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UNC Lineberger Cancer Network
CANCER TREATMENT IN NORTH CAROLINA RESEARCH TO PRACTICE
Live Lecture

UNC CANCER CARE

Genitourinary Oncology Update 2021

Matthew Milowsky MD

April 28, 2021

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Disclosures

- **Employment** - none
- **Leadership** - none
- **Stock and Other Ownership Interests** – none
- **Honoraria** - none
- **Consulting or Advisory Role** – none
- **Speaker's Bureau** - none
- **Research Funding (institution)**– Merck, Roche/Genentech, Bristol-Myers Squibb, Seagen, Astellas Pharma, Clovis Oncology, Inovio Pharmaceuticals, Mirati Therapeutics, Constellation Pharmaceuticals, Syndax, Incyte, Amgen, Regeneron, Arvinas, Pfizer, Johnson & Johnson/Janssen
- **Patents, Royalties, Other Intellectual Property** – none
- **Expert Testimony** - none
- **Travel, Accommodations, Expenses** - none
- **Other Relationship** - none

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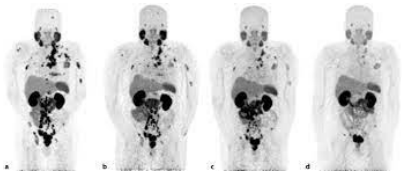
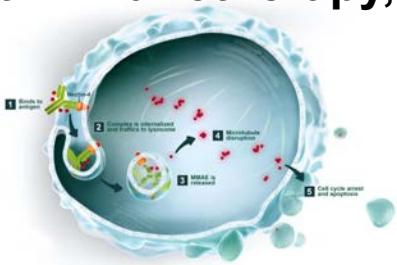
2021 GU Cancers Symposium Highlights

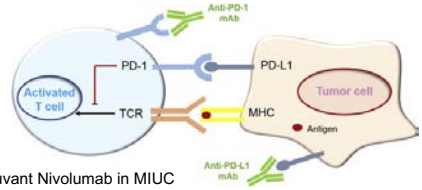
ADC, radioligand therapy, adjuvant immunotherapy,



Lu-177-PSMA therapy for prostate cancer



Enfortumab Vedotin for advanced urothelial cancer



Adjuvant Nivolumab in MIUC

and more…

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Prostate Cancer Update

1. **TheraP (ANZUP 1603) – Lu-177-PSMA in mCRPC**
2. **ACIS – Apa/Abi vs. Abi in mCRPC**

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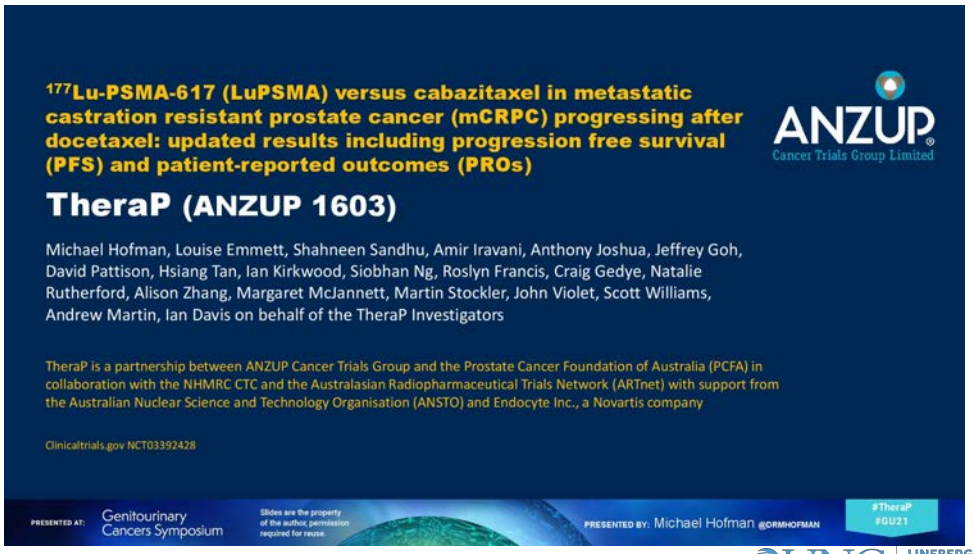
TheraP (ANZUP 1603)



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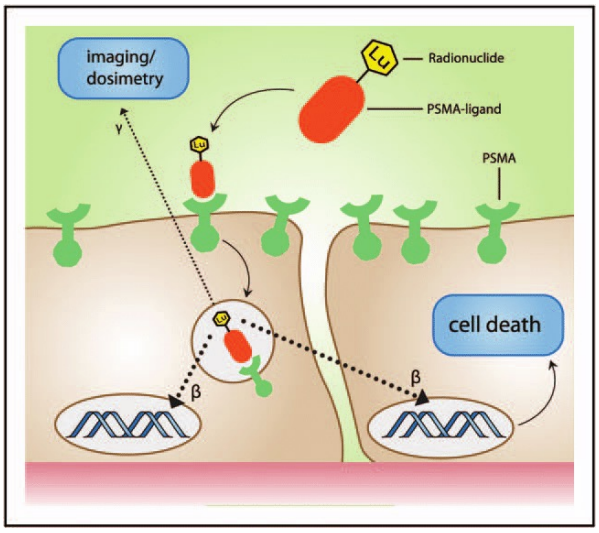
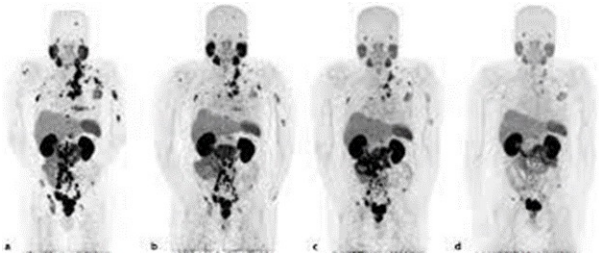
177-Lu-PSMA-617





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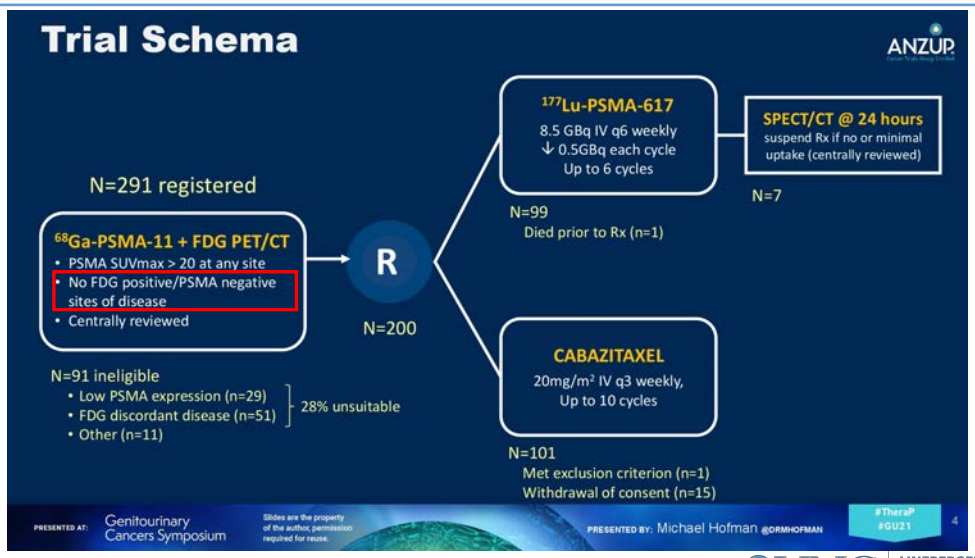
TheraP (ANZUP 1603)



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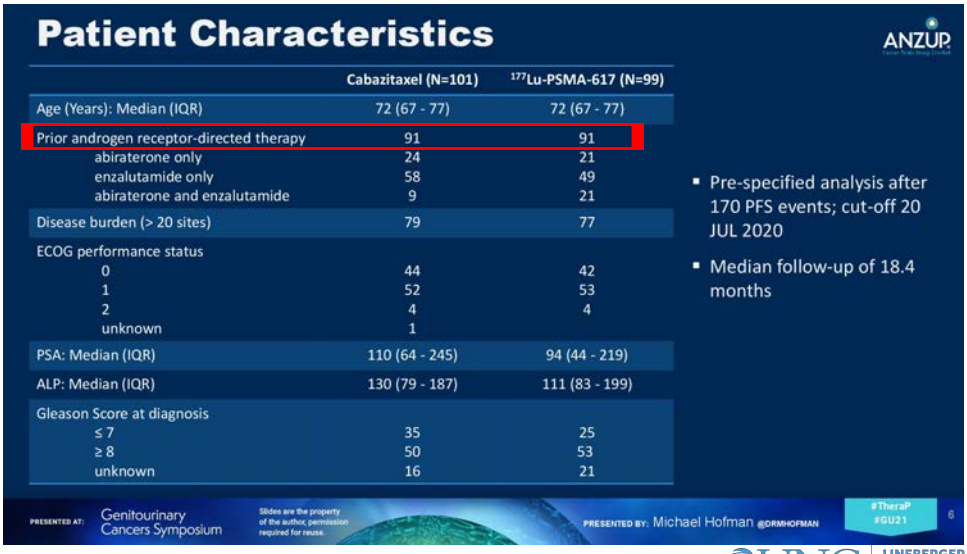
TheraP (ANZUP 1603)



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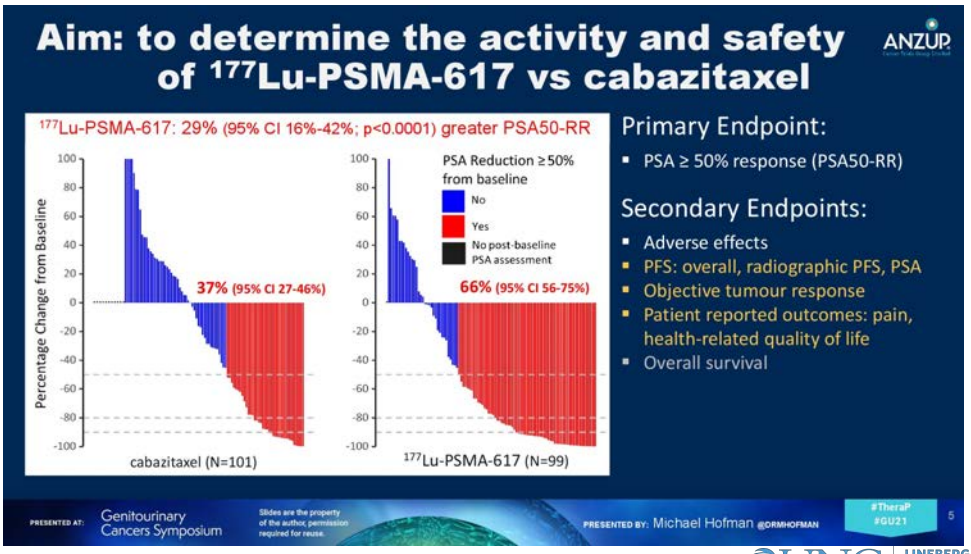
TheraP (ANZUP 1603)



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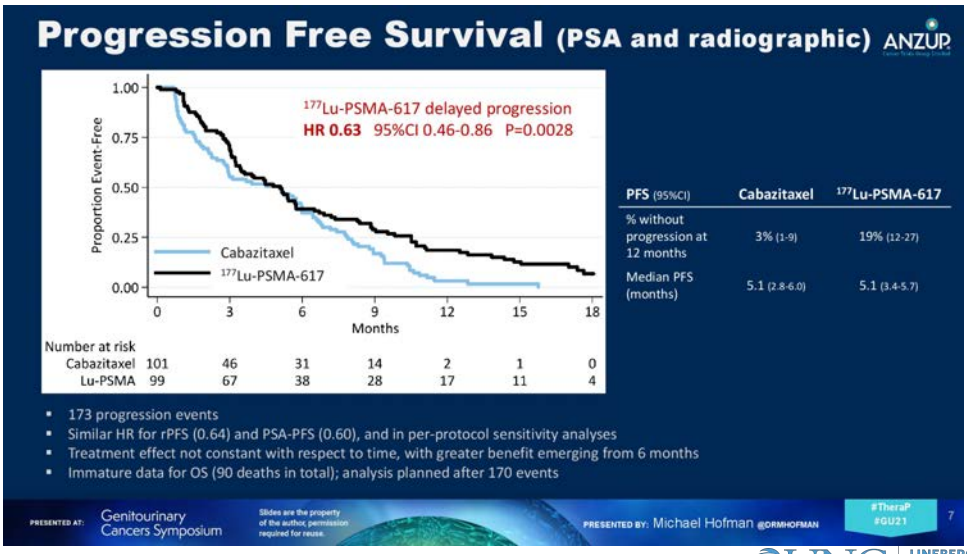
TheraP (ANZUP 1603)



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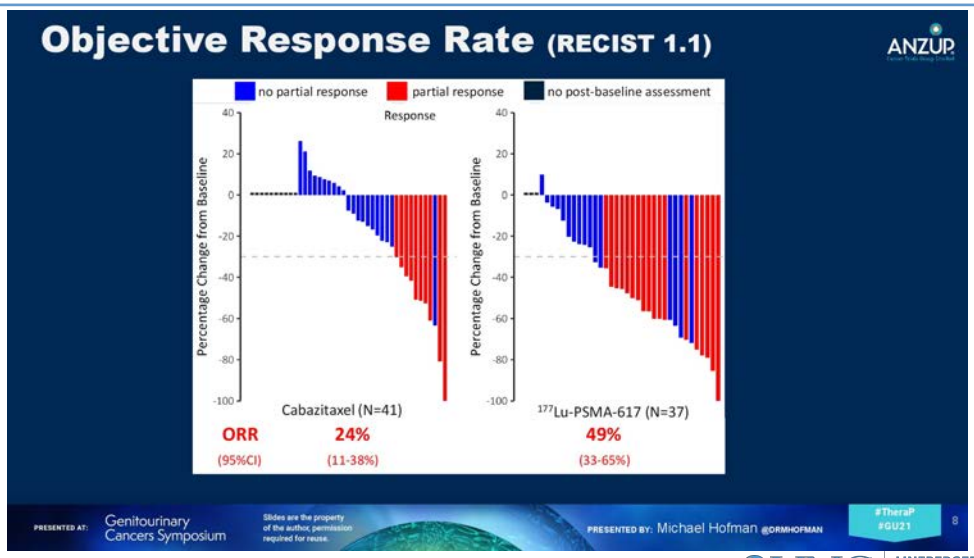
TheraP (ANZUP 1603)



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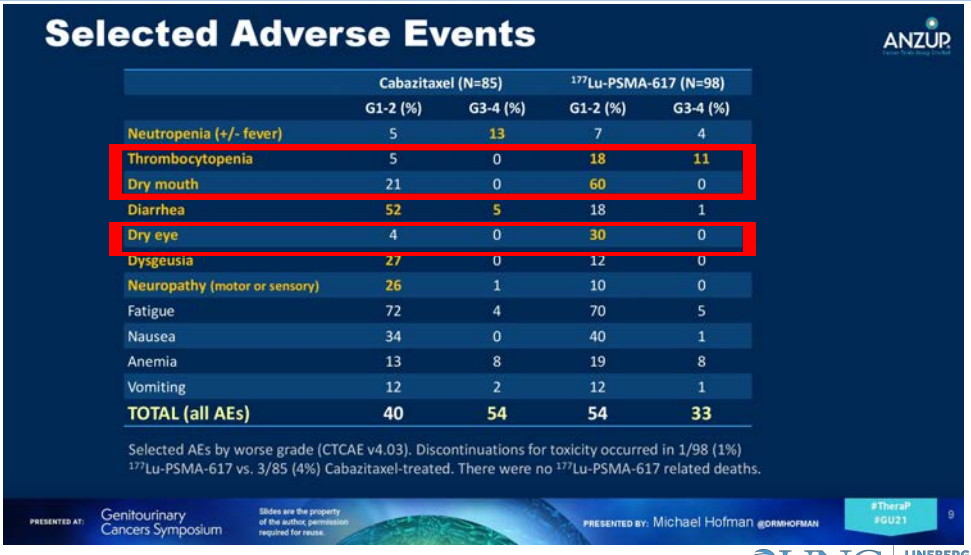
TheraP (ANZUP 1603)



	Cabazitaxel (N=85)		177Lu-PSMA-617 (N=98)	
	G1-2 (%)	G3-4 (%)	G1-2 (%)	G3-4 (%)
Neutropenia (+/- fever)	5	13	7	4
Thrombocytopenia	5	0	18	11
Dry mouth	21	0	60	0
Diarrhea	52	5	18	1
Dry eye	4	0	30	0
Dysgeusia	27	0	12	0
Neuropathy (motor or sensory)	26	1	10	0
Fatigue	72	4	70	5
Nausea	34	0	40	1
Anemia	13	8	19	8
Vomiting	12	2	12	1
TOTAL (all AEs)	**40**	**54**	**54**	**33**

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Press Release (3/23/2021): Phase III VISION study

Novartis announces positive result of phase III study with radioligand therapy 177Lu-PSMA-617 in patients with advanced prostate cancer

- *Phase III VISION study with ^{177}Lu-PSMA-617 met both primary endpoints, significantly improving overall survival (OS) and radiographic progression-free survival (rPFS) in patients with PSMA-positive metastatic castration-resistant prostate cancer[1]*

Likely practice changing (awaiting data)

https://www.novartis.com/news/media-releases/novartis-announces-positive-result-phase-iii-study-radioligand-therapy-177lu-psma-617-patients-advanced-prostate-cancer

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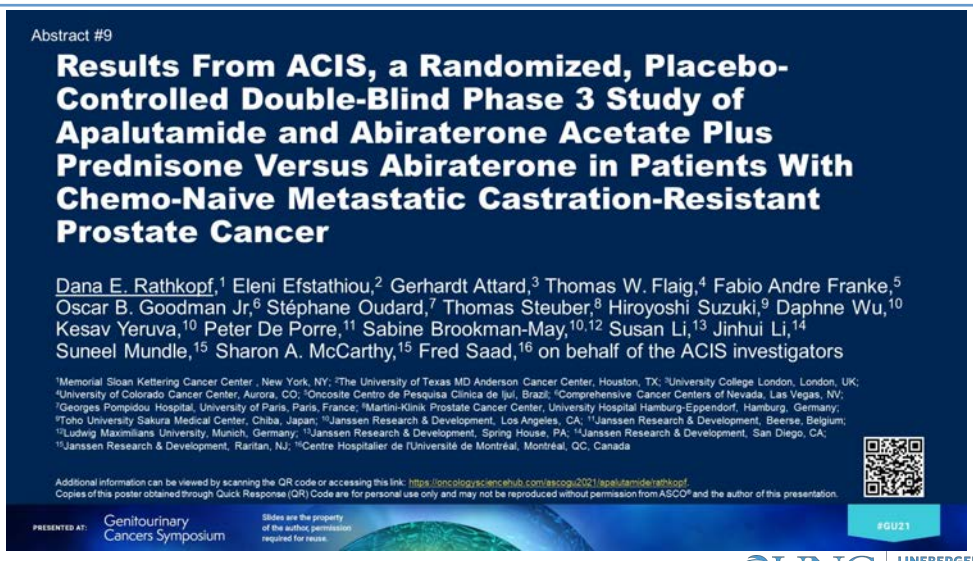
ACIS



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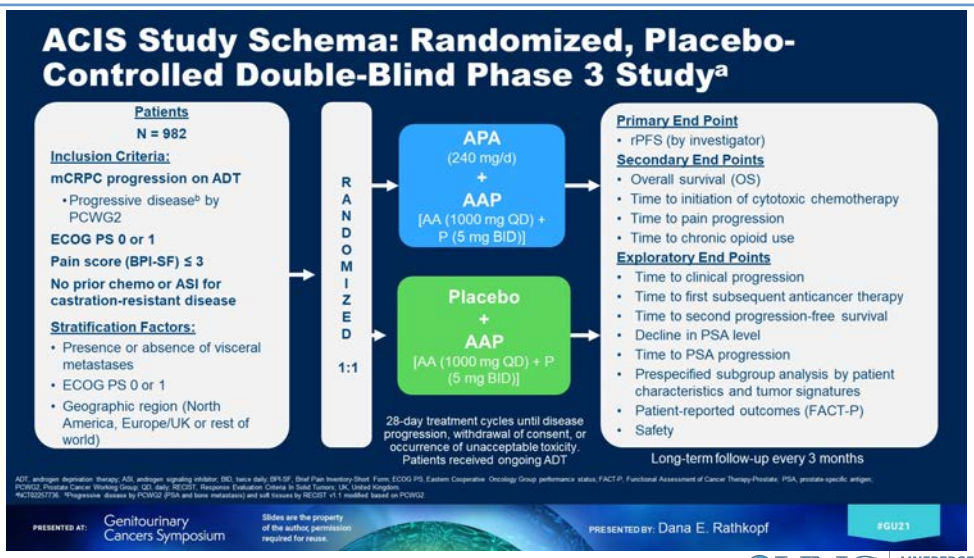
ACIS



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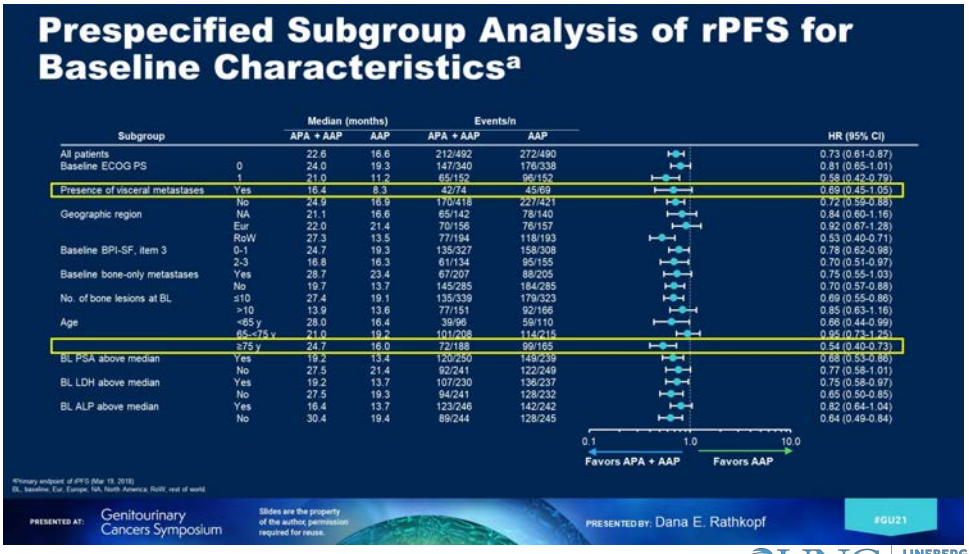
ACIS



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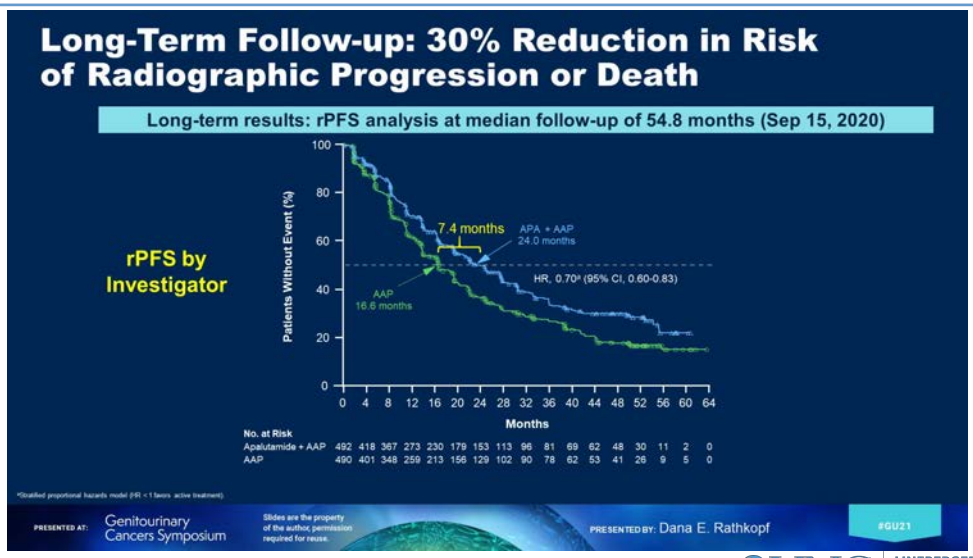
ACIS



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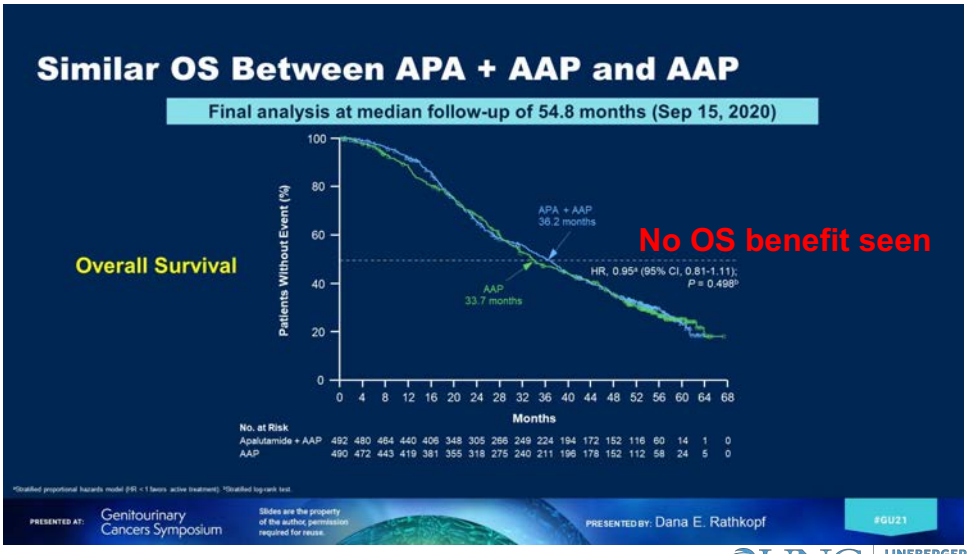
ACIS



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ACIS

APA + AAP Combination Safety Consistent With Previously Reported Profiles: No New Safety Signals

n (%)	APA + AAP (n = 490)		AAP (n = 489)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any TEAE	484 (98.8)	310 (63.3)	473 (96.7)	275 (56.2)
SAE	192 (39.2)	183 (37.3)	165 (33.7)	152 (31.1)
TEAE leading to discontinuation	83 (16.9)	46 (9.4)	61 (12.5)	31 (6.3)
TEAE associated with death[a]	17 (3.5)		37 (7.6)	
TEAEs of special interest[b]				
Fatigue	213 (43.5)	23 (4.7)	183 (37.4)	19 (3.9)
Hypertension	158 (32.2)	101 (20.6)	130 (26.6)	61 (12.5)
Fall	107 (21.8)	16 (3.3)	93 (19.0)	3 (0.6)
Skin rash	101 (20.6)	22 (4.5)	49 (10.0)	2 (0.4)
Cardiac disorders[c]	93 (19.0)	44 (9.0)	94 (19.2)	28 (5.7)
Hypokalemia	79 (16.1)	17 (3.5)	74 (15.1)	20 (4.1)
Peripheral edema	92 (18.8)	1 (0.2)	93 (19.0)	4 (0.8)
Fracture and osteoporosis	74 (15.1)	20 (4.1)	59 (12.1)	7 (1.4)
Ischemic cerebrovascular disorders	9 (1.8)	3 (0.6)	14 (2.9)	6 (1.2)
Seizures	3 (0.6)	1 (0.2)	1 (0.2)	0

SAE, serious adverse event; TEAE, treatment emergent adverse event.
[a]Includes cardiac disorders (APA + AAP: n = 6 [1.2%]; AAP: n = 13 [2.7%]). [b]Based on grouped terms. [c]Includes atrial fibrillation, which occurred in 4.3% and 4.1% of patients treated with APA + AAP and AAP, respectively.

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ACIS – Not practice changing without improvement in OS

ACIS Conclusions

- ACIS met its primary end point of rPFS, as assessed by investigator, in chemotherapy-naive mCRPC
  - rPFS was extended by 6 months in primary per-protocol analysis and by 7.4 months in the updated final analysis with APA + AAP versus AAP ($P < 0.0001$)
  - The rPFS benefit was observed versus AAP, an active comparator
- Secondary end points, including OS, were similar between arms
- No new safety signals were observed
- Slightly higher rates of TEAEs were seen with APA + AAP; however, the quality of life was comparable between treatment arms (FACT-P Total)
- Clinical/biomarker subgroups of patients may derive greater benefit with APA + AAP

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Bladder Cancer Update

1. **EV-301– EV vs. Chemotherapy in mUC (previously treated)**
2. **EV-201 – EV in cisplatin-unfit mUC (prior IO)**
3. **CheckMate 274 – adjuvant Nivolumab in high-risk MIUC**

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EV-301

Primary Results of EV-301: A Phase 3 Trial of Enfortumab Vedotin vs Chemotherapy in Patients With Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

Thomas Powles, MD[1a]; Jonathan E Rosenberg, MD[2a]; Guru P Sonpavde, MD[3]; Yohann Loriot, MD, PhD[4]; Ignacio Durán, MD, PhD[5]; Jae-Lyun Lee, MD, PhD[6]; Nobuaki Matsubara, MD[7]; Christof Vulsteke, MD, PhD[8]; Chunzhang Wu, PhD[9]; Mary Campbell, MD[10]; Maria Matsangou, MBChB, MD[9]; Daniel P Petrylak, MD[11]

[1]Barts Cancer Centre, Queen Mary University of London, London, United Kingdom; [2]Memorial Sloan Kettering Cancer Center, New York City, NY, USA; [3]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [4]Gustave Roussy, Université Paris-Saclay, Villejuif, France; [5]Hospital Universitario Marques de Valdecilla, IDIVAL, Cantabria, Spain; [6]Asan Medical Center and University of Ulsan College of Medicine, Seoul, South Korea; [7]National Cancer Center Hospital East, Chiba, Japan; [8]Center for Oncological Research (CORE), University of Antwerp, Integrated Cancer Center Ghent, Ghent, Belgium; [9]Astellas Pharma, Inc., Northbrook, IL, USA; [10]Seagen Inc., Bothell, WA, USA; [11]Smilow Cancer Center, Yale School of Medicine, New Haven, CT, USA

[a]Dual first authorship; Drs. Powles and Rosenberg contributed equally to this presentation.

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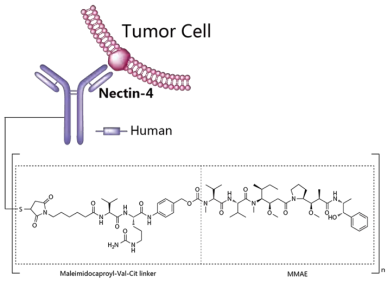
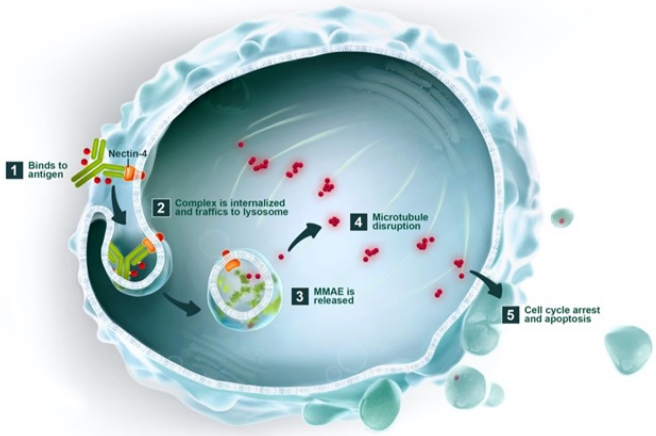
Enfortumab Vedotin





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EV-301

EV-301 Open-Label Phase 3 Trial Design

Key eligibility criteria:
- Histologically/cytologically confirmed UC, including with squamous differentiation or mixed cell types
- Radiographic progression or relapse during or after PD-1/L1 treatment for advanced UC
- Prior platinum-containing regimen for advanced UC[b]
- ECOG PS 0 or 1

1:1 randomization with stratification[a]

Enfortumab vedotin (N=301)
1.25 mg/kg on Days 1, 8, and 15 of each 28-day cycle

Preselected Chemotherapy (N=307)[c]
Docetaxel 75 mg/m² or Paclitaxel 175 mg/m² or Vinflunine[d] 320 mg/m² on Day 1 of each 21-day cycle

Primary endpoint: Overall survival

Secondary endpoints:
- Progression-free survival
- Disease control rate
- Overall response rate
- Safety

→ Investigator-assessed per RECIST v1.1

[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.

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EV-301

Results – Demographics and Disease Characteristics

Parameter		Enfortumab Vedotin N=301	Chemotherapy N=307
Age, median		68 years	68 years
Male sex		79%	76%
Geographic region	Western Europe	42%	42%
	United States	14%	14%
	Rest of the world	44%	44%
ECOG performance status[b]	0	40%	40%
	1	60%	60%
Bellmunt risk score	0-1	67%	68%
	≥2	30%	31%
Liver metastasis[a]		31%	31%
Prior lines of systemic therapy	1-2	87%	88%
	≥3	13%	12%
Response to prior CPI		20%	16%

[a]Indicates stratification variables: ECOG performance status (0 or 1), regions of the world (US, western Europe, or rest of world), liver metastasis (yes or no).
Abbreviations: CPI, checkpoint inhibitor; ECOG, Eastern Cooperative Oncology Group.

Data cut-off: July 15, 2020

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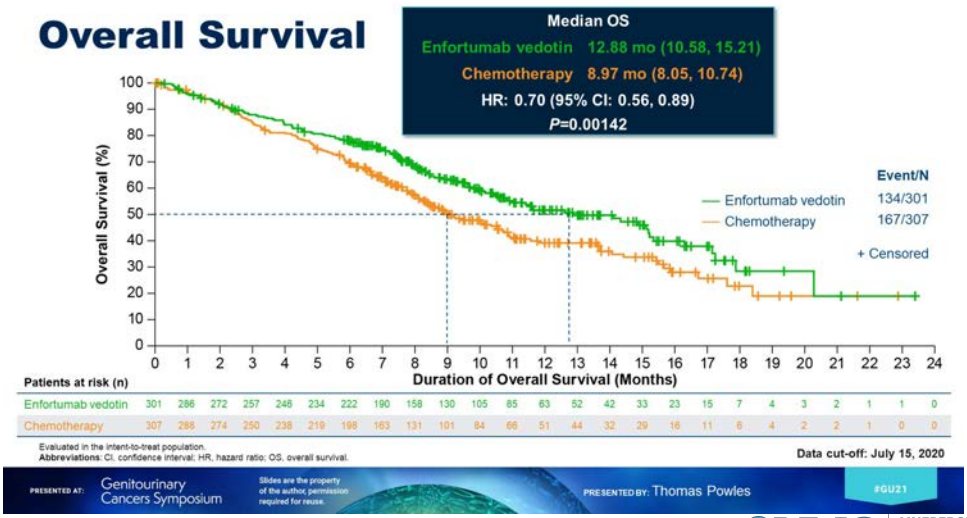
EV-301

Overall Survival



Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

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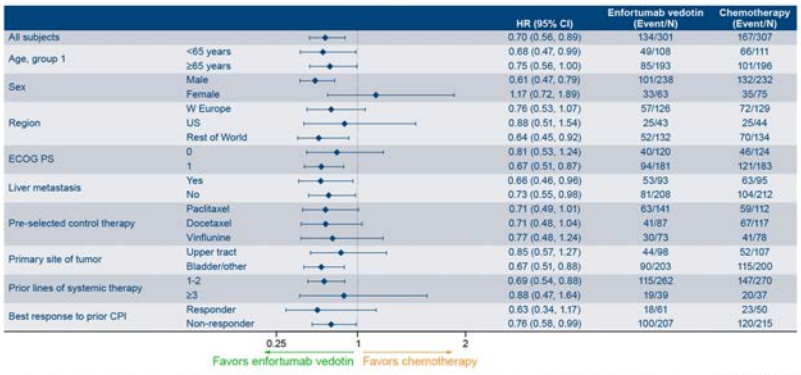
EV-301

Overall Survival: Subgroup Analyses



Abbreviations: CI, confidence interval; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; US, United States; W, western.

Data cut-off: July 15, 2020

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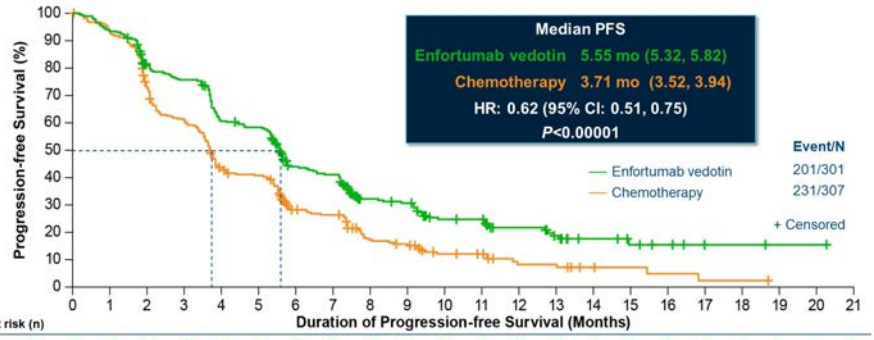
EV-301

Progression-free Survival



Patients at risk (n)

Enfortumab vedotin	301	269	224	208	165	158	102	95	60	56	38	36	23	17	11	7	5	2	2	1	1	0
Chemotherapy	307	259	200	166	116	107	62	57	33	29	18	16	8	8	4	3	2	1	0	0	0	0

Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Data cut-off: July 15, 2020

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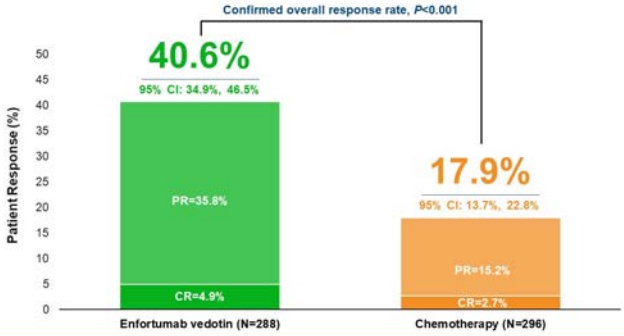
EV-301

Investigator-Assessed Overall Response



Disease control rate,[a] % (95% CI)	71.9 (66.3, 77.0)	53.4 (47.5, 59.2)	P<0.001

Evaluated in the response-evaluable population. Response is as assessed by the investigator per RECIST v1.1.
[a]Indicates the proportion of patients who had a best overall response of confirmed CR, PR, or SD (at least 7 weeks); enfortumab vedotin vs chemotherapy.
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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EV-301

Treatment-Related Adverse Events

Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any adverse event	**94%**	**51%**	**92%**	**50%**
Alopecia	45%	0	36%	0
Peripheral sensory neuropathy	34%	3%	21%	2%
Pruritus	32%	1%	4%	0
Fatigue	31%	6%	23%	4%
Decreased appetite	31%	3%	23%	2%
Diarrhea	24%	3%	16%	2%
Dysgeusia	24%	0	7%	0
Nausea	23%	1%	22%	1%
Rash maculopapular	16%	7%	2%	0
Anemia	12%	3%	20%	8%
Neutrophil count decreased	10%	6%	17%	13%
Neutropenia	7%	5%	8%	6%
White blood cell decreased	5%	1%	11%	7%
Febrile neutropenia	1%	1%	5%	5%
Serious adverse events[a]	23%	-	23%	-
Leading to treatment withdrawal	14%	-	11%	-

TRAEs leading to death, excluding disease progression, occurred in 7 patients (2.4%) treated with EV and 3 (1.0%) treated with chemotherapy.

Evaluated in the safety population; displaying adverse events (AEs) occurring in ≥20% or grade ≥3 AEs occurring in ≥5% of patients in either treatment group. Dashes indicate 'not applicable.'
Treatment-related AEs are events with a reasonable possibility of relationship to treatment (investigator-assessed) or missing relationship and are not time-adjusted.
This slide contains updated data in the chemotherapy arm to adjust for compounded rounding.
[a]AEs that were deemed "serious" in the view of the investigator or sponsor and based upon predefined criteria.
Abbreviations: AE, adverse event; EV, enfortumab vedotin; TRAEs, treatment-related adverse events.

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EV-301 – Practice changing

EV-301: Conclusions

Efficacy

Enfortumab vedotin had superior overall survival compared with chemotherapy in patients with advanced UC who had previously received platinum-based chemotherapy and a PD-1/L1 inhibitor

- Enfortumab vedotin showed superior progression-free survival and response rates compared with chemotherapy
- Subgroup analyses also broadly showed benefit in the enfortumab vedotin arm
- Results were consistent with phase 1 and 2 studies

Safety

Enfortumab vedotin demonstrated a tolerable and manageable safety profile

- No new safety signals were identified; safety profile was consistent with prior enfortumab vedotin studies
- Adverse events of special interest (eg, skin reactions, peripheral neuropathy, and hyperglycemia) were generally mild/moderate in severity and consistent with those reported in prior studies

Overall

Enfortumab vedotin is the first drug, beyond chemotherapy and immunotherapy, to show significant survival advantage in previously treated advanced UC

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EV-201

EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors (NCT03219333)

Arjun V. Balar, Bradley McGregor, Jonathan Rosenberg, Michiel S. van der Heijden, Se Hoon Park, Jae Lyun Lee, Michael R. Harrison, Elisabeth I. Heath, Mark N. Stein, Yohann Loriot, Andrea Necchi, Joyce Steinberg, Shang-Ying Liang, Eric Kim, Janet Trowbridge, Mary Campbell, Daniel P. Petrylak, and Evan Y. Yu

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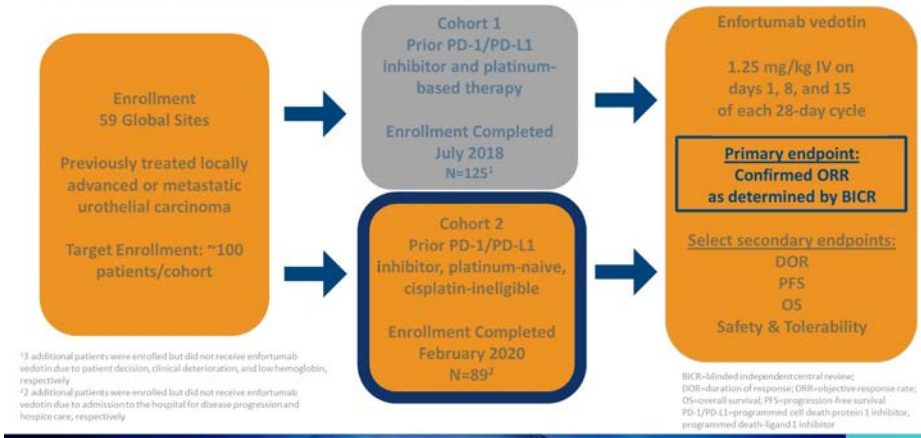
EV-201

EV-201: Non-Comparative, Pivotal Phase 2 Trial



[1]3 additional patients were enrolled but did not receive enfortumab vedotin due to patient decision, clinical deterioration, and low hemoglobin, respectively
[2]2 additional patients were enrolled but did not receive enfortumab vedotin due to admission to the hospital for disease progression and hospice care, respectively

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PD-1/PD-L1=programmed cell death protein 1 inhibitor, programmed death-ligand 1 inhibitor

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EV-201

EV-201 Cohort 2: Key Eligibility Criteria

- Key inclusion criteria:
  - Locally advanced unresectable or metastatic urothelial carcinoma (including divergent differentiation)
  - Previously treated with a PD-1/PD-L1 inhibitor
  - Ineligible for cisplatin-containing chemotherapy[1] and no prior exposure to platinum-containing chemotherapy in the locally advanced or metastatic setting
  - Progression during or following most recent treatment
- Key exclusion criteria:
  - Ongoing sensory or motor neuropathy ≥Grade 2
  - Active CNS metastases
  - Uncontrolled diabetes mellitus[2]

[1]Defined as meeting any of the following criteria: impaired renal function ([CrCl] ≥30 and <60 mL/min), hearing loss ≥Grade 2, ECOG performance status score >2
[2]Hemoglobin A1C (HbA1c) ≥8% or HbA1c of 7% to <8% with associated diabetes symptoms, polyuria or polydipsia, that were not otherwise explained

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EV-201

EV-201 Cohort 2: Key Demographics and Disease Characteristics

Characteristic	Patients (N=89)	Characteristic	Patients (N=89)
Median age (range), years	75 (49, 90)	Primary tumor location	
Male sex	66 (74%)	Upper tract[1]	38 (43%)
ECOG performance status		Bladder/other	51 (57%)
0 or 1	78 (88%)	Metastasis sites	
2	11 (12%)	Lymph nodes only	18 (20%)
Body mass index ≥30 kg/m^2	13 (15%)	Visceral disease[2]	70 (79%)
Renal function based on creatinine clearance		Liver	21 (24%)
Normal/Mild decrease ≥60 mL/min	27 (30%)	Received prior PD-1/PD-L1 therapy in first line	87 (98%)
Moderate decrease: ≥30 and <60 mL/min	60 (67%)	Responder[3] to PD-1/PD-L1-containing therapy	22 (25%)
Severe decrease: ≥15 and <30 mL/min	2 (2%)		

[1]Includes renal pelvis and ureter.
[2]Sites of visceral disease include liver, lung, intra-thoracic or intra-abdominal soft tissue, kidney, spleen, ovary, adrenal glands, and bone.
[3]Responses were investigator reported.

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EV-201

EV-201 Cohort 2: Best Overall Response per BICR

ORR per RECIST v 1.1 assessed by BICR	Patients (N=89) %
Confirmed ORR, 95% CI[1]	52 (40.8, 62.4)
Best overall response[2]	
Confirmed complete response	20
Confirmed partial response	31
Stable disease	30
Progressive disease	9
Not evaluable[3]	9

ORR = Objective Response Rate; RECIST = Response Evaluation Criteria in Solid Tumors; BICR = Blinded Independent Central Review
[1]CI = Confidence Interval, Computed using the Clopper-Pearson method
[2]Best overall response according to RECIST v1.1. Complete response and partial response were confirmed with repeat scans ≥28 days after initial response.
[3]Includes five subjects who did not have response assessment post-baseline, two subjects whose post-baseline assessment did not meet the minimum interval requirement for stable disease, and one subject whose response cannot be assessed due to incomplete anatomy.

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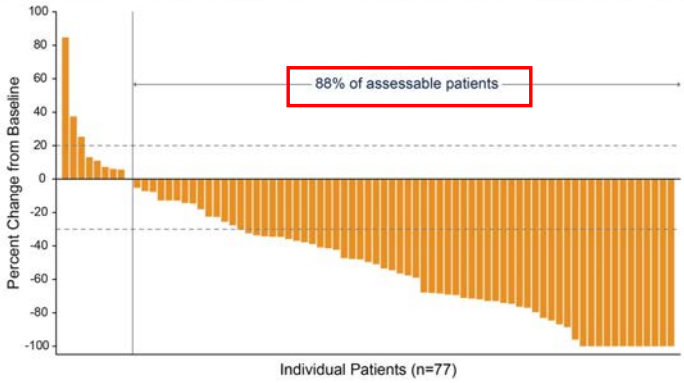
EV-201

EV-201 Cohort 2: Change in Tumor Measurements per BICR



Data are not available for 12 subjects due to no response assessment post-baseline (n=5), incomplete assessment of target lesions post-baseline (n=1), or no measurable disease at baseline per BICR (n=6).

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#GU21

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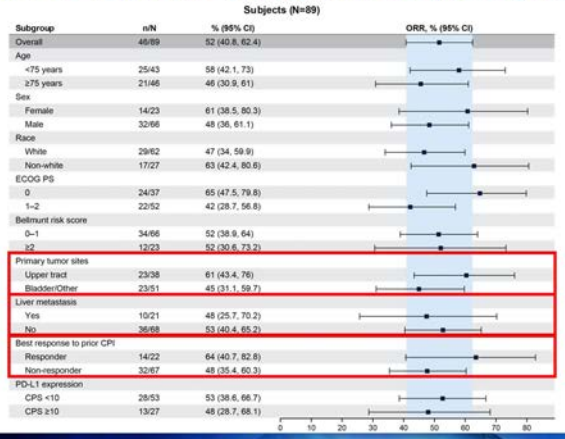
EV-201

EV-201 Cohort 2: Responses by Subgroup per BICR



Responses were observed across all subgroups, including patients:
- with primary tumor sites in the upper tract (ORR=61%)
- with liver metastasis (ORR=48%)
- who did not respond to prior PD-1/PD-L1 inhibitors (ORR=48%)

BICR = Blinded Independent Central Review; ORR = Objective Response Rate; ECOG PS= Eastern Cooperative Oncology Group Performance Score; CPI = Checkpoint Inhibitor; PD-1 = programmed cell death protein 1 inhibitor; PD-L1 = programmed death-ligand 1; CPS = combined positive score

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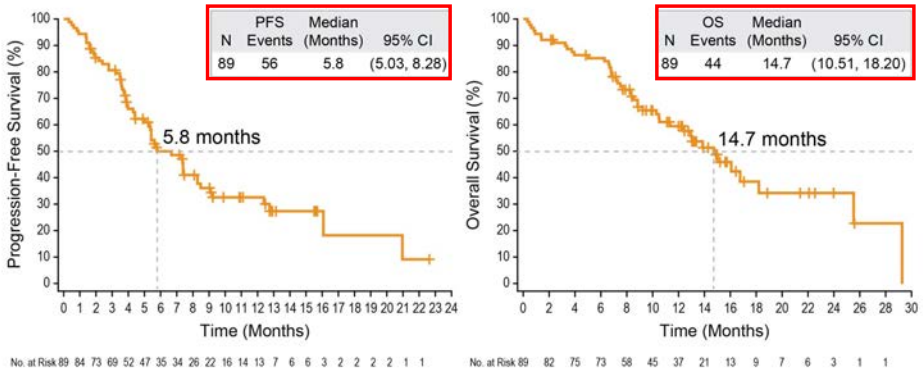
EV-201

EV-201 Cohort 2: Progression-Free Survival and Overall Survival



Median follow-up: 13.4 months

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EV-201 – Promising but not practice changing at this time

EV-201 Cohort 2: Summary and Conclusions

- Following immunotherapy, cisplatin-ineligible patients need effective treatment options
- The response rates to EV in this study are numerically the highest observed for any regimen in cisplatin-ineligible patients with advanced urothelial carcinoma
  - 52% ORR, with 20% CR rate
  - 10.9 months median duration of response
  - Response rates were consistent across all subgroups
- Tolerable safety profile in an elderly patient population ineligible for cisplatin
- Activity demonstrated in EV-201 Cohort 2 builds upon the overall survival benefit shown in PD-1/PD-L1 inhibitor and platinum-treated patients in EV-301
- These data support continued investigation of EV across the spectrum of urothelial carcinoma and may support a new standard of care for this population with unmet need

ORR = Objective Response Rate; CR = Complete Response
Ongoing enfortumab vedotin trials: **EV-103:** EV alone or in combination with pembrolizumab and/or chemotherapy (NCT03288545) **EV-302:** EV in combination with pembrolizumab vs. chemotherapy alone (NCT04223856)

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CheckMate 274

CheckMate 274

Study design

- CheckMate 274 is a phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors

- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status

R 1:1

- NIVO IV 240 mg Q2W
- PBO IV Q2W

Treat for up to 1 year of adjuvant therapy

Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IHC, immunohistochemistry; ITT, intent-to-treat; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; R, randomized.

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CheckMate 274

CheckMate 274

Statistical design

- Two primary objectives
  - To compare **DFS for NIVO versus PBO in all randomized patients (ITT)**
  - To compare **DFS for NIVO versus PBO in all randomized patients with PD-L1 ≥ 1%**
- Sample size calculation (~700 patients)

	ITT	PD-L1 ≥ 1%
Power considerations	~410 DFS events would provide ~87% power to detect an average HR of 0.72 with an overall type I error of 2.5% (2-sided)	~162 DFS events would provide ~80% power to detect an average HR of 0.61 with an overall type I error of 2.5% (2-sided)
Interim analysis	One interim analysis planned at ~85% of targeted DFS events	
Adjusted alpha level at interim analysis	0.01694 (based on 348 observed DFS events)	0.01131 (based on 137 observed DFS events)

- Key secondary objective
  - OS (secondary endpoint) to be tested using hierarchical procedure in each population, per the statistical analysis plan

HR, hazard ratio.

4

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Select baseline demographic and disease characteristics in all randomized patients

	NIVO (N = 353)	PBO (N = 356)
Mean age (range), years	65.3 (30-92)	65.9 (42-88)
Male, %	75.1	77.2
Region, %		
United States	13.9	14.9
Europe	48.2	48.0
Asia	22.7	20.8
Rest of the world	15.3	16.3
ECOG PS,[a] %		
0	63.5	62.1
1	34.6	35.1
2[b]	2.0	2.5
Tumor origin at initial diagnosis, %		
Urinary bladder	79.0	78.9
Upper tract disease	21.0	21.1
Minor histological variants present, %	41.1	39.6
PD-L1 ≥ 1% by IVRS, %	39.7	39.9
Prior neoadjuvant cisplatin, %	43.3	43.5
Pathologic T stage at resection,[c,d] %		
pT0-2	22.7	24.2
pT3	58.4	57.3
pT4a	16.1	17.4
Other	2.5	0.8
Nodal status at resection,[d] %		
N+	47.3	47.2
N0/x with < 10 nodes removed	26.6	27.8
N0 with ≥ 10 nodes removed	25.8	24.7

[a]Not reported for 1 patient in the PBO arm. [b]ECOG PS of 2 was permitted only for patients who did not receive cisplatin-based neoadjuvant chemotherapy and are ineligible for adjuvant cisplatin-based chemotherapy. [c]The T staging included patients with N+, N0, or NX. [d]Not reported for 1 patient in each arm.
ECOG PS, Eastern Cooperative Oncology Group performance status; IVRS, interactive voice-response system.

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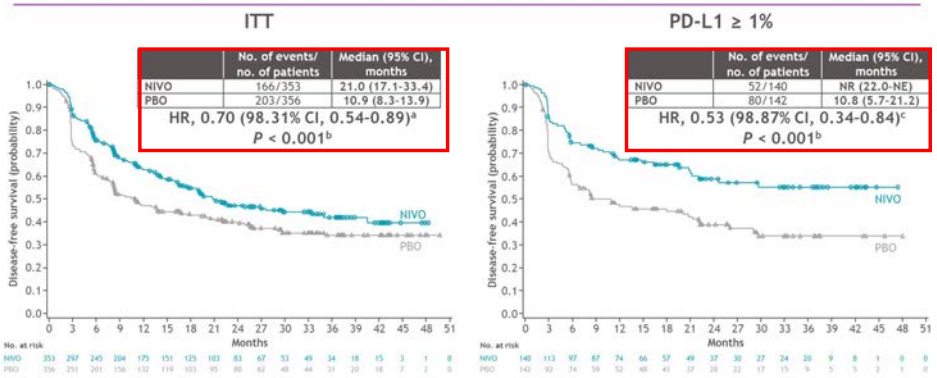
CheckMate 274

CheckMate 274

Disease-free survival



Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

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CheckMate 274

CheckMate 274

Non-urothelial tract recurrence-free survival

ITT

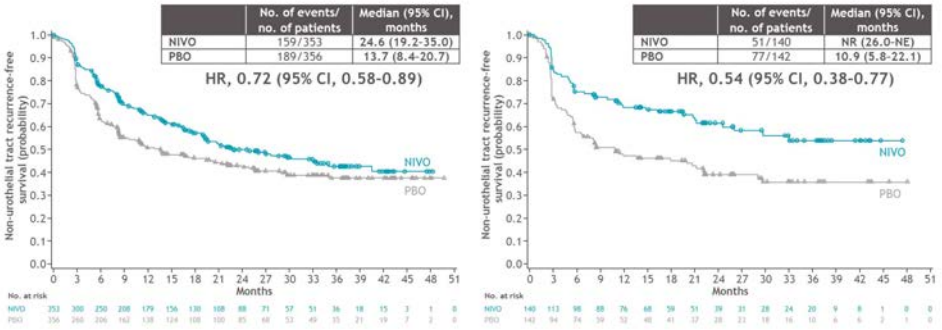
	No. of events/ no. of patients	Median (95% CI), months
NIVO	159/353	24.6 (19.2-35.0)
PBO	189/356	13.7 (8.4-20.7)

HR, 0.72 (95% CI, 0.58-0.89)

PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	51/140	NR (26.0-NE)
PBO	77/142	10.9 (5.8-22.1)

HR, 0.54 (95% CI, 0.38-0.77)



Minimum follow-up, 5.9 months.
NUTRFS was defined as the time between the date of randomization and the date of first local non-urothelial tract or distant recurrence or death.

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Distant metastasis-free survival

ITT

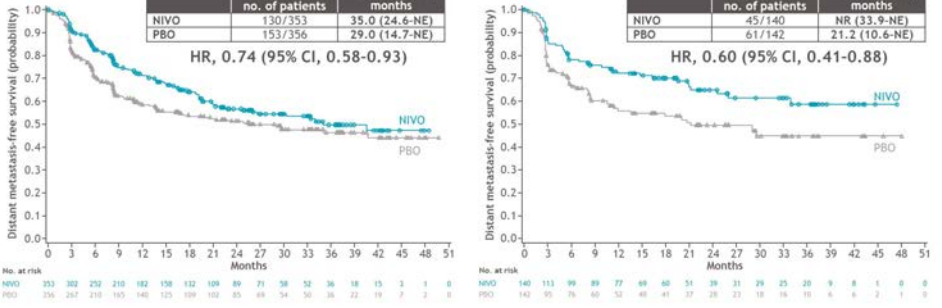
	No. of events/ no. of patients	Median (95% CI), months
NIVO	130/353	35.0 (24.6-NE)
PBO	153/356	29.0 (14.7-NE)

HR, 0.74 (95% CI, 0.58-0.93)

PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	45/140	NR (33.9-NE)
PBO	61/142	21.2 (10.6-NE)

HR, 0.60 (95% CI, 0.41-0.88)



Minimum follow-up, 5.9 months.
DMFS was defined as the time between the date of randomization and the date of first distant recurrence (non-local) or date of death.

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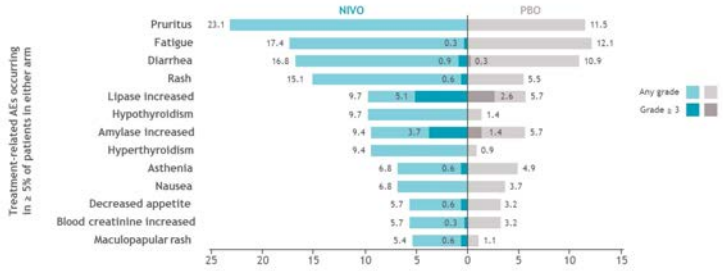
CheckMate 274

CheckMate 274

Safety summary in all treated patients

	NIVO (N = 351)[a]		PBO (N = 348)[a]	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any-cause AEs, %	98.9	42.7	95.4	36.8
Treatment-related AEs,[b] %	77.5	17.9	55.5	7.2
Treatment-related AEs leading to discontinuation, %	12.8	7.1	2.0	1.4



[a]Includes all treated patients. [b]There were 2 treatment-related deaths due to pneumonitis in the NIVO arm. There were no treatment-related deaths in the PBO arm. Includes events reported between the first dose and 30 days after the last dose of study therapy.

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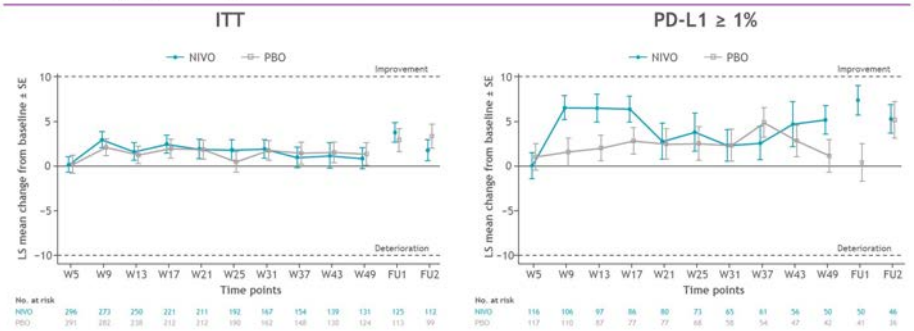
CheckMate 274

Health-related quality of life: change from baseline in EORTC-QLQ-C30 global health status score



- No deterioration in HRQoL with NIVO versus PBO was observed in either the ITT or PD-L1 ≥ 1% populations

Number of patients displayed is the number of patients included in the mixed effects linear regression for repeated measures analysis at each visit. SE is the robust SE calculated using empirical variance estimator.
FU, follow-up visit; LS, least square; SE, standard error.

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CheckMate 274 – Potential to be practice changing…

CheckMate 274

Summary

- Adjuvant NIVO significantly improved DFS in patients with high-risk MIUC after radical surgery, both in the ITT and PD-L1 ≥ 1% populations
- NUTRFS (secondary endpoint) and DMFS (exploratory endpoint) were also improved with NIVO versus PBO in both study populations
- The safety and tolerability of NIVO monotherapy was consistent with previous reports in other tumor types, including in patients with metastatic UC[1-3]
- No deterioration in HRQoL, as measured by change in EORTC QLQ-C30 global health status score, was observed with NIVO versus PBO
- NIVO is the first systemic immunotherapy to demonstrate a statistically significant and clinically meaningful improvement in outcomes when administered as adjuvant therapy to patients with MIUC[4,5]
- These results support NIVO monotherapy as a new standard of care in the adjuvant setting for patients with high-risk MIUC after radical surgery, regardless of PD-L1 status and prior neoadjuvant chemotherapy

1. Sharma P et al. *Lancet Oncol* 2016;17:1590-1598. 2. Sharma P et al. *Lancet Oncol* 2017;18:312-322. 3. Motzer R et al. *N Engl J Med* 2015;373:1803-1813. 4. Kim HS et al. *Investig Clin Urol* 2018;59:285-296. 5. Hussain MHA et al. *J Clin Oncol* 2020;38(suppl 15):5000.

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IMvigor 010

IMvigor010 Study Design

Key eligibility[a]
- **High-risk MIUC (bladder, renal pelvis, ureter)**
- **Radical cystectomy/nephroureterectomy with LN dissection** within ≤ 14 weeks
  - **ypT2-T4a or ypN+** for patients treated with **NAC[b]**
  - **pT3-T4a or pN+** for patients **not treated with NAC[b]**
- No postsurgical radiation or AC
- If no prior NAC given, patient had to be ineligible for, or declined, cisplatin-based AC
- ECOG PS 0-2
- **Tissue sample for PD-L1 testing**

R 1:1

Atezolizumab 1200 mg q3w *(16 cycles or 1 year)*

No crossover allowed

Observation[c] q3w

Disease recurrence/ survival follow-up

Tumor assessments: q12w for years 1-3, (q24w for years 4-5 and at year 6)

Stratification factors
- Number of LNs resected (< 10 vs ≥ 10)
- Prior NAC (Yes vs No)
- LN status (+ vs –)
- Tumor stage (≤ pT2 vs pT3/pT4)
- PD-L1 status[a] (IC0/1 vs IC2/3)

- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b] Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c] Alternating clinic visits and phone calls.

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Hussain M. IMvigor010 primary analysis [abs 5000] https://bit.ly/2SKSAD3

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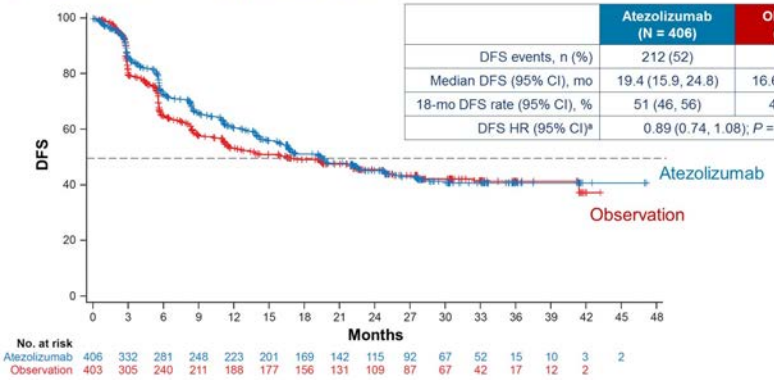
IMvigor 010

DFS in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); $P = 0.2446$[b]	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a]Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b]2-sided.

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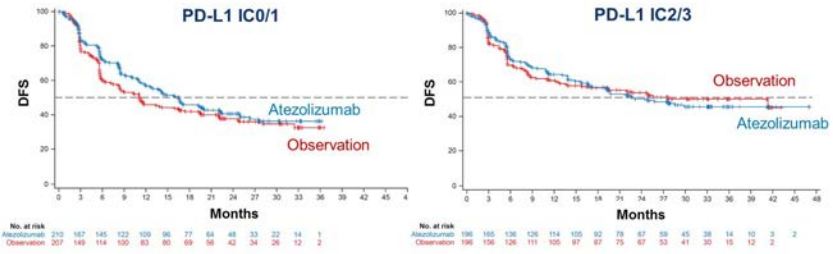
IMvigor 010

DFS by PD-L1 Status



	Atezolizumab (n = 210)	Observation (n = 207)
DFS events, n (%)	118 (56)	120 (58)
HR (95% CI)[a]	0.81 (0.63, 1.05)	

	Atezolizumab (n = 196)	Observation (n = 196)
DFS events, n (%)	94 (48)	88 (45)
HR (95% CI)[a]	1.01 (0.75, 1.35)	

Data cutoff: November 30, 2019. IC2/3, PD-L1–expressing IC on ≥ 5% of tumor area (VENTANA SP142 assay); IC0/1, < 5%. [a]Stratified by tumor stage and nodal status.

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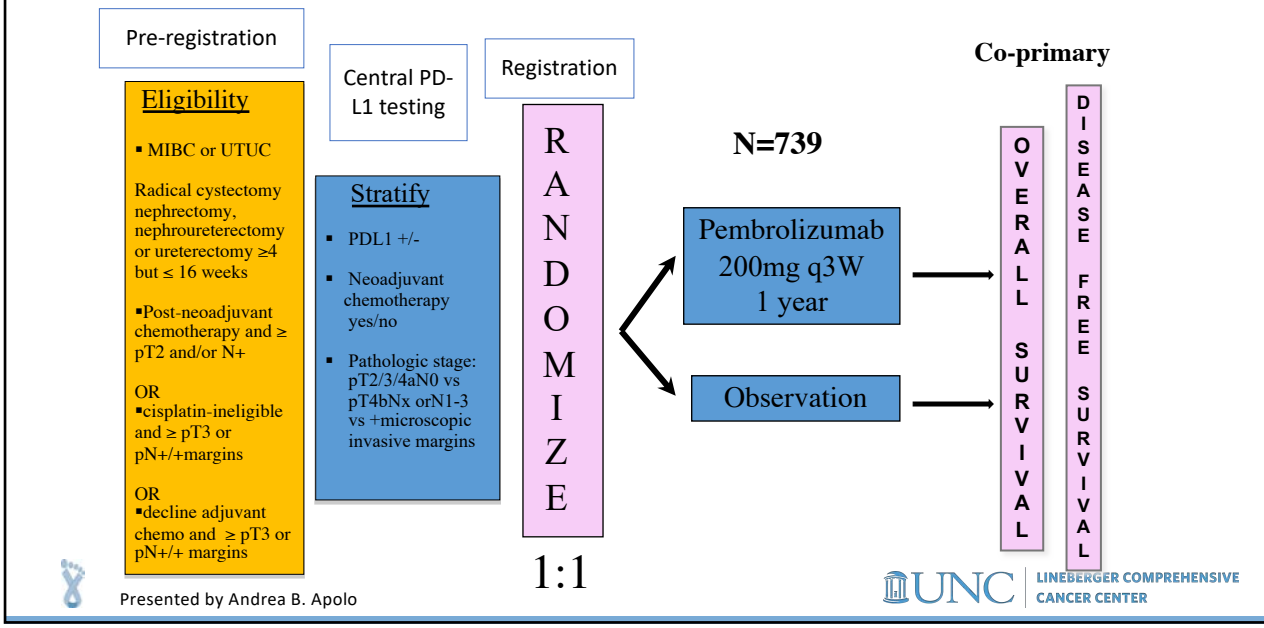
ALLIANCE A031501: Phase III randomized "Adjuvant study of peMBrolizumAb in muScle invaSive and locAlly aDvanced urOthelial carcinoma" (AMBASSADOR) versus observation



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Kidney Cancer Update

1. **CLEAR – Len/Pem in advanced ccRCC**
2. **SWOG 1500 – Cabo in pRCC**

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CLEAR

Phase 3 trial of lenvatinib plus pembrolizumab or everolimus versus sunitinib monotherapy as a first-line treatment for patients with advanced renal cell carcinoma (CLEAR study)

Robert Motzer[1], Camillo Porta[2], Masatoshi Eto[3], Thomas Powles[4], Viktor Grünwald[5], Thomas E. Hutson[6], Boris Alekseev[7], Sun Young Rha[8], Evgeny Kopyltsov[9], María José Méndez-Vidal[10], Sung-Hoo Hong[11], Anil Kapoor[12], Teresa Alonso Gordoa[13], Jeffrey C. Goh[14], Jaime R. Merchan[15], Alan D. Smith[16], Kalgi Mody[17], Rodolfo F. Perini[18], Dongyuan Xing[17], and Toni K. Choueiri[19]

[1]Memorial Sloan Kettering Cancer Center; New York, NY, USA; [2]San Matteo University Hospital Foundation, Pavia, Italy; [3]Kyushu University, Fukuoka, Japan; [4]The Royal Free NHS Trust, London, England, UK; [5]University Hospital Essen, Essen, Germany; [6]Texas Oncology, Dallas, TX, USA; [7]P.A. Hertsen Moscow Cancer Research Institute, Moscow, Russia; [8]Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; [9]State Institution of Healthcare "Regional Clinical Oncology Dispensary", Omsk, Russia; [10]Maimonides Institute for Biomedical research of Cordoba (IMIBIC) Hospital Universitario Reina Sofía, Medical Oncology Department, Córdoba, Spain; [11]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [12]McMaster University Hamilton, Ontario, Canada; [13]Hospital Universitario Ramón y Cajal, Madrid, Spain; [14]ICON Research, South Brisbane & University of Queensland, St Lucia, Queensland, Australia; [15]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [16]Eisai Ltd., Hatfield, UK; [17]Eisai Inc., Woodcliff Lake, NJ, USA; [18]Merck & Co., Inc., Kenilworth, NJ, USA; [19]Dana-Farber Cancer Institute, Boston, MA, USA.

PRESENTED AT: Genitourinary Cancers Symposium

Abstract #269 #GU21

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CLEAR

Study Design

Key eligibility criteria
- Advanced clear-cell RCC
- Treatment-naïve
- Karnofsky performance status ≥70
- Measurable disease
- Adequate organ function

Stratification factors
- **Geographic region:** Western Europe and North America vs Rest of the World
- **MSKCC risk category:** Favorable, Intermediate, or Poor

R (1:1:1)

- **Lenvatinib** 20 mg oral QD + **Pembrolizumab*** 200 mg IV Q3W
- **Lenvatinib** 18 mg oral QD + **Everolimus** 5 mg oral QD
- **Sunitinib** 50 mg oral QD 4 weeks on / 2 weeks off

Primary endpoint
- PFS by IRC per RECIST v1.1

Secondary endpoints
- OS
- ORR by IRC per RECIST v1.1
- Safety
- HRQoL

Key exploratory endpoints
- DOR
- Biomarkers

*Patients could receive a maximum of 35 pembrolizumab treatments.
DOR, duration of response; HRQoL, Health-related quality of life; IRC, Independent Review Committee; MKSCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; R, randomization.

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Baseline Characteristics

	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUN (n = 357)
Median age (range) — years	64 (34–88)	62 (32–86)	61 (29–82)
Geographic region — %			
Western Europe and North America	55.8	56.0	55.7
Rest of the World	44.2	44.0	44.3
MSKCC prognostic risk group — %			
Favorable / Intermediate / Poor	27.0 / 63.9 / 9.0	27.5 / 63.6 / 9.0	27.2 / 63.9 / 9.0
IMDC risk group — %			
Favorable / Intermediate / Poor	31.0 / 59.2 / 9.3	31.9 / 54.6 / 11.8	34.7 / 53.8 / 10.4
Sarcomatoid features — %	7.9	6.7	5.9
PD-L1 expression — %			
≥ 1 / < 1 / not available	30.1 / 31.5 / 38.3	32.5 / 33.1 / 34.5	33.3 / 28.9 / 37.8
Prior nephrectomy — %	73.8	72.8	77.0

IMDC, International Metastatic RCC Database Consortium; PD-L1, programmed death ligand 1.

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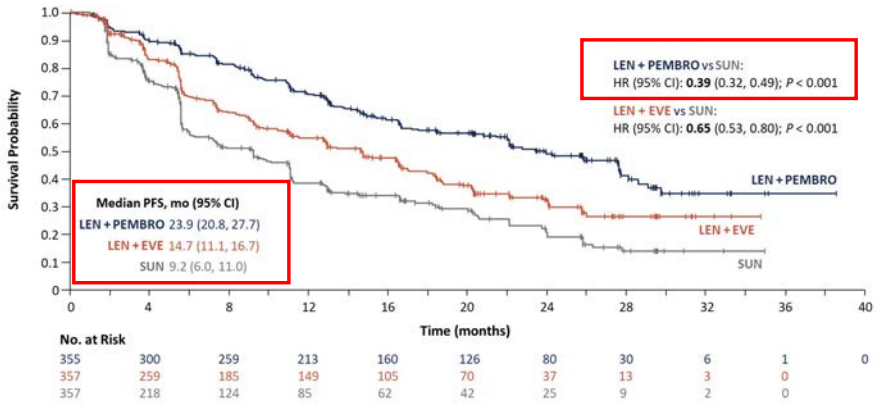
Progression-free Survival*



*By Independent Review Committee per RECIST v1.1.

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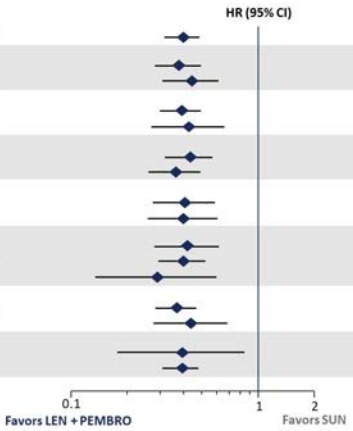
Progression-free Survival* With Lenvatinib Plus Pembrolizumab in Key Subgroups

Subgroup	LEN + PEMBRO Events / no. of patients	SUN Events / no. of patients	HR (95% CI)
Overall	160/355	205/357	0.39 (0.32–0.49)
Age			
< 65 years	88/194	134/225	0.37 (0.28–0.49)
≥ 65 years	72/161	71/132	0.43 (0.31–0.61)
Sex			
Male	120/255	158/275	0.38 (0.30–0.49)
Female	40/100	47/82	0.42 (0.27–0.66)
Geographic region			
Western Europe and NA	86/198	108/199	0.42 (0.32–0.57)
Rest of the World	74/157	97/158	0.36 (0.26–0.49)
PD-L1 expression			
≥ 1	51/107	78/119	0.40 (0.27–0.58)
< 1	48/112	58/103	0.39 (0.26–0.59)
IMDC risk group			
Favorable	43/110	67/124	0.41 (0.28–0.62)
Intermediate	97/210	110/192	0.39 (0.29–0.52)
Poor	18/33	26/37	0.28 (0.13–0.60)
Prior nephrectomy			
Yes	107/262	163/275	0.37 (0.28–0.47)
No	53/93	42/82	0.44 (0.28–0.68)
Sarcomatoid features			
Yes	19/28	16/21	0.39 (0.18–0.84)
No	141/327	189/336	0.38 (0.31–0.48)



*By Independent Review Committee per RECIST v1.1.
NA, North America.

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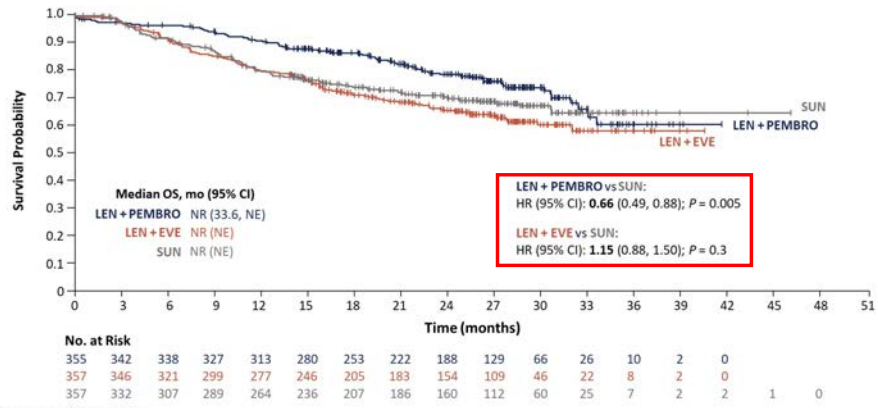
Overall Survival



No. at Risk

355	342	338	327	313	280	253	222	188	129	66	26	10	2	0	
357	346	321	299	277	246	205	183	154	109	46	22	8	2	0	
357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

NE, not estimable; NR, not reached.

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Confirmed Objective Response Rate*

	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUN (n = 357)
Objective response rate (95% CI) — %	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Best overall response — %			
Complete response	16.1	9.8	4.2
Partial response	54.9	43.7	31.9
Stable disease	19.2	33.6	38.1
Progressive disease	5.4	7.3	14.0
Unknown / not evaluable	4.5	5.6	11.8
Relative risk versus SUN (95% CI)	1.97 (1.69–2.29)	1.48 (1.26–1.74)	--
P-value	< 0.001	< 0.001	--

*By Independent Review Committee per RECIST v1.1.

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Treatment Exposure, Safety, and Discontinuation

	LEN + PEMBRO (n = 352)	LEN + EVE (n = 355)	SUN (n = 340)
Median duration of treatment, months (range)	17.0 (0.1–39.1)	11.0 (0.1–40.0)	7.8 (0.1–37.0)
Patients with any TRAEs (%)	96.9	97.7	92.1
Grade ≥ 3*	71.6	73.0	58.8
Patients with any TRAEs leading to dose reductions (LEN or SUN) (%)	67.3	69.3	49.7
Patients with any grade TRAEs leading to discontinuation (%)			
LEN or SUN	18.5	16.1	10.0
PEMBRO or EVE	25.0	19.2	--
LEN + PEMBRO or LEN + EVE	9.7	13.5	--

*Grade 5 TRAEs were observed in 1.1% of patients in the LEN + PEMBRO arm, 0.8% of patients in the LEN + EVE arm, and 0.3% of patients in the SUN arm.
TRAE, treatment-emergent adverse event.

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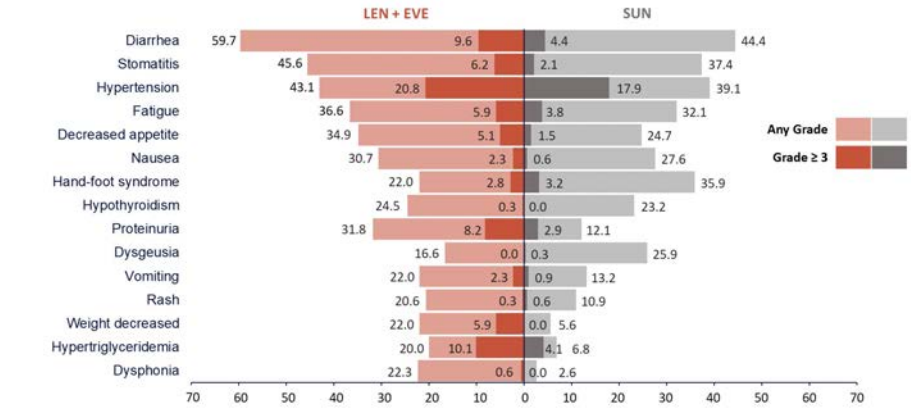
TRAEs With Frequency ≥ 20%



Alanine aminotransferase/aspartate aminotransferase increased in 10.4/11.5% (grade 3: 2.0/1.4%) of patients in the LEN + EVE arm and 8.8/8.8% of patients (grade 3: 1.8/0.6%) in the SUN arm.

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CLEAR – Practice changing as another IO/VEGFR TKI combo

Conclusions

- Lenvatinib plus pembrolizumab demonstrated significant improvements in PFS, OS, and ORR versus sunitinib
- Lenvatinib plus everolimus demonstrated significant improvements in PFS and ORR but not OS versus sunitinib
- The safety profiles of lenvatinib plus pembrolizumab and lenvatinib plus everolimus were consistent with each drug's known profile and manageable, as needed, through dose modifications
- These results support lenvatinib plus pembrolizumab as a potential first-line treatment for patients with advanced RCC

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First-line options for metastatic ccRCC

	Checkmate 214 (Int/Poor)	Keynote 426 (Pem/Axi)	Checkmate 9ER (Nivo/Cabo)	CLEAR (Pem/Lenva)
IMDC Fav/Int/Poor	23/61/17	32 / 55 / 13	22 / 58/ 20	31 / 59 / 9
Sarc features	13	18	12	8
PD-L1 positive			25.5	
Prior CN	82	83	69	74
ORR CR	42 9	59 6	56 (vs 27) 8 (vs 4.6)	71 16
Median PFS HR	11.2 (vs 8.3) 0.7 (0.65-0.90) (int/poor)	15.4 (vs 11.1) 0.69 (0.6-0.8)	16.6 (vs 8.3) 0.51 (0.41-0.64)	23.9 (vs 9.2) 0.39 (0.3-0.5)
1 yr OS Median OS Sunitinib arm HR	 48.1 26.6 0.66 (0.5-0.8)(int/poor)	 NR 35.7 0.53 (0.4-0.7)	86% vs 76% NR NR 0.60 (0.4-0.9)	 NR NR 0.66 (0.5-0.9)
PRO's	Pos	Neg	Pos	?
>= Gr 3 TRAE >=3 transaminitis >=3 HTN Steroids	48 vs 64	63 vs 58	61 vs 51 10% 12.5% 19%	72 vs 59

c/o Dr. Tracy Rose, UNC

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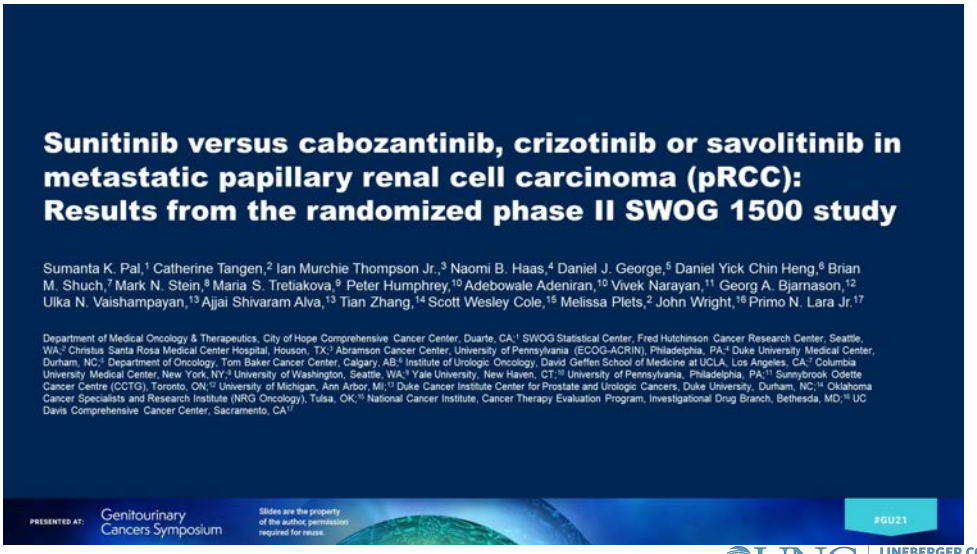
SWOG 1500



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SWOG 1500

Key Eligibility

- Pathologically verified PRCC
- Available tissue submission for retrospective central adjudication of PRCC subtype
- Up to one prior systemic therapy, excluding VEGF- or MET-directed agents
- Zubrod performance status of 0-1
- Adequate organ and marrow function

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SWOG 1500

Results: Accrual and Futility Analysis

- From April 2016 to December 2019, 152 patients were enrolled at 65 centers throughout the US and Canada

mPRCC
- Histologically confirmed diagnosis of PRCC
- Measurable disease
- 0-1 prior lines of therapy
- No prior therapy with sunitinib
- Zubrod 0-1

Randomization

- Sunitinib
- Cabozantinib
- Crizotinib
- Savolitinib

Primary Endpoint:
- Progression-free survival

Secondary Endpoints:
- Overall survival
- Response rate
- Adverse events
- Exploratory evaluation of:
  - MET mutational status
  - MET expression

- Savolitinib and crizotinib arms closed for futility in December of 2018

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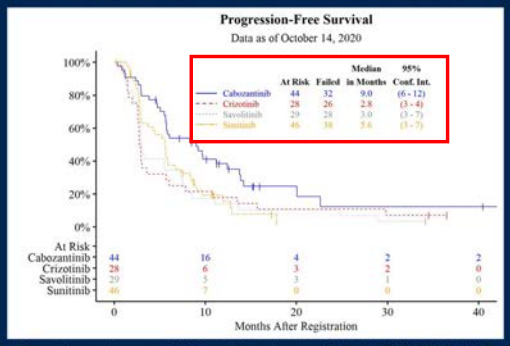
Primary Endpoint

Results: Progression-Free Survival



- Cabozantinib significantly prolonged PFS relative to sunitinib (HR 0.60 (95%CI 0.37-0.97 [1-sided P-value=0.019])

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SWOG 1500

Secondary Endpoint

Results: Efficacy

	Sunitinib [n (%)]	Cabozantinib [n (%)]	Crizotinib [n (%)]	Savolitinib [n (%)]
Complete Response	0 (0)	2 (5)	0 (0)	0 (0)
Partial Response (PR)	2 (4)	8 (18)	0 (0)	1 (3)
Unconfirmed Partial Response	1 (2)	2 (5)	1 (4)	2 (7)
Stable Disease	23 (50)	23 (51)	7 (25)	8 (28)
Increasing Disease	11 (24)	4 (9)	12 (43)	8 (28)
Symptomatic Deterioration	1 (2)	1 (2)	3 (11)	1 (3)
Early Death	1 (2)	1 (2)	0 (0)	0 (0)
Assessment Inadequate	7 (15)	3 (7)	5 (18)	9 (31)
Total	46 (100)	44 (100)	28 (100)	29 (100)

- Confirmed overall response rate with cabozantinib (23%) significantly higher than with sunitinib (4%) (2-sided P-value= 0.010)

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SWOG 1500 – Practice changing as new standard for pRCC

Conclusions

- SWOG 1500 is the first randomized trial exclusively in patients with metastatic pRCC to complete accrual
- Cabozantinib was shown to significantly prolong PFS relative to sunitinib, meeting the study's primary endpoint (HR 0.60 (95%CI 0.37-0.97 [1-sided P-value=0.019])
- Cabozantinib also significantly increased response rate relative to sunitinib (23% vs. 4% [2-sided P-value=0.010])
- Savolitinib and crizotinib study arms were terminated prematurely in a futility analysis; neither showed benefit in PFS relatively to sunitinib
- Regardless of subtype classification (by either local or central review), cabozantinib had a homogeneous treatment effect across subtypes
- Cabozantinib should be considered the new reference standard for systemic therapy in patients with metastatic pRCC

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2021 GU Cancers Symposium Highlights

- **Thank you for your attention.**

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