BT5528-100:
End of Phase I escalation top-line results

- September 2022

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Agenda

Introduction	**Kevin Lee** Chief Executive Officer
Review of BT5528 Phase I clinical data	**Dominic Smethurst** Chief Medical Officer
Q&A	**Executive Management Team**

Overview of BT5528 Phase I results

- BT5528 demonstrates anti-tumor activity in heavily pre-treated ovarian and urothelial cancer patients
- Emerging safety profile distinguishes it from other EphA2-targeted molecules
- Dosing at recommended Phase II dose (RP2D) of 6.5 mg/m^2 q2w in expansion cohorts is ongoing

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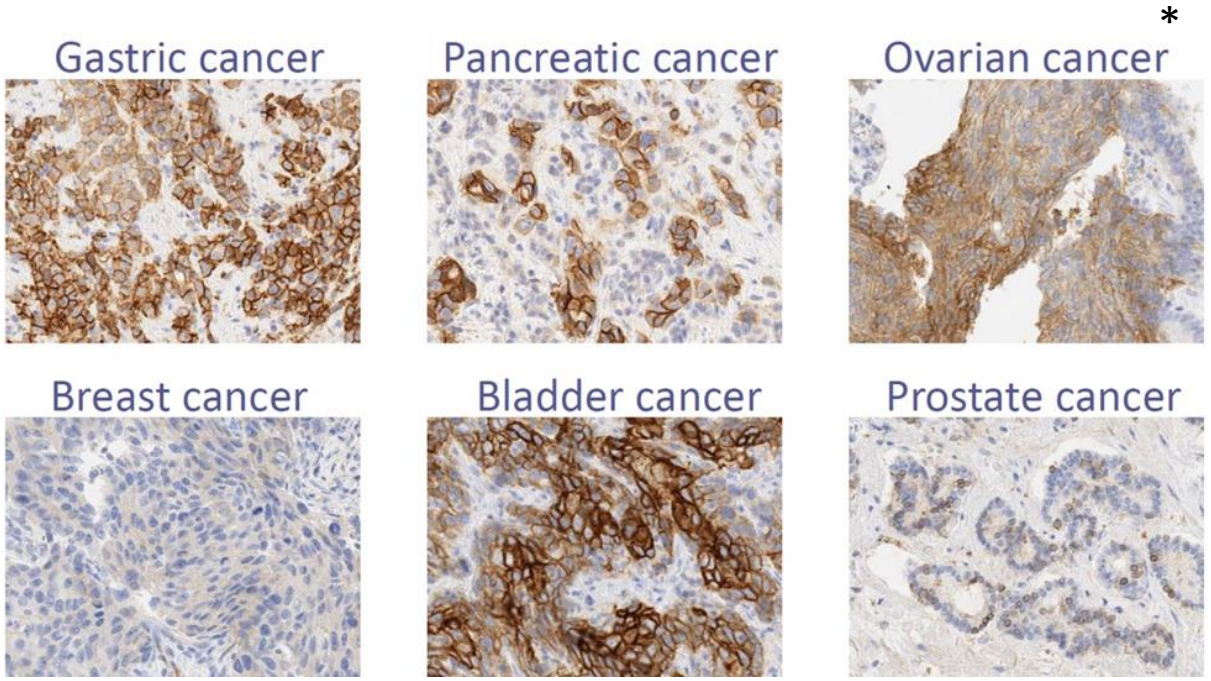
- Background on EphA2 and BT5528

EphA2 is a high value target for the treatment of cancer

- EphA2, a member of Eph subfamily of receptor tyrosine kinases
- Regulates cell migration, adhesion, proliferation and differentiation
- Highly expressed in many human cancers and correlates with tumor progression
  - Ovarian
  - Urothelial
  - NSCLC
  - Head & Neck
  - Gastric
  - TNBC



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*Kamoun, et al, Nanoliposomal Targeting of Ephrin Receptor A2 (EphA2): Clinical Translation, Merrimack Pharmaceuticals

Multiple approaches targeting EphA2-expressing tumors have failed

- MEDI-547 (MedImmune) ADC: halted following first dose-cohort coagulopathy[1]
- DS-8895a (Daiichi) antibody: limited efficacy in EphA2+ gastric and esophageal cancer, significant infusion reactions. Discontinued because of poor risk-benefit profile[2]
- MM-310 (Merrimack) antibody-targeted nanoliposome: terminated - “unable to reach optimal therapeutic index”[3]

Invest New Drugs (2013) 31:77–84
DOI 10.1007/s10637-012-9801-2

PHASE I STUDIES

Phase 1, open-label study of MEDI-547 in patients with relapsed or refractory solid tumors

Christina M. Annunziata · Elise C. Kohn · Patricia LoRusso · Nicole D. Houston · Robert L. Coleman · Manuela Buzoianu · Gabriel Robbie · Robert Lechleider

Investigational New Drugs
https://doi.org/10.1007/s10637-022-01237-3

PHASE I STUDIES

A phase 1 safety and bioimaging trial of antibody DS-8895a against EphA2 in patients with advanced or metastatic EphA2 positive cancers

Hui K. Gan[1,2,3] · Sagun Parakh[1,2,3] · F. T. Lee[1] · Niall C. Tebbutt[3] · Malaka Ameratunga[3] · Sze Ting Lee[1,2,4,5] · Graeme J. O'Keefe[1,4] · Sylvia J. Gong[1,4] · Christine Vanrenen[3] · Jaren Caine[3] · Mara Giovannetti[6] · Carmel Murone[1] · Fiona E. Scott[1,2] · Nancy Guo[1] · Ingrid J. G. Burvenich[1,2] · Cameron Paine[4] · Mary J. Macri[6] · Masakatsu Kotsuma[7] · Giorgio Senaldi[7] · Ralph Venhaus[6] · Andrew M. Scott[1,2,4,5]

Clinical Trial · J Immunother Cancer. 2019 Aug 14;7(1):219. doi: 10.1186/s40425-019-0679-9.

Safety, tolerability, pharmacokinetics, and pharmacodynamics of the afucosylated, humanized anti-EPHA2 antibody DS-8895a: a first-in-human phase I dose escalation and dose expansion study in patients with advanced solid tumors

Kohei Shitara [1], Taroh Satoh [2], Satoru Iwasa [3], Kensei Yamaguchi [4], Kei Muro [5], Yoshito Komatsu [6], Tomohiro Nishina [7], Taito Esaki [8], Jun Hasegawa [9], Yasuyuki Kakurai [9], Emi Kamiyama [9], Tomoko Nakata [9], Kota Nakamura [9], Hayato Sakaki [9], Ichinosuke Hyodo [10]

merrimack

Merrimack Discontinues Development of MM-310

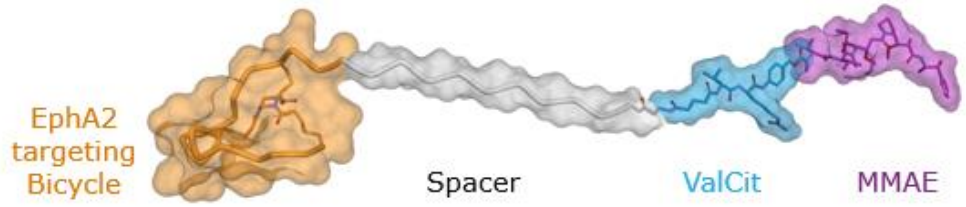
April 4, 2019

-- Safety update shows Phase 1 study unable to reach optimal therapeutic index for MM-310 due to continued observation of cumulative peripheral neuropathy --

-- Company expects to reduce workforce reflective of narrowed preclinical development pipeline; continues to prudently advance programs while completing the assessment of its strategic alternatives --

1. Annunziata et al, Invest New Drugs. 2013 Feb;31(1):77-84
2. Shitara et al, Journal for ImmunoTherapy of Cancer. 2019 7: 219-230 (Ph1 study); Gan et al, Invest New Drugs. 2022 40(4) 747-755
3. Merrimack Pharmaceuticals Inc., press release April 4, 2019

BT5528 is a first-in-class BTC-targeting EphA2



- BT5528 has potential to penetrate solid tumors; approximately 40X smaller than an ADC
- Toxin is released and retained in tumor cells, resulting in tumor cell death and bystander killing
- PK profile distinct from ADCs; renally eliminated, bypassing liver metabolism

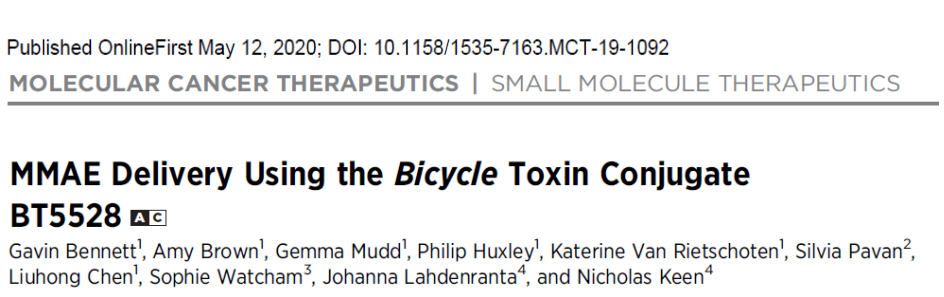

Journal of Medicinal Chemistry

pubs.acs.org/jmc Article

Identification and Optimization of EphA2-Selective Bicycles for the Delivery of Cytotoxic Payloads

Gemma E. Mudd,* Amy Brown, Liuhong Chen, Katerine van Rietschoten, Sophie Watcham, Daniel P. Teufel, Silvia Pavan, Rachid Lani, Philip Huxley, and Gavin S. Bennett

Cite This: https://dx.doi.org/10.1021/acs.jmedchem.9b02129 Read Online


Published OnlineFirst May 12, 2020; DOI: 10.1158/1535-7163.MCT-19-1092

MOLECULAR CANCER THERAPEUTICS | SMALL MOLECULE THERAPEUTICS

MMAE Delivery Using the *Bicycle* Toxin Conjugate BT5528 ADC

Gavin Bennett[1], Amy Brown[1], Gemma Mudd[1], Philip Huxley[1], Katerine Van Rietschoten[1], Silvia Pavan[2], Liuhong Chen[1], Sophie Watcham[3], Johanna Lahdenranta[4], and Nicholas Keen[4]

BT5528-100:
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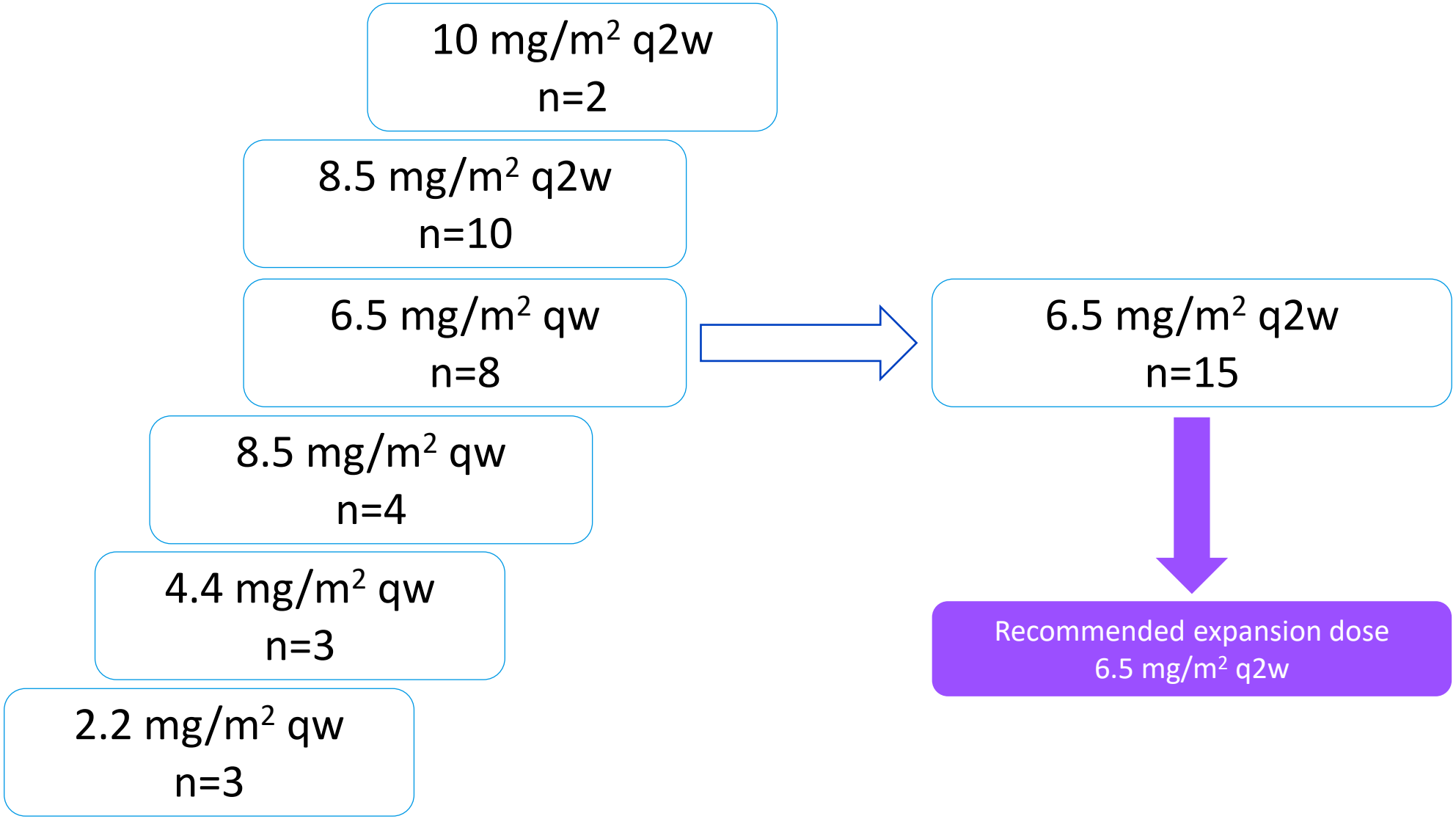
- Study design and results

BT5528 Monotherapy dose escalation



Overview of patient demographics and baseline characteristics – heavily pre-treated population

Demographics	All Cohorts N=45 n (%)	6.5 mg/m^2 q2w N=15 n (%)
Age, years, mean (range)	62 (49-76)	61 (51-75)
Sex, n (%)		
Male	15 (33)	9 (60)
Female	30 (67)	6 (40)
ECOG at baseline, n (%)		
0 (Good performance status)	18 (40)	5 (33)
1	27 (60)	10 (67)
Prior therapies[1], median (range)	7 (3-21)[2]	6 (3-21)

All data as of 01 Aug 2022

1. Includes all prior therapies. Total lines of therapy: 4 (1-13) for total population, 4 (2-13) for 6.5mg/m^2 q2w cohort
2. As of Oct 2021, the min number of prior therapies was cited as 1. A patient receiving Folfirinox was previously reported as having 1 prior therapy. This has been re-categorized as 4 therapies

Overview of patient disease indications

Primary Diagnosis (tumor type)	All Cohorts N=45 n (%)[1]	6.5 mg/m^2 q2w N=15 n (%)
Ovarian[2]	21 (47)	3 (20)
Urothelial[3]	8 (18)	6 (40)
Pancreatic	8 (18)	1 (7)
Lung[4]	4 (9)	2 (13)
Other[5]	4 (9)	3 (20)

1. Sum of percentages does not add to 100 due to rounding
2. Includes ovarian, fallopian tube
3. Includes bladder, urethra, urinary bladder, and urothelial carcinoma
4. Includes lung, NSCLC
5. Includes bone, rectal, stomach, and squamous of unknown origin

Most frequent treatment-related adverse events (≥15%) – well tolerated at RP2D

Treatment-Related Adverse Event	All Cohorts N=45 All Grades n (%)	All Cohorts N=45 Grade ≥3 n (%)	6.5 mg/m^2 q2w N=15 All Grades n (%)	6.5 mg/m^2 q2w N=15 Grade ≥3 n (%)
Nausea	20 (44)	1 (2)	8 (53)	0
Diarrhea	16 (36)	1 (2)	7 (47)	1 (7)
Fatigue	15 (33)	2 (4)	6 (40)	0
Neutrophil count decrease[1]	14 (31)	10 (22)	2 (13)	0
Vomiting	12 (27)	1 (2)	3 (20)	0
Anemia	10 (22)	4 (9)	4 (27)	2 (13)
Decreased appetite	7 (16)	0	4 (27)	0
Alopecia	7 (16)	0	1 (7)	0
Peripheral neuropathy[2]	7 (16)	0	2 (13)	0

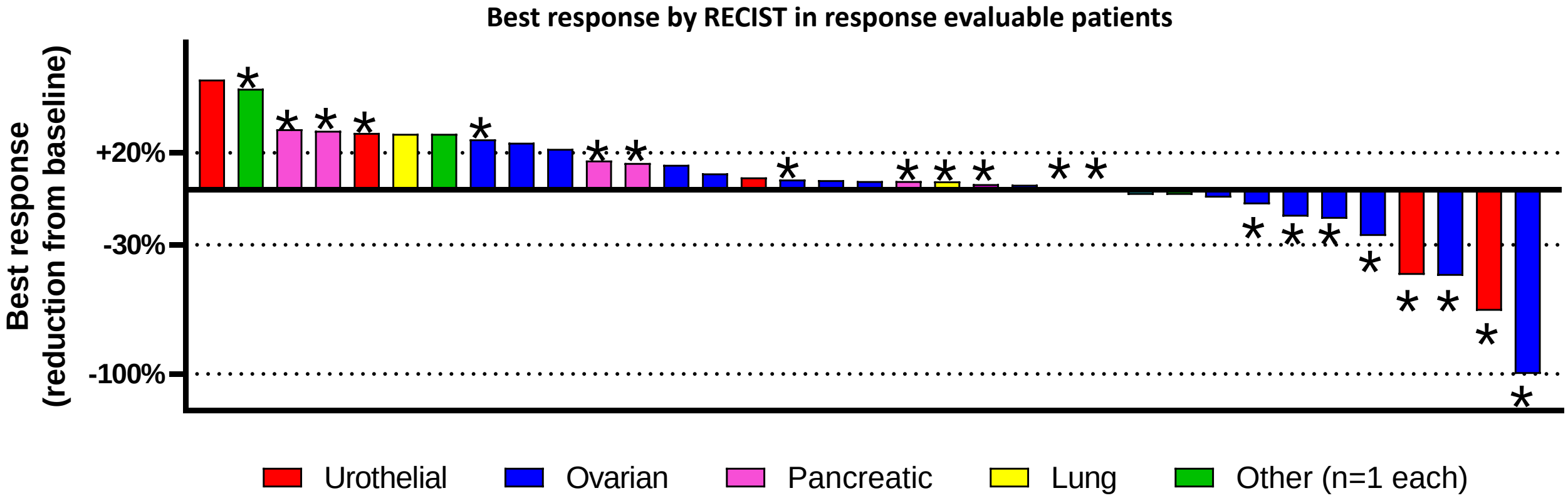
1. Neutrophil count decrease also includes neutropenia
2. Peripheral neuropathy events include neuropathy peripheral, muscular weakness, peripheral sensory neuropathy, gait disturbance, neuralgia, paresthesia

Treatment-related adverse events of interest – low incidence across all doses

Treatment-Related Adverse Event	All Cohorts N=45 All Grades n (%)	All Cohorts N=45 Grade ≥3 n (%)	6.5 mg/m^2 q2w N=15 All Grades n (%)	6.5 mg/m^2 q2w N=15 Grade ≥3 n (%)
Skin rash[1]	2 (4)	0	0	0
Hemorrhage	0	0	0	0
Eye disorders[2]	2 (4)	0	1 (7)	0

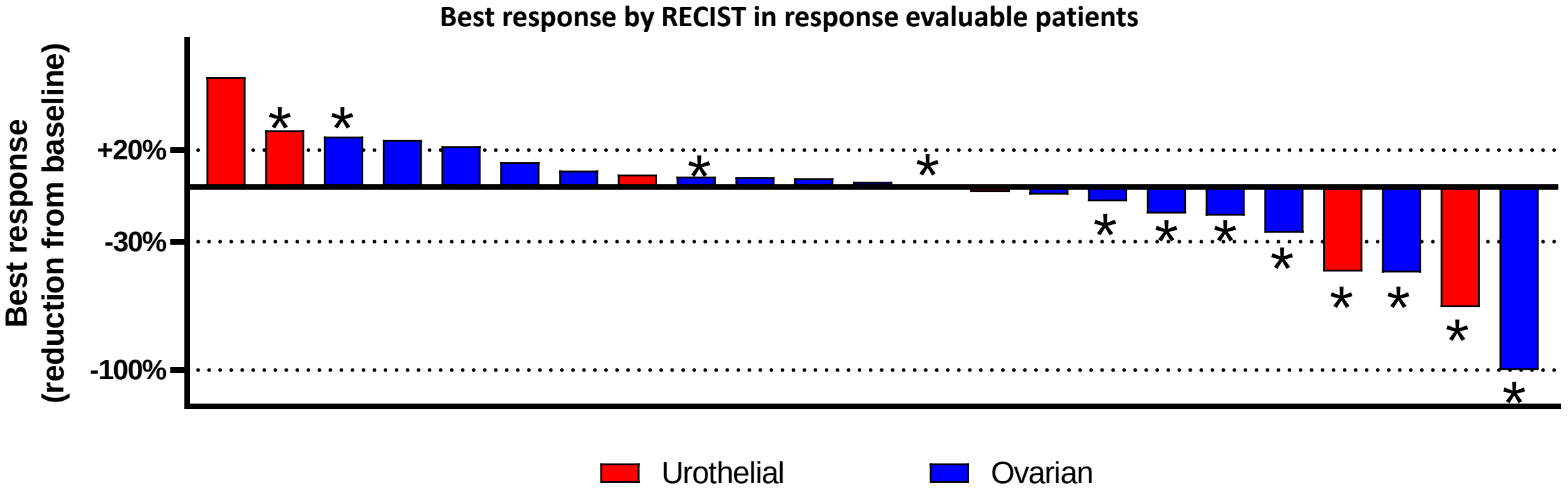
1. Both skin rash TRAEs were maculopapular
2. Eye disorder TRAEs were dry eye, visual impairment, and visual blurred

Potential relationship between EphA2 expression and response



*EphA2 positive=IHC Tumor proportion score (TPS) >1

Potential relationship between EphA2 expression and response in ovarian and urothelial cancers



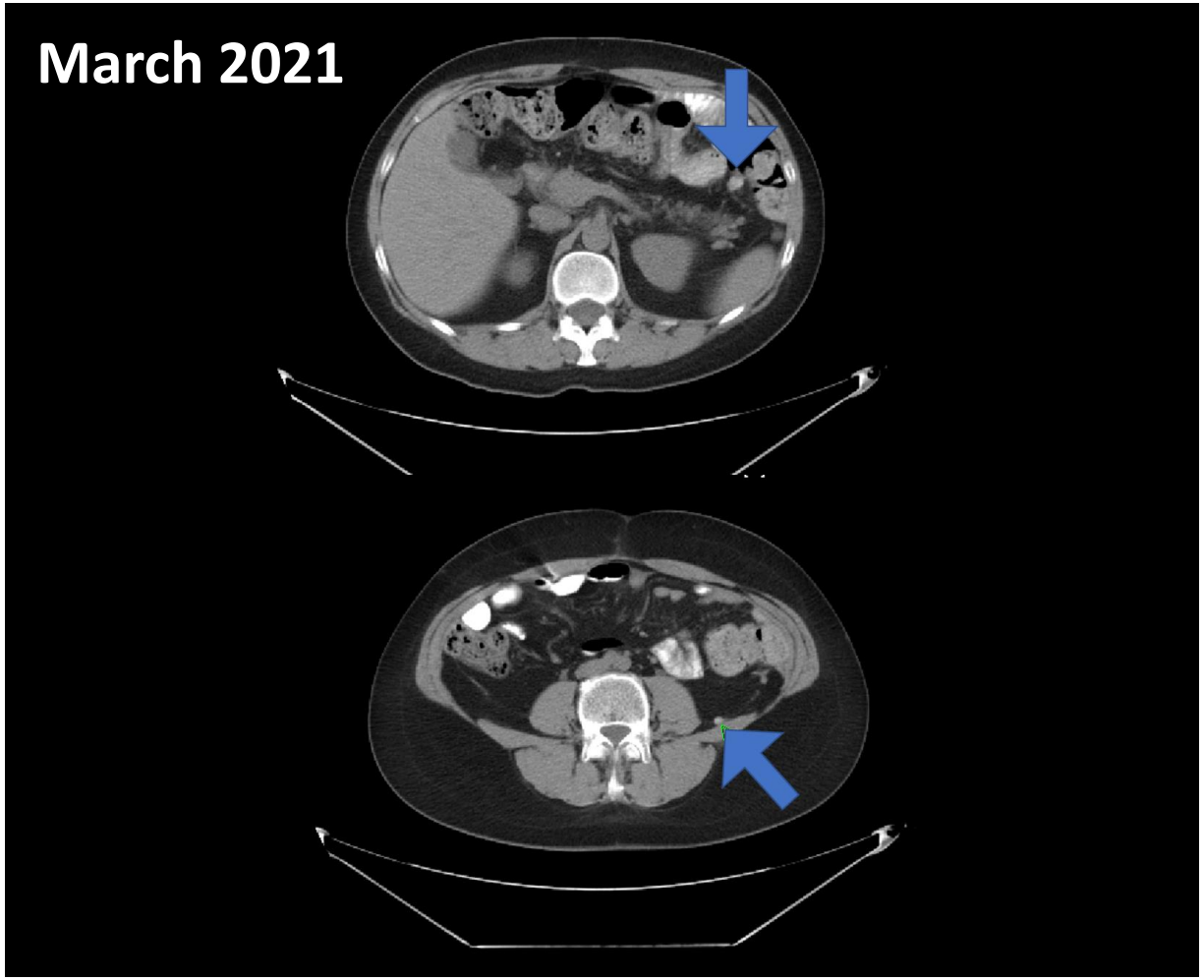
*EphA2 positive=IHC Tumor proportion score (TPS) >1

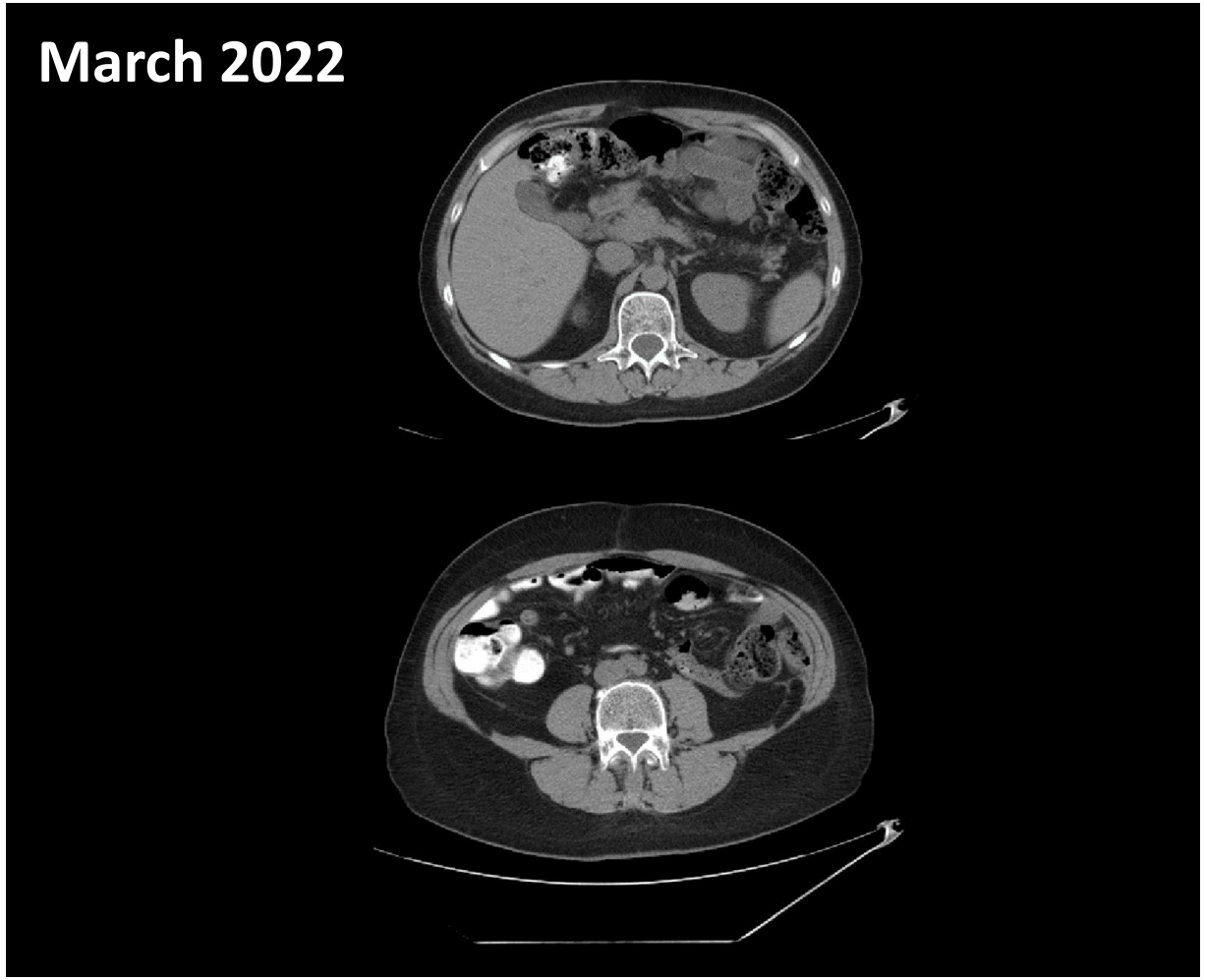
Summary of responses among EphA2+ response evaluable patients across cohorts

Best overall response	Ovarian EphA2+ N=9 n (%)	Urothelial EphA2+ N=3 n (%)
Complete Response (CR)	1 (11)[1]	0
Partial Response (PR)	1 (11)[2]	2 (67)[3,4]
Stable Disease (SD)	4 (44)	0
Progressive Disease	3 (33)	1 (33)
ORR (CR+PR)	**2 (22)**	**2 (67)**
DCR (CR+PR+SD)	**6 (67)**	**2 (67)**

1. Ovarian CR patient started at 8.5 mg/m^2 q2w and reduced to 6.5 mg/m^2 q2w after 12 28-day cycles. Patient remains on therapy >16 months
2. Ovarian PR patient started at 6.5 mg/m^2 q2w and remains on therapy >4 months
3. A urothelial responder started at 8.5 mg/m^2 q2w and reduced to 6.5 mg/m^2 q2w after 1 dose. They remained on therapy ~6 months
4. A urothelial responder started at 10 mg/m^2 q2w and reduced to 6.5 mg/m^2 q2w after 1 dose. They remained on therapy ~3 months

Complete response in ovarian cancer





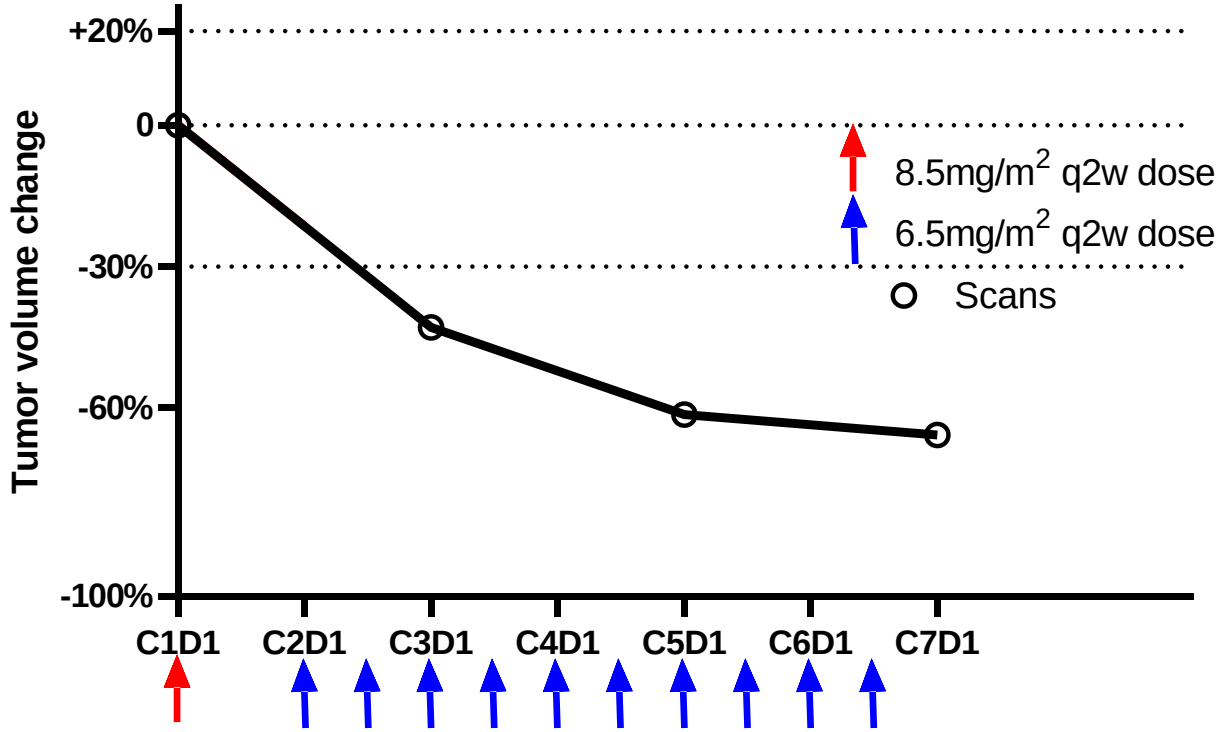
Comparative scans of ovarian cancer patient with Complete Response. Images show pre-dose scans vs end of Cycle 12 scans

Patient initially received 8.5mg/m^2 q2w, later reduced to 6.5mg/m^2 q2w. Patient now in Cycle 19

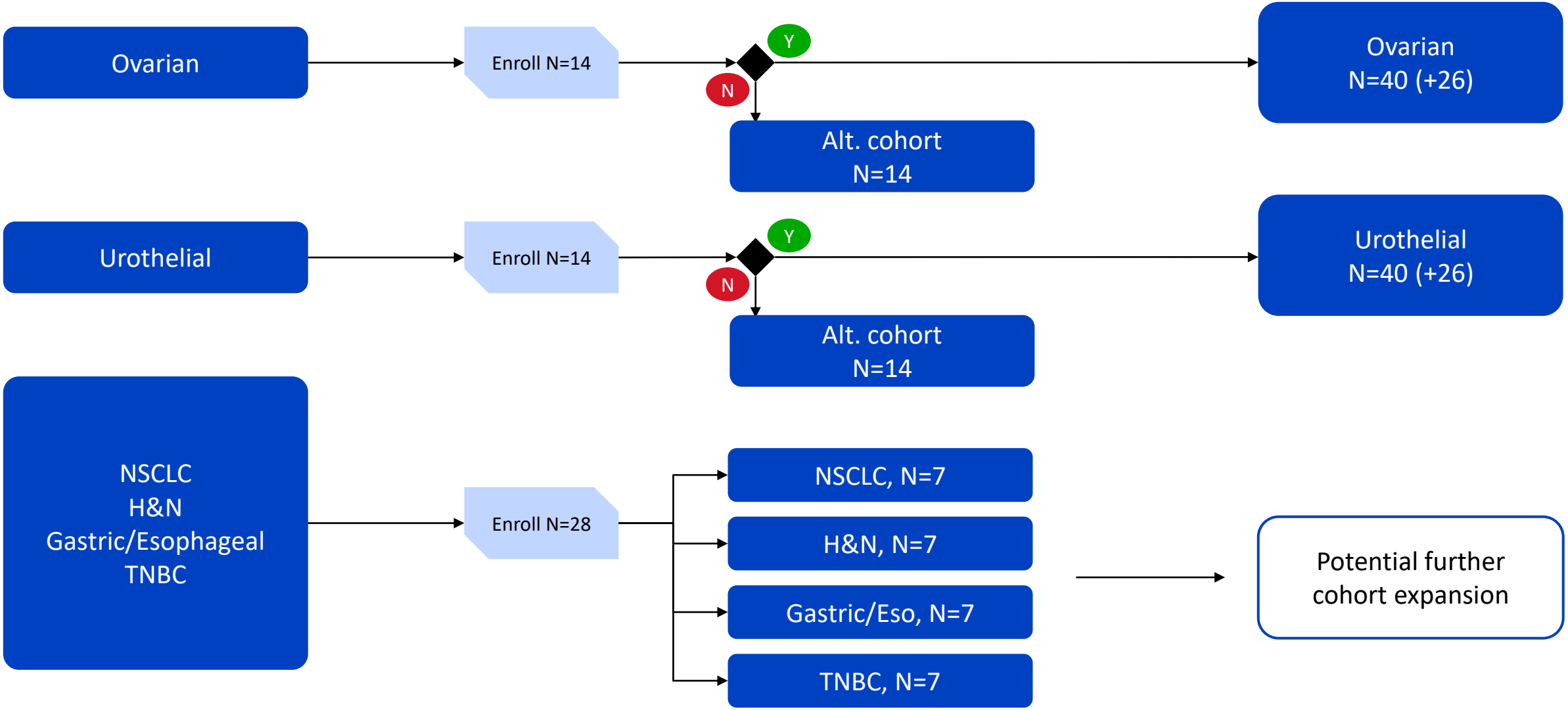
Urothelial cancer responder

Patient: Female, 76

- 4 prior lines of therapy
  - Neoadjuvant: Cisplatin + Gemcitabine (14 weeks): PD
  - 1st Line: Pembrolizumab (32 weeks): PD
  - 2nd Line: Enfortumab vedotin (15 weeks): PR (stop due to tox, pancreatitis)
  - 3rd Line: Carboplatin + Gemcitabine (17 weeks): CR (stop due to tox)
- Tumor at Study entry: Metastatic Urothelial Cancer. Target lesions: Lung and Adrenal Gland; Non target lesions: Lymph Nodes and Liver
  - Patient enrolled in Cohort 5 (8.5mg/m^2 q2w)
  - C1D1 at 8.5mg/m^2 q2w
  - Dose interrupted C1D15 due to neutropenia Gr3
  - Dose reduced to 6.5mg/m^2 q2w, C2D1-C6D15
  - Reason for discontinuation: progression due to brain metastases



BT5528 Expansion: Overall trial design



In conclusion…

- BT5528 demonstrates anti-tumor activity in heavily pre-treated ovarian and urothelial cancer patients
- Emerging safety profile distinguishes it from other EphA2-targeted molecules
- Dosing at recommended Phase II dose of 6.5 mg/m^2 q2w in expansion cohorts is ongoing
- Further BT5528 update in 2023