UCDAVIS COMPREHENSIVE CANCER CENTER

UC DAVIS HEALTH

Bladder Cancer: New Strategies

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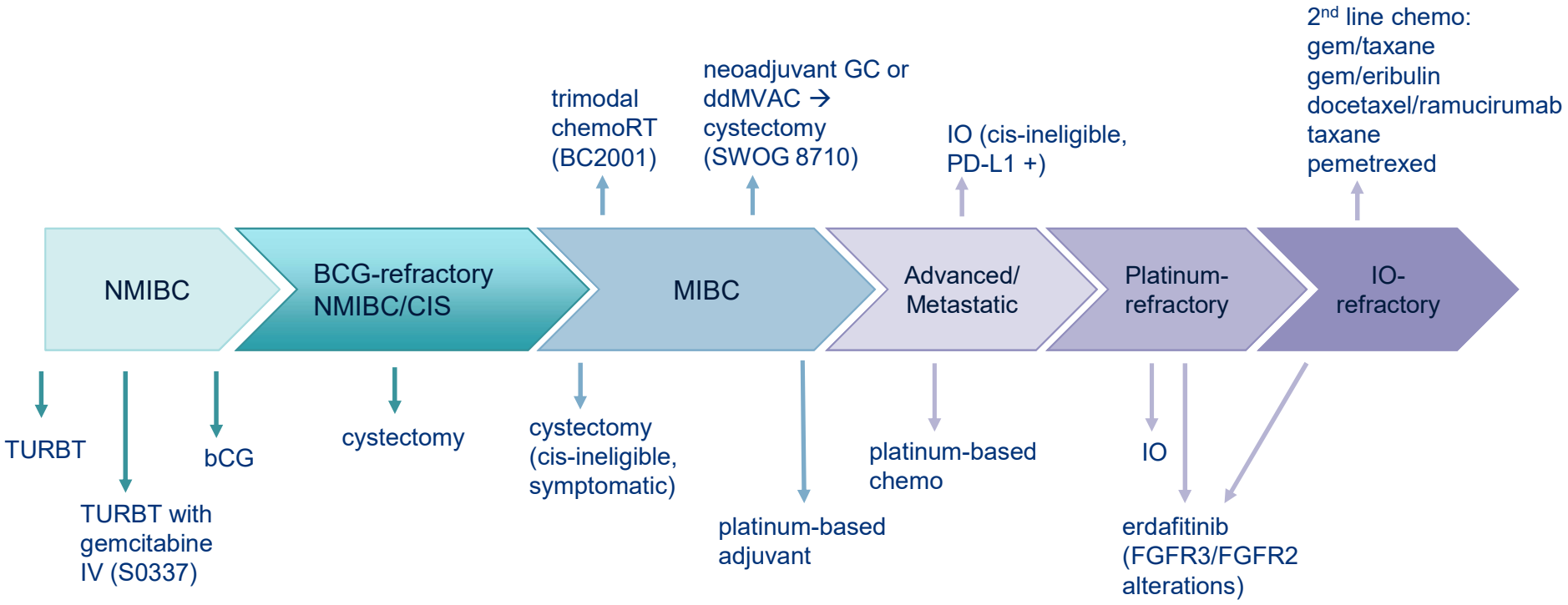
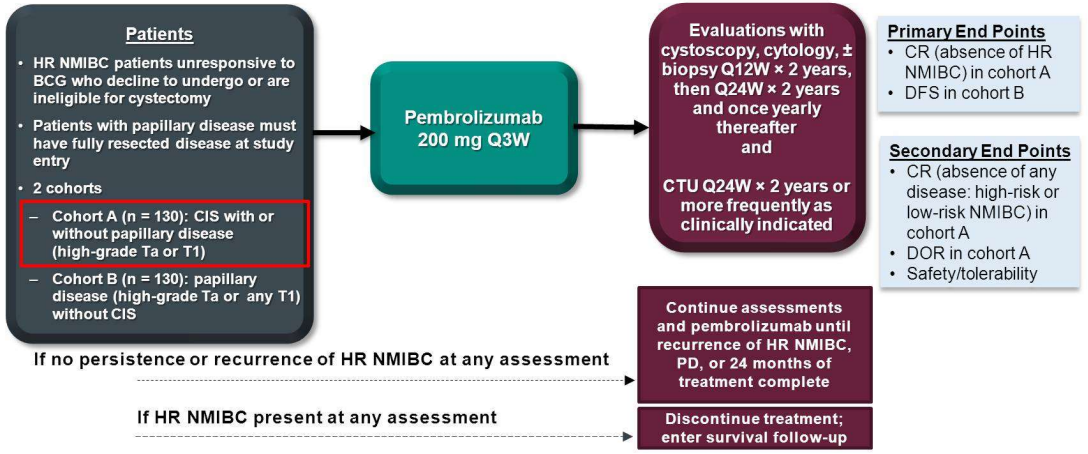
Bladder Cancer: "Old" Strategies



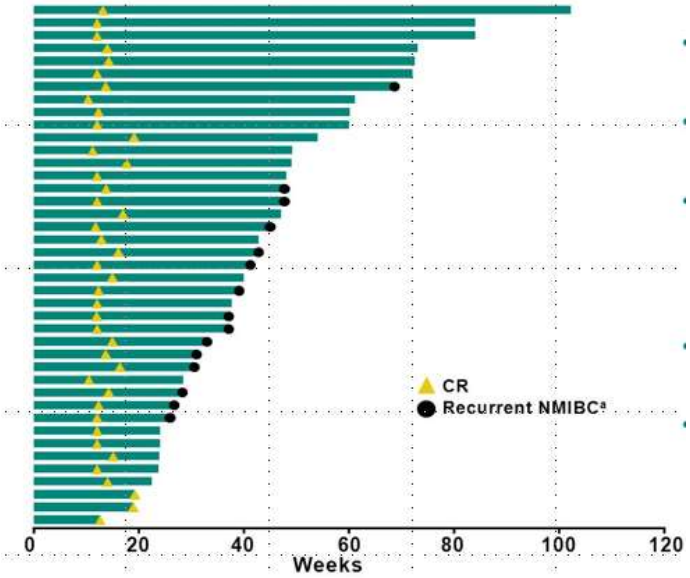
NMIBC | **BCG-refractory NMIBC/CIS** | MIBC | Advanced/ Metastatic | Platinum-refractory | IO-refractory

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



KEYNOTE-057

- January 2020: pembrolizumab approved for BCG-unresponsive, high-risk NMIBC with CIS with or without papillary tumors

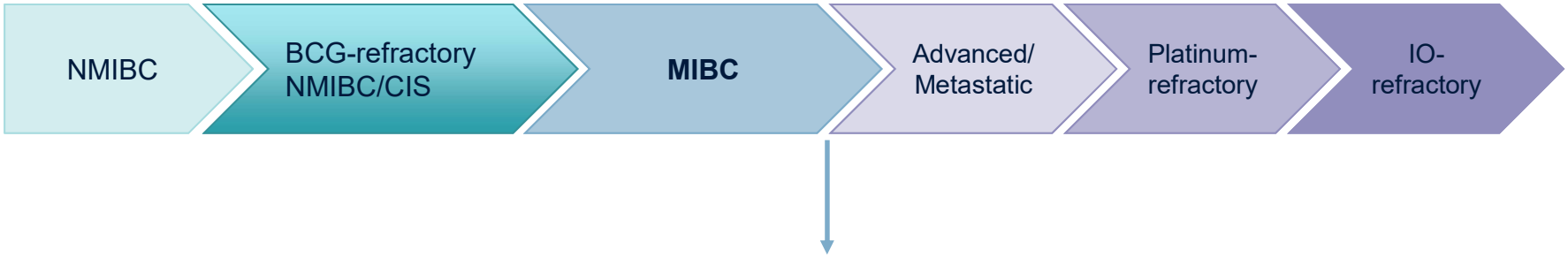


- n=148, but BCG-unresponsive CIS: n=96
- CR: 41%
- 46% of CRs ≥ 12 months
- median DOR: 16.2 months

IO-based neoadjuvant approaches

Study Title	Study Agents	pCR %	path CR/evaluable
ABACUS	**atezolizumab**	**29%**	20/68
PURE-01	**pembrolizumab**	**42%**	21/50
NABUCCO	**nivolumab + ipilimumab**	**45%**	10/22
GU14-188	**pembrolizumab + GC**	**45%**	14/31
BLASST-1	**nivolumab + GC**	**49%**	20/41

Adjuvant Approaches- in progress…



Study	Agent	Endpoint
CheckMate 274	nivolumab	DFS (by PD-L1+, all)
IMvigor 010	atezolizumab	DFS
AMBASSADOR	pembrolizumab	DFS & OS
PROOF 302	infigratinib	DFS

**met DFS endpoint

Platinum-based combinations in Advanced Disease

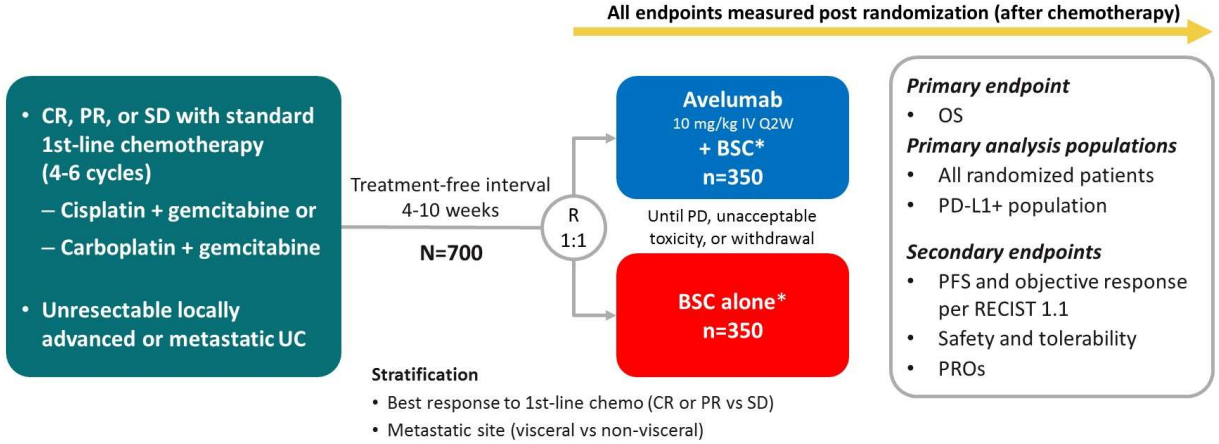
PHII-135
Gem-cis +/- VX-970: results pending

IMvigor 130
atezolizumab plus platinum-based chemo v platinum-based chemo alone v atezolizumab alone
- PFS benefit (Arm A v Arm C) but no significant difference in OS

Arm	n	PFS	OS
Atezo + CTx	451	8.2 m	16.0 m
Atezo	362	--	15.7 m
CTx	400	6.3 m	13.4 m

NMIBC → BCG-refractory NMIBC/CIS → MIBC → **Advanced/ Metastatic** → Platinum-refractory → IO-refractory

JAVELIN Bladder 100 study design (NCT02603432)

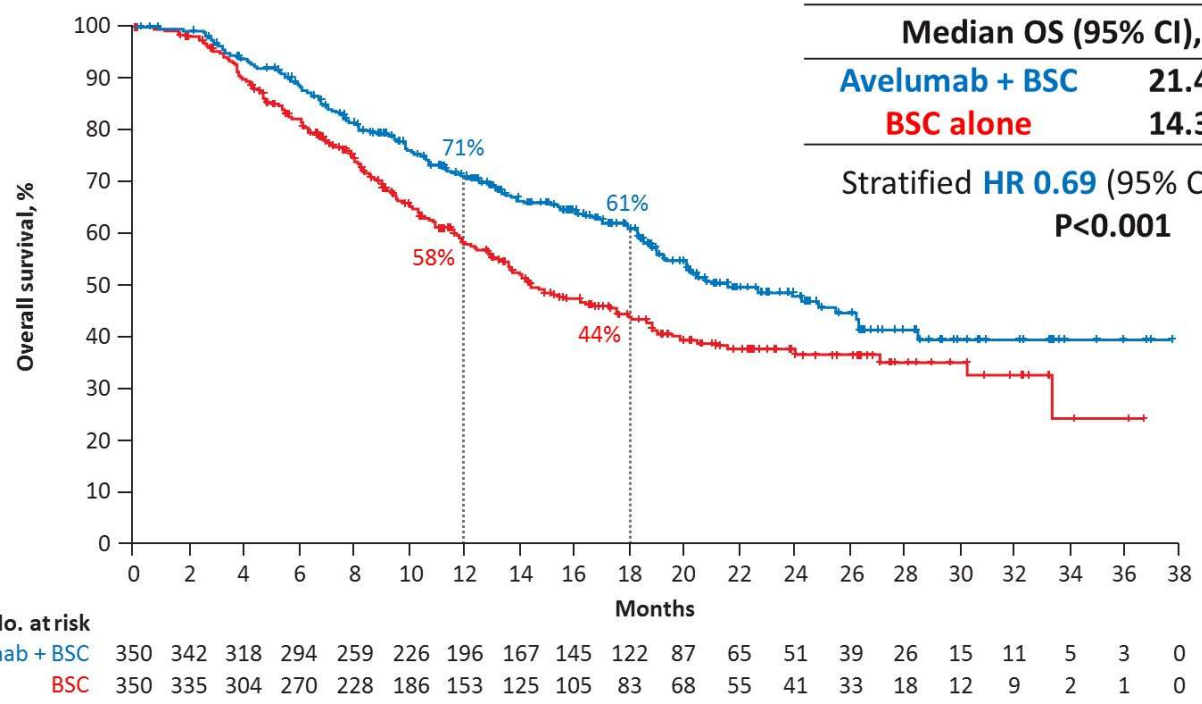


PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

BSC, best supportive care; **CR,** complete response; **IV,** intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W,** every 2 weeks; **R**, randomization; **RECIST 1.1,** Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

OS in the overall population

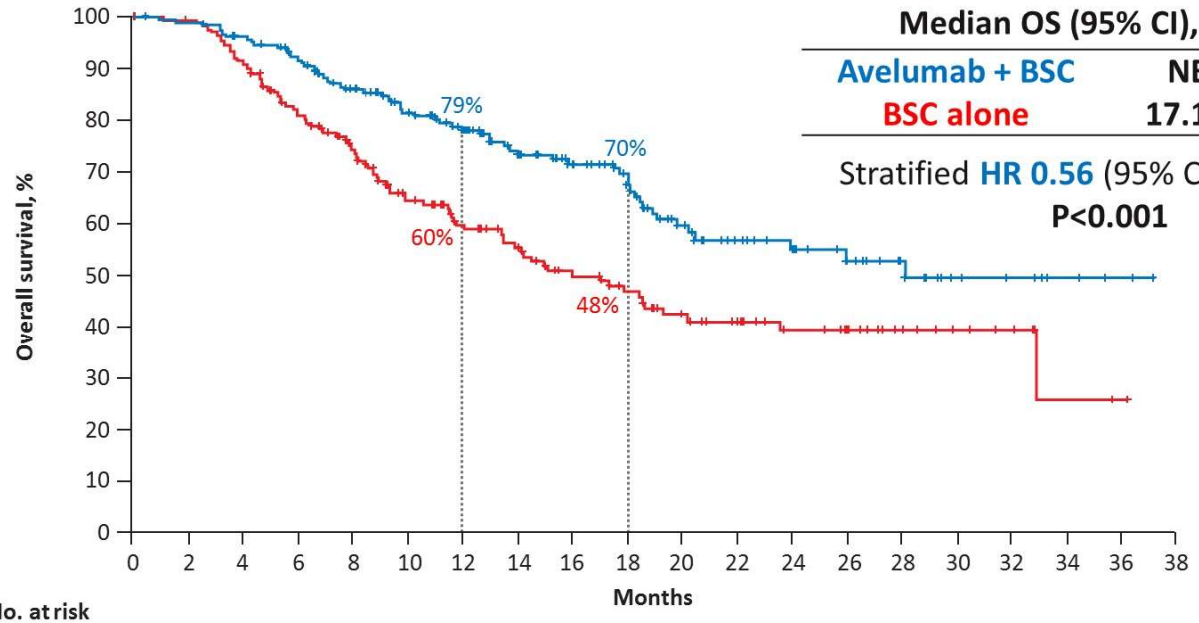


Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

Stratified **HR 0.69** (95% CI, 0.56, 0.86)
P<0.001

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

OS in the PD-L1+ population



Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.3, NE)
BSC alone	**17.1** (13.5, 23.7)

Stratified **HR 0.56** (95% CI, 0.40, 0.79)
P<0.001

No. at risk																				
Avelumab + BSC	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
BSC	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). **NE**, not estimable

Antibody Drug Conjugate Approaches to Refractory UC

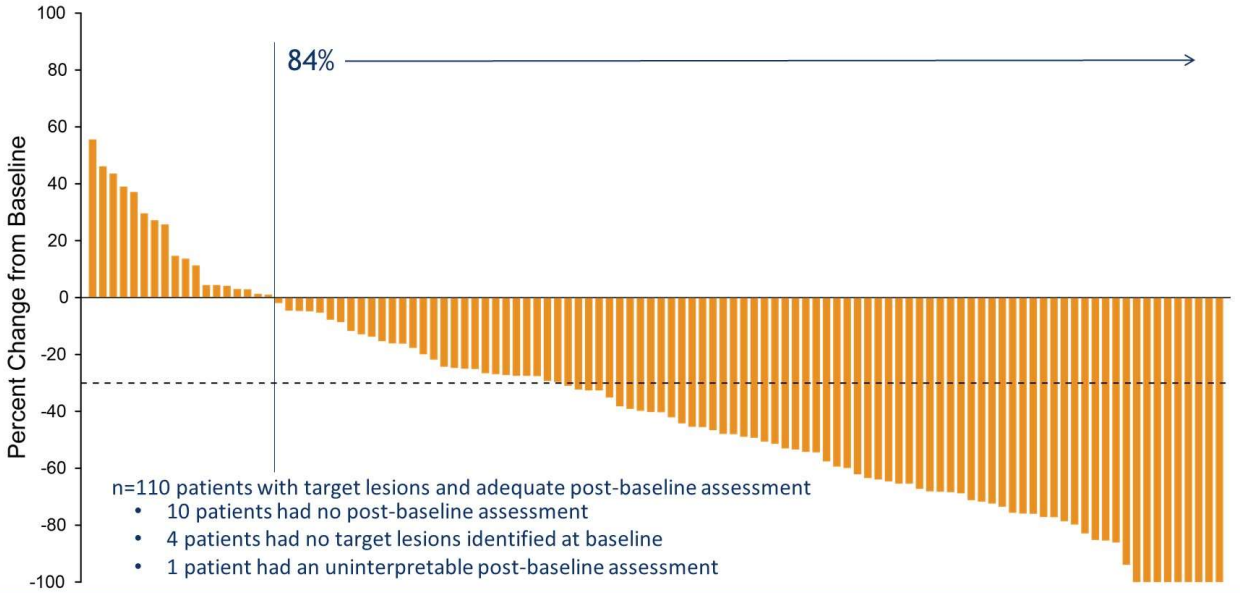
- Sacituzumab govitecan (TROP2 ADC)
  - Phase I/II ORR: 31%
  - Phase II ORR: 29%

IMMU-132-01
TROPHY-U-01
Cohort 1

NMIBC → BCG-refractory NMIBC/CIS → MIBC → Advanced/ Metastatic → **Platinum-refractory** → **IO-refractory**

EV-201: Cohort 1 Change in Tumor Measurements per BICR

EV-2



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ORR: 44% (35.1-53.2)
CR: 12%
PR: 32%
SD: 28%

Updated median OS (ESMO 2020): 12.4 months

Enfortumab vedotin (Nectin 4 ADC)

- December 2019 - Accelerated FDA Approval
- EV-301: randomized, Phase III trial of enfortumab vedotin vs chemotherapy (docetaxel, paclitaxel, vinflunine)
  - Stopped early due to positive results at planned interim
  - OS HR= 0.70 (95% CI: 0.56, 0.89; p=0.001)
  - PFS HR= 0.61 (95% CI: 0.50,0.75; p<0.00001)
- EV-201 Cohort 2 (prior IO, platinum-naive): 52% ORR

EV-103 – First-line Cohorts of Enfortumab Vedotin + Pembrolizumab

Enfortumab vedotin 1.25 mg/kg + pembrolizumab (200 mg) in 1L cisplatin-ineligible la/mUC patients (N=45)

Patient Population	Dose Escalation[1]	Dose Expansion Cohort A
Locally Advanced or Metastatic Urothelial Carcinoma	enfortumab vedotin + pembrolizumab cisplatin-ineligible (n=5)	enfortumab vedotin + pembrolizumab cisplatin-ineligible (n=40)

Dosing: Enfortumab vedotin on days 1 and 8 and pembrolizumab on day 1 of every 3-week cycle

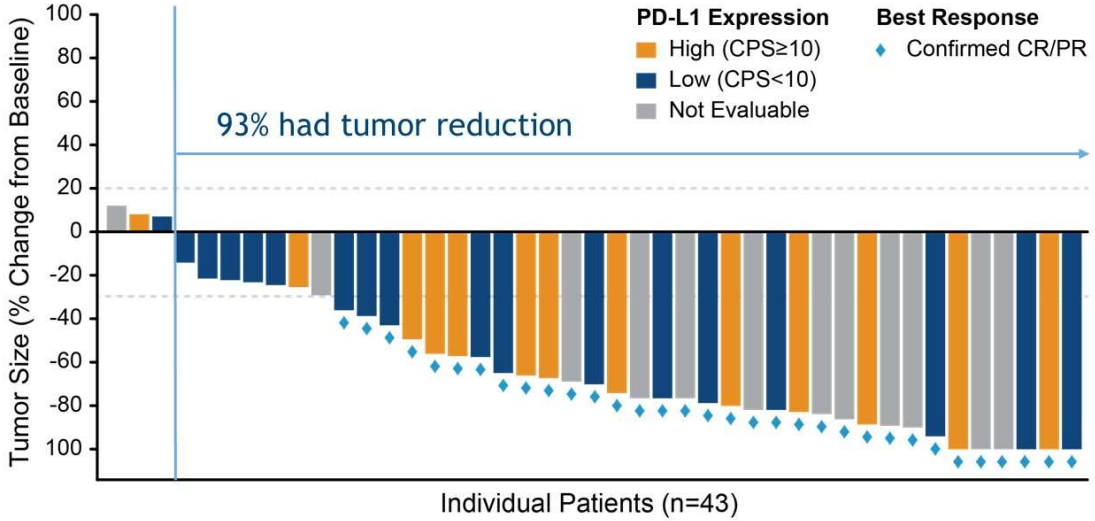
Enfortumab vedotin exposure: Comparable to enfortumab vedotin monotherapy on 4-week schedule (Days 1, 8, and 15)[2]

Primary endpoints: safety and tolerability

Key secondary endpoints: dose-limiting toxicities, ORR, DOR, PFS, OS

[1] Not included in the current analysis: three 1L patients treated with EV 1 mg/kg + pembrolizumab 200 mg and two 2L patients treated with EV 1.25 mg/kg + pembrolizumab 200 mg
[2] Rosenberg et al. *J Clin Oncol.* 2019;37(29):2592-600.

Maximal Target Lesion Reduction by PD-L1 status and Objective Response Rate per Investigator



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

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

- Responses observed regardless of PD-L1 expression level

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

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

Treatment-Related Adverse Events of Clinical Interest (AECI)

- Rates of peripheral neuropathy, rash, and hyperglycemia similar to enfortumab vedotin monotherapy
- No new safety signal with the combination

AECI: categorized by related MedDRA terms	Patients (N=45) n (%)		Time to first onset (months) median (min, max)
	Any Grade	≥Grade 3[1]	Any Grade
Peripheral neuropathy	25 (56)	2 (4)	2.3 (1, 12)
Rash	28 (62)	6 (13)	0.7 (0, 12)
Hyperglycemia[2]	5 (11)	3 (7)	0.5 (0, 3)

AECI: determined by investigator	Patients (N=45) n (%)	
	Any Grade	≥Grade 3[1]
Immune-mediated AE requiring systemic steroids	13 (29)	8 (18)[3]

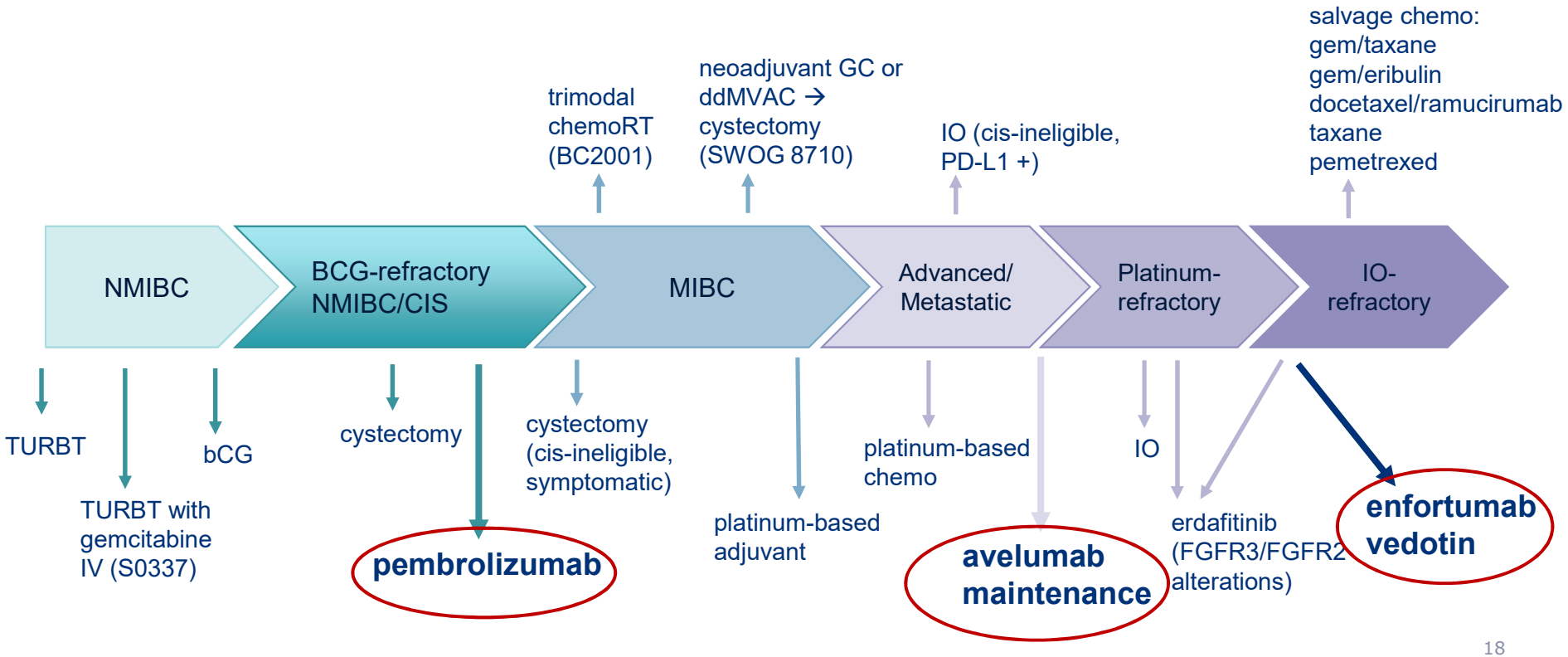
[1] No Grade 5 TRAE of Clinical Interest
[2] Blood glucose assessments were non-fasting.
[3] Grade 3 events: arthralgia, dermatitis bullous, pneumonitis, lipase increased, rash erythematous, rash maculo-papular, tubulointerstitial nephritis; Grade 4: dermatitis bullous, myasthenia gravis

IO-ADC approaches

EV-103 – EV + pembro
SGN22E-02 – EV vs EV + pembro

TROPHY-U-01 Cohort 3: SG + pembro

Current Bladder Cancer Treatment Paradigm



Stay Tuned!

- Considerations:
  - Earlier IO & combo therapy → possible earlier CRs
  - Increased need for new treatments/approaches for advanced disease

Questions?