ASCO GU Update

Andrea Harzstark, M.D.
Department of Urology
Kaiser Permanente Northern California
8/25/18

Agenda

- Cytoreductive nephrectomy for metastatic RCC
- Erdafitinib for TCC
- Enfortumab vedotin for TCC

CARMENA

In the era of targeted therapy, is cytoreductive nephrectomy still necessary ?

CARMENA: Prospective, multicenter, open-label, randomized, phase 3 non-inferiority study

- Confirmed metastatic clear cell RCC / Biopsy
- ECOG-PS 0-1
- Amenable to nephrectomy
- Eligible for sunitinib
- Brain metastases absent/controlled by treatment
- No prior systemic therapy for RCC

R 1:1

Stratification
- MSKCC risk group
- Center location

Arm A
nephrectomy → 3-6 weeks → Sunitinib 50 mg QD 4 wks on / 2 wks off

Arm B
Sunitinib 50 mg QD 4 wks on / 2 wks off

Primary endpoint: Overall survival

Secondary endpoints: Progression-free survival, objective response rate, clinical benefit, safety

LPI, last patient included; MSKCC, Memorial Sloan Kettering Cancer Center; QD, once daily; R, randomization; RCC, renal cell carcinoma

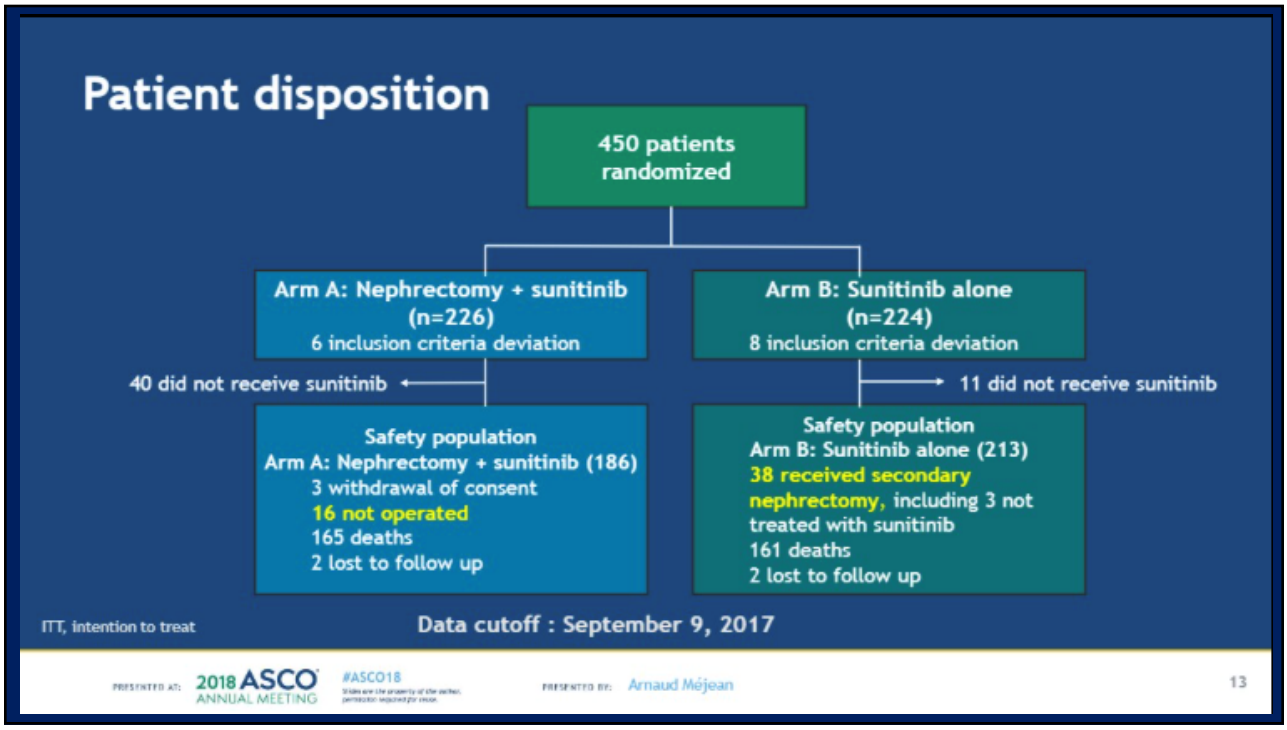
Statistical hypothesis : non inferiority design

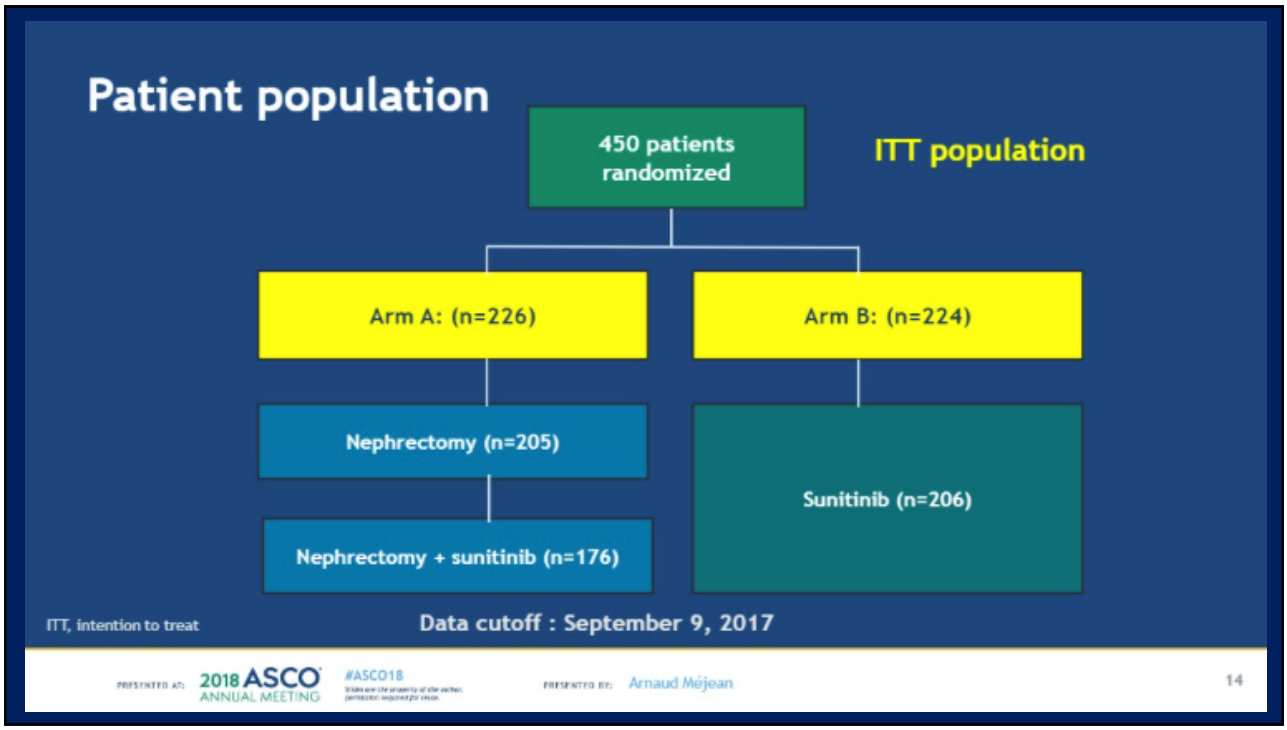
- The study was designed to have 80% power at a 1-sided significance level of 5% (risk alpha)
- Non-inferiority margin of HR: upper 95% CI ≤1.20 for sunitinib alone
- Enrolment of 576 patients needed to observe 456 events for demonstration of non-inferiority
  - Two interim analyses were planned (after 152 and 302 events)
  - Monitored by independent DSMB

CI, confidence interval; HR, hazard ratio

Study conduct

- From Sept. 2009 to Sept. 2017, **450 patients were enrolled**
- Second interim analysis, cutoff Sept. 9, 2017: **326 events had occurred**
- Median follow-up 50.9 months
- Based on overall survival results, the Steering Committee decided to stop the trial and considered this interim analysis as final


Patient disposition
450 patients randomized
Arm A: Nephrectomy + sunitinib (n=226)
6 inclusion criteria deviation
Arm B: Sunitinib alone (n=224)
8 inclusion criteria deviation
40 did not receive sunitinib
11 did not receive sunitinib
Safety population
Arm A: Nephrectomy + sunitinib (186)
3 withdrawal of consent
16 not operated
165 deaths
2 lost to follow up
Safety population
Arm B: Sunitinib alone (213)
38 received secondary nephrectomy, including 3 not treated with sunitinib
161 deaths
2 lost to follow up
ITT, intention to treat
Data cutoff : September 9, 2017
PRESENTED AT: 2018 ASCO ANNUAL MEETING
#ASCO18
PRESENTED BY: Arnaud Méjean
13


Patient population
450 patients randomized
ITT population
Arm A: (n=226)
Arm B: (n=224)
Nephrectomy (n=205)
Nephrectomy + sunitinib (n=176)
Sunitinib (n=206)
ITT, intention to treat
Data cutoff : September 9, 2017
PRESENTED AT: 2018 ASCO ANNUAL MEETING
#ASCO18
PRESENTED BY: Arnaud Méjean
14

Demographic and Clinical Characteristics of the Patients at Baseline.*

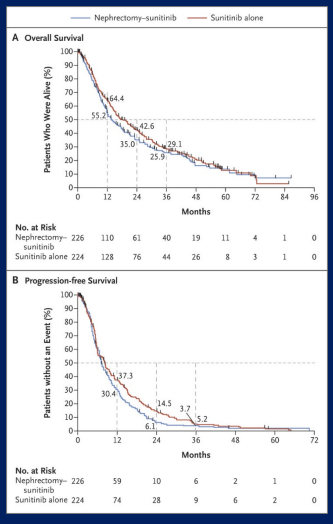
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Nephrectomy–Sunitinib (N = 226)	Sunitinib Alone (N = 224)
Median age (range) — yr	63 (33–84)	62 (30–87)
Male sex — no. (%)	169 (74.8)	167 (74.6)
MSKCC risk category — no./total no. (%)†		
Intermediate risk	125/225 (55.6)	131/224 (58.5)
Poor risk	100/225 (44.4)	93/224 (41.5)
ECOG performance-status score — no. (%)‡		
0	130 (57.5)	122 (54.5)
1	96 (42.5)	102 (45.5)
Fuhrman grade of renal-cell carcinoma — no./total no. (%)§		
1 or 2	77/150 (51.3)	82/156 (52.6)
3 or 4	73/150 (48.7)	74/156 (47.4)
Tumor–node–metastasis stage — no./total no. (%)¶	71/207 (34.3)	50/194 (25.8)
Tumor stage		
T1	5/67 (7.5)	7/49 (14.3)
T2	13/67 (19.4)	13/49 (26.5)
T3 or 4	47/67 (70.1)	25/49 (51.0)
Tx	2/67 (3.0)	4/49 (8.2)
Node stage		
N0	23/66 (34.8)	18/49 (36.7)
N1	13/66 (19.7)	6/49 (12.2)
N2	7/66 (10.6)	13/49 (26.5)
Nx	23/66 (34.8)	12/49 (24.5)
Median primary tumor size (range) — mm	88 (6–200)	86 (12–190)
Median no. of metastatic sites (range)	2 (1–5)	2 (1–5)
Median tumor burden (range) — mm‖	140 (23–399)	144 (39–313)
Location of metastases — no./total no. (%)		
Lung	172/217 (79.3)	161/221 (72.9)
Bone	78/217 (35.9)	82/221 (37.1)
Lymph nodes	76/217 (35.0)	86/221 (38.9)
Other	78/217 (35.9)	90/221 (40.7)

* The characteristics of the patients at baseline were well balanced between the treatment groups.
† The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic factors regarding risk were: a Karnofsky performance-status score of less than 80 (on a scale from 0 to 100, with lower scores indicating greater disability), a lactate dehydrogenase level of 1.5 times the upper limit of the normal range, a hemoglobin level that was less than the lower limit of the normal range, a corrected serum calcium level of more than 10 mg per deciliter (2.5 mmol per liter), and a time from diagnosis to treatment of less than 1 year. Patients with one or two prognostic factors were classified as having intermediate-risk disease and those with three or more were classified as having poor-risk disease.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability and a score of 5 indicating death.
§ The Fuhrman grade of renal-cell carcinoma is assessed on a scale of 1 to 4, with grade 1 indicating the least atypia and grade 4 the most.
¶ The tumor–node–metastasis stage was determined according to the criteria of the Union for International Cancer Control TNM Classification of Malignant Tumours.[14] Metastasis was an eligibility criterion in all patients.
‖ Tumor burden was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

A Méjean et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1803675

Kaplan–Meier Estimates of Survival.



A Méjean et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1803675

Overall survival by patient population

Population	Arm A (Nephrectomy + sunitinib)			Arm B (Sunitinib)			HR (95% CI), stratified by MSKCC risk group
	n	Events, n (%)	Median (95% CI), months	n	Events, n (%)	Median (95% CI), months	
ITT	226	165 (73)	13.9 (11.8-18.3)	224	161 (72)	18.4 (14.7-23.0)	0.89 (0.71-1.10)
PP1*	205	149 (73)	14.5 (11.9-20.2)	206	143 (69)	20.5 (15.6-25.2)	0.87 (0.69-1.1)
PP2#	176	122 (64)	18.3 (13.7-23.2)	206	143 (69)	20.5 (15.6-25.2)	0.98 (0.77-1.25)

*The PP1 analysis included only patients who had nephrectomy in Arm A, and patients who receive sunitinib in Arm B.
#The PP2 analysis included only patients who had nephrectomy and receive sunitinib after nephrectomy in Arm A, and patients who receive sunitinib in Arm B.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; MSKCC, Memorial Sloan Kettering Cancer Center; PP, per-protocol.

Progression free survival by patient population

Population	Arm A: Nephrectomy + sunitinib			Arm B: Sunitinib alone			HR (95% CI), stratified by MSKCC risk group
	n	Events, n (%)	Median (95% CI), months	n	Events, n (%)	Median (95% CI), months	
ITT	226	194 (86)	7.2 (6.7-8.5)	224	196 (87)	8.3 (6.2-9.9)	0.82 (0.67-1.00)
PP1*	205	178 (87)	7.6 (6.8-9.4)	206	181 (88)	8.5 (7.5-10.2)	0.82 (0.66-1.01)
PP2#	176	154 (87)	8.7 (7.2-10.2)	206	181 (88)	8.5 (7.5-10.2)	0.87 (0.70-1.08)

*The PP1 analysis included only patients who had nephrectomy in Arm A, and patients who receive sunitinib in Arm B.
#The PP2 analysis included only patients who had nephrectomy and receive sunitinib after nephrectomy in Arm A, and patients who receive sunitinib in Arm B.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; MSKCC, Memorial Sloan Kettering Cancer Center; PP, per-protocol.

Tumor Response Outcomes.*

Table 2. Tumor Response Outcomes.*

Response	Nephrectomy–Sunitinib (N=186)	Sunitinib Alone (N=213)
Best overall response — no./total no. (%)		
Complete response	1/178 (0.6)	0/208
Partial response	50/178 (28.1)	62/208 (29.8)
Stable disease	64/178 (36.0)	97/208 (46.6)
Progression of disease	49/178 (27.5)	40/208 (19.2)
Could not be evaluated	14/178 (7.9)	9/208 (4.3)
Objective response rate — % (95% CI)†	27.4 (21.1–34.4)	29.1 (23.1–35.7)
Disease control rate — % (95% CI)‡	61.8 (54.4–68.8)	74.6 (68.2–80.3)
Clinical benefit — no. (%)§	68 (36.6)	102 (47.9)

* Tumor response was analyzed in patients who received sunitinib. Some patients could not be evaluated for tumor response because of adverse events during treatment or deterioration of condition.
† Objective response was defined as a complete or partial response.
‡ Disease control was defined as a complete or partial response or stable disease.
§ Clinical benefit was defined as disease control beyond 12 weeks (P=0.02 for this comparison).

A Méjean et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1803675

The NEW ENGLAND JOURNAL of MEDICINE

Secondary nephrectomy in Arm B (sunitinib alone)

- 38 patients required secondary nephrectomy
  - For emergency treatment of the primary tumor
  - For CR or near CR in metastatic sites (> 6 months)
- Median 11.1 months (range 0.7-85.4) from randomisation to surgery
- 31.3% of patients with secondary nephrectomy restarted sunitinib

	Arm B: Sunitinib alone (N = 224)
Secondary nephrectomy, n (%)	
No	185 (83.0)
Yes	38 (17.0)
Missing	1
Emergency	
Yes	7 (18.9)
No	30 (81.1)
Missing	1

2018 ASCO ANNUAL MEETING

Arnaud Méjean

27

Summary of Severe Adverse Events in Sunitinib-Treated Patients.*

Table 3. Summary of Severe Adverse Events in Sunitinib-Treated Patients.*

Event	Nephrectomy–Sunitinib (N = 186)	Sunitinib Alone (N = 213)
	no. of patients (%)	
Any adverse event of grade 3 or 4†	61 (32.8)	91 (42.7)
Asthenia	16 (8.6)	21 (9.9)
Inflammation of mucosa	1 (0.5)	6 (2.8)
Edema	0	4 (1.9)
Neutropenia	5 (2.7)	10 (4.7)
Thrombocytopenia	7 (3.8)	5 (2.3)
Anemia	5 (2.7)	11 (5.2)
Hand–foot syndrome	8 (4.3)	12 (5.6)
Intratumoral hemorrhage	0	1 (0.5)
Pulmonary embolism	2 (1.1)	2 (0.9)
Severe high blood pressure	6 (3.2)	7 (3.3)
Left ventricular failure	0	1 (0.5)
Heart failure	0	1 (0.5)
Hepatitis	1 (0.5)	1 (0.5)
Liver failure	0	2 (0.9)
Severe hypothyroidism	3 (1.6)	1 (0.5)
Musculoskeletal or systemic disorder	2 (1.1)	5 (2.3)
Respiratory, thoracic, or mediastinal disorder	3 (1.6)	4 (1.9)
Renal or urinary tract disorder‡	1 (0.5)	9 (4.2)
Gastrointestinal perforation	1 (0.5)	2 (0.9)
Seizure or convulsions	0	1 (0.5)
Other	34 (18.3)	47 (22.1)

* Shown are adverse events of grade 3 or 4 that were observed among patients who received sunitinib.
† P = 0.04.
‡ P = 0.051.

A Méjean et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1803675

The NEW ENGLAND JOURNAL of MEDICINE

Author's Conclusions:

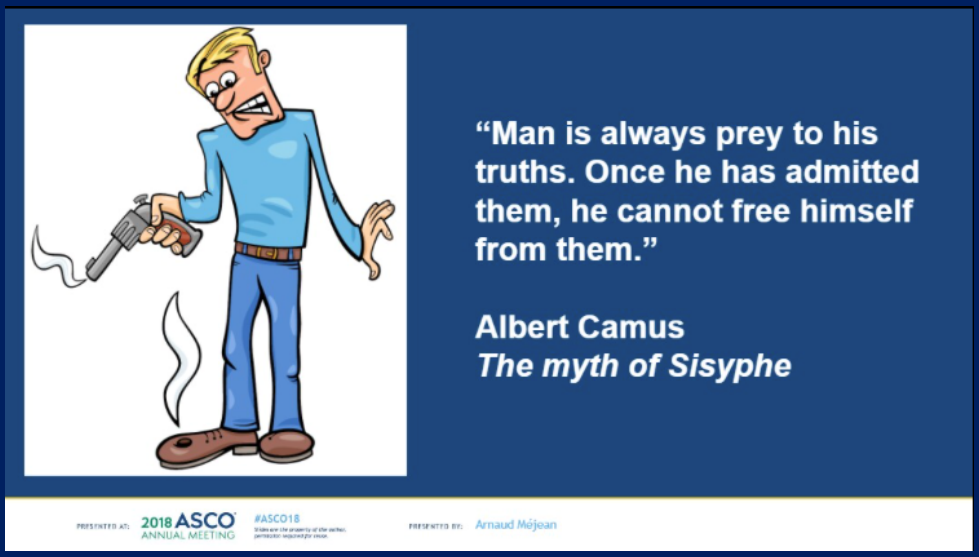
Conclusions

- Sunitinib alone is non-inferior to cytoreductive nephrectomy followed by sunitinib for OS, both in intermediate- and poor-risk patients with mRCC
- Clinical benefit was significantly higher in sunitinib alone arm
- Cytoreductive nephrectomy should no longer be considered the standard of care in mRCC, at least when medical treatment is required

CN, cytoreductive nephrectomy; mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression-free survival

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Arnaud Méjean 28

Author's Conclusions:



Issues

- Population weight toward poor outcome (44% MSKCC poor risk), tumor burden by RECIST 14 cm, median size of primary 8.8 cm
- 40/226 (18%) on nephrectomy arm didn't receive sutent, 38/226 (17%) on sutent arm had secondary nephrectomy
- Study took 8 years to enroll
- PATIENT SELECTION!!!
- Bottom line: this does NOT change the standard of care, consider debulking nephrectomy with unchanged caveats: poor risk disease, extensive RP or mediastinal LAD, extensive liver or bone mets, brain mets, removal of 75% of disease

Targeting FGFR Alterations in Bladder Cancer

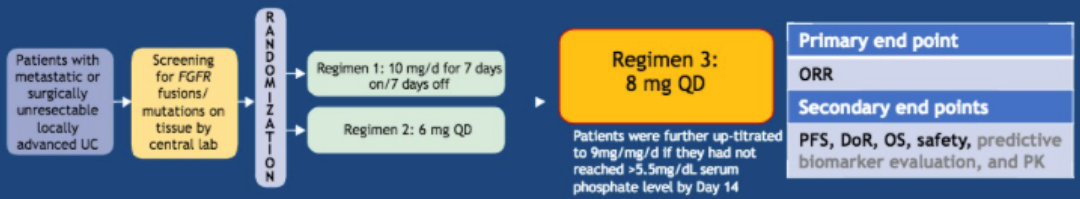
- Urothelial carcinoma has high rates of somatic alterations including FGFR mutations and fusions (15-20%)
- No current approved targeted therapies for urothelial carcinoma

FGFR targeted agents	Administration	Target
Erdafitinib (JNJ-42756493)[1]	oral	pan-FGFR (1-4)
ARQ 087[2]	oral	pan-FGFR (1-4)
Dovitinib (TKI258)[3]	oral	FGFR, VEGFR, PDGFRβ, CSF-1R, CKIT, RET, TrkA, and FLT3
BGJ398[4]	oral	FGFR (1-3)

[1]Loriot Y et al., J Clin Oncol 36, 2018 (suppl 6S; abstr 411); [2]Papadopoulos KP et al., Br J Cancer 2017;117 (11) [3]Milowsky MI et al., Eur J Cancer. 2014 Dec;50(18); [4]Pal S et al., Cancer Discovery 2018.

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Andrea B. Apolo, MD

Preliminary results presented at GU ASCO 2018:
Ongoing Phase 2 Study of Erdafitinib (JNJ-42756493) in Patients With Metastatic or Surgically Unresectable Urothelial Carcinoma and *FGFR* Alterations



Erdafitinib GU ASCO 2018 (abstract 411)	Regimen 1 10mg intermittent dose	Regimen 2 6mg continuous dose	Regimen 3 8mg continuous dose
Evaluable patients, n	33	78	59
ORR n(%)	8(24)	27 (35)	25 (42)
Survival at 1 year	31%	32%	57%

* Loriot Y et al., J Clin Oncol 36, 2018 (suppl 6S; abstr 411).

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Andrea B. Apolo, MD

Abstract 4503

Phase 2 Study of Erdafitinib (JNJ-42756493) in Patients With Metastatic or Surgically Unresectable Urothelial Carcinoma and *FGFR* Alterations

Patients with metastatic or surgically unresectable locally advanced UC → Screening for *FGFR* fusions/ mutations on tissue by central lab → Regimen 3[a]: 8 mg QD with PD Up-titration to 9mg QD **n = 99**

Primary endpoint

ORR

Secondary endpoints

PFS, DoR, OS, safety, predictive biomarker evaluation, and PK

Patients

- Progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo OR
- Chemo-naïve: cisplatin-ineligible per protocol criteria
- Prior immunotherapy was allowed

Primary hypothesis:

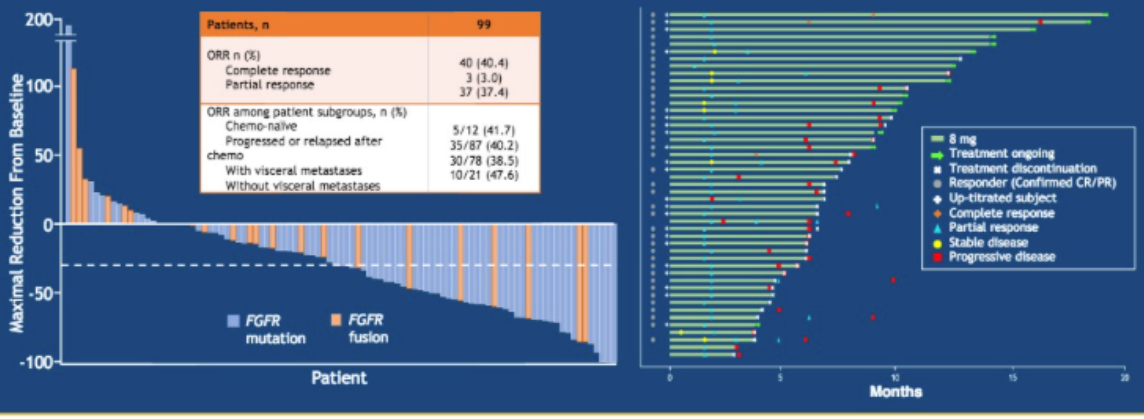
- ORR in Regimen 3 is > 25%
- One-sided α = 0.025
- 85% power

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Andrea B. Apolo, MD

Abstract 4503

Phase 2 Study of Erdafitinib (JNJ-42756493) in Patients With Metastatic or Surgically Unresectable Urothelial Carcinoma and *FGFR* Alterations

1. **Clinical activity:**

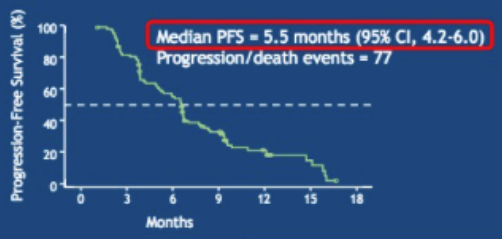


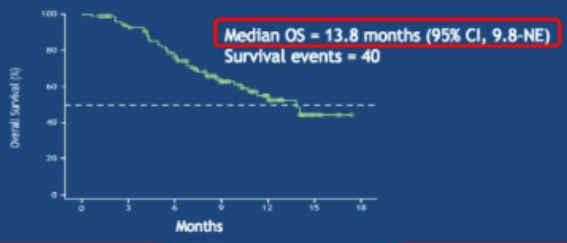
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Andrea B. Apolo, MD

Abstract 4503

Phase 2 Study of Erdafitinib (JNJ-42756493) in Patients With Metastatic or Surgically Unresectable Urothelial Carcinoma and *FGFR* Alterations

1. Clinical activity:





KEYNOTE-045* Phase III Trial	Pembrolizumab	Paclitaxel/Docetaxel/ Vinflunine	Erdafitinib
ORR (%)	21	11	40
mPFS (months)	2.1	3.3	5.5
mOS (months)	10.3	7.4	13.8
Duration of Response (months)	NR ((range, 1.6+ to 15.6+)	4.3	5.6

*Bellmunt J, et al. NEJM. 2017;376:1015-26.

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Andrea B. Apolo, MD

Abstract 4503

Phase 2 Study of Erdafitinib (JNJ-42756493) in Patients With Metastatic or Surgically Unresectable Urothelial Carcinoma and *FGFR* Alterations

2. Tolerable toxicity to continue drug?: YES

Most Common Treatment-Related AEs

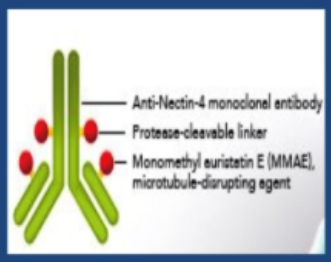
Reported in >20% of patients	8 mg continuous dose (n = 99)	
Patients with AEs, n (%)	Any grade	Grade 3
Hyperphosphatemia	72 (73)	2 (2)
Stomatitis	54 (55)	9 (9)
Dry mouth	43 (43)	0
Diarrhea	37 (37)	4 (4)
Dysgeusia	35 (35)	1 (1)
Dry skin	32 (32)	0
Alopecia	27 (27)	0
Decreased appetite	25 (25)	0
Hand-foot syndrome	22 (22)	5 (5)
Fatigue	21 (21)	2 (2)

- 7 patients discontinued therapy because of AEs of special interest
- Ocular events, including blurry vision, increased lacrimation, and conjunctivitis, were common, but manageable
- Central serous retinopathy led to discontinuation in 3 patients

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Andrea B. Apolo, MD

Enfortumab Vedotin, an Antibody-Drug Conjugate Targeting Nectin-4

- Antibody-drug conjugates are made up of 3 parts:
  - The antibody: Anti-nectin-4
  - The payload: MMAE
  - The linker (stable in circulation, but releases the cytotoxic agent in the target cell)
- The goal of antibody-drug conjugates is to highly select tumor antigen, have less off-target toxicity (from the cytotoxic payload).
- Payload must be cytotoxic to the tumor
- Nectin-4 is highly expressed in metastatic urothelial cancer patients not necessitating tumor screening
- The payload MMAE (plus linker) is vedotin, a microtubule-disrupting agent (200x more potent than vinblastine)



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Andrea B. Apolo, MD

Abstract 4504

Updated Results From the Enfortumab Vedotin Phase 1 (EV-101) Study in Patients With Metastatic Urothelial Cancer

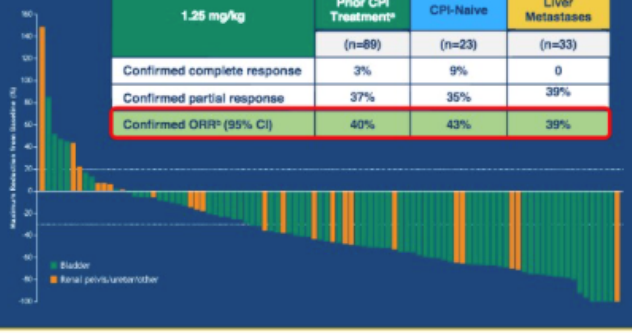
1. Clinical activity

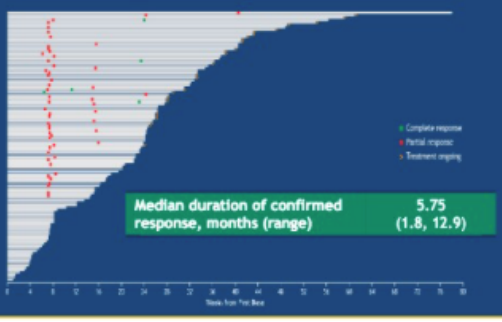
Part A (closed to accrual)
Cohort 4: 1.25 mg/kg IV D1, 8, & 15 q28 days (N= 23)
Nectin-4-expressing tumors, including mUC

RP2D 1.25 mg/kg

Part C (closed to accrual)
Dose expansion: 1 cohort (N=89)
- CPI-treated mUC patients (1.25 mg/kg)

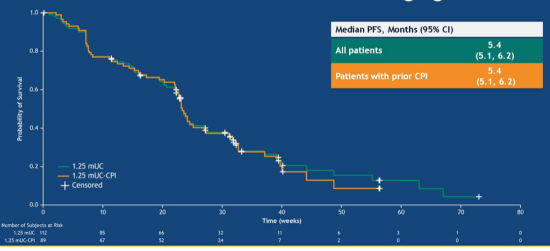
1.25 mg/kg	Prior CPI Treatment[a] (n=89)	CPI-Naive (n=23)	Liver Metastases (n=33)
Confirmed complete response	3%	9%	0
Confirmed partial response	37%	35%	39%
Confirmed ORR[b] (95% CI)	40%	43%	39%





PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Andrea B. Apolo, MD

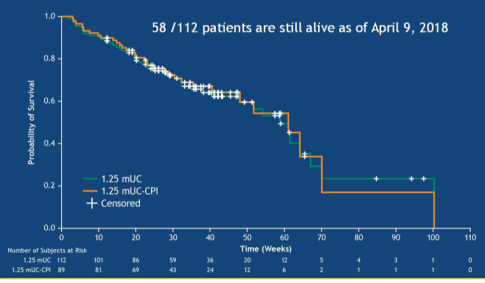
Progression-Free Survival in Patients With mUC Treated With Enfortumab Vedotin 1.25 mg/kg



Median PFS, Months (95% CI)	
All patients	5.4 (5.1, 6.2)
Patients with prior CPI	5.4 (5.1, 6.2)

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Jonathan E. Rosenberg 16

Preliminary Overall Survival in Patients With mUC Treated With Enfortumab Vedotin 1.25 mg/kg



Population	Median OS, Months (95% CI)
All patients	13.6 (11.0, 15.4)
Patients with prior CPI	14.0 (11.0, 16.1)
Estimated Overall Survival Rates	
OS rate at 6 months, %	
All patients	74.4
Patients with prior CPI	75.6
OS rate at 12 months, %	
All patients	56.3
Patients with prior CPI	54.2

Data cut-off date is April 9, 2018.

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Jonathan E. Rosenberg 17

Abstract 4504

Updated Results From the Enfortumab Vedotin Phase 1 (EV-101) Study in Patients With Metastatic Urothelial Cancer

2. Tolerable toxicity to continue drug?: YES

Treatment-Related Adverse Events (in ≥25% of Patients)

	Patients With mUC 1.25 mg/kg (N=112)	
	All Grades	Grade ≥3
Fatigue	54%	1%
Alopecia	45%	0
Decreased appetite	40%	1%
Dysgeusia	38%	0
Nausea	36%	1%
Pruritus	35%	1%
Peripheral neuropathy	35%	0
Diarrhea	32%	1%
Maculo-papular rash	25%	3%

Adverse events listed are individual preferred terms.

	1.25 mg/kg EV (N=112)
Subjects continuing treatment	24%
Treatment discontinuations	76%
Disease progression (radiographic)	50%
Disease progression (clinical symptoms)	6%
Adverse event	11%
Subject withdrew consent	3%
Investigator's decision	4%
Other	2%
Median time on treatment, weeks (range)	23.7 (1.1, 78.0)

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Andrea B. Apolo, MD

Current status

- Both drugs with FDA fast track status (with expected approval 2019)
- Erdafitinib phase 3 compared with vinflunine, docetaxel, or pembrolizumab (enrollment completion expected 2020)
- Enfortumab vedotin phase 2, also phase I in combination with pembrolizumab or atezolizumab
- Both drugs will be in post-checkpoint inhibitor space