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May 29-June 2, 2015

Chicago, Illinois

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American Society of Clinical Oncology

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4516 Poster Discussion Session; Displayed in Poster Session (Board #186), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Expanded cohort results from CheckMate 016: A phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). First Author: Hans J. Hammers, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: Nivolumab (N), a fully human IgG4 immune checkpoint inhibitor antibody, has shown durable response and encouraging overall survival (OS) in mRCC. Previously in CheckMate 016, N + ipilimumab (I) demonstrated manageable safety and promising antitumor activity in mRCC. Here, we report results from expansion cohorts in this study (NCT01472081). **Methods:** Patients (pts) with mRCC were randomized to N 3 mg/kg + I 1 mg/kg (N3 + I1), N 1 mg/kg + I 3 mg/kg (N1 + I3) or N 3 mg/kg + I 3 mg/kg (N3 + I3) IV Q3W for 4 doses, then N 3 mg/kg IV Q2W until progression or toxicity. Primary endpoint: safety. Other endpoints: objective response rate (ORR), duration of response (DOR), OS. DOR and OS were assessed by Kaplan-Meier method. **Results:** Pts randomized to N3 + I1 and N1 + I3 cohorts were expanded to 47 pts per arm; N3 + I3 (n = 6) arm showed early toxicity and did not proceed to expansion. 53% and 47% of pts were treatment naive and previously treated in N3 + I1; 45% and 55% were in N1 + I3. Median (range) follow-up was 34.3 (15.4 – 80.1) wks in N3 + I1 and 31.3 (4.6 – 79.9) wks in N1 + I3. Treatment-related AEs were seen in 88% of pts. Discontinuations for any grade AE occurred in 16% of pts. Grade 3-4 treatment-related AEs occurred in 34% and 64% of pts in N3 + I1 and N1 + I3, respectively; most common: ↑ lipase (13% and 26%), ↑ ALT (4% and 19%), diarrhea (2% and 15%), colitis (0 and 13%), ↑ AST (4% and 9%), and ↑ amylase (4% and 9%). Most common grade 3-4 select AEs were GI and hepatic (N3 + I1, N1 + I3); GI: 2%, 23%; hepatic: 4%, 21%. Efficacy is summarized in the table below. **Conclusions:** Updated results from expanded cohorts in CheckMate 016 confirm initial safety findings and promising antitumor activity for N + I in pts with mRCC. OS results for N + I in mRCC appear encouraging and support further development of this combination in the first-line setting. Clinical trial information: NCT01472081.

	N3 + I1 n = 47	N1 + I3 n = 47
OS, mos (range)	NR (3.5 – 18.4+)	NR (1.1 – 18.4+)
Overall ORR ^a , n (%)	18 (38)	20 (43)
Stable disease, n (%)	19 (40)	18 (38)
Median DOR ^b , wks (range)	NR (4.1+ – 67.1+)	53.9 (6.1+ – 66.0+)
Median PFS, wks (range)	30.3 (4.7+ – 72.6+)	36.0 (4.1+ – 77.9+)
PFS, 24 wks, % (95% CI)	53 (37 – 67)	64 (47 – 77)

^aConfirmed response + unconfirmed response; ^bConfirmed response. NR, not reached.

4518 Poster Discussion Session; Displayed in Poster Session (Board #188), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

RECORD-4: A multicenter, phase II trial of second-line everolimus (EVE) in patients (pts) with metastatic renal cell carcinoma (mRCC). First Author: Robert Motzer, Memorial Sloan Kettering Cancer Center, New York, NY

Background: In the pivotal RECORD-1 trial, EVE was superior to placebo in pts with mRCC previously treated with sunitinib, sorafenib, or both; prior treatment with cytokines, bevacizumab, and chemotherapy was permitted (*Cancer* 2010; 116:4256). The RECORD-4 study assessed EVE in pts with mRCC who progressed after 1 prior anti-VEGF or cytokine. **Methods:** RECORD-4 enrolled pts with clear cell mRCC into 3 cohorts based on prior first-line therapy: sunitinib, other anti-VEGF, or cytokines. Pts received EVE 10 mg/d until progression of disease (PD; RECIST, v1.0) or intolerance. Primary endpoint was PFS per investigator review. Data cutoff was Sept 1, 2014. **Results:** Enrolled pts (N = 134) previously received sunitinib (n = 58), other anti-VEGF therapy (n = 62; 23 sorafenib, 16 bevacizumab, 13 pazopanib, 10 other), or cytokines (n = 14). Demographics were balanced among cohorts; overall 90% of pts had good/intermediate MSKCC prognosis; most were white (56%) or Asian (41%). At data cutoff, 88% of pts had discontinued, mainly due to PD (54%). Median duration of exposure was 5.8 mo. Median overall PFS (95% CI) was 7.8 (5.7-11.0) mo, 5.7 (3.7-11.3) mo with prior sunitinib, and 7.8 (5.7-11.0) mo with prior other anti-VEGFs (Table). Overall response rate (ORR) was 7.5% (95% CI, 3.6-13.3%); most pts achieved stable disease (67%) as best overall response. Overall rate of grade 3 or 4 adverse events (AEs) was 56%. **Conclusions:** RECORD-4 results reinforce the clinical benefit of EVE in the second line setting after sunitinib and other first-line therapies. EVE safety profile was consistent with previous experience. (ClinicalTrials.gov ID, NCT01491672). Clinical trial information: NCT01491672.

Key efficacy and safety results.

	Overall population N=134	Prior therapy Sunitinib N=58	Other anti-VEGF N=62	Cytokines N=14
Median PFS (95% CI), mo	7.8 (5.7-11.0)	5.7 (3.7-11.3)	7.8 (5.7-11.0)	12.9 (2.6-NE)
ORR, % (95% CI)	7.5 (3.6-13.3)	6.9 (1.9-16.7)	4.8 (1.0-13.5)	21.4 (4.7-50.8)
Safety set	N=133	N=58	N=61	N=14
Grade 3/4 AEs ^a , n (%)				
Anemia	17 (13)	6 (10)	7 (11)	4 (29)
Stomatitis/mouth ulceration	10 (8)	4 (7)	4 (7)	2 (14)
Hyperglycemia	6 (5)	2 (3)	4 (7)	0 (0)
Hypertriglyceridemia	6 (5)	3 (5)	3 (5)	0 (0)

NE, not evaluable. ^aCommonly reported (incidence ≥ 4%).

4517 Poster Session (Board #197), Mon, 1:15 PM-4:45 PM

Effectiveness of adjuvant chemotherapy (AC) versus observation in patients with ≥ pT3 and/or pN+ bladder cancer (BCa). First Author: Matt D. Galsky, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Though Level I evidence supports the use of neoadjuvant chemotherapy in BCa, the data supporting AC has been mixed. Experience suggests an adequately powered trial to definitively assess the role of AC is unlikely to be completed. Alternative approaches to evidence development are necessary. **Methods:** Patients undergoing cystectomy for ≥ pT3 and/or pN+ M0 BCa were identified from the National Cancer Database. Patients who received neoadjuvant chemotherapy and/or diagnosed after 2006 (most recent year with survival data) were excluded. Logistic regression was used to calculate propensity scores representing the predicted probabilities of assignment to observation versus AC based on: age, demographics, year of diagnosis, pT stage, margin status, lymph node density, distance to hospital, hospital cystectomy volume, and hospital type and location. Missing data were handled by multiple imputation. A propensity score-matched (1:1) cohort of AC versus observation patients was created using these variables. Stratified Cox proportional hazards regression was used to estimate the hazard ratio (HR) for the matched sample. Sensitivity analyses examined the impact of an alternative adjustment approach and comorbidities. **Results:** 4360 patients undergoing cystectomy alone and 1293 patients undergoing cystectomy plus AC met inclusion criteria. Patients receiving AC were significantly more likely to be younger, have more lymph nodes examined and involved, have positive margins, reside in the Northeast, and have private insurance. HR are shown in the Table. Subset analyses explored the impact of nodal status [pN+ HR = 0.63 (0.56-0.70), pN- HR = 0.76 (0.63-0.90)] and age [≤ 70 HR = 0.80 (0.72-0.88), ≥ 70 HR = 0.71 (0.61-0.82)]. The results were robust to sensitivity analysis for comorbidities. **Conclusions:** AC was associated with improved survival in patients with ≥ pT3 and/or pN+ BCa in this large comparative effectiveness analysis.

HR for overall survival with AC versus observation.

Model	HR [95% CI]
Matched Sample – Cox Model Stratified	0.71 [0.63-0.80]
Cox Model Weighted by Inverse Probability of Treatment Weight	0.78 [0.74-0.81]

4519 Poster Discussion Session; Displayed in Poster Session (Board #189), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Activating genomic mutations in the mTOR pathway to predict responses to everolimus and temsirolimus in patients with metastatic renal cell carcinoma (mRCC): Results from a large multi-institutional cohort. First Author: Andre Poisl Fay, Oncology Service and Oncology Research Unit, HSL/ PUCRS, Porto Alegre, Brazil

Background: Mammalian target of rapamycin (mTOR) inhibitors are approved in mRCC, but only a subset of patients derives clinical benefit. Recently, case reports have suggested that mutations in mTOR pathway genes might be associated with response to everolimus and temsirolimus in several malignancies, including mRCC. **Methods:** We amassed a large international cohort of mRCC patients with available tumor specimens who received mTOR inhibitors and had distinct clinical outcomes: responders were defined as complete response (CR), partial response (PR) or stable disease with any tumor shrinkage or no tumor growth for at least 6 months (R); non-responders were defined as disease progression within the first 3 months of therapy (NR). Tumor DNA from 94 patients was analyzed using a targeted next-generation sequencing panel covering 504 cancer genes. We performed a blinded analysis to investigate the correlation between mutations in mTOR pathway genes and response status. **Results:** Samples from 79 of 94 patients were successfully sequenced and were included in the analysis. Mutations are summarized in Table 1. Mutations in *MTOR*, *TSC1* or *TSC2* were more common in R (12/43) than NR (4/36) (OR: 3.05; *p* = 0.06; primary hypothesis). Similarly, mutations in *TSC1* or *TSC2* were more common in R (9/43) than NR (2/36) (OR: 4.42; *p* = 0.05; secondary hypothesis). In an exploratory analysis, 5/12 with PR/CR had mutations in *MTOR*, *TSC1* or *TSC2* vs 4/35 NR (OR: 5.28; *p* = 0.04). **Conclusions:** In this large cohort of mRCC patients, mutations in *MTOR*, *TSC1* or *TSC2* were more common in patients with clinical benefit from everolimus or temsirolimus than in NR. Mutations in those 3 genes were associated with PR/CR to mTOR inhibitors. In contrast, neither PTEN nor PIK3CA mutations showed any association with response. These findings suggest that a personalized medicine approach has value for selection of mTOR inhibitors in mRCC.

Gene Mutation	NR (n = 36) n (%)	R (n = 43) n (%)	Total (N = 79) n (%)
MTOR (activating)	2 (6)	3 (7)	5 (6)
PTEN (inactivating)	5 (14)	5 (12)	10 (13)
TSC1 (inactivating)	2 (6)	8 (19)	10 (13)
TSC2 (inactivating)	0	1 (2)	1 (1)
PIK3CA (activating)	0	1 (2)	1 (1)

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