Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Bladder Cancer (Part 2 of a 2-Part Series)

Friday, February 18, 2022

6:30 PM – 8:00 PM PT

Faculty

Shilpa Gupta, MD
Daniel P Petrylak, MD
Guru Sonpavde, MD

Moderator

Sumanta Kumar Pal, MD

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Faculty

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Taussig Cancer Institute, Cleveland Clinic
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Dana-Farber Cancer Institute
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Professor of Internal Medicine (Medical Oncology) and Urology
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New Haven, Connecticut

Moderator

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Professor, Department of Medical Oncology and Therapeutics Research
City of Hope
Duarte, California

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Commercial Support

This activity is supported by educational grants from Astellas and Seagen Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, and Gilead Sciences Inc.

Research To Practice CME Planning Committee Members, Staff and Reviewers

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Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
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Agenda

Module 1 – Integrating Novel Agents into the Treatment Paradigm for Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Pal

Module 2 – Current and Future Front-Line Management of Metastatic UBC (mUBC) — Dr Gupta

Module 3 – Selection and Sequencing of Therapy for Relapsed/Refractory mUBC — Dr Petrylak

Module 4 – Tolerability/Toxicity of Novel Treatment Strategies and Practical Considerations in the Management of UBC — Dr Sonpavde

Bladder Cancer Survey Respondents

Neeraj Agarwal, MD

Andrea B Apolo, MD

Joaquim Bellmunt, MD, PhD

Robert Dreicer, MD, MS

Terence Friedlander, MD

Petros Grivas, MD, PhD

Shilpa Gupta, MD

Peter H O'Donnell, MD

Sumanta Kumar Pal, MD

Daniel P Petrylak, MD

Thomas Powles, MBBS, MRCP, MD

Jonathan E Rosenberg, MD

A Oliver Sartor, MD

Susan F Slovin, MD, PhD

Matthew R Smith, MD, PhD

Guru Sonpavde, MD

Evan Y Yu, MD

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MODULE 1: Integrating Novel Agents into the Treatment Paradigm for Nonmetastatic Urothelial Bladder Cancer (UBC) — Dr Pal

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Integrating Novel Agents into the Treatment Paradigm for Nonmetastatic Urothelial Bladder Cancer (UBC)

Sumanta Kumar Pal, MD

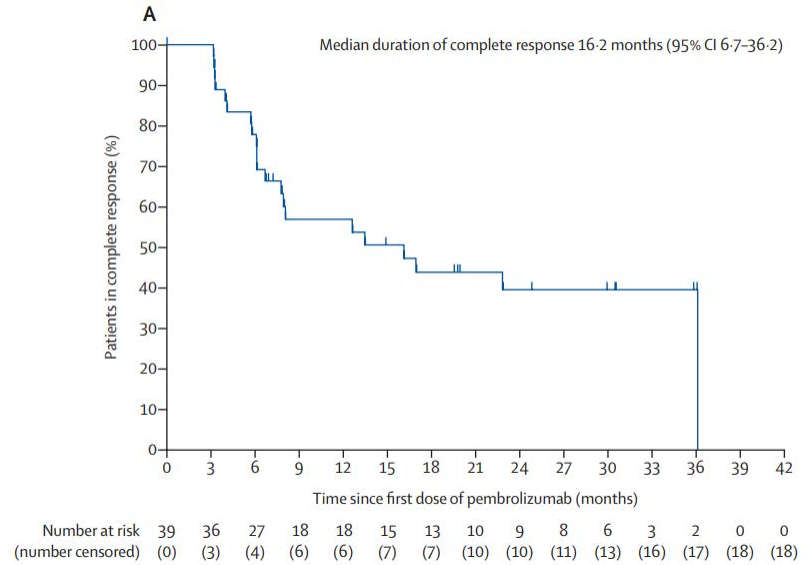
Dr Pal (Moderator) — Disclosures

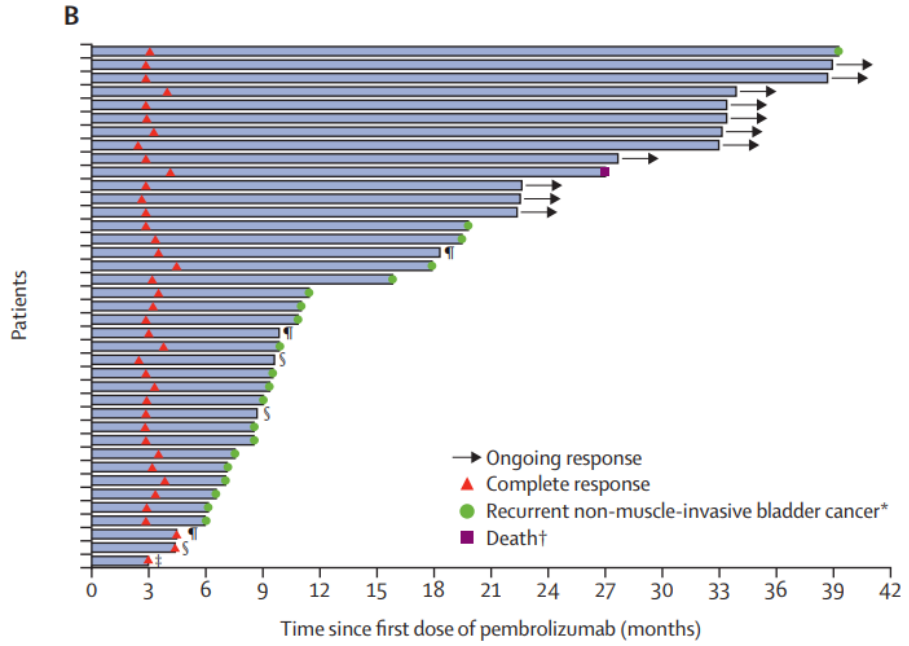
No relevant conflicts of interest to disclose

Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Arjun V Balar, Ashish M Kamat, Girish S Kulkarni, Edward M Uchio, Joost L Boormans, Mathieu Roumiguié, Laurence E M Krieger, Eric A Singer, Dean F Bajorin, Petros Grivas, Ho Kyung Seo, Hiroyuki Nishiyama, Badrinath R Konety, Haojie Li, Kijoeng Nam, Ekta Kapadia, Tara Frenkl, Ronald de Wit

	Cohort A efficacy population (n=96)*
Complete response	39 (41%, 30·7–51·1)
Non-complete response	56 (58%, 47·8–68·3)
Persistent disease†‡	40 (42%, 31·7–52·2)
Recurrent disease	6 (6%, 2·3–13·1)
Non-muscle-invasive bladder cancer stage progression§	9 (9%, 4·4–17·1)
Non-bladder malignancy¶	1 (1%, 0·0–5·7)
Progression to muscle-invasive disease (T2)	0 (NA–NA)
Non-evaluable‖	1 (1%, 0·0–5·7)





- Multicenter, phase II study across 54 sites in 14 countries
- Patients had to have BCG-unresponsive bladder cancer, ECOG 0-2 and decline radical cystectomy
- Patients received pembrolizumab every 3 weeks for 24 mos or until centrally confirmed disease persistence, recurrence or progression
- Primary endpoint was complete response rate (absence of high-risk NMIBC)
- 334 patients were screened → 101 eligible patients enrolled with a median follow-up of 36.4 months
- 39 of 96 patients (41%) had a complete response at 3 months
- Grade 3 or 4 treatment-related Aes occurred in 13% of pts

Balar, Arjun V., Ashish M. Kamat, Girish S. Kulkarni, Edward M. Uchio, Joost L. Boormans, Mathieu Roumiguié, Laurence E. M. Krieger, et al. "Pembrolizumab Monotherapy for the Treatment of High-Risk Non-Muscle-Invasive Bladder Cancer Unresponsive to BCG (KEYNOTE-057): An Open-Label, Single-Arm, Multicentre, Phase 2 Study." *The Lancet Oncology* 22, no. 7 (July 1, 2021): 919–30. https://doi.org/10.1016/S1470-2045(21)00147-9.

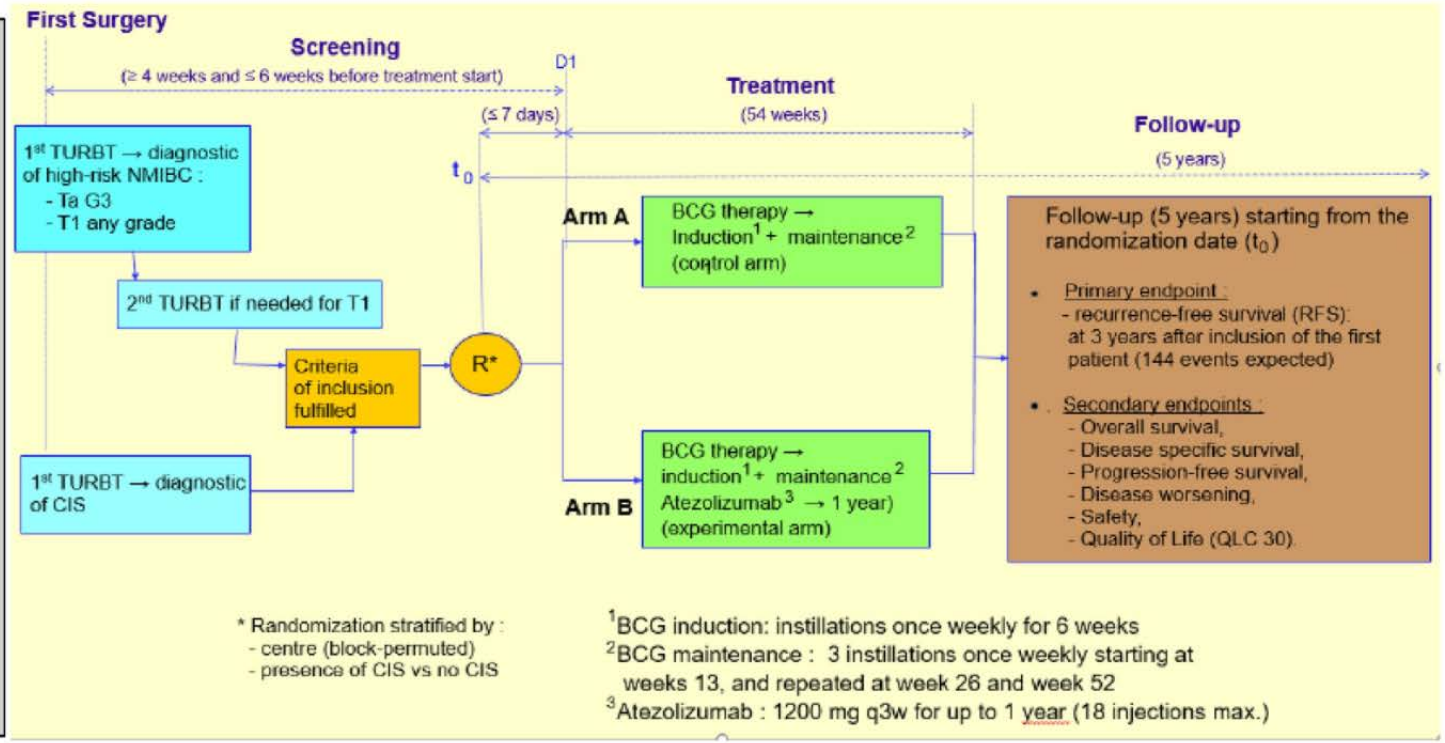
ALBAN: An open label, randomized, phase III trial, evaluating efficacy of Atezolizumab in addition to one year BCG (Bacillus CaLmette-Guerin) bladder instillation in BCG-naive patients with high-risk non-muscle invasive Bladder cANcer (AFU-GETUG 37) (NCT03799835)

Morgan Rouprêt[1], Yann Neuzillet[2], Aurélie Bertaut[3], Géraldine Pignot[4], Nadine Houédé[5], Stéphane Champiat[6], Maggy Chausson[7], Soazig Nénan[7], Yohann Loriot[6]
[1]Hôpital Pitié-Salpêtrière, Paris; [2]Hôpital Foch, Suresnes, [3] Centre Georges François Leclerc, Dijon, [4]Institut Paoli-Calmettes, Marseille, [5]CHU Nîmes, [6]Gustave Roussy, Villejuif, [7]Unicancer, Paris
Morgan.roupret@psl.aphp.fr - yohann.loriot@gustaveroussy.fr

Patient population

N=614

- Histologicall-confirmed NMIBC with predominant TCC histology
- **High risk NMIBC** defined
  - High grade and/or
  - T1 and/or
  - In situ carcinoma
- PS 0-2
- BCG naive
- Prior TURBT ≥ 4 weeks but ≤ 6 weeks before therapy
- Tumor samples available for PDL1 status assessment



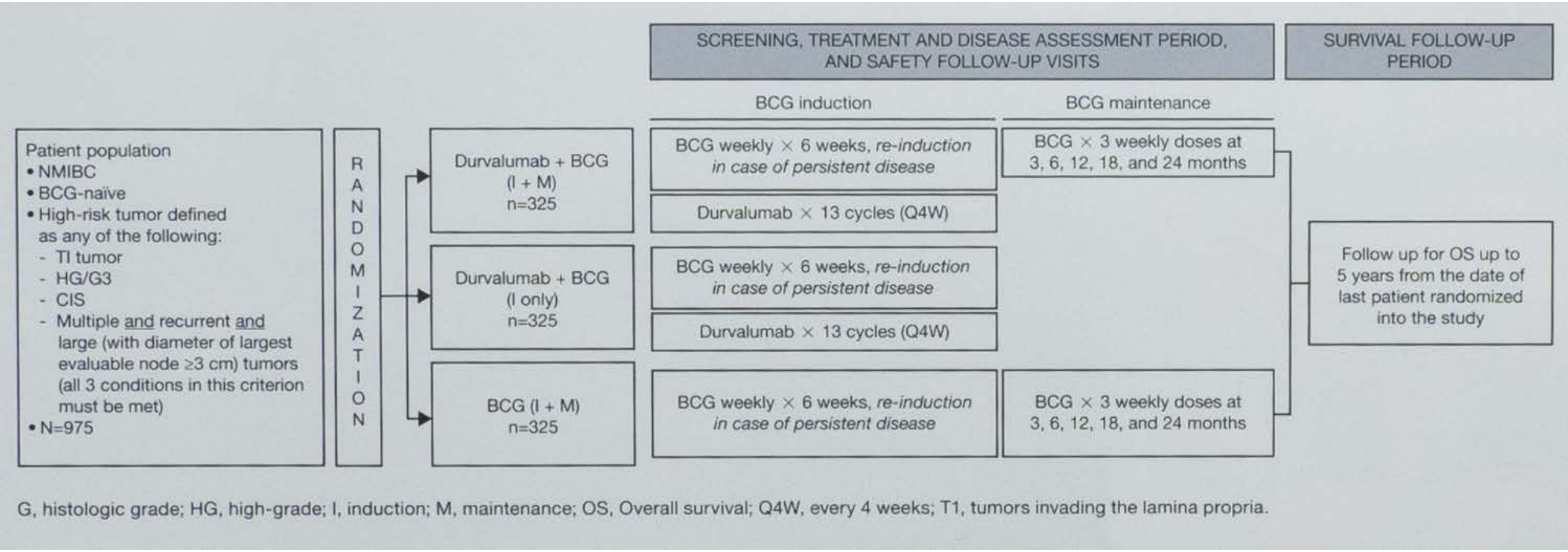
Roupret, M et al. "ALBAN: An Open Label, Randomized, Phase III Trial, Evaluating Efficacy of Atezolizumab in Addition to One Year BCG (Bacillus Calmette-Guerin) Bladder Instillation in BCG-Naive Patients with High-Risk Nonmuscle Invasive Bladder Cancer (AFU-GETUG 37)." *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019): TPS4589–TPS4589. https://doi.org/10.1200/JCO.2019.37.15_suppl.TPS4589.

A Phase 3, Randomized, Open-Label, Multicenter, Global Study of Durvalumab and Bacillus Calmette-Guérin (BCG) Versus BCG Alone in High-Risk, BCG-Naïve Non–Muscle-Invasive Bladder Cancer (NMIBC) Patients (POTOMAC)

De Santis M,[1] Abdrashitov R,[2] Hegele A,[3] Kolb M,[2] Parker S,[2] Palou Redorta J,[4] Nishiyama H,[5] Xiao F,[2] Gupta A,[2] Shore N[6]

[1]Charité University Hospital, Berlin, Germany and Department of Urology, Medical University of Vienna, Austria; [2]AstraZeneca, Gaithersburg, MD; [3]Department of Urology and Paediatric Urology, Philipps-Universität Marburg, Marburg, Germany; [4]Department of Urology, Fundació Puigvert, Barcelona, Spain; [5]Department of Urology, University of Tsukuba, Tsukuba, Japan; [6]Carolina Urologic Research Center, Myrtle Beach, SC

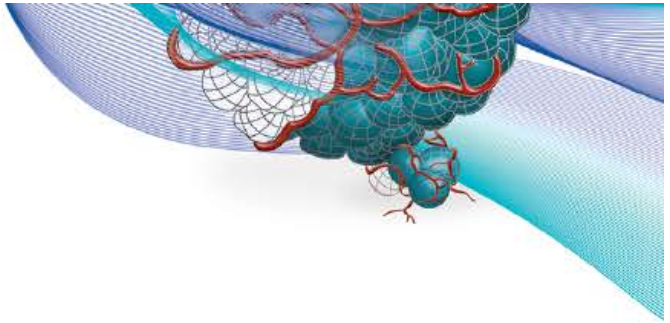
Poster No. N10



G, histologic grade; HG, high-grade; I, induction; M, maintenance; OS, Overall survival; Q4W, every 4 weeks; T1, tumors invading the lamina propria.

De Santis, Maria, Ramil Abdrashitov, Axel Hegele, Margaret Kolb, Suzanne Parker, Juan Palou Redorta, Hiroyuki Nishiyama, Feng Xiao, Ashok Kumar Gupta, and Neal D. Shore. "A Phase III, Randomized, Open-Label, Multicenter, Global Study of Durvalumab and Bacillus Calmette-Guérin (BCG) versus BCG Alone in High-Risk, BCG-Naïve Non-Muscle-Invasive Bladder Cancer (NMIBC) Patients (POTOMAC)." *Journal of Clinical Oncology* 37, no. 7_suppl (March 1, 2019): TPS500–TPS500. https://doi.org/10.1200/JCO.2019.37.7_suppl.TPS500.

KEYNOTE-676: Phase III study of BCG and pembrolizumab for persistent/recurrent high-risk NMIBC



Ashish M Kamat*,[1], Neal Shore[2], Noah Hahn[3], Shaheen Alanee[4], Hiroyuki Nishiyama[5], Shahrokh Shariat[6], Kijoeng Nam[7], Ekta Kapadia[8], Tara Frenkl[8] & Gary Steinberg[9]

Stratification
- PD-L1 CPS ≥10 vs <10
- NMIBC disease history:
  - Persistent or recurrent at 0–≤6 months
  - Recurrent at >6–≤12 months
  - Recurrent at >12–≤24 months

Disease assessments
- Q12W for years 1–2
- Q24W for years 3–5
- With cystoscopy, urine cytology, and biopsies (as applicable)
- CTU every 18 months through year 5

Patient population
- Histologically confirmed† NMIBC with predominant TCC histology
  - T1, high-grade Ta and/or CIS
- Persistent or recurrent HR NMIBC after adequate BCG induction
- Prior cystoscopy/TURBT within 12 weeks prior to randomization
- ECOG PS 0–2

R 1:1

Pembrolizumab + BCG

BCG monotherapy

Treatment discontinuation

Post-treatment follow-up:
- Safety
- Survival

Kamat, Ashish M., Neal Shore, Noah Hahn, Shaheen Alanee, Hiroyuki Nishiyama, Shahrokh Shariat, Kijoeng Nam, Ekta Kapadia, Tara Frenkl, and Gary Steinberg. "KEYNOTE-676: Phase III Study of BCG and Pembrolizumab for Persistent/Recurrent High-Risk NMIBC." *Future Oncology (London, England)* 16, no. 10 (April 2020): 507–16. https://doi.org/10.2217/fon-2019-0817.

CheckMate 274: Adjuvant Nivolumab

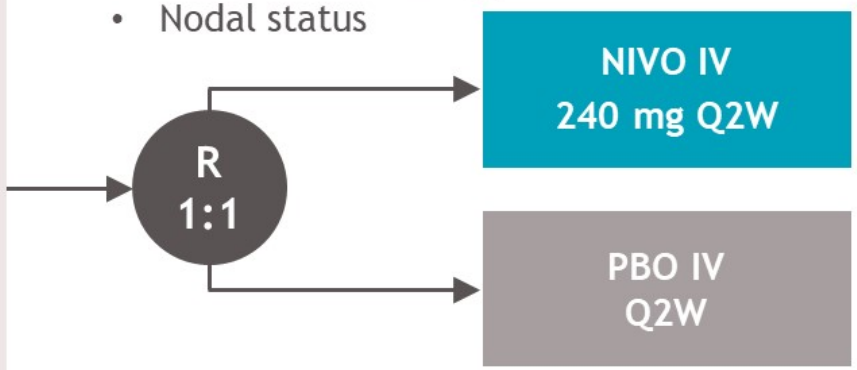
N = 709

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



Treat for up to 1 year of adjuvant therapy

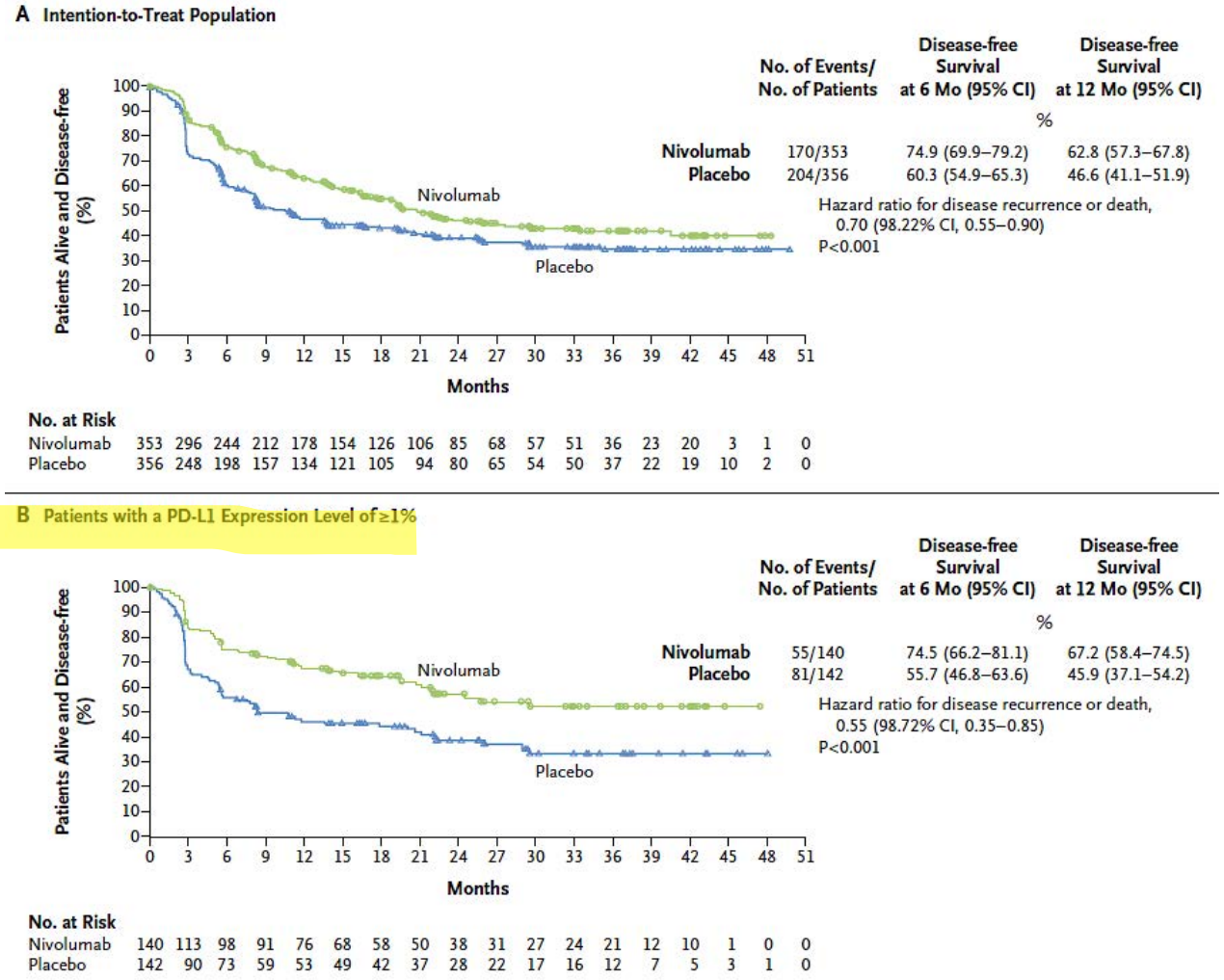
Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

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

Bajorin, Dean F., J. Alfred Witjes, Jürgen E. Gschwend, Michael Schenker, Begoña P. Valderrama, Yoshihiko Tomita, Aristotelis Bamias, et al. "Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma." *New England Journal of Medicine* 384, no. 22 (June 3, 2021): 2102–14. https://doi.org/10.1056/NEJMoa2034442.

CheckMate 274: Adjuvant Nivolumab

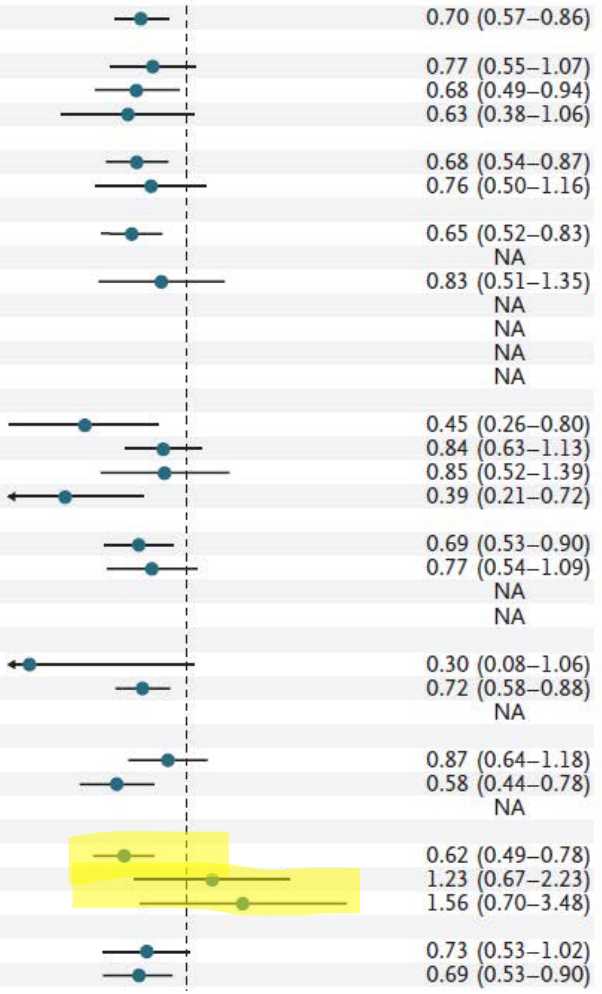
Characteristic	Nivolumab (N=353)	Placebo (N=356)
Age		
Mean (range) — yr	65.3 (30–92)	65.9 (42–88)
<65 yr — no. (%)	155 (43.9)	136 (38.2)
≥65 yr — no. (%)	198 (56.1)	220 (61.8)
Sex — no. (%)		
Male	265 (75.1)	275 (77.2)
Female	88 (24.9)	81 (22.8)
Race or ethnic group — no. (%)†		
White	264 (74.8)	272 (76.4)
Asian	80 (22.7)	75 (21.1)
Black	2 (0.6)	3 (0.8)
American Indian or Alaska Native	1 (0.3)	0
Other	6 (1.7)	5 (1.4)
Not reported	0	1 (0.3)
ECOG performance-status score — no. (%)‡		
0	224 (63.5)	221 (62.1)
1	122 (34.6)	125 (35.1)
2	7 (2.0)	9 (2.5)
Not reported	0	1 (0.3)
Tumor origin at initial diagnosis — no. (%)		
Urinary bladder	279 (79.0)	281 (78.9)
Renal pelvis	44 (12.5)	52 (14.6)
Ureter	30 (8.5)	23 (6.5)
Time from initial diagnosis to randomization — no. (%)		
<1 yr	325 (92.1)	324 (91.0)
≥1 yr	28 (7.9)	32 (9.0)
PD-L1 expression level of ≥1% by IVRS — no. (%)	140 (39.7)	142 (39.9)



Bajorin, Dean F., J. Alfred Witjes, Jürgen E. Gschwend, Michael Schenker, Begoña P. Valderrama, Yoshihiko Tomita, Aristotelis Bamias, et al. "Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma." *New England Journal of Medicine* 384, no. 22 (June 3, 2021): 2102–14. https://doi.org/10.1056/NEJMoa2034442.

CheckMate 274: Adjuvant Nivolumab

Subgroup	No. of Patients	Nivolumab	Placebo	Hazard Ratio for Disease Recurrence or Death (95% CI)
		no. of events/no. of patients		
All patients	709	170/353	204/356	0.70 (0.57–0.86)
Age				
<65 yr	291	74/155	70/136	0.77 (0.55–1.07)
≥65 yr and <75 yr	295	64/131	100/164	0.68 (0.49–0.94)
≥75 yr	123	32/67	34/56	0.63 (0.38–1.06)
Sex				
Male	540	125/265	156/275	0.68 (0.54–0.87)
Female	169	45/88	48/81	0.76 (0.50–1.16)
Race or ethnic group				
White	536	126/264	162/272	0.65 (0.52–0.83)
Black	5	1/2	3/3	NA
Asian	155	37/80	35/75	0.83 (0.51–1.35)
American Indian or Alaska Native	1	1/1	0	NA
Native Hawaiian or other Pacific Islander	0	0	0	NA
Other	11	5/6	3/5	NA
Not reported	1	0	1/1	NA
Geographic region				
United States	102	24/49	36/53	0.45 (0.26–0.80)
Europe	341	87/170	96/171	0.84 (0.63–1.13)
Asia	154	37/80	34/74	0.85 (0.52–1.39)
Rest of the world	112	22/54	38/58	0.39 (0.21–0.72)
ECOG performance-status score at baseline				
0	445	105/224	126/221	0.69 (0.53–0.90)
1	247	64/122	71/125	0.77 (0.54–1.09)
2	16	1/7	7/9	NA
Not reported	1	0	0/1	NA
Hemoglobin level at baseline				
<10 g/dl	46	8/19	17/27	0.30 (0.08–1.06)
≥10 g/dl	653	162/332	185/321	0.72 (0.58–0.88)
Not reported	10	0/2	2/8	NA
Creatinine clearance at baseline				
<60 ml/min	309	83/151	91/158	0.87 (0.64–1.18)
≥60 ml/min	388	86/199	111/189	0.58 (0.44–0.78)
Not reported	12	1/3	2/9	NA
Initial tumor origin				
Urinary bladder	560	129/279	166/281	0.62 (0.49–0.78)
Renal pelvis	96	24/44	25/52	1.23 (0.67–2.23)
Ureter	53	17/30	13/23	1.56 (0.70–3.48)
Minor histologic variants				
Yes	286	70/145	76/141	0.73 (0.53–1.02)
No	423	100/208	128/215	0.69 (0.53–0.90)



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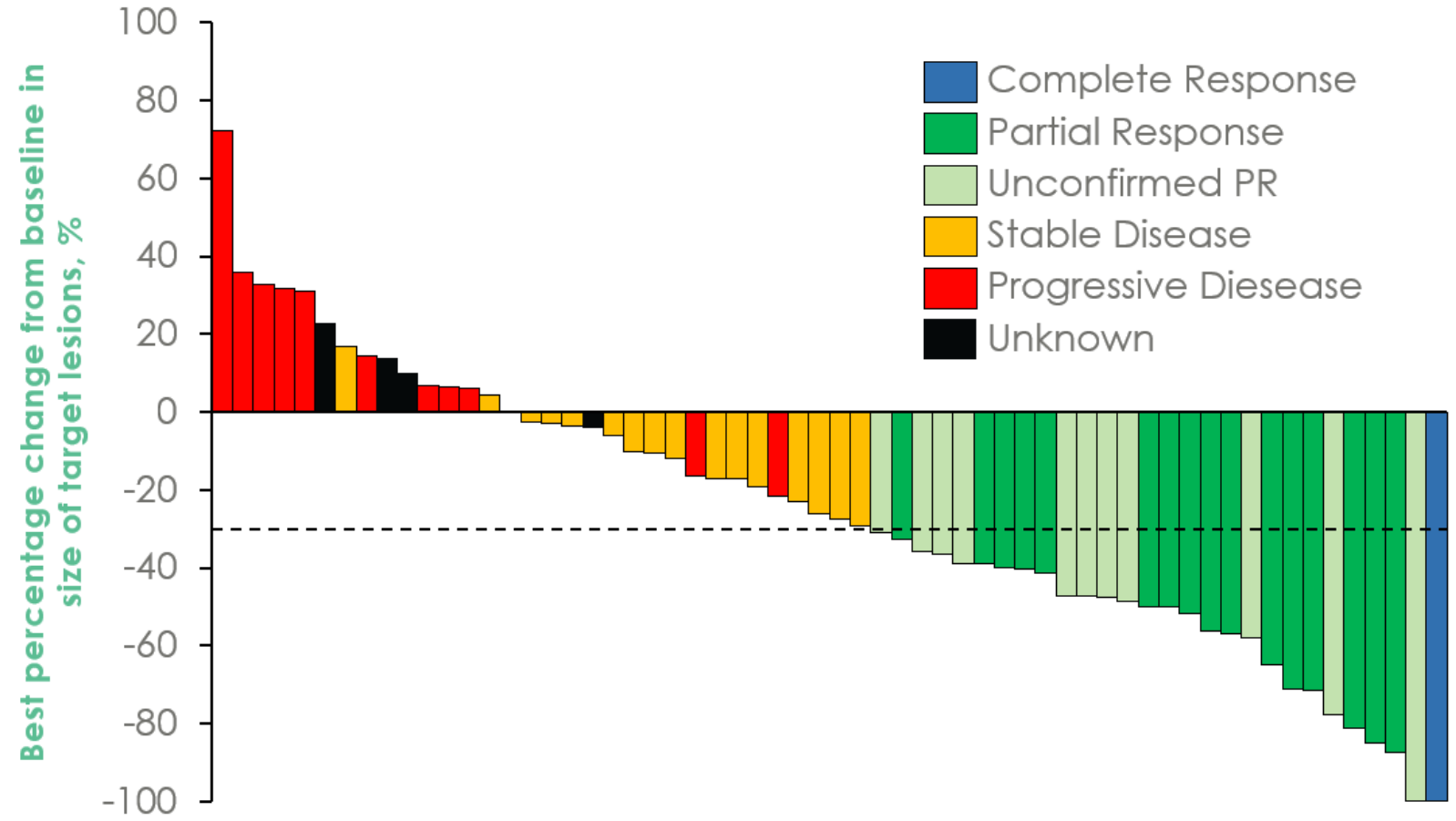
Infigratinib: FGFR3 inhibitor

Phase 1 expansion cohort advanced urothelial carcinoma with FGFR GAs (N=67)



25% confirmed ORR

42% BOR (including unconfirmed responses)

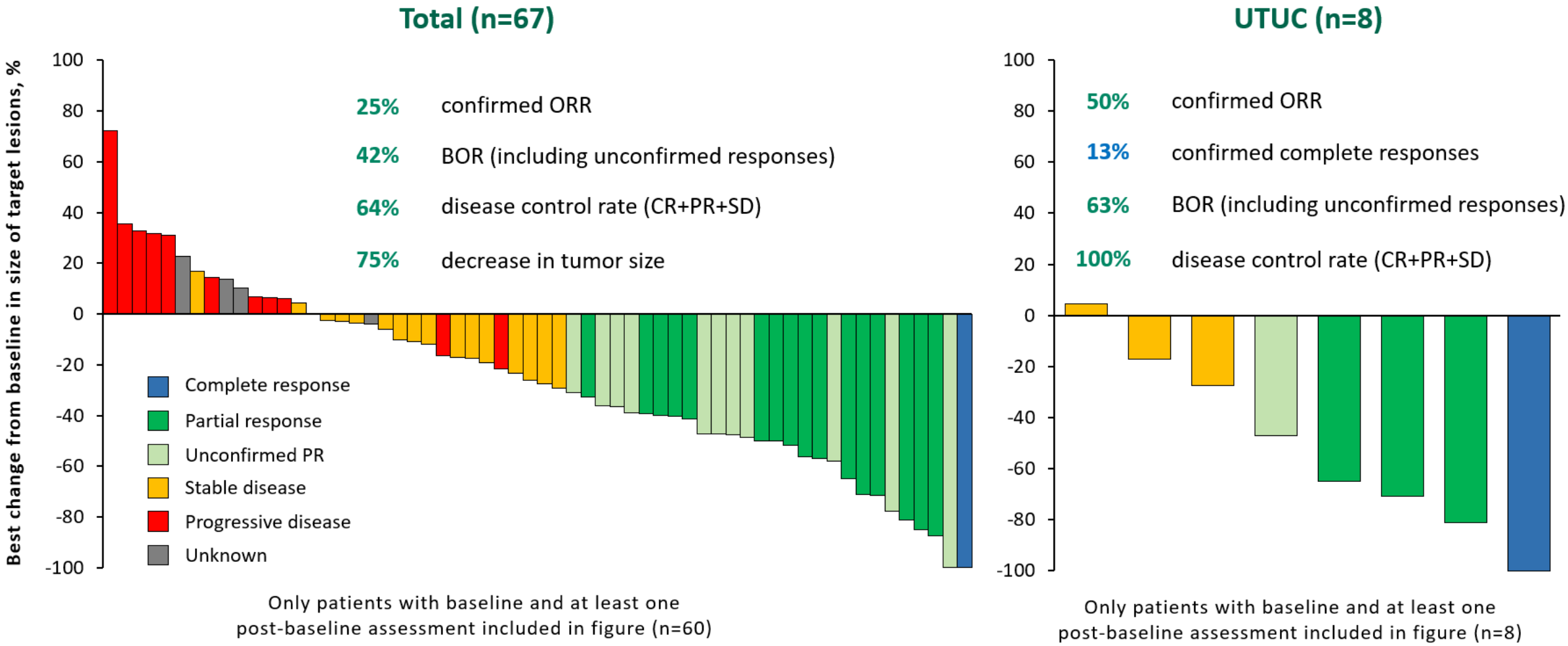
64% disease control rate (CR+PR+SD)

75% decrease in tumor size

Only patients with baseline and at least one post-baseline assessment included in figure (N=60)

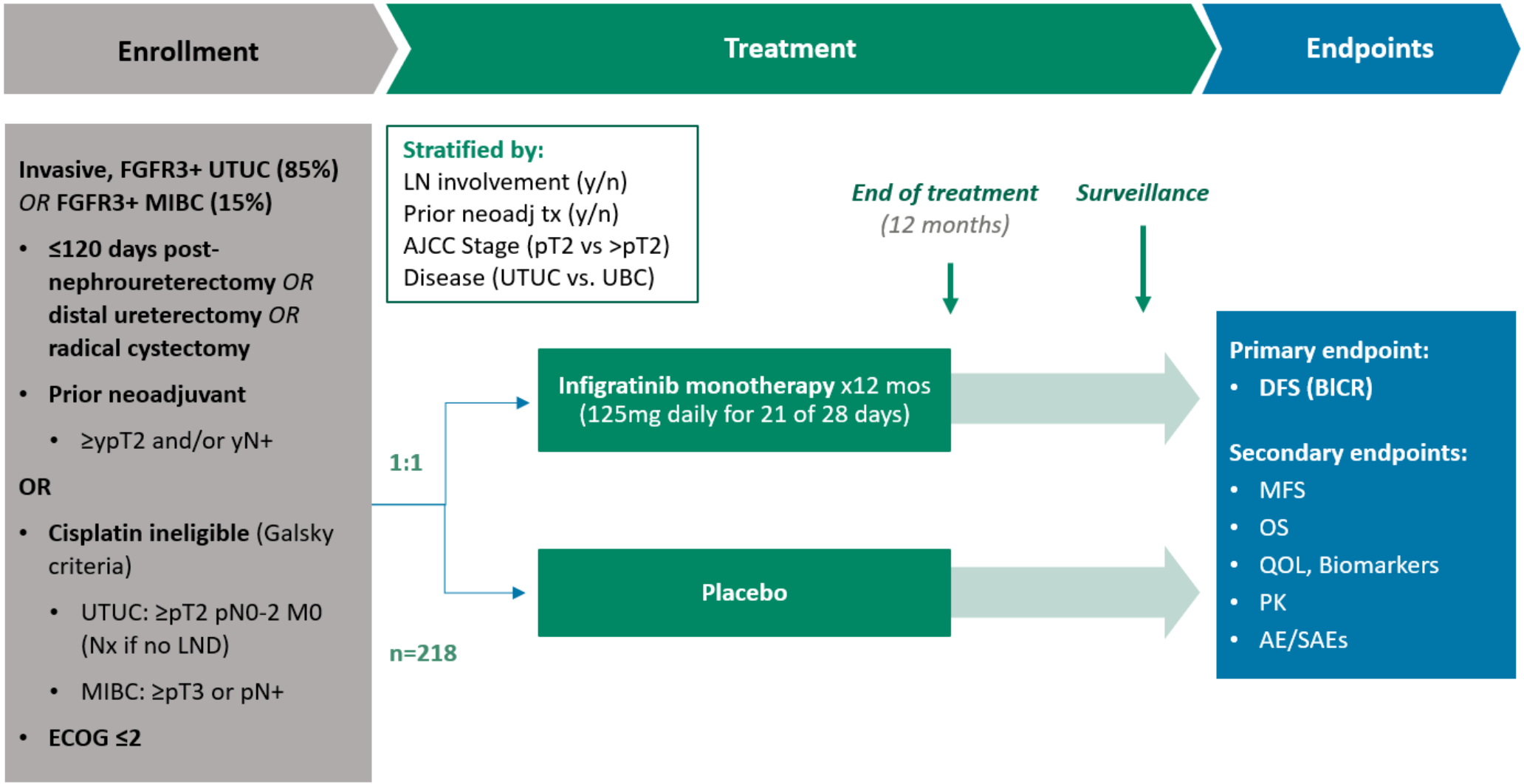
Pal, Sumanta K., Jonathan E. Rosenberg, Jean H. Hoffman-Censits, Raanan Berger, David I. Quinn, Matthew D. Galsky, Juergen Wolf, et al. "Efficacy of BGJ398, a Fibroblast Growth Factor Receptor 1-3 Inhibitor, in Patients with Previously Treated Advanced Urothelial Carcinoma with FGFR3 Alterations." *Cancer Discovery* 8, no. 7 (July 2018): 812–21. https://doi.org/10.1158/2159-8290.CD-18-0229.

Responses seen in urothelial patients



Pal, Sumanta K., Siamak Daneshmand, Surena F. Matin, Yohann Loriot, Srikala S. Sridhar, Petros Grivas, Shilpa Gupta, et al. "PROOF 302: A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Infigratinib as Adjuvant Therapy in Patients with Invasive Urothelial Carcinoma Harboring FGFR3 Alterations." *Journal of Clinical Oncology* 38, no. 6_suppl (February 20, 2020): TPS600–TPS600. https://doi.org/10.1200/JCO.2020.38.6_suppl.TPS600.

PROOF 302: adjuvant infigratinib vs. placebo for invasive urothelial carcinoma with susceptible *FGFR3* alterations



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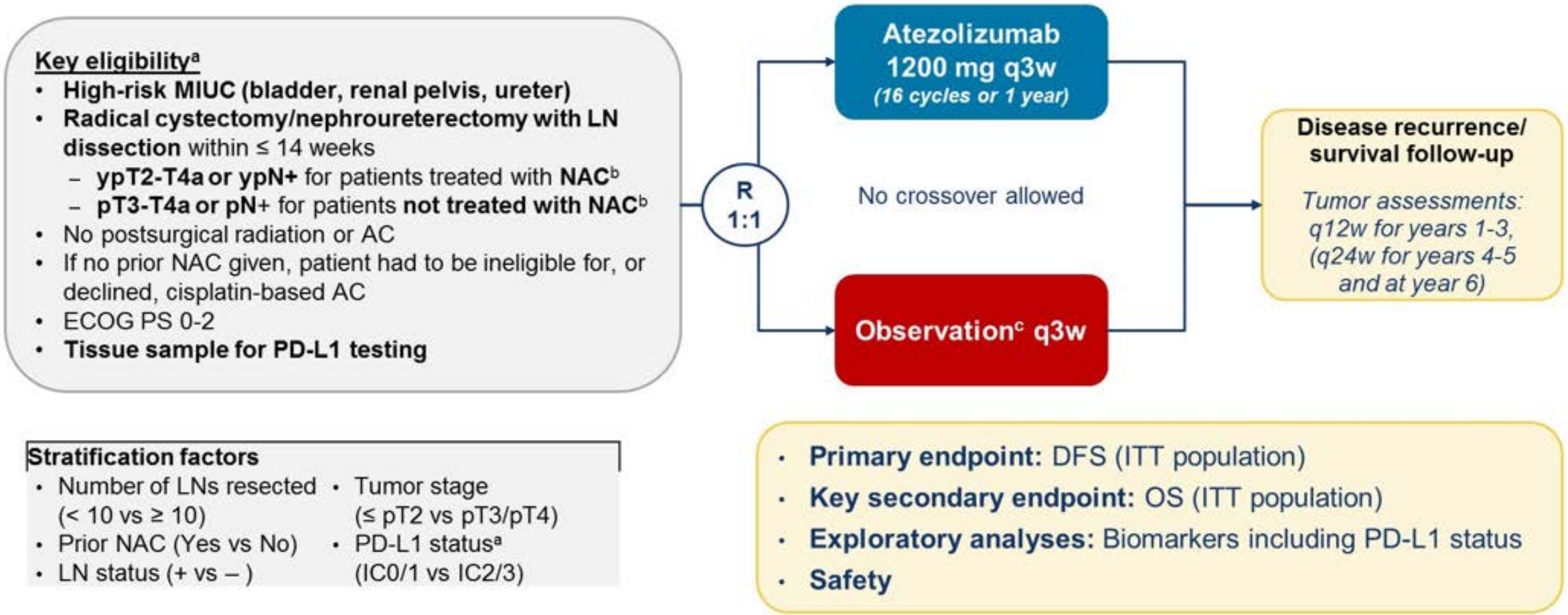
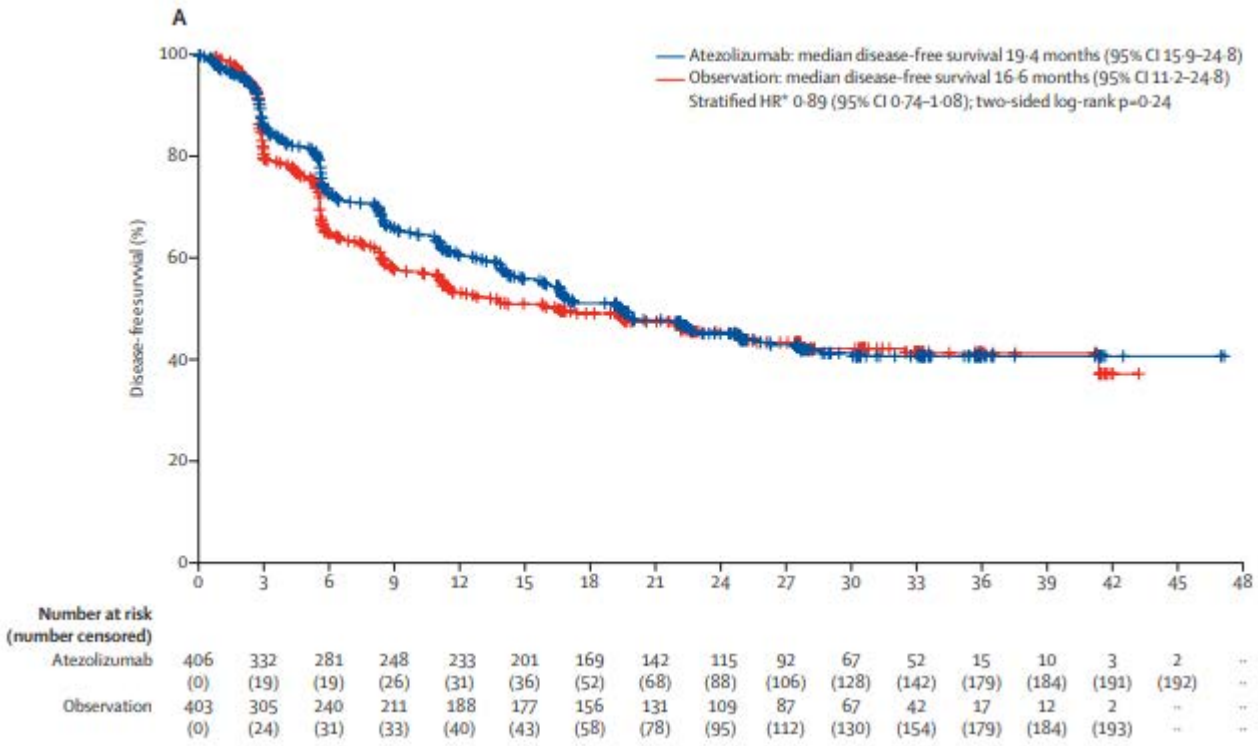
IMvigor010 Study Design



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.

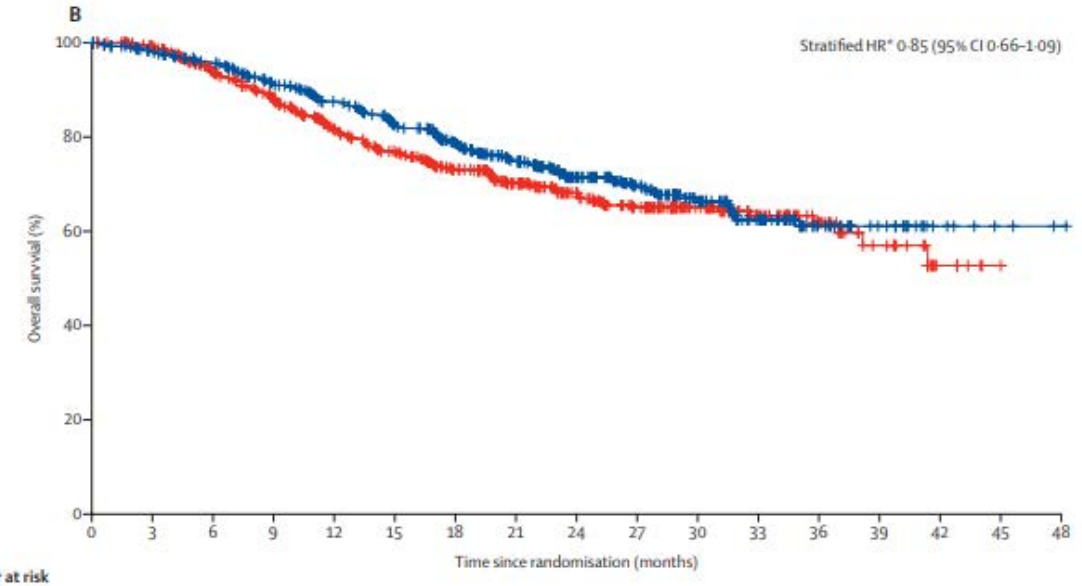
Bellmunt, Joaquim, Maha Hussain, Jürgen E. Gschwend, Peter Albers, Stephane Oudard, Daniel Castellano, Siamak Daneshmand, et al. "Adjuvant Atezolizumab versus Observation in Muscle-Invasive Urothelial Carcinoma (IMvigor010): A Multicentre, Open-Label, Randomised, Phase 3 Trial." *The Lancet Oncology* 22, no. 4 (April 1, 2021): 525–37. https://doi.org/10.1016/S1470-2045(21)00004-8.

Disease-Free Survival



Number at risk (number censored)																	
Atezolizumab	406	332	281	248	233	201	169	142	115	92	67	52	15	10	3	2	..
	(0)	(19)	(19)	(26)	(31)	(36)	(52)	(68)	(88)	(106)	(128)	(142)	(179)	(184)	(191)	(192)	..
Observation	403	305	240	211	188	177	156	131	109	87	67	42	17	12	2	..	..
	(0)	(24)	(31)	(33)	(40)	(43)	(58)	(78)	(95)	(112)	(130)	(154)	(179)	(184)	(193)	..	..

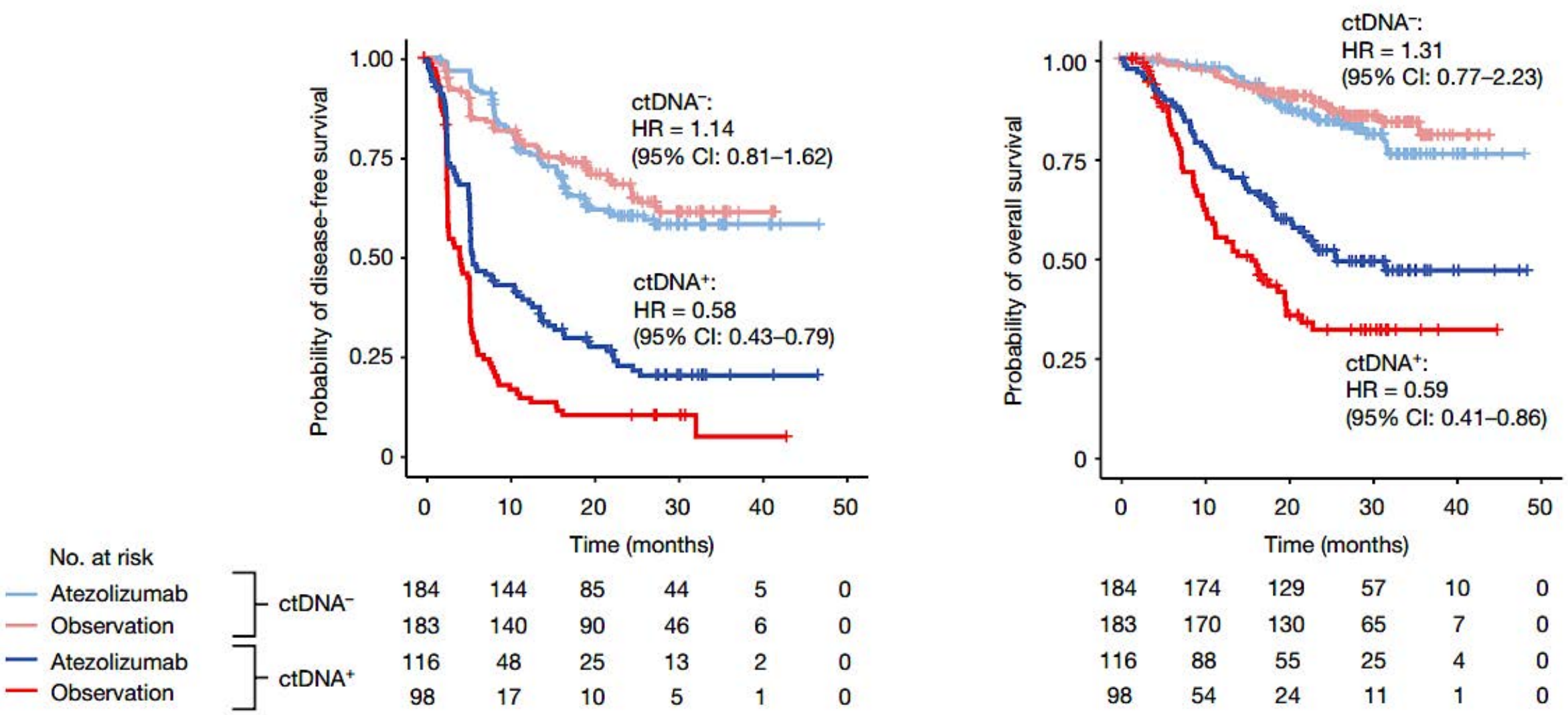
Overall Survival



Number at risk (number censored)																	
Atezolizumab	406	383	369	350	328	306	267	229	185	144	100	72	35	22	8	4	2
	(0)	(16)	(21)	(23)	(30)	(33)	(59)	(85)	(119)	(156)	(195)	(217)	(253)	(266)	(280)	(284)	(286)
Observation	403	377	345	318	289	270	235	199	163	134	100	65	36	20	6	1	..
	(0)	(23)	(35)	(40)	(46)	(49)	(71)	(98)	(129)	(151)	(185)	(218)	(246)	(260)	(273)	(278)	..

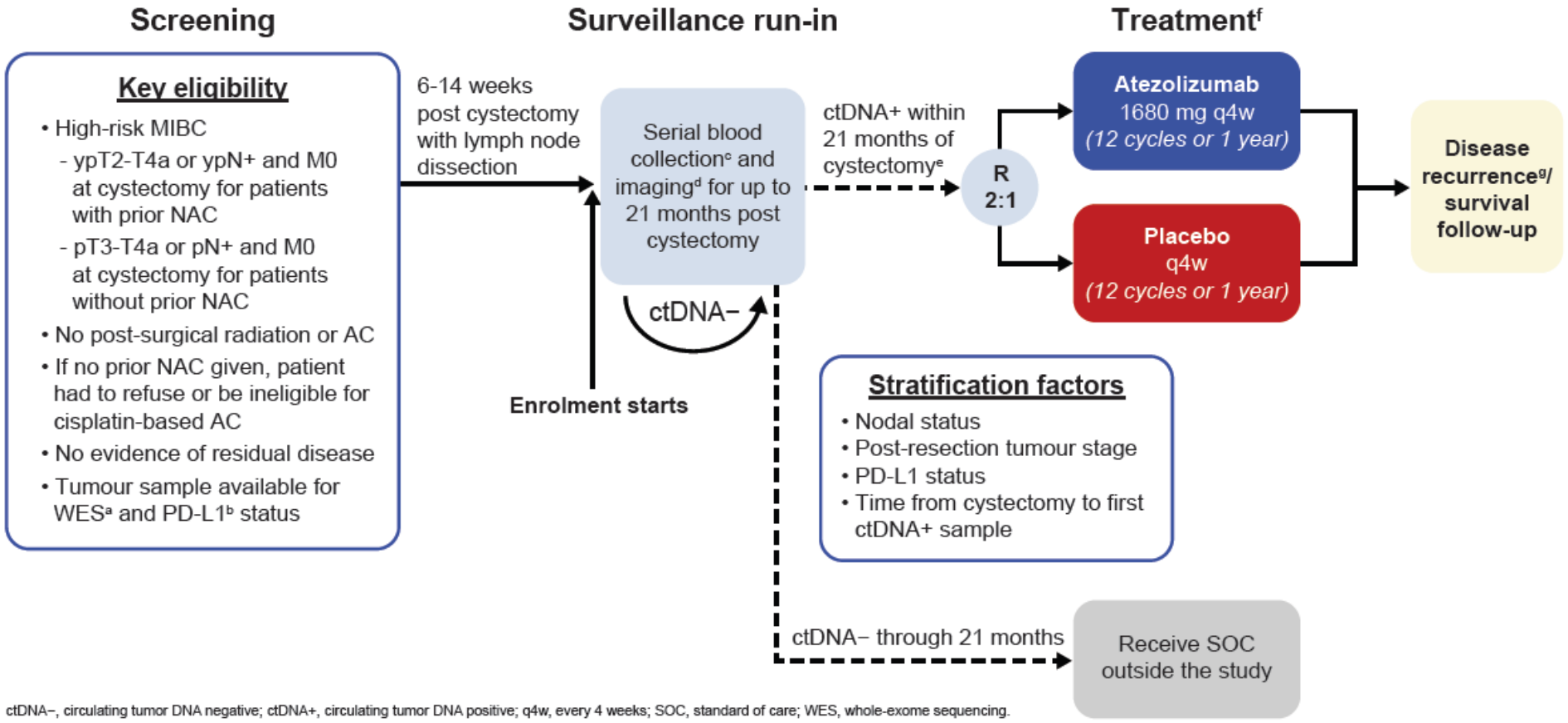
Key Difference: Observation on Control Arm

Bellmunt, Joaquim, Maha Hussain, Jürgen E. Gschwend, Peter Albers, Stephane Oudard, Daniel Castellano, Siamak Daneshmand, et al. "Adjuvant Atezolizumab versus Observation in Muscle-Invasive Urothelial Carcinoma (IMvigor010): A Multicentre, Open-Label, Randomised, Phase 3 Trial." *The Lancet Oncology* 22, no. 4 (April 1, 2021): 525–37. https://doi.org/10.1016/S1470-2045(21)00004-8.



Powles, Thomas, Zoe June Assaf, Nicole Davarpanah, Romain Banchereau, Bernadett E. Szabados, Kobe C. Yuen, Petros Grivas, et al. “CtDNA Guiding Adjuvant Immunotherapy in Urothelial Carcinoma.” *Nature* 595, no. 7867 (July 2021): 432–37. https://doi.org/10.1038/s41586-021-03642-9.

Figure 1. IMvigor011 Study Design



ctDNA−, circulating tumor DNA negative; ctDNA+, circulating tumor DNA positive; q4w, every 4 weeks; SOC, standard of care; WES, whole-exome sequencing.

[a] Evaluable WES data for development of a personalised multiplex PCR (mPCR) ctDNA assay from post-surgical blood samples (Signatera assay) are required.

[b] Per the VENTANA SP142 IHC assay.

[c] Every 6 weeks up to 36 weeks and q12w (every 12 weeks) up to 21 months.

[d] q12w up to Week 84 or until 21 months from date of cystectomy, whichever occurs first.

[e] ctDNA positivity is defined as ≥2 mutations per ctDNA mPCR assay. Patients will be randomised to treatment at the first ctDNA+ sample; full recovery from cystectomy and no evidence of disease recurrence within 28 days of treatment initiation is required.

[f] Imaging and blood draws q9w (every 9 weeks) starting at Week 9 up to Week 54.

[g] Assessed q9w up to Year 3; less often up to Year 6.

Powles, Thomas, Zoe June Assaf, Nicole Davarpanah, Romain Banchereau, Bernadett E. Szabados, Kobe C. Yuen, Petros Grivas, et al. “CtDNA Guiding Adjuvant Immunotherapy in Urothelial Carcinoma.” *Nature* 595, no. 7867 (July 2021): 432–37. https://doi.org/10.1038/s41586-021-03642-9.

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journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Bladder Cancer
Editorial by Constance Thibault, Pernelle Lavaud and Yohann Loriot on pp. 447–448 of this issue

Updated Results of PURE-01 with Preliminary Activity of Neoadjuvant Pembrolizumab in Patients with Muscle-invasive Bladder Carcinoma with Variant Histologies

Andrea Necchi[a,], Daniele Raggi[a], Andrea Gallina[b], Russell Madison[c], Maurizio Colecchia[a], Roberta Lucianò[b], Rodolfo Montironi[d], Patrizia Giannatempo[a], Elena Farè[a], Filippo Pederzoli[b], Marco Bandini[b], Marco Bianchi[b], Renzo Colombo[b], Giorgio Gandaglia[b], Nicola Fossati[b], Laura Marandino[a], Umberto Capitanio[b], Federico Dehò[b], Siraj M. Ali[c], Jon H. Chung[c], Jeffrey S. Ross[c,e], Andrea Salonia[b,f], Alberto Briganti[b,f], Francesco Montorsi[b,f]*

[a] *Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [b] *San Raffaele Hospital and Scientific Institute, Milan, Italy;* [c] *Foundation Medicine, Cambridge, MA, USA;* [d] *Polytechnic University of the Marche Region, Ancona, Italy;* [e] *Upstate Medical University, Syracuse, NY, USA;* [f] *Vita-Salute San Raffaele University, Milan, Italy*

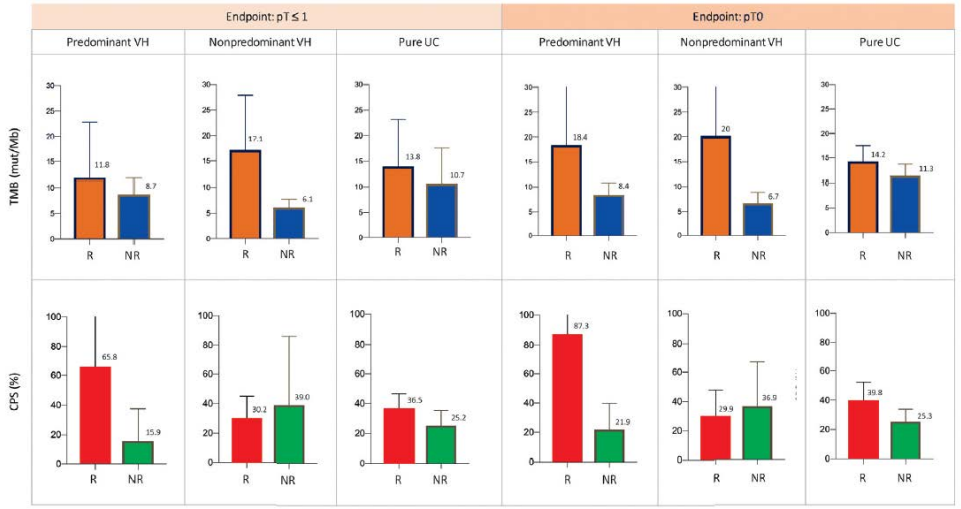


Table 2 – Updated pathological response outcomes and their distribution according to histological category.

Endpoint	Total population (N = 114)		Predominant VH patients (N = 19)		Nonpredominant VH patients (N = 15)		Pure UC patients (N = 80)	
	N (%)	95% CI	*N* (%)	95% CI	*N* (%)	95% CI	*N* (%)	95% CI
pT0N0	42 (37)	28–46	3 (16)	3.4–40	8 (53)	27–79	31 (39)	28–50
pT ≤ 1N0	63 (55)	46–65	8 (42)	21–67	10 (67)	38–88	45 (56)	45–67
pT2N0	11 (9.6)		3 (16)		1 (6.7)		7 (8.8)	
pT3–4N0	11 (9.6)		3 (16)		2 (13)		6 (7.5)	
pTany pN1–3	19 (17)		4 (21)		0		15 (19)	
Number of LNs removed, median (IQR)[a]	27 (21–34)		27 (23–42)		30 (20–35)		27 (22–34)	
Clinical PD, no cystectomy[b]	1 (0.9)		0		1 (6.7)		0	
Additional NAC before RC[c]	7 (6.1)		0		1 (6.7)		6 (7.5)	
Refusal of RC	2 (1.8)		1 (5.3)		0		1 (1.2)	

CI = confidence interval; NAC = neoadjuvant chemotherapy; PD = progression of disease; RC = radical cystectomy; TURB = transurethral resection of the bladder; UC = urothelial carcinoma; VH = variant histology.

[a] Lymphadenectomy template of the extended nodal dissection included removal of the obturator, internal, external, and common iliac nodes, up to the intersection with the ureter, as well as the presacral nodes.

[b] A male patient with *FGFR3-TACC3* fusion found in the TURB sample: this patient developed a bone metastasis during pembrolizumab therapy and was discontinued from the study. He was subsequently enrolled in the fight-201 study (NCT02872714) and received pemigatinib, benefiting from a complete response to treatment, which is still ongoing.

[c] Cisplatin-based chemotherapy. The pathological responses were the following: pT0 (*N* = 1); pT ≤ 1 (*N* = 3); pT3–4N+ (*N* = 3).

Necchi, Andrea, Daniele Raggi, Andrea Gallina, Russell Madison, Maurizio Colecchia, Roberta Lucianò, Rodolfo Montironi, et al. "Updated Results of PURE-01 with Preliminary Activity of Neoadjuvant Pembrolizumab in Patients with Muscle-Invasive Bladder Carcinoma with Variant Histologies." *European Urology* 77, no. 4 (April 2020): 439–46. https://doi.org/10.1016/j.eururo.2019.10.026.

LETTERS
https://doi.org/10.1038/s41591-019-0628-7
nature medicine

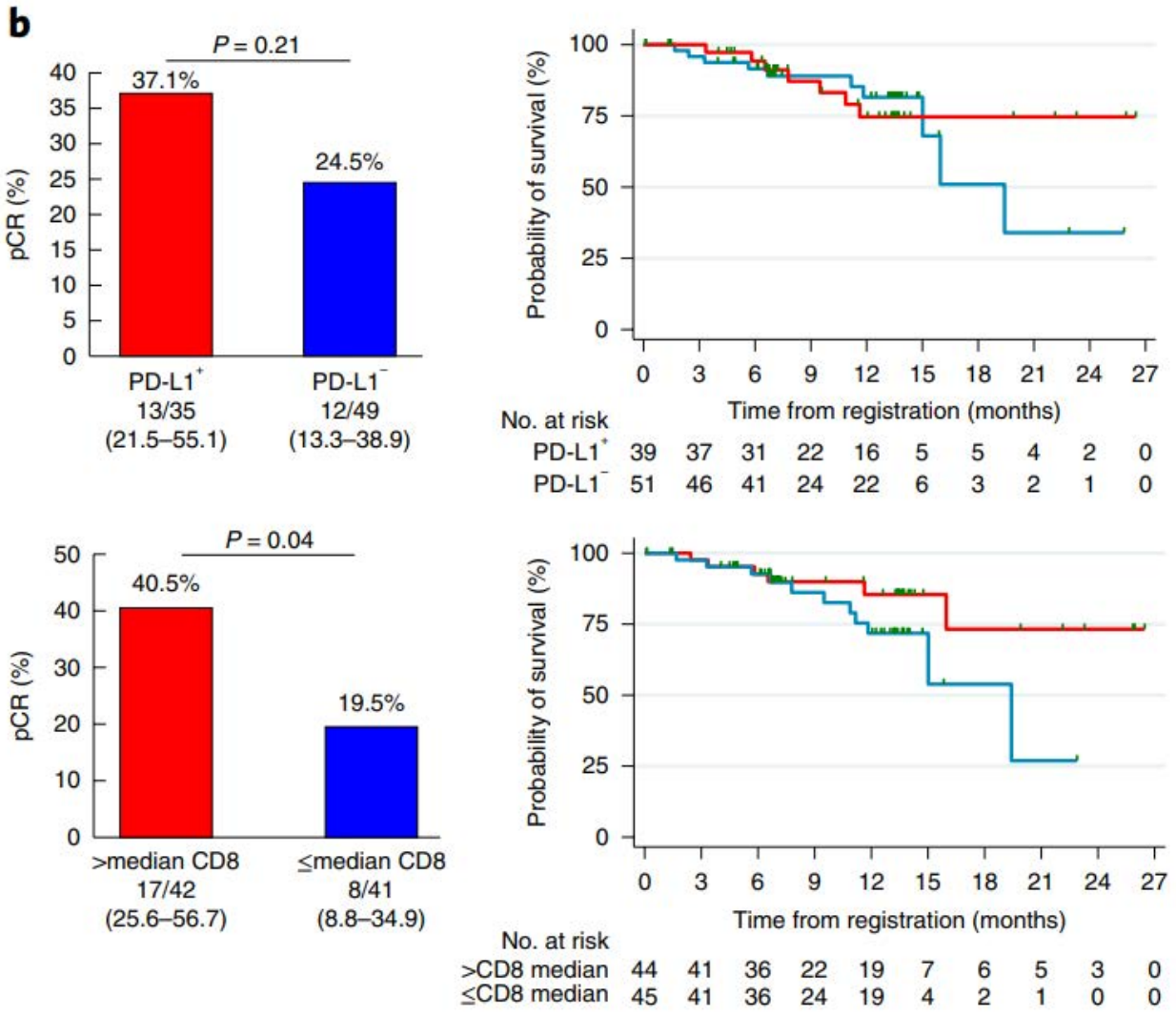
There are amendments to this paper

Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial

Thomas Powles[1*], Mark Kockx[2], Alejo Rodriguez-Vida[3], Ignacio Duran[4], Simon J. Crabb[5], Michiel S. Van Der Heijden[6], Bernadett Szabados[1], Albert Font Pous[7], Gwenaelle Gravis[8], Urbano Anido Herranz[9], Andrew Protheroe[10], Alain Ravaud[11], Denis Maillet[12], Maria Jose Mendez[13], Cristina Suarez[14], Mark Linch[15], Aaron Prendergast[1], Pieter-Jan van Dam[2], Diana Stanoeva[2], Sofie Daelemans[2,16], Sanjeev Mariathasan[17], Joy S. Tea[17], Kelly Mousa[1], Romain Banchereau[17,19] and Daniel Castellano[18,19]

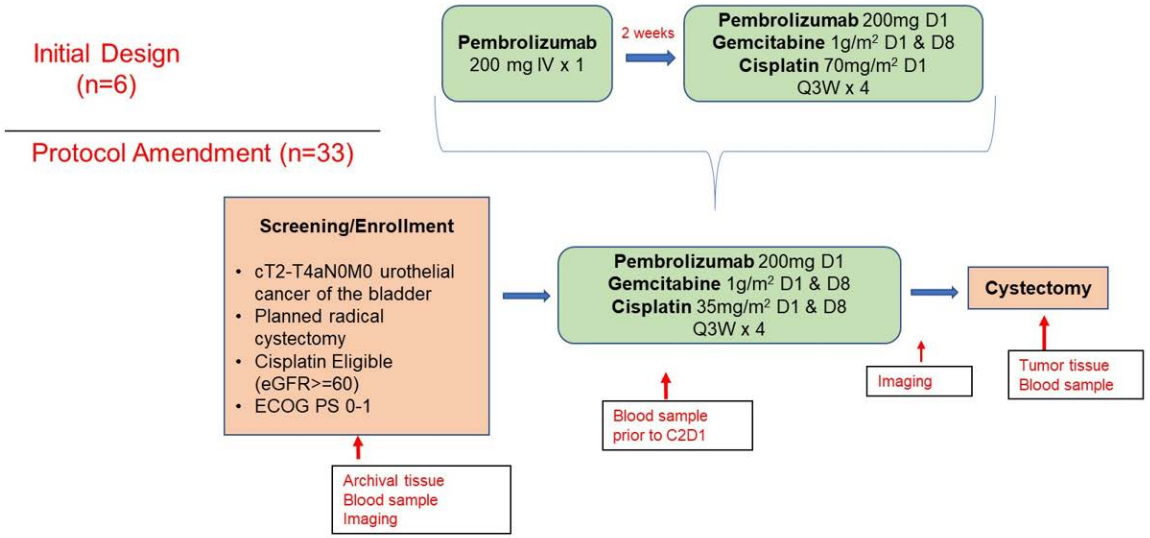
Table 1 | Patient characteristics at baseline

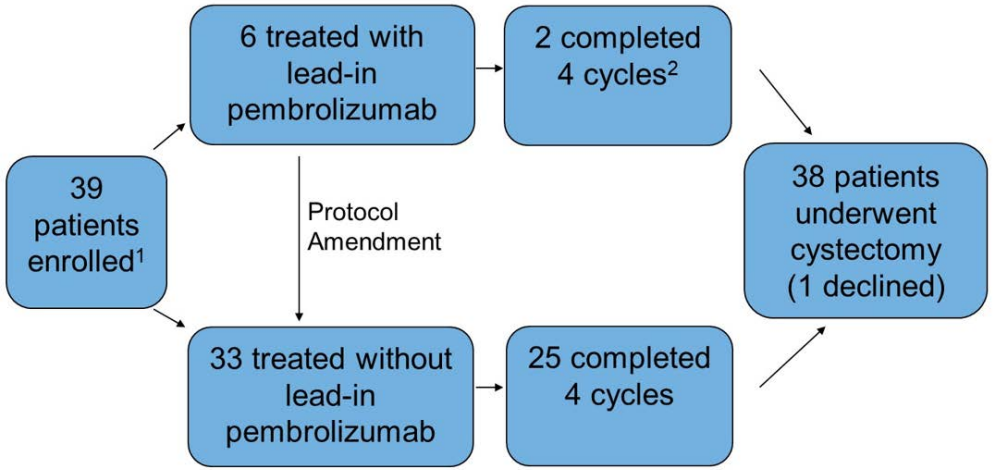
	Treated population (*N* = 95)	Clinical primary endpoint population (*N* = 88)	pCR population (*N* = 27)
Age (years), median (IQR)	73 (68-77)	72 (67-76)	73 (68-79)
Male sex, *n* (%)	81 (85)	75 (85)	24 (89)
TNM stage, *n* (%)			
T2	70 (74)	64 (73)	23 (85)
T3	17 (18)	17 (19)	3 (11)
T4	8 (8)	7 (8)	1 (4)
N positive	0	0	0
M1	0	0	0
Previous non-muscle-invasive disease, *n* (%)	14 (15)	14 (16)	3 (11)



Powles, Thomas, Mark Kockx, Alejo Rodriguez-Vida, Ignacio Duran, Simon J. Crabb, Michiel S. Van Der Heijden, Bernadett Szabados, et al. “Clinical Efficacy and Biomarker Analysis of Neoadjuvant Atezolizumab in Operable Urothelial Carcinoma in the ABACUS Trial.” *Nature Medicine* 25, no. 11 (November 2019): 1706–14. https://doi.org/10.1038/s41591-019-0628-7.

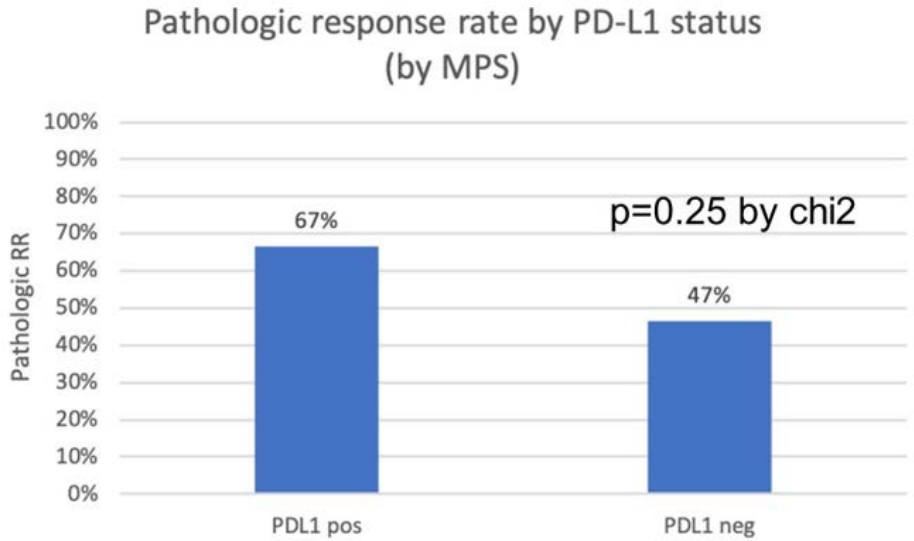
LCCC1520: Schema





Pathologic Response	Patients (n=39)
<pT2N0M0	22 (56%)
T0N0	14 (36%)
Ta	1 (3%)
Tis	4 (11%)
T1	3 (8%)

Progression prior to cystectomy 0



Rose, Tracy L., Michael R. Harrison, Allison M. Deal, Sundhar Ramalingam, Young E. Whang, Blaine Brower, Mary Dunn, et al. "Phase II Study of Gemcitabine and Split-Dose Cisplatin Plus Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Bladder Cancer." *Journal of Clinical Oncology* 39, no. 28 (October 1, 2021): 3140–48. https://doi.org/10.1200/JCO.21.01003.

HCRN GU16-257

76 patients

cT2-4aN0M0

Gemcitabine + Cisplatin + Nivolumab X 4 cycles

64 patients

Clinical Restaging

Cysto + biopsies
Urine cytology
MRI

31 patients

Clinical CR

30 patients

No cystectomy → **Nivo x 4 mos**

* Treatment based on patient choice

Cystectomy

1 patient

33 patients

No Clinical CR → **Cystectomy**

Clinical complete response rate = 48% (95% CI 36%, 61%)

Galsky, Matt D., Siamak Daneshmand, Kevin G. Chan, Tanya B. Dorff, Jeremy Paul Cetnar, Brock O Neil, Anishka D'souza, et al. "Phase 2 Trial of Gemcitabine, Cisplatin, plus Nivolumab with Selective Bladder Sparing in Patients with Muscle- Invasive Bladder Cancer (MIBC): HCRN GU 16-257." *Journal of Clinical Oncology* 39, no. 15_suppl (May 20, 2021): 4503–4503. https://doi.org/10.1200/JCO.2021.39.15_suppl.4503.

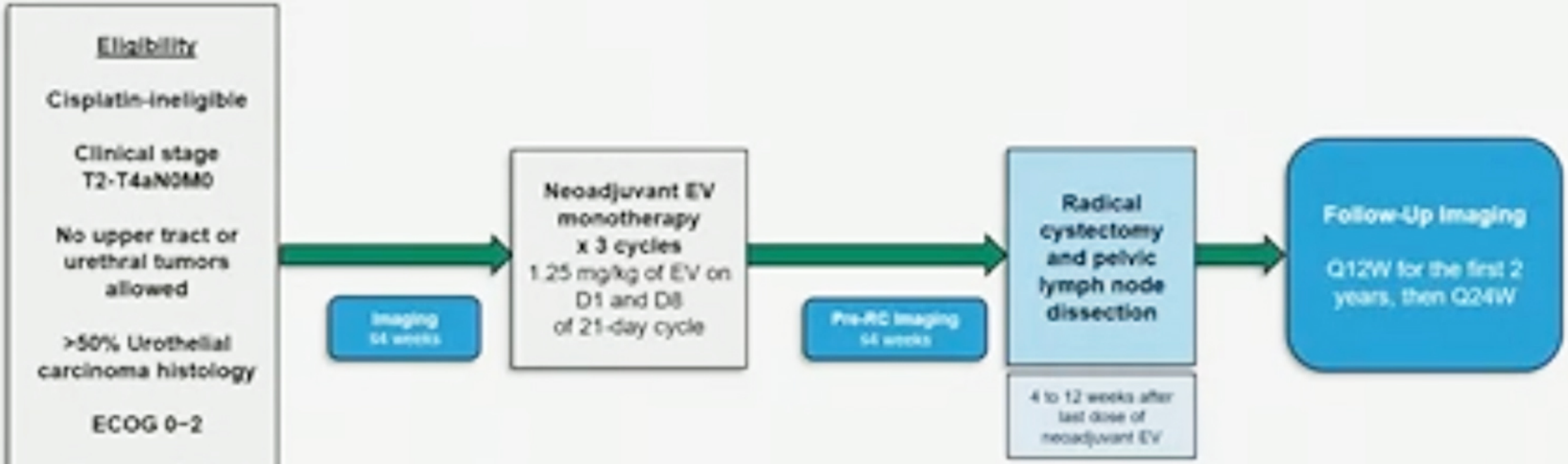
ASCO Genitourinary Cancers Symposium

Study EV-103 Cohort H: Antitumor activity of neoadjuvant treatment with enfortumab vedotin monotherapy in patients with muscle invasive bladder cancer (MIBC) who are cisplatin-ineligible

Daniel P. Petrylak, Yale University, New Haven, CT; Thomas W. Flaig, University of Colorado Comprehensive Cancer Center, Aurora, CO; Nataliya Mar, UC Irvine, Irvine, CA; Theodore S. Gourdin, Hollings Cancer Center, Medical University of South Carolina, Charleston, SC; Sandy Srinivas, Stanford University Medical Center, Palo Alto, CA; Jonathan E. Rosenberg, Memorial Sloan Kettering Cancer Center, New York, NY; Maria Guseva, Astellas Pharma Inc., Northbrook, IL; Yao Yu, Seagen Inc., Bothell, WA; Sujata Narayanan, Seagen Inc., Bothell, WA; Christopher J. Holmes, Duke University, Duke Cancer Institute, Durham, NC

Dr. Daniel P. Petrylak, Speaker

EV-103 Cohort H Study Design



DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; EFS: Event-free survival; EV: Enfortumab vedotin; OS: Overall survival; pCR: pathological Complete Response rate; pOS: pathological Downstaging; RC+PLND: radical cystectomy + pelvic lymph node dissection; PROs: Patient-reported outcomes; TURBT: transurethral resection of bladder tumor

Dr. Daniel P. Petrylak

Efficacy: Central Pathology Review

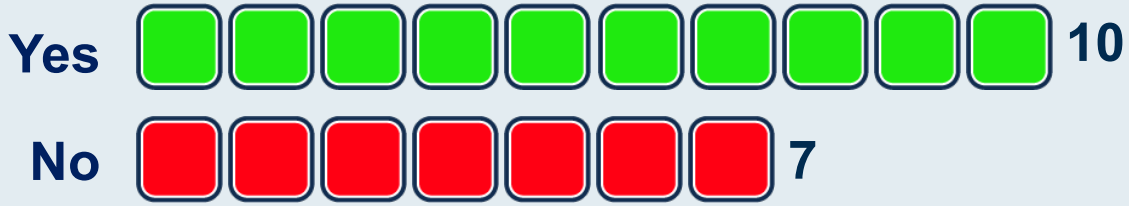
Pathological Response	Central Pathology Results (N=22) n (%) [95% Confidence Interval]
Pathological Complete Response Rate (defined as absence of any viable tumor tissue: ypT0 and N0)	**8 (36.4%)** [17.2–59.3]
Pathological Downstaging Rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	**11 (50.0%)** [28.2–71.8]

Clinical Investigator Survey Results

In general, would you recommend pembrolizumab to a patient with BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC) who is…

65 years old, otherwise healthy and prefers not to undergo cystectomy

70 years old, with minor comorbidities



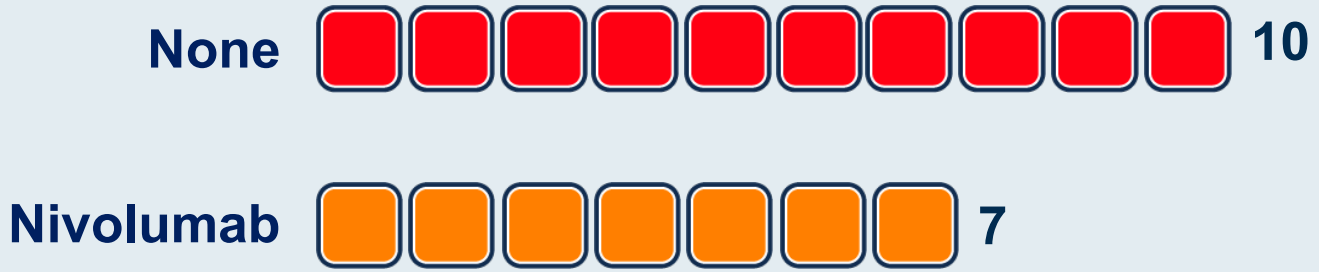
80 years old, with significant comorbidities and not a candidate for cystectomy

Survey of genitourinary cancer clinical investigators

A 65-year-old man receives neoadjuvant dose-dense MVAC for PD-L1-positive MIBC and undergoes cystectomy, which reveals significant residual disease and a positive pelvic lymph node. Regulatory and reimbursement issues aside, what adjuvant systemic therapy, if any, would you recommend?

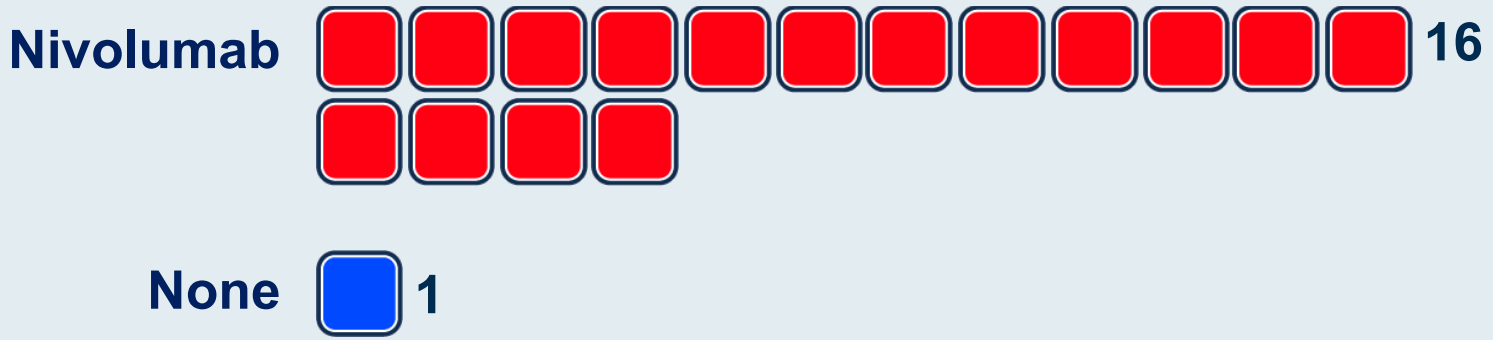
Survey of genitourinary cancer clinical investigators

A 65-year-old man receives neoadjuvant dose-dense MVAC for PD-L1-positive MIBC and undergoes cystectomy, which reveals small amounts of residual disease and negative pelvic lymph nodes. Regulatory and reimbursement issues aside, what adjuvant systemic therapy, if any, would you recommend?



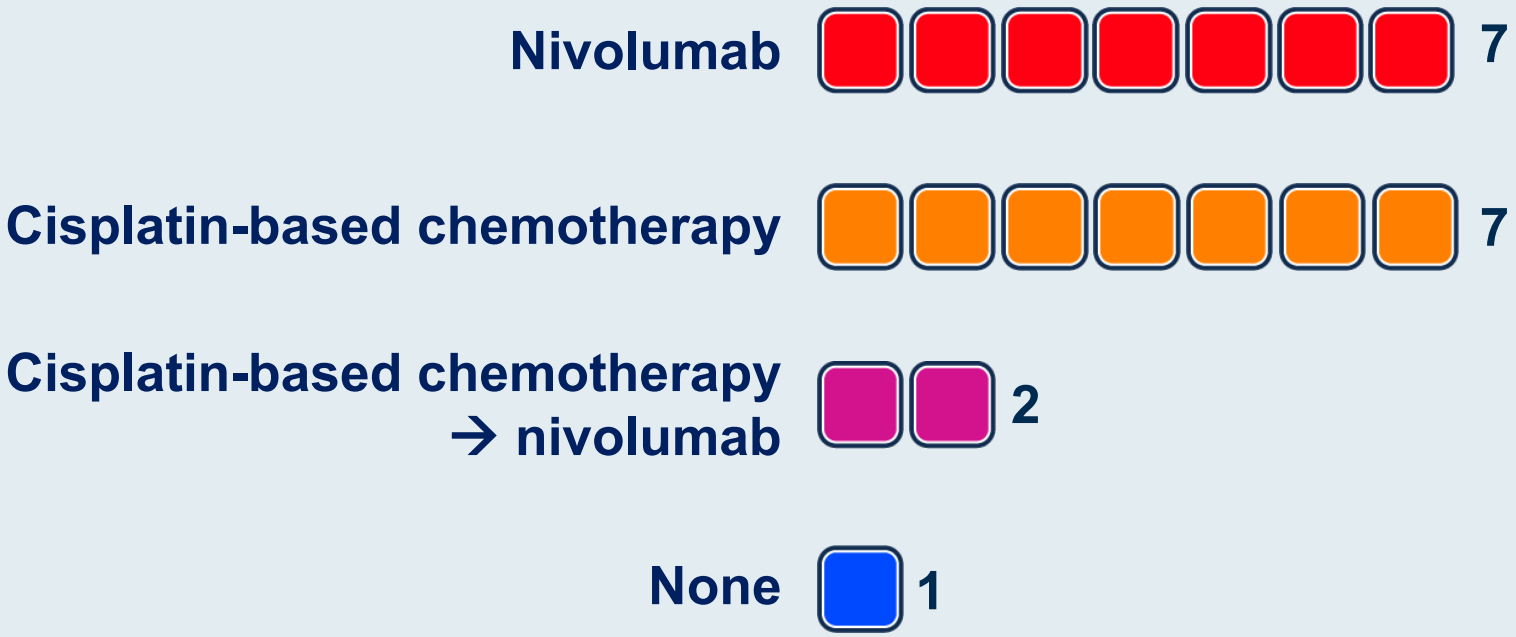
Survey of genitourinary cancer clinical investigators

A 65-year-old man receives neoadjuvant dose-dense MVAC for PD-L1-negative MIBC and undergoes cystectomy, which reveals significant residual disease and a positive pelvic lymph node. Regulatory and reimbursement issues aside, what adjuvant systemic therapy, if any, would you recommend?



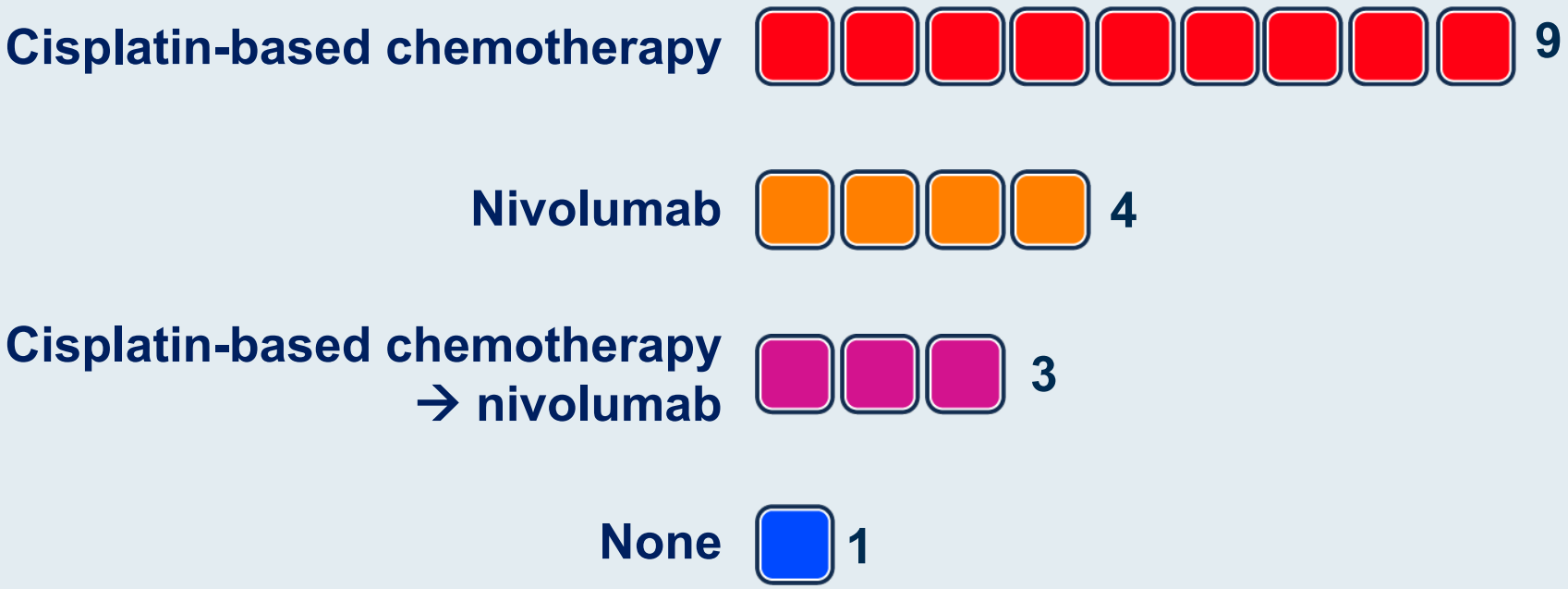
Survey of genitourinary cancer clinical investigators

A 65-year-old man is diagnosed with MIBC and undergoes cystectomy, which reveals pT3N1 PD-L1-positive disease. Regulatory and reimbursement issues aside, what adjuvant systemic therapy, if any, would you recommend?



Survey of genitourinary cancer clinical investigators

A 65-year-old man is diagnosed with MIBC and undergoes cystectomy, which reveals pT3N1 PD-L1-negative disease. Regulatory and reimbursement issues aside, what adjuvant systemic therapy, if any, would you recommend?



Survey of genitourinary cancer clinical investigators

MODULE 2: Current and Future Front-Line Management of Metastatic UBC (mUBC) — Dr Gupta

Cleveland Clinic

Current and Future Front-Line Management of Metastatic UBC (mUBC)

Shilpa Gupta, M.D.
Associate Professor
Director, Genitourinary Oncology Program
Cleveland Clinic Taussig Cancer Institute
Cleveland,OH

Dr Gupta — Disclosures

Advisory Committee	Aveo Pharmaceuticals, EMD Serono Inc, Gilead Sciences Inc, Lilly, Pfizer Inc
Consulting Agreements	Aveo Pharmaceuticals, Bristol-Myers Squibb Company, EMD Serono Inc, Gilead Sciences Inc, Janssen Biotech Inc, Lilly, Pfizer Inc
Ownership Interest	Nektar
Speakers Bureau	Bristol-Myers Squibb Company, Gilead Sciences Inc, Janssen Biotech Inc, Seagen Inc

RTP
RESEARCH
TO PRACTICE

Platinums are the backbone of first-line therapy in mUBC

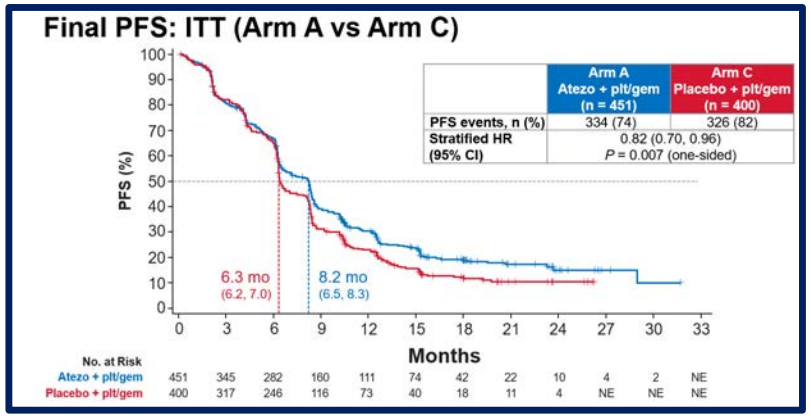
- Gemcitabine-Cisplatin (GC): Median OS ~ 14 months, ORR 49%
- ddMVAC: Median OS ~ 15 months, ORR 70%
- Gemcitabine-Carboplatin: Recent trials show median OS~ 13 months ORR 43%
- Only a minority of patients receive 2nd-line therapy for mUC
- An unmet need to improve survival with 1st-line treatment

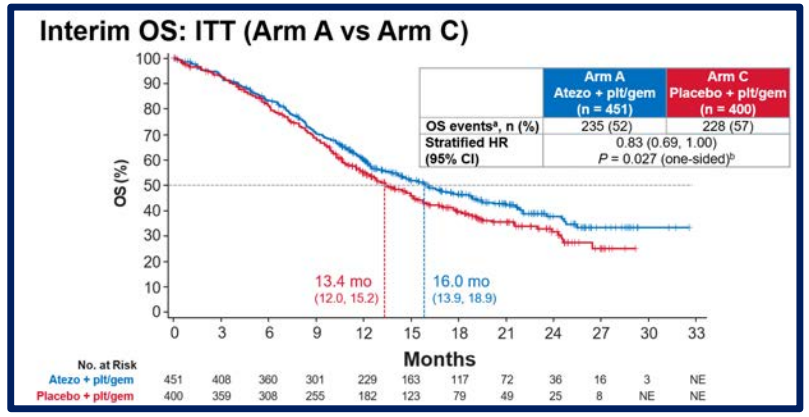
Von der Maase H et al. JCO 2005 Sternberg CN Eur J Cancer 2006, Galsky MD Lancet 2020, Flannery K et al. Future Oncol 2019, Powles T ASC) GU 2021

First-line Chemo-IO did not improve OS compared to Chemo

IMvigor130

- Atezolizumab + Chemo
- Atezolizumab
- Placebo + Chemo



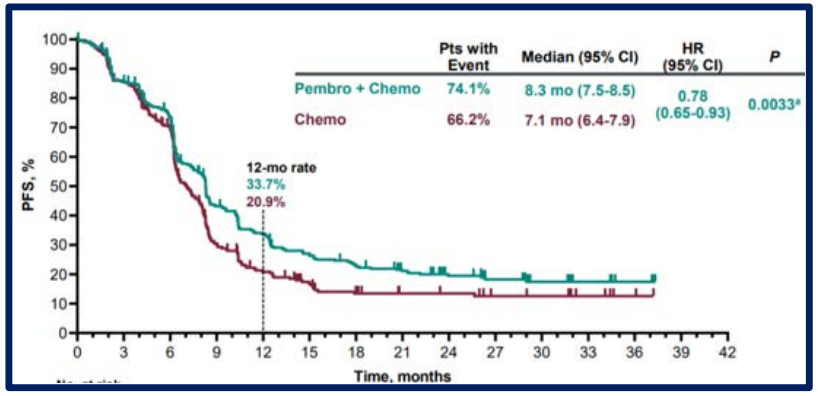


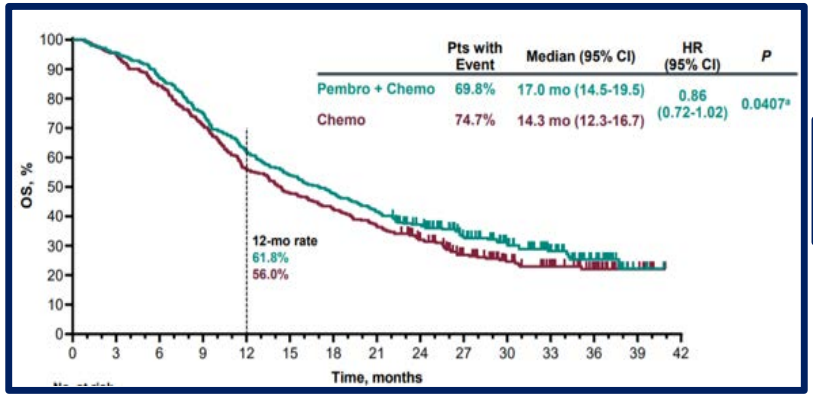
PFS improvement not clinically meaningful

No significant OS benefit so far

KEYNOTE-361

- Pembrolizumab + Chemo
- Pembrolizumab
- Chemo

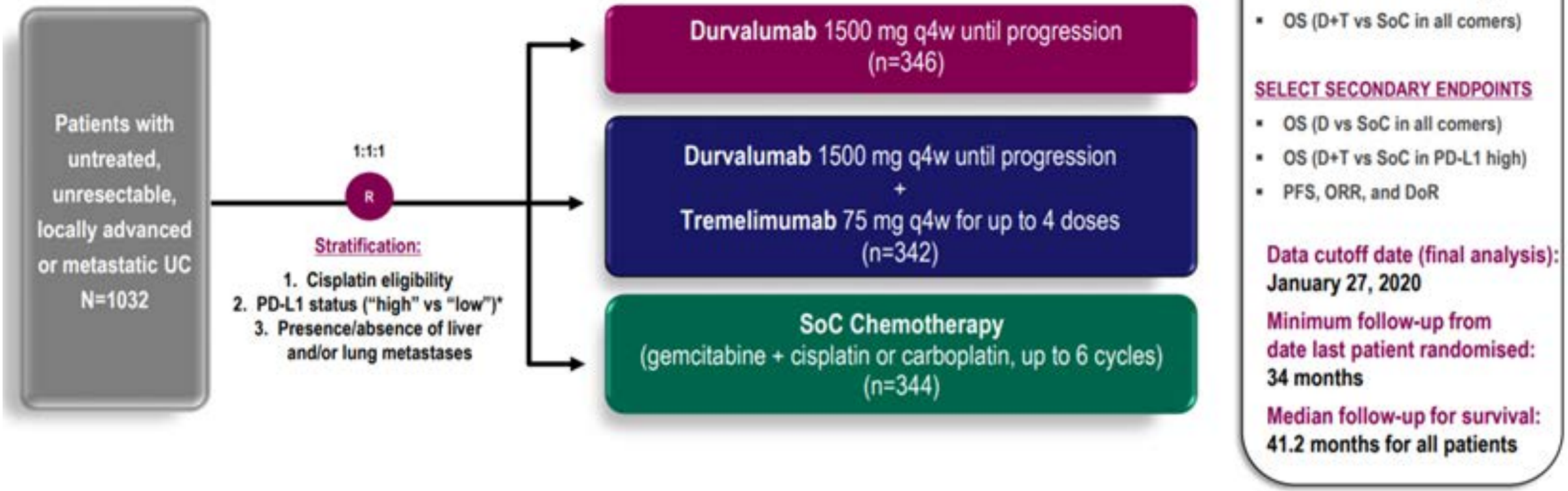




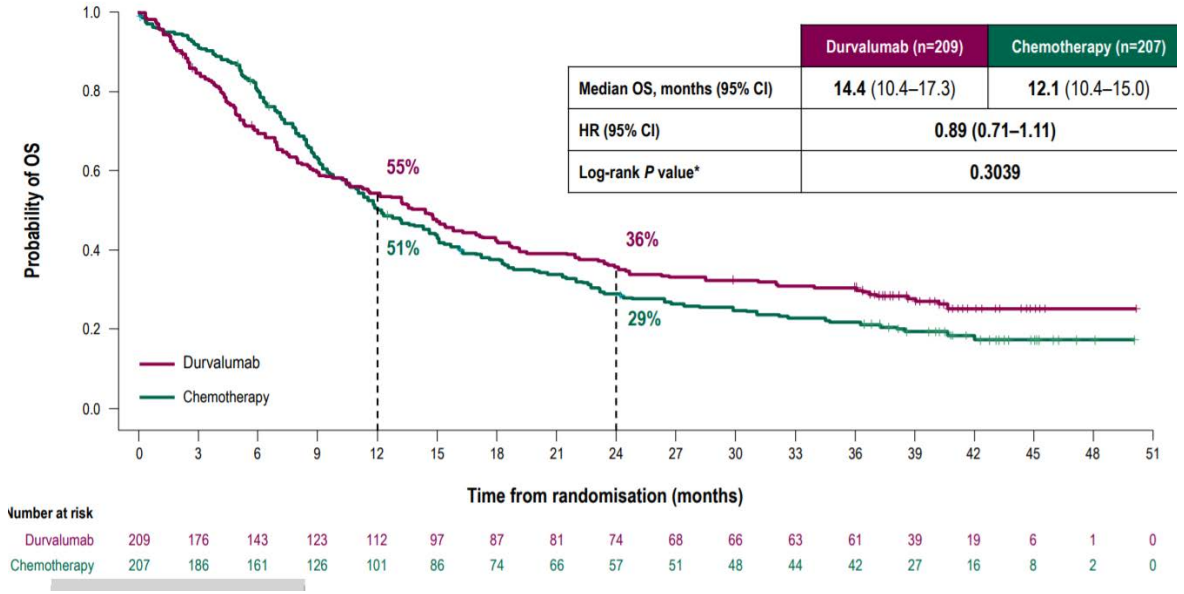
No PFS or OS improvement

Cleveland Clinic

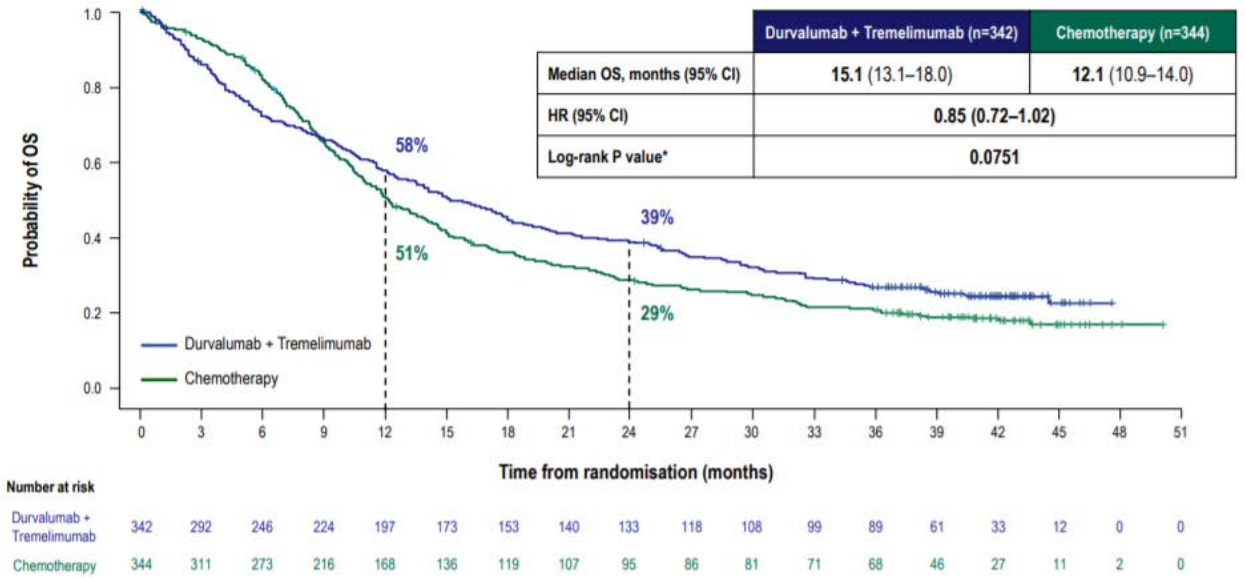
DANUBE: First-line durvalumab +/- tremelimumab versus SOC chemotherapy in Ia/mUC



Durva and Durva/Tremi did not improve OS compared to chemo in ITT population



	Durvalumab (n=209)	Chemotherapy (n=207)
Median OS, months (95% CI)	**14.4** (10.4–17.3)	**12.1** (10.4–15.0)
HR (95% CI)	**0.89 (0.71–1.11)**	
Log-rank *P* value*	**0.3039**	



	Durvalumab + Tremelimumab (n=342)	Chemotherapy (n=344)
Median OS, months (95% CI)	**15.1** (13.1–18.0)	**12.1** (10.9–14.0)
HR (95% CI)	**0.85 (0.72–1.02)**	
Log-rank P value*	**0.0751**	

February 22, 2021: Voluntary Withdrawal Announced of Durvalumab Indication for Previously Treated Locally Advanced or Metastatic Bladder Cancer

Cleveland Clinic

Thomas Powles ESMO 2020

Evolution of First-Line Therapy in Cisplatin-Ineligible mUC

De Santis M et al. JCO 2021
.Balar AV Lancet 2017
Balar AV et al. Lancet 2017
Powles T et al. NEJM 2020

KEYNOTE-361: Pembro Alone or Combined with Chemo vs Chemo

Response Rates and Disease Control Rates Lower with Pembro Compared to Carbo-Gem

Total Patients

Confirmed Response	Pembro N = 170	Carbo + Gem N = 196
ORR (95% CI)	**27.6% (21.1–35.0)**	**41.8% (34.8–49.1)**
DCR (95% CI)	**45.3% (37.7–53.1)**	**73.5% (66.7–79.5)**
CR	10.0%	10.7%
PR	17.6%	31.1%
SD	17.6%	31.6%
PD	37.6%	11.7%
Non-CR/non-PD	2.9%	5.1%
Non-evaluable or no assessment	14.1%	9.7%

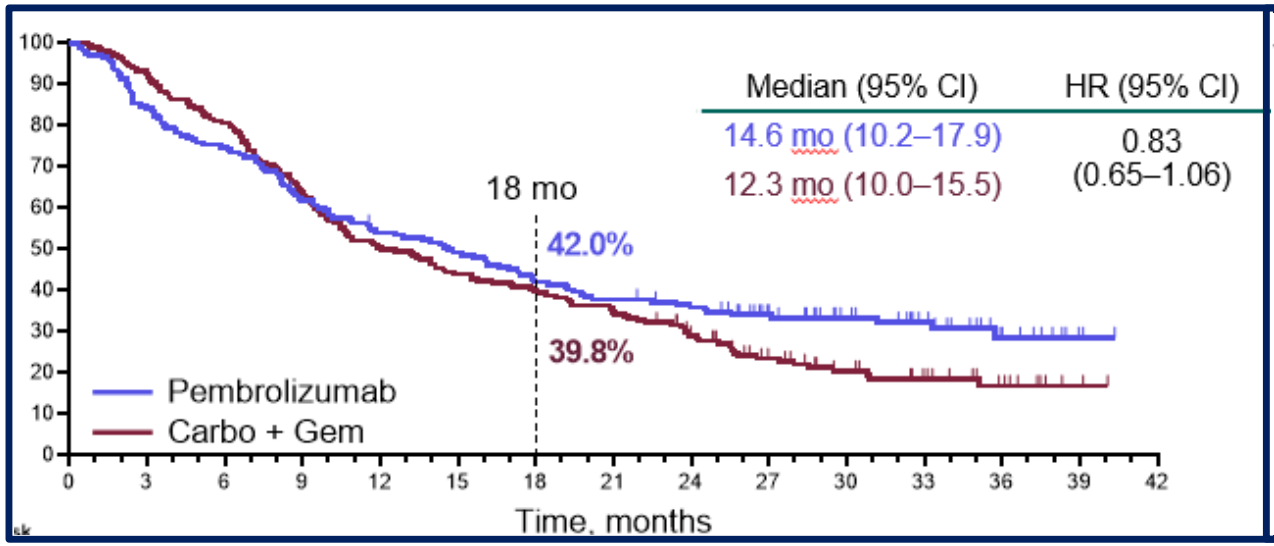
CPS ≥10

Confirmed Response	Pembro N = 84	Carbo + Gem N = 89
ORR (95% CI)	**29.8% (20.3–40.7)**	**46.1% (35.4–57.0)**
DCR (95% CI)	**48.8% (37.7–60.0)**	**73.0% (62.6–81.9)**
CR	11.9%	18.0%
PR	17.9%	28.1%
SD	19.0%	27.0%
PD	36.9%	7.9%
Non-CR/non-PD	1.2%	5.6%
Non-evaluable or no assessment	13.1%	13.5%

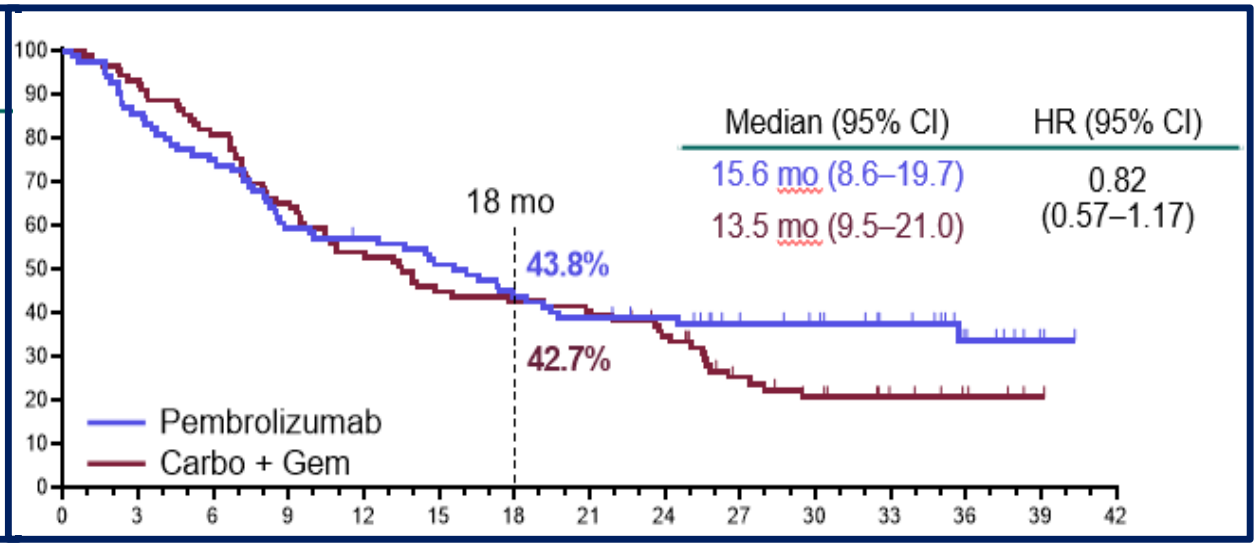
KEYNOTE-361: Pembro Alone or Combined with Chemo vs Chemo

OS for Pembro catches up but DOES NOT cross significantly enough for a positive trial

Total Patients



CPS ≥10



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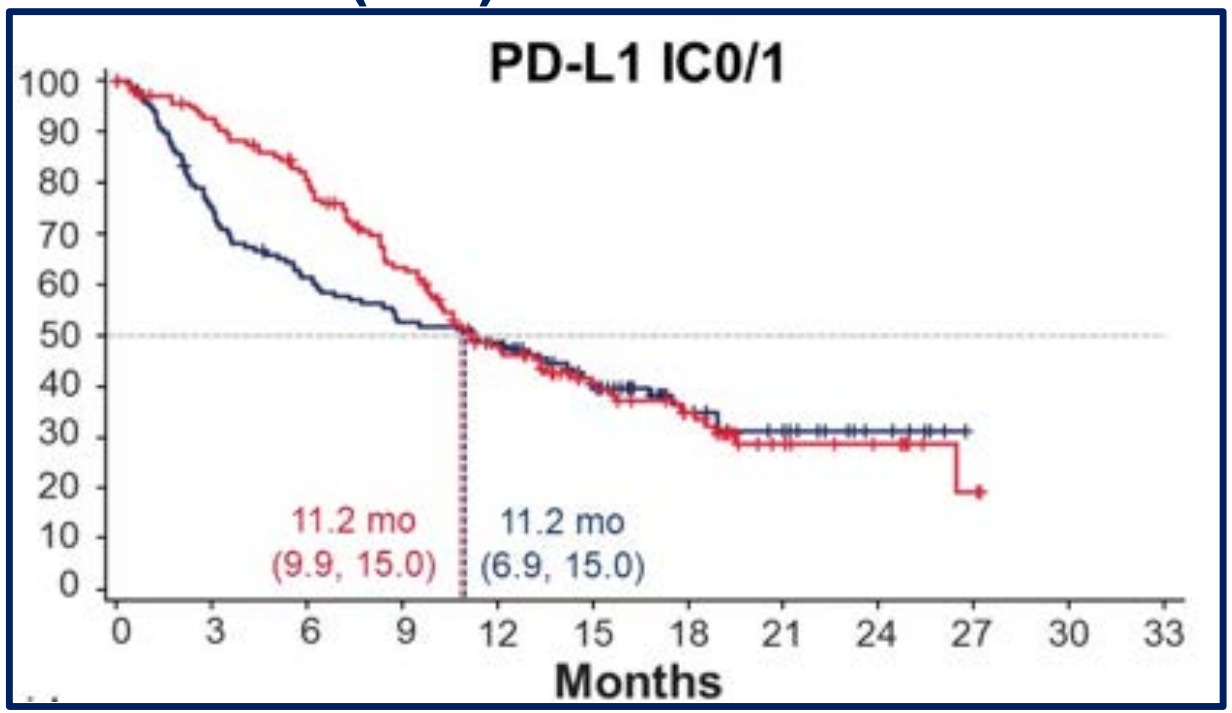
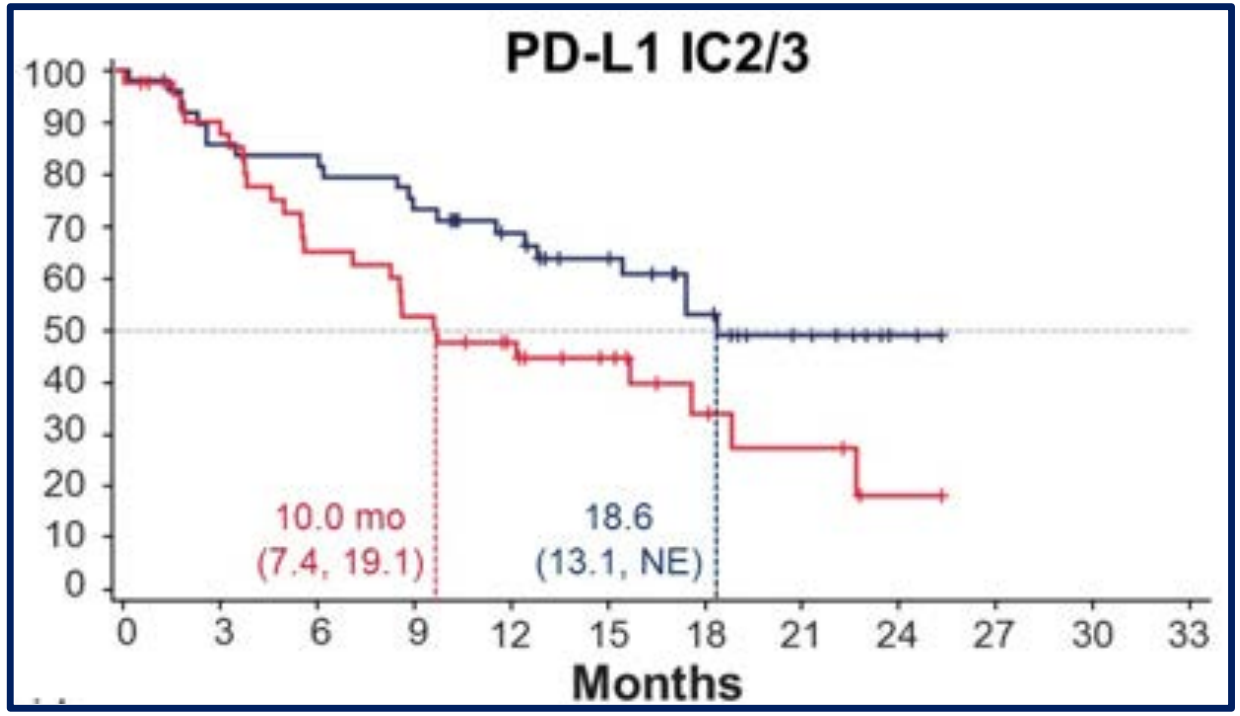
IMvigor130 Exploratory Analysis: Atezo vs Chemo in Cis-Ineligible Patients (OS)



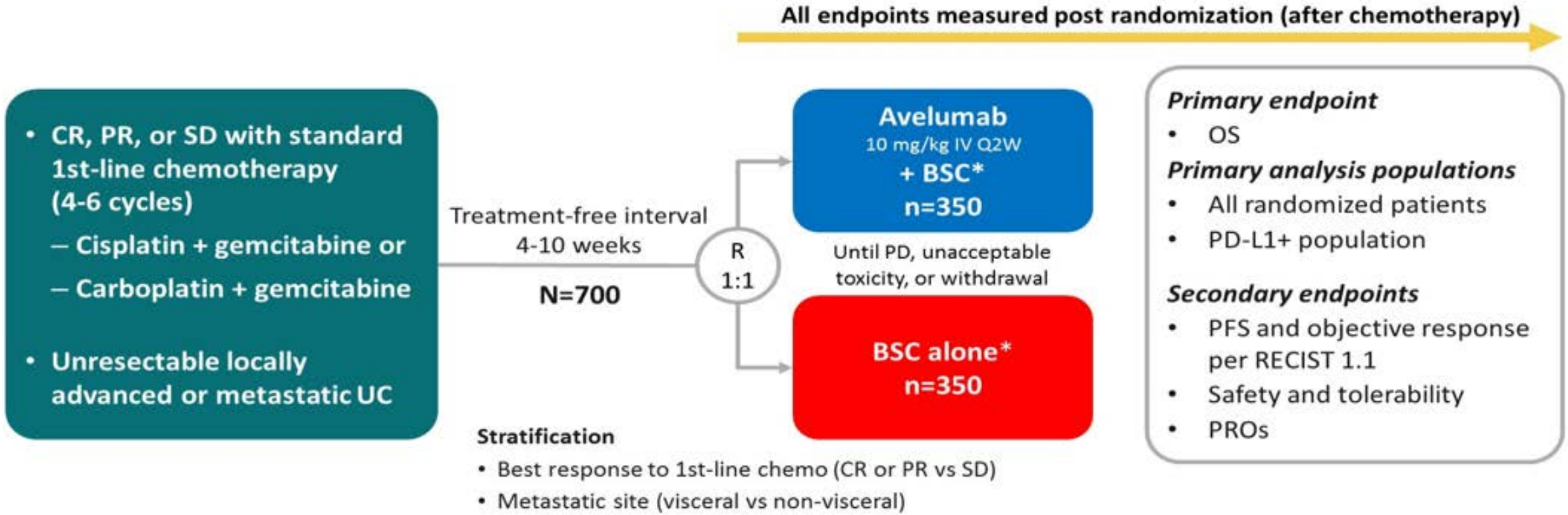


	Atezolizumab (Arm B) (n=140)	Placebo + plt/gem (Arm C) (n=140)
OS events	85	85
OS HR (95% CI)	1.11 (0.82, 1.51)	
ORR (95% CI), %[a]	16 (10, 23)	42 (34, 51)

	Atezolizumab (Arm B) (n=50)	Placebo + plt/gem (Arm C) (n=43)
OS events	21	26
OS HR (95% CI)	0.53 (0.30, 0.94)	
ORR (95% CI), %	38 (25, 53)	33 (19, 49)

PD-L1 seems to predict responses to atezo in this exploratory analysis

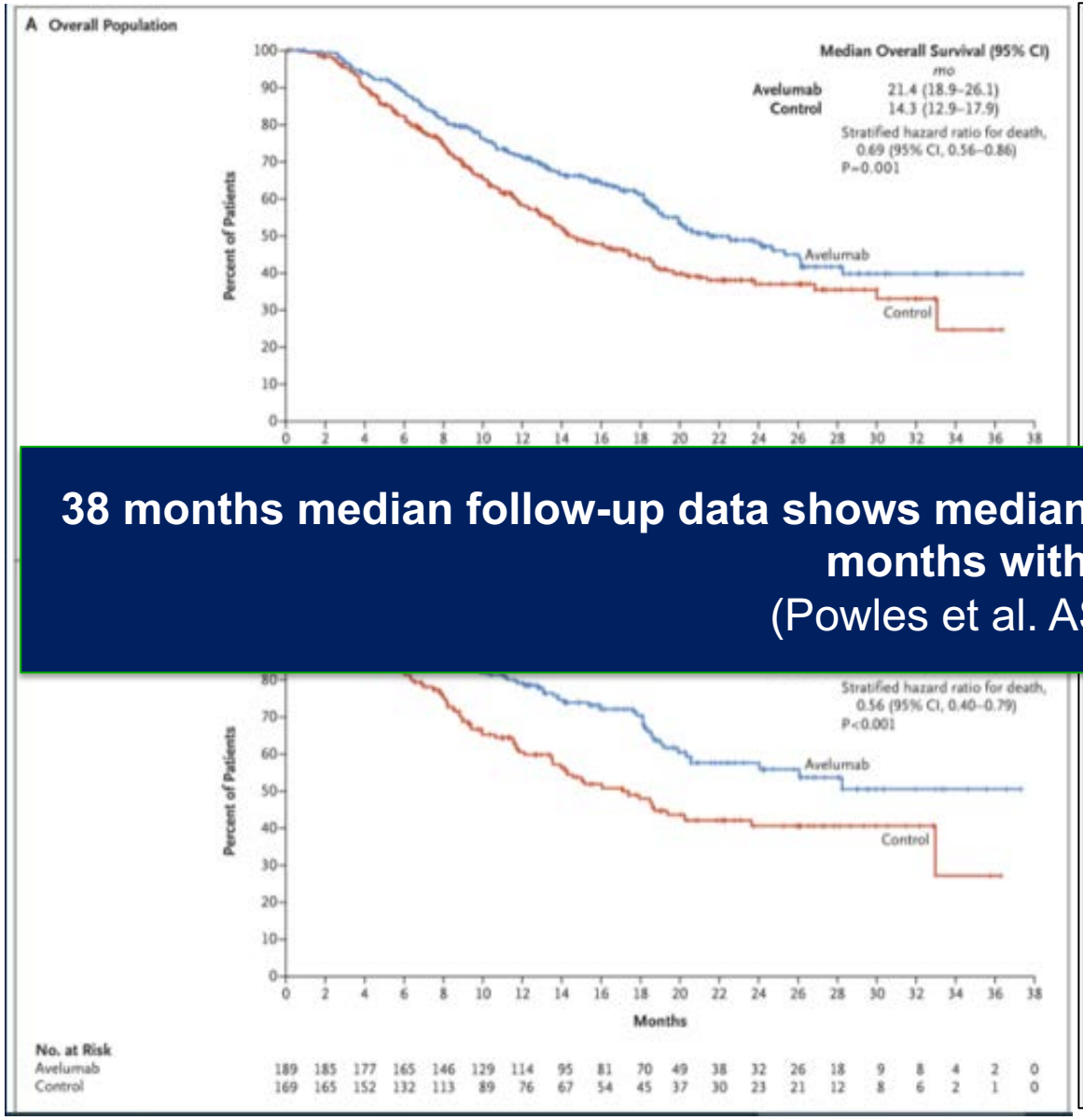
JAVELIN Bladder 100 study design (NCT02603432)

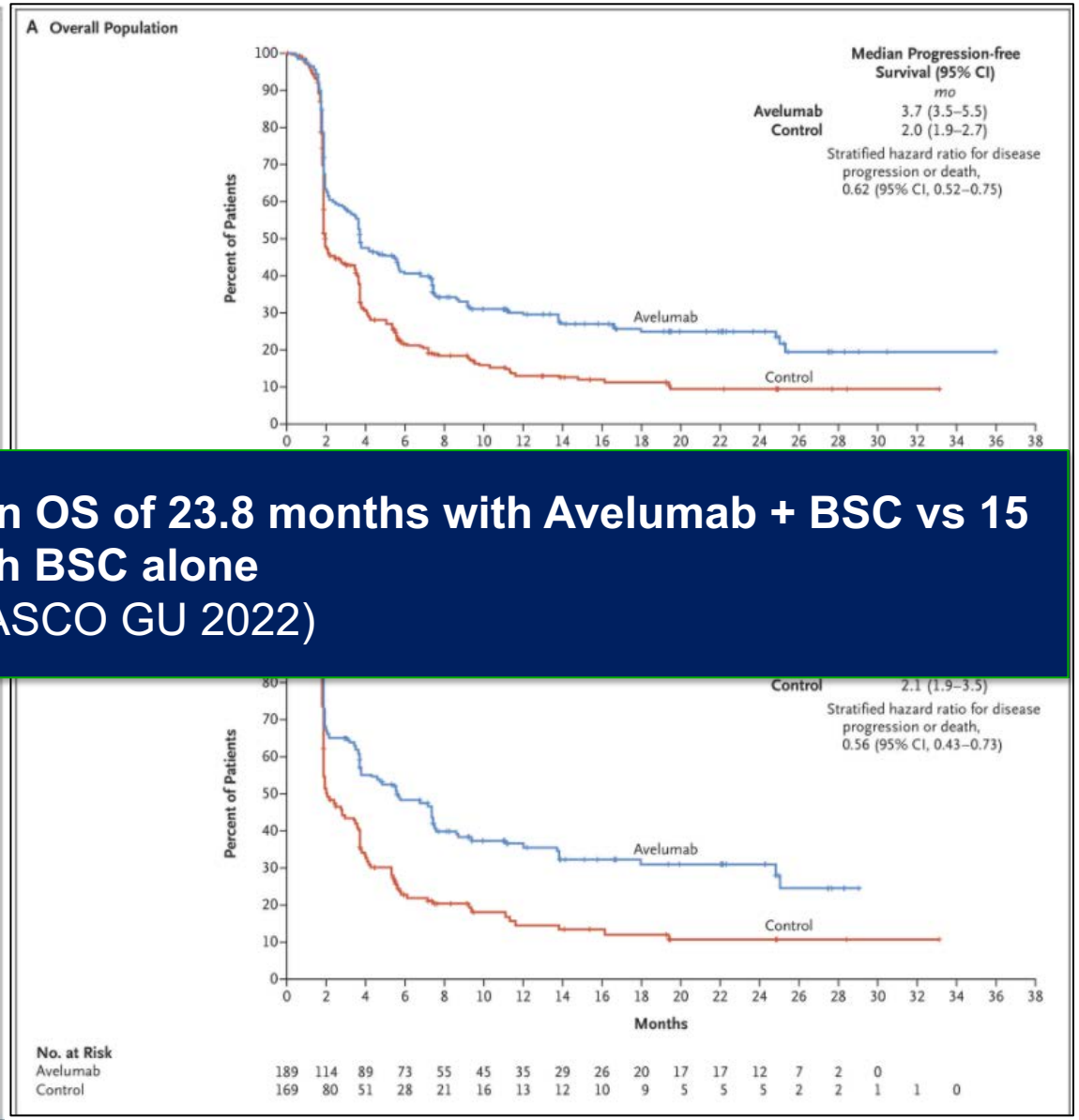


PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

Thomas Powles ASCO 2020

Maintenance Avelumab improves OS and PFS





38 months median follow-up data shows median OS of 23.8 months with Avelumab + BSC vs 15 months with BSC alone
(Powles et al. ASCO GU 2022)

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Table 2. Responses in the Overall Population and the PD-L1–Positive Population.*

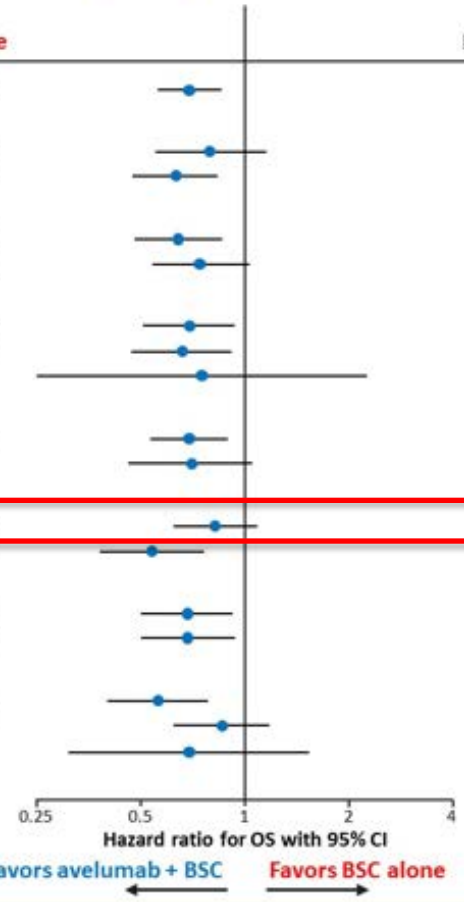
Variable	Overall Population			PD-L1–Positive Population		
	Avelumab Group (N=350)	Control Group (N=350)	Stratified Odds Ratio (95% CI)	Avelumab Group (N=189)	Control Group (N=169)	Stratified Odds Ratio (95% CI)
Confirmed objective response (95% CI) — %	9.7 (6.8–13.3)	1.4 (0.5–3.3)	7.46 (2.82–24.45)	13.8 (9.2–19.5)	1.2 (0.1–4.2)	12.70 (3.16–114.12)
Confirmed best overall response — no. (%)						
Complete response	21 (6.0)	3 (0.9)		18 (9.5)	1 (0.6)	
Partial response	13 (3.7)	2 (0.6)		8 (4.2)	1 (0.6)	
Stable disease	44 (12.6)	46 (13.1)		19 (10.1)	23 (13.6)	
Non–complete response or non–progressive disease†	66 (18.9)	45 (12.9)		38 (20.1)	22 (13.0)	
Progressive disease	130 (37.1)	169 (48.3)		59 (31.2)	82 (48.5)	
Could not be evaluated	76 (21.7)‡	85 (24.3)§		47 (24.9)¶	40 (23.7)‖	
Disease control — no. (%)**	144 (41.1)	96 (27.4)		83 (43.9)	47 (27.8)	
Median time to objective response (range) — mo	2.0 (1.7–16.4)	2.0 (1.8–7.0)		2.0 (1.7–16.4)	2.8 (1.8–3.8)	

Table 3. Adverse Events (Safety Population).*

Event	Avelumab Group (N=344)		Control Group (N=345)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	337 (98.0)	163 (47.4)	268 (77.7)	87 (25.2)
Fatigue	61 (17.7)	6 (1.7)	24 (7.0)	2 (0.6)
Pruritus	59 (17.2)	1 (0.3)	6 (1.7)	0
Urinary tract infection	59 (17.2)	15 (4.4)	36 (10.4)	9 (2.6)
Diarrhea	57 (16.6)	2 (0.6)	17 (4.9)	1 (0.3)
Arthralgia	56 (16.3)	2 (0.6)	19 (5.5)	0
Asthenia	56 (16.3)	0	19 (5.5)	4 (1.2)
Constipation	56 (16.3)	2 (0.6)	31 (9.0)	0
Back pain	55 (16.0)	4 (1.2)	34 (9.9)	8 (2.3)
Nausea	54 (15.7)	1 (0.3)	22 (6.4)	2 (0.6)
Pyrexia	51 (14.8)	1 (0.3)	12 (3.5)	0
Decreased appetite	47 (13.7)	1 (0.3)	23 (6.7)	2 (0.6)
Cough	44 (12.8)	1 (0.3)	16 (4.6)	0
Vomiting	43 (12.5)	4 (1.2)	12 (3.5)	2 (0.6)
Hypothyroidism	40 (11.6)	1 (0.3)	2 (0.6)	0
Rash	40 (11.6)	1 (0.3)	4 (1.2)	0
Anemia	39 (11.3)	13 (3.8)	23 (6.7)	10 (2.9)
Hematuria	36 (10.5)	6 (1.7)	37 (10.7)	5 (1.4)
Infusion-related reaction	35 (10.2)	3 (0.9)	0	0

Subgroup analysis of OS in the overall population

Subgroup		Events/patients, n: Avelumab + BSC	Events/patients, n: BSC alone	Hazard ratio (95% CI)
All patients		145/350	179/350	**0.69** (0.56, 0.86)*
Age	<65 years	61/129	53/107	**0.79** (0.55, 1.15)
	≥65 years	84/221	126/243	**0.63** (0.47, 0.83)
ECOG PS score	0	77/213	101/211	**0.64** (0.48, 0.86)
	≥1	68/137	78/139	**0.74** (0.54, 1.03)
1st-line chemotherapy regimen	Gemcitabine + cisplatin	71/183	98/206	**0.69** (0.51, 0.94)
	Gemcitabine + carboplatin	68/147	73/122	**0.66** (0.47, 0.91)
	Gemcitabine + cisplatin/carboplatin	6/20	7/20	**0.75** (0.25, 2.25)
Best response to 1st-line chemotherapy	CR or PR	104/253	127/252	**0.69** (0.53, 0.89)
	SD	41/97	52/98	**0.70** (0.46, 1.05)
Site of baseline metastasis	Visceral	93/191	101/191	**0.82** (0.62, 1.09)
	Nonvisceral	52/159	78/159	**0.54** (0.38, 0.76)
Creatinine clearance	≥60 mL/min	74/181	97/196	**0.68** (0.50, 0.92)
	<60 mL/min	71/168	81/148	**0.68** (0.50, 0.94)
PD-L1 status	Positive	61/189	82/169	**0.56** (0.40, 0.78)
	Negative	76/139	72/132	**0.86** (0.62, 1.18)
	Unknown	8/22	25/49	**0.69** (0.31, 1.53)



Error bars show 95% CI

*Stratified (all other analyses are unstratified)

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Powles T et al. NEJM 2020

Maintenance PARP inhibitors in mUC

Abstract 436
Crabb SJ et al
A randomized, double blind, biomarker selected, phase II clinical trial of maintenance PARP inhibition following chemotherapy for metastatic urothelial carcinoma (mUC): Final analysis of the ATLANTIS rucaparib arm

Abstract 442
Vignani F et al
Randomized phase II study of niraparib plus BSC vs BSC alone as maintenance treatment in patients with advanced UC whose disease did not progress after first-line platinum-based chemotherapy: The Meet-URO12 trial

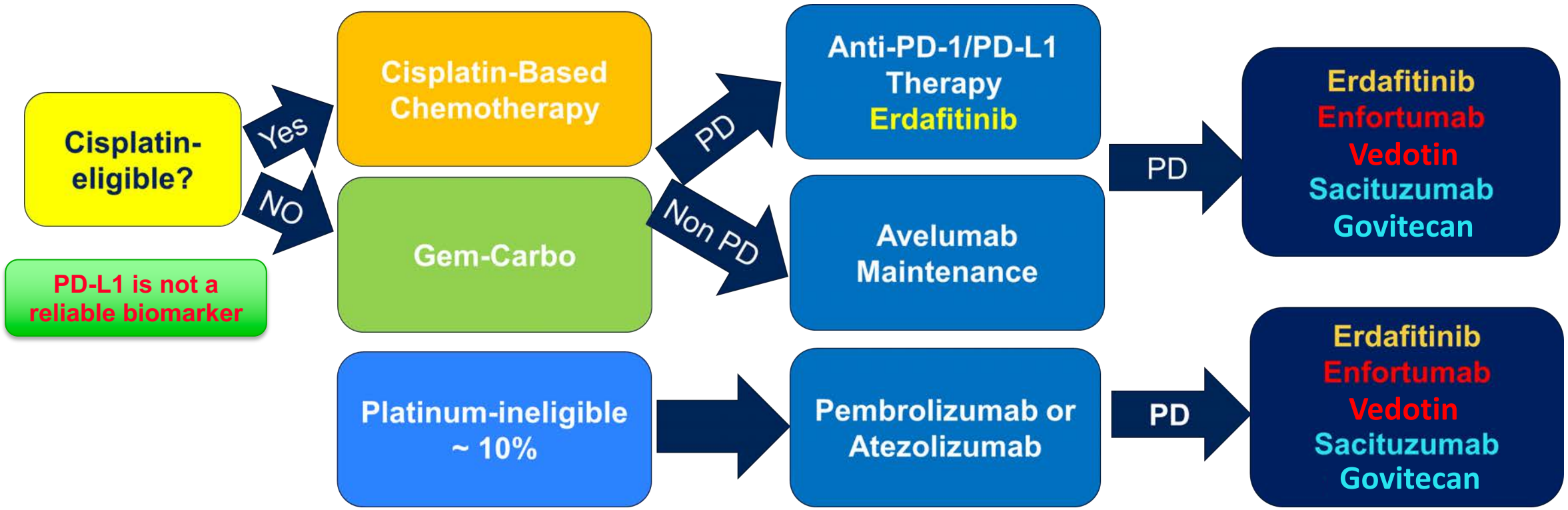
Patient Selection for first-line treatment in mUBC

- PD-L1 is not a reliable biomarker (KEYNOTE-361) and FDA has restricted pembrolizumab label only to platinum-ineligible mUBC pts

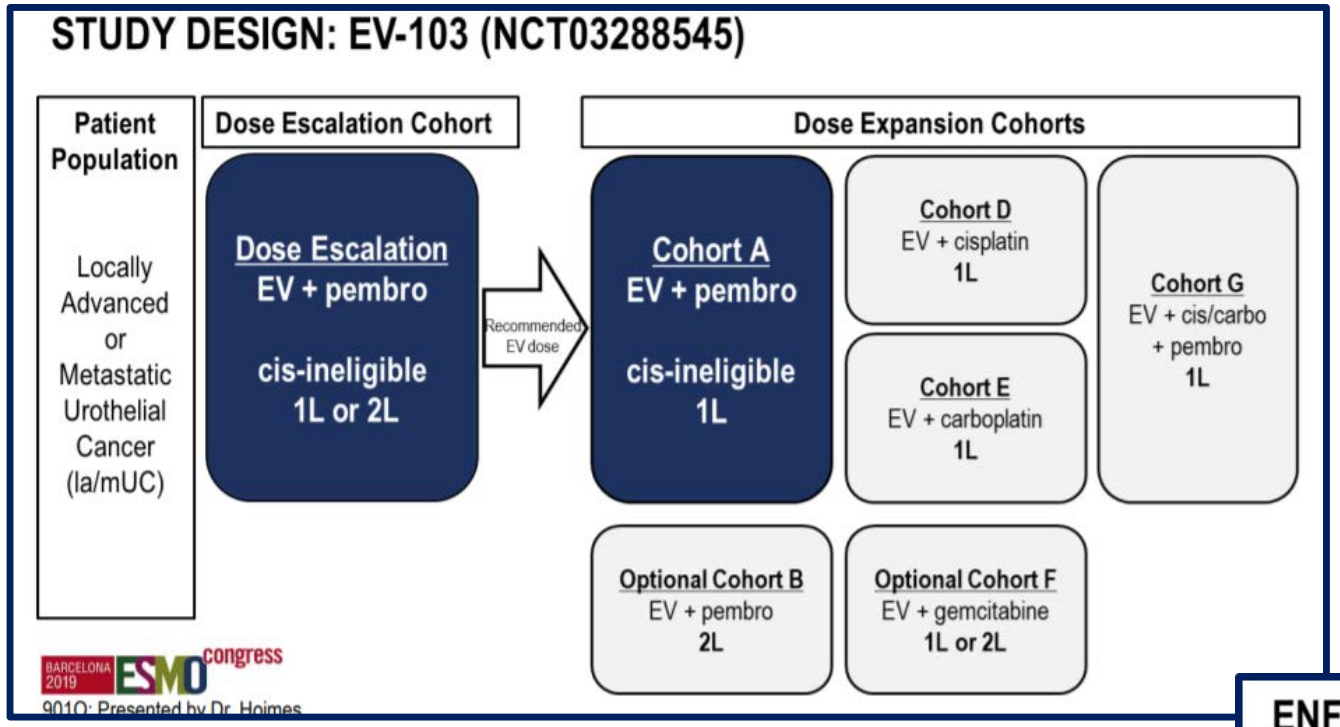
- Our group proposed a consensus definition for “platinum-ineligibility” for standardization using 1 of the 5 parameters:
  - ECOG PS ≥ 3
  - Cr Cl < 30 ml/min
  - Peripheral neuropathy ≥ 3
  - NYHA Heart Failure Class > 3
  - ECOG PS 2 and Cr Cl < 30 ml/min

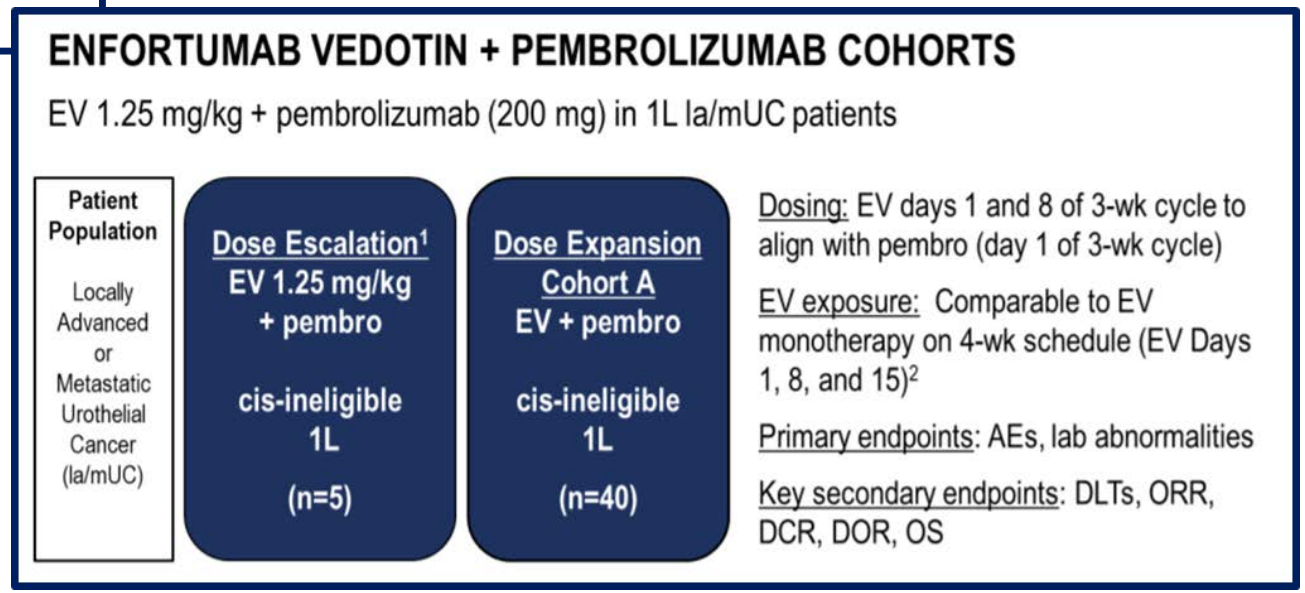
Gupta, S et al. ASCO GU 2019

Treatment Paradigm for mUBC in 2022



Enfortumab vedotin and pembrolizumab in first-line cisplatin-ineligible mUC





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Hoimes et al. ESMO 2019

EV 1.25 mg/kg + pembrolizumab in 1L setting 18 June 2019 data cut-off	Patients (N=45) n (%)
Male sex, n (%)	36 (80)
Age, yrs, Median (min, max)	69 (51, 90)
ECOG performance status, n (%)	
0	16 (36)
1	23 (51)
2	6 (13)
Primary tumor location, n (%) [1]	
Lower tract	31 (69)
Upper tract	13 (29)
Metastasis sites, n (%)	
Lymph nodes only	4 (9)
Visceral disease	41 (91)
Liver	15 (33)
PD-L1 status by combined positive score, [2] **n (%)**	
<10	19 (42)
≥10	13 (29)
Not evaluable/Not available	13 (29)

TREATMENT-RELATED ADVERSE EVENTS (TRAE)

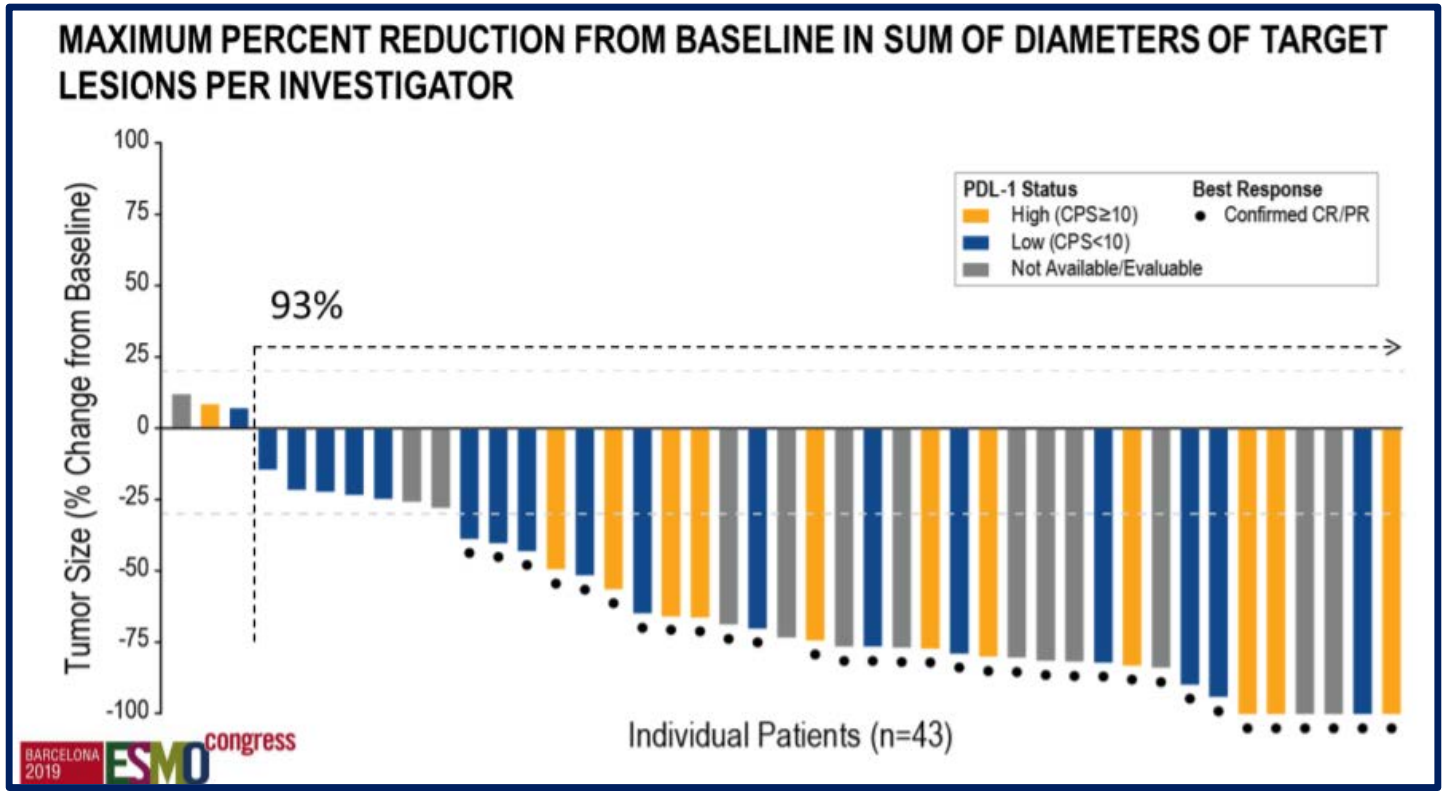
TRAEs by preferred term Any grade in ≥20% of patients and ≥Grade 3 in ≥10% of patients	Patients (N=45) n (%)	
	Any Grade	≥Grade 3
Overall	43 (96)	23 (51)
Fatigue	22 (49)	4 (9)
Alopecia	21 (47)	N/A
Peripheral sensory neuropathy	21 (47)	2 (4)
Diarrhea	18 (40)	2 (4)
Decreased appetite	15 (33)	0
Dysgeusia	14 (31)	N/A
Nausea	13 (29)	0
Pruritus	12 (27)	1 (2)
Rash maculo-papular	12 (27)	3 (7)
Weight decreased	10 (22)	0
Anemia	9 (20)	2 (4)
Lipase increased	7 (16)	6 (13)

N/A: Non-applicable

- **7 patients had treatment-related serious AEs (16%)**
- **4 treatment-related discontinuations of EV + pembro due to AEs (9%)**
  - Peripheral sensory neuropathy most common: 2 patients
- **1 treatment-related death as reported by investigator (2%)**
  - Multiple organ dysfunction syndrome
  - Confounded by concomitant acute onset of atrial fibrillation, corticosteroids, and amiodarone

BARCELONA 2019 ESMO congress

Hoimes et al. ESMO 2019



ASCO GU 2021: Updated median follow-up of 24.9 mo

- Median PFS 12.3 mos. and median OS is not reached
- The most TRAEs were peripheral sensory neuropathy (56%, 4% ≥G3), fatigue (51%, 11% ≥G3), and alopecia (49%)
- 1 treatment-related death
- ORR 73.3%; CR 17.8%, ORR 57% in liver metastases

Fridlander TW et al. ASCO GU 2021

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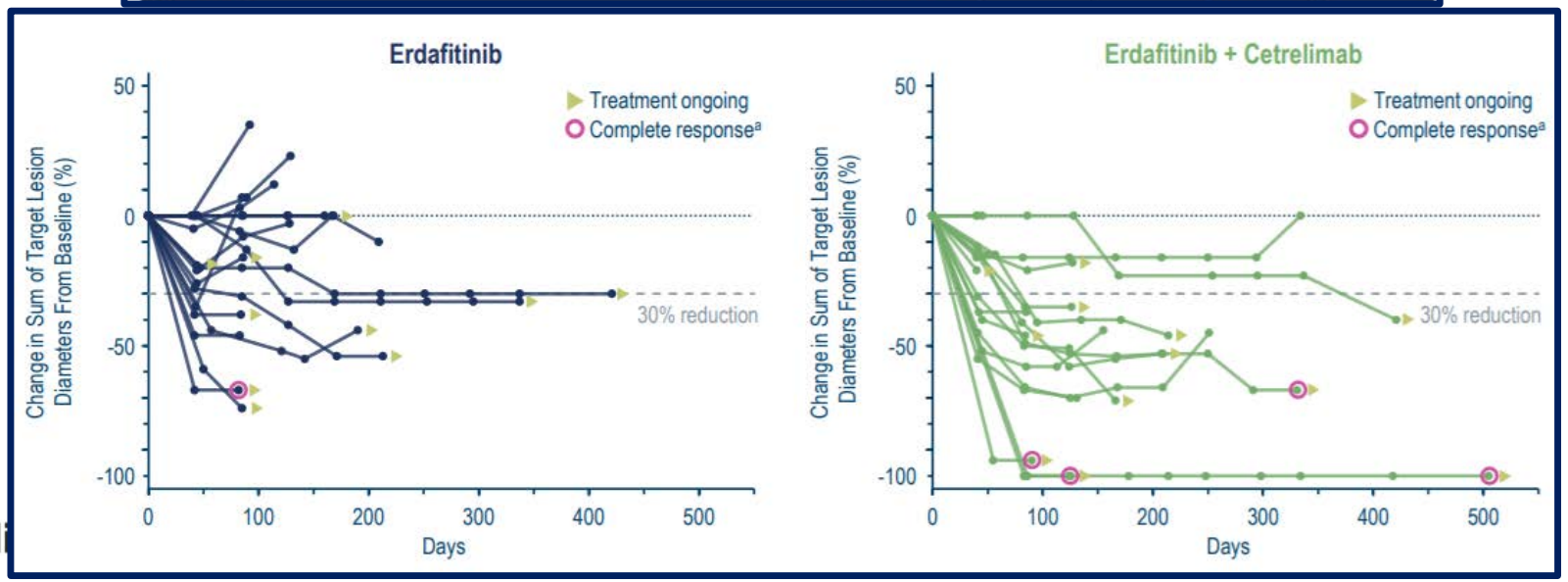
Erdafitinib (FGFRi) + Cetrelimab (anti-PD-L1) in 1L mUC: NORSE Study

	Erdafitinib (n = 18)	Erdafitinib + Cetrelimab (n = 19)
ORR[a], n (%) [95% CI]	6 (33%) [13%-59%]	13 (68%) [43%-87%]
Complete response, n (%)	1 (6%)	4 (21%)
Partial response, n (%)	5 (28%)	9 (47%)
DOR, median, months [95% CI]	NE [4.4-NE]	6.9 [1.6-NE]
Responses ongoing, n (%)	5 (28%)	10 (53%)
Time to response, median (range), months	2.3 (1-6)	1.8 (1-4)
DCR, n (%) [95% CI]	18 (100%) [82%-100%]	17 (90%) [67%-99%]



Powles T ESMO 2021

Reinvigorating the role of PARP inhibitors in mUBC
Durvalumab + olaparib for first-line treatment of platinum-ineligible patients with mUC (BAYOU)

- Platinum-ineligible mUC population, N=154
- Randomized to receive durva+olaparib vs durva+placebo
- 20% had an HRRm

	D+O	D+PBO
ITT population	n = 78	n = 76
Median PFS, mo (95% CI)	4.2 (3.6–5.6)	3.5 (1.9–5.1)
HR (95% CI)	0.94 (0.64–1.39)	
Log-rank p-value	0.789	
HRRm subset*	n = 17	n = 14
Median PFS, mo (95% CI)	5.6 (1.9–8.1)	1.8 (1.7–2.2)
HR (95% CI)	0.18 (0.06–0.47)	
Log-rank p-value	< 0.001	

How will 1st-line therapy in mUC evolve in future?

Key Ongoing Phase 3 Trials

CheckMate 901	NILE	EV-302
Gem + Cis/Carbo	Gem + Cis/Carbo Durvalumab	EV + Pembrolizumab
Gem + Cis/Carbo Nivolumab	Gem + Cis/Carbo Durva/Tremi	Gem + Cis/Carbo
Ipi/Nivo	Gem + Cis/Carbo	

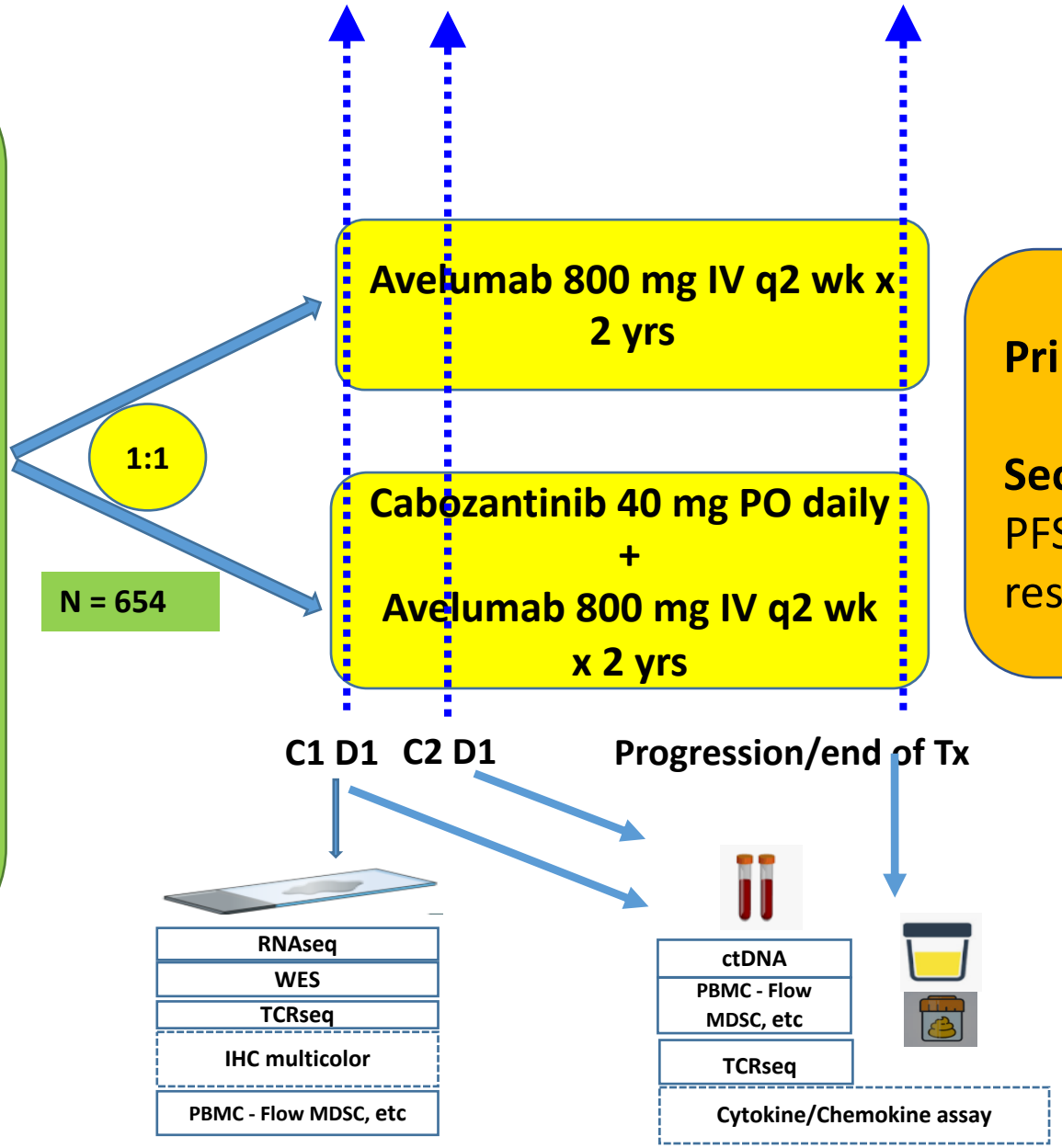
A032001: MAINCAV- Phase III randomized trial of maintenance cabozantinib and avelumab vs maintenance avelumab after 1L platinum-based chemotherapy in patients with mUC (including N3 only disease) (NCT05092958)

Patients with locally advanced/mUC, N3 only disease allowed

CR/PR/SD with standard 1st-line platinum-based chemotherapy (4-6 cycles)

Stratification:

- **Best response to 1st-line chemo (CR vs PR vs SD)**
- **Sites of metastases: visceral vs non-visceral**



Primary endpoint: OS

Secondary endpoints: PFS, Safety, Tumor response, HRQOL

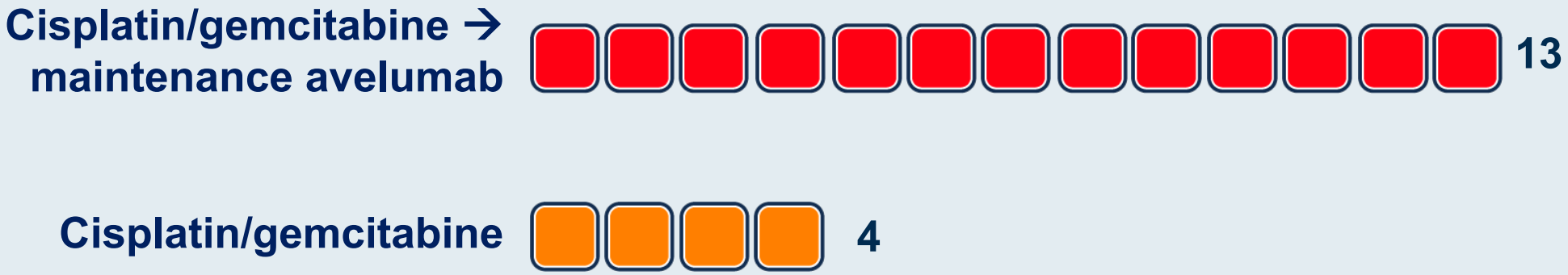
Study Chair: Shilpa Gupta

Conclusions

- Platinum-based chemotherapy is the kingpin in 1L mUC and addition of more agents is NOT better
- PD-L1 does not appear to be predictive for IO benefit
- Maintenance immunotherapy improves outcomes
- Ongoing first-line trials will establish the role of novel chemo-sparing combinations

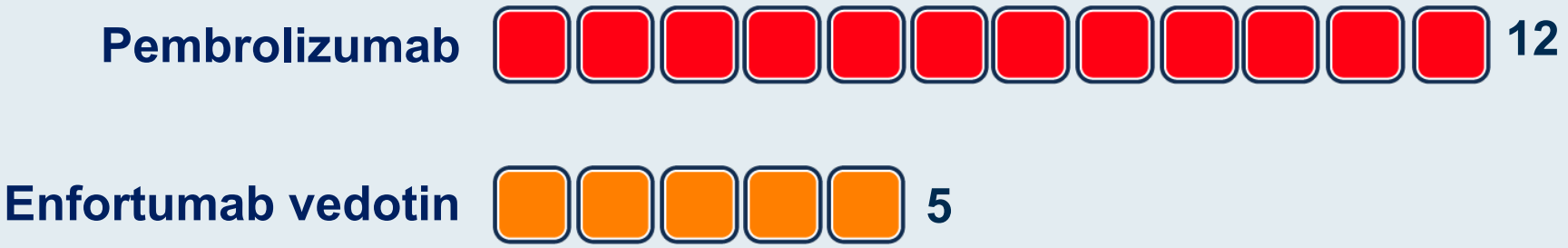
Clinical Investigator Survey Results

What would be your preferred first-line treatment regimen for a 65-year-old patient with de novo metastatic urothelial bladder cancer (UBC)?



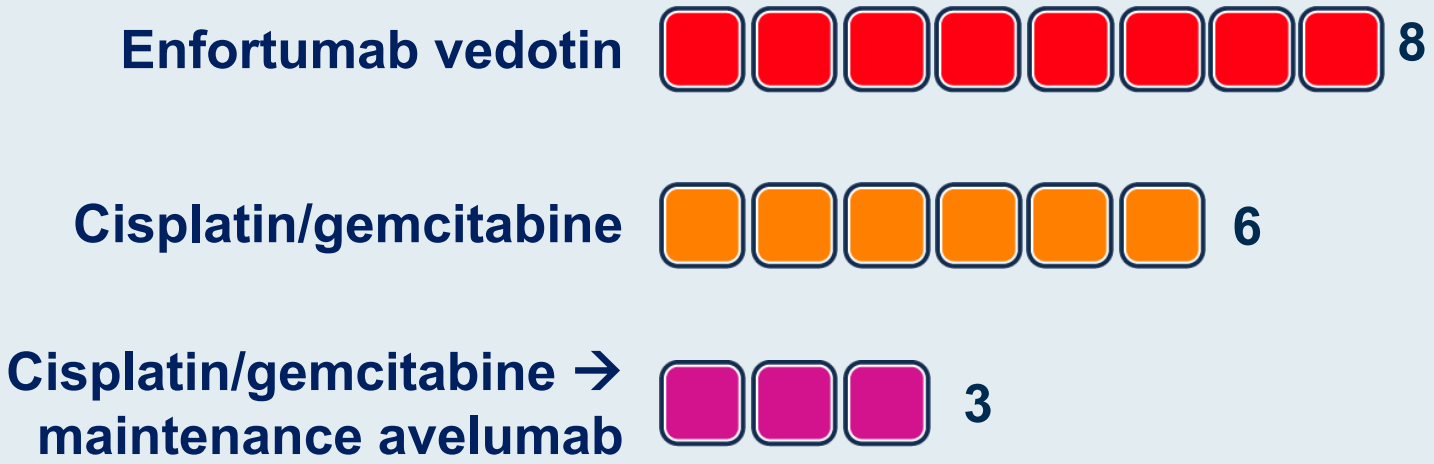
Survey of genitourinary cancer clinical investigators

What would you generally recommend for a 65-year-old patient who experiences disease recurrence in the liver 9 months after cystectomy and adjuvant gemcitabine/cisplatin for muscle-invasive FGFR wild-type UBC?



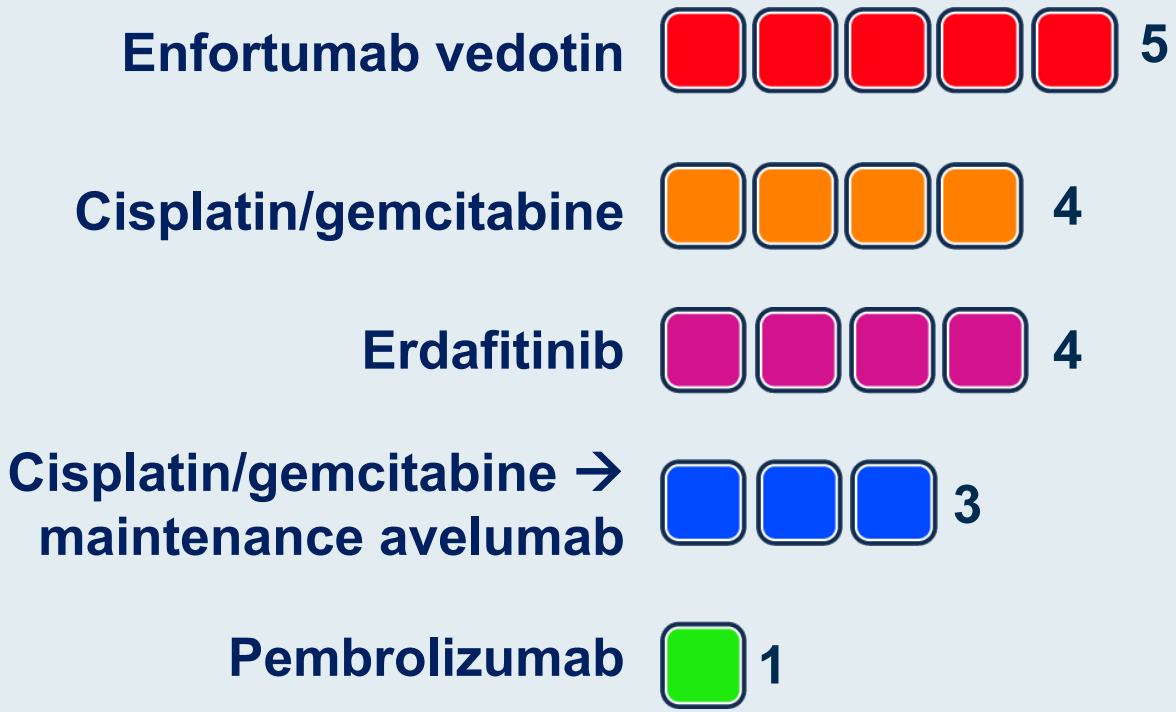
Survey of genitourinary cancer clinical investigators

What would you generally recommend for a 65-year-old patient who experiences disease recurrence in the liver 9 months after cystectomy and adjuvant nivolumab for muscle-invasive FGFR wild-type UBC?



Survey of genitourinary cancer clinical investigators

What would you generally recommend for a 65-year-old patient who experiences disease recurrence in the liver 9 months after cystectomy and adjuvant nivolumab for muscle-invasive UBC and is found to have an FGFR3 mutation?



Survey of genitourinary cancer clinical investigators

Based on current clinical trial data and your personal experience, do you believe pembrolizumab in combination with enfortumab vedotin will result in superior outcomes compared to currently available up-front regimens for metastatic UBC?

Survey of genitourinary cancer clinical investigators

MODULE 3: Selection and Sequencing of Therapy for Relapsed/Refractory mUBC — Dr Petrylak

Selection and Sequencing of Therapy for Relapsed/Refractory mUBC

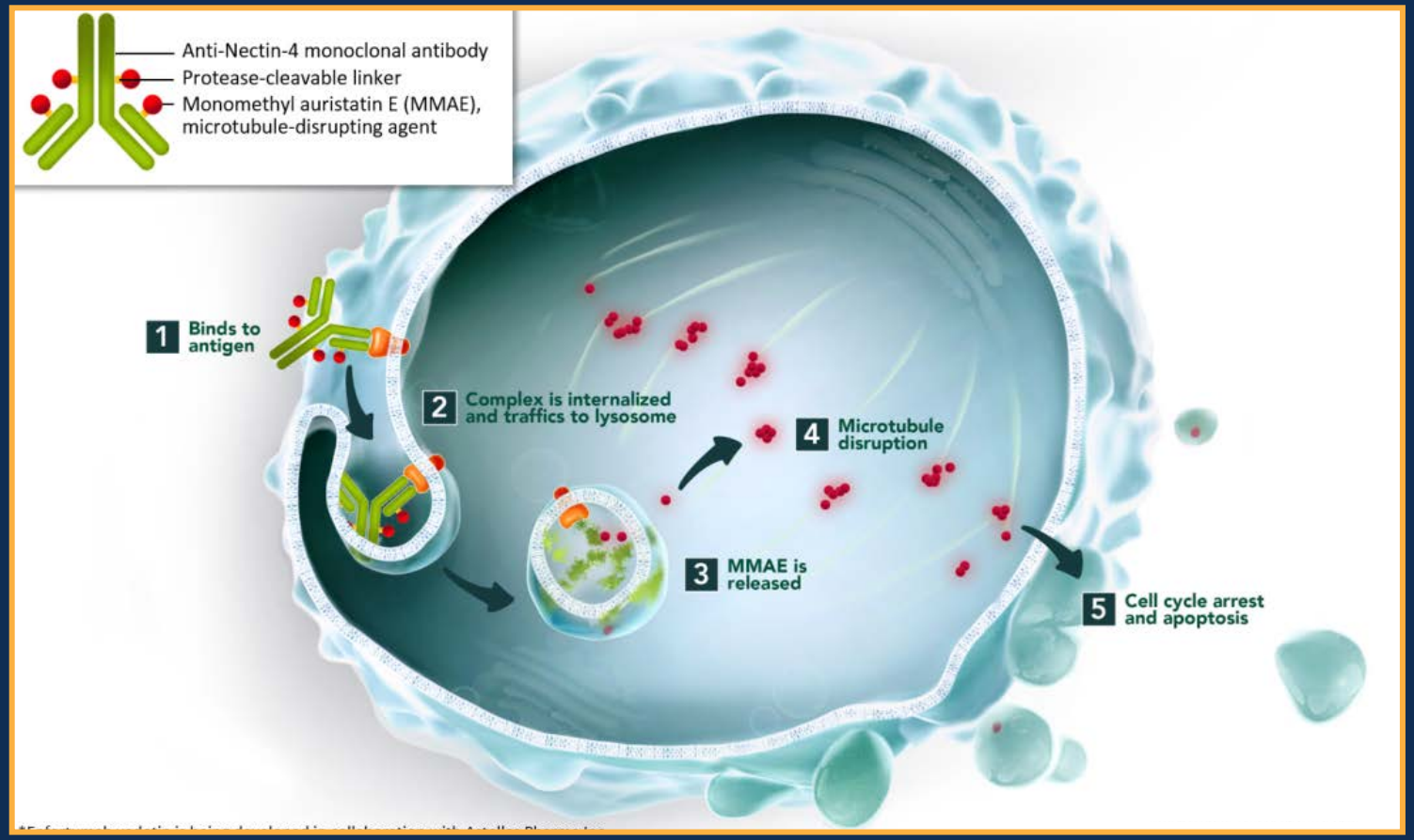
Daniel P. Petrylak, MD
Professor of Medicine and Urology
Director, GU Translational Working Group
Co Director, Cell Signaling Program
Smilow Cancer Center, Yale University

Dr Petrylak — Disclosures

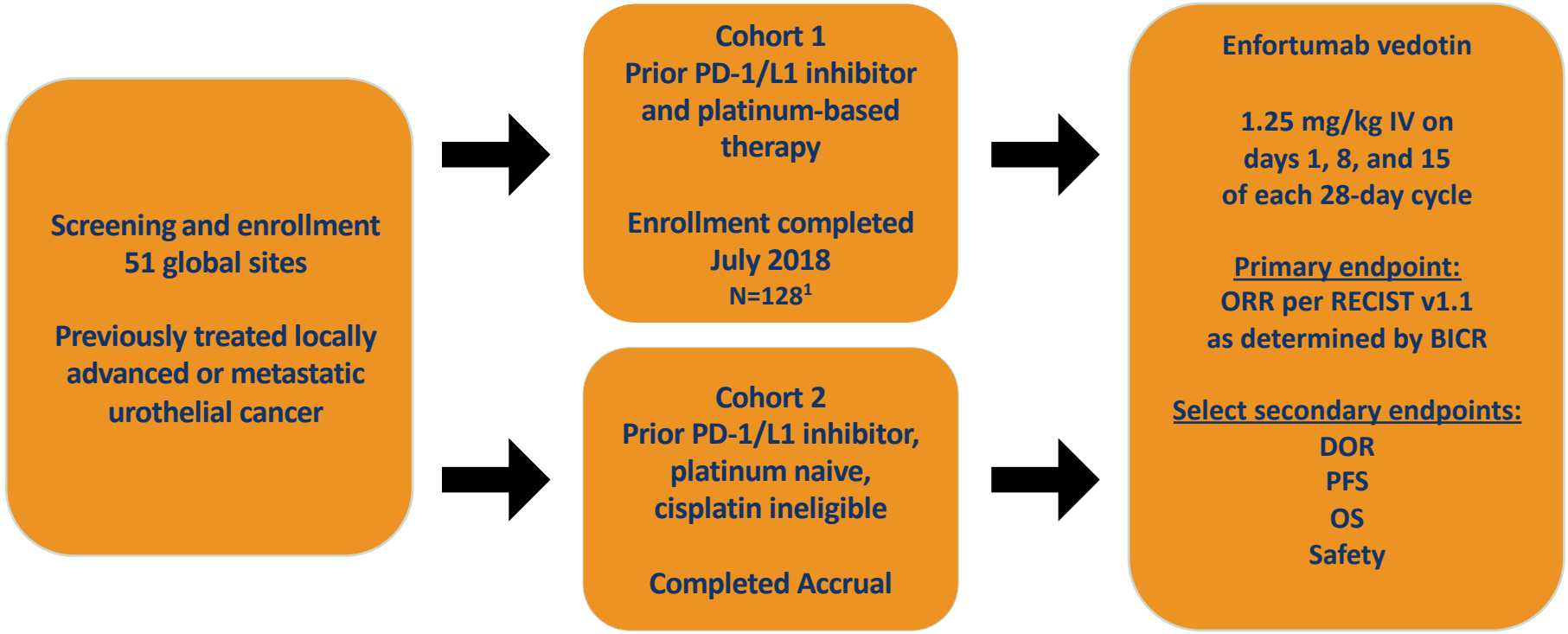
Consulting Agreements	Gilead Sciences Inc, Ipsen Biopharmaceuticals Inc
Contracted Research	Gilead Sciences Inc

RTP
RESEARCH
TO PRACTICE

Enfortumab Vedotin: Proposed Mechanism of Action



EV-201: Single-Arm, Pivotal Phase 2 Trial



[1] 3 patients did not receive enfortumab vedotin treatment: one each due to clinical deterioration, patient decision, and low hemoglobin after enrollment

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Balar AV et al. ASCO GU 2021;Abstract 394.

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

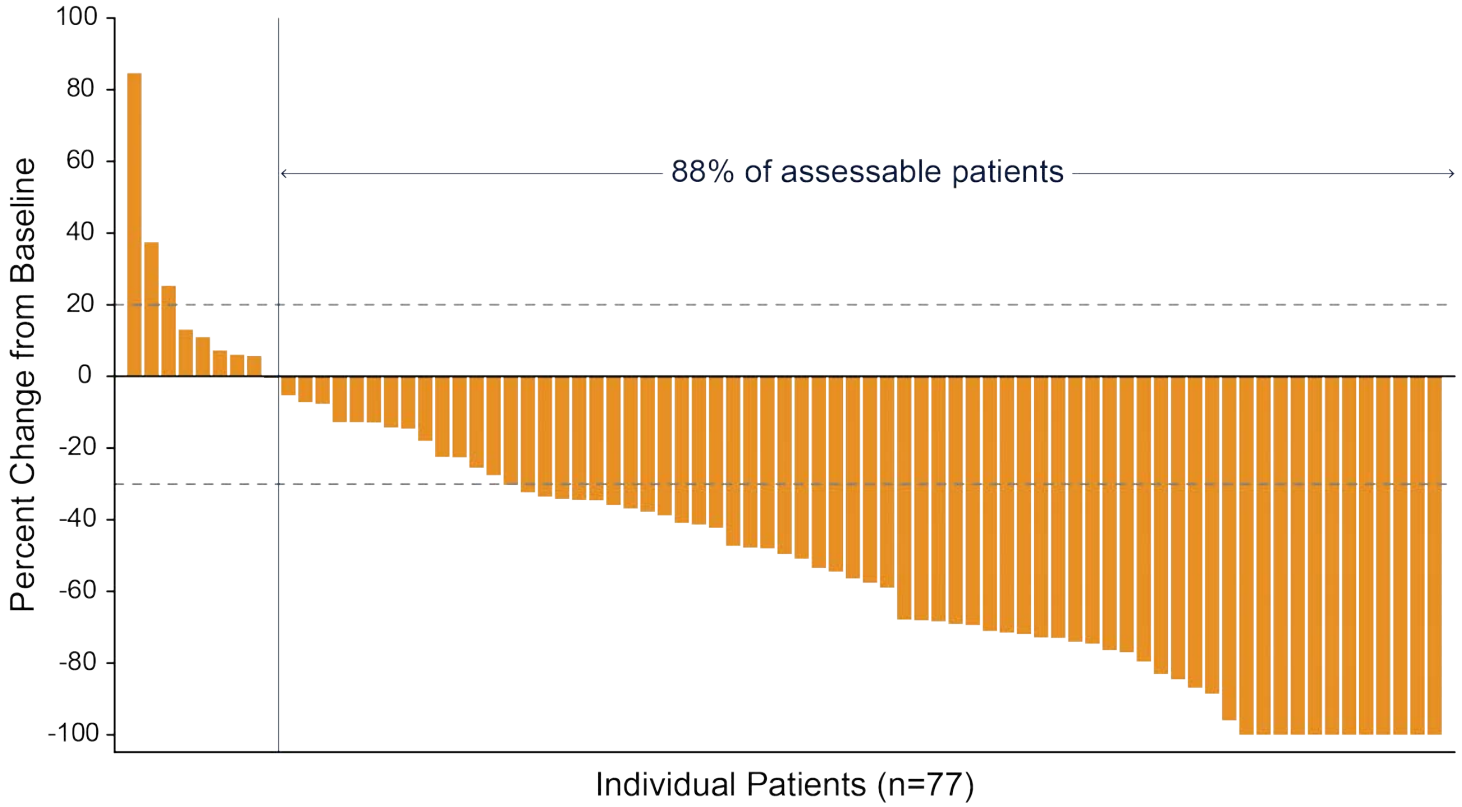
[1]CI = Confidence Interval, Computed using the Clopper-Pearson method

[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.

Balar AV et al. ASCO GU 2021;Abstract 394.

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



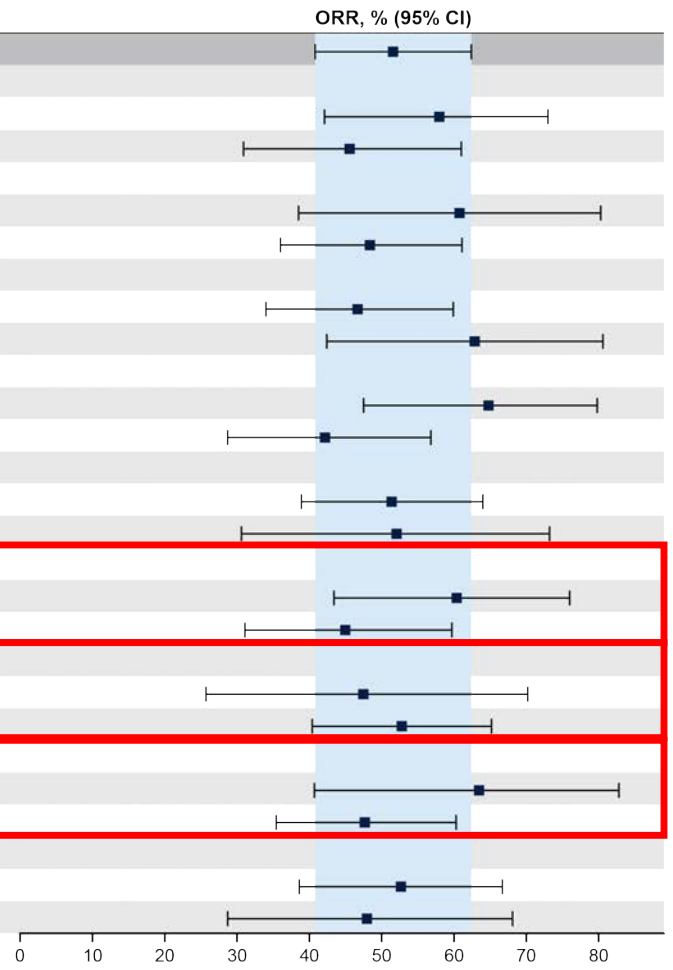
Data are not available for 12 subjects due to no response assessment post-baseline (n=5), incomplete assessment of target lesions post-baseline (n=1), or no measurable disease at baseline per BICR (n=6).

Balar AV et al. ASCO GU 2021;Abstract 394.

EV-201 Cohort 2: Responses by Subgroup per BICR

Subjects (N=89)

Subgroup	n/N	% (95% CI)
Overall	46/89	52 (40.8, 62.4)
Age		
<75 years	25/43	58 (42.1, 73)
≥75 years	21/46	46 (30.9, 61)
Sex		
Female	14/23	61 (38.5, 80.3)
Male	32/66	48 (36, 61.1)
Race		
White	29/62	47 (34, 59.9)
Non-white	17/27	63 (42.4, 80.6)
ECOG PS		
0	24/37	65 (47.5, 79.8)
1–2	22/52	42 (28.7, 56.8)
Bellmunt risk score		
0–1	34/66	52 (38.9, 64)
≥2	12/23	52 (30.6, 73.2)
Primary tumor sites		
Upper tract	23/38	61 (43.4, 76)
Bladder/Other	23/51	45 (31.1, 59.7)
Liver metastasis		
Yes	10/21	48 (25.7, 70.2)
No	36/68	53 (40.4, 65.2)
Best response to prior CPI		
Responder	14/22	64 (40.7, 82.8)
Non-responder	32/67	48 (35.4, 60.3)
PD-L1 expression		
CPS <10	28/53	53 (38.6, 66.7)
CPS ≥10	13/27	48 (28.7, 68.1)



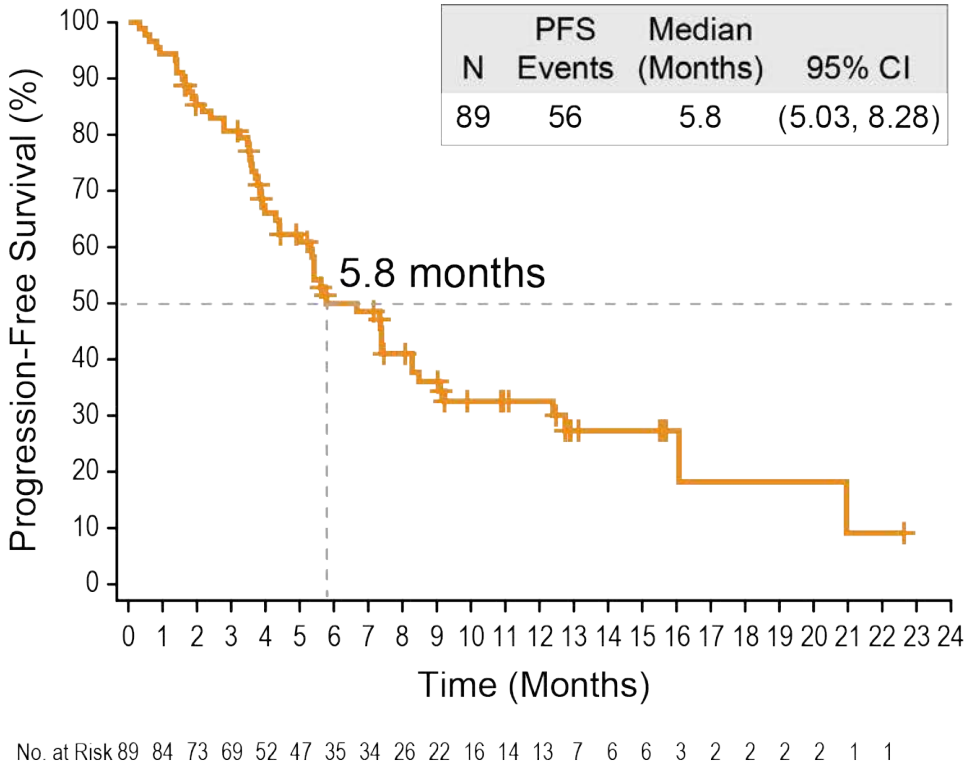
Responses were observed across all subgroups, including patients:

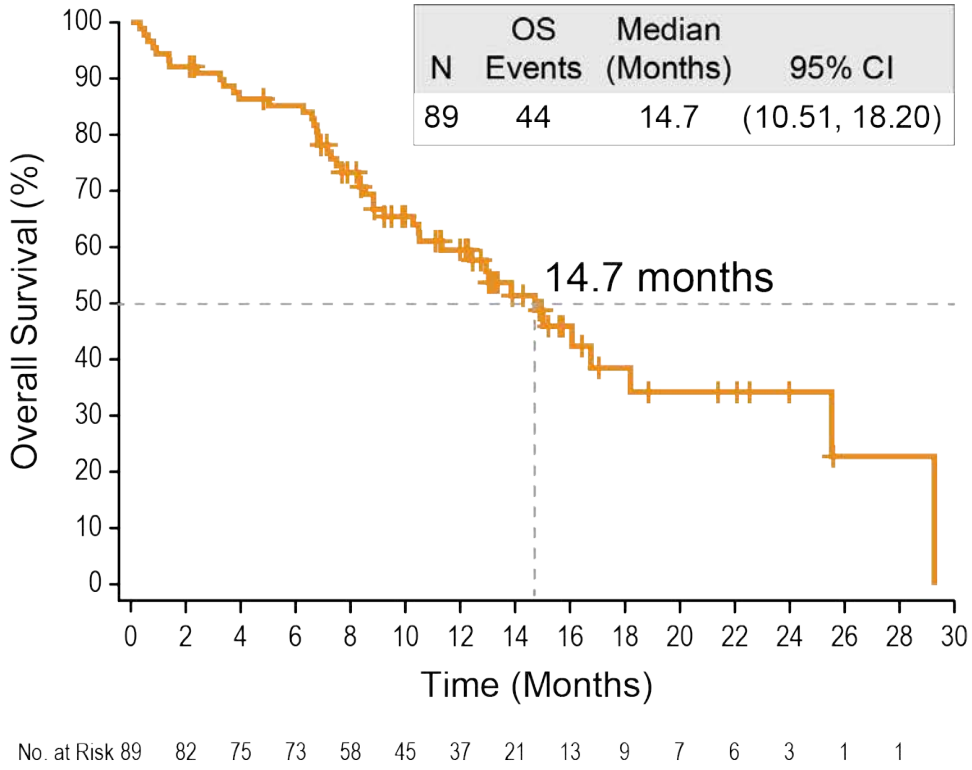
- with primary tumor sites in the upper tract (ORR=61%)
- with liver metastasis (ORR=48%)
- who did not respond to prior PD-1/PD-L1 inhibitors (ORR=48%)

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

Balar AV et al. ASCO GU 2021;Abstract 394.

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





Median follow-up: 13.4 months

Balar AV et al. ASCO GU 2021;Abstract 394.

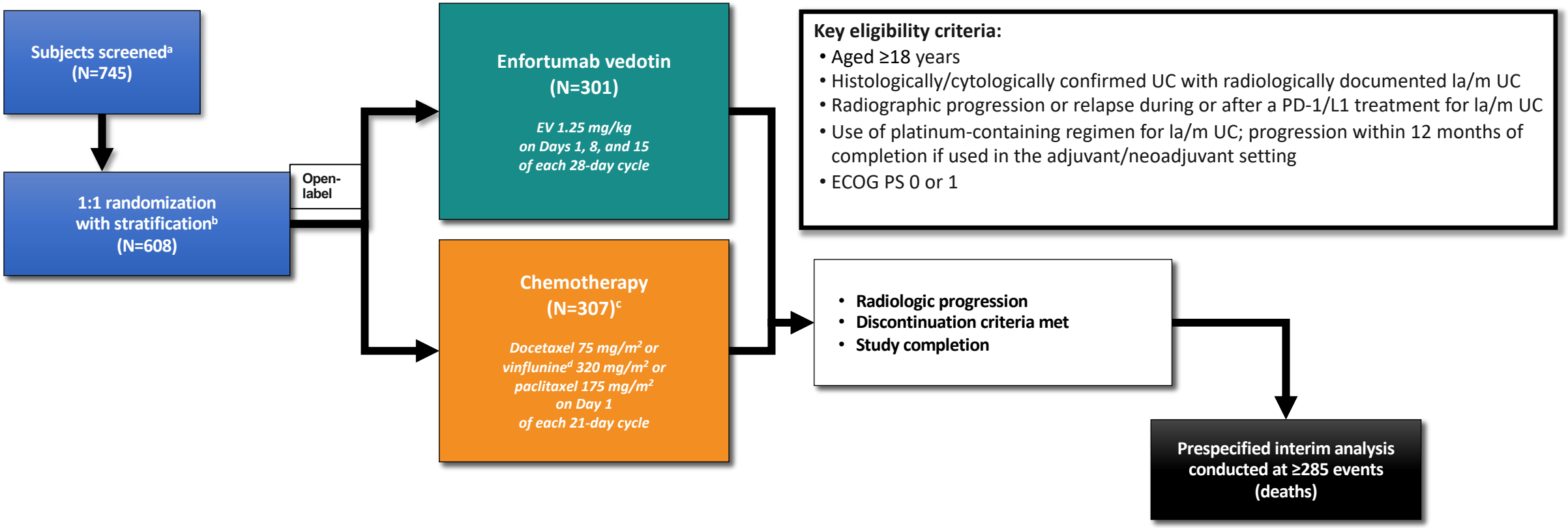
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

Thomas Powles, M.D., Jonathan E. Rosenberg, M.D., Guru P. Sonpavde, M.D., Yohann Loriot, M.D., Ph.D., Ignacio Durán, M.D., Ph.D., Jae-Lyun Lee, M.D., Ph.D., Nobuaki Matsubara, M.D., Christof Vulsteke, M.D., Ph.D., Daniel Castellano, M.D., Chunzhang Wu, Ph.D., Mary Campbell, M.D., Maria Matsangou, M.B., Ch.B., M.D., and Daniel P. Petrylak, M.D.

Methods – EV-301 Phase 3 Trial Design

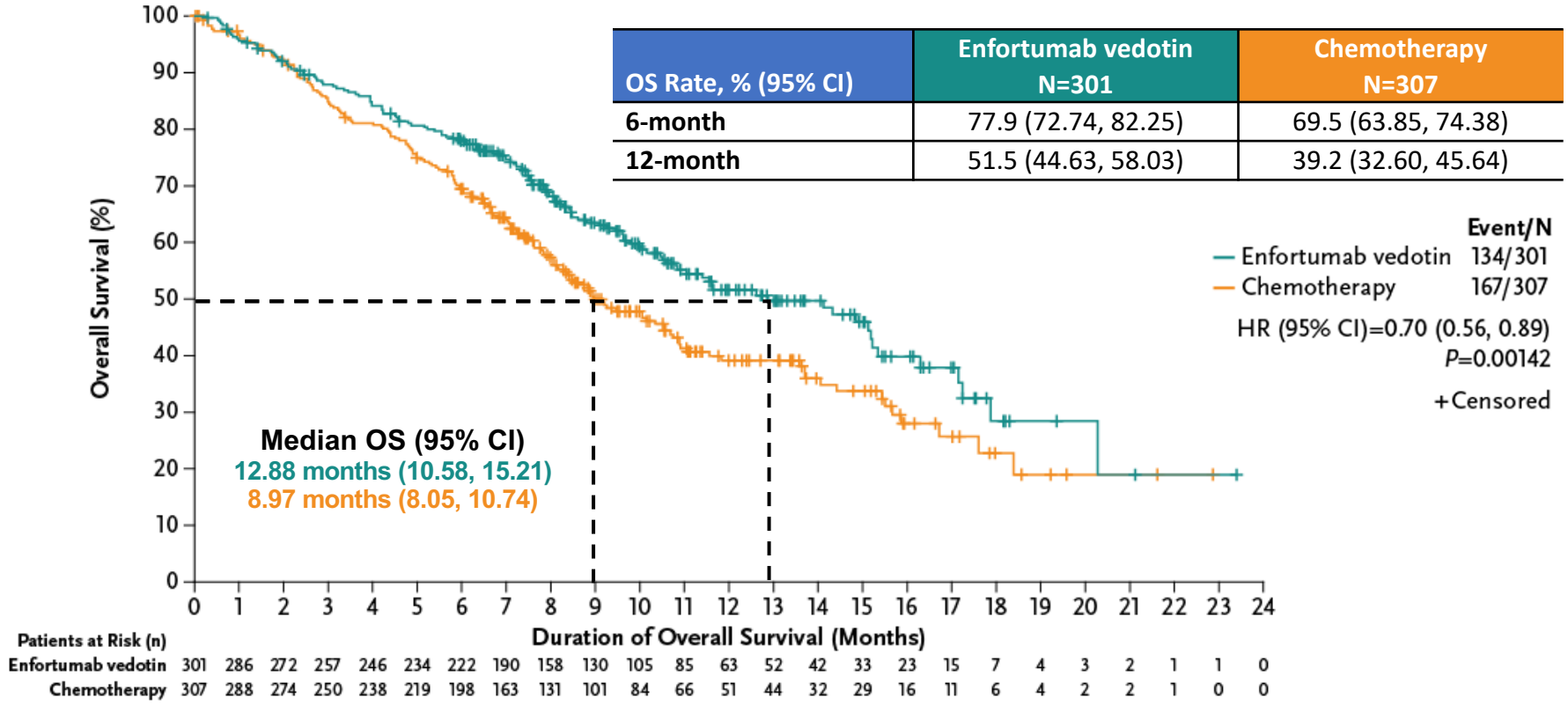


[a]Screening at 185 study centers in North America, Europe, Asia Pacific, and Latin America.
[b]Stratification variables were ECOG performance status (0 or 1), regions of the world (US, western Europe, or rest of world), liver metastasis (yes or no).
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine will be capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; la/m, locally advanced or metastatic; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; UC, urothelial carcinoma.

Powles T et al. N Engl J Med 2021

Overall Survival (Intention-to-Treat Population)

OS Rate, % (95% CI)	Enfortumab vedotin N=301	Chemotherapy N=307
6-month	77.9 (72.74, 82.25)	69.5 (63.85, 74.38)
12-month	51.5 (44.63, 58.03)	39.2 (32.60, 45.64)

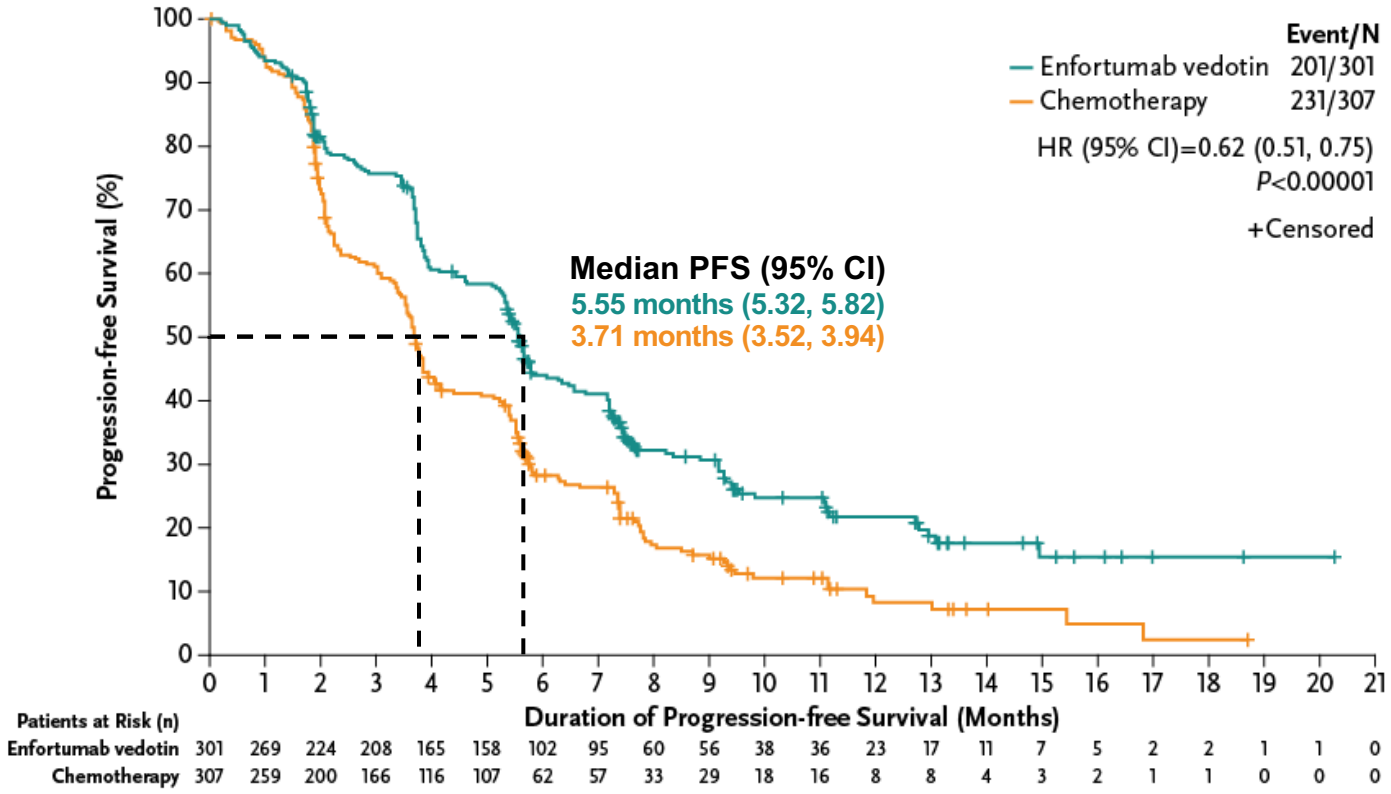


Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off: July 15, 2020

Powles T et al. N Engl J Med 2021

Progression-Free Survival (Intention-to-Treat Population)

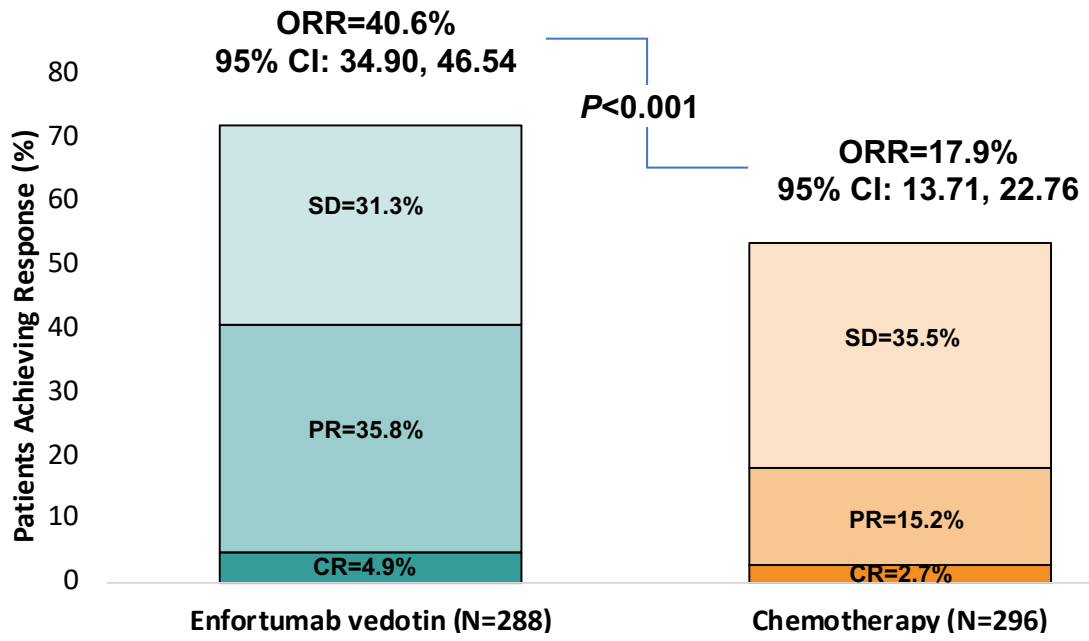


Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Data cut-off: July 15, 2020

Powles T et al. N Engl J Med 2021

Best Overall Response (Response-Evaluable Population)



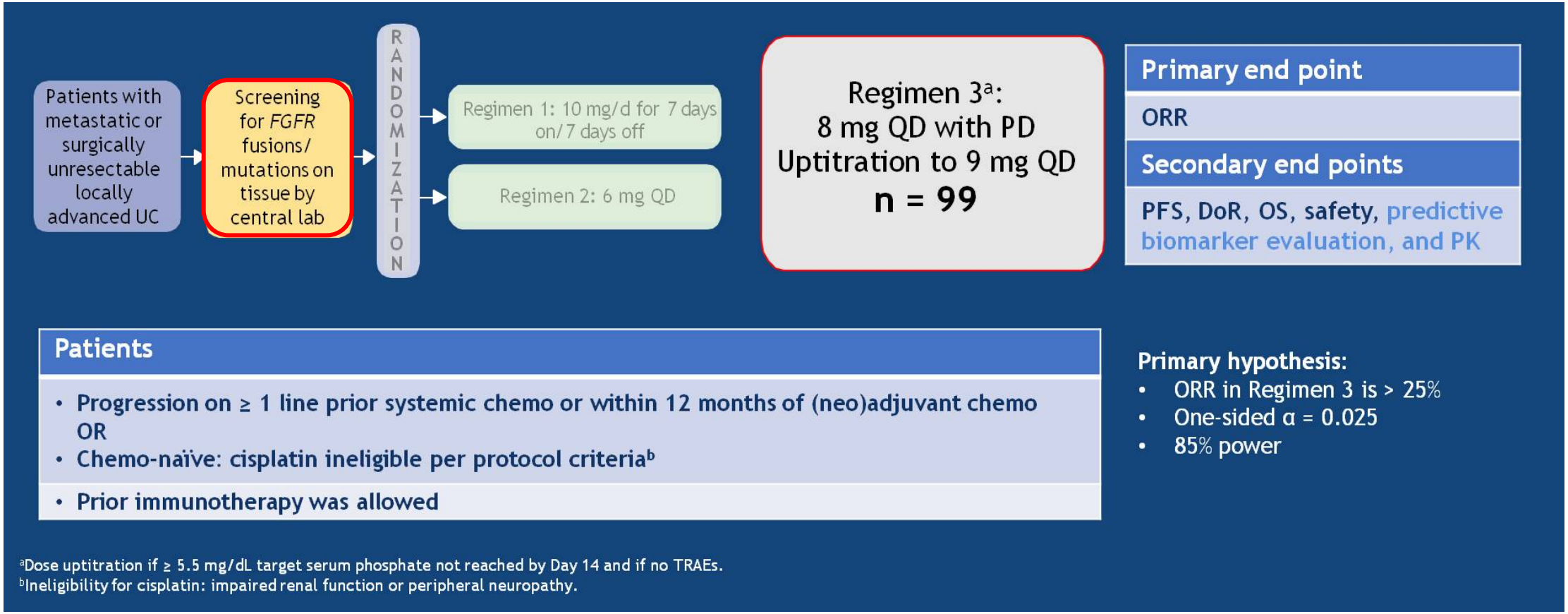
Disease control rate, % (95% CI)	**71.9 (66.30, 76.99)**	**53.4 (47.52, 59.17)**	***P*<0.001**

*Disease control rate is defined as the proportion of patients who had a best overall response of confirmed CR, PR, or SD (at least 7 weeks).
Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

Data cut-off: July 15, 2020

Powles T et al. N Engl J Med 2021

Phase II BLC2001 Study of Erdafitinib: Design



Siefker-Radtke AO, et al. ASCO 2018. Abstract 4503. Siefker-Radtke AO, et al. ASCO 2016. Abstract TPS4575. ClinicalTrials.gov. NCT02365597.

Phase II BLC2001 Study of Erdafitinib: Antitumor Activity

		[95% CI]
Patients, n	99	
Response per investigator assessment[a,b], n (%)		
ORR	**40 (40.4)**	[30.7-50.1]
Complete response	3 (3.0)	
Partial response	37 (37.4)	
Stable disease	39 (39.4)	
Progressive disease	18 (18.2)	
Median time to response	1.4 months	
Median duration of response	5.6 months	[4.2-7.2]
ORR among patient subgroups, n (%)		
Chemo-naïve vs progressed/relapsed after chemo	5/12 (41.7) vs 35/87 (40.2)	
With vs without visceral metastases	30/78 (38.5) vs 10/21 (47.6)	

[a]Confirmed with second scan at least 6 weeks following the initial observation of response.
[b]Response in 2 patients was unknown.

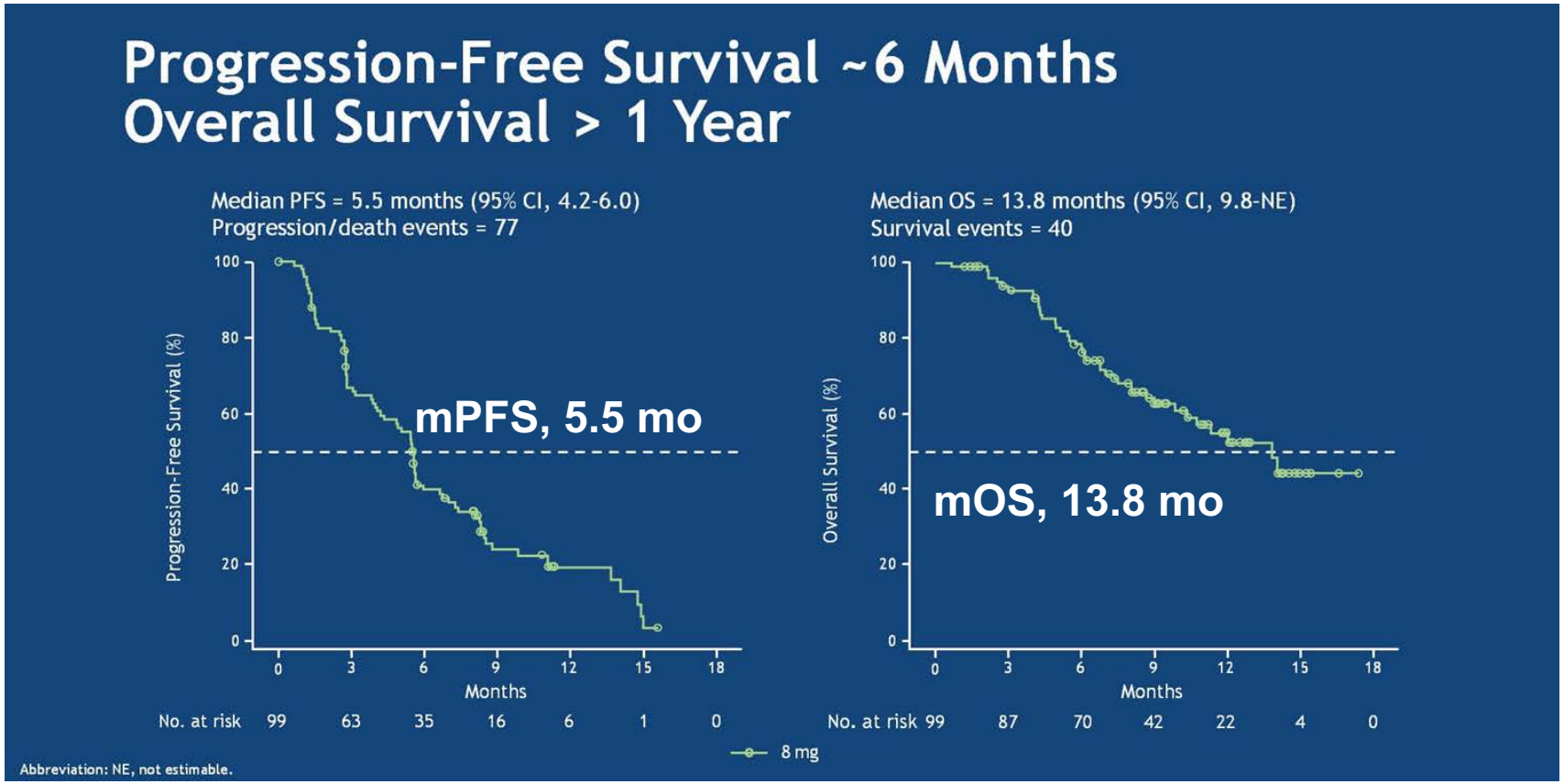
Prior IO ORR, 59%

ORR to Prior IO, 5%

Siefker-Radtke AO, et al. ASCO 2018. Abstract 4503.

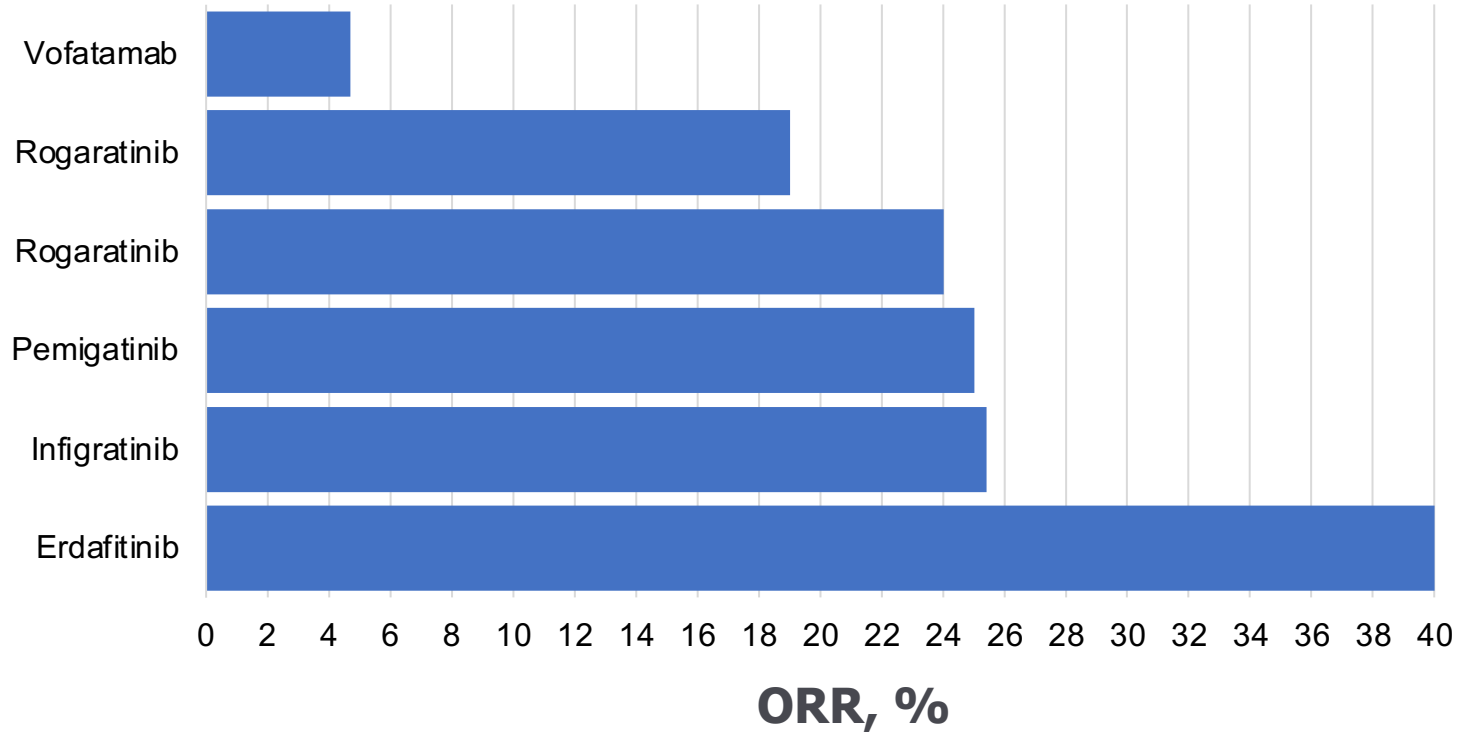
Phase II BLC2001 Study of Erdafitinib: Survival

- At follow-up of 11 mos, 21.2% of patients remained on erdafitinib



Siefker-Radtke AO, et al. ASCO 2018. Abstract 4503.

Response Rates with FGFR Inhibitors in **Urothelial Cancer**

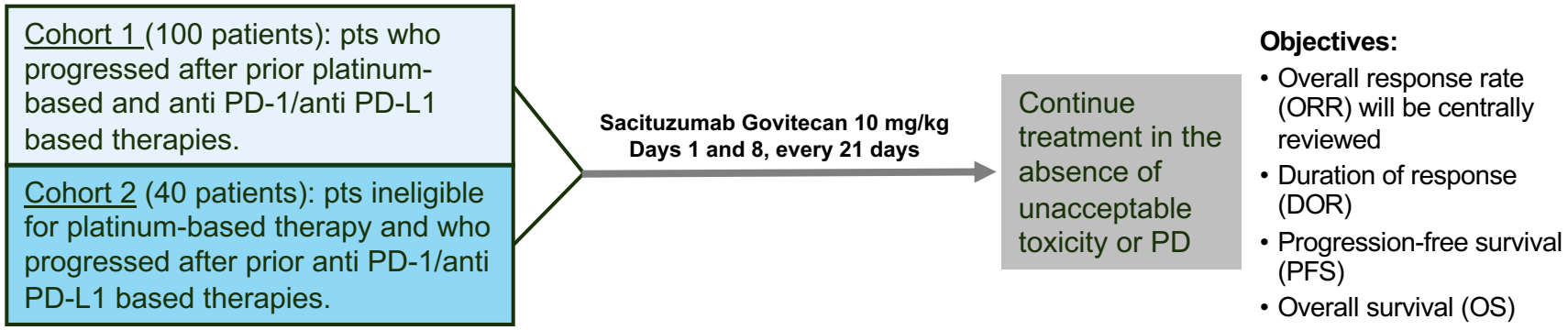


1. Necchi A et al. *J Clin Oncol*. 2019;37(7 suppl)409-409. 2. Quinn DI et al. *J Clin Oncol.* 2020;38(6 suppl):489. 3. Kempf E et al. *J Clin Oncol.* 2020;38(6 suppl):527.
4. Necchi A et al. *Ann Oncol.* 2018;29(suppl 8):900P. 5. Pal SK et al. *Cancer Discov.* 2018;8:812-821. 6. Loriot Y et al. *N Engl J Med.* 2019;381:338-348.

TROPHY-U-01 (IMMU-132-06) Study

A Phase II Open Label Study of IMMU-132 in Metastatic Urothelial Cancer After Failure of Platinum-based Regimen or Anti-PD-1/ PD-L1 Based Immunotherapy

- Results from the Study-01 basket trial warranted further investigation in a dedicated phase 2 trial.
- TROPHY-U-01 (NCT03547973) is an international, single-arm, open-label, phase 2 trial evaluating the antitumor activity and safety of sacituzumab govitecan in 140 pts with advanced UC.



NCT Trial Number: 03547973

PD-1, programmed cell death-1; PD-L1, programmed death ligand-1.

TROPHY-U-01 Cohort 1: Response Assessments[a]

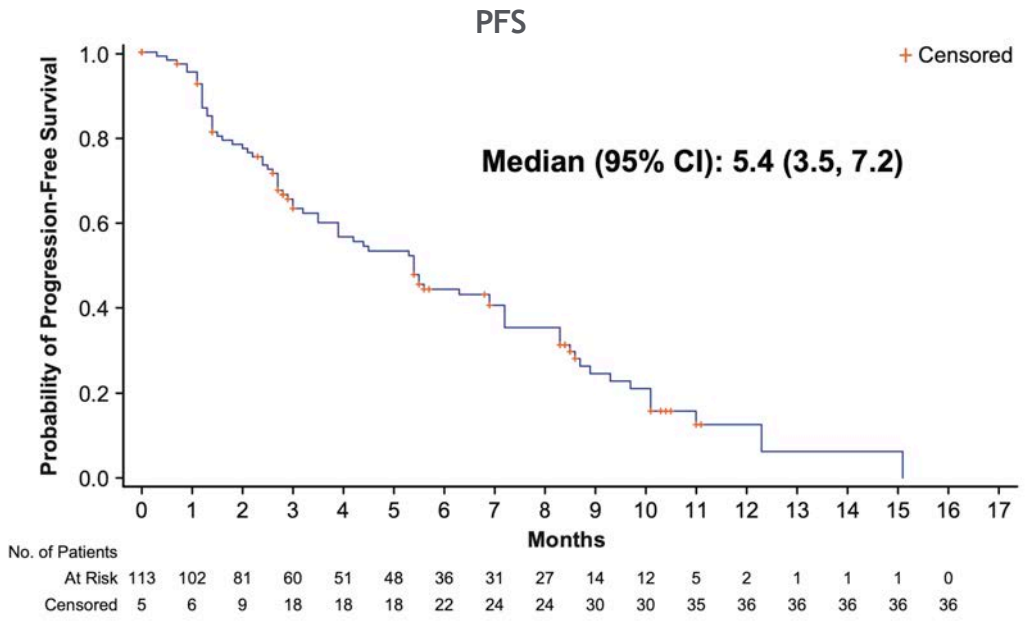
- ORR and mDOR values were consistent with investigator assessments

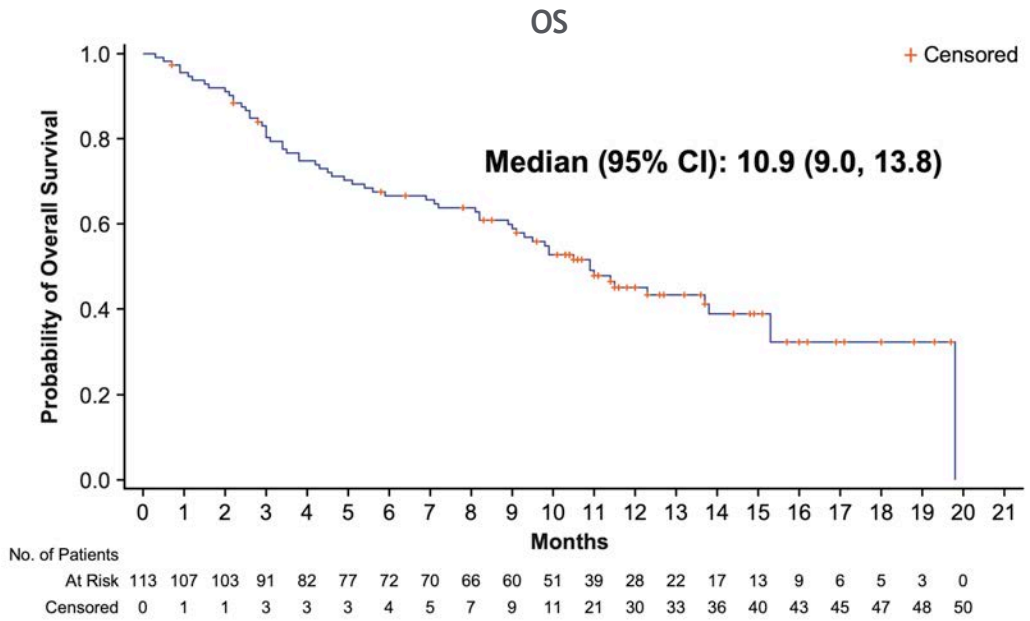
	Sacituzumab Govitecan (n=113)
Overall Response Rate	
ORR, n (%) [95% CI]	31 (27.4) [19.5, 36.6]
CR, n (%) PR, n (%)	6 (5.3) 25 (22.1)
Response duration	
mDOR, months 95% CI Range	7.2 4.7-8.6 1.4-13.7

Subjects with visceral metastasis involving the liver had an ORR of 31.6% compared with 25.3% in those without liver involvement

[a] Assessments were per blinded independent review assessment, RECIST v1.1.
CR, complete response; mDOR, median duration of response; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
Tagawa ST, et al. TROPHY-U-01: A Phase 2 Open-label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-based Chemotherapy and Checkpoint Inhibitors. *J Clin Oncol*. 2021. In press.

TROPHY-U-01 Cohort 1: Survival Outcomes[a]





OS, overall survival; PFS, progression-free survival.

[a] Median follow-up time was 6.3 months, defined as time from informed consent date to death date, end of study date or data cutoff date, whichever occurs first.

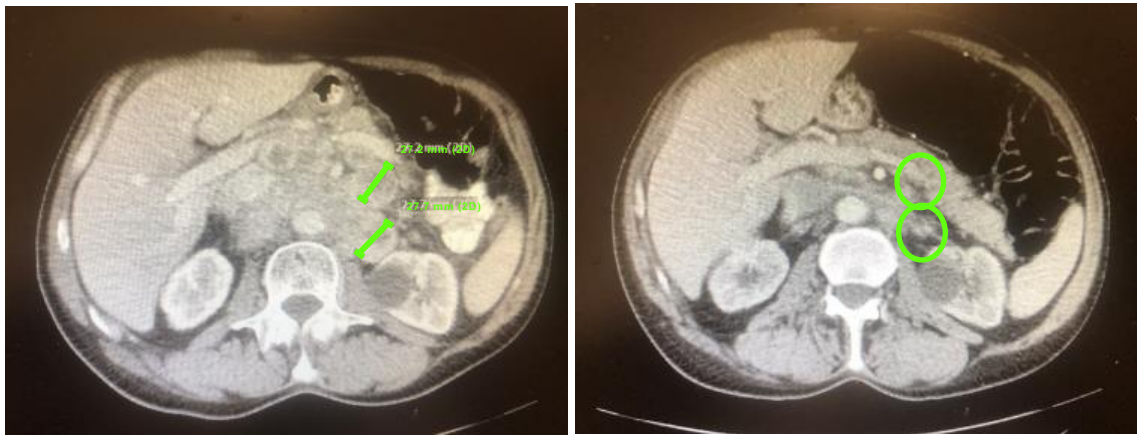
Orange hash marks indicate data censoring.

Tagawa ST, et al. TROPHY-U-01: A Phase 2 Open-label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-based Chemotherapy and Checkpoint Inhibitors. *J Clin Oncol*. 2021. In press.

Case: Retroperitoneal Lymph Node Metastasis

- 61 year-old male with past medical history of G1 neuropathy and RLE edema, with target lesions consisting of periportal, retroperitoneal, and mesenteric adenopathy
- Refractory to adjuvant tx: Cisplatin/gemcitabine
- Prior metastatic regimens:
  - Atezolizumab (24 mon)
  - Enfortumab vedotin (8 mon)
  - Pemetrexed (3 mon)
- **Confirmation of PR after cycle 4 with SG treatment[a]**
  - **No worsening of neuropathy reported**
  - **Significant reduction in lower extremity edema**
  - **On treatment for 7 mon and ongoing at time of data cut-off**

Images provided by Daniel P. Petrylak from the Yale School of Medicine, New Haven, CT



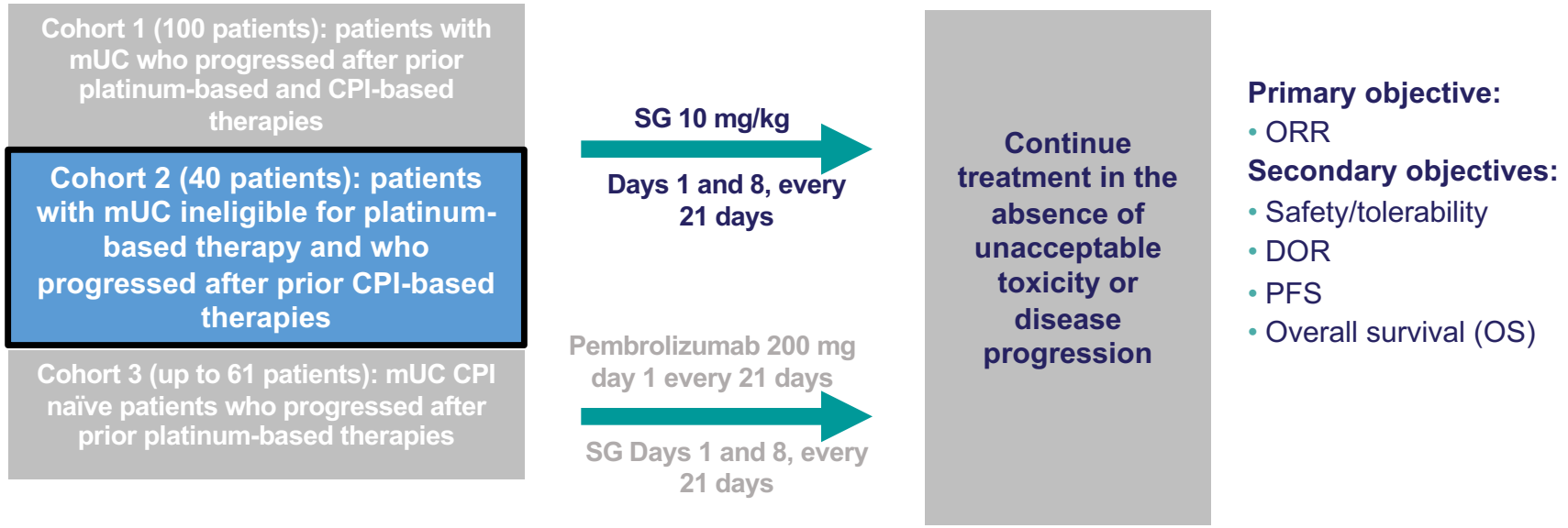
Baseline CT

Follow-up CT
(after 10 cycles of SG)

70% reduction of target lesions

[a]Assessed by investigator using RECISTv1.1.
CT, computed tomography; G1, grade 1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; RLE, right leg extremity; SG, sacituzumab govitecan.

Figure 3. TROPHY-U-01: Phase II trial of SG in stage IV urothelial cancer after failure of a platinum-based regimen and/or anti-PD-1/PD-L1-based therapies



CPI therapy (includes anti-PD-1/anti-PD-L1–based therapies).
CPI, checkpoint inhibitor; DOR, duration of response; mUC, metastatic urothelial cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973; IMMU-132-06 study.

Petrylak DP et al. ASCO 2020;Abstract 5027

Exposure and Response Outcomes

- Median treatment cycles (range): 5 (1-15)
- Median duration of treatment (range): 4.5 months (0.3 – 15.6)
- Median dose intensity: 92%

- At a median follow-up of 6.8 months, ORR was 29% (6/21) with 6 confirmed PRs

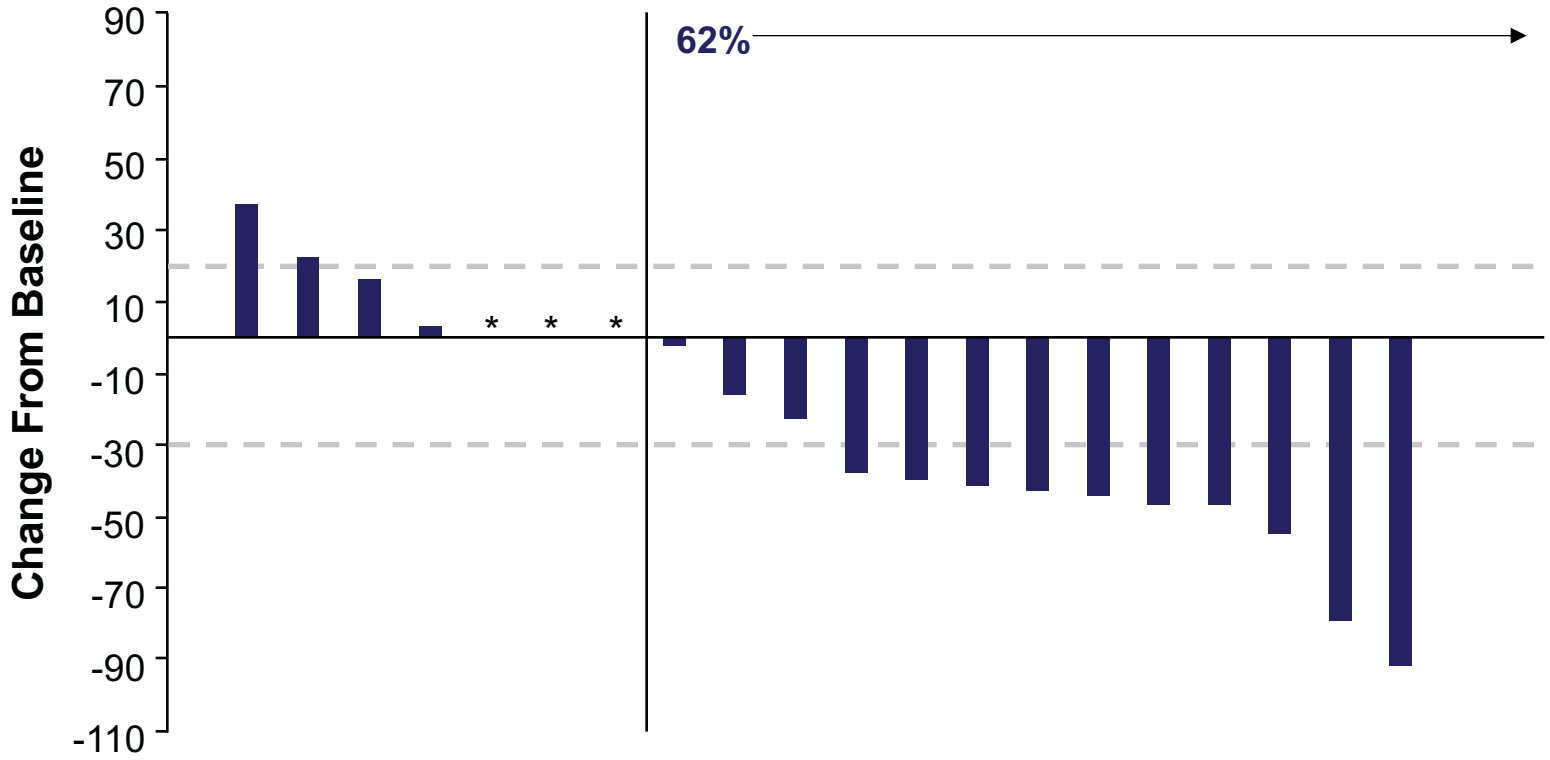
Response Outcomes

Endpoint	N=21
Median (range) follow-up, mon	6.8 (1.6–18.9)
Patients continuing treatment, n (%)	9 (43)
ORR, n (%) [95% CI]	6 (29) [12–54]
CR, n (%)	0 (0)
PR, n (%)	6 (29)
SD, n (%)	10 (48)
Median TTR, (range), mon	1.3 (1.1–1.5)
CBR, n (%) [95% CI]	7 (33) [15–59]
Median DOR (95% CI), mon	NR (4.3–NR)

CBR, clinical benefit rate defined as CR + uCR + PR + uPR or (SD >= 6 months); CI, confidence interval; DOR, duration of response; mon, month; NR, not reached; ORR, objective response; PR, partial response; SD, stable disease; TTR, time to response

Petrylak DP et al. ASCO 2020;Abstract 5027

62% (13/21) of Patients Demonstrated a Reduction in Tumor Size

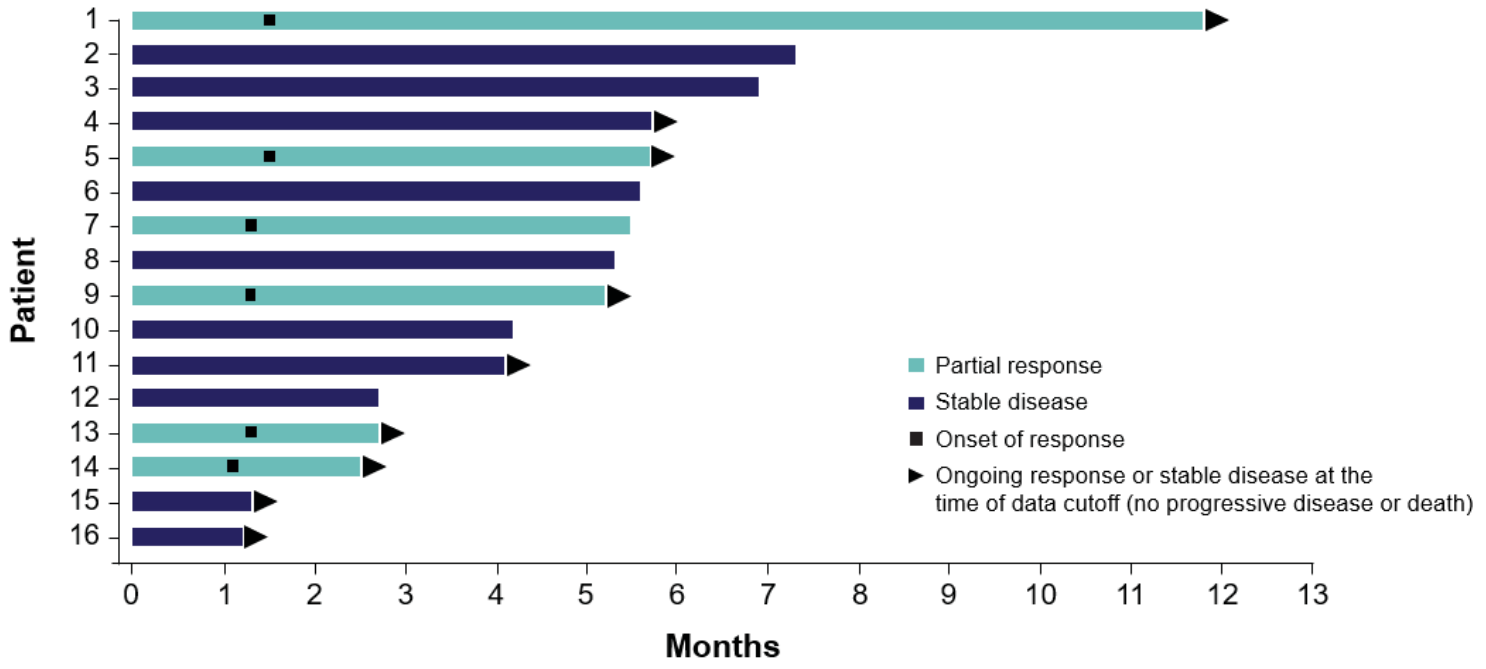


*Denotes patients who had a 0% change from baseline in tumor size.
One patient had only screening data and thus is not represented.

Petrylak DP et al. ASCO 2020;Abstract 5027

Duration of Response (Local Assessment)

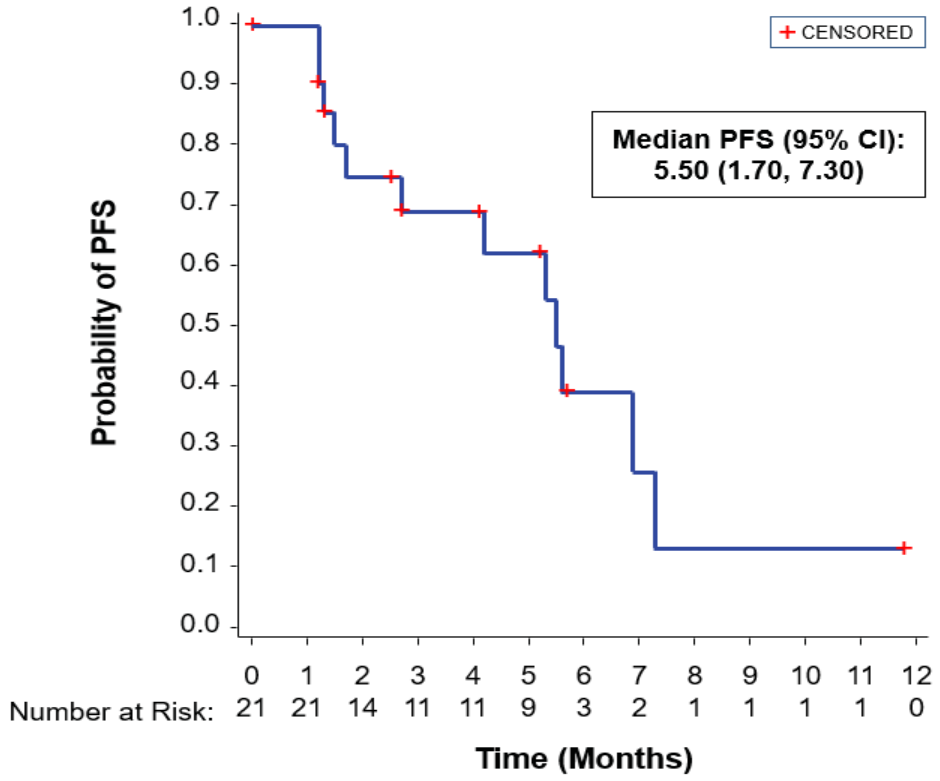
- Median DOR not reached
- The DOR of responders ranged from 1.4+ to 10.4+ months, with 3 of 6 responders having a duration of ≥4 months
- Five of 6 responders have an ongoing response

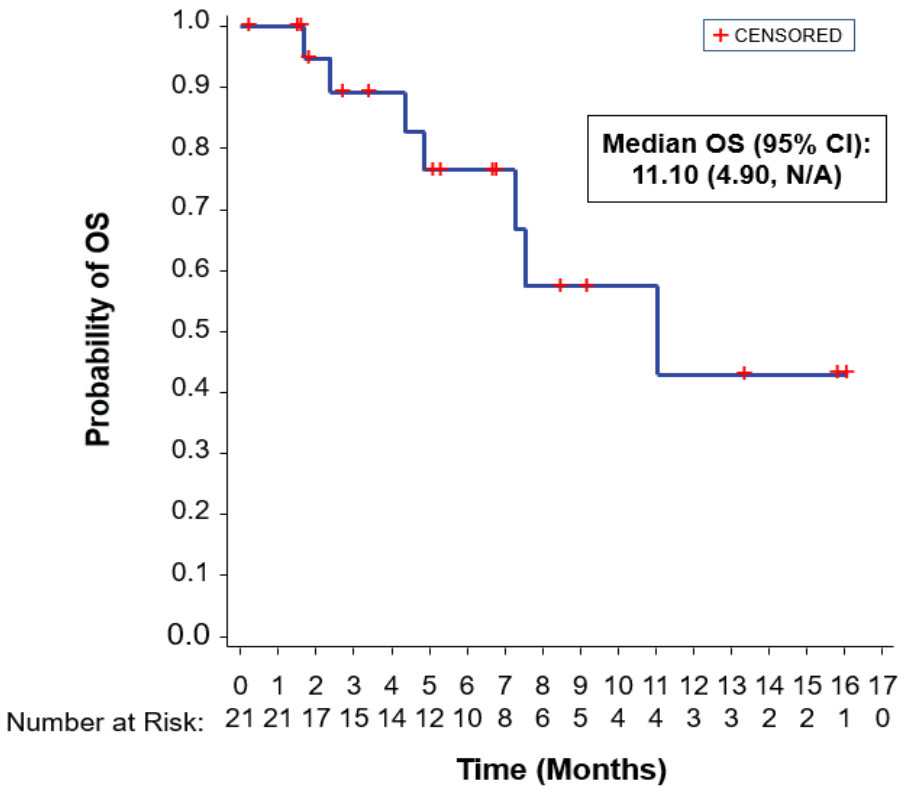


DOR, duration of response.

Petrylak DP et al. ASCO 2020;Abstract 5027

Survival Outcomes

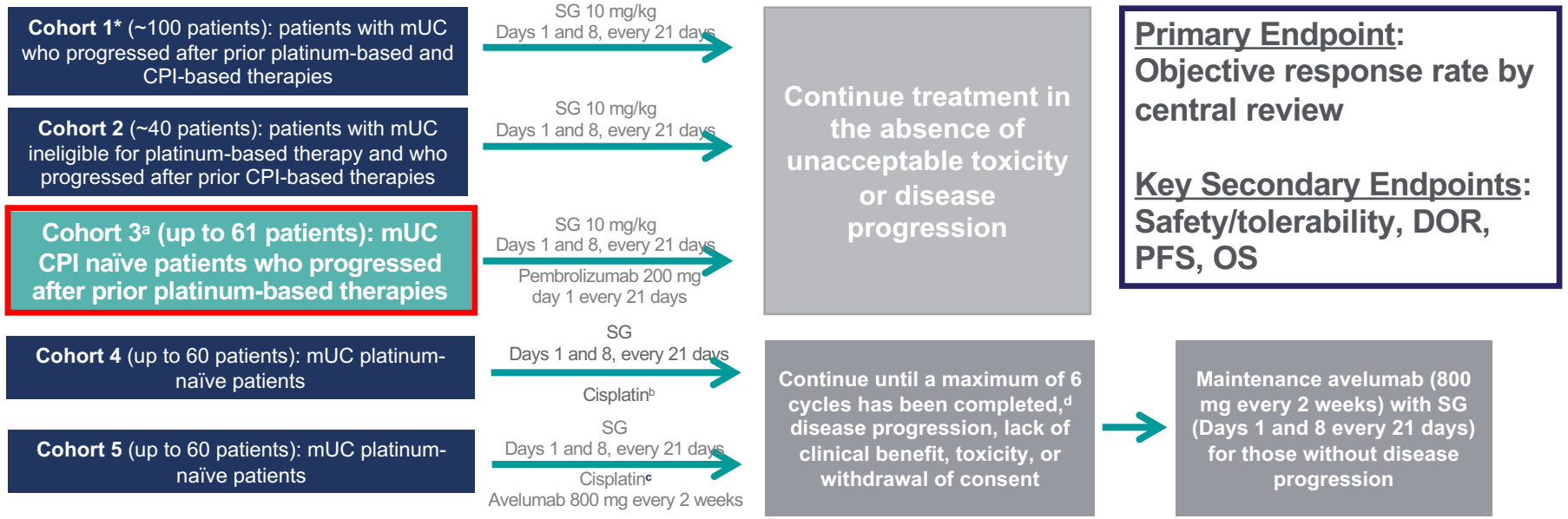




- At this early follow-up, the median PFS and OS compare favorably to current standards of care for platinum-ineligible patients with mUC who have progressed after CPI therapy
- The OS rate (95% CI) at 6 months and 12 months was: 76.4% (48.4–90.5) and 43.0% (13.1–70.4), respectively

Petrylak DP et al. ASCO 2020;Abstract 5027

TROPHY-U-01 Is a Registrational, Open-Label, Multicohort Phase 2 Trial in Patients With mUC



Key Inclusion Criteria: Age ≥18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥30 mL/min,[b,c] adequate hepatic function
Key Exclusion Criteria: Immunodeficiency, active Hepatitis B or C, active secondary malignancy, or active brain metastases

***Accelerated FDA approval for treatment of patients with locally advanced or mUC who previously received platinum-containing chemotherapy and PD-1/L1 inhibitor[1]**

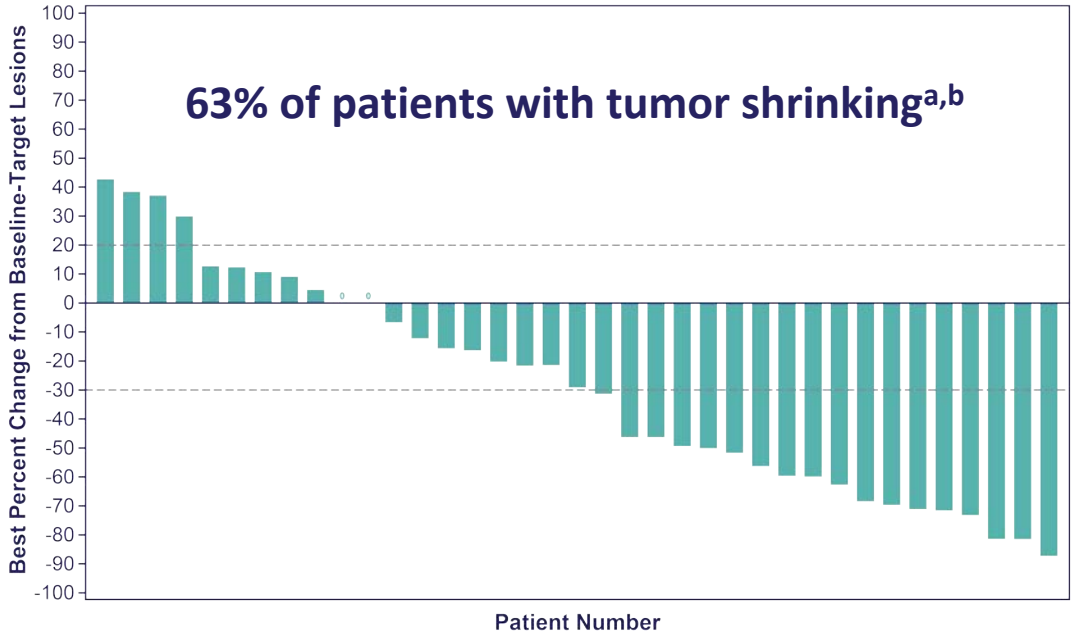
[a]Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. [b]In patients with CrCl ≥60 mL/min; [c]In patients with creatinine clearance 50–60 mL/min. [d]For patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 2 weeks beginning cycle 1, day 1 and every 2 weeks thereafter) followed by SG on days 1 and 8 every 21 days.
CBR, clinical benefit rate; CPI, checkpoint inhibitor; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.

1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

Grivas P et al. ASCO GU 2022;Abstract 434.

Overall Response and Best % Change From Baseline in Tumor Size

- **Median follow-up: 5.8 months (data cutoff date: 2021-09-24)**
- **Median time to response: 2 months (1.3–2.8; n=14)**
- **Median DOR not yet reached: N/A (2.80-N/A)**
- **Median PFS (95% CI), 5.5 months (1.7–NR); median OS, not reached**

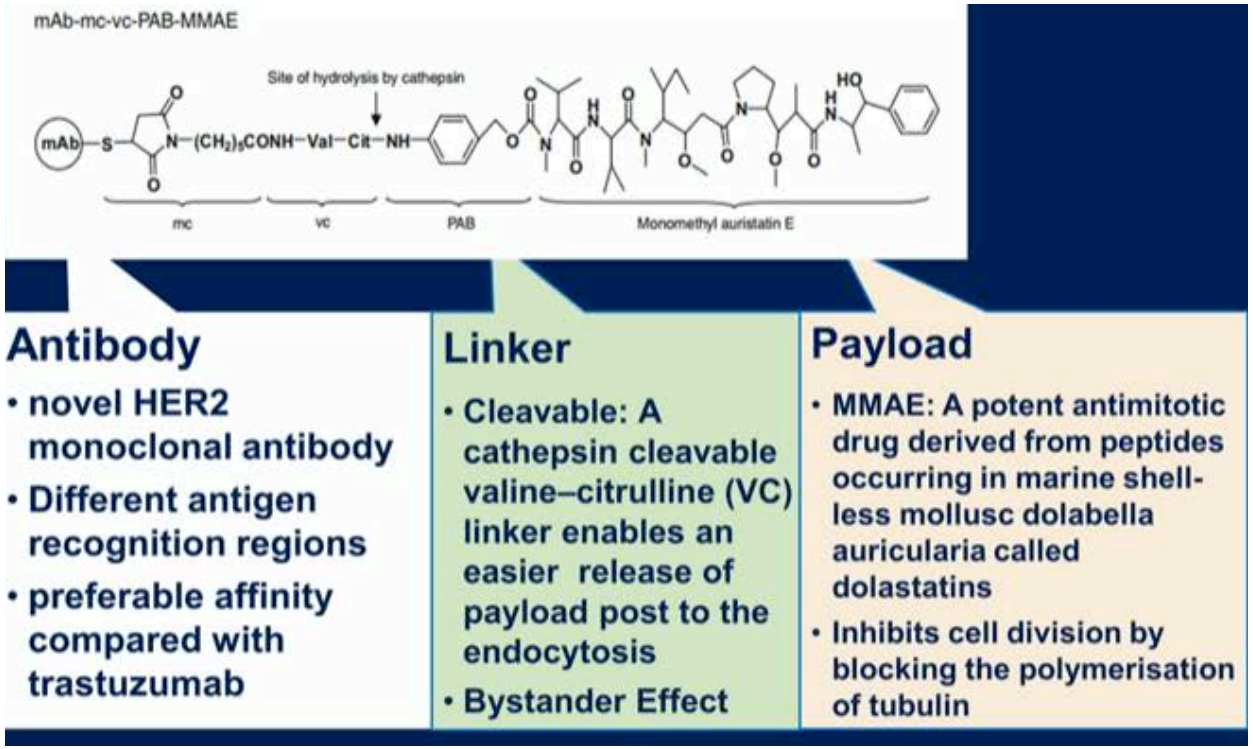


[a]Responses assessed by investigator in the intent-to-treat population. [b]Patients without post-baseline assessments are not shown here.
CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

	Cohort 3[a] (N=41)
Objective response rate (CR + PR), n (%) [95%CI]	**14 (34) [20.1-50.6]**
Objective response rate (CR + PR), evaluable patients, n (%)	14 (38)
Best overall response, n (%)	
CR	1 (2)
PR	13 (32)
SD	11 (27)
SD ≥ 6 months	*4 (10)*
PD	12 (29)
Not assessed	4 (10)
Clinical Benefit Rate (CR + PR + SD), n (%) [95%CI]	25 (61) [44.5-75.8]

Grivas P et al. ASCO GU 2022;Abstract 434.

Disitamab Vedotin for Patients with HER2-Overexpressing mUBC



- 43 HER2^{+} (IHC status 3+ or 2+) locally advanced or mUC who previously failed at least one line of systemic chemotherapy
- ORR=51.2%
- The median PFS and OS were 6.9 months (95% CI, 5.6–8.9) and 13.9 months (95% CI, 9.1–NE)
- The most common treatment-related adverse events (TRAE) were hypoesthesia (60.5%), alopecia (55.8%), and leukopenia (55.8%)

Wang J et al. ASCO 2021;Abstract 1022. Xinan Sheng et al. Clin Cancer Res 2021;27:43-51

ASCO Genitourinary Cancers Symposium

Primary Analysis From DS8201-A-U105: A Phase 1b, 2-Part, Open-Label Study of Trastuzumab Deruxtecan (T-DXd) With Nivolumab in Patients With HER2-Expressing Urothelial Carcinoma (UC)

Matthew D. Galsky, Gianluca Del Conte, Silvia Foti, Evan Y. Yu, Jean-Pascal H. Machiels, Bernard Doger, Andrea Necchi, Filippo G. De Braud, Erika P. Hamilton, Audrey Hennequin, Tom Van den Mooter, Philip R. Debruyne, Irene Moreno, Hendrik-Tobias Arkenau, Zenta Tsuchihashi, Fu-Chih Cheng, Bincy Augustine, Ben Cheng, Daniel Barrios, Diana Lüftner

Matthew D. Galsky, MD
Icahn School of Medicine at Mount Sinai, New York, NY

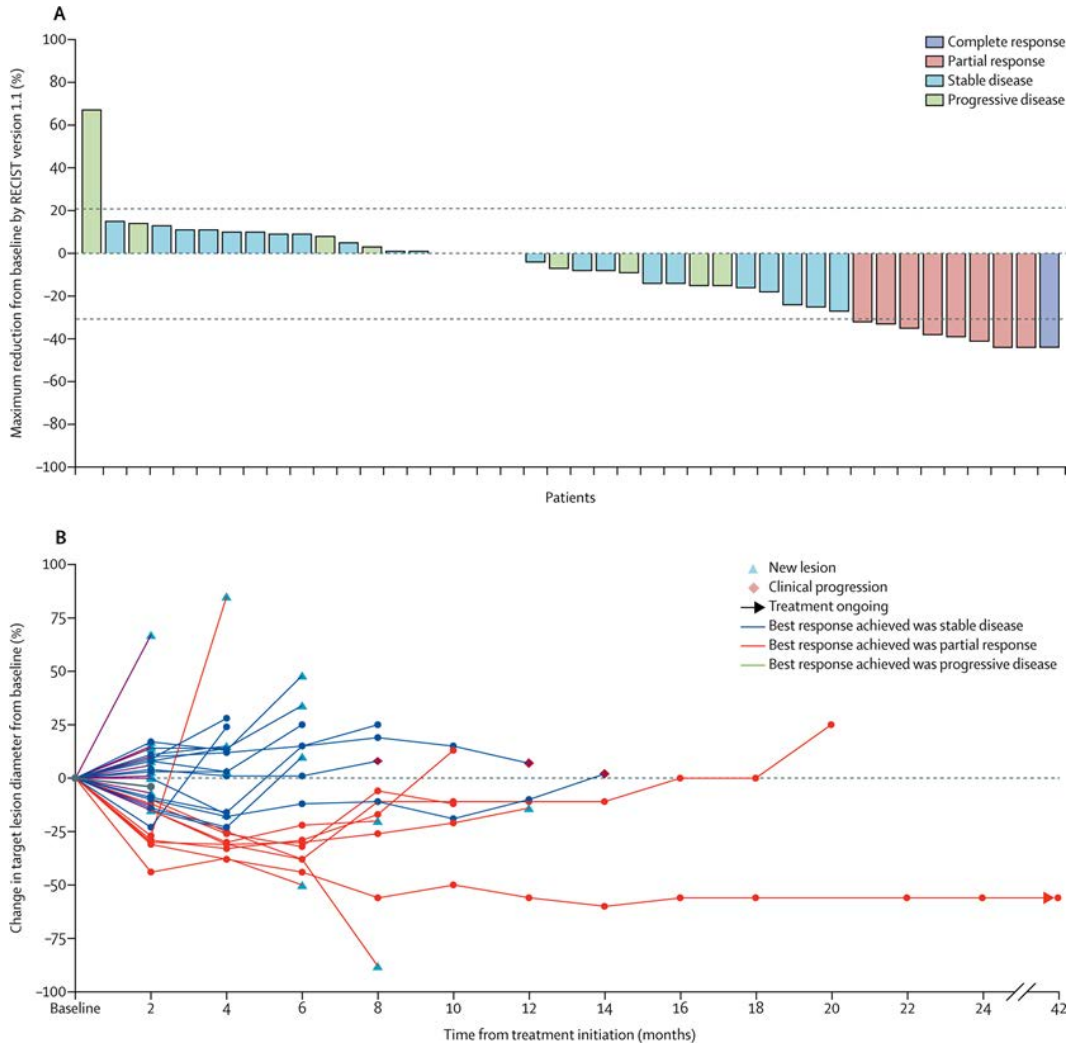
Summary of Efficacy Results in UC Cohorts

	Cohort 3 HER2 IHC 3+/2+ n = 30
Confirmed ORR by ICR (ORR, CR + PR)	
n (%)	**11 (36.7)**
95% CI	(19.9-56.1)
Best overall response, n (%)	
CR	4 (13.3)
PR	7 (23.3)
SD	12 (40.0)
PD	5 (16.7)
NE[a]	2 (6.7)
DOR, median (95% CI), months	13.1 (4.1-NE)
PFS, median (95% CI), months	6.9 (2.7-14.4)
TTR, median (95% CI), months	1.9 (1.2-6.9)
OS, median (95% CI), months	11.0 (7.2-NE)
Treatment duration, median (range), months	
T-DXd	3.9 (1-21)
Nivolumab	4.1 (1-20)

- Data cutoff: July 22, 2021
- In cohort 3:
  - HER2 IHC 3+: 62.5% (5/8) patients had a confirmed objective response, including 2 CR (25%)
  - HER2 IHC 2+: 27.3% (6/22) patients had a confirmed objective response, including 2 CR (9.1%)
- In cohort 4 (HER2 IHC 1+)[b]:
  - 2 patients had a PR
  - 1 patient had SD
  - 1 patient had PD

CR, complete response; DOR, duration of response; ICR, independent central review; NE, nonevaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.
[a]Patients were missing postbaseline scans.
[b]For cohort 4, efficacy endpoints are not summarized because of the small sample size (n = 4).

Cabozantinib in Platinum Refractory Metastatic Urothelial Cancer



ORR=19%

Lancet Oncol 2020;21: 1099–109

Conclusions: Treatment of Metastatic Urothelial Cancer

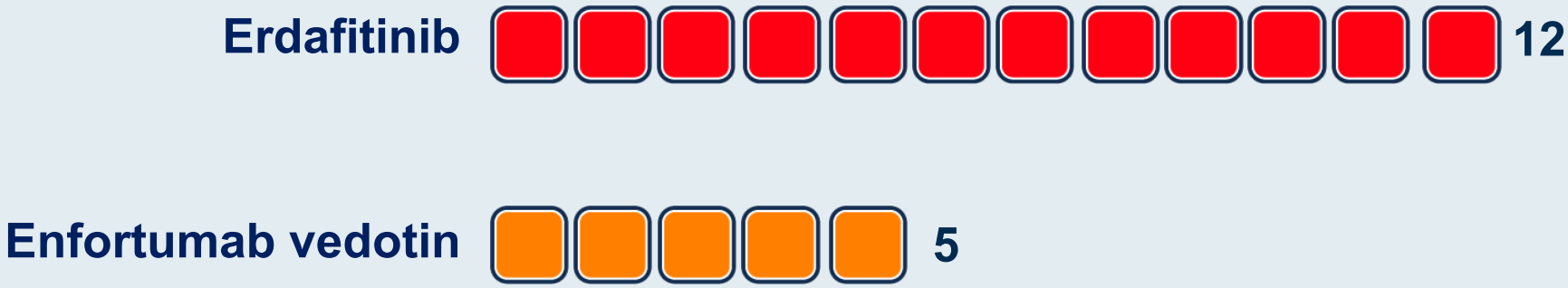
- Enfortumab Vedotin is FDA approved as third line therapy in patients who have progressed on chemotherapy and checkpoint inhibition therapy
- Enfortumab Vedotin has accelerated approval in patients who are cisplatin ineligible and have progressed on 1 prior treatment
- Sacituzumab Govetecan (phase 2) is FDA approved and has promising activity in patients who have failed 2 or more prior therapies
- Studies are evaluating the combination of checkpoint inhibition with targeted therapies
- All metastatic urothelial cancer patients should be checked for FGF-R3 mutations; erdafitinib had a 40% response rate in this patient population

Clinical Investigator Survey Results

What would you generally recommend as second-line therapy for a 65-year-old patient with FGFR wild-type UBC metastatic to the liver whose disease progresses on first-line cisplatin/gemcitabine followed by avelumab maintenance?

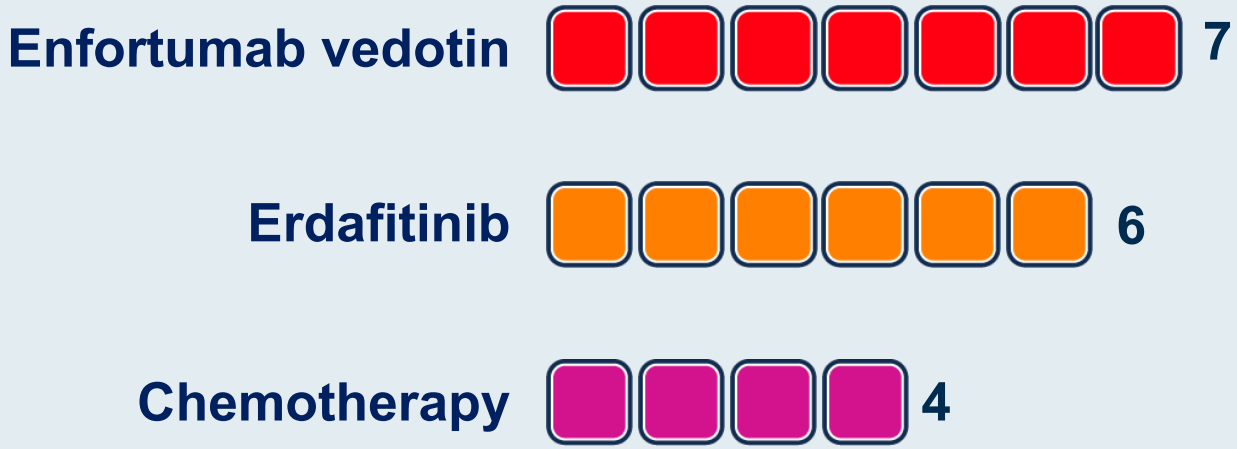
Survey of genitourinary cancer clinical investigators

What would you generally recommend as second-line therapy for a 65-year-old patient with FGFR3 mutation-positive UBC metastatic to the liver whose disease progresses on first-line cisplatin/gemcitabine followed by avelumab maintenance?



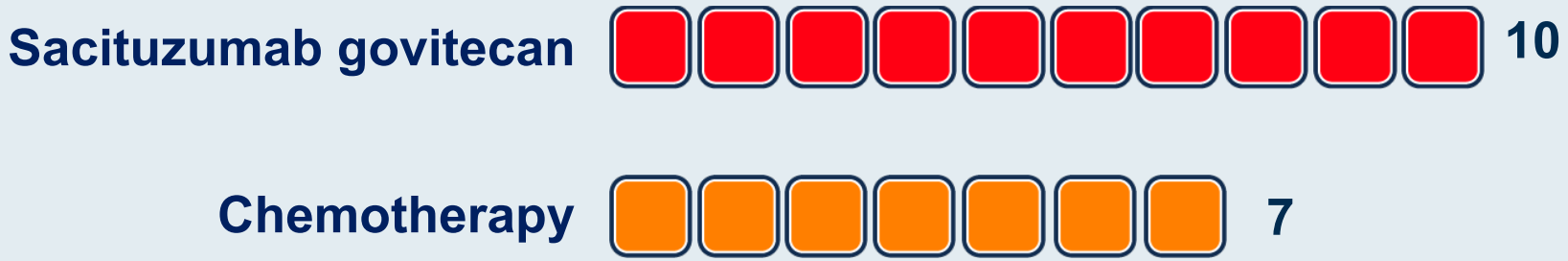
Survey of genitourinary cancer clinical investigators

What would you generally recommend as second-line therapy for an 80-year-old patient with FGFR3 mutation-positive UBC metastatic to the liver whose disease progresses on first-line pembrolizumab?



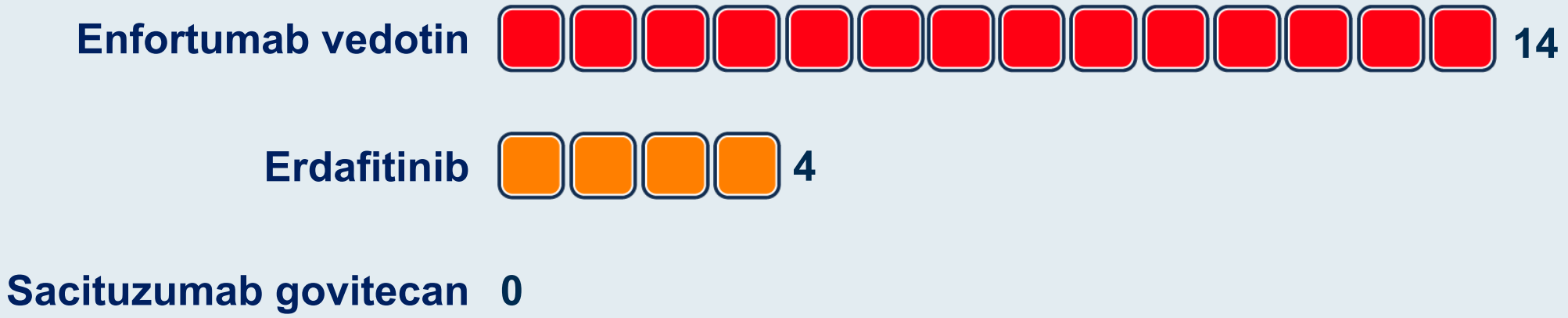
Survey of genitourinary cancer clinical investigators

What would you generally recommend as third-line therapy for an 80-year-old patient with FGFR wild-type metastatic UBC whose disease has progressed on first-line pembrolizumab and second-line enfortumab vedotin?



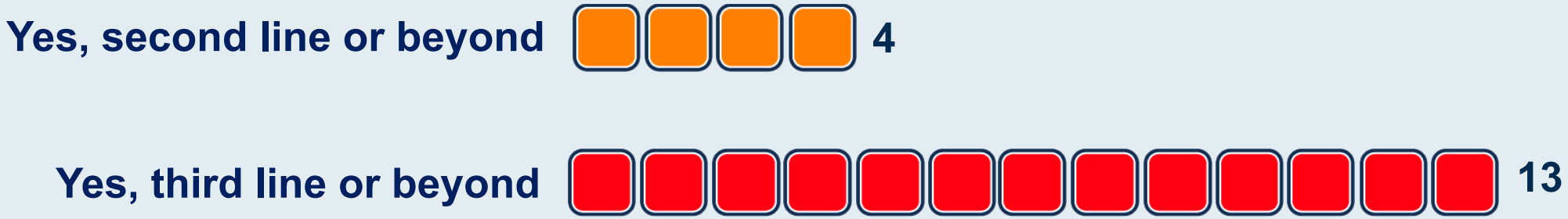
Survey of genitourinary cancer clinical investigators

Which of the following would you generally recommend first for a patient with metastatic UBC who is eligible to receive all 3 agents?



Survey of genitourinary cancer clinical investigators

If disitamab vedotin were available for patients with HER2-positive metastatic UBC, would you use it?



Survey of genitourinary cancer clinical investigators

MODULE 4: Tolerability/Toxicity of Novel Treatment Strategies and Practical Considerations in the Management of UBC — Dr Sonpavde

RTP
RESEARCH
TO PRACTICE

Toxicities of Novel Treatment Strategies and Practical Considerations in the Management of Urothelial Carcinoma

Guru Sonpavde, MD
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, MA

Dr Sonpavde — Disclosures

Advisory Committee	Astellas, AstraZeneca Pharmaceuticals LP, Bicycle Therapeutics, Bristol-Myers Squibb Company, EMD Serono Inc, Exelixis Inc, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Immunomedics Inc, Infinity Pharmaceuticals Inc, Janssen Biotech Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Pfizer Inc, Sanofi Genzyme, Scholar Rock, Seagen Inc
Consulting Agreements (Paid)	AstraZeneca Pharmaceuticals LP, Debiopharm, EMD Serono Inc
Consulting Agreements (Unpaid)	Bavarian Nordic, Bristol-Myers Squibb Company, G1 Therapeutics Inc, QED Therapeutics, Seagen Inc
Travel Cost	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company
Writing/Editor Fees	Elsevier Practice Update Bladder Cancer Center of Excellence

Urothelial Carcinoma Therapy: *metastatic disease*

Dramatic advances in therapeutic landscape

Treatment	First-line	Second-line	Post-platinum & PD1/L1	Late salvage
Cisplatin-eligible	GC/(dd)-MVAC→ Avelumab	Post-platinum •Pembrolizumab (or nivolumab or avelumab) •Erdafitinib (FGFR2/3) •EV (cis-ineligible) Post-PD1/L1 inhibitor •Gem-Carbo* •EV (cis-ineligible)	•EV •SG •Erdafitinib (FGFR2/3)	•Taxane •Vinflunine
Cisplatin-ineligible	•Gem-Carbo* →Avelumab •Atezolizumab if PD-L1+			
Platinum-ineligible	•Pembrolizumab •Atezolizumab			

*Split dose weekly cisplatin + gemcitabine reasonable alternative to gem-carbo in selected patients with CrCl ≥40 ml/min (no Phase III data)

EV: Enfortumab Vedotin, **SG**: Sacituzumab Govitecan

Urothelial Carcinoma Therapy: *Peri-operative disease*

Adjuvant nivolumab added to therapeutic armamentarium

Setting	Cisplatin-eligibility	Therapy
Neoadjuvant	Cisplatin-eligible	•GC x 4 •ddMVAC x 4 •MVAC x 3
	Cisplatin-ineligible	•Surgery
Adjuvant	Cisplatin-eligible, no prior NAC (if ≥ypT3 or N+)	•GC x 4 •ddMVAC x 4 •MVAC x 3
	Cisplatin-eligible, prior NAC	•Nivolumab x 1 year (if ≥ypT2 or N+)
	Cisplatin-ineligible (no NAC)	•Nivolumab x 1 year (if ≥ypT3 or N+) •Gem-Carbo x 4 (Only if upper tract ≥ypT2/N+)

Immune related adverse events from ICIs

Any organ (patient education, vigilance, high index of suspicion, collaboration with specialties)-common (fatigue) or rare unpredictable symptoms (visual)-prevent pregnancy

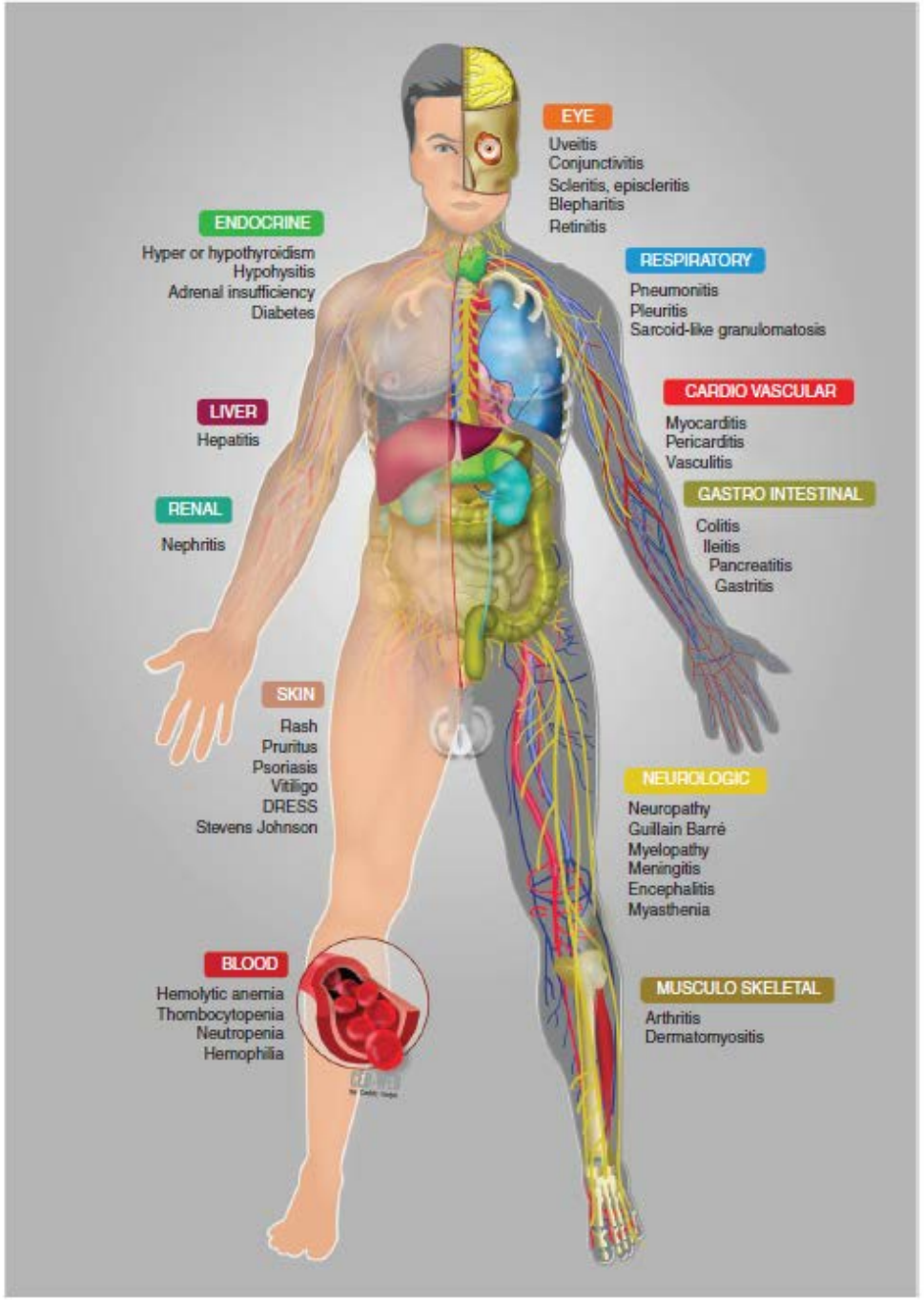
Severe irAEs in 10-15% with PD1/L1 inhibitor monotherapy (PD1 > PD-L1), and 30-60% of combination PD1/L1 + CTLA4 inhibitors

Life-threatening if not promptly and appropriately managed.

irAEs can affect >1 organ system (pneumonitis-NSCLC↑; dermatitis- melanoma↑)

Median time to onset 2-3 months, can occur early and even years after discontinuing the ICI

Infusion reactions with avelumab ~20% (needs premedication with diphenhydramine, acetaminophen for first 4 infusions)



Champiat S, et al. Ann Oncol 27: 559–574, 2016

Laboratory monitoring of patients on ICI

Laboratory	Baseline	Every cycle	Every 6-12 weeks
CBC	X	X	
CMP	X	X	
TSH, FT4	X		X
UA	X		X
EKG	X		X
Troponins	X		X
Lipase, Amylase	X		X

Brahmer JR, *et al*. SITC guidelines. *J Immunother Cancer* 2021;9:e002435.

Fatal irAEs from ICIs

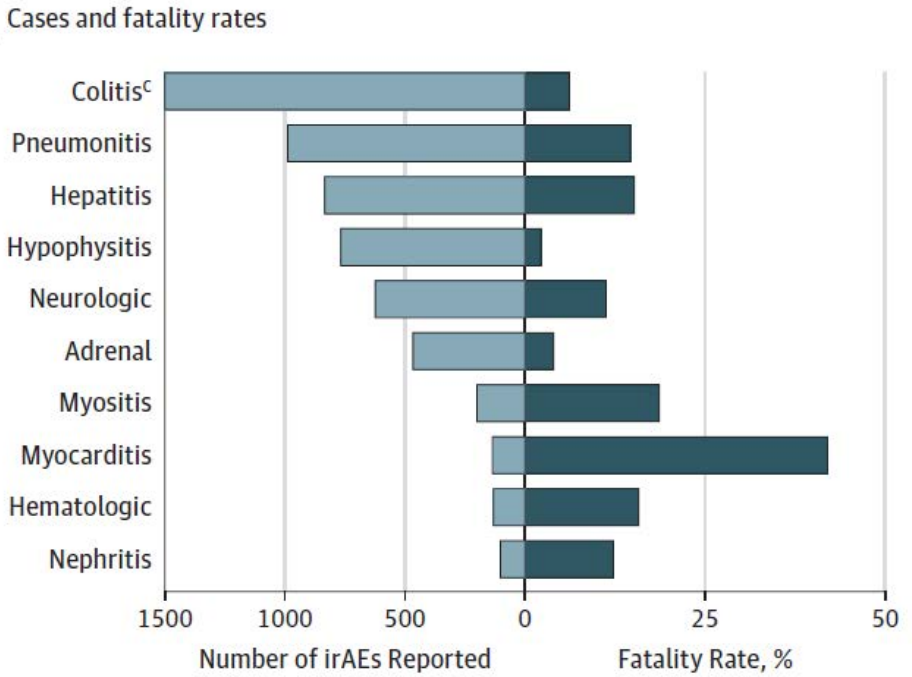
•Number of cases (light blue) and fatality rate (dark blue).

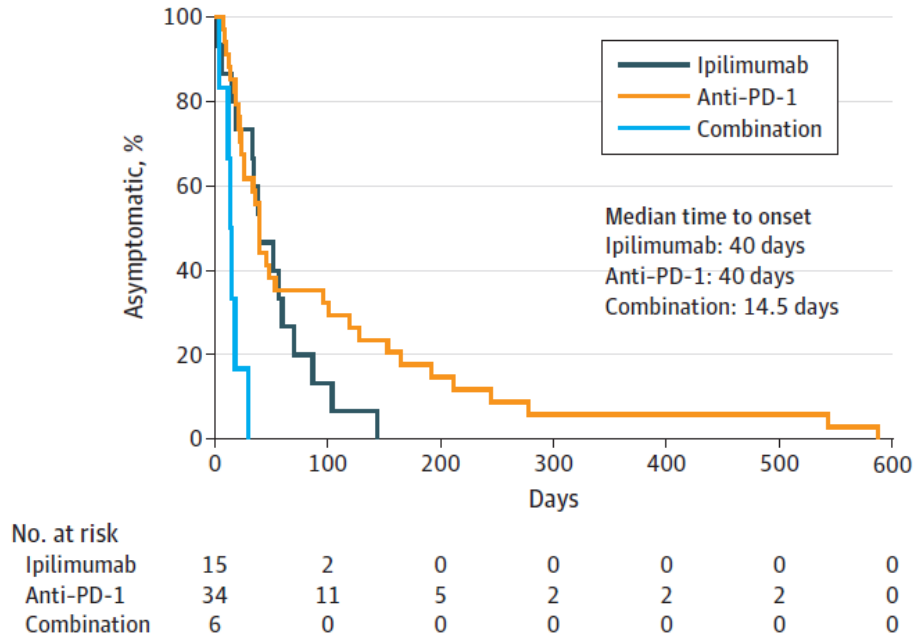
•Toxic fatal event onset occurred early.

•Retrospective review of 3545 patients: 0.6% fatality rates; cardiac and neurologic events were prominent (43%).

•Meta-analysis of 112 trials (19 217 patients) showed toxic fatality rates of 0.36% (anti–PD-1), 0.38% (anti–PD-L1), 1.08% (anti–CTLA-4), and 1.23% (PD-1/PD-L1 plus CTLA-4).

•613 fatal ICI toxic events in Vigilyze database:
- CTLA4i deaths from colitis (70%)
- anti–PD1/L1 fatalities from pneumonitis (35%), hepatitis (22%), and neurotoxicities (15%)
- Combination PD-1/CTLA-4 deaths from colitis (37%) and myocarditis (25%).





Wang DY, et al. JAMA Oncol 2018 Dec 1;4(12):1721-1728.

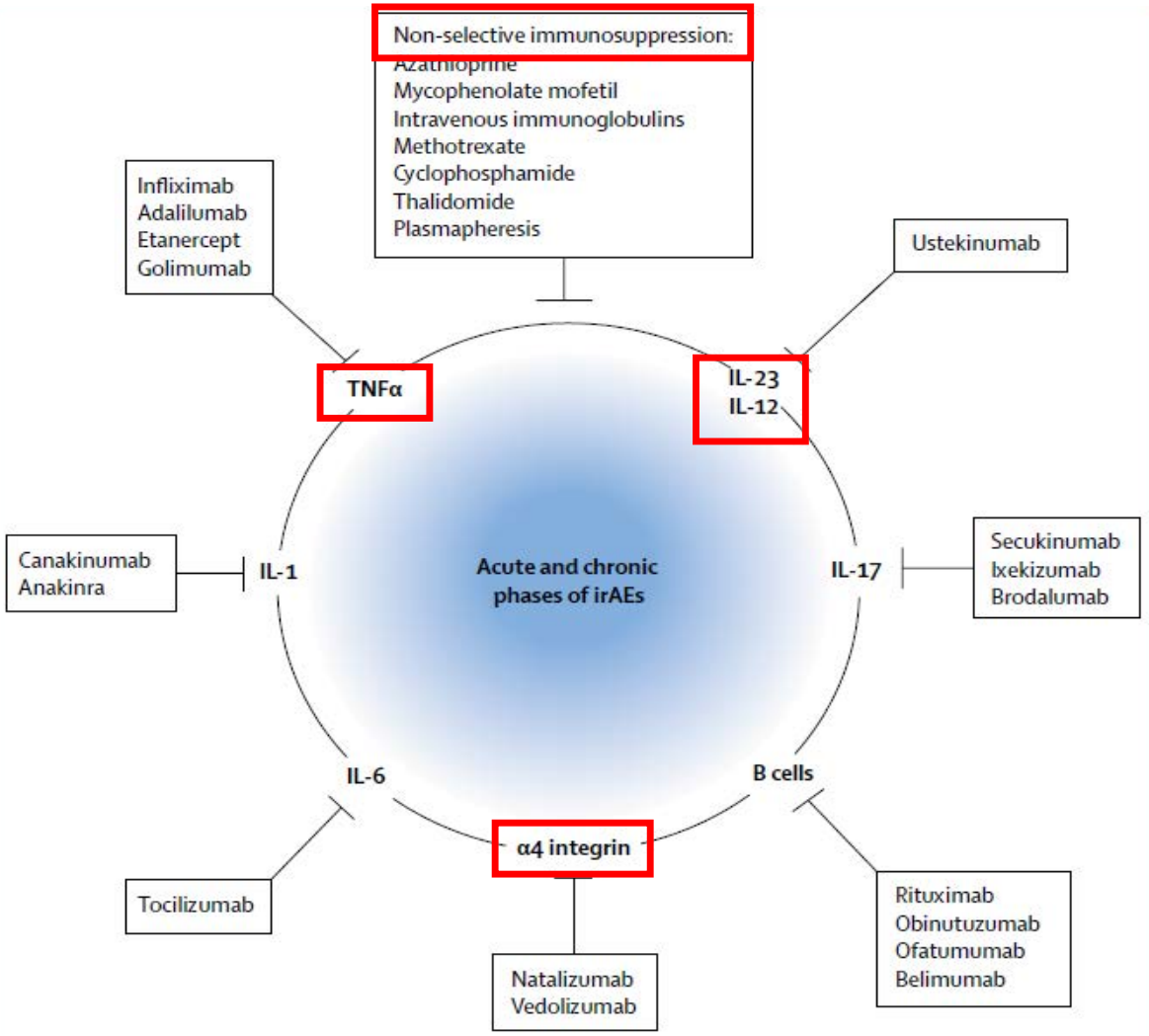
Principles of managing irAEs from immune checkpoint inhibitors

ASCO / ESMO guidelines

- Grade 1: continue ICI with close monitoring, except for some neurologic, hematologic and cardiac toxicities.
- Grade 2: ICI therapy may be suspended, consider resuming when symptoms revert to grade 1. Corticosteroids (Prednisone 0.5-1 mg/kg/d) may be administered (arthritis may respond to very low doses 0.25 mg/kg/d; Antibiotic prophylaxis if >20 mg/d >4 wk).
- Grade 3: suspension of ICIs and initiate high-dose corticosteroids (Prednisone 1.0-2.0 mg/kg/d) tapered over at least 4-6 weeks.
- Grade 4: permanent discontinuation of ICI, except for endocrinopathies that have been controlled by hormone replacement; High-dose corticosteroids
- Evaluate after 72 hours of corticosteroids to adapt therapy

Schneider B, et al. JCO 2021 Dec 20;39(36):4073-4126.
Haanen J, et al. ESMO IO Dec 2021

Steroid-Refractory irAEs



Strategy aims to inhibit key inflammatory components in the pathophysiology of irAEs, while limiting potential adverse effects of immuno-suppression on tumor response.

- Colitis: Infliximab, vedolizumab
- Pneumonitis: Infliximab
- Nephritis: Infliximab, mycophenolate, azathioprine
- Hepatitis: Mycophenolate, tocilizumab (NO infliximab)
- Neurotoxicity: IVIG, rituximab, plasmapheresis
- Psoriasis: Ustekinumab
- Dermatitis: Dupilumab (IL-4, IL-13 inh), rituximab, CSA
- Myocarditis: Infliximab, mycophenolate, IVIG, ATG
- Arthritis: Adalimumab, etanercept, tocilizumab

Martins F, et al. Lancet Oncol 2019 Jan;20(1):e54-e64.

Underlying autoimmune disease and ICIs

- In 123 patients with autoimmune diseases, 92 (75%) had exacerbation of preexisting autoimmune disease, irAEs, or both.
- No differences in patients with active versus inactive disease.
- Patients receiving immunosuppressive therapy at initiation of CPI therapy had fewer adverse events.
- Most flares and irAEs were managed with corticosteroids; 16% required other immunosuppressive therapies.

Abdel-Wahab N, et al. Ann Intern Med. 2018 Jan 16;168(2):121-130.

- In 112 patients, autoimmune disease flare and/or other irAE(s) occurred in 79 patients (71%).
- Immunosuppressive therapy in 48 patients (43%) and permanent discontinuation of ICI in 24 patients (21%).
- Median PFS was shorter in patients receiving immunosuppression at ICI initiation (Prednisone ≥10 mg/d at baseline may compromise efficacy-study confounded by comorbidity requiring steroids).
- Median PFS shorter in patients who experienced flare of autoimmune disease/irAE.

Tison A, et al. Athritis Rheumatol 2019 Dec;71(12):2100-2111.
Ricciuti B, et al. JCO 2019;37(22):1927-1934.

Enfortumab Vedotin Adverse Events

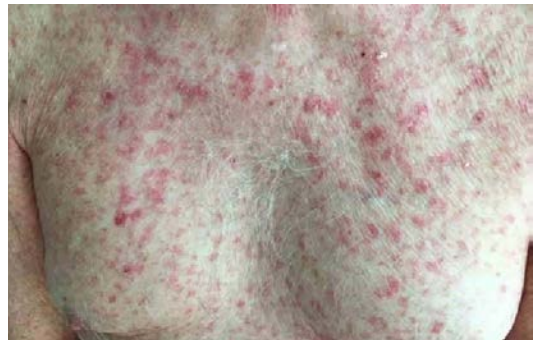
Adverse Event, %	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any adverse event	**94**	**51**	**92**	**50**
Alopecia	45	0	36	0
Peripheral sensory neuropathy	34	3	21	2
Pruritus	32	1	5	0
Fatigue	31	6	23	5
Decreased appetite	31	3	23	2
Diarrhea	24	3	17	2
Dysgeusia	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	6	6
Serious adverse events	23	-	23	-
Leading to treatment withdrawal	14	-	11	-

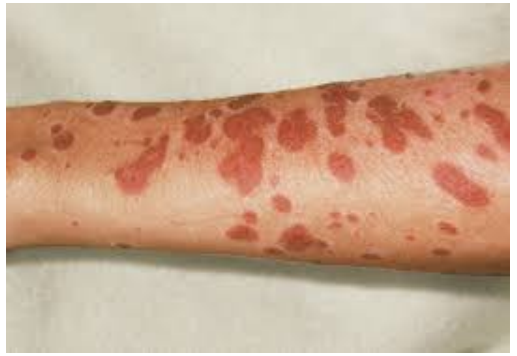
Data cut-off: July 15, 2020

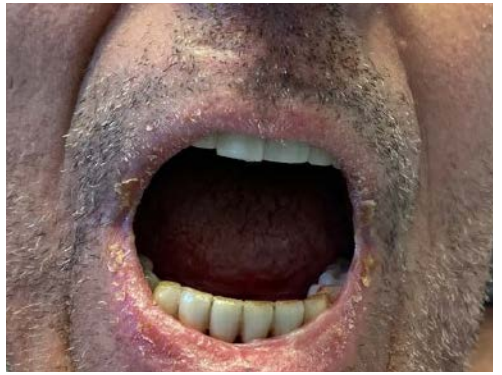
Powles, et al. NEJM Feb 2021

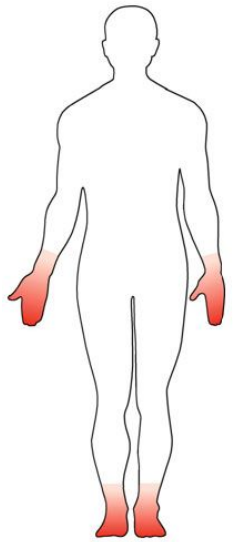
Skin toxicities with EV

- Skin reactions occurred in 55% of 680 patients treated with EV in trials: 23% maculopapular rash and 33% pruritus.
- Grade 3-4 skin reactions in 13%: maculopapular rash (erythematous), dermatitis bullous/exfoliative, palmar-plantar erythrodysesthesia.
- Median time to severe skin reactions 0.6 mo (0.1 to 6.4 mo).
- After interruption, those who restarted EV (n=59), 24% at same dose and 16% of patients at reduced dose experienced recurrent severe rash.
- Skin reactions led to discontinuation of EV in 2.6%.
- Severe/fatal reactions: Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN).
- Discontinue EV for SJS/TEN or Grade 4 or recurrent Grade 3 events.
- Refer to dermatology for suspected SJS/TEN or Grade 3-4 skin events.









EV associated neuropathy

Incidence

- Peripheral neuropathy in 52% of 680 patients treated with EV in trials including 39% sensory neuropathy, 7% muscular weakness and 6% motor neuropathy.
- 4% experienced Grade 3-4 reactions.
- Occurred in patients treated with EV with or without preexisting peripheral neuropathy.
- The median time to onset of Grade ≥2 peripheral neuropathy was 4.6 months (0.1 to 15.8 mo).
- Neuropathy led to treatment discontinuation in 5% of patients.

Management

- Permanently discontinue EV if Grade ≥3 peripheral neuropathy
- Prevent: dose reductions/interruptions, exercise, cryotherapy
- Non-pharmacologic therapy: Acupuncture, Scrambler therapy (electro-cutaneous stimulation), Neurofeedback
- Topical therapy: Menthol, Capsaicin
- Pharmacologic therapy (pain+):
  - Duloxetine
  - Gabapentin
  - Venlafaxine
  - Pregabalin

Hyperglycemia with EV

- Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials.
- Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus.
- The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20.3 months).
- 14% of the 680 trial patients treated with EV developed hyperglycemia.
- 7% of patients developed Grade 3-4 hyperglycemia.
- Grade 3-4 hyperglycemia increased in patients with higher BMI and higher baseline A1C.
- 5% of patients required insulin therapy.
- Hyperglycemia led to discontinuation of EV in 0.6% of patients.
- Closely monitor blood glucose levels in patients with, or at risk for, DM or hyperglycemia.
- If blood glucose is elevated (>250 mg/dL), withhold EV.

Eye toxicities with EV

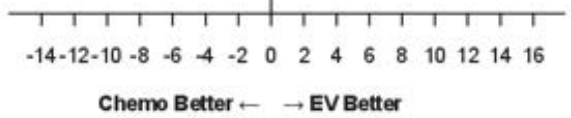
- Ocular events were reported in 40% of 384 patients treated with EV in trials in which ophthalmologic exams were scheduled.
- Events involved the cornea: dry eye, keratitis, blurred vision, lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy.
- Dry eye in 34%, and blurred vision in 13% of patients.
- The median time to onset of symptomatic ocular disorder was 1.6 months (0 to 19.1 months).
- Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur.
- Consider dose interruption, reduction of EV and topical steroids for severe symptoms.

Quality of Life, Functioning, and Symptoms in Patients With Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma From EV-301: A Randomized Phase 3 Trial of Enfortumab Vedotin vs Chemotherapy

Ronac Mamtani[1], Jonathan E Rosenberg[2], Thomas Powles[3], Guru P Sonpavde[4], Yohann Loriot[5], Ignacio Duran[6], Jae Lyun Lee[7], Nobuaki Matsubara[8], Christof Vulsteke[9], Daniel Castellano[10], Srikala S Sridhar[11], Helle Pappot[12], Howard Gurney[13], Jens Bedke[14], Michiel van der Heijden[15], Chunzhang Wu[16], Zsolt Hepp[17], Caroline McKay[18], Daniel P Petrylak[19]

Figure 3. QLQ-C30 Functioning Domains at Week 12 by Treatment

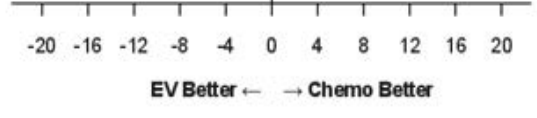
Domain	LSMean (SE) at W12 EV	LSMean (SE) at W12 Chemo	Contrast EV vs Chemo [95%CI]
Global Health Status	-2.83 (1.35)	-5.00 (1.48)	2.17 [-1.48; 5.82]
Physical Functioning Score	-2.86 (1.46)	-6.18 (1.60)	3.32 [-0.65; 7.29]
Role Functioning Score	-5.37 (2.01)	-9.93 (2.21)	4.56 [-0.91; 10.02]
Emotional Functioning Score	2.92 (1.34)	2.26 (1.47)	0.66 [-2.96; 4.28]
Cognitive Functioning Score	-0.97 (1.34)	-1.00 (1.47)	0.03 [-3.58; 3.64]
Social Functioning Score	-4.77 (1.92)	-4.83 (2.10)	0.06 [-5.12; 5.23]
Summary Score	-1.85 (1.08)	-2.61 (1.19)	0.76 [-2.13; 3.65]



Abbreviations: BL, baseline; chemo, chemotherapy; CI, confidence interval; EV, enfortumab vedotin; LS, least squares; QLQ-C30, Quality of Life Questionnaire Core 30; SE, standard error; W, week.

Figure 4. QLQ-C30 Symptom Scales at Week 12 by Treatment

Domain	LSMean (SE) at W12 EV	LSMean (SE) at W12 Chemo	Contrast EV vs Chemo [95%CI]
Financial Difficulties Symptom Score	0.12 (1.49)	1.50 (1.65)	-1.38 [-5.47; 2.72]
Fatigue Symptom Score	5.86 (1.75)	5.99 (1.92)	-0.13 [-4.87; 4.61]
Nausea and Vomiting Symptom Score	1.47 (1.05)	0.57 (1.16)	0.90 [-1.96; 3.76]
Pain Symptom Score	-5.62 (1.86)	0.11 (2.04)	-5.73 [-10.80; -0.66]
Dyspnea Symptom Score	3.22 (1.78)	7.12 (1.97)	-3.90 [-8.74; 0.93]
Insomnia Symptom Score	-1.49 (2.01)	-1.85 (2.23)	0.37 [-5.15; 5.89]
Appetite Loss Symptom Score	8.55 (2.34)	1.26 (2.57)	7.29 [0.90; 13.69]
Constipation Symptom Score	-2.89 (1.77)	-2.03 (1.95)	-0.85 [-5.62; 3.92]
Diarrhea Symptom Score	4.79 (1.61)	1.13 (1.78)	3.66 [-0.73; 8.04]



Abbreviations: BL, baseline; chemo, chemotherapy; CI, confidence interval; EV, enfortumab vedotin; LS, least squares; QLQ-C30, Quality of Life Questionnaire Core 30; SE, standard error; W, week.

TROPHY-U-01: Toxicities with Sacituzumab Govitecan post-platinum and PD1/L1 inhibitors

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	**Neutropenia**	**46**	**22**	**12**
	Leukopenia	26	12	5
	Anemia	34	14	0
	Lymphopenia	12	5	2
	Febrile neutropenia	**10**	**7**	**3**
Gastrointestinal	**Diarrhea[b]**	**65**	**9**	**1**
	Nausea	**58**	**4**	**0**
	Vomiting	28	1	0
General disorders & administrative site conditions	**Fatigue**	**50**	**4**	**0**
Skin & subcutaneous tissue	**Alopecia**	**47**	**0**	**0**
Metabolism & nutrition	Decreased appetite	36	3	0
Infections & infestations	Urinary tract infection	8	6	0

- 7 (6%) pts discontinued due to TRAEs
  - 4 discontinued due to neutropenia or its complications
- 30% GCSF usage
- One treatment-related death (sepsis due to febrile neutropenia)
- 2-drug antiemetic regimen recommended (3-drug regimen for persistent nausea and vomiting)

Loriot Y, et al. ESMO September 2020; Tagawa S, JCO 2021

Pre-medications for Sacituzumab Govitecan

Pooled safety population (ASCENT, IMMU-132-01, and TROPHY U-01) at dose of 10 mg/kg:

- **Hypersensitivity reactions** within 24 hrs in 37%.
- Grade 3-4 hypersensitivity in 2%.
- Permanent discontinuation 0.3%.
- Anaphylactic reactions 0.3%.
- Closely monitor for hypersensitivity and infusion-related reactions during each SG infusion and for at least 30 minutes after completion of each infusion.
- Premedication using antipyretics and H1 (histamine 1) and H2 (histamine 2) blockers; corticosteroids (e.g. hydrocortisone 50 mg) for patients who had prior infusion reactions.
- First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose.
- Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe during the infusion and for at least 30 minutes after infusion.

Erdafitinib Treatment-Related AEs

Metabolic

GI

Skin / Nail

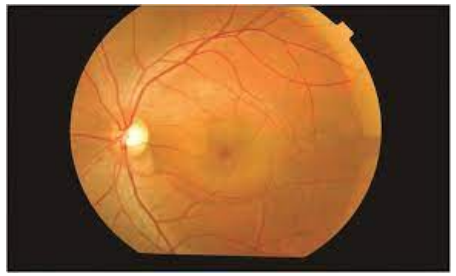
Eye

Adverse Event	Any Grade	Grade 1	Grade 2	Grade ≥3
	number of patients (percent)			
Hyperphosphatemia	76 (77)	53 (54)	21 (21)	2 (2)
Stomatitis	57 (58)	21 (21)	26 (26)	10 (10)
Diarrhea	50 (51)	31 (31)	15 (15)	4 (4)
Dry mouth	45 (46)	34 (34)	11 (11)	0
Decreased appetite	38 (38)	18 (18)	20 (20)	0
Dysgeusia	37 (37)	23 (23)	13 (13)	1 (1)
Fatigue	32 (32)	12 (12)	18 (18)	2 (2)
Dry skin	32 (32)	24 (24)	8 (8)	0
Alopecia	29 (29)	23 (23)	6 (6)	0
Constipation	28 (28)	19 (19)	8 (8)	1 (1)
Hand–foot syndrome	23 (23)	6 (6)	12 (12)	5 (5)
Anemia	20 (20)	9 (9)	7 (7)	4 (4)
Asthenia	20 (20)	2 (2)	11 (11)	7 (7)
Nausea	20 (20)	13 (13)	6 (6)	1 (1)
Dry eye	19 (19)	14 (14)	4 (4)	1 (1)
Onycholysis	18 (18)	6 (6)	10 (10)	2 (2)
Alanine aminotransferase increased	17 (17)	13 (13)	2 (2)	2 (2)
Paronychia	17 (17)	3 (3)	11 (11)	3 (3)
Blurred vision	17 (17)	10 (10)	7 (7)	0
Nail dystrophy	16 (16)	5 (5)	5 (5)	6 (6)

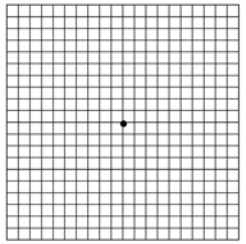
Low Phosphate diet at baseline

Avoid nuts, fish, processed meats, baked food, hard cheese, cola drinks

Loriot Y, NEJM 2019



Monitoring and management of ocular toxicities of Erdafitinib



Incidence

•Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) in 25% - median time to onset 50 days.

•Grade 3 CSR/RPED, involving central field of vision in 3% of patients.

•CSR/RPED resolved in 13% and was ongoing in 13% at the study cutoff.

•CSR/RPED led to dose interruptions and reductions in 9% and 14% of patients, respectively and 3% discontinuations.

Monitoring & management

•Baseline and monthly ophthalmology exams during the first 4 months- then every 3 months (self-exam with Amsler's grid).

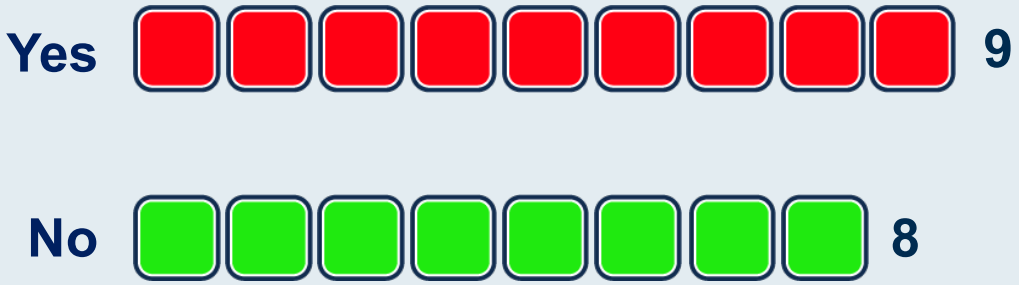
•Urgent eye exam any time for visual symptoms.

•Ophthalmological exam includes:
- visual acuity
- slit lamp examination
- fundoscopy
- optical coherence tomography.

•Hold erdafitinib for CSR and discontinue if no resolution within 4 weeks or Grade 4.

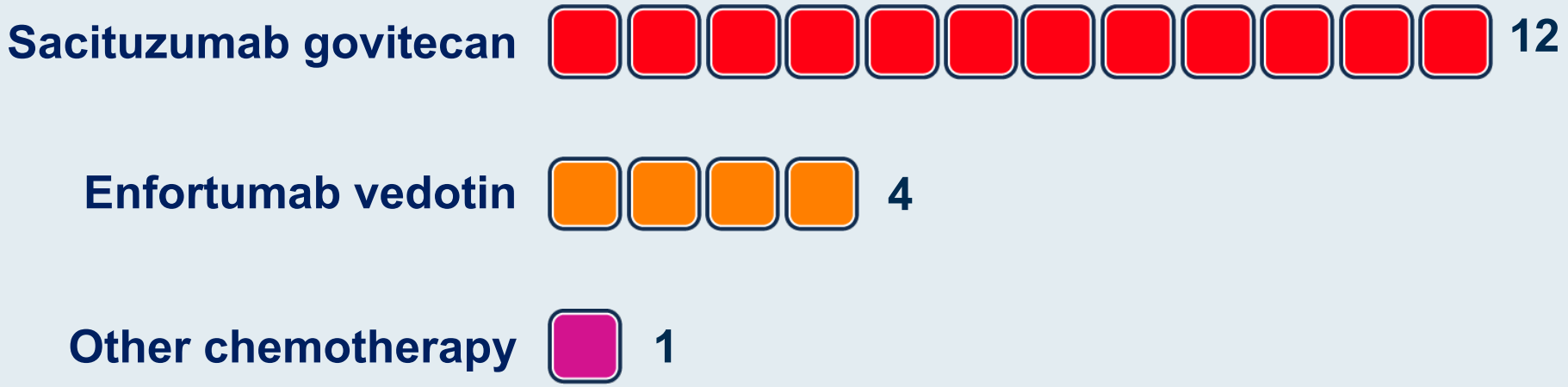
Clinical Investigator Survey Results

Is there a baseline Hgb A1C level beyond which you would not consider treating a patient with metastatic UBC with enfortumab vedotin?



Survey of genitourinary cancer clinical investigators

What would you generally recommend as second-line therapy for a 65-year-old patient with a history of poorly controlled diabetes and FGFR wild-type UBC metastatic to the liver whose disease progresses on first-line cisplatin/gemcitabine followed by avelumab maintenance?



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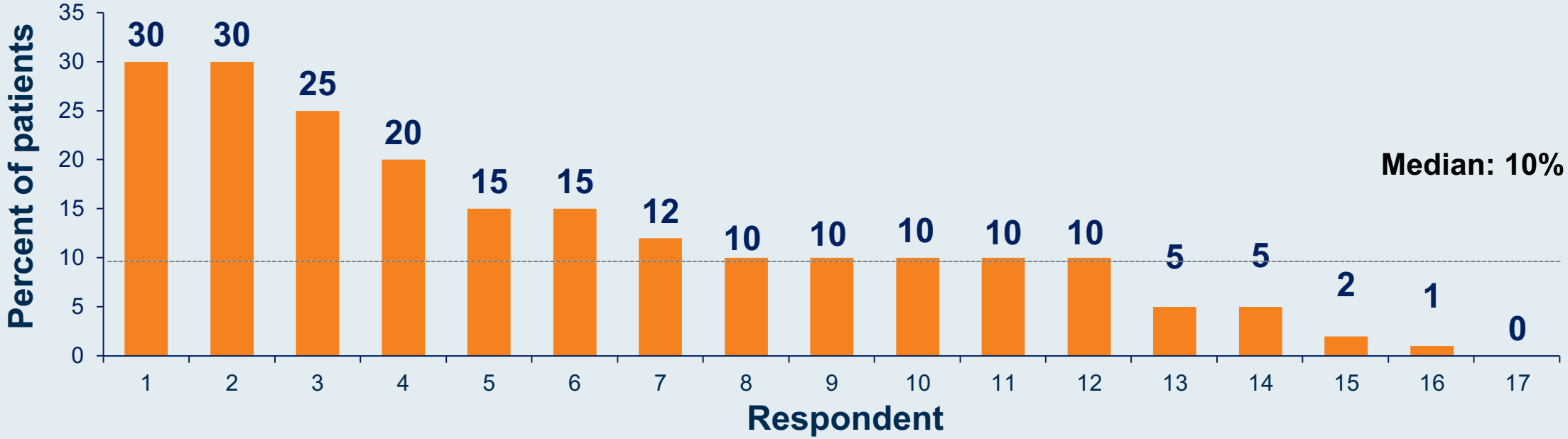
Approximately what proportion of your patients with metastatic UBC receiving erdafitinib develop clinically significant ocular toxicity?



Do you recommend regular ophthalmologic examinations to your patients with metastatic UBC receiving erdafitinib?

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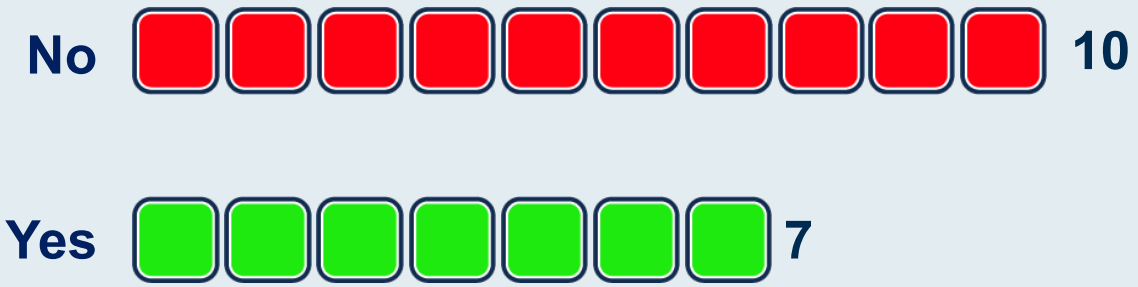
In general, when you administer sacituzumab govitecan for metastatic UBC, do you preemptively prescribe growth factors for the prevention of treatment-related neutropenia?



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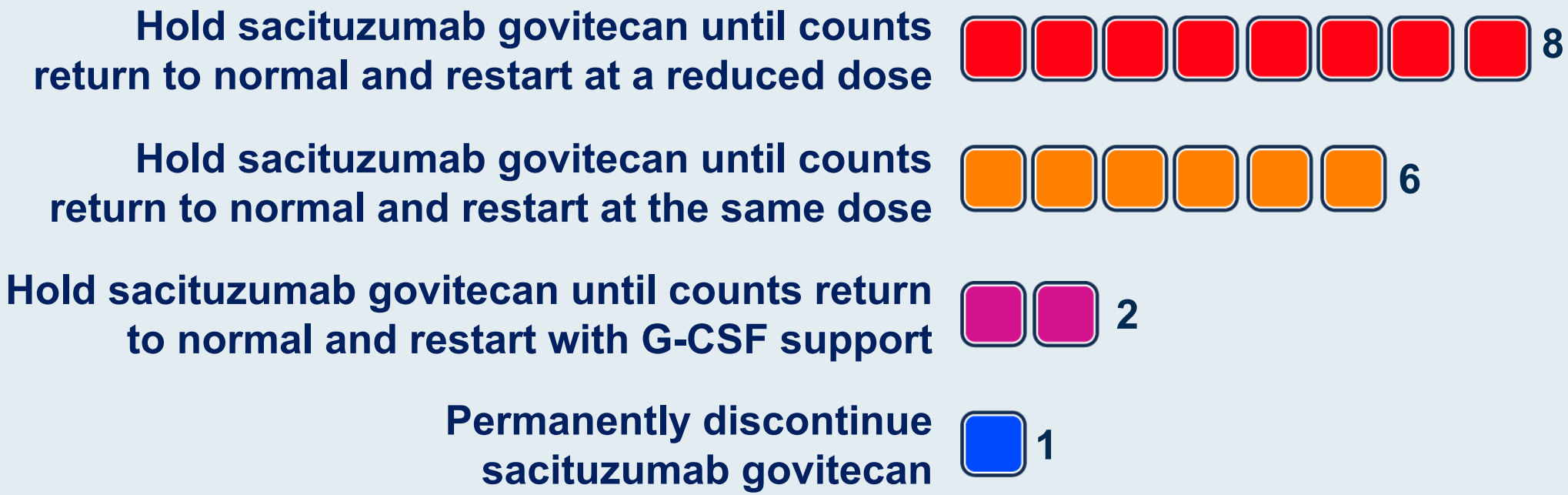
A patient who is experiencing a good response to sacituzumab govitecan for metastatic UBC is found to have an absolute neutrophil count of 900/mm^3 without fever. What would you recommend?



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Thank you for attending!

CME Credit Information

For those participating in person today, please remit your CME credit form as you exit the meeting room.

For all others, a CME credit link will be provided in the chat room at the conclusion of the program.

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