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Society for Immunotherapy of Cancer

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Sitravatinib + Nivolumab Demonstrates Clinical Activity in Platinum-Experienced Urothelial Carcinoma Patients Who Progressed on Prior Checkpoint Inhibitor

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Presenter Disclosure Information

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The following relationships exist related to this presentation:

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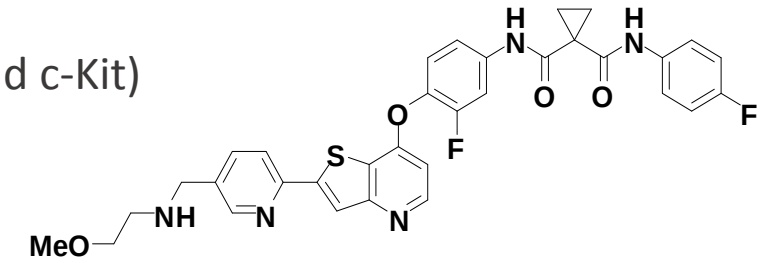
Takeda Pharmaceutical Company

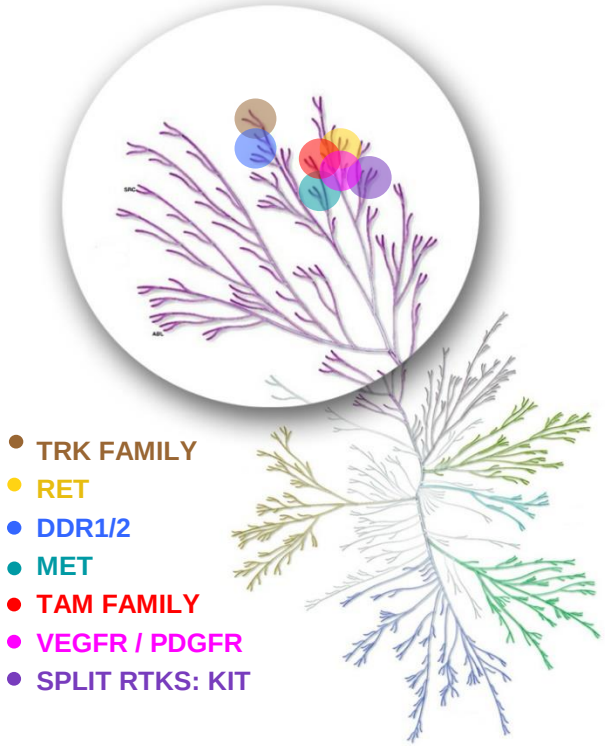
There will be discussion about the use of products for non-FDA approved indications in this presentation

Sitravatinib (MGCD516): A Spectrum-Selective Kinase Inhibitor

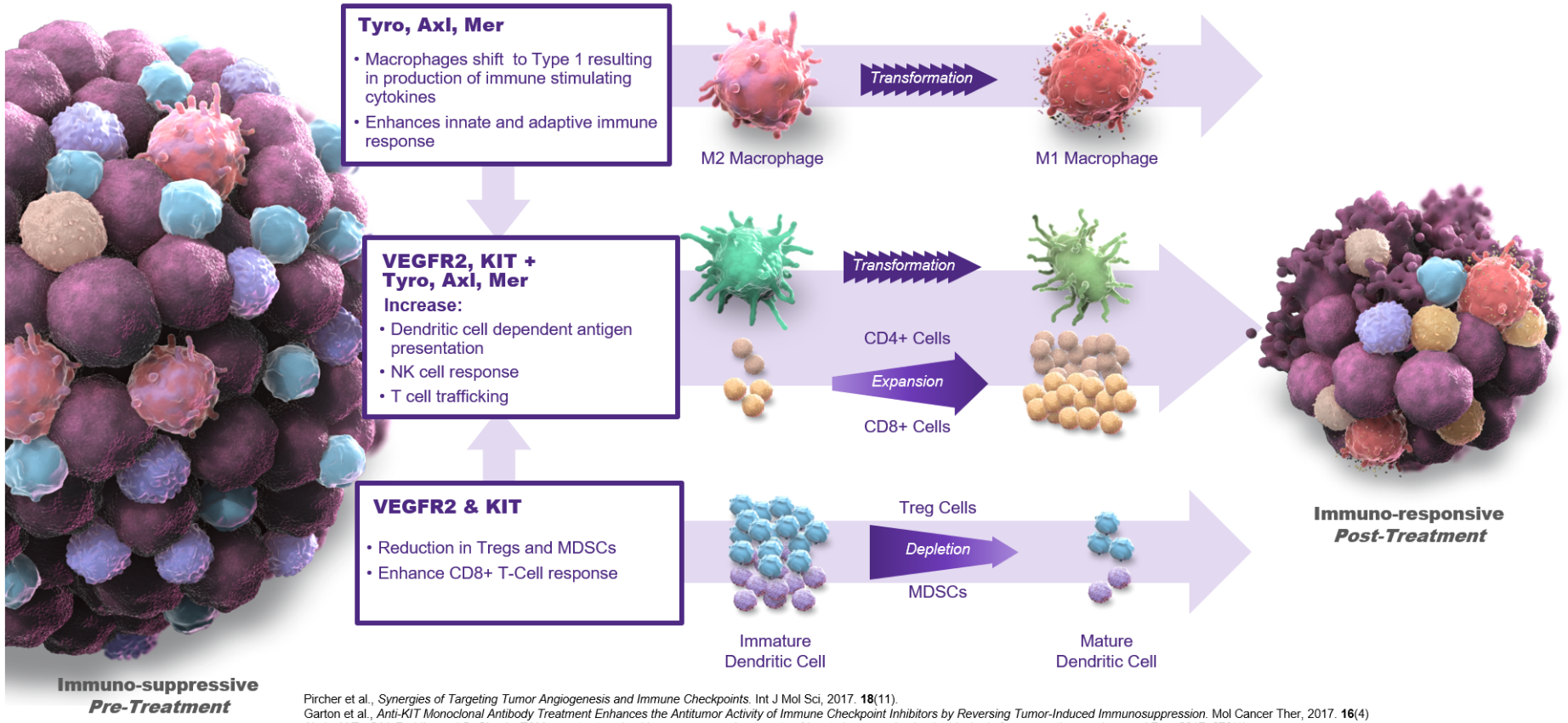
- **Sitravatinib is an orally available small molecule that inhibits a spectrum of related receptor tyrosine kinases (RTKs) including:**
  - TAM family (Tyro3, Axl, MerTK)
  - Split family (VEGFR2/PDGFR and c-Kit)
  - c-Met



- **Inhibition of these target classes may enhance anti-tumor activity through:**
  - Modulation of the immunogenic status of tumors
  - Improvement of tumor perfusion by reducing intratumoral pressure
  - Modulating subsets of immune cells



Sitravatinib in the Tumor Microenvironment (TME)



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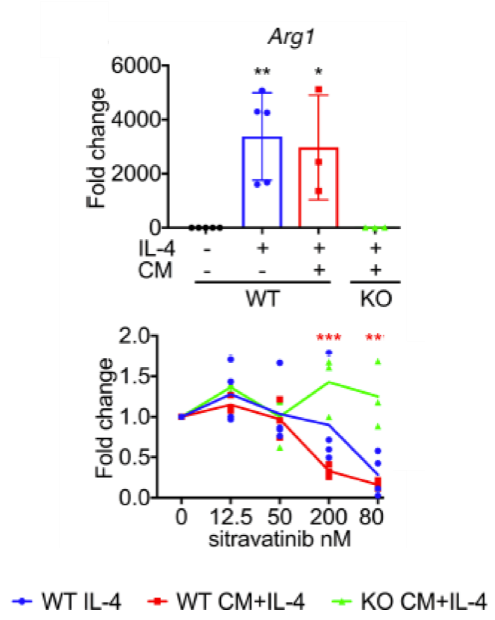
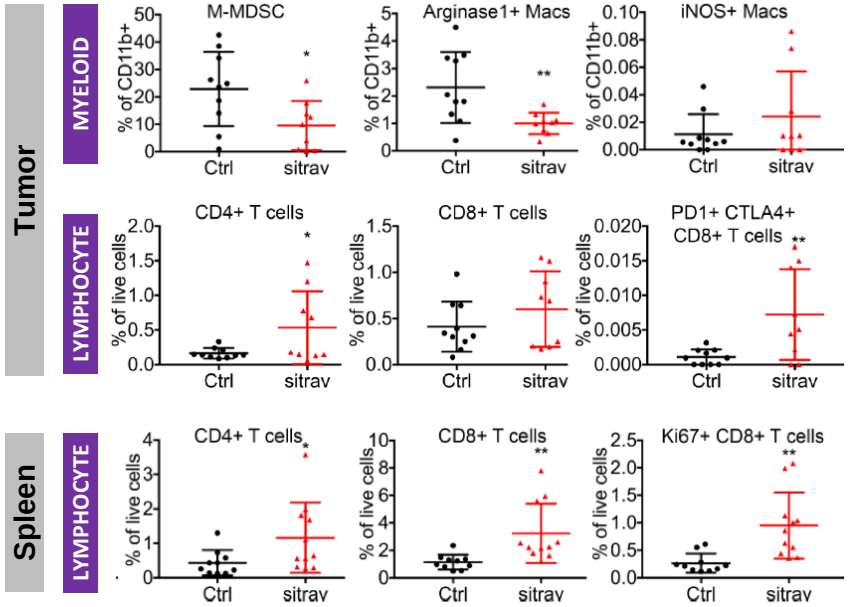
Sitravatinib Inhibits Immunosuppressive Immune Populations and Augments Checkpoint Inhibitor Therapy

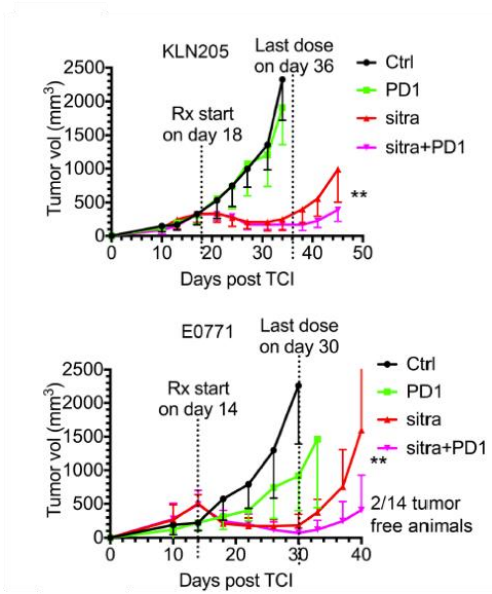
Inhibition of M2 macrophage polarization by sitra or MERTK KO *ex vivo*



Sitravatinib decreases M2 MΦs, M-MDSCs and increases CD4 and CD8 cells in a syngeneic model



Sitravatinib augments PD-1 therapy in CPI refractory models



Du W, et al, *Sitravatinib potentiates immune checkpoint blockade in refractory cancer models*. JCI Insight, 2018

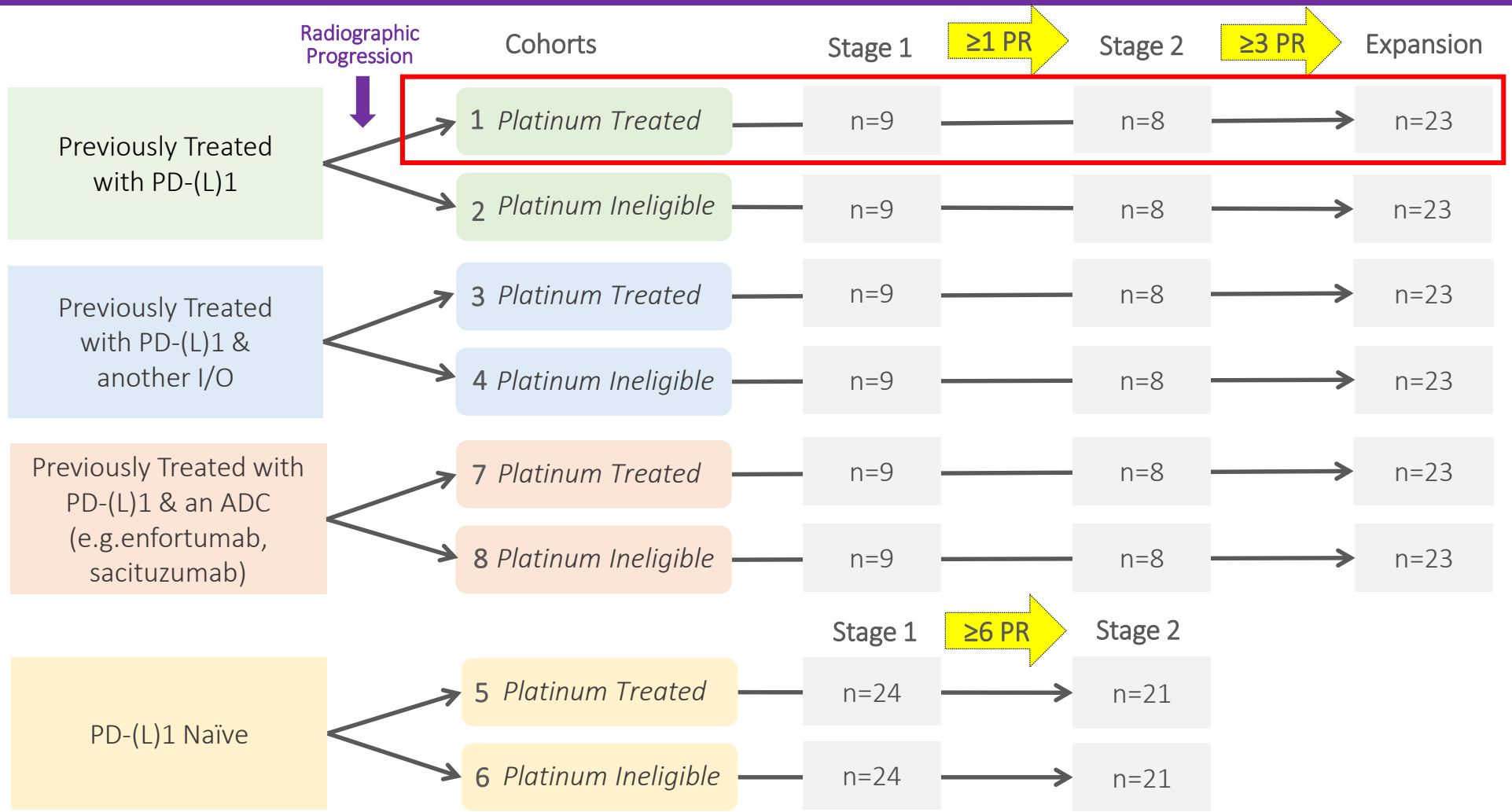
- Sitravatinib shifts macrophage polarization M2 → M1, depletes MDSCs and increases CD8+ T cells in tumor-bearing syngeneic mice
- Sitravatinib augments PD-1 therapy in CPI-refractory models and in mice with complete responses to sitravatinib + PD-1 therapy, tumors do not form upon re-innoculation, confirming an adaptive immunity-based mechanism

Urothelial Carcinoma Background

- **Results in approximately 165,000 deaths per year worldwide**
- **Platinum-based chemotherapy is the cornerstone of first-line therapy**
  - Most patients experience treatment resistance or intolerance
- **Since 2016, treatment options for platinum-refractory or platinum-ineligible advanced UC have been expanded to include anti-PD-1 and anti-PD-L1 checkpoint inhibitors (CPI)**
  - Single agent CPI response rates in UC are relatively low (around 20%)
  - Durable clinical responses in a subset of patients
- **Strategies to improve clinical efficacy and overcome acquired or primary resistance to CPI therapy are needed**
  - Combine an anti-PD-1 or anti-PD-L1 CPI with an agent that has both immune modulatory and antitumor properties

516-003 Study Design

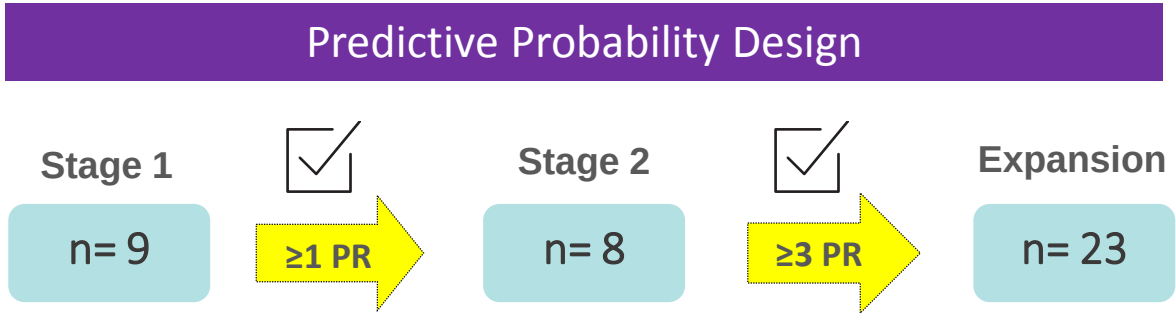
Open-label, multi-center Phase 2 Study to evaluate sitravatinib + nivolumab in patients with locally-advanced or metastatic UC



516-003 Cohort 1

- **Hypothesized that the combination of sitravatinib + nivolumab will restore or enhance CPI clinical activity in pts with immunotherapy-refractory UC**
  - *Could enhance the antitumor activity observed with either agent alone*
  - *Sitravatinib + nivolumab has also been shown to be well-tolerated in other indications, including NSCLC and RCC*
- **Cohort 1 patients (data cut-off of 17 October 2019)**
  - *UC patients who have progressed on or after treatment with a CPI, as the most treatment prior to the study*
  - *AND were previously treated with platinum-based chemotherapy*
- **Completed enrollment into the expansion phase**

Continuous 28-day Cycles
Sitravatinib 120 mg QD orally
+
Nivolumab 240 mg IV Q2W or 480 mg IV Q4W
Tumor Assessments performed Q8W



516-003 Objectives & Eligibility Criteria

OBJECTIVES/ENDPOINTS

- **PRIMARY**
  - Clinical activity by ORR per RECIST Version 1.1
- **SECONDARY**
  - Safety & tolerability
  - Secondary efficacy endpoints including DOR, CBR, PFS & OS
  - Pharmacokinetics (PK) of sitravatinib
  - PK of sitravatinib in patients with renal impairment
- **EXPLORATORY**
  - Circulating PD-L1, immune cell populations and cytokines
  - Tumor cell PD-L1 expression, tumor infiltrating immune cell populations & gene expression signatures
  - Tumor gene alterations in circulation & in tumor tissue

KEY ELIGIBILITY CRITERIA

- Histologically-confirmed transitional cell UC that is locally advanced or metastatic & is unresectable
- Most recent treatment must have included anti-PD-1 or anti-PD-L1 CPI with radiographic PD on or after the CPI
  - *No prior treatment with other immunotherapies (e.g. anti-CTLA-4, anti-OX40 and anti–CD137)*
- Received prior platinum-based chemotherapy
  - *If peri-operative setting, must have PD ≤ 1 yr of last dose*
- Measurable disease, as per RECIST Version 1.1
- ECOG 0-1
- GFR ≥ 30 mL/min per CKD-EPI
- No active brain metastases, unless adequately treated & neurologically-stable off treatment

516-003 Cohort 1 Patient Disposition

Enrolled Population	33
Safety Population (received ≥1 dose)	33 (100%)
Early treatment discontinuations (prior to 1st tumor assessment) • Unrelated AE • Global deterioration of health • Withdrew consent	4 2 1 1
Too early for 1st tumor assessment (<8 wks on study)	7
Evaluable Population (≥1 on-study tumor assessment)	22 (67%)

516-003 Cohort 1 Safety Population Characteristics (N=33)

Age, years	Median (range)	68 (47, 83)
	≥75 years, n (%)	8 (24)
Gender, n (%)	Male	23 (70)
	Female	10 (30)
Race, n (%)	Caucasian	30 (91)
	Black or African American	2 (6)
	Other *(refused to provide)*	1 (3)
ECOG PS, n (%)	0	15 (45)
	1+	18 (55)
Smoking, n (%)	Former smoker	17 (52)
	Never smoker	14 (42)
	Current smoker	2 (6)

* Patients with 1 prior therapy had a platinum-based chemotherapy and a PD-(L)1 inhibitor in combination

Disease stage at study entry, n (%)	Metastatic	30 (91)
	Locally advanced	3 (9)
Metastasis sites at baseline, n (%)	Visceral disease	23 (70)
	Liver	10 (30)
	Lymph node only	7 (21)
	Lymph node + brain/bone	3 (9)
Hemoglobin at baseline, n (%)	<10 g/dL	7 (21)
Bellmunt prognostic factors, n (%)	≥2 adverse factors	8 (24)
Number of prior systemic therapy in advanced/metastatic setting, n (%)	Median (range)	2 (1, 4)
	1*	1 (3)
	2	27 (82)
	3	2 (6)
	4	3 (9)

516-003 Preliminary Sitravatinib Pharmacokinetics

- The PK exposure values attained in UC patients Cohort 1 are consistent with the PK levels historically observed
- In the current study, limited exposure parameters were derived due to the sparse sampling collections (0, 2 and 4hrs on C1D1 and C1D15)
- The 120 mg QD dose resulted in a single dose geometric mean Cmax of 21 ng/mL reached after approximately 3 hrs. At steady state the geometric mean Ctrough and Cmax values were 50 and 72.5 ng/mL, respectively
- A renal impairment sub-study is ongoing to compare PK in patients with mild or moderate renal impairment to patients with no renal impairment

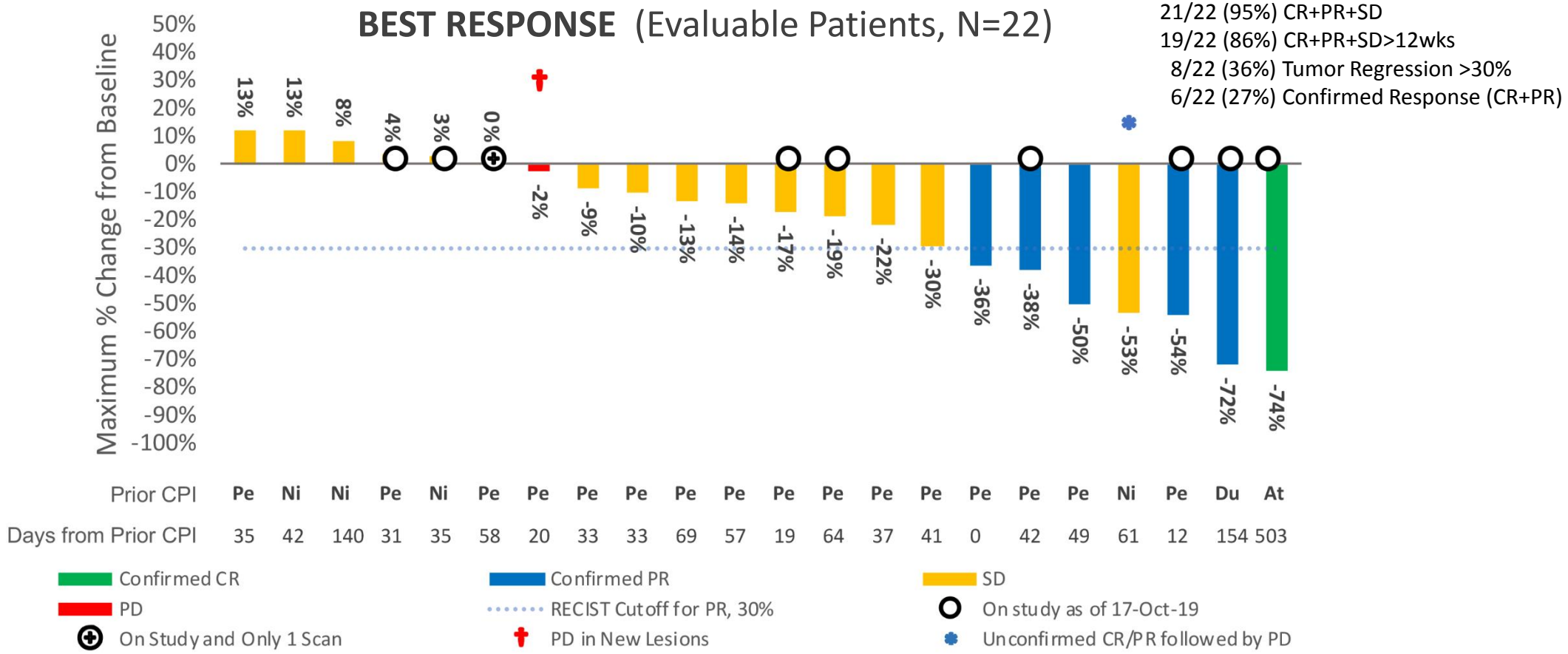
516-003 Safety | Most Frequent (>15%) Related Treatment-Emergent Adverse Events (Sitravatinib and/or Nivolumab)

Adverse Event (Preferred Term)	Safety Population (N=67, Cohorts 1-6; N=33, Cohort 1 only)			
	Cohorts 1-6 All Grades n (%)	Cohort 1 All Grades n (%)	**Cohorts 1-6 Grade 3 n (%)**	Cohort 1 Grade 3 n (%)
Fatigue	**36 (54%)**	19 (58%)	**6 (9%)**	4 (12%)
Diarrhea	**33 (49%)**	16 (48%)	**5 (8%)**	3 (9%)
Decreased appetite	**22 (33%)**	11 (33%)	**1 (2%)**	1 (3%)
Dysphonia	**20 (30%)**	11 (33%)	**0**	0
Nausea	**16 (24%)**	11 (33%)	**1 (2%)**	0
Alanine aminotransferase increased	**16 (24%)**	7 (21%)	**0**	0
Palmar-plantar erythrodysesthesia syndrome (PPE)	**14 (21%)**	6 (18%)	**2 (3%)**	1 (3%)
Aspartate aminotransferase increased	**12 (18%)**	5 (15%)	**0**	0
Hypertension	**12 (18%)**	4 (12%)	**9 (13%)**	4 (12%)
Lipase increased	**11 (16%)**	6 (18%)	**4 (6%)**	3 (9%)
Vomiting	**11 (16%)**	6 (18%)	**0**	0

No treatment-related Grade 4 or Grade 5 AEs were reported

516-003 Cohort 1: Efficacy

PD-(L)1-Refractory
Platinum-Experienced

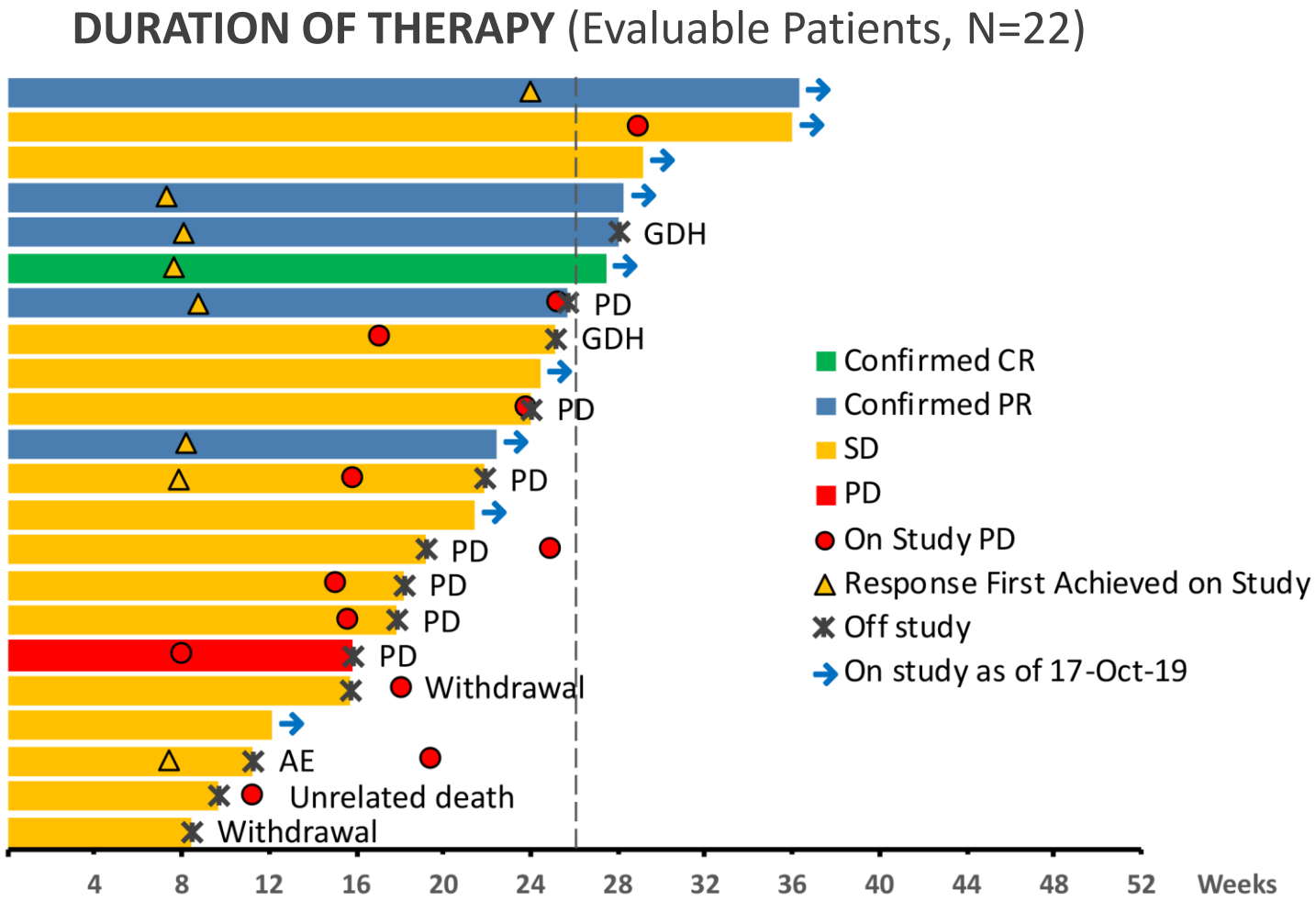


21/22 (95%) CR+PR+SD
19/22 (86%) CR+PR+SD>12wks
8/22 (36%) Tumor Regression >30%
6/22 (27%) Confirmed Response (CR+PR)

Abbreviations: At=atezolizumab; Du=durvalumab; Ni=nivolumab; Pe=pembrolizumab

516-003 Cohort 1: Duration of Therapy

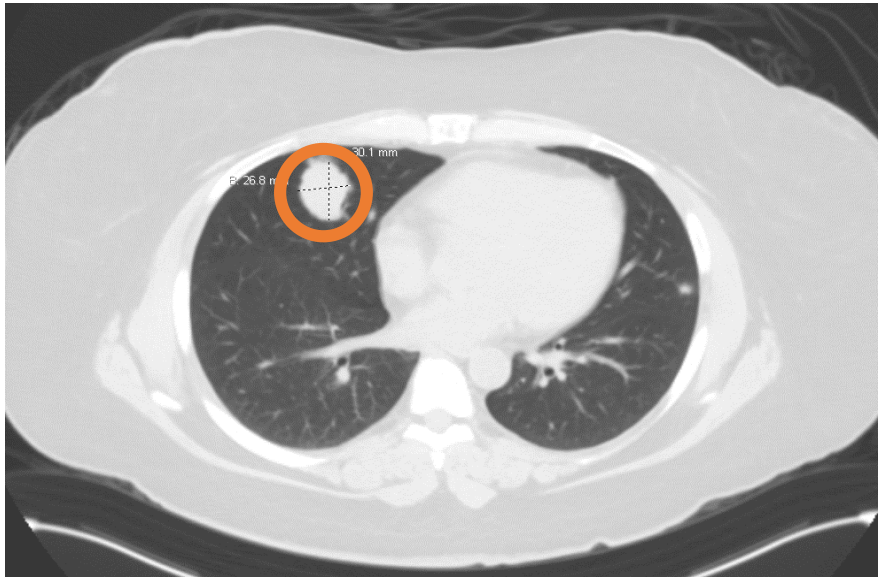
PD-(L)1-Refractory
Platinum-Experienced



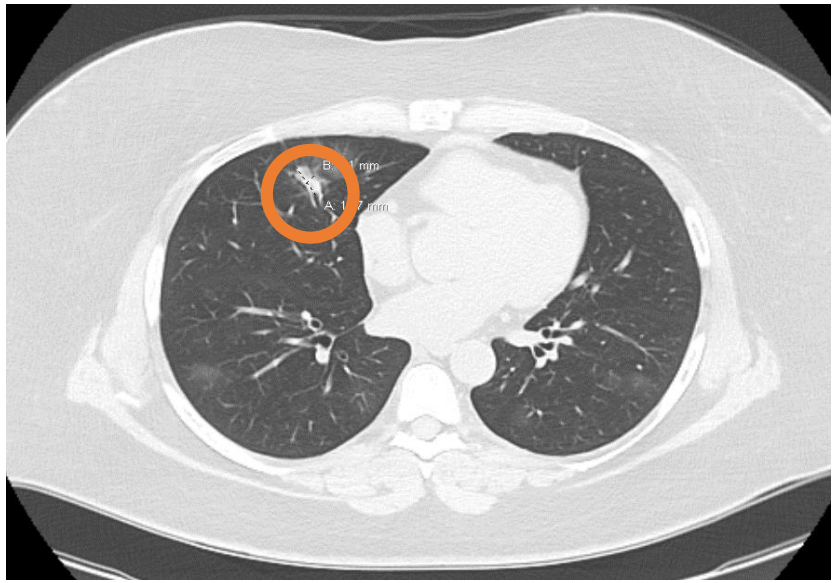
Cohort 1: Case Study #1

- 10/2017: metastatic UC of bladder
- 10/2017: neoadjuvant ddMVAC x 4 cycles
- 2/2018: cystectomy

- 9/2018: new lung mets → 11/2018: pembrolizumab
- 1/2019: disease progression
  → 2/2019: nivolumab + sitravatinib



1/11/2019 (Baseline)

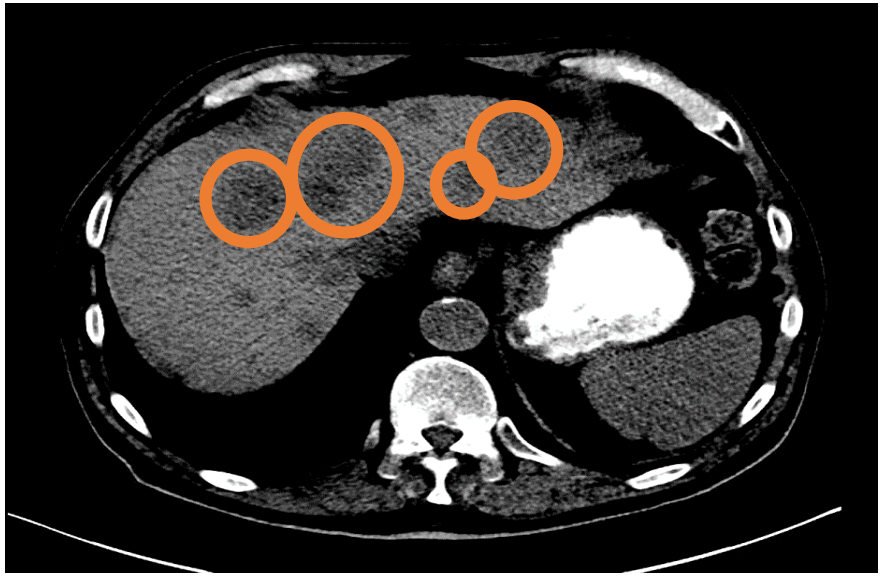


9/15/2019 (Wk16): confirmatory PR scan (-50%)

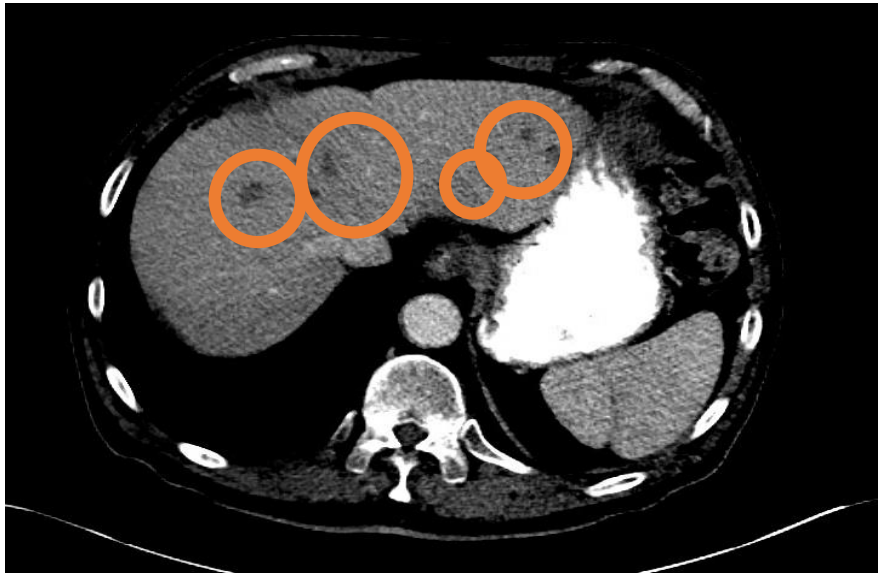
Cohort 1: Case Study #2

- 5/2018: metastatic UC of urethra/prostatic duct
- 7/2018: carboplatin/gemcitabine x 6 cycles
- 1/2019: progression in bone and LNs
  → 11/2018: pembrolizumab

- 5/2019: progression in bone, LNs and innumerable new liver metastases
  → 5/2019: nivolumab + sitravatinib



5/2/2019 (Baseline)



9/17/2019 (Wk16): confirmatory PR scan (-50%) – remains in PR (-54%)

516-003 Cohort 1 Conclusion

- The combination of sitravatinib with nivolumab is a rational approach to restoring or enhancing the clinical activity of anti-PD-(L)1 CPI in patients with immunotherapy resistant UC
- The combination has an acceptable toxicity profile with manageable AEs
- This ongoing study continues to show promising clinical activity, including tumor regression & prolonged duration on treatment in patients who have progressed following prior CPI
- The study is open at 25 sites in the US & recruitment is ongoing in 7 Cohorts
- Preliminary clinical activity has been seen in several other cohorts, with decisions regarding expansion awaiting for additional enrollment & maturing data

Acknowledgements

- Thank you to all the patients and their families
- Participating study investigators and clinical sites
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