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ASCO 2022: Sets the Stage for Improved and Practice-Changing Results

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Dear Colleagues,

This year's annual meeting of the American Society of Clinical Oncology (ASCO22) held June 3 through 7, was hybrid in nature with attendees joined both in-person and virtually from over 100 countries. Tens of thousands of physicians, clinical trial investigators, R&D scientists, academics, patient advocates, and biopharma leaders descended upon Chicago for the first in-person ASCO meeting after a two-year hiatus due to the COVID-19 pandemic. This year's ASCO22 has provided an opportunity to explore the latest advancements in cancer research, treatment, and patient care with featured abstracts in more than 120 subcategories including all major disease sites and research areas. Presentations at ASCO22 have unearthed a wealth of exciting data across the oncology spectrum, especially for oncologists and physicians around the world, and also gave glimpses into what is next for the field. With a mix of live and on-demand content, there was no shortage of cutting-edge research available to attendees —including more than 2,000 abstracts, 85 live stream sessions, and more than 2,500 poster presentations and poster discussion sessions, clinical science symposia, education sessions, etc. Topics span the spectrum of hematology/oncology, including new drugs; treatment advances in prostate, breast, lung, and blood cancers, as well as screening, prevention, access to care, immunotherapy, and precision medicine.

The theme for ASCO 2022 was "Advancing Equitable Cancer Care Through Innovation" with more than 200 sessions offering resources and research on this topic. Inequitable access to cancer care and management, compounded by the unprecedented effects of global COVID-19 impact, presents a daunting, global challenge for both governments and stakeholders —as well as opportunities for innovative solutions. Presentations at the meeting sought to address inequitable access issues and develop equitable cancer strategies through innovation. "The COVID-19 pandemic has laid bare the inequities that exist in our global health care systems," noted Everett E. Vokes, MD, FASCO, 2021-2022 ASCO President, in his program communication to attendees. "It has also provided us an opportunity to reinvent cancer care delivery and test promising approaches to a more equitable future in health care. In oncology, innovation can be seen around every corner. Opportunities range from new therapies and smarter use of existing treatments and offering patients broader and easier access through telemedicine, to rethinking clinical trial eligibility and much more" he concluded. ASCO'22 provided the perfect backdrop to dive into strategies we can collectively drive patient-centric oncology research and drug development. Many important discussions on how to help address inequities in cancer care have drawn leaders in the field to seek solutions quickly.

The science of immunotherapy has come a long way in the last decade since the approval of the first checkpoint immunotherapy in 2011, as the meeting presentations highlighted that tremendous scientific advances are unlocking more of immunotherapy's potential each passing year. While the immuno-oncology combinations continued their impressions, newly developed strategies viz. HIF2a inhibitor and GAS6-AXL inhibitor also showcased their promising outcomes in renal cell carcinoma. More than 160 abstracts and talks focused on therapies for renal cell carcinoma were delivered during poster and oral sessions. Following high-profile clinical

trials have delivered some interesting and impactful data at the meeting: EVEREST (everolimus, SWOG S0931, NCT01120249; abstract LBA4500), CheckMate 9ER (nivolumab plus cabozantinib; NCT03141177; abstract 4501), CheckMate 214 (nivolumab plus ipilimumab; NCT02231749; abstract 4502), CALYPSO (durvalumab plus savolitinib; NCT02819596; abstract LBA4503), LITESPARK-001 (belzutifan; NCT02974738; abstract 4509), AVB-S6-500 (batiraxcept; NCT04300140; abstract 4511), KEYNOTE-564 (pembrolizumab; NCT03142334; abstract 4512), KEYNOTE-426 (Pembrolizumab plus axitinib; NCT02853331; abstract 4513), TiNivo-2 (tivozanib plus nivolumab; NCT04987203; abstract TPS4605) and CLEAR (lenvatinib plus pembrolizumab; NCT02811861; abstract 4514) etc. A full list of abstracts that I have picked is available in the special ASCO22 section in detail. These studies presented at ASCO22 demonstrated statistically significant and clinically meaningful benefits or deeper responses over their respective comparator drug as well as made tremendous strides in the renal cancer space. Altogether, ASCO 2022 offered impactful novel data that will continue to transform clinical practice and cancer drug development for a variety of cancers. Most importantly, the implementation of the scientific advances we learned at ASCO 2022 will improve the quality of life and length of our cancer patients.

In this issue, an exclusive roundtable discussion that I chaired, provide key perspectives on the efficacy and tolerability of tivozanib plus nivolumab combination therapy. Following distinguished kidney cancer investigators joined the conversation: Dr. Robert Motzer, Dr. Toni Choueiri, and Dr. Laurence Albiges discuss the full potential of tivozanib plus ICI combinations in a rapidly changing treatment paradigm of renal carcinoma. A manuscript by Paquin et al provides the framework for comprehensive research on the demographic, increased risk factor and genetic pathway differences between papillary renal cell carcinoma type 1 and type 2 tumors. In another review work, Zhang *et al* outlined the current state of using engineered T cell therapy especially CAR-T cell therapy for the treatment of patients with advanced RCC and also described the toxicity and challenges and CAR-T cell therapy. Also, Dr. Yasser Ged and Dr. Nirmish Singla provided meeting coverage for our featured ASCO22 section in this issue.

Sincerely,
Robert A Figlin, MD

Kidney Cancer Research Highlights from ASCO 2022 Annual Meeting

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ABSTRACT

The 2022 American Society of Clinical Oncology (ASCO) annual meeting was held June 3-7, 2022, in Chicago, Illinois. This hybrid meeting gathered international cancer experts across multidisciplinary specialties and was held both virtually and in-person. Here, we highlight key kidney cancer research updates presented at the meeting. Slides from the meeting's presentations are available on the ASCO meeting library website.

Adjuvant Therapy Updates

Locally advanced kidney cancer has traditionally been managed surgically alone1. However, approximately 30% of patients develop recurrent metastatic disease after surgical resection despite curative intent, and the optimal approaches to integrate surgery with systemic therapies in a neoadjuvant or adjuvant approach to reduce the risk of recurrence has been an area of active research.[2] The U.S. Food and Drug Administration (FDA) has approved two adjuvant therapies in renal cell carcinoma (RCC) thus far, including sunitinib in 2017 and most recently pembrolizumab in 2021.[3,4] The use of adjuvant sunitinib has been limited despite FDA approval because of its increased toxicity and lack of overall survival benefit.[5] Pembrolizumab is the first approved adjuvant immunotherapy for clear cell RCC patients with intermediate-high or high risk of recurrence after nephrectomy based on the phase 3 double-blind, multicenter, randomized KEYNOTE-564 study (NCT03142334).[4]

Updated analysis from KEYNOTE-564 was presented at the meeting evaluating the time to first

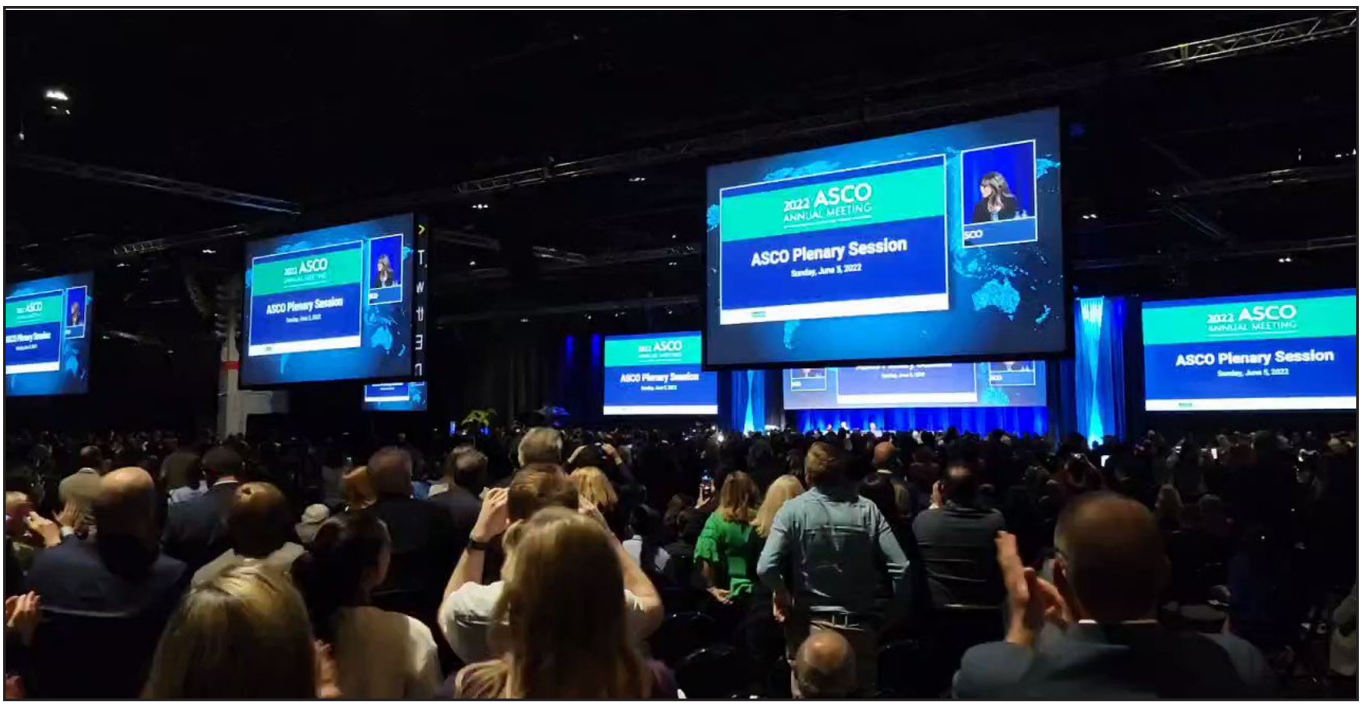

Figure 1. Oral presentation at the 2022 American Society of Clinical Oncology (ASCO22).

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subsequent drug treatment or any-cause death (TFST) and time from randomization to progression on next line of therapy or any-cause death (PFS2) after treatment with pembrolizumab or placebo in the study.[6] Overall 67 patients (13.5%) in the pembrolizumab group and 99 patients (19.9%) in the placebo group received ≥1 line of subsequent anticancer drug therapy. A total of 108 PFS2 events were observed, 40 (8.1%; 12 death events and 28 progression events) in the pembrolizumab group and 68 (13.7%; 14 death events and 54 progression events) in the placebo group. PFS2 was also delayed with pembrolizumab compared with placebo (HR, 0.57; 95% CI, 0.39-0.85; medians not reached). The authors concluded that treatment with adjuvant pembrolizumab reduced risk for TFST and PFS2 compared with placebo. LITESPARK-022 (NCT05239728) is the next iteration of the KEYNOTE-564 study which is a phase 3 study designed to compare the efficacy and safety of belzutifan plus pembrolizumab with that of placebo plus pembrolizumab as adjuvant treatment for clear cell RCC after nephrectomy, and this study is currently actively enrolling.

Multiple adjuvant and neoadjuvant vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKIs) studies in RCC were reported previously.[5] To better understand the role of mammalian target of rapamycin (mTOR) inhibitors in the adjuvant setting, the *Southwest Oncology Group* (SWOG) launched the phase 3 study of everolimus in treating patients with kidney cancer who have undergone surgery (EVEREST) study (NCT01120249), which was reported at ASCO 2022.[7] Individuals with clear or non-clear cell RCC immediately post-nephrectomy whose tumors show intermediate high-risk to high risk features were included in the study. Between 4/2011 and 9/2016, 1545 patients were randomized to either 12 months of adjuvant everolimus (n = 775) or placebo (n = 770) including 83% with clear cell RCC and 17% with non-clear cell RCC. With a median follow-up of 76 months, the recurrence free survival was improved with everolimus compared to placebo (HR 0.85, 95% CI, 0.72 – 1.00; P (one sided) = 0.0246), narrowly missing the pre-specified, one-sided significance level of 0.022 which accounted for interim analyses, and the effect of everolimus was especially pronounced in patients with very high risk disease. Adverse events were consistent with safety profiles of everolimus, although there was a high discontinuation rate of everolimus in this population (47%).

First Line Metastatic Kidney Cancer Treatment Updates

The first line treatment landscape of metastatic RCC has rapidly evolved in recent years.[8] New updates on some of the registration first line metastatic RCC studies were

Figure 2. ASCO poster session

presented during the meeting.

The CheckMate 9ER trial is a phase 3 trial which compared nivolumab plus cabozantinib versus sunitinib in patients with untreated advanced clear cell RCC and demonstrated superior overall survival (OS), progression free survival (PFS) and objective responses of the nivolumab plus cabozantinib combination9. Updated analysis from the depth of response was presented at ASCO 2022.[10] Patients' responses were classified as complete response (CR) or partial response (PR) subdivided by a tumor reduction of ≥80%–<100% (PR1), ≥60%–<80% (PR2), or ≥30%–<60% (PR3). Overall, greater proportions of patients receiving nivolumab plus cabozantinib had deeper responses versus sunitinib (CR, PR1, PR2), and deeper responses with nivolumab plus cabozantinib were associated with improved 12-months PFS rate versus sunitinib for CR (94.9% vs 82.4%), PR1 (81.3% vs 37.5%), and PR2 (72.1% vs 53.2%).

Updates on health-related quality of life (HRQoL) from the CheckMate-214 phase 3 clinical trial, which compared nivolumab plus ipilimumab versus sunitinib in patients with untreated advanced clear cell RCC, were also presented during the meeting.[11,12] As previously reported, nivolumab plus ipilimumab was associated with improved HRQoL compared to sunitinib. At ASCO 2022, the investigators reported on a post-hoc analysis on the prognostic ability of HRQoL to inform the risk of disease progression or death. The results of the analysis showed that higher (better) baseline scores were associated with significantly reduced risk of death (HR [95% CI] for FKSI-19 Total Score and DRS score was 0.83 [0.80-0.87] and 0.80 [0.76-0.84], respectively). Furthermore, patients with improved/stable HRQoL had a 52% reduction in risk of death compared to patients who had worsened (HR 0.48 [95% CI: 0.39-0.59]).

Post-hoc exploratory analyses of PFS2 were conducted in the KEYNOTE 426 (phase 3 study comparing pembrolizuamb plus axitinib versus sunitinib in patients with untreated advanced clear cell RCC)[13,14] and the CLEAR (phase 3 study comparing pembrolizumab plus lenvatinib versus sunitinib in patients with untreated advanced clear cell RCC)[15,16] studies. Both analyses demonstrated prolongation of PFS2 in patients who received pembrolizumab plus axitinib in KEYNOTE 426 study and pembrolizumab plus lenvatinib in the CLEAR study.

Novel Kidney Cancer Therapies Highlights

Several exciting data were presented on novel therapies in RCC. Batiraxcept is a GAS6-AXL inhibitor, a pathway which is overexpressed in clear cell RCC.[17] Interim results of a phase 1b study of batiraxcept plus cabozantinib 60 mg daily were presented at the meeting.[18] A total of 26 patients were enrolled in the phase 1b study so far, and the recommended phase 2 dose of batiraxcept was identified as 15 mg/kg every 2 weeks. Encouraging early anti-tumor efficacy results of the combination were observed with an objective response rate of 67% and 6 months PFS of 79%.

Hypoxia-inducible factor 2α (HIF-2α) is a key oncogenic driver in RCC.[19] Belzutifan is a HIF-2α inhibitor which was recently approved by the FDA for patients with VHL syndrome and currently under investigation in sporadic RCC.[20,21] LITESPARK-001 is a phase 1 study which was designed to evaluate belzutifan in heavily pretreated RCC and showed durable antitumor activity and an acceptable safety profile.[21] An update of the clear cell RCC cohort in the study with more than 3 years of total follow-up was presented at the meeting.[22] With extended follow-up of 41 months, the objective response rate was 25% with 80% disease control rate and median PFS of 14.5 months (95% CI, 7.3-22.1). Belzutifan monotherapy continued to show a high rate of disease control and durable responses in this heavily pre-treated population.

The CALYPSO study results were presented at the meeting as well.[23] This is a randomized phase II study of durvalumab alone or with savolitinib or tremelimumab in previously treated advanced clear cell RCC. Savolitinib is a potent MET inhibitor with established dosing and activity in papillary RCC; however, its role in clear cell RCC is unclear.[24] Between 2017 and 2021, 139 patients were randomized across the treatment arms. Savolitinib alone and in combination with duravlumab was associated with modest confirmed response rates (5% and 13%, respectively) compared to confirmed response rates of 10% for durvalumab and 28% for durvalumab plus tremelimumab. All regimens studied in the trial appeared to be safe and tolerable.

SUMMARY

In summary, ASCO 2022 was enriched with novel results and concepts continually expanding the field of kidney cancer research. Indeed, the data presented are both hypothesis-generating and practice-informing. Herein, we highlighted a snapshot of some of the oral presentations from the meeting in the kidney cancer space; however, there are considerably more exciting abstract and poster presentations that are available for review on the meeting's website. In addition to the scientific content, ASCO 2022 also provided ample opportunities for networking and collaborations among the academic kidney cancer community, with the first in-person option since the beginning of the COVID-19 pandemic.

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These recommended abstracts from ASCO22 Annual meeting have been selected by Robert A. Figlin, MD, Editor-in-Chief of the Kidney Cancer Journal. The chosen abstracts provided here highlight some of the most important trends in ongoing trials and reflect the foremost research and strategies from latest clinical trials that impact the current standard of care in renal cancer.

ABSTRACT LBA4500: EVEREST: Everolimus for renal cancer ensuing surgical therapy—A phase III study (SWOG S0931, NCT01120249). *Ryan CW et al.*

BACKGROUND: Patients (pts) who undergo resection of renal cell carcinoma (RCC) with curative intent remain at risk for disease relapse. We conducted a phase III, double-blind, placebo (PB)-controlled, intergroup study to determine the effect of adjuvant treatment with the mTOR inhibitor everolimus (EVE) on recurrence-free survival (RFS).

METHODS: Pts with treatment-naïve, non-metastatic, fully-resected RCC at intermediate high- (pT1 G3-4 No to pT3a G1-2 No) or very high-risk (pT3a G3-4 to pT4 G-any or N+) for recurrence were randomized 1:1 to EVE 10 mg PO daily x 54 weeks or PB within 12 weeks of radical or partial nephrectomy. Randomization was stratified by risk group, histology (clear vs. non-clear cell), and performance status (0 vs. 1). RFS was the primary end point; secondary endpoints included overall survival (OS) and adverse events (AEs). The study was designed to detect an 18% reduction in the risk of RFS with EVE compared to PB, corresponding to an improvement of median RFS from 6.75 (based on E2805 ASSURE) to 8.23 years. Final analysis, using a stratified logrank test, was to occur after 804 total events or by 3/2022, whichever occurred first.

RESULTS: Between 4/2011 and 9/2016, 1545 pts were randomized to EVE (n = 775) or PB (n = 770). Overall pt characteristics included: intermediate high-/very high-risk 45%/55%; clear cell/non-clear cell 83%/17%. The DSMC recommended study continuation after each of 4 pre-specified interim analyses. 556 DFS events among 1499 eligible pts occurred by the time of final study analysis on 2/23/2022. The median follow-up was 76 months. RFS was improved with EVE vs. PB (HR 0.85, 95% CI, 0.72 – 1.00; P1-sided= 0.0246), narrowly missing the pre-specified, one-sided significance level of 0.022 which accounted for interim analyses. Median RFS was not reached; the 6-year RFS estimate was 64% for EVE and 61% for PB. RFS improvement with EVE vs. PB was observed in the very high-risk group (HR 0.79, 95% 0.65-0.97; P1-sided= 0.011) but not in the intermediate high-risk group (HR 0.99, 95% CI 0.73-1.35, P1-sided= 0.48) (P for interaction = 0.22). With 290 deaths, OS was similar between arms (HR 0.90, 95% CI, 0.71 – 1.13; P1-sided= 0.178). Fewer pts completed all 54 weeks of study treatment in the EVE group (45% v 69%). In the EVE group, 37% withdrew due to AEs (vs 5% in PB). Grade 3-4 AEs occurred in 46% of pts treated with EVE and 11% with PB. The most common grade 3-4 AEs were mucositis (14% v 0%), hypertriglyceridemia (11% vs. 2%), and hyperglycemia (5% vs. 0%).

CONCLUSIONS: Adjuvant EVE improved RFS in RCC pts after nephrectomy, but the nominal significance level was narrowly missed. The RFS improvement was seen despite a high rate of early treatment discontinuation. A 21% improvement in RFS with EVE was observed in pts with very high-risk disease, a group for whom adjuvant therapy may be most relevant. Clinical trial information: NCT01120249.

ABSTRACT 4501- Association between depth of response (DepOR) and clinical outcomes: Exploratory analysis in patients with previously untreated advanced renal cell carcinoma (aRCC) in CheckMate 9ER. *Suárez C et al.*

BACKGROUND: Among patients (pts) with untreated aRCC in the CheckMate 9ER trial, superior progression-free survival (PFS; hazard ratio [HR], 0.56) and overall survival (OS; HR, 0.70) were maintained, and objective response and complete response (CR) rates were doubled for nivolumab plus cabozantinib (N+C) vs sunitinib (SUN) with extended 25.4 mo minimum (32.9 mo median) follow-up. This exploratory analysis evaluated the relationship between DepOR and clinical outcomes in CheckMate 9ER.

METHODS: Eligible pts received N (240 mg) every 2 weeks plus C (40 mg) once daily or SUN (50 mg once daily; 4 weeks of each 6-week cycle). In this analysis, DepOR subgroups were based on best overall response (blinded independent central review [BICR] per RECIST v1.1) and best tumor reduction threshold, as follows: CR; partial response subdivided by a tumor reduction of ≥80%–<100% (PR1); ≥60%–<80% (PR2); or ≥30%–<60% (PR3); stable disease (SD); and progressive disease (PD). PFS (per BICR) and OS by DepOR subgroups were analyzed after a 6-mo post-randomization landmark. Treatment-related adverse events (TRAEs) were assessed in DepOR subgroups.

RESULTS: Of 323 and 328 pts randomized to N+C or SUN, 236 and 157 pts were progression-free and alive and 293 and 253 pts were alive at the 6-mo landmark and were categorized by DepOR subgroup. Overall, greater proportions of pts receiving N+C had deeper responses vs SUN (CR, PR1, PR2; Table). Deeper responses with N+C were associated with improved 12-mo PFS rate vs SUN for CR (94.9% vs 82.4%), PR1 (81.3% vs 37.5%), and PR2 (72.1% vs 53.2%). In both arms, an increasingly deeper response led to better OS outcome; yet OS rates and medians were comparable between arms for CR, PR1, PR2, and PR3 (Table). No meaningful patterns for overall TRAE rates by DepOR subgroup were identified in either arm.

CONCLUSIONS: In CheckMate 9ER, more pts receiving N+C achieved deeper responses vs SUN. Deeper responses were generally associated with improved PFS and OS. Clinical trial information: NCT03141177.CONCLUSIONS: At 30 months of follow-up, adjuvant pembrolizumab continued to demonstrate a consistent and clinically meaningful improvement in DFS vs placebo in pts with RCC at high risk of recurrence. No new safety signals were observed with pembrolizumab in the adjuvant setting. Clinical trial information: NCT03142334.

	N+C						SUN					
	PFS[a] N = 236			OS[a] N = 293			PFS[a] N = 157			OS[a] N = 253		
DepOR	n	12 morate, %[b,c]	Median (95% CI), mo	n	18 morate, %[c]	Median (95% CI), mo	n	12 morate, %[b,c]	Median (95% CI), mo	n	18 morate, %[c]	Median (95% CI), mo
CR	40	94.9	NR (26.0–NE)	40	97.5	NR (NE–NE)	17	82.4	NR (15.9–NE)	17	100	NR (30.2–NE)
PR1	32	81.3	24.3 (17.0–NE)	33	97.0	NR (28.9–NE)	8	37.5	6.5 (0.9–NE)	9	100	NR (19.7–NE)
PR2	37	72.1	24.8 (13.4–NE)	38	83.5	NR (31.7–NE)	18	53.2	12.0 (7.9–NE)	18	88.2	NR (NE–NE)
PR3	62	46.7	10.4 (5.5–14.0)	69	78.3	NR (30.5–NE)	45	57.0	15.9 (6.8–21.6)	49	75.3	NR (25.1–NE)
SD	65	33.5	6.3 (4.0–10.6)	99	59.6	28.7 (17.8–NE)	69	22.6	5.2 (3.7–6.7)	123	68.0	NR (24.6–NE)
PD	0	–	–	14	35.7	10.1 (4.8–25.1)	0	–	–	37	39.1	13.7 (6.4–18.6)

[a]At the 6 mo landmark. [b]12 mo PFS rate is presented due to low patient numbers at later timepoints. [c]12 mo and 18 mo rates are from 6 mo landmark.CI, confidence interval; NE, not evaluable; NR, not reached.

ABSTRACT 4502: The relationship between health-related quality of life (HRQoL) and clinical outcomes in patients with advanced renal cell carcinoma (aRCC) in CheckMate (CM) 214. *Cella D et al.*

BACKGROUND: In CM 214, when compared to sunitinib (S), nivolumab plus ipilimumab (N+I) was associated with both clinical benefit and improved HRQoL as first-line treatment for intermediate/poor (I/P)-risk patients (pts). This analysis investigates the direct association between HRQoL and clinical outcomes in aRCC pts.

METHODS: I/P-risk population included 425 and 422 pts in the N+I and S arms, respectively. HRQoL was assessed using the FKSI-19 (Total Score and Disease Related Symptoms [DRS]). Three separate analyses (A, B, and C) were conducted. A: Changes in individual item scores from baseline to last assessment prior to progression were descriptively assessed. B: For each FKSI-19 score, multivariable Cox regression, adjusted for treatment and stratification factors, was used to evaluate the prognostic significance of baseline and time-dependent HRQoL scores in separate models. Hazard ratios (HR) were calculated based on the risk of death per improvement in HRQoL scores, defined using the clinically meaningful change threshold (5 points for FKSI-19 Total and 3 points for DRS). Pts with overall survival (OS) events were censored if their survival event was not within 12 weeks of the last available HRQoL assessment. C: The association between HRQoL change status (ie, improvement or maintenance vs. worsening from baseline in the FKSI-19 Total Score), irrespective of treatment arm, and OS was further assessed using a landmark analysis at the month 6 (mo-6) landmark. Additional landmark time points were explored in sensitivity analysis.

RESULTS: Items related to fatigue and perceived bother of the side-effects of treatment had the largest percentage of pts worsening prior to progression. In both baseline and time-dependent HRQoL analyses, OS was independently associated with both HRQoL measures. Higher (better) baseline scores were associated with significantly reduced risk of death (HR [95% CI] for FKSI-19 Total Score and DRS was 0.83 [0.80-0.87] and 0.80 [0.76-0.84], respectively). Every 5-point increase (improvement) in FKSI-19 Total Score and 3-point increase in DRS was associated with a 31% decreased risk of death (P< 0.01). At mo-6, 301 pts showed improvement or maintenance in HRQoL. Pts with improved/stable HRQoL had a 52% reduction in risk of death compared to pts who had worsened (HR 0.48 [95% CI: 0.39-0.59]).

CONCLUSIONS: Results demonstrate there is an association between HRQoL and clinical outcomes in CM 214. Baseline HRQoL scores are a potential predictor for survival in aRCC, and HRQoL changes are informative for pts' expected survival. HRQoL change status at mo-6 was significantly and positively associated with subsequent survival. Thus, patient-reported outcomes may be useful for both describing pt experience in clinical trials and providing valuable clinical insights during routine practice. Clinical trial information: NCT02231749.

ABSTRACT LBA4503 - CALYPSO: A three-arm randomized phase II study of durvalumab alone or with savolitinib or tremelimumab in previously treated advanced clear cell renal cancer. *Powles T et al.*

BACKGROUND: New drug combinations are required in advanced clear cell renal cancer (RCC). These potentially include MET inhibition with savolitinib (S) or CTLA-4 inhibition with tremelimumab (T). In this study these agents were given alone or in combination with the PD-L1 inhibitor durvalumab (D).

METHODS: A multinational open-label randomised phase II study assigning patients to one of D, S, DT or DS was performed. Patients with RCC, who had previously received VEGF targeted therapy but not immune checkpoint inhibitors or MET inhibitors were included. Confirmed response rate (cRR) was the primary endpoint. A response rate of at least 50% was required for further exploration. The S arm was closed early due to a lack of efficacy. DNA alterations were measured using Foundation One and PD-L1 analysis was performed with SP263. This abstract details the pre-planned 12-month interim analyses after the cohort completed randomisation.

RESULTS: Between 2017 and 2021, 139 patients were randomised (D N=39, S N=22, DT N=39, DS N=39). The median age was 62 years (range: 28 – 85). cRRs for the 4 arms were D=10%, S=5%, DT=28%, DS=13%, which did not meet the primary objective. cRRs in the MET-driven patients (N=17) were D=0% (0/7), S=0% (0/2), DT=50% (1/2), DS=17% (1/6). cRRs in PD-L1+ves for DT and D were 14% (1/7) and 33% (2/6) respectively. 12-month progression-free survival (PFS) rates were D=26% (80% confidence interval [CI]: 17% - 36%), S=21% (80% CI: 10% - 35%), DT=33% (80% CI: 24% - 43%), DS=17% (80% CI: 10% - 26%). Median overall survival for D=26.1 (80% CI: 16.2 – 32.0) months, S=23.1 (80% CI: 20.6 – 29.7) months, DT=21.9 (80% CI: 16.3 – 31.5) months, DS=16.1 (80% CI: 10.3 – 18.8) months. There was 1 treatment related death in the DT arm. Of the 136 patients who received treatment, grade 3 or more treatment related adverse events occurred in D=10% (4/39), S=26% (5/19), DT=23% (9/39), DS=23% (9/39).

CONCLUSIONS: This randomised phase II study did not demonstrate significant efficacy for S alone or in combination with D in RCC. The addition of T to D did not demonstrate clearly superior efficacy to D in this setting. Clinical trial information: NCT02819596.

ABSTRACT 4509: Phase 1 LITESPARK-001 (MK-6482-001) study of belzutifan in advanced solid tumors: Update of the clear cell renal cell carcinoma (ccRCC) cohort with more than 3 years of total follow-up. *Jonasch E et al.*

BACKGROUND: Hypoxia-inducible factor 2α (HIF-2α) is a key oncogenic driver in RCC. Antitumor activity of the HIF-2α inhibitor belzutifan has been observed in RCC and is approved for treatment in patients (pts) with VHL disease who require therapy for associated RCC, CNS hemangioblastomas, or pNETs not requiring immediate surgery. Previous data from the phase 1 LITESPARK-001 trial (NCT02974738) designed to evaluate belzutifan in heavily pretreated RCC showed durable antitumor activity and an acceptable safety profile. After more than 3 years of follow-up for pts with ccRCC still receiving treatment, updated data are presented.

METHODS: Pts enrolled in the ccRCC cohort were previously treated with ≥1 therapy, had RECIST-measurable disease, ECOG PS score of 0 or 1, adequate organ function, and life expectancy of ≥6 months. Pts received oral belzutifan 120 mg once daily. The primary end point was safety. Secondary end points were ORR, DCR (CR + PR + SD), PFS, and DOR per RECIST v1.1 by investigator. The data cutoff date was July 15, 2021.

RESULTS: Of 55 pts enrolled in the ccRCC cohort, 9 (16%) remain on treatment as of the data cutoff date of July 15, 2021; the primary reason for discontinuation was progressive disease (n = 34; 62%). Pts received a median of 3 prior therapies (range, 1-9); 39 (71%) received prior VEGF and immunotherapy. Pts were followed while on treatment and for 30 days after the last dose for a median of 41.2 months (range, 38.2-47.7). Twenty-two pts (40%) experienced grade 3 TRAEs. The most common (≥10%) grade 3 TRAEs were anemia (n = 13; 24%) and hypoxia (n = 7; 13%). There were no grade 4 or 5 TRAEs. ORR was 25%, with 1 confirmed CR (2%) and 13 PRs (24%); DCR was 80%. Median DOR was not reached (range, 3.1+ to 37.9+ months); 8 of 14 responding pts (57%) remain in response as of the data cutoff date. Per IMDC risk, 4 of 13 pts with favorable risk achieved response (ORR = 31%; all PRs) and 10 of 42 pts with intermediate/poor risk achieved response (ORR = 24%; 1 CR, 9 PRs). DCR was 92% for pts with favorable risk and 76% for pts with intermediate/poor risk. For pts who received prior VEGF and immunotherapy, 8 of 39 pts achieved response (ORR = 21%; 1 CR; 7 PR); DCR was 74%. For the 16 pts who did not receive prior VEGF/immunotherapy, 6 achieved response (ORR = 38%; all PRs); DCR was 94%. Median PFS for the total cohort was 14.5 months (95% CI, 7.3-22.1); PFS rate at 156 weeks (36 months) was 34%.

CONCLUSIONS: As seen after a median follow-up of > 3 years for pts still receiving treatment, belzutifan monotherapy continued to show a high rate of disease control and durable

responses in previously treated pts with advanced ccRCC. Belzutifan exhibited a favorable safety profile, and no new safety signals were observed. In several phase 3 studies, belzutifan is being evaluated as monotherapy and combined therapy for ccRCC. Clinical trial information: NCT02974738.

ABSTRACT 4511: A phase 1b/2 study of batiraxcept (AVB-S6-500) in combination with cabozantinib in patients with advanced or metastatic clear cell renal cell (ccRCC) carcinoma who have received front-line treatment (NCT04300140).

Shah N et al.

BACKGROUND: AXL is up-regulated by hypoxia-inducible factor-1 signaling in both VHL-deficient and hypoxic tumor cells and plays a critical role in the metastatic phenotype of ccRCC. Batiraxcept is a recombinant fusion protein containing an extracellular region of human AXL combined with the human immunoglobulin G1 heavy chain (Fc), demonstrating highly potent, specific AXL inhibition.

METHODS: Batiraxcept at doses of 15 and 20 mg/kg, plus cabozantinib 60 mg daily, was evaluated using a 3+3 dose escalation study design. The primary objective was safety; secondary and exploratory objectives included identification of the recommended phase 2 dose (RP2D), overall response rate (ORR), and duration of response (DOR). Correlation of serum soluble AXL (sAXL)/GAS6 with ORR was evaluated. Key eligibility criteria include previously treated (2L+) ccRCC patients; prior treatment with cabozantanib was not allowed. sAXL/GAS6 was evaluated at baseline.

RESULTS: Data as of 4-February-2022, Phase 1b enrolled 26 patients, 16 patients treated with 15 mg/kg and 10 patients with 20 mg/kg dose of batiraxcept. Baseline characteristics: median age 60 (40-81); male 22 (85%); median prior line of therapy 1 (1-5); IMDC risk group of favorable 6 (23%); prior VEGF inhibitor 15 (58%); 100% with prior immunotherapy. At median follow up of 4.9 months, 92% (n=24) patients remained on the study. No dose limiting toxicities were observed at either 15 mg/kg or 20 mg/kg dose. Batiraxcept and cabozantinib related adverse events (AEs) occurred in 17 subjects (65%). Most common related AEs include decreased appetite 31% (n=8), diarrhea and fatigue 23% (n=6). Grade 3 related AEs occurred in 4 patients (15%) including diarrhea, thromboembolism, hypertension, small bowel obstruction, and thrombocytopenia (n=1, 4% each) being most common. No grade 4 or 5 related AEs were observed. The ORR was 46% (n=12, partial response [PR]; Table). No patients had primary progressive disease. Among the patients who had a baseline sAXL/GAS6 ratio of ≥ 2.3, the ORR was 67% (12/18). Regardless of baseline sAXL/GAS6 ratio, 3-month DOR was 100%; and 6-month progression free survival was 79%. Batiraxcept PK levels were similar across both doses and GAS6 levels suppressed through the dosing period.

CONCLUSIONS: Batiraxcept plus cabozantinib is well tolerated. The RP2D of batiraxcept was identified as 15 mg/kg. Early efficacy signals were observed including 100% DOR at 3 months. Baseline sAXL/GAS6 may serve as a potential biomarker to enrich the population. Clinical trial information: NCT04300140.

	Entire cohort	Batiraxcept 15 mg/kg cohort	Batiraxcept 20 mg/kg cohort
	N=26 (%)	N=16 (%)	N=10 (%)
ORR (confirmed + unconfirmed)	12 PR (46)	9 PR (56)	3 PR (30)
DOR (3-month)	26 (100)	26 (100)	Not reached
Any grade-related AEs	17 (65)	11 (69)	6 (60)
Grade ≥3 related AEs	4 (15)	2 (13)	2 (20)

ABSTRACT 4512: Adjuvant pembrolizumab for postnephrectomy renal cell carcinoma (RCC): Expanded efficacy analyses from KEYNOTE-564.

Choueiri TK et al.

RESULTS: Of 994 patients, 496 were randomly assigned to receive pembrolizumab and 498 to placebo. Median time from randomization to the data cutoff date (June 14, 2021) was 30.1 months (range, 20.8-47.5). Overall, 67 patients (13.5%) in the pembrolizumab group and 99 patients (19.9%) in the placebo group received ≥1 line of subsequent anticancer drug therapy. Of patients who received ≥1 line of subsequent drug therapy, most in the pembrolizumab group (90.0% [60/67]) and placebo group (85.9% [85/99]) received a VEGF/VEGFR-targeted therapy; 23.9% of patients (16/67) in the pembrolizumab group and 59.6% (59/99) in the placebo group received an anti–PD-1/PD-L1 agent. Seventy-seven TFST events were observed in the pembrolizumab group; 110, in the placebo group. Compared with placebo, adjuvant treatment with pembrolizumab delayed TFST (HR, 0.67; 95% CI, 0.50-0.90; medians not reached). A total of 108 PFS2 events were observed, 40 (8.1%; 12 death events and 28 progression events) in the pembrolizumab group and 68 (13.7%; 14 death events and 54 progression events) in the placebo group. PFS2 was also delayed with pembrolizumab compared with placebo (HR, 0.57; 95% CI, 0.39-0.85; medians not reached).

CONCLUSIONS: Treatment with adjuvant pembrolizumab reduced risk for TFST and PFS2 compared with placebo. Results of this exploratory analyses suggest sustained clinical benefit of adjuvant pembrolizumab and support the use of adjuvant pembrolizumab after nephrectomy as standard of care for patients with localized RCC at increased risk for recurrence. Clinical trial information: NCT03142334.

ABSTRACT 4513: Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Analysis of progression after first subsequent therapy in KEYNOTE-426.

Powles T et al.

BACKGROUND: The randomized, open-label, phase 3 KEYNOTE-426 study (NCT02853331) met its primary and key secondary end points of improved OS, PFS, and ORR with pembro + axi versus sunitinib as first-line treatment for patients with advanced ccRCC. Extended follow-up (42.8-mo median follow-up) continued to show the superior efficacy of pembro + axi versus sunitinib in this patient population. We describe the results of PFS2 for all randomly assigned patients and across IMDC risk categories.

METHODS: Treatment-naive patients with advanced ccRCC, Karnofsky Performance Status Scale score ≥70% and measurable disease per RECIST v1.1 were randomly assigned 1:1 to receive pembro 200 mg IV every 3 weeks for up to 35 doses (~ 2 y) + axi 5 mg orally twice daily or sunitinib 50 mg orally once daily on a 4-wk on/2-wk off schedule. The end point of this exploratory analysis was PFS2, defined as time from randomization to progression after first subsequent therapy or any-cause death. The Kaplan-Meier method was used to estimate PFS2 and hazard ratios were estimated using a Cox regression model.

RESULTS: Of 861 patients, 432 were assigned to receive pembro + axi; 429, to sunitinib. Median time from randomization to the database cutoff date (January 11, 2021) was 42.8 mo (range, 35.6-50.6). Overall, 47.2% of patients (204/432) in the pembro + axi arm and 65.5% of patients (281/429) in the sunitinib arm received ≥1 line of subsequent anticancer therapy. For patients who received subsequent therapy, anti–PD-1/PD-L1 agents were the first subsequent treatment for 11.3% of patients (23/204) in the pembro + axi arm and 54.8% of patients (154/281) in the sunitinib arm. In the pembro + axi arm, 82.8% of patients (169/204) received a VEGF/VEGFR inhibitor as first subsequent therapy, as did 43.4% (122/281) in the sunitinib arm. PFS2 results are displayed in the Table.

CONCLUSIONS: In this exploratory analysis, PFS2 was longer for patients randomized to pembro + axi compared to sunitinib. Results were consistent across IMDC risk groups. These data support use of pembro + axi for the first-line treatment of patients with advanced ccRCC. Clinical trial information: NCT02853331.

	ITT		IMDC favorable risk		IMDC intermediate/poor risk	
	Pembro + axi N = 432	Sunitinib N = 429	Pembro + axi n = 138	Sunitinib n = 131	Pembro + axi n = 294	Sunitinib n = 298
Received ≥1 line of subsequent anticancer therapy, n (%)	204 (47.2)	281 (65.5)	64 (46.4)	87 (66.4)	140 (47.6)	194 (65.1)
Median (95% CI) PFS2, mo	40.1 (34.9–43.8)	27.7 (23.1–29.9)	46.0 (43.8 to NR)	39.9 (33.5 to NR)	32.1 (27.9–39.3)	20.1 (15.9–25.1)
HR (95% CI)	0.63 (0.53–0.75)		0.68 (0.47–0.98)		0.62 (0.51–0.76)	

ABSTRACT 4514: Impact of subsequent therapies in patients (pts) with advanced renal cell carcinoma (aRCC) receiving lenvatinib plus pembrolizumab (LEN + PEMBRO) or sunitinib (SUN) in the CLEAR study. *Voss MH et al.*

BACKGROUND: In the open-label, randomized, phase 3 CLEAR study, LEN + PEMBRO had significant PFS (primary endpoint) and OS (key secondary endpoint) benefits over SUN among pts with aRCC in the 1L setting (Motzer 2021, NEJM). We evaluated PFS on next-line therapy ("PFS2") and explored the effect of subsequent anticancer therapy on OS in the LEN + PEMBRO and SUN treatment arms of CLEAR.

METHODS: PFS2 was defined as time from randomization to disease progression (as assessed by investigator) on next-line treatment or death from any cause (whichever occurred first). PFS2 was evaluated in all pts randomly assigned to LEN 20 mg orally QD + PEMBRO 200 mg IV Q3W (n=355) or SUN 50 mg orally QD (4 wks on/2 wks off) (n=357) using Kaplan-Meier estimates, and compared between treatment arms via a log-rank test stratified by geographic region and MSKCC prognostic groups. The HR and corresponding CI were estimated using the Cox regression model with Efron's method for ties, using the same stratification factors. A post hoc analysis accounting for the effect of subsequent anticancer therapy on OS in the LEN + PEMBRO and SUN arms using 2-stage estimation was conducted.

RESULTS: Among pts who received subsequent anticancer therapy in the LEN + PEMBRO (n=117 pts) and SUN (n=206 pts) arms (Table), median time to next-line therapy was 12.2 mos (range 1.45–37.36) and 6.4 mos (range 0.39–28.52), respectively. Median duration of first subsequent anticancer therapy was 5.2 mos (range 0.10–30.23) in the LEN + PEMBRO arm and 6.8 mos (range 0.03–30.72) in the SUN arm. Among all pts, PFS2 was longer with LEN + PEMBRO than with SUN (median not reached vs 28.7 mos; HR, 0.50; 95% CI 0.39–0.65; nominal P<0.0001); PFS2 rates at 24 and 36 mos are in the Table. The unadjusted OS HR for LEN + PEMBRO vs SUN (from the primary analysis [Motzer 2021, NEJM]) was 0.66 (95% CI 0.49–0.88); the HR for OS adjusted for subsequent therapy was 0.54 (bootstrap 95% CI 0.39–0.72).

CONCLUSION: LEN + PEMBRO had a statistically significant and clinically meaningful benefit over SUN in the CLEAR study. These findings remained consistent after accounting for subsequent therapies, as evidenced by prolonged PFS2 and adjusted OS. Results further support LEN + PEMBRO as a standard of care in 1L aRCC. Clinical trial information: NCT02811861.

Parameter	LEN + PEMBRO (n=355)	SUN (n=357)
Pts receiving any subsequent systemic anticancer therapy[a], n (%)	117 (33.0)	206 (57.7)
Anti-VEGF	108 (30.4)	120 (33.6)
PD-1/PD-L1 checkpoint inhibitor	29 (8.2)	154 (43.1)
MTOR Inhibitor	6 (1.7)	17 (4.8)
CTLA-4 Inhibitor	6 (1.7)	18 (5.0)
Other	12 (3.4)	20 (5.6)
PFS2, median (95% CI)	Not reached (NE–NE)	28.7 mos (23.0–NE)
PFS2 HR (95% CI)	0.50 (0.39–0.65)	
Nominal *P* value	<0.0001	
PFS2 rate at 24/36 mos, % (95% CI)	72.7 (67.3, 77.4) / 61.9 (53.7, 69.0)	54.2 (48.4, 59.6) / 42.9 (32.8, 52.5)

[a]Monotherapy or in combination. NE, not estimable.

ABSTRACT TPS4605 TiNivo-2: A phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib in combination with nivolumab to tivozanib monotherapy in subjects with renal cell carcinoma who have progressed following one or two lines of therapy where one line has an immune checkpoint inhibitor. *Choueiri et al.*

BACKGROUND: Tivozanib, a highly selective and potent vascular endothelial growth factor receptor tyrosine kinase inhibitor, has demonstrated single-agent efficacy in advanced renal cell carcinoma (aRCC) along with minimal off-target toxicities and a favorable adverse event (AE) profile (Rini et al Lancet Oncol 2020). Tivozanib was approved by the FDA on March 10, 2021, for the treatment of patients with aRCC who had progressed on 2 or more prior systemic therapies. Tivozanib was combined with Nivolumab in the phase 1b/2 TiNivo trial (NCT03136627), showing an objective response rate of 56%, disease control rate of 96%, median PFS of 18.9 months and a tolerable safety profile (Albiges et al Ann Oncol. 2021).

METHODS: TiNivo-2 (NCT04987203) is a phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib in combination with nivolumab to tivozanib monotherapy in subjects with renal cell carcinoma who have progressed following 1-2 lines of therapy including an immune checkpoint inhibitor. Eligibility criteria include age >18 years, clear cell RCC, ECOG PS 0-1, and disease progression during or following at least 6 weeks of treatment with ICI for RCC. Subjects will be stratified by IMDC risk category and whether ICI was received in most recent line of treatment or not. Subjects will receive tivozanib 1.34 mg orally once daily for 21 consecutive days followed by 7 days off, on the monotherapy arm, and tivozanib 0.89 mg at the same schedule in addition to nivolumab 480mg intravenously every 4 weeks on the combination arm. Study assessments include CT scan or MRI of the chest, abdomen, and pelvis every 8 weeks following Cycle 1 Day 1 for 2 years and every 12 weeks thereafter until disease progression is confirmed by independent radiology review (IRR). The primary objective is to compare the progression-free survival (PFS) of tivozanib in combination with nivolumab to tivozanib. A sample size of 326 subjects, with 191 events will provide at least 80% power to detect a 50% improvement in PFS, 12 mos v. 8 mos, as assessed by an IRR. Secondary endpoints include assessment of overall survival (OS), objective response rate (ORR), and duration of response (DoR), as well as safety and tolerability. Exploratory endpoints are to assess the quality of life (FKSI-DRS and EORTC QLQ C-30) and to investigate the pharmacokinetics of tivozanib. TiNivo-2 is actively enrolling and planning to open at 190 sites in the United States, and the European Union. Clinical trial information: NCT04987203.

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Nivolumab, nivolumab-ipilimumab, and VEGFR-tyrosine kinase inhibitors as first-line treatment for metastatic clear-cell renal cell carcinoma (BIONIKK): a biomarker-driven, open-label, non-comparative, randomised, phase 2 trial. *Vano YA et al. Lancet Oncol. 2022 May;23(5):612-624. doi: 10.1016/S1470-2045(22)00128-0*

FINDINGS: Between June 28, 2017, and July 18, 2019, 303 patients were screened for eligibility, 202 of whom were randomly assigned to treatment (61 to nivolumab, 101 to nivolumab–ipilimumab, 40 to a VEGFR-TKI). In the nivolumab group, two patients were excluded due to a serious adverse event before the first study dose and one patient was excluded from analyses due to incorrect diagnosis. Median follow-up was 18·0 months (IQR 17·6–18·4). In the ccrcc1 group, objective responses were seen in 12 (29%; 95% CI 16–45) of 42 patients with nivolumab and 16 (39%; 24–55) of 41 patients with nivolumab–ipilimumab (odds ratio [OR] 0·63 [95% CI 0·25–1·56]). In the ccrcc4 group, objective responses were seen in seven (44%; 95% CI 20–70) of 16 patients with nivolumab and nine (50% 26–74) of 18 patients with nivolumab–ipilimumab (OR 0·78 [95% CI 0·20–3·01]). In the ccrcc2 group, objective responses were seen in 18 (50%; 95% CI 33–67) of 36 patients with a VEGFR-TKI and 19 (51%; 34–68) of 37 patients with nivolumab–ipilimumab (OR 0·95 [95% CI 0·38–2·37]). In the ccrcc3 group, no objective responses were seen in the four patients who received a VEGFR-TKI, and in one (20%; 95% CI 1–72) of five patients who received nivolumab–ipilimumab. The most common treatment-related grade 3–4 adverse events were hepatic failure and lipase increase (two [3%] of 58 for both) with nivolumab, lipase increase and hepatobiliary disorders (six [6%] of 101 for both) with nivolumab–ipilimumab, and hypertension (six [15%] of 40) with a VEGFR-TKI. Serious treatment-related adverse events occurred in two (3%) patients in the nivolumab group, 38 (38%) in the nivolumab–ipilimumab group, and ten (25%) patients in the VEGFR-TKI group. Three deaths were treatment-related: one due to fulminant hepatitis with nivolumab–ipilimumab, one death from heart failure with sunitinib, and one due to thrombotic microangiopathy with sunitinib.

Health-related quality-of-life outcomes in patients with advanced renal cell carcinoma treated with lenvatinib plus pembrolizumab or everolimus versus sunitinib (CLEAR): a randomised, phase 3 study. *Motzer R et al.* Lancet Oncol. 2022 Jun;23(6):768-780. doi: 10.1016/S1470-2045(22)00212-1.

FINDINGS: Between Oct 13, 2016, and July 24, 2019, 355 patients were randomly assigned to the lenvatinib plus pembrolizumab group, 357 to the lenvatinib plus everolimus group, and 357 to the sunitinib group. Median follow-up for HRQOL analyses was 12·9 months (IQR 5·6-22·3). Because of the promising efficacy and safety results of lenvatinib plus pembrolizumab in the first-line setting, we focus the HRQOL results in this report on that combination versus sunitinib. Mean change from baseline in the lenvatinib plus pembrolizumab group compared with the sunitinib group was -1·75 (SE 0·59) versus -2·19 (0·66) for FKSI-DRS, -5·93 (0·86) versus -6·73 (0·94) for EORTC QLQ-C30 global health status/quality of life (GHS/QOL), and -4·96 (0·85) versus -6·64 (0·94) for the EQ-5D visual analogue scale (VAS). Median time to first deterioration in the lenvatinib plus pembrolizumab group compared with the sunitinib group was 9·14 weeks (95% CI 6·43-12·14) versus 12·14 weeks (9·14-15·29; HR 1·13 [95% CI 0·94-1·35], log-rank p=0·20) for FKSI-DRS, 12·00 weeks (7·29-15·14) versus 9·14 weeks (6·29-12·14; 0·88 [0·74-1·05], log-rank p=0·17) for EORTC QLQ-C30 GHS/QOL, and 9·43 weeks (6·43-12·29) versus 9·14 weeks (6·29-12·00; 0·83 [0·70-0·99], log-rank p=0·041) for the EQ-5D VAS. Median time to definitive deterioration in the lenvatinib plus pembrolizumab group compared with the sunitinib group was 134·14 weeks (95% CI 120·00-not estimable) versus 117·43 weeks (90·14-131·29; HR 0·70 [95% CI 0·53-0·92], log-rank p=0·0081) for FKSI-DRS, 114·29 weeks (102·14-153·29) versus 75·14 weeks (57·29-105·14; 0·60 [0·47-0·77], log-rank p<0·0001) for EORTC QLQ-C30 GHS/QOL, and 124·86 weeks (94·71-134·57) versus 74·86 weeks (54·14-96·00; 0·67 [0·53-0·85], log-rank p=0·0012) for the EQ-5D VAS. No outcomes on any of the instruments significantly favoured sunitinib over lenvatinib plus pembrolizumab. Most HRQOL comparisons of lenvatinib plus everolimus versus sunitinib were similar or favoured sunitinib.

Efficacy and safety of avelumab plus axitinib in elderly patients with advanced renal cell carcinoma: extended follow-up results from JAVELIN Renal 101. *Tomita Y. ESMO Open . 2022 Apr;7(2):100450.*

RESULTS: In the avelumab plus axitinib and sunitinib arms, 271/138/33 and 275/128/41 patients aged <65, ≥65 to <75, and ≥75 years, respectively, were randomized. At data cut-off (January 2019), median PFS [95% confidence interval (CI)] with avelumab plus axitinib versus sunitinib in these respective age groups was 11.6 (8.4-19.4) versus 6.9 (5.6-8.4) months [hazard ratio (HR), 0.63; 95% CI 0.501-0.786], 13.8 (11.1-18.0) versus 11.0 (7.8-16.6) months (HR, 0.88; 95% CI 0.627-1.231), and 13.8 [7.0-not estimable (NE)] versus 9.8 (4.3-NE) months (HR, 0.76; 95% CI 0.378-1.511). Median OS (95% CI) in the respective age groups was not reached (NR) (NE-NE) versus 28.6 (25.5-NE) months (HR, 0.74; 95% CI 0.541-1.022), 30.0 (30.0-NE) versus NR (NE-NE) months (HR, 0.89; 95% CI 0.546-1.467), and 25.3 (19.9-NE) versus NR (19.4-NE) months (HR, 0.87; 95% CI 0.359-2.106). ORR (95% CI) in the respective age groups was 49.4% (43.3% to 55.6%) versus 27.3% (22.1% to 32.9%), 60.9% (52.2% to 69.1%) versus 28.9% (21.2% to 37.6%), and 42.4% (25.5% to 60.8%) versus 22.0% (10.6% to 37.6%). In the avelumab plus axitinib arm, grade ≥3 adverse events (AEs) and immune-related AEs occurred in 76.9%/81.2%/72.7% and 45.5%/48.1%/36.4% in the respective age groups.

CONCLUSIONS: First-line avelumab plus axitinib demonstrated favorable efficacy across age groups, including patients aged ≥75 years. OS data were still immature; follow-up is ongoing. The safety profile was generally consistent across age groups..

Bempegaldesleukin plus nivolumab in first-line renal cell carcinoma: results from the PIVOT-02 study.
Tannir NM, et al. J Immunother Cancer. 2022 Apr;10(4):e004419. doi: 10.1136/jitc-2021-004419.

RESULTS: At a median follow-up of 32.7 months, the ORR was 34.7% (17/49 patients); 3/49 patients (6.1%) had a complete response. Of the 17 patients with response, 14 remained in response for >6 months, and 6 remained in response for >24 months. Median PFS was 7.7 months (95% CI 3.8 to 13.9), and median OS was not reached (95% CI 37.3 to not reached). Ninety-eight per cent (48/49) of patients experienced ≥1 treatment-related adverse event (TRAE) and 38.8% (19/49) had grade 3/4 TRAEs, most commonly syncope (8.2%; 4/49) and increased lipase (6.1%; 3/49). No association between exploratory biomarkers and ORR was observed. Limitations include the small sample size and single-arm design.

CONCLUSIONS: BEMPEG plus NIVO showed preliminary antitumor activity as first-line therapy in patients with advanced clear-cell RCC and was well tolerated. These findings warrant further investigation.

A phase 1-2 trial of sitravatinib and nivolumab in clear cell renal cell carcinoma following progression on antiangiogenic therapy. *Msaouel P. Sci Transl Med. 2022 Apr 20;14(641):eabm6420.*

ABSTRACT: The accumulation of immune-suppressive myeloid cells is a critical determinant of resistance to anti-programmed death-1 (PD-1) therapy in advanced clear cell renal cell carcinoma (ccRCC). In preclinical models, the tyrosine kinase inhibitor sitravatinib enhanced responses to anti-PD-1 therapy by modulating immune-suppressive myeloid cells. We conducted a phase 1-2 trial to choose an optimal sitravatinib dose combined with a fixed dose of nivolumab in 42 immunotherapy-naïve patients with ccRCC refractory to prior antiangiogenic therapies. The combination demonstrated no unexpected toxicities and achieved an objective response rate of 35.7% and a median progression-free survival of 11.7 months, with 80.1% of patients alive after a median follow-up of 18.7 months. Baseline peripheral blood neutrophil-to-lymphocyte ratio correlated with response to sitravatinib and nivolumab. Patients with liver metastases showed durable responses comparable to patients without liver metastases. In addition, correlative studies demonstrated reduction of immune-suppressive myeloid cells in the periphery and tumor microenvironment following sitravatinib treatment. This study provides a rationally designed combinatorial strategy to improve outcomes of anti-PD-1 therapy in advanced ccRCC.

Results from the INMUNOSUN-SOGUG trial: a prospective phase II study of sunitinib as a second-line therapy in patients with metastatic renal cell carcinoma after immune checkpoint-based combination therapy. *Grande E, ESMO Open. 2022 Apr;7(2):100463.*

RESULTS: Twenty-one assessable patients were included in the efficacy and safety analyses. Four patients [19.0%, 95% confidence interval (CI) 2.3% to 35.8%] showed an objective response (OR), and all of them had partial responses. Additionally, 14 (67%) patients showed a stable response, leading to clinical benefit in 18 patients (85.7%, 95% CI 70.7% to 100%). Among the four assessable patients who showed an OR, the median duration of the response was 7.1 months (interquartile range 4.2-12.0 months). The median progression-free survival (PFS) was 5.6 months (95% CI 3.1-8.0 months). The median overall survival (OS) was 23.5 months (95% CI 6.3-40.7 months). Patients who had better antitumor response to first-line ICI-based treatment showed a longer PFS and OS with sunitinib. The most frequent treatment-emergent adverse events were diarrhea (n = 11, 52%), dysgeusia (n = 8, 38%), palmar-plantar erythrodysesthesia (n = 8, 38%), and hypertension (n = 8, 38%). There was 1 patient who exhibited grade 5 pancytopenia, and 11 patients experienced grade 3 adverse events. Eight (38%) patients had serious adverse events, four of which were considered to be related to sunitinib.
CONCLUSION: Although the INMUNOSUN trial did not reach the pre-specified endpoint, it demonstrated that sunitinib is active and can be safely used as a second-line option in patients with mRCC who progress to new standard ICI-based regimens.

Telaglenastat Plus Cabozantinib or Everolimus for Advanced or Metastatic Renal Cell Carcinoma: An Open-Label Phase I Trial. *Meric-Bernstam F, et al.* Clin Cancer Res. 2022 Apr 14;28(8):1540-1548. doi: 10.1158/1078-0432.CCR-21-2972.

RESULTS: Twenty-seven patients received TelaE, 13 received TelaC, with median 2 and 3 prior therapies, respectively. Treatment-related adverse events were mostly grades 1 to 2, most common including decreased appetite, anemia, elevated transaminases, and diarrhea with TelaE, and diarrhea, decreased appetite, elevated transaminases, and fatigue with TelaC. One dose-limiting toxicity occurred per cohort: grade 3 pruritic rash with TelaE and thrombocytopenia with TelaC. No maximum tolerated dose (MTD) was reached for either combination, leading to a recommended phase II dose of 800-mg telaglenastat twice daily with standard doses of E or C. TelaE disease control rate (DCR; response rate + stable disease) was 95.2% [20/21, including 1 partial response (PR)] among 21 patients with clear cell histology and 66.7% (2/3) for papillary. TelaC DCR was 100% (12/12) for both histologies [5/10 PRs as best response (3 confirmed) in clear cell].
CONCLUSIONS: TelaE and TelaC showed encouraging clinical activity and tolerability in heavily pretreated mRCC patients.

Safety and efficacy of nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 CheckMate 920 trial. *Tykodi SS. J Immunother Cancer. 2022 Feb;10(2):e003844.*

RESULTS: Fifty-two patients with nccRCC (unclassified histology, 42.3%; papillary, 34.6%; chromophobe, 13.5%; translocation-associated, 3.8%; collecting duct, 3.8%; renal medullary, 1.9%) received treatment. With 24.1 months minimum study follow-up, median duration of therapy (range) was 3.5 (0.0-25.8) months for nivolumab and 2.1 (0.0-3.9) months for ipilimumab. Median (range) number of doses received was 4.5 (1-28) for nivolumab and 4.0 (1-4) for ipilimumab. Grade 3-4 immune-mediated AEs were diarrhea/colitis (7.7%), rash (5.8%), nephritis and renal dysfunction (3.8%), hepatitis (1.9%), adrenal insufficiency (1.9%), and hypophysitis (1.9%). No grade 5 immune-mediated AEs occurred. ORR (n=46) was 19.6% (95% CI 9.4 to 33.9). Two patients achieved complete response (papillary, n=1; unclassified, n=1), seven achieved partial response (papillary, n=4; unclassified, n=3), and 17 had stable disease. Median TTR was 2.8 (range 2.1-14.8) months. Median DOR was not reached (range 0.0+-27.8+); eight of nine responders remain without reported progression. Median PFS (n=52) was 3.7 (95% CI 2.7 to 4.6) months. Median OS (n=52) was 21.2 (95% CI 16.6 to not estimable) months.
CONCLUSIONS: Nivolumab plus ipilimumab for previously untreated advanced nccRCC showed no new safety signals and encouraging antitumor activity.

Baseline circulating unswitched memory B cells and B-cell related soluble factors are associated with overall survival in patients with clear cell renal cell carcinoma treated with nivolumab within the NIVOREN GETUG-AFU 26 study. *J Immunother Cancer. 2022 May;10(5):e004885. doi: 10.1136/jitc-2022-004885.PMID: 35640928*

RESULTS: Among the 44 patients, baseline unswitched memory B cells (NSwM B cells) were enriched in responders (p=0.006) and associated with improved OS (HR=0.08, p=0.002) and PFS (HR=0.54, p=0.048). Responders were enriched in circulating T follicular helper (Tfh) (p=0.027) and tertiary lymphoid structures (TLS) (p=0.043). Circulating NSwM B cells positively correlated with Tfh (r=0.70, p<0.001). Circulating NSwM B cells correlated positively with TLS and CD20 +B cells at the tumor center (r=0.59, p=0.044, and r=0.52, p=0.033) and inversely correlated with BCA-1/CXCL13 and BAFF (r=-0.55 and r=-0.42, p<0.001). Tfh cells also inversely correlated with BCA-1/CXCL13 (r=-0.61, p<0.001). IL-6, BCA-1/CXCL13 and BAFF significantly associated with worse OS in the discovery (n=40) and validation cohorts (n=313).
CONCLUSION: We report the first fresh blood immune-monitoring of patients with m-ccRCC treated with nivolumab. Baseline blood concentration of NSwM B cells was associated to response, PFS and OS in patients with m-ccRCC treated with nivolumab. BCA-1/CXCL13 and BAFF, inversely correlated to NSwM B cells, were both associated with worse OS in discovery and validation cohorts. Our data confirms a role for B cell subsets in the response to immune checkpoint blockade therapy in patients with m-ccRCC. Further studies are needed to confirm these findings.

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