INDIGO: A global, randomized, double-blinded, phase 3 study of vorasidenib versus placebo in patients with residual or recurrent grade 2 glioma with an IDH1/2 mutation.

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Background: Grade 2 gliomas are slowly progressive, malignant brain tumors with a poor long-term prognosis. Current treatments (surgery followed by observation or adjuvant radiation and chemotherapy) are not curative and can be associated with short- and long-term toxicities. Mutations in isocitrate dehydrogenase (IDH) 1 or 2 occur in approximately 80% and 4% of grade 2 gliomas, respectively, and are a disease defining characteristic in the World Health Organization (WHO) 2021 definition. Vorasidenib (VOR) – an oral, brain-penetrant, dual inhibitor of mutant (m)IDH1/2 enzymes has shown a tolerable safety profile and preliminary clinical activity in phase 1 studies. Methods: In this randomized, double-blind, placebo-controlled phase 3 study (NCT04164901) patients (pts) were randomized 1:1 to receive VOR 40 mg daily or placebo (PBO) daily in 28-day cycles. Patients were stratified by 1p19q status and baseline tumor size. Key eligibility criteria included: age ≥12; KPS >80; residual or recurrent grade 2 IDH1m or IDH2m oligodendroglioma or astrocytoma; measurable non-enhancing disease; no prior treatment for glioma with most recent surgery 1-5 years from randomization; and not in immediate need of chemotherapy/radiation. Primary endpoint: radiographic progression-free survival (PFS) by blinded independent radiology committee (BIRC). Key secondary endpoint: time to next intervention (TTNI). Results: As of 6Sep2022 (2nd planned interim analysis data cutoff), 331 pts were randomized across 10 countries: 168 to VOR and 163 to PBO. Of the 331 pts: median age: 40.4 years (range, 16 to 71); KPS =100: 53.5%; histological subtype: oligodendroglioma: 172 and astrocytoma: 159; median time from last surgery until randomization: 2.4 years. Two hundred twenty-six (68.3%) pts remained on treatment (131VOR; 95PBO). PFS by BIRC was statistically significant in favor of the VOR arm (HR, 0.39; 95% CI, (0.27, 0.56); P=0.000000067). Median PFS: VOR: 27.7 mos; PBO: 11.1 mos. TTNI was statistically significant in favor of the VOR arm (HR, 0.26; 95% CI, (0.15, 0.43); P=0.000000019). Median TTNI: PBO: 17.8 mos; VOR: not reached. All reported P values are one-sided. All-grade adverse events (AEs) occurring in >20% pts receiving VOR vs PBO were alanine aminotransferase increased (38.9% vs 14.7%), COVID-19 (32.9% vs 28.8%), fatigue (32.3% vs 31.9%), aspartate aminotransferase increase (28.7% vs 8.0%), headache (26.9% vs 27.0%), diarrhea (24.6% vs 16.6%), nausea (21.6% vs 22.7%). Common grade ≥3 AEs (≥5%): ALT increased (9.6% vs 0%). Conclusions: This is the first prospective, randomized phase 3 study of a targeted therapy in grade 2 mIDH glioma. VOR significantly improved PFS by BIRC compared with PBO with a manageable safety profile. These data demonstrate the clinical benefit of VOR in this pt population for whom chemotherapy and radiotherapy are being delayed. Clinical trial information: NCT04164901. Research Sponsor: Servier.
PROSPECT: A randomized phase III trial of neoadjuvant chemoradiation versus neoadjuvant FOLFOX chemotherapy with selective use of chemoradiation, followed by total mesorectal excision (TME) for treatment of locally advanced rectal cancer (LARC) (Alliance N1048).

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Background: Radiation with sensitizing fluoropyrimidine (5FUCRT) is a standard curative intent treatment for LARC. It improves disease-free survival (DFS) by decreasing pelvic recurrence but has short- and long-term toxicity. The PROSPECT trial compares FOLFOX chemotherapy with selective use of 5FUCRT (intervention) to 5FUCRT (control) for neoadjuvant treatment prior to TME for LARC.

Methods: Eligible patients (pts) had cT2N+, cT3N-, cT3N+ rectal cancers deemed appropriate for neoadjuvant therapy prior to low anterior resection with TME. Pts with distal, T4 tumors, threatened radial margins or > 4 enlarged lymph nodes were ineligible. Pts were randomized 1:1 without blinding. Pts in the control group received 5FUCRT with 5040 cGy over 5.5 weeks with either capecitabine or 5FU. Pts in the intervention group had 6 cycles of mFOLFOX6 followed by restaging. If tumor regression was > 20%, then TME was performed without radiation; if < 20%, 5FUCRT was given before TME. DFS was the 1st outcome, defined as time from randomization to any recurrence or death, analyzed in the per-protocol population. One interim analysis was conducted with $\alpha$ spending = 0.001. Noninferiority (NI) of the intervention could be claimed if the upper limit of the 2-sided 90.2% confidence interval (CI) of the DFS hazard ratio did not exceed 1.29 (NI margin). Secondary endpoints included overall survival (OS), local recurrence free survival, R0 resection, pathologic complete response (CR), and toxicity.

Results: From June 2012 to December 2018, 1194 pts were randomized and 1128 initiated protocol-assigned treatment. Median age was 57, 34.5% were women and 61.9% had clinically positive nodes. 53 of 585 pts in the intervention group (9%) received preop 5FUCRT. DFS was analyzed after 227 events and median follow-up of 58 months. Conclusions: FOLFOX chemotherapy with selective use of 5FUCRT is non-inferior to 5FUCRT for neoadjuvant treatment of LARC prior to low anterior resection with TME. Patients and physicians have alternative strategies for management of LARC. Clinical trial information: NCT01515787. Research Sponsor: U.S. National Institutes of Health.
LBA3

Plenary Session

Overall survival analysis from the ADAURA trial of adjuvant osimertinib in patients with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC).

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Background: Osimertinib is a third-generation, central nervous system (CNS) active EGFR-TKI, that potently and selectively inhibits EGFR-TKI sensitizing and EGFR T790M resistance mutations. In the primary analysis from the Phase III ADAURA study (NCT02511106), adjuvant osimertinib demonstrated a clinically meaningful, statistically significant, and practice-changing disease-free survival (DFS) benefit vs placebo in patients with completely resected EGFRm (ex19del/L858R) NSCLC ± adjuvant chemotherapy. In an updated DFS analysis, with 2 years additional follow-up, DFS and CNS DFS benefit with adjuvant osimertinib were sustained (stage II–IIIA DFS hazard ratio [HR] 0.23; 95% confidence interval [CI] 0.18, 0.30; stage IB–IIIA DFS HR 0.27; 95% CI 0.21, 0.34; stage II–IIIA CNS DFS HR 0.24; 95% CI 0.14, 0.42), with a tolerable safety profile observed over the extended treatment duration. Here, we report the planned final overall survival (OS) analysis from ADAURA. Methods: Eligible patients (aged ≥18 years [≥20 in Japan and Taiwan], WHO PS 0/1 with completely resected EGFRm (ex19del/L858R) stage IB, II or IIIA [AJCC/UICC 7th edition] NSCLC; adjuvant chemotherapy allowed) were randomized 1:1 to osimertinib 80 mg once daily or placebo until disease recurrence, treatment completion (3 years), or a discontinuation criterion was met. The primary endpoint was investigator-assessed DFS in stage II–IIIA. Key secondary endpoints: DFS in stage IB–IIIA, OS and safety. Data cut-off: January 27, 2023. Results: Globally, 682 patients were randomized; osimertinib n=339, placebo n=343. Adjuvant osimertinib significantly improved OS vs placebo. In patients with stage II–IIIA disease, OS HR was 0.49 (95% CI 0.33, 0.73; p=0.0004; 100/470 events, 21% maturity); 5-year OS rate was 85% with osimertinib vs 73% with placebo. Median follow-up for OS in stage II–IIIA was 59.9 months (osimertinib) and 56.2 months (placebo). In the overall population (stage IB–IIIA), OS HR was 0.49 (95% CI 0.34, 0.70; p<0.0001; 124/682 events, 18% maturity); 5-year OS rate was 88% with osimertinib vs 78% with placebo, with a median follow-up for OS of 60.4 months (osimertinib) and 59.4 months (placebo). Median OS was not reached in either population or treatment group. Conclusions: Adjuvant osimertinib demonstrated an unprecedented, highly statistically significant and clinically meaningful OS benefit in patients with EGFRm stage IB–IIIA NSCLC after complete tumor resection, with or without adjuvant chemotherapy. ADAURA is the first global Phase III study to demonstrate a statistically significant DFS and OS benefit with targeted treatment for patients with EGFRm stage IB–IIIA NSCLC. Clinical trial information: NCT02511106. Research Sponsor: AstraZeneca.
**LBA4**  
**Plenary Session**

**SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL).**

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**Background:** The addition of BV to initial chemotherapy improves overall survival (OS) in adults and PFS in pediatric patients (pts) with AS HL. However, frontline BV adds toxicity, most pediatric pts receive radiation therapy (RT), and 7-20% of pts still develop relapsed/refractory (RR) HL. The PD-1 pathway is central to the pathogenesis of HL and PD-1 blockade is effective in RR HL. The adult and pediatric cooperative groups of the National Clinical Trials Network (NCTN) conducted the randomized, phase 3 S1826 trial to evaluate N-AVD vs BV-AVD in pts with newly diagnosed AS HL. 

**Methods:** Eligible pts were $12 years (y) with stage 3-4 HL. Pts were randomized 1:1 to either 6 cycles of N-AVD or BV-AVD. Recipients of BV-AVD were required to receive G-CSF neutropenia prophylaxis vs optional with N-AVD. Pre-specified pts could receive RT to residually metabolically active lesions on end of treatment PET. Pts were stratified by age, international prognostic score (IPS), and intent to use RT. Response and disease progression were assessed by investigators using 2014 Lugano Classification. The primary endpoint was PFS; secondary endpoints included OS, event-free survival, patient-reported outcomes (PRos), and safety. 

**Results:** 994 pts were enrolled from 7/9/19 to 10/5/22; 976 were eligible and randomized to N-AVD (n=489) or BV-AVD (n=487). Median age was 27y (range, 12-83y), 56% of pts were male, 76% were white, and 13% were Hispanic. 24% of pts were $18y, 10% were $>60y, and 32% had IPS 4-7. So far, < 1% of pts received RT. At the planned 2nd interim analysis (50% of total PFS events) the SWOG Data and Safety Monitoring Committee recommended to report the primary results because the primary PFS endpoint crossed the protocol-specified conservative statistical boundary. 30 PFS events occurred after N-AVD vs 58 events after BV-AVD. With a median follow-up of 12.1 months, PFS was superior in the N-AVD arm \[HR 0.48, 99% CI 0.27-0.87, one-sided p=0.0005\]; 1y PFS: N-AVD, 94%, BV-AVD, 86%. 11 deaths (7 due to adverse events, AE) were observed after BV-AVD compared to 4 after N-AVD (3 due to AE). The rate of grade (gr) $3 hematologic AE was 48.4% (45.1% gr $3 neutropenia) after N-AVD compared to 30.5% (23.9% gr $3 neutropenia) after BV-AVD. Rates (any gr) of febrile neutropenia (5.6% N vs 6.4% BV), pneumonitis (2.0% N vs 3.2% BV), ALT elevation (30.7% N vs 39.8% BV), and colitis (1% N vs 1.3% BV) were similar. Hypo/hyperthyroidism was more frequent after N-AVD (7%/3% N vs 1% BV) while peripheral neuropathy (any gr) was more common after BV-AVD (sensory: 28.1% N vs 54.2% BV; motor: 4% N vs 6.8% BV). 

**Conclusions:** N-AVD improved PFS vs BV-AVD in pts with AS HL. Few immune AEs were observed and < 1% of pts received RT. Longer follow-up is needed to assess OS and PRos. S1826, the largest HL study in NCTN history, is a key step towards harmonizing the pediatric and adult treatment of AS HL. Funding provided by: National Cancer Institute of the National Institutes of Health U10CA180888 and U10CA180819 and Bristol-Myers Squibb. Clinical trial information: NCT03907488. Research Sponsor: U.S. National Institutes of Health; Bristol Myers Squibb; NIH/NCI/NCTN: U10CA180888 and U10CA180819.

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KEYNOTE-671: Randomized, double-blind, phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early stage NSCLC.

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Background: In patients (pts) with NSCLC, pembrolizumab (pembro) has shown efficacy as monotherapy in the adjuvant (adj) and advanced settings and in combination with chemotherapy(chemo) in metastatic disease. KEYNOTE-671 (NCT03425643), evaluated the addition of pembro to platinum-based chemo as neoadjuvant therapy followed by resection and pembro vs placebo as adj therapy in patients with early stage NSCLC. Methods: Eligible pts with stage II, IIIA, or IIIB (N2) resectable NSCLC per AJCC v8 and ECOG PS 0-1 were randomized 1:1 to 4 cycles of pembro 200 mg or placebo + cisplatin based chemo followed by surgery and adj pembro or placebo for up to an additional 13 cycles. Stratification factors were stage (II vs III), PD-L1 TPS (<50% vs ≥50%), histology (squamous vs nonsquamous), and region (east Asia vs not east Asia). Dual primary end points were EFS (time from randomization to local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST 1.1 by investigator assessment, or death) and OS (time from randomization to all-cause death) in the ITT population. Secondary end points included mPR (≤10% viable tumor cells in resected primary tumor and lymph nodes) and pCR (ypT0/Tis ypN0) by blinded independent pathology review, and safety. Results: 797 pts were randomized to pembro (n=397) or placebo (n=400). As of July 29, 2022, data cutoff, median follow-up was 25.2 month (range, 7.5-50.6). Baseline characteristics were balanced between arms. EFS was significantly improved with pembro + chemo followed by resection and adj pembro over placebo + chemo followed by resection and adj placebo (HR 0.58 (95% CI, 0.46-0.72); P<0.00001). Median EFS was not reached (NR) (95% CI, 14.3-22) with placebo + chemo (2-year EFS rate, 62.4% vs 40.6%). With only 177 events, the significance boundary for OS was not crossed (HR 0.73 (95% CI, 0.54-0.99); P=0.02124). In the pembro arm 80.6% underwent definitive surgery compared to 75.5% in the placebo arm, of these 92% and 84% had an R0 resection, respectively. The mPR and pCR rates were 30.2% vs 11% (difference: 19.2% (95% CI: 13.9, 24.7); p<0.00001) and 18.1% vs 4% (difference: 14.2% (95% CI: 10.1, 18.7); P<0.00001) in the pembro vs placebo arms, respectively. Treatment-related (TR) Grade ≥3 AEs occurred in 44.9% of pts in the pembro arm vs 37.3% in the placebo arm; TRAEs led to discontinuation of all treatment in 12.6% vs 5.3% and death in 1% vs. 0.8%; immune-mediated AEs of any grade occurred in 25.3% vs 10.5%. Conclusions: Pembrol + chemo followed by resection and adjuvant pembro provided a statistically significant and clinically meaningful improvement in EFS, pCR and mPR in pts with resectable stage II, IIIA, and IIIB (N2) NSCLC. The safety profile of pembro was as expected. OS will be tested at future analyses according to the statistical plan. Clinical trial information: NCT03425643. Research Sponsor: Merck.

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Effect of CBM588 in combination with cabozantinib plus nivolumab for patients (pts) with metastatic renal cell carcinoma (mRCC): A randomized clinical trial.

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Background: We have previously demonstrated that the live bacterial product CBM588 may augment clinical outcomes in pts with mRCC receiving 1st-line (1L) therapy with dual immune checkpoint inhibitors (ICIs; Dizman et al Nature Medicine 2022). As tyrosine kinase inhibitors (TKIs) in combination with ICIs also represent a 1L standard of care in mRCC, we sought to determine if CBM588 would augment clinical outcome with the TKI cabozantinib (cabo) with nivo.

Methods: Eligible pts were \(18\) yrs old (Karnofsky performance status \(\geq 70\%\)) with histologically verified (clear-cell, papillary or sarcomatoid component) mRCC and no prior systemic therapy for metastatic disease. Patients were randomized 1:2 to receive either cabo/nivo at the standard dose/schedule (40mg PO QD and 480mg IV monthly, respectively) alone or with CBM588 dosed at 80mg PO BID. The primary endpoint was the relative abundance of Bifidobacterium spp. in stool specimens at baseline and after 12 weeks of treatment. Secondary endpoints included assessment of response rate, overall survival, progression-free survival (PFS), systemic immunomodulation, and toxicity. A two-group t-test with a one-sided type I error of 0.05 was used to assess the study’s primary endpoint, hypothesizing an increase in Bifidobacterium spp. with CBM588 therapy.

Results: A total of 30 (20:10 M:F) pts were recruited; median age was 65 (36-84) and 5 pts (17%) had sarcomatoid features and 2 pts (7%) had predominant papillary histology. 12 (40%), 12 (40%) and 6 pts (20%) had good, intermediate and poor risk, respectively. Metagenomic sequencing of paired stool specimens showed a significant decrease in diversity from baseline to week 12 in patients receiving cabo/nivo (P=0.02); no significant difference was observed in those treated with cabo/nivo+CBM588. No significant change in Bifidobacterium spp. was observed. RR was 63% in pts receiving cabo/nivo+CBM588 vs 33% in pts receiving cabo/nivo alone. Median PFS was not reached in pts receiving CBM588 vs 5.8 mos in pts receiving cabo/nivo alone (P=0.03). Grade 3/4 toxicities were observed in 44% and 42% of patients on control and experimental arms, respectively. Conclusions: In the second prospective trial assessing the addition of CBM588 to ICI-based therapy in mRCC, a consistent result with improved PFS and RR was observed. Further translational efforts are underway to characterize the mechanism through which CBM588 augments clinical activity. Clinical trial information: NCT05122546. Research Sponsor: Exelixis.
First phase 3 results from CARTITUDE-4: Cilta-cel versus standard of care (PVd or DPd) in lenalidomide-refractory multiple myeloma.

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Background: CARTITUDE-4 is a global, phase 3, randomized, controlled trial (NCT04181827) of ciltacabtagene autoleucel (cilta-cel), a dual-binding, BCMA-targeting CAR-T cell therapy, vs standard of care (SOC; pomalidomide, bortezomib, and dexamethasone [PVd] or daratumumab, pomalidomide, and dexamethasone [DPd]) in lenalidomide (len)-refractory patients (pts).

Methods: Eligible pts had 1–3 prior lines of therapy (LOT), including PI and IMiD, and were len-refractory. After apheresis, pts randomized to cilta-cel received PVd or DPd (physician’s choice) bridging therapy, then 1 cilta-cel infusion 5–7 days after lymphodepletion. In the SOC arm, pts received PVd or DPd until progression. Primary endpoint was progression-free survival (PFS) in the intent-to-treat (randomized) population.

Results: 419 pts were randomized (cilta-cel, n=208; SOC, n=211 [PVd, n=28; DPd, n=183]). 176 pts received cilta-cel as study treatment (tx), 20 more received it after PD on bridging therapy, and 208 received SOC. There were no manufacturing failures. Baseline characteristics were balanced (cilta-cel vs SOC: 59% vs 63% cytogenetic high risk [including gain/amp 1q]; 50% vs 46% PI refractory; 24% vs 22% anti-CD38 refractory; 33% vs 32% had 1 prior LOT). Median dose was $3 \times 10^6$ CAR+ viable T cells/kg. At Nov 1, 2022, data cut-off, median follow-up was 16 mo (range, 0.1–27). Primary endpoint was met; cilta-cel reduced risk of progression/death by 74% (HR=0.26; $P$, 0.0001). Cilta-cel vs SOC significantly improved ORR, rate of $\geq$CR, and overall MRD negativity rate (Table), with a positive trend in OS (HR, 0.78; 95% CI, 0.5–1.2). 97% and 94% of pts treated in the cilta-cel or SOC arms, respectively, had grade (gr) 3/4 AEs, including infections (27% vs 25%) and cytopenias (94% vs 86%). In the cilta-cel and SOC arms, respectively, 39 and 46 pts died (14 and 30 due to PD). In pts who received cilta-cel as study tx (n=176), 76% had CRS (1% gr 3; no gr 4/5) and 5% had ICANS (all gr 1/2). 1 pt had a gr 1 movement/neurocognitive TEAE.

Conclusions: A single cilta-cel infusion significantly improved PFS vs SOC in len-refractory pts with 1–3 prior LOT, with a favorable benefit/risk profile across pt populations. The 74% reduction in progression/death and high rates of CR and MRD negativity highlight the potential for cilta-cel to become a key therapy for pts with MM after first relapse.

Clinical trial information: NCT04181827. Research Sponsor: Janssen Research & Development, LLC; Legend Biotech USA Inc.

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<th>Cilta-cel vs SOC outcomes (ITT).</th>
<th>Cilta-cel (n=208)</th>
<th>SOC (n=211)</th>
<th>HR*</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>NE (23–NE)</td>
<td>12 (10–14)</td>
<td>0.26 (0.18–0.38)</td>
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</tr>
<tr>
<td>12-mo PFS, % (95% CI)</td>
<td>76 (69–81)</td>
<td>49 (42–55)</td>
<td>0.0001</td>
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<tr>
<td>ORR, n (%)b</td>
<td>176 (85)</td>
<td>142 (67)</td>
<td>3 (P&lt;0.0001)</td>
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<tr>
<td>$\geq$CRb</td>
<td>152 (73)</td>
<td>46 (22)</td>
<td>10 (P&lt;0.0001)</td>
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<tr>
<td>$10^{-5}$ MRD negative,c n (%)</td>
<td>126 (61)</td>
<td>33 (16)</td>
<td>9 (P&lt;0.0001)</td>
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*Per computerized algorithm by constant piecewise weighted log-rank test. bIn 176 pts who received cilta-cel as study tx: ORR, 175 (99%); $\geq$CR, 152 (86%). cFor MRD-evaluable pts: cilta-cel, 88% (126/144); SOC, 33% (33/101).
Primary overall survival analysis of the phase 3 randomized ZUMA-7 study of axicabtagene ciloleucel versus standard-of-care therapy in relapsed/refractory large B-cell lymphoma.

Jason Westin, Olalekan O. Oluwole, Marie José Kersten, David Bernard Miklos, Miguel-Angel Perales, Armin Ghobadi, Aaron Rapoport, Anna Sureda, Caron Alyce Jacobson, Umar Farooq, Tom van Meerten, Matthew L. Ulrickson, Mahmoud Elsawy, Lori A. Leslie, Sridhar Chaganti, Michael Dickinson, Yin Yang, Marco Andreas Schupp, Christina Ann To, Frederick L. Locke; University of Texas MD Anderson Cancer Center, Houston, TX; Vanderbilt University Cancer Center, Nashville, TN; Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; Stanford University School of Medicine, Stanford, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Washington University School of Medicine, St. Louis, MO; University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD; Hematology Department, Institut Català d’Oncologia-Hospital, Barcelona, Spain; Dana-Farber Cancer Institute, Boston, MA; University of Iowa, Iowa City, IA; University Medical Center Groningen, Groningen, Netherlands; Banner MD Anderson Cancer Center, Gilbert, AZ; Division of Hematology and Hematologic Oncology, Department of Medicine, Dalhousie University and QEII Health Sciences Center, Halifax, NS, Canada; John Theurer Cancer Center, Hackensack, NJ; Centre for Clinical Haematology, University Hospitals Birmingham NHS Trust, Birmingham, United Kingdom; The Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Vic, VIC, Australia; Kite, a Gilead Company, Santa Monica, CA; Moffitt Cancer Center, Tampa, FL

Background: In ZUMA-7 (NCT03391466), axicabtagene ciloleucel (axi-cel) was superior to standard of care (SOC; hazard ratio [HR], 0.398; P<.0001) in the primary analysis of event-free survival as second-line therapy in patients with early relapsed or refractory large B-cell lymphoma (R/R LBCL; Locke et al. NEJM. 2022). In a preplanned interim analysis, median overall survival (OS) was not reached in the axi-cel arm and was 25.7 mo in the SOC arm (HR, 0.71; 95% CI, 0.52-0.97; Locke et al. TCT 2022. Abstract 1). We now report the primary OS analysis of ZUMA-7. Methods: Study procedures and eligibility were previously reported. The intention-to-treat (ITT) primary OS analysis occurred 5 years after the first patient was randomized (01/25/2018) per protocol. A log-rank test stratified by randomization stratification factors compared OS between the 2 arms. In addition to the ITT analysis and to account for subsequent treatment with cellular immunotherapy off protocol in the SOC arm, prespecified sensitivity analyses of OS were conducted using the Rank-Preserving Structural Failure Time (RPSFT) and Inverse Probability of Censoring Weights (IPCW) models. Other endpoints included progression-free survival (PFS) per investigator assessment, OS in key subgroups, and safety. Results: In total, 359 patients were randomly assigned, 180 to axi-cel and 179 to SOC. As of 01/25/2023, at a median follow-up of 47.2 mo, axi-cel demonstrated a statistically significant improvement in OS over SOC (HR [95% CI], 0.726 [0.540-0.977]; stratified log-rank 1-sided P=0.0168 [efficacy boundary, 0.0249]). Median OS was longer with axi-cel vs SOC (not reached vs 31.1 mo, respectively). OS benefit with axi-cel vs SOC was consistent in prespecified key subgroups, including age ≥65 years, primary refractory, early relapse, high-grade B-cell lymphoma, and high second-line age-adjusted IPI. In the SOC arm, 102 (57%) patients received subsequent cellular immunotherapy off protocol. Prespecified OS sensitivity analyses, conducted to address the confounding effects of treatment-switching in the SOC arm, showed an even greater OS benefit with axi-cel vs SOC, with stratified HR (95% CI) of 0.608 (0.449-0.824) by RPSFT and 0.633 (0.409-0.981) by IPCW. PFS by investigator confirmed benefit of axi-cel over SOC (HR [95% CI], 0.506 [0.383-0.669]), with 48-mo PFS estimates of 41.8% vs 24.4%, respectively. No new cytokine release syndrome or neurologic events and no new treatment-related deaths occurred since the primary EFS analysis. The safety profile of axi-cel remained consistent with prior studies. Conclusions: Axi-cel as second-line therapy demonstrated a significant improvement in overall survival over historical standard of care in patients with early relapsed/refractory LBCL. Clinical trial information: NCT03391466. Research Sponsor: Kite, a Gilead Company.
Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer: Primary results from the phase III NATALEE trial.

Dennis J. Slamon, Daniil Stroyakovskiy, Denise A. Yardley, Chiun-Sheng Huang, Peter A. Fasching, John Crown, Aditya Bardia, Stephen Chia, Seock-Ah Im, Miguel Martin, Sherene Loi, Binghe Xu, Sara A. Hurvitz, Carlos Barrios, Michael Untch, Rebecca L. Moroose, Fran Visco, Rodrigo Fresco, Tetiana Taran, Gabriel N. Hortobagyi; David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA; Moscow City Oncology Hospital No.62, Moscow, Russian Federation; Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN; National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taipei, Taiwan; University Hospital Erlangen, Comprehensive Cancer Center (CCC) Erlangen-EMN, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany; St. Vincent’s University Hospital, Dublin, Ireland; Medical Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; British Columbia Cancer Agency, Vancouver, BC, Canada; Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; Instituto de Investigación Sanitaria Gregorio Marañón, Centro de Investigación Biomática en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense, Madrid, Spain; Peter MacCallum Cancer Centre, Melbourne, Australia; Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; University of California Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA; Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; Interdisciplinary Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; Orlando Health Cancer Institute, Orlando, FL; National Breast Cancer Coalition, Washington, DC; TRIO - Translational Research in Oncology, Montevideo, Uruguay; Novartis Pharma AG, Basel, Switzerland; Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: RIB + ET has demonstrated significant survival benefits in pre- and postmenopausal pts with HR+/HER2− metastatic BC. To investigate whether RIB + ET also improves outcomes in early BC (EBC), the Phase III NATALEE trial (NCT03701334) evaluated adjuvant RIB + ET in a broad population of pts with stage II or III HR+/HER2− EBC at risk for recurrence, including pts with no nodal involvement (NO). As extended duration of tx is crucial to prolong cell cycle arrest and drive more tumor cells into senescence or death, a 3- y duration of RIB tx at a dose of 400 mg was chosen to improve tolerability while maintaining efficacy. Results from a prespecified interim analysis of invasive disease–free survival (iDFS; primary endpoint) are presented. Methods: Men and pre- or postmenopausal women were randomized 1:1 to RIB (400 mg/day; 3 wk on/1 wk off for 3 y) + ET (letrozole 2.5 mg/day or anastrozole 1 mg/day, for ≥ 5 y) or ET alone. Men and premenopausal women also received goserelin. Eligible pts had an ECOG PS of 0-1 and BC anatomic stage IIA (either NO with additional risk factors or 1-3 axillary lymph nodes [N1]), stage IIB, or stage III per AJCC (8th ed); prior (neo)adjuvant ET was allowed if initiated ≤ 12 mo before randomization. Stratification factors were menopausal status, disease stage, prior (neo)adjuvant chemotherapy, and geographic region. This prespecified interim analysis of iDFS, defined per STEEP criteria, was planned after ≥ 425 iDFS events (≥ 85% of planned total events). iDFS was evaluated by Kaplan-Meier methods, and statistical comparison was made by a stratified log-rank test, with a protocol-defined Lan-DeMets (O’Brien-Flemming) stopping boundary of a 1-sided P < .0128 for superior efficacy. Results: From 10 Jan 2019 to 20 April 2021, 5101 pts were randomized (RIB+ET, n = 2549; ET alone, n = 2552). As of the data cutoff (11 Jan 2023), median follow-up was 34 mo (min, 21 mo). 3- and 2-y RIB tx was completed by 515 pts (20.2%) and 1449 pts (56.8%), respectively; 3810 (74.7%) remained on study tx (RIB+ET, n = 1984; ET alone, n = 1826). iDFS was evaluated after 426 events (RIB + ET, n = 189; ET alone, n = 237). RIB + ET demonstrated significantly longer iDFS than ET alone (HR, 0.748; 95% CI, 0.618-0.906; P = .0014); 3-y iDFS rates were 90.4% vs 87.1%. iDFS benefit was generally consistent across stratification factors and other subgroups. Secondary endpoints of overall survival, recurrence-free survival, and distant disease–free survival consistently favored RIB. RIB at 400 mg had a favorable safety profile with no new signals. Conclusions: Ribociclib added to standard-of-care ET demonstrated a statistically significant, clinically meaningful improvement in iDFS with a well-tolerated safety profile. The NATALEE results support ribociclib + ET as the treatment of choice in a broad population of pts with stage II or III HR+/HER2− EBC, including pts with NO disease. Clinical trial information: NCT03701334. Research Sponsor: Novartis Pharmaceuticals Corporation.
Background: PHERGain is assessing the feasibility of a CT-free treatment based on a dual HER2 blockade with trastuzumab and pertuzumab (HP) in patients (pts) with HER2[+] EBC using a PET-based, pathologic complete response (pCR)-adapted strategy. In an earlier analysis of this study, a total of 227 (79.7%) of 285 pts included in group B were PET-responder (RX), of whom 86 of 227 (37.9%, 95% CI, 31.6 to 44.5; p<0.0001) achieved a pCR, reaching the first primary endpoint (Perez-Garcia JM, Lancet Oncol 2021).

Methods: Details of the trial design and study population have been previously reported. Here, we present the results of the second primary endpoint, 3-year iDFS, among pts included in group B who underwent surgery based on an intent-to-treat (ITT) analysis. In brief, group B included centrally-confirmed, stage I-IIIA, HER2[+] EBC pts that were initially treated with HP (± endocrine therapy), introducing CT in pts without PET response after two treatment cycles and/or pCR. The binomial design tested the null hypothesis that the true 3-year iDFS rate was =89.0% against the alternative that the 3-year iDFS was >95%. We estimated that enrolling 284 pts in group B would provide 80% power at a nominal level of one-sided α of 0.025, assuming a 25% dropout rate.

Results: Between June 26, 2017 and April 24, 2019, 356 pts were randomly assigned (71 pts in group A and 285 pts in group B) and 63 (89.0%) and 267 (93.7%) pts proceeded to surgery in groups A and B, respectively. In group B, the 3-year iDFS rate for the ITT population was 95.4% (95% CI, 92.8 to 98), meeting the second primary endpoint (p<0.001). After a median follow-up of 43.3 months (range, 2.4-63.0), a total of 12 iDFS events were reported, including eight distant recurrences (3.0%), three locoregional ipsilateral recurrences (1.1%), and one non-related death (0.4%). Among group B/PET-RX pts with pCR that did not receive CT as part of study treatment (n = 86), only one patient had an invasive event (locoregional ipsilateral recurrence) for a 3-year iDFS rate of 98.8% (95% CI, 96.3 to 100.0). Treatment-related adverse events (AEs) and serious adverse events (SAEs) were higher in pts allocated to group A than to group B (grade ≥3, 61.8% vs. 32.9% [p<0.001]; SAEs, 27.9% vs. 13.8% [p<0.01]). Group B/PET-RX pts with pCR presented the lowest incidence of treatment-related grade ≥3 AEs (1.2%) without any SAEs. No treatment-related deaths were reported.

Conclusions: Among HER2[+] EBC pts, a PET-based, pCR-adapted strategy was associated with a substantial 3-year iDFS. These results appear comparable to those reported in several studies for the combination of neoadjuvant CT and dual HER2 blockade. This strategy identifies about a third of HER2[+] EBC pts who may safely omit CT with significantly reduced toxicity. Clinical trial information: NCT5732164. Research Sponsor: Roche.
LBA520
Poster Discussion Session

Oral paclitaxel, carboplatin, and dostarlimab (OPE/Cb/D) without and with trastuzumab in early-stage, high-risk breast cancer: Results from the neoadjuvant I-SPY 2 TRIAL.

Kay T Yeung, Kevin Kalinsky, Christina Yau, Amy Jo Chien, Judy Caroline Boughey, Erica Michelle Stringer-Reasor, Carla Isadora Falkson, Kathy S. Albain, Ingrid A. Mayer, Meghna S. Trivedi, Rita Nanda, Emily H. Douglas, Coral Oghenerukewwe Omene, Hope S. Rugo, Claudine Isaacs, Beverly Parker, Angela DeMichele, Douglas Yee, Laura Esserman, I-SPY Investigators; University of California, San Diego, La Jolla, CA; Emory University Hospital, Atlanta, GA; University of California, San Francisco, San Francisco, CA; Mayo Clinic, Rochester, MN; University of Alabama at Birmingham, Birmingham, AL; University of Rochester Medical Center Department of Medical Oncology, Rochester, NY; Loyola University Medical Center, Maywood, IL; Vanderbilt University, Nashville, TN; Columbia University, New York, NY; University of Chicago, Chicago, IL; Wake Forest University School of Medicine, Winston-Salem, NC; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; University of California Comprehensive Cancer Center, San Francisco, CA; Lombardi Cancer Center, Georgetown University, Washington, DC; Living Beyond Breast Cancer, Naperville, IL; University of Pennsylvania, Philadelphia, PA; Masonic Cancer Center, Minneapolis, MN

Background: I-SPY 2 is a multicenter trial using response-adaptive randomization within biomarker subtypes including MammaPrint (MP) risk to evaluate novel neoadjuvant agents in high-risk breast cancer. Oral paclitaxel and encequidar (OPE) is an oral combination of paclitaxel (P) with a p-glycoprotein pump inhibitor, encequidar, to enhance gastrointestinal (GI) absorption. Dostarlimab (D) is an anti-PD-1 monoclonal antibody.

Methods: Women with tumors ≥ 2.5 cm and MP high-risk cancers were screened and treated starting Oct 5, 2020. Treatment included Oral Paclitaxel 205mg/m2 and encequidar 12.9 mg on days 1-3, Carboplatin (Cb) AUC 1.5 on day 1 weekly x 12, and Dostarlimab (D) 500 mg every 3 weeks x 4, followed by doxorubicin/ cyclophosphamide (AC) every 2-3 weeks x 4. The control arm was IV P weekly x 12 followed by AC every 2-3 weeks x 4. For patients with HER2+ disease, weekly Trastuzumab (T) was administered during the first 12 weeks. The arm was eligible for graduation [≥ 85% chance of success in a 300-person phase 3 neoadjuvant trial with a pathologic complete response (pCR) endpoint] in 10 predefined signatures. Results: 106 patients (44 HR+HER2-, 56 HR-HER2- (TN), 6 HER2+) received OPE/Cb/D. The control arm included 388 historical controls (201 HR+HER2-, 156 TN, 31 HER2+). 22 patients (20 HR+, 2 HR-) in OPE/Cb/D were MP1 (MP high) and 84 patients (29 HR+, 55 HR-) were MP2 (MP ultra-high). OPE/Cb/D graduated in the TN signature and accrual was stopped.

Conclusions: OPE/Cb/D graduated in the TN signature with a higher predicted pCR rate compared to control. OPE and D have been, individually, shown to have efficacy in other settings. The lower-than-expected pCR rate and lower irAEs with triplet therapy (taxane, platinum, immune checkpoint inhibitor [ICI]) in TN compared to prior IV chemo + ICI arms on I-SPY 2 suggests a possible interference of OPE with ICI. Changes in gut microbiome is being investigated as an explanation. Clinical trial information: NCT01042379. Research Sponsor: U.S. National Institutes of Health; U.S. National Institutes of Health; Quantum Leap Healthcare Collaborative.

<table>
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<tr>
<th>Signature</th>
<th>Estimated pCR rate (95% Probability Interval)</th>
<th>Probability OPE/Cb/D Superior to Control</th>
<th>Predictive Probability of Success in Phase 3</th>
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<tr>
<td>HR-HER2- (TN)</td>
<td>0.49 (0.39-0.59)</td>
<td>0.97</td>
<td>0.79</td>
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<td>HR-</td>
<td>0.49 (0.39-0.60)</td>
<td>0.89</td>
<td>0.62</td>
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<tr>
<td>HER2+</td>
<td>0.32 (0.26-0.39)</td>
<td>0.95</td>
<td>0.56</td>
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<tr>
<td>HR+</td>
<td>0.32 (0.26-0.31)</td>
<td>0.97</td>
<td>0.79</td>
</tr>
<tr>
<td>MP2</td>
<td>0.32 (0.26-0.30)</td>
<td>0.89</td>
<td>0.60</td>
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</table>

Safety events for OPE/Cb/D versus control included increased rates of nausea (89%, 3.8% g3), diarrhea (76%; 7.5% g3), neutropenia (69.4%; 41.5% g3), anemia (35.8%), urinary tract infections (27.9% g2), febrile neutropenia (10.4%), immune-related adverse events (irAEs: hypothyroidism 12.3%, adrenal insufficiency 3.8%), but decreased rates of peripheral neuropathy (27.4% g1; 4.7% g2; 0% g3) and alopecia (28.3% g2).

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Oral paclitaxel and dostarlimab with or without trastuzumab in early-stage, high-risk breast cancer: Results from the neoadjuvant ISPY 2 TRIAL.

Rebecca Arielle Shatsky, Alexandra Thomas, Christina Yau, Amy Jo Chien, Carla Isadora Falkson, Erica Michelle Stringer-Reasor, Coral Oghenerukevwe Omene, Meghna S. Trivedi, Judy Caroline Boughey, Amy Sanford, Mili Arora, Tara B. Sanft, Rita Nanda, Claudine Isaacs, Thelma Brown, Nola Hylton, Angela DeMichele, Douglas Yee, Laura Esserman, I-SPY Investigators; University of California San Diego Medical Center, La Jolla, CA; Wake Forest University School of Medicine, Winston-Salem, NC; University of California, San Francisco, San Francisco, CA; University of Rochester Medical Center Department of Medical Oncology, Rochester, NY; University of Alabama at Birmingham, Birmingham, AL; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Columbia University, New York, NY; Mayo Clinic, Rochester, MN; Sanford Health, Sioux Falls, SD; UC Davis Comprehensive Cancer Center, Sacramento, CA; Yale University, New Haven, CT; University of Chicago, Chicago, IL; Lombardi Cancer Center, Georgetown University, Washington, DC; Susan G. Komen, Birmingham, AL; University of California San Francisco, San Francisco, CA; University of Pennsylvania, Philadelphia, PA; Masonic Cancer Center, Minneapolis, MN

Background: I-SPY2 is a multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes including MammaPrint (MP) status to evaluate novel neoadjuvant agents in high-risk breast cancer. The primary endpoint is pathologic complete response (pCR). Oral Paclitaxel and encequidar (OPE) is an oral combination of paclitaxel (P) with a p-glycoprotein pump inhibitor, encequidar. Dostarlimab (D) is an intravenous (IV) PD-1 inhibitor. Methods: Women with tumors $\geq 2.5\text{cm}$ and MP high risk cancers (MP1 = MP high; MP2 = MP ultra-high) were treated starting Oct 5, 2020. Treatment included OPE (Oral P 205mg/m2 + encequidar 12.9mg) on days 1-3 weekly x 12 and D 500 mg IV given q 3 weeks x 4, followed by doxorubicin/cyclophosphamide (AC) q 2-3 weeks x 4. Patients with HER2+ disease received IV weekly trastuzumab (T) during the first 12 weeks. The control arm was weekly IV P x 12 with or without trastuzumab followed by AC q 2-3 weeks x 4. OPE + D was eligible to graduate [85% chance of success in a 300-person phase 3 neoadjuvant trial with a pCR endpoint] in any of the pre-defined signatures. Results: 113 (78 HR+HER2-, 17 HR-HER2- and 18 HER2+ patients) received OPE + D +/- T. The control arm included 388 historical controls (201 HR+Her2-, 156 HR-HER2-, 31 HER2+). 77 patients (70 HR+ and 7 HR-) were MP1 and 36 patients (24 HR+ and 12 HR-) were MP2. Safety events of note for OPE + D versus IV P include increased rates of nausea (85% vs. 72%) diarrhea (77% vs. 41%). There was no significant difference in rates of neutropenia (23% vs.17%). Peripheral neuropathy (37% vs. 64%) and alopecia (59% vs. 66%) were significantly decreased. Immune related adverse events (irAEs) were lower than expected. Conclusions: Although both OPE and D have both been shown to have efficacy in other settings, combination therapy with OPE + D did not graduate in any of the predefined subtypes. In the HR+ signature where we would not expect a benefit of D, we see equal response to OPE with decreased rates of peripheral neuropathy and alopecia, which suggest this oral agent may be an attractive alternative to IV P in this subgroup and is under consideration in ISPY 2.2. We did not observe the expected improvement in pCR rates seen with PD-1 inhibitors in the HR- or MP2 subtypes (over P alone historic control). In addition, the irAEs were less than expected. Together these findings suggest interference of OPE with D. A potential mechanism of interference could be change in microbiome with the use of OPE vs. IV P, as the microbiome is known to influence the efficacy of immunotherapy. The source of interference is being investigated. Clinical trial information: NCT01042379. Research Sponsor: U.S. National Institutes of Health; Quantum Leap Healthcare Collaborative.

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<tr>
<th>Estimated pCR rates.</th>
<th>Estimated pCR rate</th>
<th>Probability OPE+D Superior to Control</th>
<th>Predictive Probability of Success in Phase 3</th>
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<td>HR+</td>
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<tr>
<td>MP2</td>
<td>0.282</td>
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LBA637 Rapid Abstract Session

Nine-weeks versus one-year trastuzumab for early-stage HER2+ breast cancer: 10-year update of the Short-HER phase III randomized trial.

Pier Franco Conte, Giancarlo Bisagni, Federico Piacentini, Samanta Sarti, Santino Minichillo, Elisa Anselmi, Michele Aieta, Vittorio Gebbia, A Schirone, Antonino Musolin, Ornella Garrone, A Beano, Anita Rimanti, Francesco Giotta, Anna Turletti, Maria Vittoria Dieci, Roberto Vicini, Sara Balduzzi, R D’Amico, Valentina Guarneri; Department of Surgery, Oncology and Gastroenterology, University of Padua, and Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Medical Oncology Unit, Clinical Cancer Centre, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy, Reggio Emilia, RE, Italy; Department of Oncology, Hematology, and Respiratory Diseases, Modena University, Modena, Italy; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRST (IRCCS) s, Forlì, Italy; Medical Oncology, Bellaria Hospital, Bolonga, Italy; Department of Oncology and Hematology, ASL Piacenza, Piacenza, Italy; Medical Oncology, IRCCS-CROB, Rionero in Vulture, Italy; Kore University, Enna and La Maddalena Clinic, Palermo, Italy; S Anna University Hospital, Ferrera, Italy; University of Parma, Parma, Italy; IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; Breast Oncology, Città della Salute e della Scienza, Torino, Italy; Azienda Ospedaliera di Mantova, Mantova, Italy; IRCCS Istituto Oncologico Giovanni Paolo II, Bari, Italy; Medical Oncology, Ospedale Martini ASL Città di Torino, Torino, Italy; Department of Surgery, Oncology and Gastroenterology, University of Padova; Oncology Unit 2, Istituto Oncologico Veneto IRCCS, Padova, Padova, Italy; University of Modena and Reggio Emilia, Modena, Italy; Department of Medical and Surgical Sciences for Children & Adults, University Hospital of Modena, Modena, Italy; Department of Medical and Surgical Sciences for Children and Adults, University Hospital of Modena, Modena, Italy; Department of Surgery, Oncology and Gastroenterology, University of Padova, Oncology 2, IOV - Istituto Oncologico Veneto IRCCS -IOV, Padova, Italy

Background: The ShortHER trial is a phase III non-inferiority, randomized trial comparing 9 weeks (short arm) versus 1 year (long arm) of adjuvant trastuzumab combined with chemotherapy in HER2+ eBC patients. The first primary end point of the study was the event-driven analysis of disease-free survival which was achieved in 2017, presented at ASCO 2017 and published in Annals of Oncology in 2018. The HR was 1.13 (90% CI 0.89-1.42) and the non-inferiority could not be claimed as the upper border of CI crossed the upper limit of 1.29 chosen as non-inferiority margin. According to a pre-planned Bayesian analysis, the probability that the short arm was not inferior to the standard one was 80%.

Methods: 1254 HER2+ early breast cancer patients were stratified according to nodal status and randomized. Median age was 55 years (range 25-78); 672 (54%) patients were node negative, 383 (30%) with 1-3 positive nodes, 198 (16%) 4 or more positive nodes. At the time of the event-driven analysis, median follow up was 6 years, 200 DFS events and 78 deaths were reported. Here we report the overall survival, which was the second co-primary end point, updated DFS and outcomes according to nodal status.

Results: Median follow-up is now 9 years, 248 DFS events and 116 deaths have been reported. The 10 year DFS is 77% in the long arm and 78% in the short arm (HR 1.06; 90% CI 0.86-1.31). The 10-year OS is 89% in the long arm and 88% in the short arm (HR 1.15; 90% CI 0.85-1.56). The DFS and OS data overall and by nodal status are summarized in the table below.

Conclusions: At a median follow-up of 9 years, the ShortHER trial shows that 1 year trastuzumab is still the standard treatment for HER2+ eBC patients as non-inferiority cannot be claimed in terms of DFS or OS. Numerically however, the differences for the patients at low risk (N0) or intermediate risk (N 1-3) is negligible and patients with 4 or more positive lymph nodes have a clear benefit with 1 year trastuzumab. This long-term date can reassure clinicians if, for any reason a patient at low/intermediate risk has to stop trastuzumab and, more important, might facilitate access to a far less expensive treatment to the thousands of patients worldwide who cannot afford the cost of one year of trastuzumab. Clinical trial information: NCT00629278. Research Sponsor: Agenzia Italiana del Farmaco (grant number FARM62MC97).

<table>
<thead>
<tr>
<th>Subgroups (n)</th>
<th>10-y Disease-Free Survival</th>
<th>10-y Overall Survival</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Long (90% CI)</td>
<td>Short (90% CI)</td>
</tr>
<tr>
<td>ITT (1,254)</td>
<td>77% (0.86-1.31)</td>
<td>78% (0.74-1.04)</td>
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<td>N0 (672)</td>
<td>81% (0.74-1.04)</td>
<td>85% (0.54-1.04)</td>
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<td>N 1-3 (383)</td>
<td>77% (0.76-1.64)</td>
<td>79% (0.74-1.04)</td>
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<td>N &gt; 4 (198)</td>
<td>63% (1.24-2.75)</td>
<td>53% (1.84-3.14)</td>
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Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC).

Gabe S. Sonke, Annemiek Van Ommen - Nijhof, Noor Wortelboer, Vincent van der Noort, Astrid C. P. Swinkel, Hedwig M. Blommestein, Aart Beeker, Karin Beelen, Lisanne C. Hamming, Joan B. Heijns, Aafke H. Honkoop, Paul C. De Jong, Quirine C. Van Rossum-Schornagel, Christa van Schaik-van de Mheen, Jolien Tol, Cathrien Tromp-Van Driel, Suzan Vrijaldenhoven, A. Elise Van Leeuwen-Stok, Inge Konings, Agnes Jager, The Netherlands Cancer Institute, Amsterdam, Netherlands; Erasmus MC Cancer Institute, Rotterdam, Netherlands; Netherlands Comprehensive Cancer Organisation (IKNL), Nijmegen, Netherlands; Erasmus School of Health Policy & Management, Rotterdam, Netherlands; Sitts Meer, Hoofddorp, Netherlands; Rijnstate Hospital, Arnhem, Netherlands; Medical Center Leeuwarden, Leeuwarden, Netherlands; Amphia Hospital, Breda, Netherlands; Isala, Zwolle, Netherlands; St. Antonius Ziekenhuis, Nieuwegein, Netherlands; Francisca Gasthuis & Vlietland, Schiedam, Netherlands; Meander Medical Center, Amersfoort, Netherlands; Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands; Gelre Hospital, Apeldoorn, Netherlands; Northwest Clinics, Alkmaar, Netherlands; Dutch Breast Cancer Research Group (BOOG), Utrecht, Netherlands; Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Background: The phase-3, randomized, investigator-initiated, nationwide SONIA trial is evaluating the efficacy, safety and cost-effectiveness of CDK4/6i added to either first- or second-line endocrine therapy (ET) in patients with HR+, HER2- ABC who have received no prior therapy for ABC. The addition of CDK4/6i to ET improves progression-free (PFS) and overall survival (OS) in HR+, HER2- ABC, as initial treatment (first-line) and after prior endocrine monotherapy (second-line). Most international guidelines advise first-line use, despite prolonged toxicity and a steep increase in costs compared to use in second-line. Evidence of superiority of first-line use over second-line based on a head-to-head comparison is lacking. Methods: Pre- and postmenopausal women (N=1050), who received no prior therapy for ABC, with measurable or evaluable disease and WHO performance status 0-2 were enrolled in 74 Dutch hospitals. (Neo)adjuvant therapy was allowed (disease-free interval after non-steroidal aromatase inhibitor (NSAI) >12 months). Patients were randomized 1:1 to receive strategy A (first-line treatment with an NSAI + CDK4/6i, followed on progression by fulvestrant (F)) or strategy B (first-line treatment with an NSAI, followed on progression by F + CDK4/6i). Choice between one of the available CDK4/6i (abemaciclib, palbociclib, ribociclib) was a stratification factor and left to the discretion of the treating physician. The primary endpoint is time from randomization to second objective disease progression, as assessed by local investigators, or death (PFS2). Secondary endpoints include OS, safety, quality of life, and cost-effectiveness. Results: After a median follow-up of 37.7 months (data cut-off 1 December 2022), median PFS2 was 31.0 months in strategy A versus 27.8 months in strategy B (hazard ratio 0.89; 95% confidence interval, 0.75 to 1.04; P=0.14). The treatment effect was consistent across the levels of pre-defined subgroups. The safety profile was characteristic for ET + CDK4/6i. Median time on CDK4/6i was 24.7 months in strategy A and 8.3 months in strategy B (Δ16.4 months). The number of grade ≥3 adverse events was 2778 for strategy A and 1620 for strategy B. Conclusions: First-line use of CDK4/6i + ET does not provide statistically significant, nor clinically meaningful PFS benefit compared to second-line use in women with HR+, HER2- ABC. Use in first-line prolongs the time on CDK4/6i by 16.4 months and increases toxicity and costs. Second-line use may thus be a preferred option for the majority of patients. (Funded by The Netherlands Organisation for Health Research and Development and Dutch Health Insurers; ClinicalTrials.gov number, NCT03425838). Clinical trial information: NCT03425838. Research Sponsor: The SONIA trial (NCT03425838) is funded by The Netherlands Organisation for Health Research and Development and Dutch Health Insurers.
TORCHLIGHT: A randomized, double-blind, phase III trial of toripalimab versus placebo, in combination with nab-paclitaxel(nab-P) for patients with metastatic or recurrent triple-negative breast cancer (TNBC).

Zefei Jiang, Quchang Ouyang, Tao Sun, Qingyuan Zhang, Yuee Teng, Jiuwei Cui, Haibo Wang, Yongmei Yin, Xiaojia Wang, Xin Zhou, Yongsheng Wang, Gang Sun, Jingfen Wang, Lili Zhang, Jin Yang, Min Yan, Xinlan Liu, Shanghai Junshi Biosciences; Department of oncology, the Fifth Medical Center of Chinese PLA General Hospital, Beijing, China; Department of Breast Medicine, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; Department of Breast Medicine, Cancer Hospital of China Medical University, Cancer Hospital of Dalian University of Technology, Liaoning Cancer Hospital and Institute, Shenyang, China, China; Harbin Medical University Cancer Hospital, Harbin, China; Department of Medical Oncology, The First Hospital of China Medical University, Shenyang, China; Department of Medical Oncology, the First Bethune Hospital of Jilin University, Changchun, China; Breast Center, The Affiliated Hospital of Qingdao University Medical College, Qingdao, China; The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; Department of Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences/Zhejiang Cancer Hospital, Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, Hangzhou, China; Chongqing Cancer Hospital, Chongqing, China; Shandong Cancer Hospital, Shandong University, Jinan, China; The Affiliated Cancer Hospital of Xuzhou Medical University, Xuzhou, China; Key Laboratory of Oncology of Xinjiang Uyghur Autonomous Region, Urumqi, China; Department II of breast, Linyi Cancer Hospital, Linyi, China; Jiangsu Cancer Hospital, Nanjing, China; The first affiliated hospital of Xi'an Jiaotong University, Xi'an, China; The first affiliated hospital of bengbu medical college, Bengbu, China; Xiangyang Central Hospital, Xiangyang, China; Henan Cancer Hospital, Zhengzhou, China; Departments of Oncology, General Hospital of Ningxia Medical University, Yinchuan, China

Background: Checkpoint blockade combined with taxanes based chemotherapy had generated mixed results as first line treatment for metastatic TNBC. Toripalimab, a humanized IgG4K monoclonal antibody specific for PD-1, provided significant clinical efficacy with a favorable safety profile in various solid tumors. The purpose of this study is to compare the efficacy and safety of toripalimab versus placebo, in combination with nab-P for metastatic or recurrent TNBC (NCT04085276). Methods: Patients with initially diagnosed metastatic or recurrent inoperable TNBC were randomized 2:1 to receive toripalimab (240mg, D1, q3w) or placebo along with nab-P on days1, 8 in 3-week cycles. Stratifications included PD-L1 expression, paclitaxel therapy history and line of prior therapy at enrollment. Primary endpoint was progression-free survival (PFS) assessed by a blinded independent central review (BICR) per RECIST v1.1, first in the PD-L1 positive population and then in the ITT population. Secondary endpoints included overall survival (OS) and safety. Results: 531 patients were randomized to toripalimab (n = 353) or placebo (n = 178); 200 and 100 patients, respectively had PD-L1 positive TNBC. At interim analysis, with the median follow-up of 14 months, a statistically significant improvement in PFS by BICR was demonstrated for the toripalimab arm in the PD-L1 positive subgroup (mPFS 8.4 vs 5.6 months; HR = 0.653, 95% CI 0.470-0.906, P = 0.0102). The PFS in the ITT population showed a similar trend (mPFS 8.4 vs 6.9 months, HR = 0.773, 95% CI 0.602-0.994). Descriptive analysis of OS showed a trend towards improved OS in the PD-L1 positive (mOS 32.8 vs 19.5 months; HR = 0.615, 95%CI 0.414-0.914) and the ITT population (mOS 33.1 vs 23.5 months; HR = 0.691, 95% CI 0.513-0.932). No new safety signals were identified. Grade≥3 adverse events (AEs) (56.4% vs 54.3%) and fatal AEs (0.6% vs 3.4%) were similar between arms, while AEs leading to discontinuation of toripalimab/placebo (8.5% vs. 3.4%) and immune-related (irAEs) (40.8% vs. 24.0%) were more frequent in the toripalimab arm. Conclusions: The addition of toripalimab to nab-P provided a significant improvement in PFS for PD-L1 positive metastatic or recurrent TNBC patients receiving first-line treatment with an acceptable safety profile. Patients will be followed for the final PFS and OS analysis. Clinical trial information: NCT04085276. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.

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Palbociclib (P) plus tamoxifen (TAM) ± goserelin in women with hormone receptor-positive (HR+)/HER2-negative (HER2−) advanced breast cancer (ABC): Primary results of NCCH1607/PATHWAY, an Asian international double-blind randomized phase 3 trial.

Takahiro Kogawa, Emi Noguchi, Takashi Yamanaka, Naohito Yamamoto, Chi-Feng Chung, Yen-Shen Lu, Dwan-Ying Chang, Joohyuk Sohn, Gun Min Kim, Kyung-Hun Lee, Soo-Chin Lee, Yoon Sim Yap, Yoshiko Umeyama, Kazuki Sudo, Tomomi Hata, Aya Kuchiba, Taro Shibata, Kenichi Nakamura, Kenji Tamura, Kan Yonemori; National Cancer Center Hospital East, Chiba, Japan; National Cancer Center Hospital, Tokyo, Japan; Kanagawa Cancer Center, Kanagawa, Japan; Chiba Cancer Center, Chiba, Japan; Koo Foundation Sun Yat-sen Cancer Center, Taipei, Taiwan; National Taiwan University Hospital, Taipei, Taiwan; Severance Hospital, Yonsei University Health System, Seoul, South Korea; Seoul National University Hospital, Seoul, South Korea; National University Cancer Institute Singapore, Singapore, Singapore; Pfizer R&D Japan, Tokyo, Japan; National Cancer Center Hospital, Toyo, Japan

Background: In Asian countries, BC incidence rates are rising, with a higher proportion of pre/perimenopausal (pre/peri-M) patients (pts). Data on treatment options for pre/peri-M pts are limited. Adding P to endocrine therapy (ET), such as aromatase inhibitor or fulvestrant, has improved progression-free survival (PFS) in phase 3 studies. However, the efficacy and safety of P in combination with TAM are still unclear in pts with HR+/HER2− ABC regardless of M status. This combination was investigated in PATHWAY (NCT03423199): a double-blind randomized phase 3 trial conducted in Japan, Korea, Taiwan, and Singapore. The study was conducted as a Clinical Research Collaboration with the National Cancer Center Hospital being the regulatory sponsor and Pfizer providing drug and financial support. Methods: Women with HR+/HER2− ABC were randomly assigned 1:1 to receive either P (125 mg once daily, days 1-21 of a 28-day cycle) or placebo in combination with TAM (20 mg once daily, continuously) as 1st or 2nd line treatment for ABC. Pre/peri-M women received concurrent ovarian function suppression with goserelin. Pts were stratified by 1st vs 2nd line ET and M status. The primary endpoint was PFS as assessed by investigators. Secondary endpoints include overall survival (OS), objective response, safety, and patient-reported outcomes. Results: A total of 184 pts were assigned to P + TAM (91 pts) and placebo + TAM (93 pts). At data cutoff date (Sep 15, 2022), 138 PFS events had occurred. Median follow-up was 40.9 months for censored pts. Median PFS was 24.4 months (95% CI: 13.1, 32.4) with P + TAM and 11.1 months (95% CI: 7.4, 14.6) with placebo + TAM (hazard ratio [HR]: 0.602 [95% CI: 0.428, 0.848], 1-sided p-value from stratified log rank test: 0.002). The HRs for PFS of the subgroups by stratification factors were as follows: for pts with 1st line ET (HR: 0.521 [95% CI: 0.332, 0.817]) or with 2nd line ET (HR: 0.707 [95% CI: 0.421, 1.189]), and for pre/peri-M pts (HR: 0.378 [95% CI: 0.192, 0.742]) or post-M pts (HR: 0.677 [95% CI: 0.456, 1.005]). While OS data were still immature, the primary analysis showed a 27% reduction in overall risk of death (median OS: not reached in both arms, HR: 0.73 [95% CI: 0.442, 1.207]). 93.4% of pts with P + TAM vs. 20.4% of pts with placebo + TAM had grade (G) ≥3 treatment-emergent adverse events (TEAEs). The most frequently observed G ≥3 TEAE was neutropenia (89.0% in P + TAM arm and 1.1% in placebo + TAM arm). There were no G5 TEAEs in either arm. Conclusions: The study achieved its primary endpoint, demonstrating a significant and clinically meaningful improvement in PFS for P + TAM compared with placebo + TAM for pts with HR+/HER2− ABC. Early OS data with P+TAM is encouraging. TEAEs were generally consistent with the known safety profile of P and ET. Clinical trial information: NCT03423199. Research Sponsor: Pfizer Inc.
A randomized trial of patient navigation with symptom-monitoring in advanced lung cancer.

Vanita Noronha, Supriya Goud, Rangita Sharma, Sucheta Bhagwan More, Akanksha Yadav, Dipti Nakti, Nandini Sharrel Menon, Ajaykumar Chandrabhan Singh, Vijay Maruti Patil, Goutam Santosh Panda, Saswata Saha, Akash Pawar, Srushti Shah, Kavita Prakash Nawale, Darshit Kalpeshkumar Shah, Shweta Jagdhankar, Shriprad Dinanath Banavali, Nishu Singh Goel, Rajendra A. Badwe, Kumar Prabhush; Tata Memorial Centre, Mumbai, India; Tata Memorial Hospital, Mumbai, India; Tata Memorial Centre (HBNI), Mumbai, India; Director, Tata Memorial Centre (TMC), Mumbai, India

Background: Early symptom identification in patients with advanced cancer is crucial to prevent morbidity. Patient navigators can facilitate early workup and therapy, potentially improving outcomes. We hypothesized that combining patient navigators with symptom monitoring would improve quality of life (QoL). Methods: Phase III randomized trial in patients with advanced lung cancer planned for palliative intent therapy. Patients in the intervention arm were paired with a navigator who facilitated workup, provided support, and administered weekly symptom proformas (eight symptoms). The navigator alerted the clinician for any symptom marked, “Severe.” The primary endpoint was the change in QoL from baseline to 12 weeks measured by the Functional Assessment of Cancer Therapy-Lung Trial Outcome Index (FACT-L TOI). Results: From Feb to Nov 2022, we enrolled 150 patients; 75 in each arm. The median age was 58 years (IQR, 50–67); 100 (66.7%) were male. There were 35 (23.3%) illiterate patients; performance status (PS) was 1, 2, and 3 in 92 (61.3%), 48 (32%), and 10 (6.7%) patients, respectively. QoL at 12 weeks by FACT-L TOI improved by at least 5 points from baseline in 34 (58.6%) patients in the intervention arm, vs 32 (56.1%) in the standard arm; \(P=0.788\). Mean FACT-L TOI increased by 7.76 points in intervention arm vs 10.85 points in control arm (\(P=0.257\); effect size: -1.41). Mean FACT-L QoL score increased by 7.21 points in intervention group vs 13.68 points in control group; \(P=0.160\); effect size: 1.17. The time to initiation of cancer treatment was significantly shorter in the intervention group; median 15 days (IQR, 8–22) vs 24 (IQR, 15.3–36) in control arm, \(P<0.001\). The median time to deterioration in PS was 26.5 days (IQR, 11 – 58.3) in intervention arm, compared to 17.5 (IQR, 9.8 – 42.5) in control; \(P=0.343\). There were 46 (61.3%) unplanned hospital/emergency room visits in intervention arm vs 38 (51.4%) in standard arm; \(P=0.219\). Treatment completion rate was 82.5% in intervention arm vs 73.2% in control arm; \(P=0.219\). Median dose intensity was 75% (IQR, 75 – 100) in intervention arm vs 100% (100 – 100) in control; \(P=0.022\). The proportion of patients with severe symptoms in the navigation arm progressively decreased through the course of the study, from 29 (38%) at baseline, to 8 (10.7%) at week 6, and none at week 12. At a median follow-up of 6.4 months, 6-month OS was 66% (SE, 0.057) vs 68.1% (SE, 0.056) in intervention vs control arms, respectively; \(P=0.343\). Conclusions: Patient navigation and weekly symptom proforma monitoring do not significantly improve QoL in patients with advanced lung cancer. However, patient navigators speed up the initiation of cancer-directed therapy by a median of 9 days, which is both statistically significant and clinically meaningful. Clinical trial information: CTRI/2020/023511. Research Sponsor: None.
A randomised phase II multicentre study of ipilimumab with temozolomide vs temozolomide alone after surgery and chemoradiotherapy in patients with recently diagnosed glioblastoma: Ipi-Glio.

Paul James Mulholland, Nicholas Fraser Brown, Catherine McBain, Lucy Brazil, Sharon Peoples, Sarah Jefferies, Fiona Harris, Puneet Plaha, Anup Vinayan, Claire Brooks, Samia Hussain, Susan J. Dutton, Stasya Ng, Stephanie Levy, Timothy Coutts; University College Hospital-London, London, United Kingdom; The Christie Hospital, Manchester, United Kingdom; Guy’s Hospital, Cancer Centre, London, United Kingdom; Western General Hospital, Edinburgh, United Kingdom; Addenbrooke’s Hospital, Cambridge, United Kingdom; Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; Oxford University Hospitals, Oxford, United Kingdom; Mount Vernon Cancer Center, Northwood, Middlesex, United Kingdom; University of Oxford, Oxford, United Kingdom; The University of Oxford, Oxford, United Kingdom

Background: Median survival for patients with glioblastoma is less than a year. Standard treatment comprises surgical debulking if feasible followed by temozolomide (TMZ) chemoradiotherapy. The objective of this clinical trial is to evaluate whether the addition of the CTLA-4 immune checkpoint inhibitor ipilimumab (IPI) improves survival.

Methods: Ipi-Glio is an academic phase II, open label, stratified randomised multicentre study of IPI + TMZ (Arm A) vs TMZ alone (Arm B), after surgery and radical radiotherapy with concomitant temozolomide in patients with recently diagnosed de-novo glioblastoma. Following completion of chemoRT, patients were randomised 2:1 Arm A:B, with stratification to extent of surgery and MGMT promotor methylation. IPI 3mg/kg was administered q3/52 for 4 cycles, and TMZ 150-200mg/m2 days 1-5 q4/52 for 6 cycles. Primary outcome was overall survival (OS), treatment difference reported as hazard ratio (HR) with 60% confidence intervals (CI) and OS at 18 months. Secondary outcomes were progression-free Survival (PFS) and safety.

Results: 119 patients were randomly assigned, 79 to Arm A and 40 to Arm B, at seven centres in the UK between Jan 2019 and April 2021. Patient characteristics (Arm A vs B): median Age 53 vs 48 years; male sex 70% vs 65%; ECOG PS0 70 vs 70%, PS1 30 vs 30%; MGMT promotor methylation 39% vs 40%; IDH mutation 11% vs 10%; surgical gross total resection 61% vs 60%. PFS (Arm A vs B): median PFS 10.9 months (m) vs 12.5mo, HR 1.252 (60%CI 1.01-1.54, p=0.369); 18m PFS 22% (60%CI 17-27%) vs 43% (34-51%). Overall Survival (Arm A vs B): median OS 22.7 vs 26.4 months, HR 1.223 (60% CI 0.986-1.516, p=0.431); 18 month OS 53% (60%CI 48-58%) vs 64% (56-70%). Adverse events (AE) reported by CTCAE grade (Arm A vs B): total reported AEs 1058 vs 329; no. of reported AEs per patient: mean 13.5 (SD 10.1) vs mean 8.2 (SD 7.3). Conclusions: No improvement in PFS or OS was observed with the addition of ipilimumab to temozolomide. This study does not support further investigation of this regimen in this setting. Clinical trial information: ISRCTN84434175. Research Sponsor: National Brain Appeal; BMS.
Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: DESTINY-PanTumor02 (DP-02) interim results.

Funda Meric-Bernstam, Vicky Makker, Ana Oaknin, Do-Youn Oh, Susana N. Banerjee, Antonio Gonzalez Martin, Kyung Hae Jung, Iwona A. Lugowska, Luis Manso, Aránzazu Manzano, Bohuslav Melichar, Salvatore Siena, Daniil Stroyakovskiy, Chiedozie Anoka, Yan Ma, Soham D. Puwada, Jung-Yun Lee; University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; Gynecologic Cancer Programme, Vall d’Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d’Hebron, Vall d’Hebron Barcelona Hospital Campus, Barcelona, Spain; Seoul National University College of Medicine, Seoul, Korea, Republic of (South); The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom; Cancer Center Clinica Universidad de Navarra, Madrid, Spain; Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South); Maria Sklodowska-Curie National Research Institute and Oncology Centre (MSCI), Warsaw, Poland; Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital Clínico San Carlos and IDISSC, Madrid, Spain; University Hospital, Palacky University, Olomouc, Czech Republic; Università degli Studi di Milano (La Statale) and Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy; Moscow City Oncology Hospital No. 62, Moscow, Russian Federation; Late-Stage Development, Oncology R&D, AstraZeneca, Gaithersburg, MD; Late-stage Development, Oncology R&D, AstraZeneca, Cambridge, United Kingdom; Yonsei University College of Medicine, Seoul, South Korea

Background: T-DXd is an antibody drug conjugate targeting HER2 and is approved in HER2-expressing breast (BC) and gastric (GC) cancers. HER2 expression is prevalent in other solid tumors. The efficacy of current treatments (Tx) in these populations, including studies with HER2-directed Tx, is modest, revealing a significant unmet medical need. Clinically meaningful activity of T-DXd was seen in HER2-expressing tumors in a phase 1 study (NCT02564900).

Methods: DP-02 (NCT04482309) is an open-label phase 2 study of T-DXd 5.4 mg/kg q3w in pts with HER2-expressing (immunohistochemistry [IHC] 3+ or IHC 2+ by local or central testing) locally advanced or metastatic disease that progressed after $\leq 1$ systemic Tx or that has no Tx options. Cohorts with biliary tract (BTC), bladder (URO), cervical (CC), endometrial (EC), ovarian (OC), pancreatic (PC), or other tumors (excluding BC, GC, colorectal cancer, and non-small cell lung cancer) were enrolled. Efficacy and safety were analyzed in all pts who received $\geq 1$ dose of T-DXd. The primary endpoint was investigator-assessed confirmed objective response rate (ORR). Secondary endpoints included duration of response (DOR), disease control rate, progression-free and overall survival, and safety.

Results: At data cutoff (16 Nov 2022; median follow-up, 9.7 mo), 267 pts had been treated (median, 2 prior lines of Tx [range, 0-13]); 75 pts were IHC 3+ and 125 were IHC 2+ by central testing. In all 267 pts, the ORR was 37.1% and median DOR (mDOR) was 11.8 mo; in pts with IHC 3+ expression, the ORR was 61.3% and mDOR was 22.1 mo. ORR per cohort is shown in all pts and those with centrally confirmed HER2 IHC 3+ or IHC 2+ expression. Grade (G) $\geq 3$ adverse events (AEs) occurred in 58.4% of pts; 11.6% discontinued Tx due to AEs. Adjudicated drug-related interstitial lung disease/pneumonitis occurred in 18 pts (6.7% [G1, n=6; G2, n=11; G5, n=1]).

Conclusions: This is the first tumor-agnostic global study of T-DXd in a broad range of HER2-expressing solid tumors. T-DXd showed encouraging ORR, particularly in pts with IHC 3+ expression, durable clinical benefit, and a manageable safety profile in this heavily pretreated population. These interim results show T-DXd to be a potential new Tx option for pts with HER2-expressing solid tumors.


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* Responses in extramammary Paget disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer. ** By investigator assessment per RECIST 1.1. Central assessment of HER2 expression was done retrospectively for pts enrolled based on local testing; 67 pts were not centrally confirmed as IHC 3+ or IHC 2+.
Phase III randomized clinical trial comparing the efficacy of neoadjuvant chemotherapy and standard treatment in patients with locally advanced colon cancer: The NeoCol trial.

Lars Henrik Jensen, Monica Linda Kjaer, Finn Ole Larsen, Niels Henrik Hollander, Hans B. Rahr, Frank Pfeffer, Laura Dines, Jan Lindebjerg, Soeren Rafael Rafaelsen, Torben Hansen, Signe Timm, Inger Marie Laes, Ismail Gogenur, Kim Wedervang, Fahimeh Andersen, Lone Norgard Petersen, Elinor Bexe Lindskog, Laurids Poulsen, Olav Dahl; Danish Colorectal Cancer Center South, University Hospital of Southern Denmark, Vejle Hospital, Vejle, Denmark; Copenhagen University Hospital, Hvidovre, Gastro Unit, Centre for Surgical Research, Hvidovre, Denmark; Department of Oncology, Copenhagen University Hospital, Herlev and Gentofte, Denmark; Department of Oncology and Palliative Units, Zealand University Hospital, Naestved, Denmark; Department of Gastrointestinal Surgery, Haukeland University Hospital and Institute of Clinical Medicine, Medical Faculty, University of Bergen, Bergen, Norway; Department of Clinical Science, University of Bergen, and Department of Oncology, Haukeland University Hospital, Bergen, Norway; Zealand University Hospital, Koege, Denmark; Department of Oncology, Hospital Soenderjylland, Sønderborg, Denmark; Hilleroed Hospital, Hillerød, Denmark; Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; Institute of Clinical Sciences, Sahlgrenska University Hospital/Östra, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; Aalborg University Hospital, Aalborg, Denmark; Department of Oncology and Radiation Physics, Haukeland University Hospital, Department of Clinical Science, Medical Faculty, University of Bergen, Bergen, Norway

Background: Locally advanced colon cancer presents a therapeutic challenge regarding improving survival and minimizing side effects by optimizing the timing of surgical and systemic treatments. Neoadjuvant chemotherapy is a widely accepted approach in numerous cancers as it aims to eliminate micrometastases and reduce tumor size. Our study aimed to assess the impact of neoadjuvant chemotherapy on locally advanced colon cancer compared to standard initial surgery. Methods: This was a randomized, controlled, phase III clinical trial. Patients aged 18 years or older with biopsy-proven colon cancer were eligible for inclusion if staged as T4 or T3 with invasion depth $\leq$5 mm, N0-2, and M0 according to CT scan evaluation. Patients were randomly assigned to either standard upfront surgery or surgery after neoadjuvant chemotherapy with either 3 cycles of CAPOX (oxaliplatin, capecitabine every 3 weeks) or 4 cycles of FOLFOX (oxaliplatin, 5FU every 2 weeks). Adjuvant chemotherapy was chosen based on the pathological stage of the cancer according to guidelines. The primary endpoint, disease-free survival (DFS), was analyzed on an intent-to-treat basis. The sample size was set at 125 patients per arm, based on a projected increase in two-year disease-free survival from 80% to 90%, with a two-sided significance level of 5%, power of 80%, 3 years of inclusion, 2 years of follow-up, and a 10% drop-out rate. Results: Nine centers in 3 countries included 122 patients in the standard group and 126 patients in the neoadjuvant group from 10/2013 to 11/2021. Forty-four % were female, the median age was 66 years, and 91% had a performance status (PS) of 0, while 9% had a PS of 1. Seventy-three % of the tumors were classified as T3, with a median outgrowth of 11 mm, while 26% were classified as T4 on the baseline CT scan. There were no significant differences in baseline characteristics. The median number of chemotherapy cycles was lower in the neoadjuvant group, 3 (IQR 1-7) vs. 4 (0-8). There were slightly more postoperative complications in the standard group regarding ileus, anastomotic leakage, and length of stay. Postoperatively, more patients in the standard arm had an indication of adjuvant chemotherapy, 88 vs. 72 (p = 0.02). DFS at 2 years was similar in the two arms (p = 0.95, logrank), as was overall survival (OS) (p = 0.95, logrank). Conclusions: Neoadjuvant chemotherapy and standard upfront surgery showed no significant difference in DFS and OS in patients with colon cancer. However, neoadjuvant chemotherapy seemed to have more favorable outcomes in terms of chemotherapy cycles, postoperative complications, and downstaging. CT scan alone may not be sufficient in identifying high-risk patients preoperatively. These findings suggest that neoadjuvant chemotherapy could be considered a viable treatment option for patients with locally advanced colon cancer. Clinical trial information: NCT01918527. Research Sponsor: None.
Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: 7-year results of PRODIGE 23 phase III trial, a UNICANCER GI trial.

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Background: We have reported that neoadjuvant chemotherapy (NACT) with FOLFIRINOX followed by chemoradiotherapy (CRT), surgery, and adjuvant chemotherapy (ACT) significantly improved outcomes in patients (pts) with locally advanced rectal cancer (LARC) compared with pts who received standard CRT, surgery, and ACT. We now report the primary and secondary endpoints with mature follow-up (F/U) in patients (pts) with locally advanced rectal cancer (LARC) compared with pts who received standard chemoradiotherapy (CRT), surgery, and adjuvant chemotherapy (ACT). We have reported that neoadjuvant chemotherapy (NACT) with FOLFIRINOX followed by CRT, surgery, and ACT significantly improved outcomes, including OS in pts with LARC vs those who received standard CRT, surgery, and ACT. Nevertheless, we observed non-PH. So we used the restricted mean survival time (RMST) to evaluate the treatment effect (Liang F & al Ann Oncol 2018, Pak K & al JAMA Oncol 2017). Methods: PRODIGE 23 is a phase III randomized clinical trial. Eligible pts had cT3 or cT4, M0 rectal adenocarcinomas <15 cm from the anal verge, age 18-75 years, and WHO PS ≤1. Randomization was stratified by center, T stage, N status, T location, and T extramural spread. Arm A pts received preoperative CRT (50 Gy, 2 Gy/fr; 25 fr + capecitabine), surgery, then ACT for 6 months (mos). Arm B pts received 6 cycles of mFOLFIRINOX, then the same preoperative CRT, surgery and 3 mos of ACT, mFOLFOX6 or capecitabine. From 6/2012 to 6/2017, pts were randomly assigned in Arm A (n=230) and B (n=231) by 35 participating centers. Analysis was performed on intent-to-treat population. For survival outcomes, HR and 95% CI were estimated by a stratified Cox proportional hazard (PH) model. However, we observed non-PH. So we used the restricted mean survival time (RMST) to evaluate the treatment effect (Liang F & al Ann Oncol 2018, Pak K & al JAMA Oncol 2017). Results: With a median F/U of 82.2 mos, death was reported for 55 pts in arm A and 42 in Arm B. All survival endpoints were better for Arm B vs Arm A. The absolute increase in 5-year survival were 7.6% for Disease-Free Survival (DFS), 6.9% for Overall Survival (OS), 9.9% for Metastasis-Free Survival (MFS), and 5.7% for Cancer Specific Survival (CSS) in Arm B compared to Arm A. Survival results at 7 years are presented in the Table. 7-year cumulative incidence of locoregional relapses are 5.3% in arm B vs 8.1% in arm A (p=0.38). Conclusions: NACT with mFOLFIRINOX followed by CRT, surgery, and ACT significantly improved all outcomes, including OS in pts with LARC vs those who received standard CRT, surgery, and ACT. Clinical trial information: NCT01804790. Research Sponsor: Institut du Cancer (INCa) France - PHRC; Ligue National contre le Cancer - France.

Survival results.

<table>
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<tr>
<th></th>
<th>Arm A: CRT</th>
<th>Arm B: mFOLFIRINOX + CRT</th>
<th>Stratified HR (95%CI) (Cox Model)</th>
<th>Difference between RMST in mos (Arm B - Arm A) (95% CI)</th>
<th>p-value (RMST test)</th>
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<tbody>
<tr>
<td>DFS</td>
<td>62.5% [95% CI 56.6-68.4]</td>
<td>67.6% [60.7-73.4]</td>
<td>0.80 [0.58-1.11]</td>
<td>5.7 [0.05-11.4]</td>
<td>0.048</td>
</tr>
<tr>
<td>RMST*</td>
<td>60.4 mos [56.2-64.7]</td>
<td>66.2 mos [62.4-69.9]</td>
<td>6.2 [1.7-12.6]</td>
<td>0.011</td>
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<tr>
<td>MFS</td>
<td>65.4% [95% CI 58.7-71.3]</td>
<td>73.6% [67.0-79.2]</td>
<td>0.73 [0.51-1.02]</td>
<td>7.1 [1.7-12.6]</td>
<td>0.011</td>
</tr>
<tr>
<td>RMST*</td>
<td>62.1 mos [57.9-66.3]</td>
<td>69.3 mos [65.7-72.8]</td>
<td>6.5 [1.8-11.1]</td>
<td>0.003</td>
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<tr>
<td>OS</td>
<td>76.1% [69.8-81.3]</td>
<td>81.9% [75.8-86.7]</td>
<td>0.73 [0.48-1.09]</td>
<td>4.3 [0.4-8.4]</td>
<td>0.033</td>
</tr>
<tr>
<td>RMST*</td>
<td>71.9 mos [68.7-75.1]</td>
<td>76.3 mos [73.8-78.8]</td>
<td>5.7 [0.5-10.4]</td>
<td>0.033</td>
<td></td>
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<tr>
<td>CSS</td>
<td>79.6% [73.5-84.4]</td>
<td>84.9% [79.1-89.2]</td>
<td>0.66 [0.42-1.05]</td>
<td>3.8 [0.02-7.7]</td>
<td>0.051</td>
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Cl= Confidence Interval * at 84 mos F/U.
**Short-course neoadjuvant FOLFIRINOX versus upfront surgery for resectable pancreatic head cancer: A multicenter randomized phase-II trial (NORPACT-1).**

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**Background:** Fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) has shown improved survival in metastatic pancreatic cancer, and promising results as downstaging chemotherapy in locally advanced pancreatic cancer. The efficacy of neoadjuvant FOLFIRINOX in patients with resectable pancreatic cancer is unknown. **Methods:** This is a randomized phase II trial with patients included from 12 Nordic centers in the period 2017-2021. Patients with resectable pancreatic head cancer were randomly assigned to receive either four neoadjuvant cycles of FOLFIRINOX followed by surgery and eight adjuvant cycles mFOLFIRINOX, or upfront surgery and adjuvant mFOLFIRINOX (12 cycles). The primary endpoint was overall survival at 18 months after date of randomization (intention-to-treat [ITT]). Overall survival was estimated with the Kaplan-Meier method, and differences between the respective treatment arms were analyzed with log rank tests. **Results:** In NORPACT-1, 140 patients were randomly assigned (neoadjuvant chemotherapy, n=77; upfront surgery, n=63). Median age was 66.5 years (IQR 59, 72), while 115 (82.1%) and 25 (17.9%) patients were ECOG 0 and 1, respectively. Median OS by ITT was 25.1 months [95% CI 17.2-34.9] with neoadjuvant chemotherapy and 38.5 months [95% CI 27.6-not reached] with upfront surgery (p=0.096). The proportion of patients alive at 18 months by ITT was 59.7 % [95% CI 48.9-70.7] and 73.0 % [95% CI 62.0-84.0], respectively (p=0.100). Resection rates were 81.8% (63/77) in the neoadjuvant group and 88.9% (56/63) in the upfront surgery group (p=0.342). In the neoadjuvant group 61 (79.2%) patients initiated neoadjuvant FOLFIRINOX. Completion of the four planned cycles was 60%, with dose reductions and delays in 70% and 28.3%. Per-protocol (PP) analysis of 60 patients with pancreatic ductal adenocarcinoma (PDAC) who received minimum one cycle neoadjuvant FOLFIRINOX compared with 55 patients in the upfront surgery arm who were explored showed median OS of 23.0 months [95% CI 16.2-34.9] and 34.4 months [95% CI 19.4-not reached] (p=0.158). Adjuvant chemotherapy initiation rate was 66.2% and 74.6% (p=0.282) by ITT. In resected PDAC patients the rate was 86.4% and 89.8% (p=0.593). Of 120 patients receiving at least one dose of neoadjuvant and/or adjuvant chemotherapy (safety population), 57.5% (42/73) in the neoadjuvant group and 40.4% (19/47) in the upfront surgery group experienced at least one grade ≥3 adverse event (p=0.067). In PP analysis neoadjuvant FOLFIRINOX was associated with significantly higher rate of N0 (p=0.002) and R0 resection (p=0.011). **Conclusions:** Neoadjuvant FOLFIRINOX did not improve OS compared with upfront surgery in resectable pancreatic head cancer. Our results do not support neoadjuvant chemotherapy as standard of care for these patients. Future trials should incorporate a biomarker-based design. Clinical trial information: NCT02919787. Research Sponsor: Norwegian Cancer Society, The Sjøberg Foundation.
Efficacy and safety of atezolizumab plus cabozantinib vs cabozantinib alone after progression with prior immune checkpoint inhibitor (ICI) treatment in metastatic renal cell carcinoma (RCC): Primary PFS analysis from the phase 3, randomized, open-label CONTACT-03 study.

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Background: ICI-based regimens are the standard of care for first-line (1L) treatment of metastatic clear cell (cc) RCC. Treatment options following disease progression during or after ICI therapy are limited but can include single-agent TKIs, such as cabozantinib (cabo). CONTACT-03 evaluated anti–PD-L1 atezolizumab (atezo) + cabo vs cabo alone in patients (pts) with metastatic RCC that progressed during or after prior ICI treatment and is the first phase 3 randomized trial to test the benefit of ICI rechallenge by direct addition to a control arm. Methods: CONTACT-03 enrolled pts with histologically confirmed, inoperable, locally advanced or metastatic cc or non-cc RCC, regardless of PD-L1 status, that progressed on or after prior ICI treatment. Randomization was 1:1 to atezo (1200 mg IV q3w) plus cabo (60 mg oral qd) or cabo alone. Stratification factors were IMDC risk factors (0 vs 1-2 vs ≥3); most recent line of prior ICI therapy (adjuvant vs 1L vs 2L); and histology (dominant cc without sarcomatoid vs dominant non-cc [papillary or unclassified] without sarcomatoid vs cc or non-cc with any sarcomatoid component). The multiple primary efficacy endpoints were centrally reviewed RECIST 1.1 PFS and OS. Key secondary endpoints were investigator (INV)-assessed PFS, centrally reviewed RECIST 1.1 ORR and DOR and safety. Results: Of 522 pts randomized to atezo + cabo (n=263) or cabo (n=259), 55% and 51% had most recent ICI in the 1L setting and 10% and 11% had sarcomatoid RCC, respectively. At the data cutoff (Jan 3, 2023), median follow-up was 15.2 mo. No PFS or OS benefit was observed with atezo + cabo vs cabo. ORR was 41% in both arms; DOR was 12.7 (95% CI: 10.5, 17.4) mo with atezo + cabo and 14.8 (95% CI: 11.3, 20.0) mo with cabo. All-cause Grade 3/4 adverse events (AEs) occurred in 68% (177/262) and 62% (158/256) of safety-evaluable pts receiving atezo + cabo or cabo, respectively; all-cause Grade 5 AEs occurred in 6% and 4%. AEs leading to treatment withdrawal occurred in 16% of pts on atezo + cabo and 4% on cabo. Conclusions: The addition of atezo to cabo did not improve clinical outcomes and led to increased toxicity in patients with RCC that progressed on or after prior ICI treatment. CONTACT-03 is the first randomized, phase III oncology trial to test the benefit of PD-(L)1 inhibitor continuation by direct addition to a standard control arm; the results prompt caution with this approach in other cancers. Clinical trial information: NCT04338269. Research Sponsor: F. Hoffmann-La-Roche.

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<tr>
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<th>Atezo + cabo (n=263)</th>
<th>Cabo (n=259)</th>
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<tr>
<td>Centrally reviewed PFS events, n (%)</td>
<td>171 (65)</td>
<td>166 (64)</td>
</tr>
<tr>
<td>Median (95% CI), mo</td>
<td>10.6 (9.8, 12.3)</td>
<td>10.8 (10.0, 12.5)</td>
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<td>Stratified HR (95% CI)</td>
<td>1.03 (0.83, 1.28)</td>
<td>1.03 (0.83, 1.28)</td>
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<td>P value</td>
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<td>0.7844</td>
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<tr>
<td>OS events, n (%)*</td>
<td>89 (34)</td>
<td>87 (34)</td>
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<td>Median (95% CI), mo</td>
<td>25.7 (21.5, NE)</td>
<td>NE (21.1, NE)</td>
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<tr>
<td>Stratified HR (95% CI)</td>
<td>0.94 (0.70, 1.27)</td>
<td>0.94 (0.70, 1.27)</td>
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<tr>
<td>P value</td>
<td>0.6902</td>
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NE, not evaluable. * Interim analysis.
Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: 5-year analysis of KEYNOTE-426.

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Background: At the first interim analysis of the randomized, open-label, phase 3 KEYNOTE-426 (NCT02853331) study, 1L pembro + axi showed statistically significant OS, PFS, and ORR over sun for advanced ccRCC. We report results with 5-y minimum follow-up. Methods: Adults with confirmed locally advanced or metastatic ccRCC with or without sarcomatoid features, no previous systemic therapy for metastatic ccRCC, KPS ≥70%, and ≤1 lesion measurable per RECIST v1.1 were randomly assigned 1:1 to receive pembro 200 mg IV Q3W for 35 doses (~2 y) + axi 5 mg PO BID or sun 50 mg PO QD on a 4-wk-on/2-wk-off schedule. Dual primary end points were OS and PFS per RECIST v1.1 by blinded independent central review (BICR). Secondary end points included ORR and DOR per RECIST v1.1 by BICR, and safety. A post hoc analysis adjusting for the effect of subsequent therapy on OS using a 2-stage adjustment model was conducted. Results: Of 861 enrolled patients (pts), 432 were assigned to pembro + axi and 429 to sun. Median study follow-up was 67.2 mo (range, 60.0-75.0). Efficacy for the ITT population and IMDC risk subgroups are shown in table. For pembro + axi vs sun, the 60-mo OS rates were 41.9% vs 37.1%, and the 60-mo PFS rates were 18.3% vs 7.3%. Median DOR (range) was 23.6 mo (1.4-68.6+) for pembro + axi and 15.3 mo (2.3-68.3) for sun. In pts who discontinued treatment, 237/381 pts (62.2%) in the pembro + axi arm and 300/406 pts (73.9%) in the sun arm received subsequent anticancer treatment. The HR for OS when adjusted for subsequent therapy was 0.67 (95% CI, 0.52-0.84). Clinical data on pts who completed 2 y of pembrolizumab will be presented. No new safety signals were observed. Conclusions: After 5 y of follow-up, pembro + axi had sustained OS, PFS, and ORR benefits over sun in advanced ccRCC. These results are the longest follow-up to date of an anti–PD-1/L1 inhibitor + VEGFR TKI in this pt population and continue to support the use of pembrolizumab + axitinib as a 1L standard of care for advanced ccRCC. Clinical trial information: NCT02853331. Research Sponsor: Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
Multicenter randomized phase III trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for muscle-invasive bladder cancer (MIBC): Overall survival (OS) data at 5 years in the GETUG/AFU V05 VESPER trial.

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Background: The optimal perioperative chemotherapy for patients (pts) with muscle-invasive bladder cancer remains open to discussion. The primary endpoint of the VESPER trial (NCT 018 12369) was previously reported with dd-MVAC improved-3 years PFS over GC schedule. In the neoadjuvant group, a better bladder local control and significant difference on 3y-PFS was observed in the dd-MVAC arm (p=0.025). Patients and Methods: Between February 2013 and February 2018, 500 pts were randomized in 28 French centers and received either 4 cycles of GC every 3 weeks or 6 cycles of dd-MVAC every 2 weeks before surgery (neoadjuvant group) or after surgery (adjuvant group). We report the final analysis of the VESPER phase III trial with the overall survival (OS) data after 5 years of follow-up from randomization. Results: 437 pts (88%) received neoadjuvant chemotherapy, 60% of patients received the planned 6 cycles in the dd-MVAC arm, 84% received 4 cycles in the GC arm, thereafter 91% and 90% of patients underwent surgery, respectively. Final median of follow-up was 5 years and 3 months and 190 deaths were reported within 5 years of follow-up. OS at 5 years was improved in the dd-MVAC arm (64% vs 56%, HR=0.77 (95% CI, 0.58-1.03), p=0.078), as was also disease-specific survival (DSS) (5-year rate: 72% vs 59%, HR=0.63 (95% CI, 0.46-0.86), p=0.004). The main cause of death was bladder cancer progression (83%), other causes included cardio-vascular events (4.2%), toxic deaths (2.1%), second cancers (2.1%), others (4.7%) and undocumented deaths (4.2%). In the neoadjuvant group, OS was significantly superior in the dd-MVAC arm (5-year rate: 66% vs 57%, HR=0.71 (95% CI, 0.52-0.97), p=0.032) as well as DSS (5-year rate: 75% vs 60%, HR=0.56 (95% CI, 0.39-0.80), p=0.001). In the adjuvant group, the results were not conclusive due to the limited sample size (n=56). Conclusions: Dose-dense MVAC provided a better OS at 5 years and improved significantly DSS over GC in the peri-operative setting of MIBC. Clinical trial information: NCT01812369. Research Sponsor: The GETUG AFU V05 VESPER trial was supported by a grant from the French Ministry of Health (PHRC 2011-037).
Phase 3 THOR study: Results of erdafitinib (erda) versus chemotherapy (chemo) in patients (pts) with advanced or metastatic urothelial cancer (mUC) with select fibroblast growth factor receptor alterations (FGFRalt).

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Background: FGFRalt are observed in ~20% of pts with mUC. Erda is an oral selective pan-FGFR tyrosine kinase inhibitor granted accelerated approval to treat locally advanced or mUC in adults with susceptible FGFR3/2alt who have progressed after platinum-containing chemo. THOR (NCT03390504), a randomized phase 3 study, assessed whether erda provided a survival advantage vs investigator’s choice of chemo in pts with mUC who progressed after 1 or 2 prior treatments, including an anti-PD-(L)1 agent. Methods: Pts (≥18 y) with unresectable advanced/mUC and select FGFR3/2alt(mutations/fusions), ECOG performance status 0-2, adequate organ function, progression on/after prior systemic therapy (tx) that included an anti-PD-(L)1 agent, and ≤2 prior lines of tx were randomized 1:1 to receive erda (8 mg with pharmacodynamically guided uptitration to 9 mg on day 14) QD or investigator’s choice of chemo (docetaxel or vinflunine) Q3W until disease progression or intolerable toxicity. The primary end point was overall survival (OS). Secondary end points included progression-free survival (PFS), objective response rate (ORR), and safety. Results: 266 pts were randomized: 136 pts assigned to erda, 130 to chemo. In all pts, median age was 67 y; 30% had 1 prior line of tx; 70% had 2 prior lines; 74% had visceral metastases; 90% were PD-L1 low (CPS <10). Median follow-up was 15.9 mo. The primary endpoint of the study was met, with erda significantly increasing OS and reducing the risk of death by 36%; median OS was 1 y (Table). These data met predefined stopping criteria for superiority. Erda also significantly improved median PFS (5.6 vs 2.7 mo) and ORR (46% vs 12%) vs chemo. No new safety signals were seen. Serious treatment-related adverse events (TRAEs) were observed in 13% and 24% of pts with erda and chemo, respectively, and grade (Gr) 3/4 TRAEs were observed in 46% and 46% of pts with erda and chemo, respectively. TRAEs leading to death were reported in 1 and 6 pts with erda and chemo, respectively. More TRAEs leading to dose reduction were observed with erda (66%) vs chemo (21%); 8% and 13% of pts had TRAEs leading to discontinuation of erda and chemo, respectively. Central serous retinopathy occurred in 23 pts (17%) with erda (Gr 1-2, 20 pts). Conclusions: In pts with FGFRalt advanced/mUC after prior treatment with PD-(L)1, erda significantly improved OS, PFS, and ORR vs investigator’s choice of chemo. Erda toxicity was consistent with the known safety profile. These results support the role of erda to treat pts with FGFRalt mUC after PD-(L)1 tx. Clinical trial information: NCT03390504. Research Sponsor: Janssen Research & Development.
Prostate irradiation in men with de novo, low-volume, metastatic, castration-sensitive prostate cancer (mCSPC): Results of PEACE-1, a phase 3 randomized trial with a 2x2 design.

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Background: PEACE-1 demonstrated that combining ADT and docetaxel with abiraterone acetate plus prednisone (AAP) improves both overall survival (OS) and radiographic progression-free-survival (rPFS) in men with de novo mCSPC. The present analysis examines the second pre-planned primary endpoint of PEACE-1 in the low-volume population: the impact of prostate irradiation (RT) in men receiving intensified systemic treatment. Methods: PEACE-1 is an academic, multicentre, international, 2x2 design, phase 3 trial. The co-primary endpoints for each question were rPFS and OS. The standard of care (SOC) was ADT alone or ADT plus docetaxel (Doce) at investigator’s discretion until 2017, then accrual was restricted to men receiving ADT+Doce. RT (74 Gy/37 fractions) was delivered after Doce completion when applicable. SOC included continuous ADT, with or without Doce at 75 mg/m² every 3 weeks for 6 cycles. AAP, 1000 mg/day with prednisone 10 mg/day was given to men randomized to the AAP arms until disease progression or intolerance. The overall type I error testing the RT effect was 5% (4.9% for OS, 0.1% for rPFS). In the low-volume population, 299 and 213 events were required to detect an HR of 0.62 for rPFS and 0.68 for OS with 80% power, respectively. Results: Between 11/2013 and 12/2018, 1172 men were randomized to receive either SOC (+/- AAP) plus RT (n=584) or SOC (+/- AAP) without RT (n=588). 505 patients had low-volume disease (0-3 bone metastases +/- lymph nodes), 252 in the RT arms, 253 in the non-RT arms. Baseline characteristics were similar across arms. With a median follow-up of 6.1 years, 303 rPFS and 214 OS events were recorded for the low-volume population. A qualitative interaction between RT and AAP was observed for rPFS (p=0.026) and therefore, each experimental arm was assessed individually. RT did not improve rPFS with a median of 3 years (99.9% CI: 2.3-4.8) for SOC vs 2.6 (1.7-4.6) for SOC+RT; HR=1.12 (0.68-1.85). When compared individually to SOC, rPFS was improved by SOC+AAP+RT (median 7.5 years (99.9% CI: 4.0-NR); HR=0.49, [0.28-0.87], p<0.0001) and borderline improved by SOC+AAP (median 4.4 years (95% CI: 2.5-7.6); HR=0.74, [0.44-1.26], p=0.066). The HR between AAP arms was 0.66 [0.36-1.19]. For OS the predefined threshold for a statistical interaction was not reached (p=0.11). OS was not improved by RT: median OS was 6.9 years (95.1% CI: 5.9-7.5) without RT vs 7.5 (6.0-NR) with RT (HR=0.97 [0.74-1.27], p=0.81). Median OS was 7.1 years in the SOC arm and not yet reached in the SOC+AAP+RT arm. Conclusions: Combining prostate RT to systemic treatment did not improve OS in men with de novo mCSPC and low metastatic burden. However, best outcomes (rPFS and OS) were observed in men receiving SOC+AAP+RT. The impact of RT on severe urinary symptom prevention will be presented. Clinical trial information: NCT01957436. Research Sponsor: Ipsen, Janssen, Sanofi; Unicancer.© 2023 by American Society of Clinical Oncology. Visit meetings.asco.org and search by abstract for disclosure information.
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Oral Abstract Session

Durvalumab with paclitaxel/carboplatin (PC) and bevacizumab (bev), followed by maintenance durvalumab, bev, and olaparib in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) without a tumor BRCA1/2 mutation (non-tBRCAm): Results from the randomized, placebo (pbo)-controlled phase III DUO-O trial.

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Background: Olaparib (ola) maintenance ( mtx) improved outcomes in pts with newly diagnosed AOC and a BRCAm (DiSilvestro J Clin Oncol 2023:41:609–17) or with bev in pts with homologous recombination deficiency (HRD+) tumours (Ray-Coquard Ann Oncol 2022: LBA29) in response to 1L treatment, but an unmet need remains. Combining an immune checkpoint inhibitor with an antiangiogenic agent and a PARP inhibitor may enhance antitumor effect (Banerjee Ann Oncol 2022: LBA29) in response to 1L treatment, but an unmet need remains. Combining an immune checkpoint inhibitor with an antiangiogenic agent and a PARP inhibitor may enhance antitumor effect (Banerjee Ann Oncol 2022: LBA29) in response to 1L treatment, but an unmet need remains. Combining an immune checkpoint inhibitor with an antiangiogenic agent and a PARP inhibitor may enhance antitumor effect (Ann Oncol 2023:34:1460–71) and then the intent-to-treat (ITT) population. Results: 1130 pts were randomized: 378 Arm 1, 374 Arm 2, and 378 Arm 3. At a prespecified interim analysis (DCO Dec 5, 2022), a statistically significant improvement in PFS was observed for Arm 3 vs Arm 1: HR 0.49 (95% CI 0.34–0.69; P<0.0001) and HR 0.63 (95% CI 0.52–0.76; P=0.0001) in the HRD+ and ITT populations, respectively; a consistent PFS effect was observed in the HRD− subgroup (HR 0.68, 95% CI 0.54–0.86). A numerical improvement in PFS was shown for Arm 2 vs Arm 1 (ITT population), but statistical significance was not reached (Table). During the study, any serious adverse events were reported in 34%, 43% and 39% of pts in Arms 1, 2 and 3, respectively. Conclusions: PC + bev + durva followed by mtx bev + durva + ola in pts with newly diagnosed non-tBRCAm AOC resulted in a statistically significant and clinically meaningful improvement in PFS vs PC + bev followed by mtx bev. Safety was generally consistent with the known profiles of each agent. Clinical trial information: NCT03737643. Research Sponsor: AstraZeneca.
Phase III MIRASOL (GOG 3045/ENGOT-ov55) study: Initial report of mirvetuximab soravtansine vs. investigator’s choice of chemotherapy in platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression.

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Background: Mirvetuximab soravtansine (MIRV), an antibody drug conjugate targeting FRα, demonstrated clinically meaningful antitumor activity in a single arm trial reported previously (Matulonis, JCO 2023). MIRASOL is a randomized phase 3 trial to confirm the efficacy of MIRV vs standard-of-care chemotherapy in patients (pts) with PROC. Methods: 453 PROC pts with high FRα expression (Roche FOLR1 Assay) with 1-3 priors were randomized 1:1 to MIRV 6 mg/kg, adjusted ideal body weight, Day 1 of a 21-day cycle or IC: paclitaxel, pegylated liposomal doxorubicin, or topotecan. The primary efficacy endpoint was progression-free survival (PFS) by investigator (INV) with key secondary endpoints ORR, overall survival (OS), and patient-reported outcomes in hierarchical order; other endpoints included safety and tolerability. Blinded independent central review (BICR) for PFS and ORR were sensitivity analyses. Results: With a data cutoff of March 6, 2023, 227 pts were randomized to the MIRV arm; 226 to the IC arm. Median follow-up was 13.1 months. Baseline characteristics were well balanced across arms; 14% of pts had one, 39% two, and 47% three prior lines of therapy; 62% received prior bev; and 55% received prior PARPi therapy. The study met its primary and key secondary endpoints with statistically significant results in PFS (INV), ORR (INV), and OS (Table). In the bev-pretreated subset (n=281), PFS HR was 0.64 (0.492, 0.842) and OS HR was 0.74 (0.535, 1.036); in the bev-naïve subset (n=172), PFS HR was 0.66 (0.459, 0.942) and OS HR was 0.51 (0.306, 0.860). The adverse event (AE) profile of MIRV was consistent with prior reports: predominantly low-grade ocular (MIRV vs IC all grade 56% vs 9%; grade 3+ 14% vs 0%) and gastrointestinal events (MIRV vs IC all grade 43% vs 9%; grade 3+ 11% vs 0%). Compared with IC, MIRV was associated with lower rates of grade 3+ treatment-emergent AEs (42% vs 54%), serious AEs (24% vs 33%), and discontinuations due to TEAEs (9% vs 16%). Fourteen percent of pts on the MIRV arm remained on study drug vs 3% on the IC arm. Conclusion: MIRV is the first treatment to demonstrate a PFS and OS benefit in PROC compared to IC. The efficacy data, along with the well-characterized safety profile, position MIRV as a new, standard of care for pts with FRα positive PROC. Clinical trial information: NCT04209855. Research Sponsor: ImmunoGen.
An international randomized phase III trial comparing radical hysterectomy and pelvic node dissection (RH) vs simple hysterectomy and pelvic node dissection (SH) in patients with low-risk early-stage cervical cancer (LRESCC): A Gynecologic Cancer Intergroup study led by the Canadian Cancer Trials Group (CCTG CX.5-SHAPE).

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Background: In the last 2 decades, there has been a trend towards less radical surgery in patients with low-risk cervical cancer. Retrospective data suggested that less radical surgery may be safe and associated with less morbidity. The objective of this non-inferiority phase III prospective randomized trial was to compare RH to SH in women with LRESCC. Methods: Women with LRESCC defined as stage 1A2 or 1B1 with lesion ≤ 2cm were randomized to RH or SH after stratification by cooperative group, intended use of sentinel node mapping, stage, histological type, and tumour grade. The primary endpoint was pelvic recurrence rate at 3 years (PRR3). Non-inferiority of SH to RH is claimed when the 95% upper one-sided confidence limit (95% UCL) for the difference in PRR3 of SH to RH (DPRR3), calculated by the Kaplan-Meier method for pelvic-relapse free survival, is lower than or equal to 4%. Primary intention to treat (ITT) analysis included all patients randomized. Per-protocol (PP) analysis included patients eligible at baseline and without evidence of more advanced disease found at the time of surgery or final pathology, based on treatment received. Secondary endpoints included extrapelvic relapse-free survival (ERFS), overall survival (OS), and quality of life (QoL). Results: 700 women (12 countries, 130 centers) were enrolled from December 2012 to November 2019. Patient characteristics were well balanced: median age was 44 (24-80); 91.7% were stage 1B1 and 61.7% had squamous histology. 50% of the hysterectomies were done laparoscopically (56% SH vs. 44% RH), 25% robotically (24% vs. 25%) and 23% abdominally (17% vs. 29%). 4.4% of patients had lymph node metastasis (4.1% SH and 5.1% RH) and 3.1% had extrauterine extension (2.6% SH and 3.7% RH). A total of 8.8% of women received post-surgical adjuvant therapy (9.2% SH and 8.4% RH). With a median follow-up of 4.5 years, 21 pelvic recurrences were identified (11 SH and 10 RH). The PRR3 was 2.5% with SH and 2.2% with RH (DPRR3 0.35% with 95% UCL 2.32%) in ITT analysis; 2.8% with SH and 2.3% with RH (DPRR3 0.42% with 95% UCL 2.56%) in PP analysis. The 3-year ERFS and OS were respectively 98.1% and 99.1% with SH; 99.7% and 99.4% with RH. RH had significantly higher surgery related incidence of urinary incontinence (11.0% vs. 4.7% with SH; p=0.003) and urinary retention (9.9% vs. 0.6% with SH; p<0.0001) during follow-up. QoL scales with significant difference between the two groups over time were all in favor of SH. Conclusions: The pelvic recurrence rate at 3 years in women with low-risk early-stage cervical cancer who underwent a simple hysterectomy is not inferior to those who received a radical hysterectomy. Fewer surgical complications and better quality of life were observed with SH. Clinical trial information: NCT01658930. Research Sponsor: Canadian Institutes of Health Research (CIHR) and Canadian Cancer Society (CCS).
PD-1 blockade with sintilimab plus induction chemotherapy and concurrent chemoradiotherapy (IC-CCRT) versus IC-CCRT in locoregionally-advanced nasopharyngeal carcinoma (LANPC): A multicenter, phase 3, randomized controlled trial (CONTINUUM).

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Background: Despite the success of PD-1 blockade plus chemotherapy in recurrent/metastatic NPC, its role in LANPC is unproven. This trial evaluated the efficacy and safety of adding sintilimab (a PD-1 inhibitor) to IC-CCRT in LANPC. Methods: Patients with non-metastatic high-risk LANPC (stage III-IVA, excluding T3-4N0/T3N1) were enrolled at 9 centers in China, and randomized (1:1; stratified by center and stage with block size four) to the Standard Arm (gemcitabine and cisplatin IC plus cisplatin CCRT), or Sintilimab Arm (sintilimab plus IC-CCRT). Sintilimab 200mg was given intravenously once every 3 weeks for up to 12 cycles (3 induction, 3 concurrent, and 6 adjuvant). The primary endpoint was event-free survival (EFS) (i.e. freedom from local/regional/distant failure or death). It is estimated that approximately 417 patients would provide 80% power to detect a hazard ratio (HR) of 0.52 with a two-sided type 1 error of 0.05. Quality of life (QoL) was assessed by EORTC-C30. Biomarkers including tertiary lymphoid structure (TLS), PD-L1, and gene expression were also analyzed. Results: Between December 2018, and March 2020, 425 patients were randomized to the Sintilimab Arm (n = 210) and Standard Arm (n = 215). After a median follow-up of 42 months (94% alive patients $\geq 36$ months), the intention-to-treat analysis showed that 3-year EFS was 86.1% in the Sintilimab Arm and 76.0% in the Standard Arm (stratified HR, 0.59; 95% confidence interval [CI], 0.38-0.92; stratified log-rank p = 0.019). Grade 3-4 adverse events (AEs) occurred in 155 (74.2%) and 140 (65.4%) patients, including immune-related AEs in 20 (9.6%) and 2 (0.9%) patients and grade 5 AEs in 2 (0.95%) and 1 (0.5%) patients in the Sintilimab and Standard Arm, respectively (Table). No minimum clinically important differences in QoL were observed. The benefit of the addition of sintilimab was observed in patients with TLS (HR 0.18; 95% CI, 0.04-0.81; p = 0.011) but not in patients without TLS (HR 0.94; 95% CI, 0.50-1.76; p = 0.85). Conclusions: The addition of sintilimab to standard IC-CCRT results in significant improvement of EFS, manageable safety profile, and comparable QoL in high-risk LANPC. TLS appears to be a predictive biomarker for benefit of sintilimab. Clinical trial information: NCT03700476. Research Sponsor: Innovent.
Phase 3 randomized study for evaluation of physician choice Rx and triple metronomic as second-line therapy in head and neck cancer (CRSF 2021-HN-001).

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Background: There are multiple options of treatment in second-line therapy in locally advanced head and neck squamous cell carcinoma (LAHNSCC) with recurrent or metastatic disease. However triple metronomic chemotherapy is oral, affordable, and requires minimal resources. Hence in this study, we compared NCCN-recommended physician choice of standard systemic therapy versus triple metronomic therapy in the second-line treatment of head and neck cancer. Methods: This was a phase 3, multicentric (16 sites), randomized study with a superiority design that was approved by the institutional ethics committees and registered with CTRI (CTRI/2021/08/036002) conducted in India under the aegis of Cancer Research Statistics Foundation. The study recruited LAHNSCC with a recurrent and metastatic disease that either was platinum-refractory or was planned for second-line chemotherapy. The key inclusion criteria were: Age ≥18 years, ECOG PS 0-2, and the presence of normal hematological and biochemical parameters. These patients underwent 1:1 central stratified randomization (Stratification - site of disease & ECOG PS) to either triple metronomic chemotherapy (methotrexate 9 mg/m² PO weekly, celecoxib 200 mg PO twice daily and erlotinib 150 mg PO once daily) or physician choice therapy (nivolumab or pembrolizumab or cetuximab or taxane or afatinib or 5-FU or capecitabine). The study drugs were administered either till disease progression or the development of intolerable side effects. The primary endpoint of the study is overall survival (OS). The secondary endpoints are adverse events (CTCAE version 5.0), progression-free survival (PFS), and quality of life (EORTC). The sample size required was 114. The OS and PFS were estimated using Kaplan-Meier method and were compared using the log-rank test. Cox proportional hazard model was constructed for the calculation of the hazard ratio. The adverse events were compared using Fisher’s test. A p-value of 0.05 was considered significant. Results: At a median follow-up of 258 (95% CI 209-306) days. The median overall survival of the triple metronomic chemotherapy was 181 days (95%CI 142.7-219.2) versus 123 days (95%CI 94-152) in the physician choice therapy arm (P=0.002). The corresponding hazard ratio of death was 0.58 (95%CI 0.33-0.79, P=0.003). The 6-month OS was 52.9% (95%CI 36.9-65.1) versus 14.8% (95%CI 6.4-26.4). The median progression-free survival was 120 days (95%CI 89.2-150.8) versus 70 days (95% CI 58.2-81.8) in metronomic chemotherapy and in the physician choice therapy arms respectively (P=0.000). The corresponding hazard ratio of progression was 0.5 (95%CI 0.33-0.74, P=0.001). Conclusions: In this phase 3 multicentric study, triple metronomic chemotherapy as second-line therapy had an overall survival and progression-free survival advantage over NCCN-recommended physician choice therapy. Clinical trial information: CTRI/2021/08/036002. Research Sponsor: Individual Donor.
Observation vs. radiotherapy in primary mediastinal B-cell lymphoma patients with complete response to standard immunochemotherapy: The IELSG37 randomized trial.

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Background: Primary mediastinal B-cell lymphoma (PMBCL) has a good prognosis if remission is rapidly achieved with dose-intensive immunochemotherapy. In these patients mediastinal radiotherapy (RT) may consolidate responses; however, it increases the risk of second malignancies and coronary or valvular heart disease. The IELSG37 trial was planned with a non-inferiority design to test whether RT can be omitted in patients who achieve a complete metabolic response (CMR) after immunochemotherapy.

Methods: Patients with newly diagnosed PMBCL were eligible. Initial rituximab and anthracycline-based therapy was chosen according to local practice. CMR was defined, upon central review of positron emission computed tomography (PET/CT) scans, as Deauville score 1 to 3, according to the Lugano classification. Responding patients were randomized to observation (OBS) or consolidation RT (30 Gy). Randomization was stratified on gender, chemotherapy regimen, country, and PET/CT score. The primary endpoint was progression-free survival (PFS) after randomization. The sample size (540 patients to enrol, and 376 to randomize) was calculated assuming a 30-month PFS probability of 0.85 in both arms, with alpha at 0.05, 80% power and a hazard ratio (HR) of 1.77 as non-inferiority margin.

Results: At a median follow-up of 30 months, the number of observed events was considerably lower than expected, hence, the Independent Data Monitoring Committee (IDMC) of the trial recommended to complete the planned total accrual without increasing the study size or duration. The primary endpoint analysis was performed, according to the IDMC recommendation, with $\geq 80\%$ of patients having a minimum follow-up of 30 months. 545 patients (209 men, 336 women) were enrolled. Induction immunochemotherapy was completed and response assessed in 530 patients, 268 of them (50.6\%) achieved a CMR and were randomly allocated to OBS (n = 132) or RT (n = 136). The PFS at 30 months was 98.5\% (95%CI, 94.3 – 99.6) in the RT arm and 96.2\% (95%CI, 91.1-98.4) in the OBS arm (P = 0.278). The estimated relative effect of radiotherapy vs observation in terms of hazard ratio (HR) was 0.47 (0.12-1.89) without adjustments and 0.79 (0.19-3.31) after stratification for the variables used for randomization. At 30 months the absolute risk reduction from RT was 2.3\% (-1.5 to 6.2) unadjusted, and 0.8\% (-3.0 to 8.3) with stratified HR. The number needed to treat is high (43 patients, unadjusted, and 126 after stratification). The 5-year overall survival was 99\% in both arms. Longer follow-up is needed to examine late toxicity. Conclusions: This study is the largest prospective study of PMBCL ever conducted and although the event rate did not reach the assumed level, its evidence supports the omission of RT in patients achieving a CMR after immunochemotherapy. Research Sponsor: Swiss Cancer League; Swiss National Science Foundation partially supported the study in Switzerland; Cancer Research UK.
IND227 phase III (P3) study of cisplatin/pemetrexed (CP) with or without pembrolizumab (pembro) in patients (pts) with malignant pleural mesothelioma (PM): A CCTG, NCIN, and IFCT trial.

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Background: The vast majority of pts with PM have unresectable disease, due to co-morbidities and/or advanced stage. In unresectable PM, standard first line treatment has been C(or carboplatin)P for 20 years but it is usually only moderately efficient, mostly on epithelioid (E)PM, with a global median overall survival (mOS) around 12 months (m), an improved quality-of-life (QoL), and mild toxicity. Trial CM743 demonstrated a significant improvement in mOS for nivolumab/ipilimumab (NI) over CP (18.1 versus 14.1 m), particularly for non-EPM, but 30% NI pts experienced grade 3 toxicity. Thus, alternative therapies to improve mOS and tolerability are needed. Methods: Canadian Cancer Trials Group (CCTG) IND 227 is an academic, open-label, randomized P3 study of the CCTG, National Cancer Institute of Naples (NCIN) and Intergroupe Francophone de Cancérologie Thoracique (IFCT). The study was supported by grants to CCTG (Canadian Cancer Society - 707213); Merck & Co. Inc provided pembrolizumab (pembro) and a grant to support study conduct. Untreated unresectable PM pts ≥ 18 years with ECOG performance status 0-1, adequate hematological, renal and hepatic function, no active autoimmune disease, brain metastases, interstitial lung disease or other active co-morbidities, were randomized 1:1 to CP with or without pembro and stratified by histology (E vs. non-E). Carboplatin was allowed if C contraindicated. Radiological review (BICR) and PD-L1 testing was centralised. mOS was the primary endpoint; median progression-free survival (PFS) and response rate (RR), QoL (EORTC QLQ-C30 + QLQ-LC13) and economic analysis were secondary. Results: A total 440 PM pts were randomized; 218 to CP and 222 to CP-pembro. Data cut-off was 16 September 2022 when the required events was observed. All pts were included in the analyses. Arms were well balanced. Seven pts opted not to receive CP. Median exposure of CP was comparable between arms, while 59 pts in CP arm (vs 17 CP-pembro pts) received immunotherapeutics. Using a stratified log rank test, mOS was 17.3m vs 16.1m for CP-pembro vs CP (HR 0.79 95%CI 0.64-0.98; p=0.0324), mPFS was 7.13m vs 7.16m (HR 0.80, 95%CI 0.65-0.99, p=0.0372). BOR was significantly higher for CP-pembro (63% vs 40%, p < 0.0001). Grade 3 or higher pembro related adverse events (AEs) occurred in 19% of patients (88% were grade 3; the most common were fatigue (5%) and diarrhea, pneumonitis and irAE (2% each)), and 16% of pts discontinued pembro per protocol for related AEs (most commonly diarrhea and pneumonitis). Conclusions: With a statistically significant improvement in mOS and acceptable tolerability. CP-pembro is an option for treatment naïve, unresectable PM. Clinical trial information: NCT02784171. Research Sponsor: Canadian Cancer Society; Merck & Co Inc.
Pemetrexed and platinum with or without pembrolizumab for tyrosine kinase inhibitor (TKI)-resistant, *EGFR*-mutant, metastatic nonsquamous NSCLC: Phase 3 KEYNOTE-789 study.

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**Background:** *EGFR* TKIs are standard 1L therapy for metastatic NSCLC with sensitizing *EGFR* mutations; however, most patients (pts) ultimately experience PD. We report the protocol-specified final analysis (FA) from the randomized, double-blind, phase 3 KEYNOTE-789 study of pemetrexed (pem) and platinum-based chemotherapy (chemo) with or without pembrolizumab (pembro) as subsequent therapy for pts with TKI-resistant, *EGFR*-mutant, metastatic nonsquamous NSCLC (NCT03515837).

**Methods:** Adults with histologically or cytologically confirmed stage IV nonsquamous NSCLC, ECOG PS of 0 or 1, documented *DEL19* or *L858R EGFR* mutation, and progression after EGFR TKI treatment were enrolled. Pts were randomized 1:1 to 35 cycles of pembro 200 mg Q3W or placebo (pbo) Q3W plus 4 cycles of pem and carboplatin or cisplatin Q3W followed by maintenance pem. Randomization was stratified by PD-L1 TPS (<50% vs ≥50%), prior osimertinib (yes vs no), and region (East Asia vs not East Asia). Dual primary endpoints were PFS per RECIST v1.1 by blinded independent central review (BICR) and OS. ORR and DOR per RECIST v1.1 by BICR and safety were secondary endpoints. Final PFS testing was completed at the second interim analysis (IA2; data cutoff, Dec 3, 2021); all other endpoints were assessed at FA (data cutoff, Jan 17, 2023). Efficacy boundaries based on actual observed events were 1-sided $P = 0.0117$ for PFS (IA2) and $P = 0.0118$ for OS (FA).

**Results:** 492 pts were randomized to pembro + chemo (n = 245) or pbo + chemo (n = 247). At IA2, median PFS (95% CI) was 5.6 (5.5–5.8) mo with pembro + chemo vs 5.5 (5.4–5.6) mo with pbo + chemo; HR 0.80 (95% CI, 0.65–0.97); $P = 0.0122$; and the results did not reach statistical significance. Median (range) time from randomization to data cutoff at FA (Jan 17, 2023) was 42.0 (29.5–53.9) mo. At IA2, median PFS (95% CI) was 5.6 (5.5–5.8) mo with pembro + chemo vs 5.5 (5.4–5.6) mo with pbo + chemo; HR 0.80 (95% CI, 0.65–0.97); $P = 0.0122$; and the results did not reach statistical significance. Median (range) time from randomization to data cutoff at FA (Jan 17, 2023) was 42.0 (29.5–53.9) mo. At FA, median OS (95% CI) was 15.9 (13.7–18.8) vs 14.7 (12.7–17.1) mo. While the HR for OS (0.84 [95% CI, 0.69–1.02]; $P = 0.0362$) favored pembro + chemo vs pbo + chemo, it did not reach statistical significance. Median (range) time from randomization to data cutoff at IA2 was 42.0 (29.5–53.9) mo. At FA, median OS (95% CI) was 15.9 (13.7–18.8) vs 14.7 (12.7–17.1) mo. While the HR for OS (0.84 [95% CI, 0.69–1.02]; $P = 0.0362$) favored pembro + chemo vs pbo + chemo, it did not reach statistical significance. OS rates at 12-mo were 61.6% vs 59.4% and at 24-mo were 30.6% vs 26.4%. HR for OS was similar in PD-L1 TPS ≥50% (HR, 0.84) and TPS <50% groups (HR, 0.85). ORR (95% CI) in ITT was 29.0% (23.4–35.1%) with pembro + chemo vs 27.1% (21.7–33.1%) with pbo + chemo. Median DOR was 6.3 (2.3 to 40.8+) mo vs 5.6 (1.8+ to 40.6+) mo. Grade 3 treatment-related AEs occurred in 43.7% of pts in pembro + chemo arm and 38.6% in pbo + chemo arm; grade 5 AEs occurred in 0.4% vs 0.8%. Grade ≥3 immune-mediated AEs and infusion reactions occurred in 4.5% of pts in the pembro + chemo arm and 2.0% in the pbo + chemo arm; 0.4% vs 0% had grade 5 events.

**Conclusions:** In the KEYNOTE-789 study, addition of pembro to chemo in pts with TKI-resistant, *EGFR*-mutant, metastatic nonsquamous NSCLC did not significantly prolong PFS and OS in comparison to pbo + chemo. AEs were manageable in both arms, and no new safety signals were identified. Clinical trial information: NCT03820986. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
Tumor Treating Field (TTFields) therapy with standard of care (SOC) in metastatic non-small cell lung cancer (mNSCLC) following platinum failure: Randomized, phase 3 LUNAR study.

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Background: TTFields are electric fields that disrupt processes critical for cancer cell viability. TTFields are delivered by a noninvasive portable device that is FDA approved for glioblastoma and mesothelioma. Preclinical NSCLC studies demonstrated that TTFields enhance the antitumor immune response, through disruption of mitosis and subsequent induction of immunogenic cell death. In addition, TTFields were shown to synergize with taxanes and immune checkpoint inhibitors (ICIs). The global, randomized, phase 3 LUNAR study (NCT02973789) assessed TTFields therapy with SOC (investigator’s choice ICI or docetaxel [DTX]) for previously treated mNSCLC. Methods: Adults with mNSCLC progressing on or after platinum therapy (prior ICI permitted) were randomized 1:1 to TTFields + SOC or SOC. TTFields therapy (150 kHz) was delivered continuously until progression or intolerable toxicity. Primary endpoint was overall survival (OS). Key secondary endpoints were OS in ICI TTFields + SOC or SOC. TTFields therapy (150 kHz) was delivered continuously until progression or intolerable toxicity. Key secondary endpoints were OS in ICI TTFields + SOC or SOC.

Results: 276 patients were randomized between Feb 2017 and Nov 2021 to receive TTFields + SOC (n=137) vs SOC (n=139). Baseline characteristics were balanced: median (m) age 64 years (range, 22–86); 65% male; 56% non-squamous; 96% ECOG PS 0–1; 89% one prior line of systemic therapy; 31% prior ICI. OS was significantly extended with TTFields + SOC vs SOC. After a minimum follow-up of 12 months (mo), mOS (95% CI) was 13.2 (10.3–15.5) mo with TTFields + SOC vs 10.0 (8.2–12.2) mo with SOC (HR 0.74; 95% CI 0.56–0.98; P=0.037). 1-year survival rates (95% CI) were 53% (44–61) and 42% (34–50), respectively (P=0.040). mPFS was 4.8 (4.1–5.7) mo and 4.1 (3.0–4.7) mo (HR 0.87; 95% CI 0.67–1.14), respectively. In patients receiving an ICI (n=134), TTFields significantly improved OS vs ICI alone: mOS (95% CI) 18.5 (10.6–30.3) vs 10.6 (8.2–17.6) mo (HR 0.63; 95% CI 0.41–0.96; P=0.032). In the DTX subgroup (n=142), patients who received TTFields had a numerically higher mOS vs DTX alone: 11.1 (95% CI 8.2–14.1) mo vs 8.9 (95% CI 6.5–12.2) mo (HR 0.87; 95% CI 0.60–1.26). The rate of AEs was similar between groups (97% TTFields + SOC vs 91% SOC). The incidence of TTFields-related AEs was 71%; majority were grade 1 and 2 local skin irritation; 8 patients (6%) reported a grade 3 AE. There were no grade 4 toxicities and no deaths attributable to TTFields. Conclusions: TTFields therapy significantly extended OS in patients with mNSCLC following platinum failure without exacerbating systemic toxicities, and with few high-grade device-related AEs. The efficacy and safety demonstrated in this phase 3 study warrant inclusion of TTFields therapy as part of second line SOC in mNSCLC. Clinical trial information: NCT02973789.

Research Sponsor: Novocure.
A phase III study comparing EGFR tyrosine kinase inhibitor (EGFR-TKI) monotherapy and EGFR-TKI with inserted cisplatin (CDDP) plus pemetrexed (PEM) as a first-line treatment in patients (pts) with advanced non-squamous non–small-cell lung cancer (NSqNSCLC) harboring EGFR activating mutation (EGFR-NSqNSCLC): JCOG1404/WJOG8214L, AGAIN study.

Background: The standard first-line treatment for pts with EGFR-NSqNSCLC is EGFR-TKI monotherapy, but acquired resistance to EGFR-TKI restricts duration of response and survival. We hypothesized that the insertion of platinum-doublet chemotherapy after the initial response to EGFR-TKI might prevent the emergence of acquired resistance to EGFR-TKI and prolong patient survival. Methods: This was an open-label, multicenter, randomized phase III study comparing two arms as below in pts with EGFR-NSqNSCLC. The key eligibility criteria were pts with advanced or recurrent NSqNSCLC harboring EGFR mutations (exon 19 deletion or exon21 L858R), age 20 to 74 years, and PS 0 or 1. In the standard arm (SA), gefitinib (GEF) or osimertinib (OSI) was administrated until disease progression. In the experimental arm (EA), GEF or OSI was reinitiated on days 1-56. Then, after a two-week drug-free period, three cycles of CDDP and PEM were administered on days 71, 92, and 113. Thereafter, GEF or OSI was reinitiated on day 134 and continued until disease progression. The primary endpoint was overall survival (OS). The planned sample size (required number of events) of 500 patients (257 deaths) provided 75% power (one-sided alpha level of 5%) to detect an OS hazard ratio (HR) of 0.749. Results: From December 2015 to October 2020, 501 pts (GEF cohort: 308 pts, OSI cohort: 193 pts) were randomized. EGFR-TKI was changed from GEF to OSI in October 2018 considering the results of FLAURA study. The median age was 65. Advanced stage and recurrent disease were 86% and 14%, exon 19 deletion and exon21 L858R were 56% and 44%, PS 0 and 1 were 47% and 53%, respectively. Median survival time (MST) was 48.0 months (95% confidence interval [CI] 40.8 to 56.4) in SA and 48.0 months (95% CI 43.2 to 54.0) in the EA (HR 0.985; 95% CI 0.772 to 1.257; one-sided p=0.4496). In GEF cohort, MST was 43.2 months (95% CI 37.2 to 51.6) in SA and 45.6 months (95% CI 40.8 to 51.6) in EA (HR 1.016; 95% CI 0.774 to 1.332). In OSI cohort, MST was not reached in both SA and EA (HR 0.835; 95% CI 0.484 to 1.442). Median progression-free survival (mPFS) was 12.0 months (95% CI 10.8 to 14.4) in SA and 18.0 months (95% CI 15.6 to 20.4) in EA (HR 0.762; 95% CI 0.628 to 0.925; one-sided p=0.0003). In GEF cohort, mPFS was 9.6 months (95% CI 9.6 to 12.0) in SA and 14.4 months (95% CI 12.0 to 18.0) in EA (HR 0.687; 95% CI 0.544 to 0.867). In OSI cohort, mPFS was 20.4 months (95% CI 20.4 to 25.2) in SA and 25.2 months (95% CI 18.0 to 34.8) in EA (HR 0.812; 95% CI 0.572 to 1.155). Conclusions: In patients with advanced EGFR-NSqNSCLC, the insertion of platinum-doublet chemotherapy after the initial response to EGFR-TKI could not prolong OS compared with EGFR-TKI, though that could prolong PFS. Clinical trial information: UMIN000020242. Research Sponsor: Japan Agency for Medical Research and Development.
Intracranial efficacy of sotorasib versus docetaxel in pretreated KRAS G12C-mutated advanced non-small cell lung cancer (NSCLC): Practice-informing data from a global, phase 3, randomized, controlled trial (RCT).

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Background: Brain metastases are common (~30%) in patients (pts) with KRAS G12C-mutated advanced NSCLC and have a negative impact on survival and quality of life (QOL). In the CodeBreaK 200 global, phase 3 RCT, sotorasib was the first oral KRASG12C inhibitor to show improved progression-free survival (PFS) and overall response rate (ORR), with a better toxicity profile and QOL, compared with intravenous docetaxel in pretreated KRASG12C-mutated advanced NSCLC. Here we describe the first RCT data evaluating the intracranial (IC) efficacy of sotorasib versus docetaxel from the CodeBreaK 200 study. Methods: Pts with KRAS G12C-mutated advanced NSCLC who progressed after platinum-based chemotherapy and a checkpoint inhibitor were randomized 1:1 to sotorasib (960 mg daily; n=171) or docetaxel (75 mg/m² every 3 weeks; n=174). Patients with treated, stable (non-progressing) brain metastases were eligible for study. Baseline brain imaging, by contrast enhanced MRI, was performed for all pts at screening. For pts with history of or brain metastasis at baseline, the brain MRI was repeated at every subsequent imaging assessment (every 6 weeks). A post-hoc analysis on IC efficacy (CNS PFS and time to CNS recurrence) was assessed by blinded independent central review (BICR) per modified Response Assessment in Neuro-Oncology Brain Metastases (mRANO-BM). Systemic response was also assessed by RECIST 1.1. Results: CNS metastases by imaging at baseline were present in 40 pts (23%) in the sotorasib arm and 29 pts (17%) in the docetaxel arm (full analysis set, FAS). With a median follow-up of 20.0 months, the median systemic PFS by RECIST 1.1 in the FAS was 6.1 months versus 4.5 months (HR 0.57 [95% CI: 0.30, 1.07], P=0.045) for sotorasib versus docetaxel, respectively. Time to CNS recurrence in the FAS was 9.6 months with sotorasib versus 5.4 months with docetaxel (HR 0.84 [95% CI: 0.32, 2.19], P=0.37). Treatment-related adverse events of any grade occurred in 77.5% of pts treated with sotorasib versus 89.7% of pts treated with docetaxel. Conclusions: In the first randomized evaluation of IC activity of any KRAS G12C inhibitor, sotorasib demonstrated a reduced risk of progression and trend towards delayed time to CNS recurrence versus docetaxel in patients with pretreated KRAS G12C-mutated advanced NSCLC who had treated, stable brain metastases. These results suggest IC activity with sotorasib to complement the overall PFS benefit observed with sotorasib versus docetaxel. Clinical trial information: NCT04303780. Research Sponsor: Amgen Inc.
First-line (1L) nivolumab (N) + ipilimumab (I) + chemotherapy (C) vs C alone in patients (pts) with metastatic NSCLC (mNSCLC) from CheckMate 9LA: 4-y clinical update and outcomes by tumor histologic subtype (THS).

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Background: In CheckMate 9LA (NCT03215706), 1L N + I + C demonstrated durable survival benefit in pts with mNSCLC vs C alone. Here, we report updated efficacy and safety with a 4-y minimum (min) follow-up (f/u) as well as exploratory analyses of efficacy by THS, a known prognostic indicator for NSCLC. Methods: Adults with stage IV/recurrent NSCLC (no known sensitizing EGFR/ALK alterations) and ECOG PS ≤ 1 were randomized 1:1 to N 360 mg Q3W + I 1 mg/kg Q6W + 2 cycles of C (n = 361) or 4 cycles of C alone (n = 358). Pts were stratified by sex, PD-L1 (≤ 1% vs ≥ 1%), and histology (squamous [SQ] vs non-squamous [NSQ]). Maintenance pemetrexed was allowed in the C arm (NSQ NSCLC). Assessments included OS, PFS, ORR, safety, treatment (tx)-free interval (TFI; time from last study dose to start of first subsequent systemic tx or death), and efficacy by THS (solid, acinar, or other, per modified WHO classification). Results: At a min f/u of 47.9 mo (database lock, Feb 2023; median f/u, 54.5 mo), N + I + C continued to provide long-term, durable OS benefit vs C in all randomized pts (HR, 0.74 [95% CI 0.63–0.87]; 4-y OS rates, 21% vs 16%, respectively). Similar clinical benefit was seen for N + I + C vs C across tumor PD-L1 or histology subgroups (table). In all pts treated with N + I + C (n = 358), median TFI was 2.2 mo, with 11% remaining tx-free and alive at 4y. In pts who discontinued all components of N + I + C due to tx-related adverse events (n = 61), 4-y OS rate was 41%; median TFI was 10.6 mo, with a 4-y TFI rate of 27%. In an exploratory analysis in pts with evaluable NSQ NSCLC tissue (n = 310; min f/u 36.1 mo), median OS was longer with N + I + C vs C in both solid (16.6 vs 9.3 mo) and acinar (18.7 vs 12.9 mo) THS. Updated efficacy by THS will be presented. No new safety signals were identified with longer f/u. Conclusions: With a 4-y min f/u, pts treated with N + I + C continued to derive long-term, durable efficacy benefit vs C regardless of tumor PD-L1 expression or histology, with greater magnitude of benefit in pts with tumor PD-L1 < 1% or SQ histology. Exploratory analyses suggested OS benefit with N + I + C vs C in both solid and acinar subtypes. Together, these data further reinforce the use of N + I + C as an efficacious 1L tx option for pts with mNSCLC. Clinical trial information: NCT03215706. Research Sponsor: Bristol Myers Squibb.
Distant metastasis-free survival results from the randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial.

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Background: mRNA-4157 is a novel mRNA-based personalized cancer vaccine which encodes up to 34 patient-specific tumor neoantigens. The open-label randomized Phase 2 mRNA-4157-P201/Keynote-942 trial met its primary endpoint of recurrence free survival (RFS) in patients with resected high-risk stage IIIB/C/D and IV melanoma. The study has shown a statistically significant and clinically meaningful improvement in RFS in the combination therapy compared to pembrolizumab monotherapy, with a reduction in the risk of recurrence or death by 44% (HR = 0.561; 95% CI: (0.309, 1.017); 1-sided p-value of 0.0266). This report provides the first analysis of the secondary efficacy endpoint of distant metastasis-free survival (DMFS). Methods: mRNA-4157-p201 is an ongoing multicenter, open-label, randomized Phase II trial in patients with completely resected, high-risk Stage IIIB/C/D and IV cutaneous melanoma. Patients were randomized 2:1 (stratified by stage) to receive mRNA-4157 in combination with pembrolizumab or pembrolizumab alone. mRNA-4157 (1mg) was administered intramuscularly every 3 weeks for a total of 9 doses and pembrolizumab (200mg) intravenously was given every 3 weeks for up to 18cycles. The primary endpoint was investigator-assessed RFS, defined as local, locoregional, distant recurrence, or new primary melanoma. The secondary endpoint of DMFS was pre-specified and hierarchically tested following positive RFS. All tests were performed at 1-sided alpha = 0.99. Results: 157 patients were randomized to the combination of mRNA-4157 with pembrolizumab (n = 107) or pembrolizumab monotherapy (n = 50). The primary analysis for the primary endpoint occurred after all patients completed a minimum of 12 months on study and 44 RFS events were observed. At a median follow-up of 23 (combination) and 24 (pembrolizumab) months in the primary analysis, RFS events were reported in 22.4% (24/107) of patients in the combination arm and 40% (20/50) of patients in the monotherapy arm. The 18-month RFS rates (95% CI) were 78.6% (69.0%, 85.6%) vs 62.2% (46.9%,74.3%) in the combination and monotherapy arms respectively. There was also a statistically and clinically significant improvement in DMFS for the combination versus pembrolizumab monotherapy (HR = 0.347; 95% CI: (0.145, 0.828); 1-sided p-value 0.0063). Distant recurrence or death was reported in 8.4% (9/107) and 24% (12/50) of patients, with 18-month DMFS rates (95% CI) were 91.8% (84.2, 95.8%) vs 76.8% (61.0%, 86.8%) in the combination and monotherapy arm, respectively. Conclusions: mRNA-4157 in combination with pembrolizumab as adjuvant therapy for resected high-risk melanoma significantly prolonged DMFS compared to pembrolizumab. These results provide further evidence that a personalized neoantigen approach is potentially beneficial for cancer patients. A phase 3 randomized study will be initiated in patients with melanoma. Clinical trial information: NCT03897881. Research Sponsor: Moderna Inc.
Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the phase 3 KEYNOTE-716 study.

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Background: Adjuvant pembrolizumab significantly improved distant metastasis-free survival (DMFS) and recurrence-free survival (RFS) in patients with resected stage IIB or IIC cutaneous melanoma per American Joint Committee on Cancer, 8th edition, guidelines and a negative sentinel lymph node biopsy. In part 1 of the study, patients were randomly assigned (1:1) to pembrolizumab 200 mg (2 mg/kg up to 200 mg for pediatric patients) or placebo every 3 weeks for up to 17 cycles (~1 year) or until disease recurrence, unacceptable toxicity, or withdrawal. Randomization was stratified by T category for adults (T3b vs T4a vs T4b), with a separate stratum for pediatric patients. The primary end point was RFS per investigator review. DMFS per investigator review was a secondary end point. The protocol-specified final DMFS analysis was based on a target of 195 DMFS events. No formal hypothesis testing was performed because DMFS and RFS end points were met at previous interim analyses. The data cutoff date for this analysis was January 4, 2023. Results: Overall, 976 patients were randomly assigned to receive pembrolizumab (n = 487) or placebo (n = 489). Median duration of follow-up (time from randomization to the data cutoff date) was 39.4 months (range, 26.0-51.4). Compared with placebo, adjuvant pembrolizumab improved DMFS (medians: not reached; hazard ratio [HR], 0.59 [95% CI, 0.44-0.79]) and RFS (medians: not reached; HR, 0.62 [95% CI, 0.49-0.79]). The 36-month DMFS rate was 84.4% with adjuvant pembrolizumab versus 74.7% with placebo; the 36-month RFS rate was 76.2% with adjuvant pembrolizumab versus 63.4% with placebo. DMFS benefit with adjuvant pembrolizumab over placebo was observed regardless of cancer stage at baseline (stage IIB HR, 0.62 [95% CI, 0.42-0.92]; stage IIC HR, 0.57 [0.36-0.88]). Similar results were observed with RFS (stage IIB HR, 0.58 [95% CI, 0.43-0.79]; stage IIC HR, 0.65 [95% CI, 0.45-0.94]). No new safety signals were observed. Conclusions: With a median follow-up of 39.4 months, adjuvant pembrolizumab for resected stage IIB and IIC melanoma continued to show DMFS and RFS benefit over placebo, with no new safety signals. Clinical trial information: NCT03553836. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
Survival after isolated hepatic perfusion as a treatment for uveal melanoma liver metastases: Results from a randomized controlled trial (the SCANDIUM trial).

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Background: Uveal melanoma is the most common primary intraocular malignancy in adults. Despite successful control of the primary tumor, metastatic disease will ultimately develop in approximately 50% of the patients, with the liver being the most common site. The median survival for patients with liver metastases is about 6-12 months, and there are only few systemic treatment options available providing only small survival benefits. The SCANDIUM trial previously demonstrated significantly superior response rate (40% vs 4.5%) and progression free survival (7.4 vs 3.3 months), compared to best alternative care, in patients with liver metastases of uveal melanoma receiving first-line treatment with isolated hepatic perfusion (IHP). Here we present the primary endpoint, overall survival (OS) rate at 24 months.

Methods: In this multicenter randomized, controlled, phase III trial, adult patients with a performance status ECOG 0-1, and with previously untreated isolated liver metastasis from uveal melanoma, were randomized 1:1 between 2013 and 2021 to receive a one-time treatment with IHP or best alternative care (control group). No crossover from the control group to the IHP group was allowed. The primary endpoint was OS rate at 24 months, with the hypothesis of a treatment effect leading to a 50% OS rate in the IHP group compared to 20% in the control group. Results: A total of 93 patients were randomized, with three patients in each group being excluded due to either withdrawal of consent or inappropriate enrollment, and a total of 87 patients were assigned to either IHP group (43 patients) or control group (44 patients). In the IHP group, 41 (89%) patients received IHP. In the control group, the first-line of treatment was chemotherapy (49%), immunotherapy (39%) or localized treatment interventions (9%). In the intention-to-treat (ITT) population, the OS rate at 24 months in the IHP group was 46.5% (95% CI, 31.2-60.4%) compared to 29.5% (95% CI, 17.0-43.2%) in the control group (p = 0.12, Fisher’s exact test). The median OS in the IHP group was 21.7 months (95% CI, 19.1-NA months) compared to 17.6 months (95% CI, 13.5-21.4 months) in the control group (p = 0.10, log-rank test), with a hazard ratio of 0.64 (95% CI 0.37-1.10) in favor of the IHP group. Conclusions: In the SCANDIUM trial, patients with metastatic uveal melanoma receiving IHP experienced a significantly improved PFS. At two years, OS was longer in patients receiving IHP, but the difference was not statistically significant. This could in part be attributed to the control group performing better than expected, potentially due to the introduction of immunotherapy during the study period. Prolonged follow-up of the cohorts will further elucidate how IHP affects OS in patients with uveal melanoma. Clinical trial information: NCT01785316. Research Sponsor: Sahlgrenska University Hospital; The Assar Gabrielsson Foundation, Gothenburg Society of Medicine, Wilhelm and Martina Lundgrens Foundation, Knut and Alice Wallenberg Foundation, Wallenberg Centre for Molecular and Translational Medicine.
Minimal residual disease by circulating tumor DNA as a biomarker of recurrence free survival in resected high-risk melanoma patients treated with mRNA-4157/V940, a personalized cancer vaccine, and pembrolizumab.

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Background: The combination of mRNA-4157/V940 and pembrolizumab improved recurrence free survival (RFS) compared to pembrolizumab monotherapy in patients with resected high-risk stage III/IV cutaneous melanoma in the randomized Phase 2 mRNA-4157-P201/KEYNOTE-942 trial (RFS event rate of 22.4% (24/107) versus 40% (20/50); HR = 0.561; 95% CI: 0.309, 1.017). Across multiple cancer types and disease settings, detection of minimal residual disease (MRD) by circulating tumor DNA (ctDNA) assays in plasma identifies patients at higher risk of relapse and progression, and can monitor presence of disease throughout treatment. Herein, we report ctDNA analyses to explore the association between minimal residual disease and the probability of recurrence.

Methods: In mRNA-4157-201, baseline tumor core biopsies and matched whole blood were subjected to whole exome sequencing (WES). The personalized amplicon-based NGS assay by Inivata (RaDaR) was used to identify and prioritize up to 48 patient-specific somatic variants to analyze ctDNA in longitudinal plasma samples for MRD detection. This method for ctDNA analysis is distinct from most prior studies in melanoma that report use of ddPCR for single mutations or fixed-gene panels. The association of MRD with RFS was evaluated with Kaplan Meier analyses and assessed with hazard ratio (95% CI) in ctDNApos and ctDNAneg subgroups and across study arms. Results: Of patients enrolled in this study with evaluable ctDNA, 88% (110/125) were ctDNAneg at start of treatment. Significantly longer RFS was observed in patients who were ctDNAneg compared to those with ctDNApos at baseline across study arms (RFS event rate of 20.9% (23/110) versus 80.0% (12/15); HR = 0.150; 95% CI: 0.073, 0.306). Within the mRNA-4157/V940 and pembrolizumab combination arm, significantly longer RFS was observed in patients with ctDNApos compared to ctDNApos samples (RFS event rate of 10.4% (8/77) versus 76.9% (10/13); HR = 0.087; 95% CI: 0.034, 0.222). This trend was also observed in the pembrolizumab arm (RFS event rate of 45.5% (15/33) versus 100% (2/2); HR = 0.008; 95% CI: 0.001, 0.088) study arm, although the small sample size in pembrolizumab arm (n = 2) limits interpretation. Conclusions: MRD detection by plasma ctDNA assay at the start of adjuvant melanoma treatment is uncommon in mRNA4157-p201 but is associated with shorter RFS. Treatment with the combination of mRNA-4157/V940 and pembrolizumab was associated with prolonged RFS compared to pembrolizumab monotherapy in patients with high-risk resectable melanoma, irrespective of MRD status. Additional analyses including assessment of longitudinal ctDNA patterns are ongoing. The association between MRD and mRNA-4157/V940 treatment effect will be further explored in upcoming planned studies. Clinical trial information: NCT03897881. Research Sponsor: Moderna Inc.
Randomized phase II trial of cabozantinib combined with PD-1 and CTLA-4 inhibition versus cabozantinib in metastatic soft tissue sarcoma.

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Background: Cabozantinib (C) has been combined successfully with either PD-1 or CTLA-4 inhibition in cancer clinical trials. The combination of nivolumab (N) and ipilimumab (I) previously was evaluated in soft tissue sarcoma (STS) and demonstrated activity as well as an acceptable safety profile. Given these data, we hypothesize that C in combination with both I and N is a therapeutic strategy that will be more effective than C alone in metastatic STS that lack translocations. Additionally, we hypothesized that C priming would enhance the efficacy of combination I and N at the time of crossover. Methods: This is a 2:1 randomized phase 2 clinical trial evaluating the overall response rate (RR) of C 40mg orally daily in combination with I (1mg/kg IV) / N (3mg/kg) for 4 doses Q3W and then maintenance N 480mg Q4W compared to C 60mg oral alone, with crossover. Secondary endpoints include progression free survival (PFS), disease control rate (DCR), RR in crossover, quality of life by FACT-G7, RR by iRECIST and safety. Correlative and biomarker analysis are preplanned. Key patient selection includes ECOG 0-1, 1-2 lines of prior therapy, and sarcomas that lack of translocations. The trial was balanced for leiomyosarcoma (LMS), liposarcoma and UPS. Results: 69 patients were randomized to C+I/N and 36 patients were randomized to C alone. 19 patients crossed over to C+I/N at progression. 54/105 patients had LMS. RR of C+I/N was 11% (5 PR and 2 CR), while the RR of C was 6% (2 PR and 0 CR) (p = NS). C+I/N responding histologies included LMS, angiosarcoma, epithelioid sarcoma, and myxofibrosarcoma. C responding histologies included 2 PRs in LMS. There were also 2 LMS PRs in crossover to C+I/N. The median PFS for C+I/N was 5.4 months and for C was 3.8 months (p = 0.016). The DCR for C+I/N was 80% (41 SD, 5 PR, 2 CR), and 42% for C (11 SD, 2 PR) (p = 0.0004). The most common grade 3-4 adverse events affecting > 10% of patients included hypothyroidism, diarrhea, mucositis, oral dysesthesia, nausea, vomiting, elevated AST and ALT, anorexia, dysgeusia, headache, pruritis, maculopapular rash, and hypertension for C+I/N and hypothyroidism, diarrhea, oral dysesthesia, fatigue, palmar-plantar erythrodynesthesia, and hypertension for C. Conclusions: The combination of C+I/N was superior to C for the treatment of non-translocation STS for DCR and PFS. Most frequent responding histology was LMS. Correlative work is ongoing. Clinical trial information: NCT04551430. Research Sponsor: BMS and Excelixis.
Effectiveness of a cardiovascular health EHR application for cancer survivors in community oncology practice: Results from WF-1804CD.

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Background: Practice guidelines recommend cardiovascular risk assessment and counseling for cancer survivors. The Automated Heart-Health Assessment study (AH-HA: WF-1804CD, NCT# 03935282) evaluated a novel electronic health record (EHR) clinical decision support tool based on American Heart Association Simple 7 cardiovascular health (CVH) factors to promote provider-patient CVH discussions in outpatient oncology. Methods: This clinic-randomized trial (R01CA226078), coordinated by the Wake Forest NCORP Research Base (UG1CA189824), randomized NCORP oncology practices using the Epic EHR to the AH-HA tool or usual care and enrolled survivors receiving routine care at least 6 months post-curative cancer treatment. The tool rendered an interactive display of risk factors, automatically populated from the EHR, alongside a tab indicating receipt of cancer treatments with cardiotoxic potential. Survivors at AH-HA sites had tool access during a routine visit; survivors at usual care sites did not. Immediately post-visit, each survivor was asked about counseling on 7 CVH factors [body mass index, physical activity, diet, smoking status, blood pressure, cholesterol, and glucose]. The primary endpoint is survivor-reported discussion of non-ideal or missing CVH factors; with 8 randomized practices (ICC=0.03), the study design had 82% power to detect a difference of 20% reported discussions in usual care versus 40% in AH-HA. Additional clinical endpoints were documentation of CVH discussions, referrals to primary care and cardiology, and change in CVH factors over 12 months (ongoing). A mixed effects logistic regression model assessed the effect of AH-HA on CVH discussions between the arms, with study arm as a fixed effect and practice as a random effect. Results: 5 usual care and 4 AH-HA practices enrolled 645 survivors from 10/1/2020- 2/28/2023. The majority had breast cancer (82%; 8% endometrial, 5% colorectal, 5% prostate, lymphoma or multiple types). Most survivors were female (96%; 84% White/non-Hispanic, 8% Black; 3% Hispanic; mean age= 62 yrs and median time since diagnosis=3.6 yrs). 18 participants (3%) did not complete necessary assessments, leaving 627 evaluable. 87% of providers (n=15) rated the tool utility and ease of use positively. Conclusions: The AH-HA tool was acceptable and effective at promoting CVH discussions during routine follow-up care for survivors and referrals to primary care. Clinical trial information: NCT03935282. Research Sponsor: U.S. National Institutes of Health.

<table>
<thead>
<tr>
<th>Model Estimate (95% CI)</th>
<th>AH-HA Tool (n=291, 4 practices)</th>
<th>Usual Care (n=336, 5 practices)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of survivors reporting ≥1 non-ideal or missing CVH factor discussed</td>
<td>97.6% (95.6, 98.7)</td>
<td>54.8% (44.8, 64.4)</td>
<td>&lt;0.001</td>
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<tr>
<td># non-ideal or missing factors discussed</td>
<td>4.06 (3.46, 4.66)</td>
<td>1.26 (0.72, 1.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td># of factors documented as discussed in EHR</td>
<td>3.83 (3.82, 5.84)</td>
<td>0.78 (1.02, 2.58)</td>
<td>0.03</td>
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<tr>
<td>Reported referral to primary care</td>
<td>38.6% (33.2, 44.4)</td>
<td>25.0% (16.8, 35.5)</td>
<td>0.03</td>
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Dexamethasone and exercise for cancer-related fatigue: A phase III randomized controlled trial.

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**Background:** Cancer-related fatigue (CRF) significantly impacts QoL of patients. Dexamethasone with physical activity may improve CRF. **Methods:** Phase III randomized study in patients with advanced cancer on palliative intent therapy, with ECOG PS 0-2, and fatigue score 4/10 on numeric rating scale. Intervention included oral dexamethasone 8 mg twice daily for 7 days, and exercise (aerobic + resistance). **Results:** From Dec 2022 to Feb 2023, we enrolled 114 pts; 56 in intervention arm, and 58 in standard arm. Median age was 56 yrs (IQR, 47.8 to 65), with 74 (64.9%) males. Common tumors were lung (75, 65.8%), head-and-neck (12, 11%), and breast (10, 8.8%). Compliance was 87.3% (n=48) for dexa, and 70.9% (n=39) for exercise. Primary endpoint of mean improvement in FACIT-Fatigue subscale on day 8 was 3.22 (SD, 12.69) in intervention, compared to 1.73 (SD, 9.97) in standard arm; \( P = 0.495 \). However, 54.5% patients in intervention had at least 3 points (minimal clinically relevant) decrease in fatigue, vs 41.8% in control; \( P = 0.182 \). By day 29, mean change in FACIT-Fatigue scores compared to baseline was similar in intervention vs control; 2.61 (SD, 14.64) vs 2.68 (SD, 12.87), respectively; \( P = 0.978 \). Although overall symptoms (ESAS) and general QoL were similar, there was a significant improvement in fatigue symptom on EORTC QLQ-C30 in intervention on day 29 compared to baseline; \( P = 0.013 \). Sleep quality also significantly improved on Day 29 in intervention; \( P = 0.018 \). On EORTC-QLQ FA12 (cancer-related fatigue QoL), physical fatigue improved significantly from baseline to Day 8 in intervention versus control; \( P = 0.035 \); with no difference in emotional or cognitive fatigue, interference with daily life, or social sequelae. There was no difference in grade 3 adverse events between groups; 18 (32.7%) in intervention group versus 18 (30.5%) in control group; \( P = 0.799 \). **Conclusions:** Dexamethasone and exercise did not lead to a statistically significant improvement in fatigue by FACT-Fatigue scale, although it resulted in greater proportion of pts with clinically relevant improvements in fatigue. The intervention significantly improved QoL fatigue symptom score and reduced physical fatigue on QoL, along with improving sleep quality. Clinical trial information: CTRI/2022/09/045678. Research Sponsor: Tata Memorial Center Research Administrative Council (TRAC).

<table>
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<tr>
<th>Changes in various scores in fatigue study.</th>
<th>Mean change in score from baseline (SD)</th>
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<tr>
<td><strong>Intervention arm</strong></td>
<td><strong>Standard arm</strong></td>
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<tr>
<td>Fatigue (FACIT-Fatigue)</td>
<td>Day 8 3.22 (12.69) 1.73 (9.97) 0.495</td>
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<tr>
<td>Day 29 2.61 (14.64) 2.68 (12.87) 0.978</td>
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<tr>
<td>Fatigue (FACT-F TOI)</td>
<td>Day 8 3.13 (21.70) 2.38 (18.18) 0.846</td>
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<tr>
<td>Day 29 8.94 (18.51) 6.18 (22.43) 0.499</td>
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<tr>
<td>Fatigue (MFI)</td>
<td>Day 8 -0.42 (11.33) -0.93 (8.64) 0.79</td>
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<td>Day 29 -0.36 (14.17) -3.16 (12.75) 0.272</td>
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<tr>
<td>Sleep quality (PSQI)</td>
<td>Day 8 -0.02 (3.70) 0.76 (4.09) 0.296</td>
</tr>
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<td>Day 29 -1.15 (3.79) 0.62 (3.81) <strong>0.018</strong></td>
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<td>Fatigue QoL (FA12)</td>
<td>Day 8 -6.26 (22.81) -0.10 (19.50) 0.131</td>
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<tr>
<td>Day 29 -11.00 (24.19) -6.50 (23.30) 0.333</td>
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<tr>
<td>Fatigue symptom on EORTC QLQ-C30</td>
<td>Day 8 -1.11 (27.22) -1.41 (28.45) 0.071</td>
</tr>
<tr>
<td>Day 29 -20.09 (31.28) -5.46 (28.04) <strong>0.013</strong></td>
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