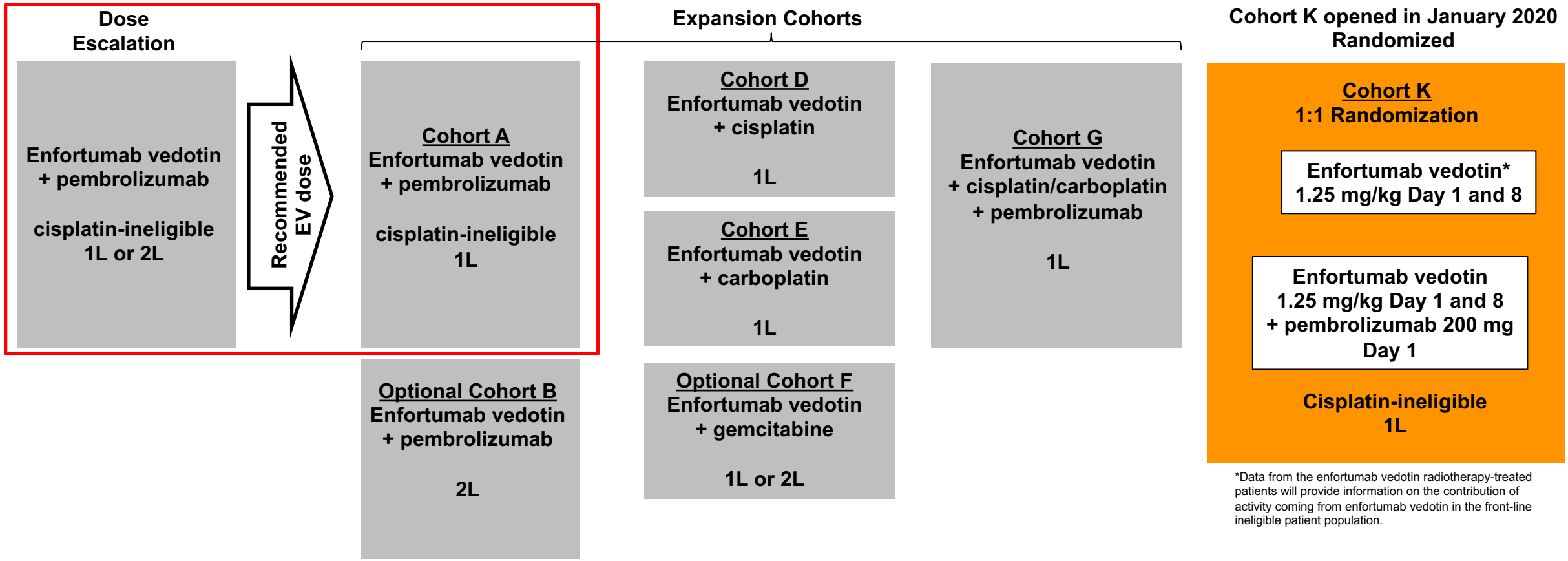
NEW DIRECTIONS IN THE MANAGEMENT OF METASTATIC UROTHELIAL BLADDER CANCER

Elisabeth Heath, MD, FACP
Associate Center Director, Translational Sciences
Hartmann Endowed Chair for Prostate Cancer Research
Chair, Genitourinary Multidisciplinary Team
Professor of Oncology and Medicine

EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC

EV-103 Study Design for Locally Advanced or Metastatic Urothelial Carcinima (la/mUC) Cohorts



*Data from the enfortumab vedotin radiotherapy-treated patients will provide information on the contribution of activity coming from enfortumab vedotin in the front-line ineligible patient population.

NCT03288545

Hoimes CJ et al. ESMO 2019. Hoimes CJ et al. J Clin Oncol 37, 2019 (suppl; abstr TPS4593).
Goldberg H. UroToday Conference Highlights 2020.

Courtesy of Elisabeth I Heath, MD

EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC

- Cis-ineligible:
  - Glomerular filtration rate (GFR) <60 mL/min and ≥ 30 mL/min
  - ECOG PS=2
  - NCI CTCAE Version 2.03 Grade 2 ≥ hearing loss
  - New York Heart Association (NYHA) Class III heart failure
- Cohort A:
  - EV 1.25 mg/kg days 1, 8 plus P 200 mg day 1 q 21 days
- Results:
  - 45 LA/mUC enrolled
  - Median age 69 years (51-90)
  - 33% liver metastasis
  - 13% ECOG PS 2

Hoimes CJ et al. ESMO 2019. Hoimes et al. J Clin Oncol 37, 2019 (suppl; abstr TPS4593).

Courtesy of Elisabeth I Heath, MD

EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC

- Results:
  - Objective Response Rate (ORR) = 71%
  - Complete Response Rate (CR) = 13%
  - Stable Disease (SD) = 22%
- Treatment-emergent adverse events:
  - Fatigue = 49%, 9% ≥ Grade 3
  - Diarrhea = 40%, 4% ≥ Grade 3
  - Rash = 27%, 7% ≥ Grade 3
  - Peripheral neuropathy = 47%, 4% ≥ Grade 3

Food and Drug Administration (FDA) Granted Breakthrough Therapy Designation on February 18, 2020

Hoimes CJ et al. ESMO 2019.

Courtesy of Elisabeth I Heath, MD

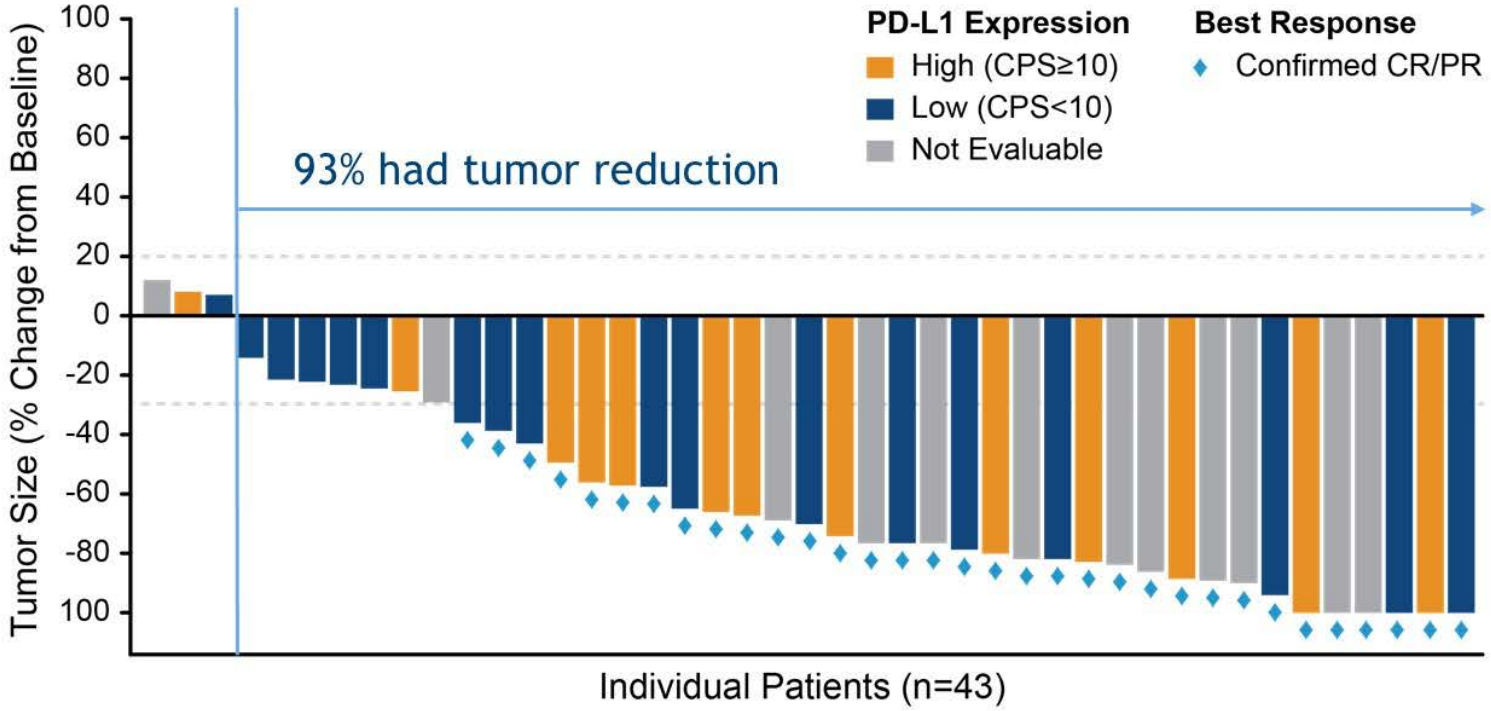
EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC

- Results (median follow-up 11.5 months):
  - ORR= 73.3%
    - ORR in patients with liver metastasis = 53.5%
    - ORR by PD-L1 Expression
      - High: 78.6%
      - Low: 63.2%
  - Complete Response Rate = 15.6%
  - Partial Response Rate = 57.8%
  - Stable Disease = 20%
- Median Progression Free Survival (PFS) = 12.3 months (95% CI 7.98,-)
- Median Overall Survival (OS) = not reached
- Median Overall Survival (OS) at 12 months = 81.6%

Rosenberg JE et al. J Clin Oncol 38, 2020 (suppl 6; abstr 441). Rosenberg JE at al. J Clin Oncol 38, 2020 (suppl; abstr 5044).

Courtesy of Elisabeth I Heath, MD

EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC



Confirmed ORR 95% CI	**73.3% (33/45)** (58.1, 85.4)
Complete response	15.6% (7/45)
Partial response	57.8% (26/45)

Best Overall Response Per RECIST v 1.1 by investigator (N=45)

- Responses observed regardless of PD-L1 expression level

Two patients did not have post-baseline response assessments before end-of-treatment: 1 withdrew consent and 1 died before any post-baseline response assessment. These patients are included in the full analysis set used to calculate ORR, but are not included in the figure above.

Horizontal lines at positive 20% and negative 30% denote thresholds for target lesions for disease progression and response, respectively.

NCT03288545

Rosenberg JE at al. J Clin Oncol 38, 2020 (suppl 6; abstr 441). Rosenberg JE at al. J Clin Oncol 38, 2020 (suppl; abstr 5044).

Courtesy of Elisabeth I Heath, MD

EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC

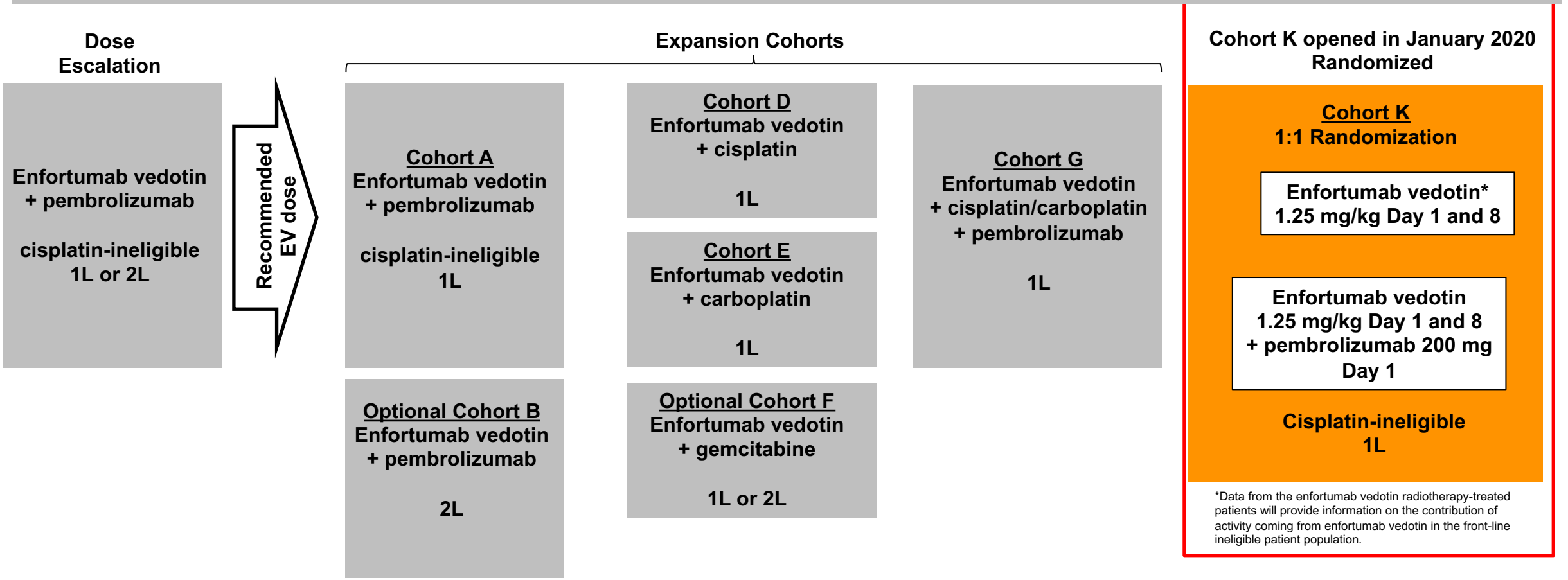
Adverse Events	Patients n (%) Any Grade	Patients n (%) ≥ Grade 3	Time to first onset (months) Median (min, max)
Peripheral neuropathy	25 (56)	2 (4)	2.3 (1, 12)
Rash	28 (62)	6 (13)	0.7 (0,12)
Hyperglycemia	5 (11)	3 (7)	0.5 (0,3)
Immune-mediated AE requiring systemic steroids	12 (29)	8 (18)	

Rosenberg JE at al. J Clin Oncol 38, 2020 (suppl 6; abstr 441). Rosenberg JE et al. J Clin Oncol 38:2020 (suppl; abstr 5044).

Courtesy of Elisabeth I Heath, MD

EV-103: Phase Ib/II Study of Enfortumab Vedotin plus Pembrolizumab for Frontline LA/mUC

EV-103 Study Design for Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC) Cohorts



NCT03288545

Rosenberg JE at al. J Clin Oncol 38, 2020 (suppl 6; abstr 441). Goldberg H. UroToday Conference Highlights 2020.
Mar N et al. J Clin Oncol 38: 2020 (suppl; abstr TPS5092)

Courtesy of Elisabeth I Heath, MD

Phase I/II CheckMate 032 Trial

- CheckMate 032: nivolumab with or without ipilimumab followed by nivolumab
- Nivolumab 1 mg/kg plus Ipilimumab 3 mg/kg
  - ORR= 38%
  - OS= 15.3 months
  - PFS= 4.9 months

- PD-1 involved in inhibition of effector T-cell and NK cell activation in peripheral tissues and in induction of Treg cell differentiation
- CTLA-4 involved in regulation of T-cell activation in lymph nodes/tissues and in suppression of dendritic cell activity by Treg cells
- Combination inhibitors should increase synergistic action to result in greater response rates

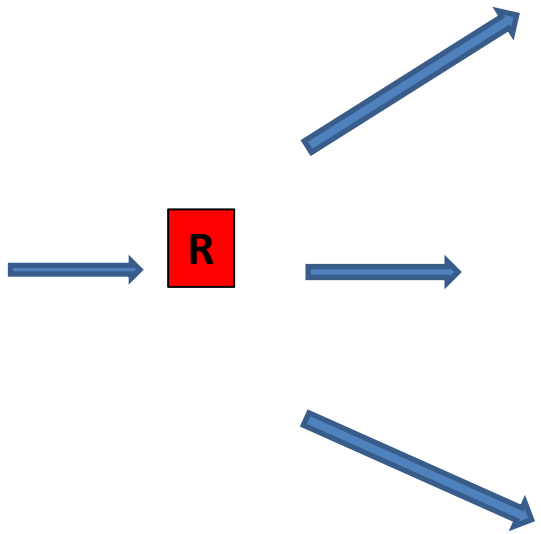
NCT01928394

Sharma P et al. J Clin Oncol 37:1608-1616, 2019. Cheng W et al. Oncogenesis (2018)7:2.

Courtesy of Elisabeth I Heath, MD

Phase III CheckMate 901 Trial

- First line unresectable or metastatic UC
- ECOG PS ≤ 1
- Co-Primary Endpoints: PFS and OS
- 897 patients



Nivolumab + Ipilimumab

Nivolumab + Gemcitabine/Cisplatin

Gemcitabine/Cisplatin OR
Gemcitabine/Carboplatin

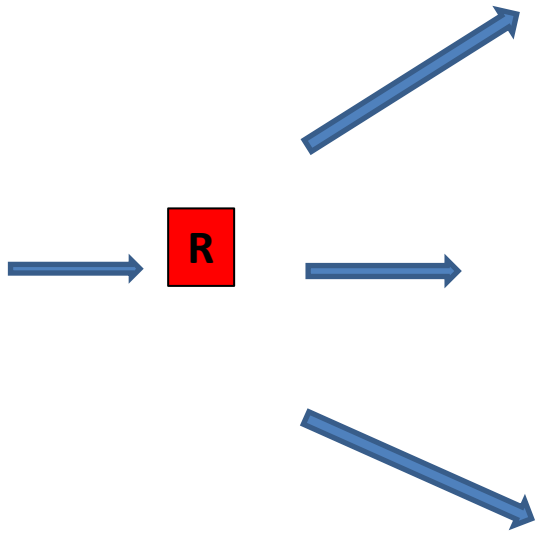
NCT01928394

www.clinicaltrials.gov, NCT03036098

Courtesy of Elisabeth I Heath, MD

Phase III NILE Trial

- First line unresectable or metastatic UC
- ECOG PS ≤ 1
- Co-Primary Endpoints: PFS and OS
- 885 patients



Durvalumab + Gemcitabine/Cisplatin OR
Durvalumab + Gemcitabine/Carboplatin

Durvalumab + Tremelimumab + Gemcitabine/Cisplatin OR
Durvalumab + Tremelimumab + Gemcitabine/Carboplatin

Gemcitabine/Cisplatin OR
Gemcitabine/Carboplatin

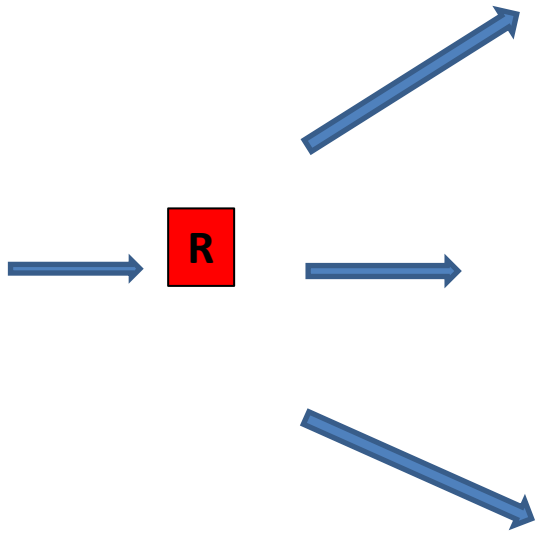
NCT03682068

www.clinicaltrials.gov, NCT03682068.

Courtesy of Elisabeth I Heath, MD

Phase III DANUBE Trial

- First line unresectable or metastatic UC
- Co-Primary Endpoints: PFS and OS
- 1005 patients



Durvalumab

Durvalumab + Tremelimumab

Gemcitabine/Cisplatin OR
Gemcitabine/Carboplatin

Press Release: March 6, 2020. DANUBE did not meet the primary endpoints of improving OS versus standard of care.

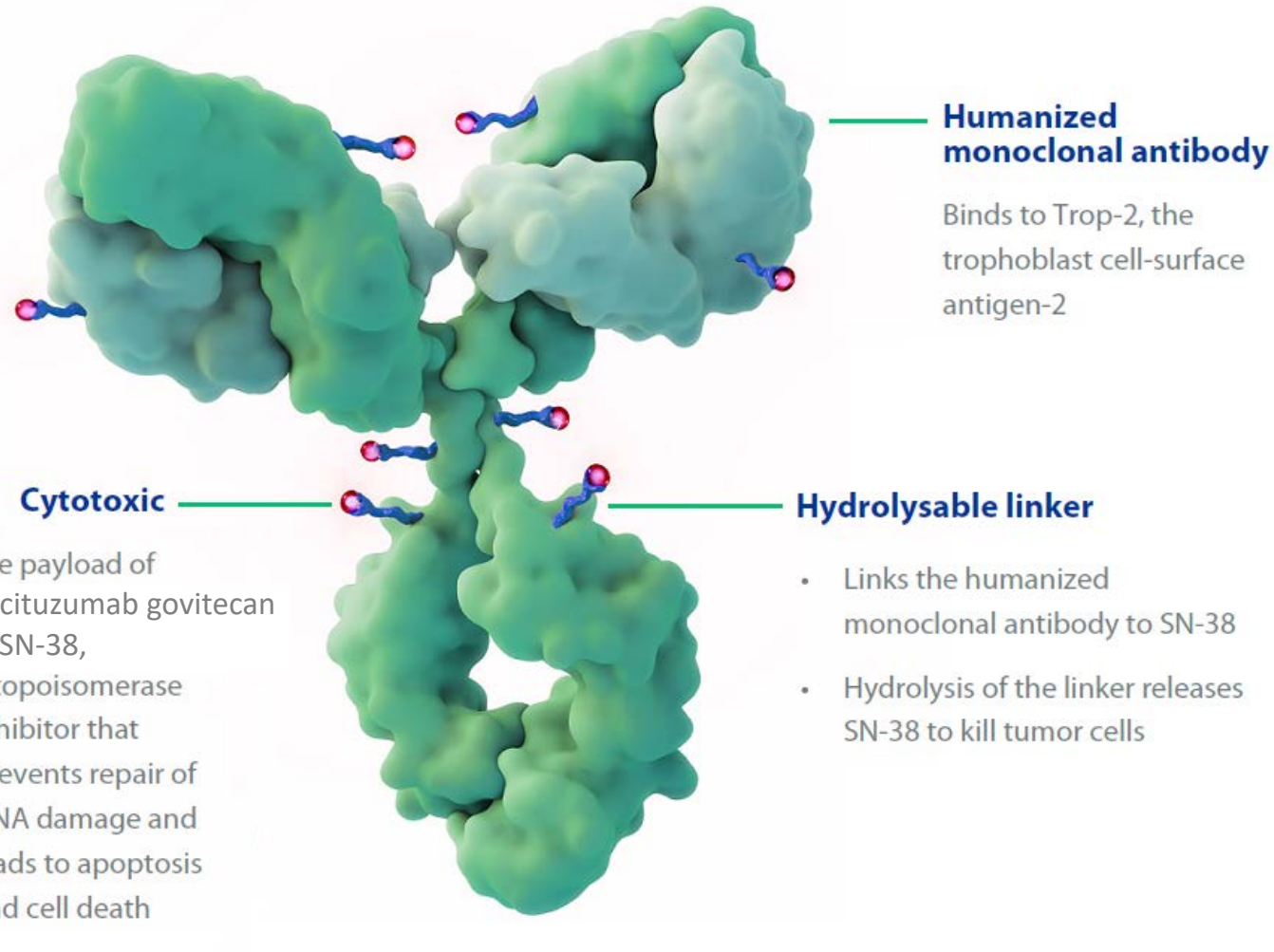
NCT02516241

www.clinicaltrials.gov, NCT02516241. Powles TB et al. Ann Oncol 2020;31(suppl 4):S1142-S1215.

Courtesy of Elisabeth I Heath, MD

Sacituzumab Govitecan

- Trop-2-directed antibody drug conjugate
- Site specific conjugate of irinotecan active metabolite (SN-38) to humanized monoclonal antibody against trophoblastic cell-surface antigen-2 (Trop-2)
- Trop-2 is a cell surface glycoprotein expressed in urothelial cancers



Courtesy of Elisabeth I Heath, MD

Sacituzumab Govitecan

- TROPHY-U-01: Phase 2 trial with multiple cohorts
- Cohort 1: post platinum-based chemotherapy and immune checkpoint inhibitor (113 pts)
  - ORR: 27% (with 76% of patients with reduction in tumor size)
  - Median PFS: 5.4 months
  - Median OS: 10.5 months
- FDA Fast Track Designation for urothelial cancer: April 9, 2020

ADVERSE EVENT	ALL GRADES (%)	GRADE 3 (%)	GRADE 4 (%)
Neutropenia	46	22	12
Febrile Neutropenia	10	7	3
Diarrhea	65	9	1
Fatigue	50	4	0

Loriot Y et al. Annals of Oncology 31(2020);S1156.

NCT03547973

Courtesy of Elisabeth I Heath, MD

Additional Sacituzumab Govitecan Clinical Trials

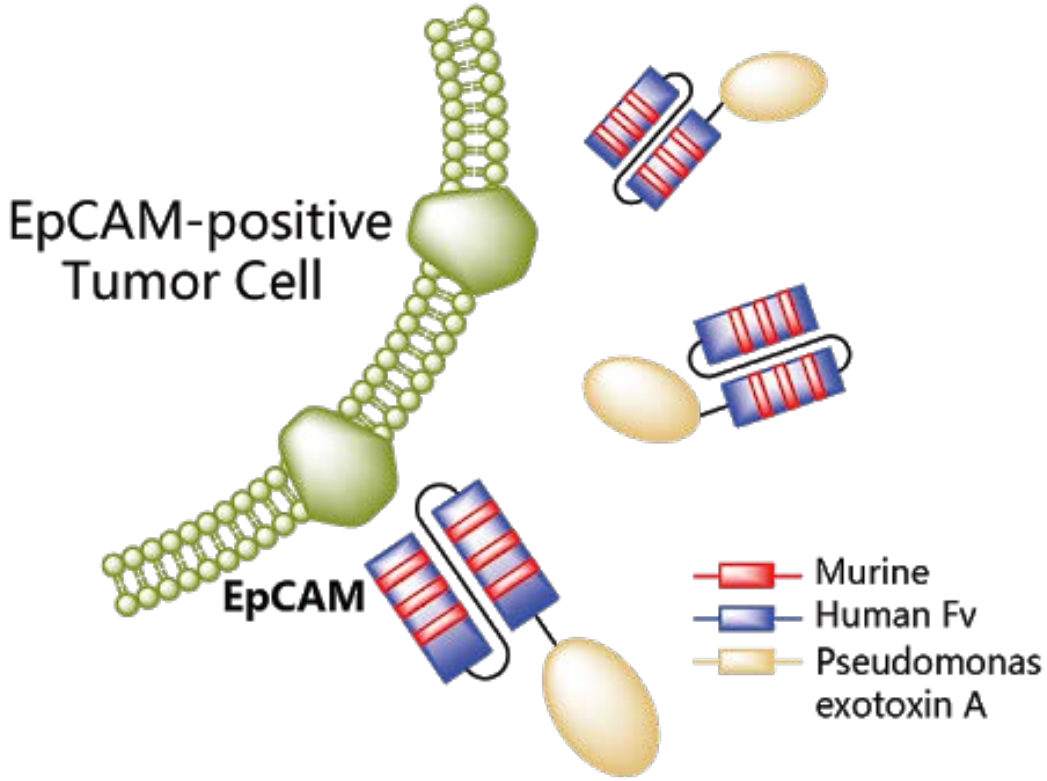
- TROPHY-U-01
  - Cohort 2: cisplatin-ineligible and one prior immune checkpoint inhibitor
  - Cohort 3: progressed after platinum-based chemotherapy and no immune checkpoint inhibitor
- TROPiCS-04
  - Phase III trial: SG versus taxane in post platinum-based chemotherapy, post PD-(L)1 antibody therapy
- MORPHEUS mUC
  - Phase I/II trial: SG plus atezolizumab in post platinum-based chemotherapy
- SEASTAR
  - Phase I/II trial: SG plus rucaparib in urothelial carcinoma with DNA repair deficiency

NCT01928394, NCT04527991, NCT03869190, NCT03992131

Courtesy of Elisabeth I Heath, MD

Oportuzumab Monatox

- Antibody-drug conjugate of humanized scFv monoclonal antibody fragments that bind to epithelial cell adhesion molecule (EpCAM) and a portion of pseudomonas exotoxin A
- VISTA-3: Phase III of VB4-845 in non-muscle invasive bladder cancer previously treated with BCG
- FDA Fast Track Designation August 16, 2018



https://www.pharmacodia.com/yaodu/html/v1/biologics/f9d81ff01aec9a8625983fe8f5c382f0.html#onlineretailersOuBiologys

NCT02449239

Courtesy of Elisabeth I Heath, MD

Disitamab Vedotin (RC48)

- HER2-directed antibody drug conjugate
- Recombinant humanized anti-HER2 monoclonal antibody-MMAE Conjugate
- Phase II:
  - 43 patients
  - HER2 IHC 2+ or 3+
  - Received at least one systemic chemotherapy
  - 86% had visceral metastasis
  - 33% had two prior lines of treatment
- ORR: 60.5%
- Median PFS: not reached
- Treatment related AEs (All Grades)
  - Leukopenia (51%)
  - Neutropenia (37%)
  - Fatigue (35%)

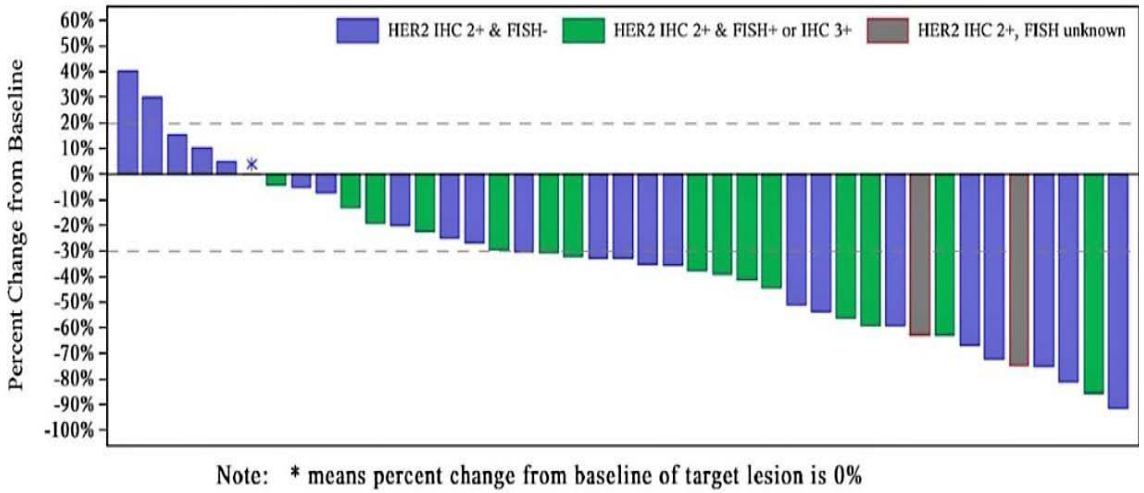
NCT03507166

Sheng et al. DOI: 10.1200/JCO.2019.37.15_suppl.4509 *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 4509-4509.

Courtesy of Elisabeth I Heath, MD

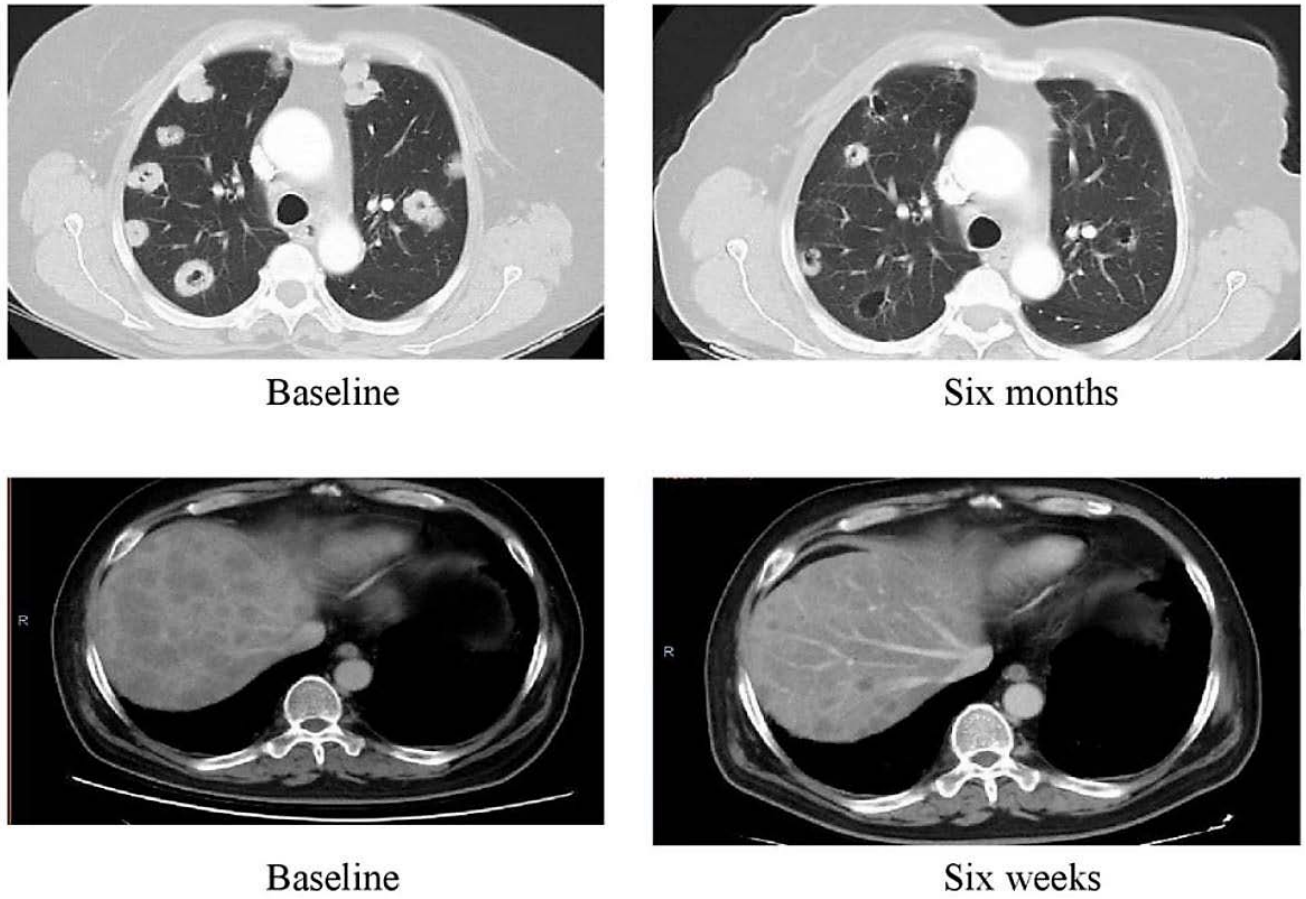
Disitamab Vedotin (RC48)

Figure 3. Best Change of Target lesion from Baseline



Note: * means percent change from baseline of target lesion is 0%

Figure 3. CT Images of Two Patients



Baseline | Six months

Baseline | Six weeks

FDA Fast Track Designation on September 25, 2020

NCT03507166

Sheng et al. DOI: 10.1200/JCO.2019.37.15_suppl.4509 *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 4509-4509.

Courtesy of Elisabeth I Heath, MD

Cabozantinib Combinations

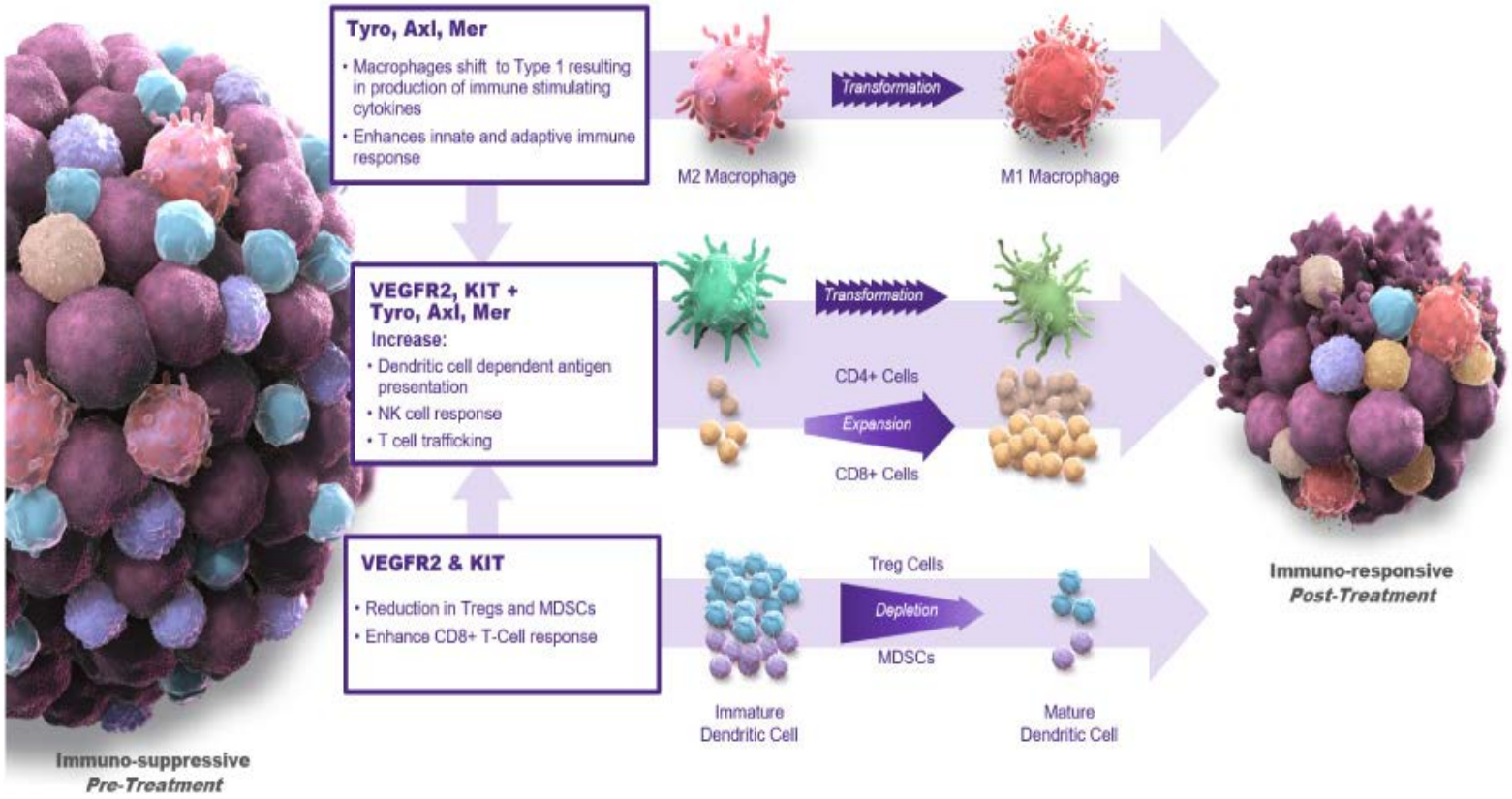
- Cabozantinib plus nivolumab and/or ipilimumab (NCT02496208)
- Cabozantinib plus durvalumab (ARCADIA)(NCT03824691)
- Cabozantinib plus atezolizumab (COSMIC-021)(NCT03170960)
  - UC expansion cohort 2
  - 30 patients with prior platinum-containing chemotherapy
  - Median follow-up 19.7 months
  - ORR= 27%, 2 CR
  - Median PFS = 5.4 months
  - AEs: asthenia (37%), diarrhea (27%), mucosal inflammation (20%)
- Cabozantinib plus niraparib (NCT03425201)

Pal SK et al J Clin Oncol 38: 2020 (suppl; abstr 5013).

Courtesy of Elisabeth I Heath, MD

Sitravatinib

- Receptor tyrosine kinase
- Involved in creating immunosuppressive tumor microenvironment
- Sitravatinib targets TAM family (TYRO3, AXL, and MER), VEGFR2, and KIT

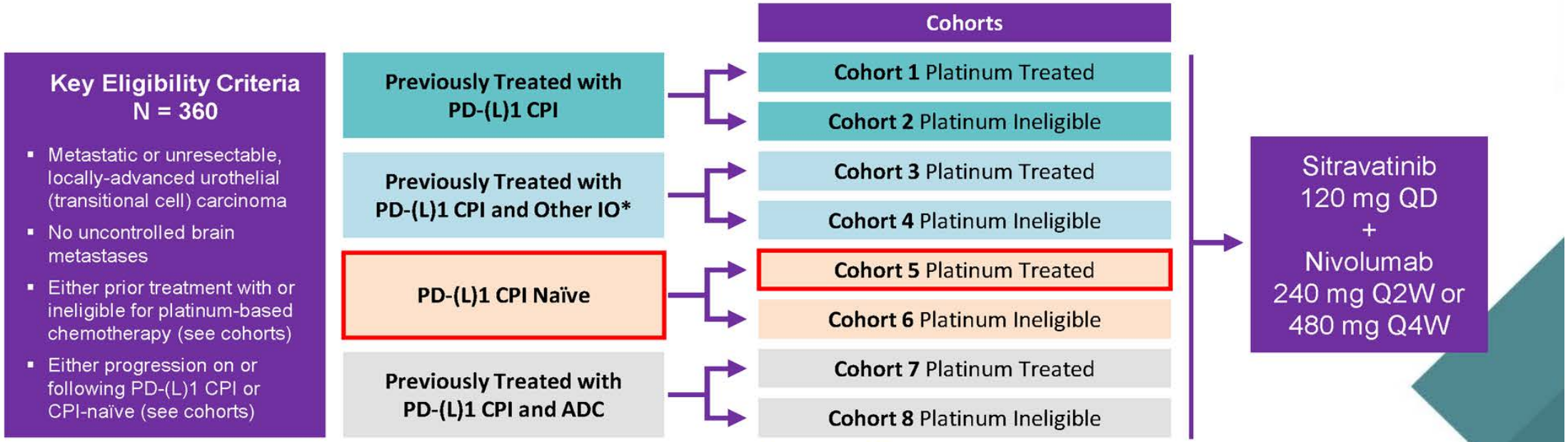


https://www.mirati.com/pipeline/sitravatinib/

Courtesy of Elisabeth I Heath, MD

VIRTUAL 2020 ESMO congress

Study 516-003: Open-Label Phase 2 Trial of Sitravatinib and PD-(L)1 CPIs in Urothelial Carcinoma



Start Date: September 11, 2018
Status: Enrolling
Sponsor: Mirati Therapeutics

Outcome Measures
Primary: ORR
Secondary: AEs, CBR, DOR, PFS, OS, PK
Exploratory: Circulating and tissue biomarkers

* Other IOs including but not limited to DNA vaccines, anti-CTLA-4, anti-OX40, anti-CD137 therapy or anti-IDO1 therapies, or recombinant IL-2 (CD-122) or IL-7 therapies
Abbreviations: ADC, antibody drug conjugate; AEs, adverse events; CBR, clinical benefit rate; CPI, checkpoint inhibitor; DOR, duration of response; IO, immune-based therapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q2/4W, every 2/4 weeks; QD, once daily
ClinicalTrials.gov. NCT03606174. Accessed August 17, 2020.

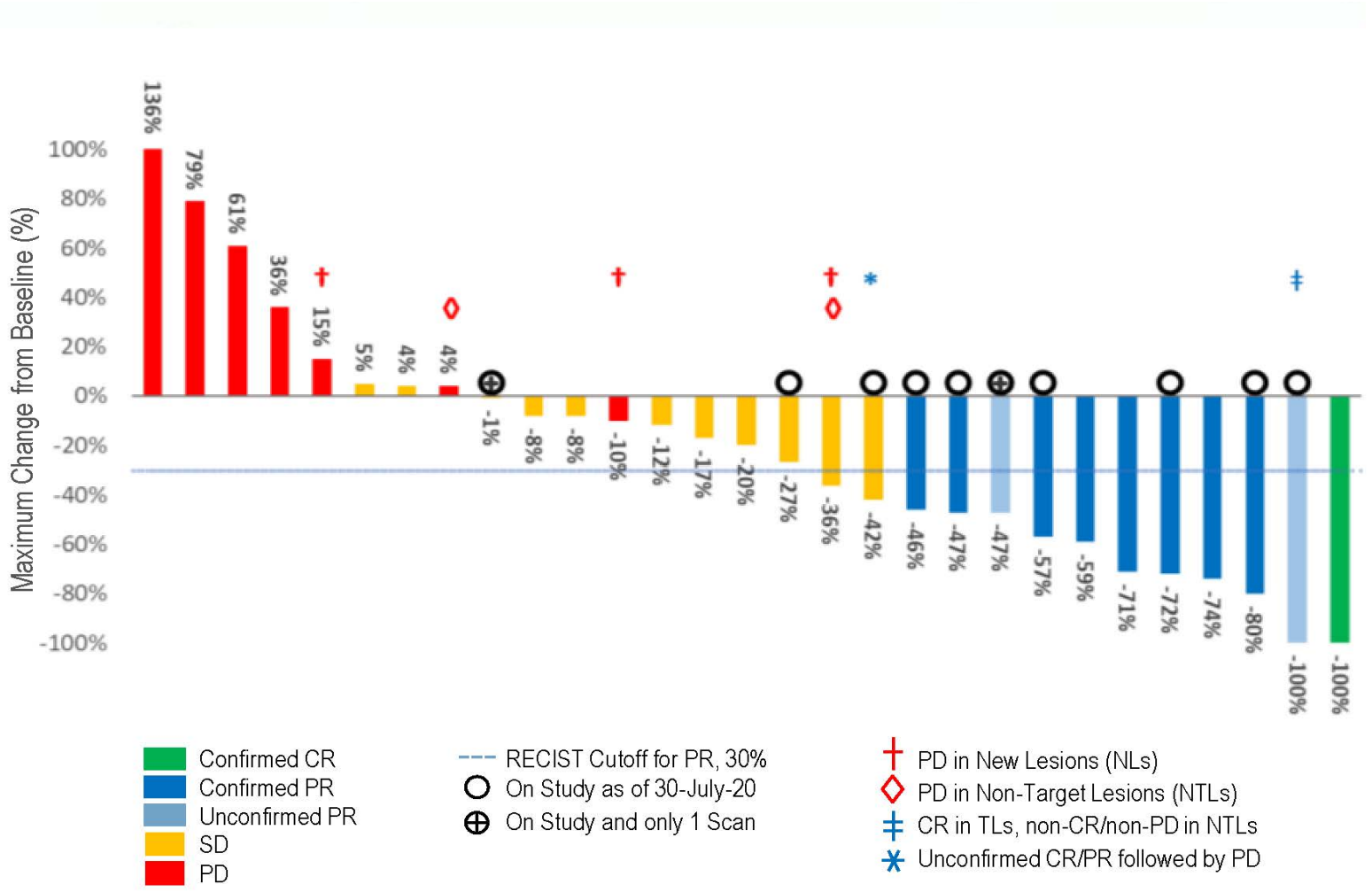
Doshi GK et al. J Clin Oncol 37, 2019 (suppl 7S; abstr TPS498). Msaouel P et al. Annals of Oncology (2020) 31 (suppl_4): S550-S550. 10.1016/annonc/annonc274.

NCT03606174

Courtesy of Elisabeth I Heath, MD

Sitravatinib

- Phase II (cohort 5)
  - 30 patients with prior platinum-based chemotherapy
  - ORR=37%
  - CR=3%
  - PR=34%
  - SD=37%
  - PD=23%
- AEs (Grades 3/4)
  - Hypertension (13%)
  - Diarrhea (8%)
  - Fatigue (5%)
  - Dysphonia (3%)



Msaouel P et al. Annals of Oncology (2020) 31 (suppl_4): S550-S550. 10.1016/annonc/annonc274.

Courtesy of Elisabeth I Heath, MD

FGFR Inhibitors

- **Rogaratinib** (pan-FGFR1-4 inhibitor)
- Phase II/III (FORT-1): rogaratinib versus chemotherapy (docetaxel/paclitaxel/vinflunine)
  - Progression after at least one platinum-containing regimen
  - Selection based on FGFR1-3 mRNA overexpression and/or FGFR3-activating mutations/translocations
  - 175 patients
  - ORR=19.5% (vs 19.3%)
  - Median PFS=2.7 months (vs 2.9 months)
  - Patients with FGFR3 DNA alterations had ORR 52.4%
- Phase Ib/II (FORT-2): rogaratinib and atezolizumab
  - Must be cisplatin-ineligible
  - Selection based on FGFR1 or FGFR3 mRNA defined as RANscope score of 3+ or 4+
  - 31 patients
  - ORR=44%
  - CR=16%
  - AEs: hyperphosphatemia (45%) and retinal pigment detachment (3%)

Schuler M et al. Lancet Oncol. 2019 Oct;20(10):1454-1466. doi: 10.1016/S1470-2045(19)30412-7.
Rosenberg J et al. Virtual Scientific Meeting ASCO 2020.

Courtesy of Elisabeth I Heath, MD

FGFR Inhibitors

- **Infigratinib** (FGFR1-3 inhibitor)
- Phase I trial: platinum-refractory, FGFR3 alterations
- 67 patients
  - ORR: 33% with hyperphosphatemia vs 5.3%
  - Different genomic alterations between upper tract and bladder
    - Upper tract: FGFR3-TACC3 fusions, FGFR3-R248C mutations

- PROOF 302: Infigratinib as adjuvant treatment
  - Undergo nephrouretectomy, distal ureterectomy, or cystectomy
  - Ineligible to receive cisplatin-based adjuvant chemotherapy (if not received neoadjuvant)
  - FGFR3 alteration

Pal SK et al. Cancer Discovery 2018 July 1;8(7):912-21.
Lyou Y et al. European Urology, 78, 6, December 2020: 916-924.
Dizman N et al. 2019 ASCO Annual Meeting.

Courtesy of Elisabeth I Heath, MD

Case 1

- 62 year old white female with 1 year history of intermittent gross hematuria
- Workup revealed T3N0 disease
- Declined neoadjuvant therapy
- Completed radical cystectomy
- Within 1 year, patient developed multiple lung lesions (1.5 cm in greatest dimension)
- Lung biopsy revealed urothelial cancer
- Genomic profiling revealed no FGFR alterations
- PD-L1 status negative
- Creatinine 1.2 with GFR 61
- Presented with clinical trial
- Enrolled in DANUBE trial

Courtesy of Elisabeth I Heath, MD

Case 2

- 67 year old Pakistani male with 6 month history of gross hematuria and flank pain
- Workup revealed T2N0 upper tract tumor
- Completed nephroureterectomy
- In year 3, patient developed persistent right knee pain
- Imaging confirmed metastatic lesion in right distal femur
- Biopsy confirmed metastatic urothelial cancer
- Genomic profiling showed FGFR3 alteration
- Underwent radiation therapy to right distal femur with major improvement in pain
- Received 8 cycles of gemcitabine/cisplatin and then progressed with new liver lesions
- Started erdafitinib with mild hyperphosphatemia
- Clinical trial with sitravatinib upon progression

Courtesy of Elisabeth I Heath, MD