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UNC Lineberger Cancer Network RESEARCH TO PRACTICE Live Lecture

UNC

Genitourinary Oncology Update 2021

Matthew Milowsky MD

April 28, 2021

1

Disclosures

- **Employment** - none
- **Leadership** - none
- **Stock and Other Ownership Interests** – none
- **Honoraria** - none
- **Consulting or Advisory Role** – none
- **Speaker's Bureau** - none
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- **Patents, Royalties, Other Intellectual Property** – none
- **Expert Testimony** - none
- **Travel, Accommodations, Expenses** - none
- **Other Relationship** - none

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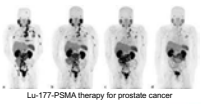
2

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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3

Prostate Cancer Update

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

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4

TheraP (ANZUP 1603)

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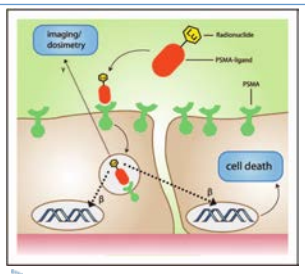
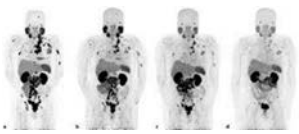
5

177-Lu-PSMA-617





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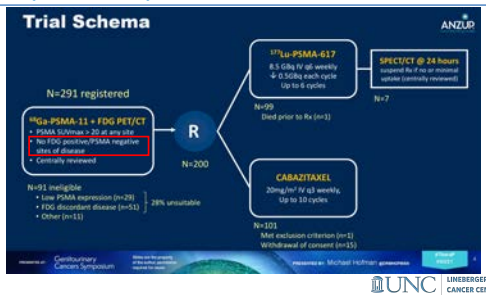
TheraP (ANZUP 1603)



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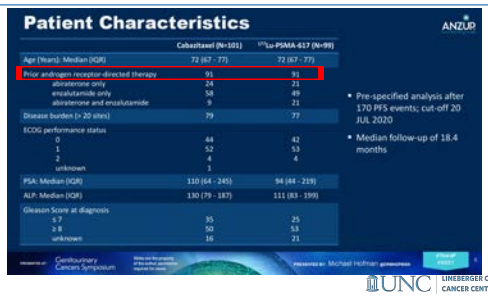

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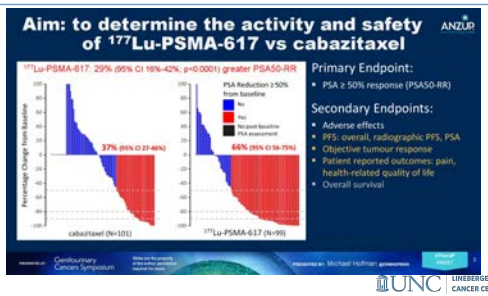

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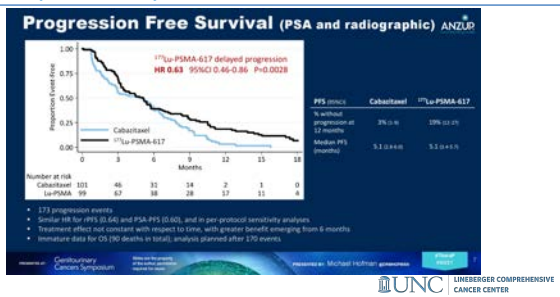

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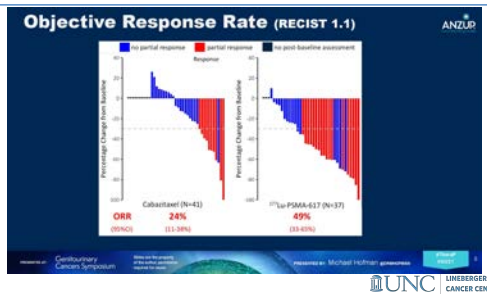

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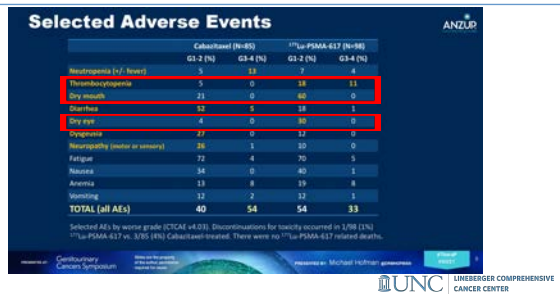
TheraP (ANZUP 1603)



12

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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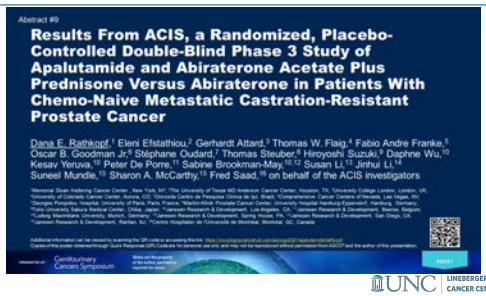
13

ACIS


Abstract #9

Results From ACIS, a Randomized, Placebo-Controlled Double-Blind Phase 3 Study of Apalutamide and Abiraterone Acetate Plus Prednisone Versus Abiraterone in Patients With Chemo-Naive Metastatic Castration-Resistant Prostate Cancer

Dana E. Rathkopf,[1] Eleni Efstathiou,[2] Gerhardt Attard,[3] Thomas W. Flaig,[4] Fabio Andre Franke,[5] Oscar B. Goodman Jr,[6] Stéphane Oudard,[7] Thomas Steuber,[8] Hiroyoshi Suzuki,[9] Daphne Wu,[10] Kesav Yeruva,[10] Peter De Porre,[11] Sabine Brookman-May,[10,12] Susan Li,[13] Jinhui Li,[14] Suneel Mundle,[15] Sharon A. McCarthy,[15] Fred Saad,[16] on behalf of the ACIS investigators

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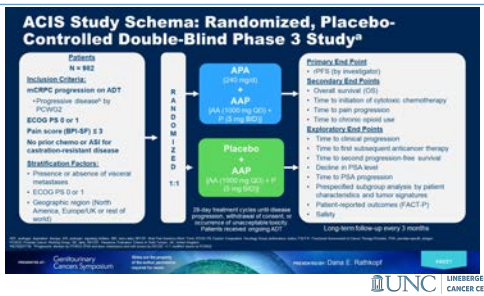
14

ACIS


ACIS Study Schema: Randomized, Placebo-Controlled Double-Blind Phase 3 Study[a]

Patients
N = 962

Inclusion Criteria:
mCRPC progression on ADT
•Progressive disease[a] by PCWG2
ECOG PS 0 or 1
Pain score (BPI-SF) ≤ 3
No prior chemo or ASI for castration-resistant disease

Stratification Factors:
• Presence or absence of visceral metastases
• ECOG PS 0 or 1
• Geographic region (North America, Europe/UK or rest of world)

RANDOMIZED 1:1

APA (240 mg/d) + AAP (AA 1000 mg QD) + P (5 mg BID)

Placebo + AAP (AA 1000 mg QD) + P (5 mg BID)

28-day treatment cycles until disease progression, withdrawal of consent, or occurrence of unacceptable toxicity. Patients received ongoing ADT

Primary End Point
• rPFS (by investigator)

Secondary End Points
• Overall survival (OS)
• Time to initiation of cytotoxic chemotherapy
• Time to pain progression
• Time to chronic opioid use

Exploratory End Points
• Time to clinical progression
• Time to first subsequent anticancer therapy
• Time to second progression-free survival
• Decline in PSA level
• Time to PSA progression
• Prespecified subgroup analysis by patient characteristics and tumor signatures
• Patient-reported outcomes (FACT-P)
• Safety

Long-term follow-up every 3 months

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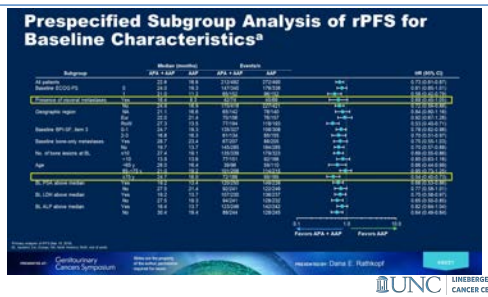
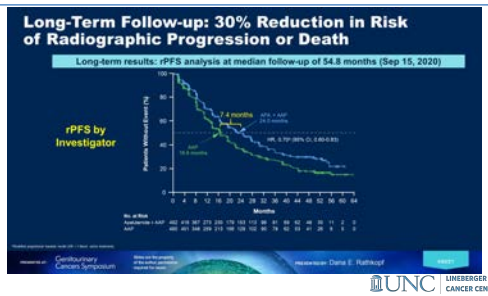
15

ACIS



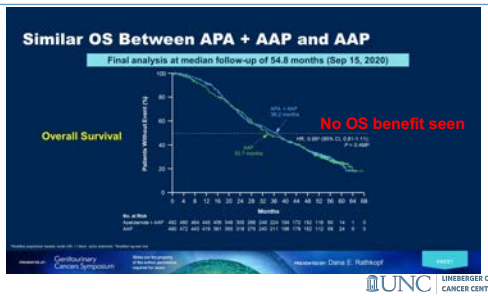
16

ACIS



17

ACIS



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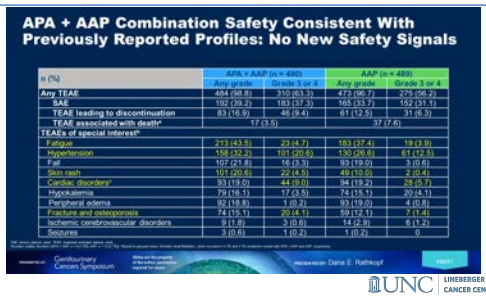
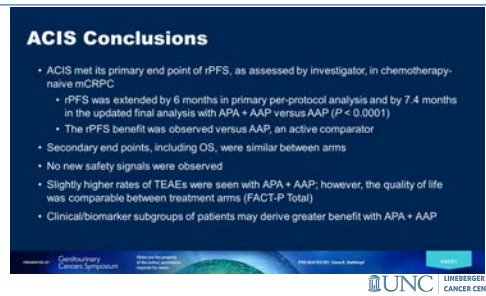
ACIS



19

ACIS – Not practice changing without improvement in OS



20

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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21

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]

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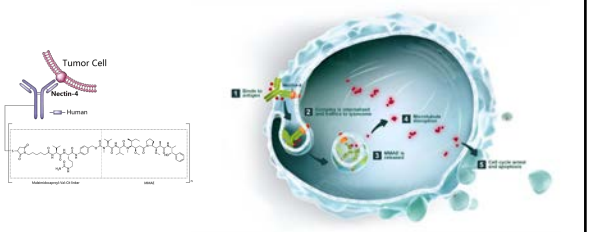
22

Enfortumab Vedotin



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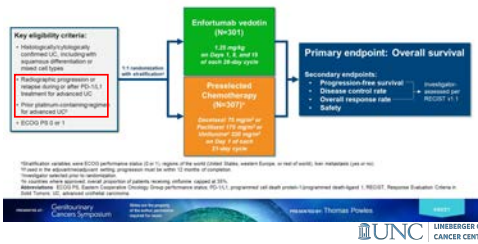
23

EV-301

EV-301 Open-Label Phase 3 Trial Design



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24

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%

Data cut-off: July 15, 2020

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25

EV-301

Overall Survival

Median OS
Enfortumab vedotin 12.88 mo (10.58, 15.21)
Chemotherapy 8.97 mo (8.05, 10.74)
HR: 0.70 (95% CI: 0.56, 0.89)
P=0.00142

Data cut-off: July 15, 2020

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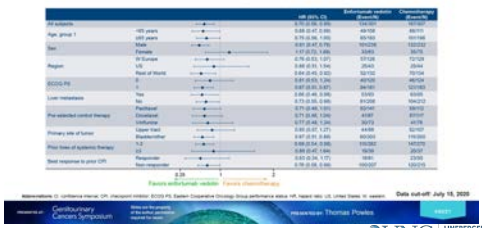
26

EV-301

Overall Survival: Subgroup Analyses



Data cut-off: July 15, 2020

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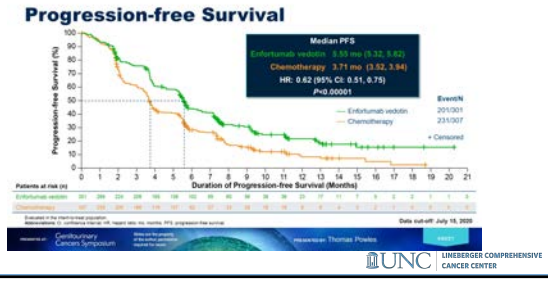
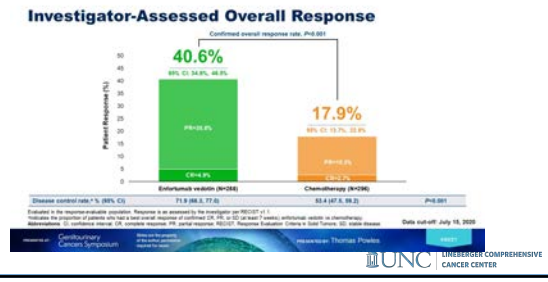
27

EV-301



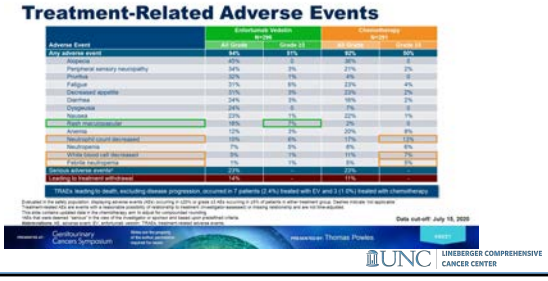
28

EV-301



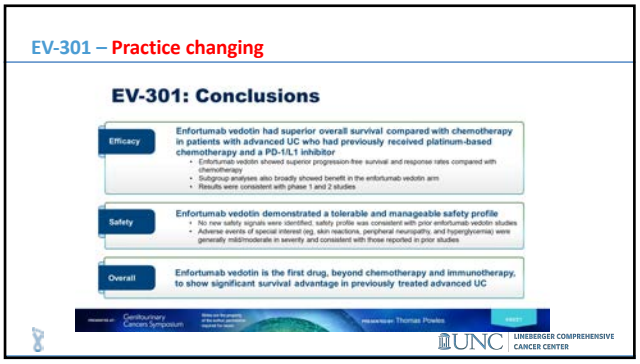
29

EV-301



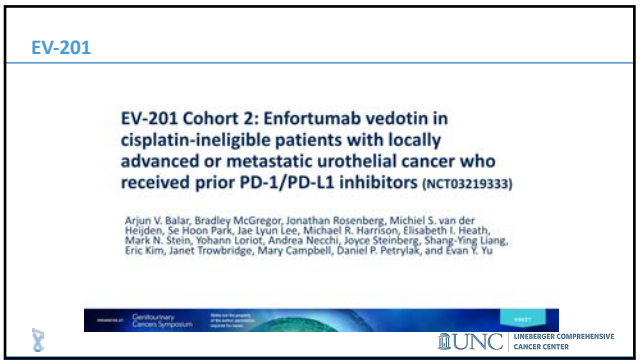
30

EV-301 – Practice changing



31

EV-201



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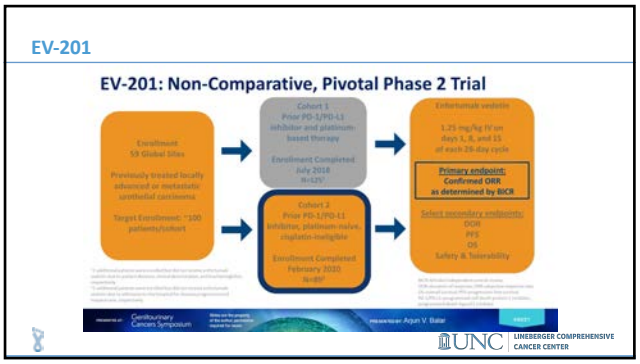
EV-201



33

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]

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Presenter: Arjun V. Balar

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34

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/m²	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%)		

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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

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Presenter: Arjun V. Balar

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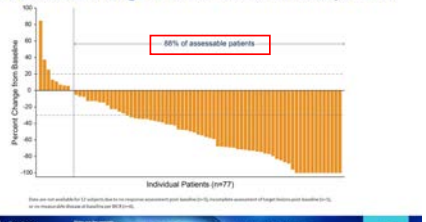
36

EV-201

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



37

EV-201

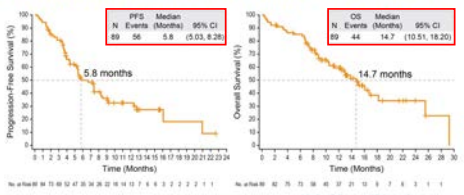
EV-201 Cohort 2: Responses by Subgroup per BICR

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%)

38

EV-201

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



Median follow-up: 13.4 months

39

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

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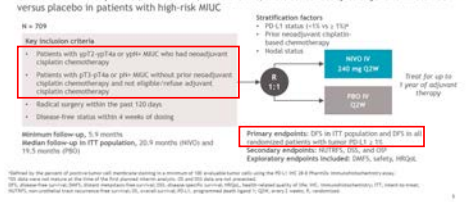
40

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



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41

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 0.63 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

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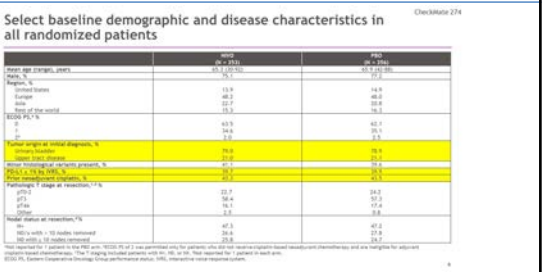
42

CheckMate 274

Select baseline demographic and disease characteristics in all randomized patients



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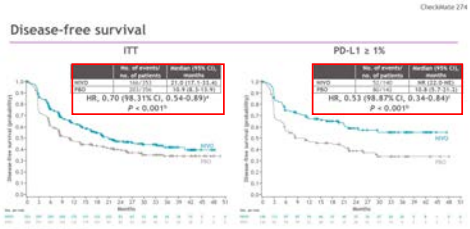
43

CheckMate 274

Disease-free survival



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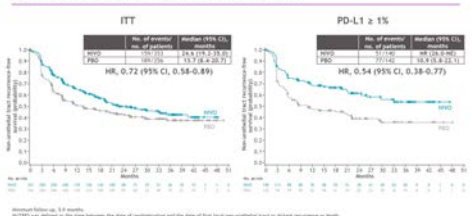
44

CheckMate 274

Non-urothelial tract recurrence-free survival



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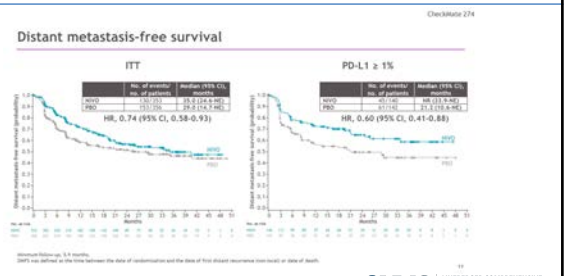
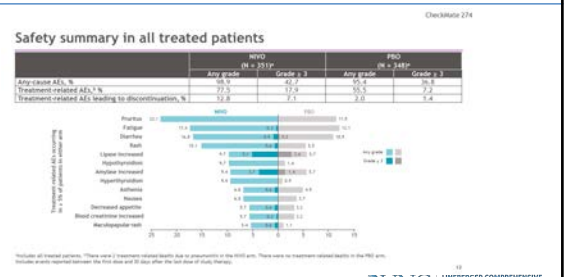
45

CheckMate 274



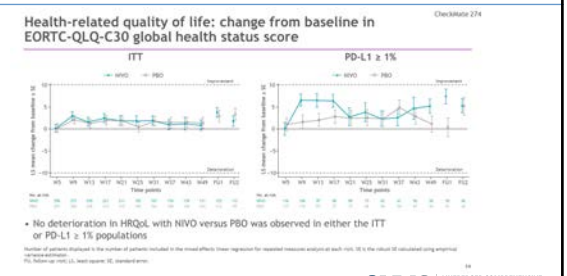
46

CheckMate 274



47

CheckMate 274



48

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

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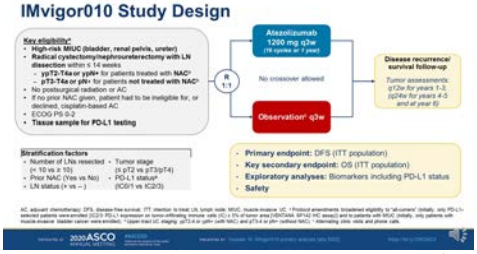
49

IMvigor 010

IMvigor010 Study Design



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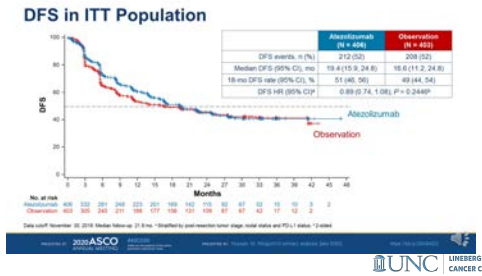
50

IMvigor 010

DFS in ITT Population



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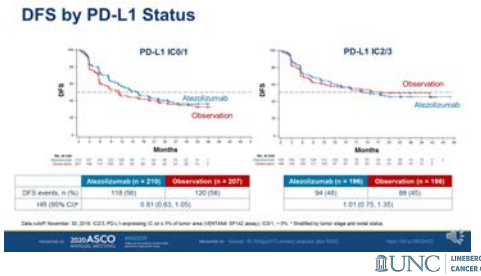
51

IMvigor 010



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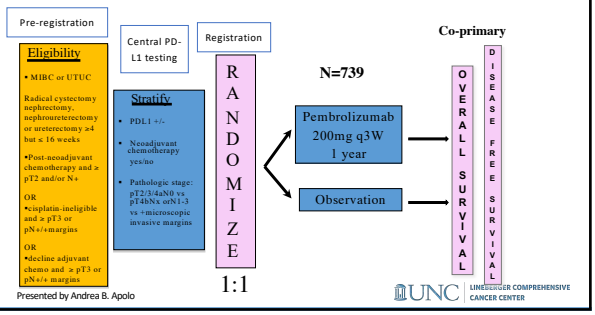
52

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



Presented by Andrea B. Apolo

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53

Kidney Cancer Update

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

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54

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]

Genitourinary Cancers Symposium Abstract #269

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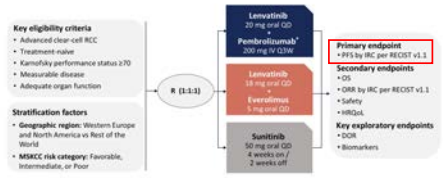
55

CLEAR

Study Design



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56

CLEAR

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

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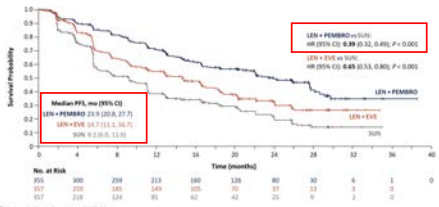
57

CLEAR

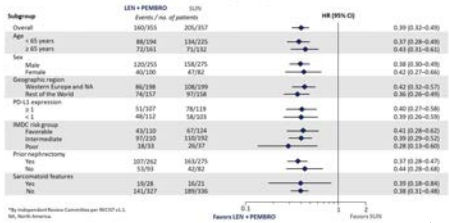
Progression-free Survival*



58

CLEAR

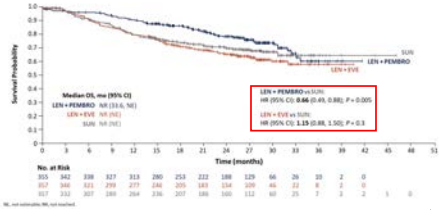
Progression-free Survival* With Lenvatinib Plus Pembrolizumab in Key Subgroups



59

CLEAR

Overall Survival



60

CLEAR

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	--

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61

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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	--

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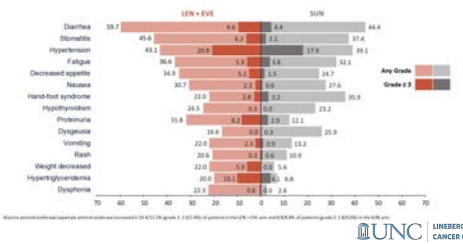
62

CLEAR

TRAEs With Frequency ≥ 20%



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63

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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65

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

67

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

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

68

SWOG 1500

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])

69

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)

Genitourinary Cancers Symposium

Presenter: Sumanta K. Pal, MD

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70

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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72