age 66, 64% males, 18% never smokers, 59% adenocarcinomas, stages: IA 8 (18%), IB 15 (34%), IIA 7 (16%), IIB 5 (11%), IIIA 9 (20%). Only 3 pts received < 3 doses due to TRAEs (7%). 34 pts had surgery post ICIs (7 not resected [7/41], 17%, [2 N, 5 NI], 3 pending). There were 10 MPRs in 41 pts overall (24%, 4 N, 6 NI), of which 6 were path CRs (15%, 2 N [9%], 4 NI [21%]). Among 34 resected pts, MPR rate was 29% (N 20%, NI 43%). Median % of viable tumor was lower post NI vs N (20% vs 65%, p = .097). ORR (RECIST v1.1) was 22% (8 PRs [5 N, 3 NI], 1 CR [NI]); 15% of pts had PD (3 N, 3 NI). The proportion of CR+PR in MPR+ was higher than in MPR- (6 [60%] vs 2 [7%], p < .001). Surgical complications included 2 bronchopleural fistulas (BPFs) in N & 8 air leaks (5 N, 3 NI). G3-G5 TRAEs included a death due to BPF post steroid-treated pneumonitis (G5, N); G3 pneumonia, hypoxia, hypermagnesemia (1 each, all N), G3 diarrhea (1 NI). CD3+ & CD103+ tissue resident memory CD8+ TILs were higher in NI- vs N-treated tumors (CD3+ 81.2% vs 54.4%, p = .028; CD8+ 56.2% vs 38.3%, p = .069). Median pre-treatment tumor PD-L1 was higher in responders (MPR+, CR+PR) vs non-responders (80% vs 1%, p = .024), and the % of viable tumor was lower in tumors with PD-L1 > 1% vs PD-L1 ≤1% (median 20% vs 80%, p = .046). Conclusions: Overall a 24% MPR rate to neoadjuvant ICIs was observed. NI induced a higher % of non-viable tumor and of tissue resident memory TILs vs N. Antitumor activity was associated with higher pre-treatment PD-L1 levels. Clinical trial information: NCT03158129.
Efficacy and safety profile of lurbinectedin in second-line SCLC patients: Results from a phase II single-agent trial.

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Background: Lurbinectedin (L) is a novel anticancer drug that inhibits activated transcription and induces DNA double-strand breaks, leading to apoptosis. Methods: A multicenter phase 2 basket trial assessed the efficacy and safety of L in several cancer types, including small cell lung cancer (SCLC). Primary endpoint was confirmed overall response rate (ORR) by RECIST v.1.1. In the SCLC cohort, a target ORR =30% was set. One-hundred and five patients (pts) with ECOG PS 0-2 who had received one prior chemotherapy line were treated with L 3.2 mg/m² as a 1-hour i.v. infusion on Day 1 q3wk. Results: Median age was 60 years (range, 40-83), 60% were male, ECOG PS 0/1/2 (32%/62%/6%), liver metastasis 41%, history of CNS involvement 3.8%, prior platinum 100%, median chemotherapy-free interval (CTFI): 3.5 (0-16.1) months; prior immunotherapy (IO): 7.6%. Pts received a median of 4 cycles (range, 1-24). Conclusions: L monotherapy is active in second-line SCLC in both resistant and sensitive disease. The acceptable and manageable safety profile is also associated to a convenient treatment administration (Day 1 q3wk). L as second-line treatment in SCLC emerges as a new promising drug for this unmet clinical need. Clinical trial information: NCT02454972.

### Overall (n=105) CTFI<90d (n=88) CTFI<90d (n=56)

| ORR, % (95% CI) (confirmed responses) | 35.2 (26.2-45.2)* | 21.3 (10.7-35.7) | 46.6 (33.3-60.1) |
| Disease Control Rate (%) at 8 wks | 64.8 | 46.8 | 79.3 |
| Median DOR (months) (95% CI) | 5.3 (3.5-6.4) | 4.7 (2.6-5.6) | 6.2 (3.4-6.9) |
| DOR rate at 6 months (95% CI) | 40.3 | 11.7 | 50.3 |
| DOR rate at 12 months (95% CI) | 10.6 | 14.7 |
| Median OS (months) (95% CI) | 10.8 (6.5-12.2) | 5.1 (4.4-8.1) | 15.2 (10.2-16.2) |

* 5 of 8 pts who failed prior IO had confirmed response DOR: duration of response. *Preliminary Myelosuppression was the most common adverse event (AE): G3 (22%) and G4 (23.8%) neutropenia, G3/4 febrile neutropenia (3.8%) and G3/4 thrombocytopenia (6.6%). Secondary prophylaxis or therapeutic G-CSF was given in 15.2%. Most common non-hematological AEs were fatigue (G3: 4.8%), nausea and vomiting (all G1-2). Related serious AEs occurred in 10.5% pts, while treatment-related discontinuations in 3.8%. No treatment-related deaths were reported.

Lung Cancer—Non-Small Cell Metastatic
RELAY: A multinational, double-blind, randomized Phase 3 study of erlotinib (ERL) in combination with ramucirumab (RAM) or placebo (PL) in previously untreated patients with epidermal growth factor receptor mutation-positive (EGFRm) metastatic non-small cell lung cancer (NSCLC).

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Background: Dual blockade of EGFR and VEGFR pathways in EGFRm NSCLC augments anti-tumor efficacy versus (v) EGFR inhibition alone. RELAY (NCT02411448) evaluated efficacy and safety of ERL, an EGFR TKI standard-of-care, plus RAM, a human IgG1 VEGFR2 antagonist, or PL in 1L EGFRm metastatic NSCLC. Methods: Eligibility included untreated metastatic NSCLC pts with Exon 19 deletion (del) or L858R and no CNS metastasis. Randomized (1:1) pts received ERL (150 mg/day) + RAM (10 mg/kg q2w) or ERL + PL, stratified by gender, geographic region (East Asia v other), EGFRm type (Ex19del v L858R) and EGFR testing method (Therascreen/Cobas v other). The primary endpoint was Investigator assessed progression free survival (PFS). Other objectives included ORR, DoR, PFS2, OS, safety, and plasma T790M mutation (Guardant NGS). Results: 449 pts were randomized characteristics were balanced between treatment arms: Asian 77%, Females 63%, Ex19del 54%. RAM + ERL significantly prolonged PFS, DoR, and PFS2 (Table). Grade ≥3 TEAEs were greater with RAM (72%) v PL (54%), largely driven by hypertension (24 v 5%, no Gr4); with 1 treatment related on study death (hemothorax) in RAM v 0 PL. EGFR T790M+ rates at progression are forthcoming. Conclusion: RAM + ERL led to superior PFS in 1L EGFRm metastatic NSCLC. Safety was consistent with the established safety profiles of the individual compounds. Clinical trial information: NCT02411448.

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<tr>
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<th>RAM + ERL (n=224)</th>
<th>PL + ERL (n=225)</th>
<th>HR (95% CI) p-value</th>
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<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Median, months (95% CI)</td>
<td>19.4 (15.4 – 21.6)</td>
<td>12.4 (11.0 – 13.5)</td>
<td>0.559 (0.461 – 0.760)</td>
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<tr>
<td>Censoring rate</td>
<td>26%</td>
<td>26%</td>
<td></td>
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<tr>
<td>Number of responders</td>
<td>171</td>
<td>168</td>
<td></td>
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<tr>
<td><strong>DoR</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median, months (95% CI)</td>
<td>18.0 (13.9 – 19.8)</td>
<td>11.1 (9.7 – 12.3)</td>
<td>0.619 (0.477 – 0.805)*</td>
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<tr>
<td>Censoring rate</td>
<td>24%</td>
<td>24%</td>
<td></td>
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<tr>
<td><strong>PFS2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Censoring rate</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Interim OS</strong></td>
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<tr>
<td>Median, months (95% CI)</td>
<td>8.3 (5.3 – 13.0)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Censoring rate</td>
<td>81%</td>
<td>NR</td>
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Median follow-up: 20.7 months NR, not reached * unstratified **Ns are based on number of responders from the ITT population
Phase III randomized trial comparing gefitinib to gefitinib with pemetrexed-carboplatin chemotherapy in patients with advanced untreated EGFR mutant non-small cell lung cancer (gef vs gef+C).

Vanita Noronha, Amit Joshi, Vijay Maruti Patil, Anuradha Chougule, Abhishek Mahajan, Amit Janu, Nilendu Purandare, Rajiv Kumar, Sucheta More, Supriya Goud, Nandkumar Kadam, Nilesh Daware, Srushti Shah, Akanksha Yadav, Amit Dutt, Vaishakh Trivedi, Vichitra Behel, Shripad Dinanath Banavali, Kumar Prabhash; Tata Memorial Centre, Mumbai, India; Tata Memorial Hospital, Mumbai, India; Gunvati J Kapoor Medical Relief Charitable Foundation, Mumbai, India; Tata Memorial Center, Mumbai, India; Advanced Centre for Treatment, Research and Education in Cancer, Navi Mumbai, India

Background: Standard first-line therapy for EGFR mutant advanced non-small cell lung cancer (NSCLC) is an EGFR-directed oral TKI. We evaluated whether adding pemetrexed-carboplatin to oral TKI would improve outcomes. Methods: Phase III randomized trial in advanced chemotherapy-naïve NSCLC harboring EGFR sensitizing mutation (exon 19, 21 or 18) with performance status (PS) 0 to 2 planned for palliative therapy. Patients were stratified for PS and EGFR mutation and randomly assigned (computer-generated randomization by independent biostatistician) 1:1 to gefitinib 250 mg orally daily (gef) or gefitinib 250 mg orally daily with pemetrexed 500 mg/m² IV and carboplatin AUC 5 IV every 3 weeks for 4 cycles, followed by maintenance pemetrexed 500 mg/m² IV every 3 weeks (gef+C). Restaging was every 2 to 3 mths; therapy continued until progression or intolerable toxicity. Primary end point was progression-free survival (PFS); secondary end points included overall survival (OS), toxicity and response rate. Survival endpoints were assessed in the intention-to-treat population. Results: Between Aug 2016 and Aug 2018, 350 patients were randomly assigned to gef (n = 177) and gef+C (n = 173). Median age was 54 yrs, 48% were females, 84% never-smokers, 21% were PS 2 and 18% had brain metastases. Median follow-up in surviving patients was 17 months (range, 7 to 30). Radiologic response rates were 81% and 69% in gef+C and gef respectively, P = 0.012. 234 patients (67%) have had events for PFS, 98 in gef+C and 136 in gef. Estimated median PFS was significantly longer with gef+C than gef (16 months, [95% CI, 13.7 to 18.3] vs. 8 months [95% CI, 7.1 to 8.9]; hazard ratio for disease progression or death, 0.5; 95% CI, 0.39 to 0.65; P < 0.001). 120 patients (34%) have died, 42 in gef+C and 78 in gef. Estimated median OS was significantly longer with gef+C than gef (not reached vs. 18 months [95% CI, 14.28 to 21.72]; hazard ratio for death, 0.45; 95% CI, 0.31 to 0.66; P < 0.001). Clinically relevant ≥ grade 3 toxicities occurred in 51% and 25% of patients in gef+C and gef arms respectively, P < 0.001. Conclusion: Adding pemetrexed-carboplatin chemotherapy to gefitinib significantly prolonged progression free and overall survival but also increased toxicity. Pemetrexed-carboplatin-gefitinib represents a new standard first-line therapy for EGFR mutant NSCLC. Clinical trial information: CTRI/2016/08/007149.
ECOG-ACRIN 5508: Pemetrexed, bevacizumab or the combination as maintenance therapy for advanced non-squamous NSCLC.

Suresh S. Ramalingam, Suzanne Eleanor Dahlberg, Chandra Prakash Belani, Joel N. Saltzman, Gopakumar S. Nambudiri, John McCann, Mohammad Asher Kassem, Mohamed K. Mohamed, Jan M. Rothman, Alan P. Lyss, Leora Horn, Tom Stinchcombe, Joan H. Schiller, ECOG-ACRIN Cancer Research Group; Winship Cancer Institute, Emory University, Atlanta, GA; Dana-Farber Cancer Institute, Boston, MA; Penn State Hershey Cancer Institute, Hershey, PA; University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH; Health East Cancer Care, Woodbury, MN; Baystate MedcI Ctr, Springfield, MA; Ann Arbor Hem Onc Assoc, Ypsilanti, MI; Mt.Sinai Hosp, Chicago, IL; Cone Health Center at Wesley Long, Greensboro, NC; The Regional Cancer Center, Erie, PA; Missouri Baptist Cancer Ctr, St Louis, MO; Vanderbilt University Medical Center, Nashville, TN; Duke Cancer Institute, Durham, NC; The University of Texas Southwestern Medical Center, Dallas, TX

Background: Maintenance therapy is a standard approach for advanced non-squamous NSCLC. Pemetrexed or bevacizumab are considered evidence-based options. The combination of bevacizumab and pemetrexed has been documented to improve progression-free survival (PFS). We conducted a phase 3 study to determine the optimal maintenance therapy for advanced NSCLC. Methods: Patients (pts) with advanced non-squamous NSCLC, no prior systemic therapy, and ECOG performance status 0/1 were treated with carboplatin (AUC = 6), paclitaxel (200 mg/m^2) and bevacizumab (15 mg/kg) every 3 weeks for up to 4 cycles (step 1). Patients with CR/PR/SD after 4 cycles were then randomized 1:1:1 to maintenance therapy with bevacizumab (15 mg/kg), pemetrexed (500 mg/m^2) or the combination of the two agents every 3 weeks until disease progression (step 2). The primary endpoint was overall survival (OS), defined as the time from randomization to death from any cause and censoring defined at the last date of followup. 1495 pts provided 81% power to detect a hazard ratio of 0.75 while controlling the 2-sided type I error at 0.025 for each comparison, assuming approximately 60% of those patients would be randomized. Results: We enrolled 1516 pts to step 1 (male 52%; ECOG PS 1 62%; adenocarcinoma 90%); After induction therapy, 874 (57%) pts were randomized to step 2 (median age 64 yrs; male 49%; ECOG PS 1 55%). Baseline characteristics were balanced across all three groups. The median follow-up in maintenance is 50.6 months. Conclusions: Single agent bevacizumab or pemetrexed is the optimal maintenance therapy for advanced non-squamous NSCLC. The combination of bevacizumab and pemetrexed cannot be recommended due to the lack of survival benefit in this definitive study. (Drs. Ramalingam, Dahlberg and Belani contributed equally to this work). Supported by the NCI: CA180820, CA180794, CA180799, CA180821, CA180838, CA180844, CA180847, CA180853, CA180857, CA180864, CA180867, CA180868, CA180870, CA180882, CA189830, CA189859, CA189863, CA189971. Clinical trial information: NCT01107626.

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<tr>
<th></th>
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<tr>
<td>Number of patients</td>
<td>287</td>
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<td>293</td>
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<tr>
<td>OS</td>
<td>14.4 m</td>
<td>15.9 m</td>
<td>16.4 m</td>
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<tr>
<td>Grade 3/4/5 Toxicity</td>
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<td>Worst Degree</td>
<td></td>
<td></td>
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<tr>
<td>Anemia</td>
<td>30%</td>
<td>37%</td>
<td>50%</td>
</tr>
<tr>
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<td>3%</td>
<td>5%</td>
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<tr>
<td>Thrombocytopenia</td>
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<td>8%</td>
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<tr>
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<tr>
<td>Hypertension</td>
<td>14%</td>
<td>1%</td>
<td>10%</td>
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Blood tumor mutational burden (bTMB) and tumor PD-L1 as predictive biomarkers of survival in MYSTIC: First-line durvalumab (D) ± tremelimumab (T) versus chemotherapy (CT) in metastatic (m) NSCLC.

Naiyer A. Rizvi, Byoung Chul Cho, Niels Reinmuth, Ki Hyeong Lee, Alexander Luft, Myung-Ju Ahn, Michel van den Heuvel, Manuel Cobo Dols, David Vicente, Alexey Smolin, Vladimir Moiseyenko, Scott Joseph Antonia, Kazuhiko Nakagawa, Sarah B. Goldberg, Edward S. Kim, Jill Walker, Rajiv Raja, Feng Liu, Urban J. Scheurig, Solange Peters; Columbia University Medical Center, New York, NY; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Asklepios Lung Clinic, Munich-Gauting, Germany; Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, South Korea; Leningrad Regional Clinical Hospital, Oncology Department, Lunacharskogo Prospect, Russian Federation; Samsung Alpert Medical School, Los Angeles, CA; Department of Thoracic Oncology, Netherlands Cancer Institute (NKI), Amsterdam, Netherlands; Hospital Universitario Regional Málaga, Instituto de Investigaciones Biomédicas Málaga (IBIMA), Málaga, Spain; Hospital Universitario Virgen Macarena, Seville, Spain; Main Military Hospital, Moscow, Russian Federation; Clinical Research Center, Pesochny, St. Petersburg, Russian Federation; Moffitt Cancer Center, Tampa, FL; Kindai University Hospital, Osaka, Japan; Yale University School of Medicine, New Haven, CT; Levine Cancer Institute, Charlotte, NC; AstraZeneca, Cambridge, United Kingdom; MedImmune, Gaithersburg, MD; AstraZeneca, Gaithersburg, MD; Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland

Background: MYSTIC, an open-label, Ph3 trial of first-line D (anti-PD-L1) ± T (anti-CTLA-4) vs platinum-based CT, showed an improvement in OS with D vs CT in pts with tumor cell PD-L1 expression ≥25% (PD-L1 TC ≥25%; HR 0.76 [97.54% CI 0.56–1.02], p = 0.036). Exploratory analyses showed bTMB was a predictive biomarker for OS with D+T vs CT. We report further exploratory analyses of OS according to PD-L1 and bTMB. Methods: Immunotherapy/CT-naive pts with mNSCLC were randomized (1:1:1) to D, D+T or CT. bTMB levels (mut/Mb) were evaluated with the GuardantOMNI platform (Guardant Health), and PD-L1 TC expression with the VENTANA PD-L1 (SP263) IHC assay.

Results: PD-L1 TC ≥25% across bTMB levels (PD-L1 TC ≥25%/bTMB ≥20 HR 0.79 [95% CI 0.45, 1.39]; PD-L1 TC ≥25%/bTMB < 20 HR 0.64 [95% CI 0.45, 0.90]). In contrast, D+T improved OS vs CT in pts with bTMB ≥20 across different PD-L1 TC expression levels (Table; PD-L1 TC ≥25%/bTMB ≥20 HR 0.44 [95% CI 0.23, 0.84]; PD-L1 TC < 1%/bTMB ≥20 HR 0.42 [95% CI 0.17, 0.97]). Additional cutoffs and outcomes in subgroups defined by both biomarkers will be presented. Conclusions: These exploratory analyses from MYSTIC support PD-L1 TC expression as an appropriate predictive biomarker for OS with D vs CT, while suggesting bTMB as a predictive biomarker for OS with D+T in mNSCLC. These biomarkers appear to be independent and both may be important for mNSCLC treatment decisions. Interpretation of these data may be limited by small sample sizes; further investigations are warranted. Clinical trial information: NCT02453282.
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<td>ASCO Oncology Practice Conference: The Business of Cancer Care</td>
<td>San Diego, CA</td>
<td>September 5, 2019</td>
<td>#OncPractice19</td>
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<td>ASCO Quality Care Symposium</td>
<td>San Diego, CA</td>
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<td>Breakthrough™: A Global Summit for Oncology Innovators</td>
<td>Bangkok, Thailand</td>
<td>October 11–13, 2019</td>
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<td>Supportive Care in Oncology Symposium: Advancing Palliative Research</td>
<td>San Francisco, CA</td>
<td>October 25–26, 2019</td>
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<tr>
<td>Gastrointestinal Cancers Symposium</td>
<td>San Francisco, CA</td>
<td>January 23–25, 2020</td>
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<td>ASCO-SITC Clinical Immuno-Oncology Symposium</td>
<td>Orlando, FL</td>
<td>February 6–8, 2020</td>
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<tr>
<td>ASCO Annual Meeting</td>
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<td>May 29–June 2, 2020</td>
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