Cabozantinib plus atezolizumab in locally advanced/metastatic adrenocortical carcinoma: Results from a multi-cohort basket phase II trial, CABATEN/GETNE-T1914.

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Background: Adrenocortical carcinoma (ACC) is a rare malignancy with a poor prognosis and limited therapeutic options. Immunotherapy and targeted therapy showed limited activity as single therapeutic strategies in ACC but synergism has been observed when combined in other genitourinary tumors such as Prostate and renal cell cancers. Therefore, we evaluated the activity and safety of cabozantinib plus atezolizumab in advanced/metastatic ACC. Methods: CABATEN was a prospective, multi-center, open-label, phase II study including patients with advanced and refractory endocrine and neuroendocrine tumors in 6 independent cohorts. Patients with locally advanced / metastatic ACC, ≥18 years old and ECOG 0–1 were included after progression to chemotherapy and/or mitotane. Prior treatment with cabozantinib or any immune checkpoint inhibitors was not allowed. Patients received atezolizumab 1200 mg IV Q3W plus cabozantinib 40 mg/day PO until progression or unacceptable toxicity. The primary endpoint was Objective Response Rate (ORR) by RECIST 1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. The study empowered a Simon II stage design, requiring 1 response out of 9 patients at 1st stage to continue accrual in a 2nd stage, for a total of 24 patients. Three responses out of the 24 patients were required in the 2nd stage to consider the study positive for the cohort. Results: From October 2020 to November 2022, 24 patients with ACC were included, 54.2% were female and the median age was 51 years. Most (87.5%) were metastatic at inclusion, 45.8% were functioning, and 20.8% presented hypercortisolism. Most patients (54.2%) had ≥ 2 prior lines of systemic therapy for advanced disease (chemotherapy 91.7%, mitotane 45.8%). Cabozantinib was administered for a median of 3 months (95% CI: 2.7–6.1) and required reduction to 20 mg/day in 20.8% of patients. Atezolizumab was administered for a median of 4.5 cycles (95% CI: 4–8). Treatment was discontinued mainly due to disease progression (79.2%). Treatment discontinuation due to toxicity occurred in 9 (9.7%) patients. The ORR was 8.3% (95% CI: 1–27), including two partial responses that lasted for 5.4 and 17.4 months respectively. After a median follow-up of 10.7 months (range: 2.1–25.7), the median PFS was 2.9 months (95% CI: 2.8–5.7) and the median OS was 13.5 months (95% CI: 8.8–NR). Treatment-related adverse events (grade ≥ 3) were observed in 20.8% of the patients, consisting of hypertension (12.5%), and transaminase increase (8.3%). Conclusions: Cabozantinib plus atezolizumab showed modest activity in locally advanced/metastatic ACC. Safety profile was consistent with previous reports. The existence of long lasting responders makes it worthwhile to continue investigating predictive factors that help select patients for this combination. Clinical trial information: EudraCT:2019-002279-32 / NCT04400474. Research Sponsor: GETNE through industry partners Ipsen and Roche.
First-line pembrolizumab plus lenvatinib for non-clear cell renal carcinomas (nccRCC): Extended follow-up of the phase 2 KEYNOTE-B61 study.

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Background: Pembrolizumab (pembro) + lenvatinib (lenva) is approved for first-line treatment of advanced/metastatic RCC based on results of the phase 3 KEYNOTE-581/CLEAR study. Previously reported results from the phase 2 KEYNOTE-B61 (NCT04704219) study with a median follow-up of 15 months further support the use of pembro + lenva in the first-line setting specifically across nccRCC. We now report updated results from KEYNOTE-B61 with median follow-up of 23 months. Methods: Adults with previously untreated, advanced nccRCC (histology assessed by investigator) and measurable disease per RECIST v1.1 received pembro 400 mg IV Q6W for #18 cycles (~2 years) + lenva 20 mg orally once daily until intolerable toxicity, progressive disease, or patient (pt) withdrawal from the study. Primary end point was ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary end points included DCR, OR, and PFS per RECIST v1.1 by BICR, OS, and safety. Results: A total of 158 pts received pembro + lenva. Median age was 60 years (range, 24–87), and the most common histologic variants of RCC were papillary (n = 93; 59%), chromophobe (n = 29; 18%), and unclassified (n = 20; 13%). Median time from first dose to the data cutoff date of July 5, 2023, was 22.8 months (range, 16.6–27.6). 86 pts had discontinued treatment (most commonly due to progressive disease, n = 56 [35%]). In all pts, ORR was 51% (95% CI, 43–59; 13 CRs [8%]; 67 PRs [42%]) and DCR was 82% (95% CI, 75–88). Median DOR was 19.5 months (range, 15.3–26.1) and median PFS and OS were 17.9 months (95% CI, 15.1–22.1) and NR (95% CI, NR–NR); estimated median PFS and OS rates were 48% and 73%. Treatment-related AEs (TRAEs) occurred in 151 pts (96%), most commonly hypertension (56%), diarrhea (46%), hypothyroidism (41%), and proteinuria (30%). Grade 3-4 TRAEs occurred in 92 pts (58%), most commonly hypertension (25%) and diarrhea, proteinuria, and decreased weight (5% each). No deaths due to TRAEs were reported. Discontinuation due to TRAEs were reported. Discontinuation due to TRAEs for pembro, lenva, or both pembro and lenva occurred in 15%, 13%, and 4% of pts, respectively. Conclusions: Consistent with prior reports, pembro + lenva had durable antitumor activity and a manageable safety profile in pts with advanced nccRCC. These results continue to support pembro + lenva as a first-line treatment option for pts with variant histologies of nccRCC. Clinical trial information: NCT04704219. Research Sponsor: Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Background: The ongoing, open-label, phase 2 LITESPARK-004 study (NCT03401788) showed that belzutifan, a HIF-2α inhibitor, exhibited antitumor activity in patients (pts) with VHL disease associated renal cell carcinoma (RCC), pancreatic neuroendocrine tumors (pNETs), and CNS hemangioblastomas. The most common adverse event (AE) of any grade was anemia and pts could have received erythropoietin-stimulating agents (ESA) and/or blood transfusions for management. This exploratory post-hoc analysis described pattern of ESA use and whether use of ESA impacted antitumor activity to belzutifan in pts with VHL disease. Methods: Pts (≥18 years) with germline VHL alterations, ≥1 measurable nonmetastatic RCC tumor, no tumor of >3 cm requiring immediate surgery, and no prior anticancer systemic treatment received oral belzutifan 120 mg once daily until disease progression, unacceptable toxicity, or pt withdrawal. End points included objective response rate (ORR) and duration of response (DOR) in VHL disease–associated RCC and non–RCC neoplasms per RECIST v1.1 by independent central review, and safety. Efficacy and safety outcomes among pts who received and did not receive ESA were evaluated. Data cutoff was April 1, 2022. Results: Of 61 treated pts, 14 (23%) received ESA and 47 (77%) did not. Median (range) time to onset of ESA use was 151 days (59-886) and median dose per pt was 5 injections (range 1-35). Duration of belzutifan exposure for ≥12 months was achieved in 100% of pts who received ESA vs 92% in pts who did not receive ESA. Median (range) relative dose intensity was 97.4 (51.4-100) and 98.8 (26.4-100) for pts who received and did not receive ESA, respectively. ORR for VHL–associated RCC was 71% (10/14, 95% CI, 42-92) for pts who received ESA and 62% (29/47, 46-76) for those who did not. Median DOR was not reached (NR) for pts who received ESA vs 12 months (5.4-35.8 months) for those who did not. Among pts with CNS hemangioblastomas, ORR was 46% (5/11, 17-77) for pts who received ESA and 42% (17/39, 28-60) for those who received pNETs, ORR was 100% (4/4, 100) for pts who received ESA and 90% (16/18, 65-99) for those who did not. Median DOR was not reached for both groups in pts with CNS hemangioblastomas and pNETs. Among pts who received and did not receive ESA, 5 (36%) and 6 (13%) pts had at least 1 dose reduction, respectively. All pts reported at least 1 AE but a larger percentage of pts who received ESA had AEs of grade 3 or higher than those who did not receive ESA (57% and 40%). Conclusions: In this exploratory, post-hoc analysis of LITESPARK-004, data suggests that administration of ESA did not adversely impact overall drug exposure or efficacy of belzutifan in pts with VHL disease associated RCC, CNS hemangioblastomas, and pNETs. Clinical trial information: NCT03401788. Research Sponsor: Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
A meta-analysis of overall survival and response in metastatic adrenocortical carcinoma: A review of 23 prospective trials of 880 patients.

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Background: Metastatic adrenocortical carcinoma (mACC) is a rare, aggressive tumour of the adrenal gland, with historically poor survival and limited established treatment modalities. The aim of this study was to systematically search for and analyse all prospective trials for mACC to establish benchmark response and survival outcomes. The study was registered on PROSPERO CRD42023430557. Methods: A systematic review and meta-analysis of five databases was performed between June 2023- July 2023. Key outcomes extracted included patient demographics, overall survival (OS), progression-free survival (PFS) and objective response rates (ORR). ORR was calculated using a random effects model and inverse variance methods. Time-to-event outcomes including PFS and OS, were extracted digitally from available Kaplan–Meier curves using the IPDfromKM tool and individual patient data (IPD) was generated as per Guyot et al. The PFS and OS data from individual studies were then pooled using a multivariate extension of the DerSimonian–Laird method to generate summary survival curves. Results: The final 23 trials (5 Phase 1b, 16 Phase II and 3 Phase 3) encompassed 880 patients were retrieved. Pooled ORR was 9.0% overall (2.9% for targeted therapy, 12.3% for chemotherapy and 15.3% for immunotherapy). Median OS was 9.9 months (95% CI 7.4–11.9) and 12-month OS of 41.6% (95% CI 33.1–51.2). Median OS was 7.4 months for patients receiving targeted therapy (95% CI 4.7–12.0), 11.2 months for patients receiving chemotherapy (95% CI 4.7–12.0) and 10.6 months for patients receiving immunotherapy (95% CI 4.4–13.2). 12-month OS was 30.4% (95% CI 15.9–58.3) for patients receiving targeted therapy, 45.4% (95% CI 33.7–61.2) for patients receiving chemotherapy and 45.3% (95% CI 36.2–56.6) for patients receiving immunotherapy. Conclusions: This study found that current treatments strategies confer limited survival and response benefit in mACC and highlight the need for research into the pathogenesis and novel strategies in the disease. Immunotherapy and chemotherapy demonstrate modest benefits for patients and future trials should attempt to surpass the survival benchmarks set in this study. Research Sponsor: None.
Rethinking the definition of stage IV disease in adrenocortical carcinoma: Assessing the impact of clinical lymph node positive disease.

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Background: Stage III (pT3N0M0 or pT1-3N1M0) adrenocortical carcinoma (ACC) encompasses both lymph node positive (LN+) and lymph node negative (LN-) disease. However, in other malignancies, prior data demonstrates that LN+ disease portends outcomes similar to metastatic, stage IV disease. We similarly wanted to examine the impact of clinical LN+ disease on oncologic outcomes in ACC. Methods: Patients with clinical stage III and stage IV (M1) disease were identified using the National Cancer Database (NCDB). Stage III patients were stratified as having either LN+ or LN- disease. Kaplan-Meier curves illustrated overall survival of the three groups – stage III LN-, stage III LN+, and stage IV. Further analysis stratified stage III LN+ and stage IV patients by whether or not patients received treatment (systemic therapy, surgery, or both). Results: A total of 917 patients were included in the analysis – 322 stage III LN-, 67 stage III LN+, and 528 stage IV. 3-year OS for patients with stage IV, stage III LN+, and stage III LN- was 15.6% (95% CI, 12.5%-19.4%), 29.4% (95% CI, 19.8%-43.6%), and 48.6% (95% CI, 43.2%-54.6%), respectively. Within the stage III LN+ group 3-year OS was 33.0% (95% CI, 18.5%-58.8%) for those who received treatment and was 27.4% (95% CI, 16.1% - 46.6%) for those who did not. Within the stage IV group 3-year OS was 29.8% (95% CI, 22.7%-39.3%) for those who received treatment and was 10.2% (95% CI, 7.4% - 14.2%) for those who did not. Conclusions: The current staging paradigm of ACC includes LN+ disease as part of the stage III classification. Herein, we see that clinical stage III LN+ disease had a 3-year OS that was more similar to clinical stage IV disease than clinical stage III LN- disease. While the survival curves appear distinct, due to the rarity of the disease and therefore small sample size there was overlapping confidence intervals. In stage IV patients there was a significant difference in OS at 3 years between those who did and did not receive treatment. This same finding was not found in stage III LN+ patients. Research Sponsor: None.