Update in Urothelial Cancers

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Urothelial Cancer: Remarkable Advances

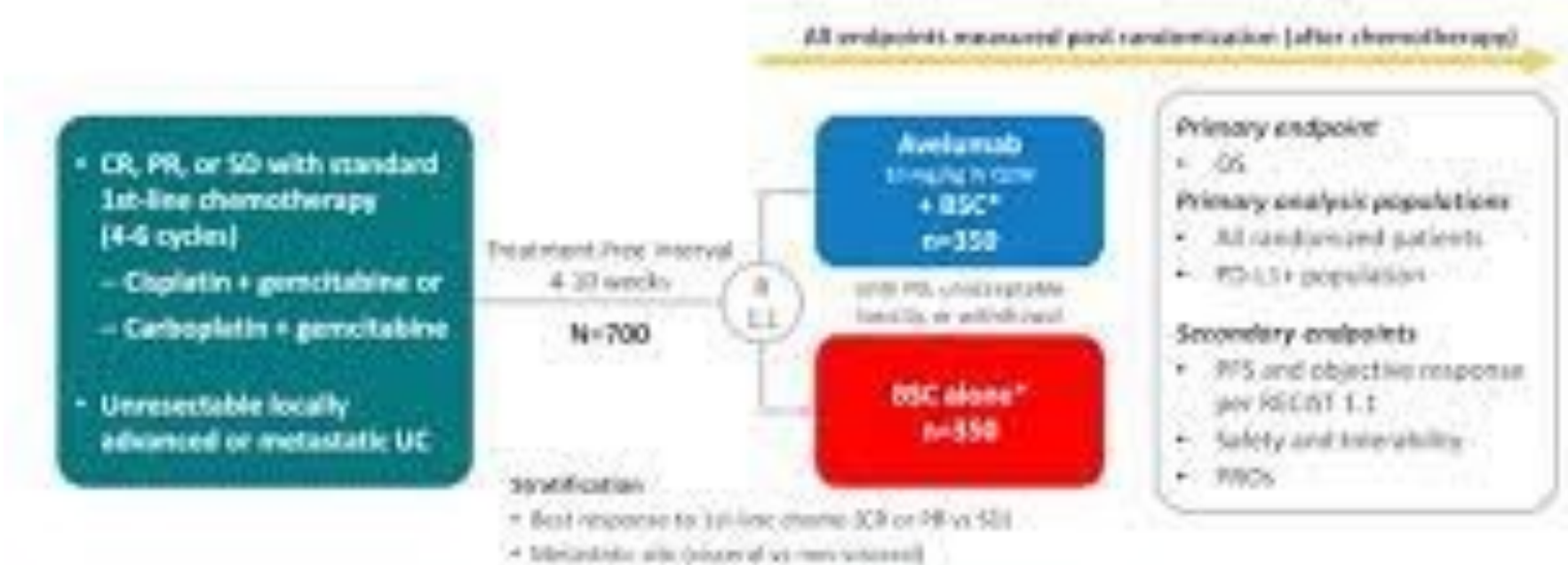
JAVELIN 100: Switch maintenance platinum +gem then avelumab

Erdafitinib shows OS benefit over taxane chemotherapy

Enfortumab + pembro shows remarkable OS benefit

Checkmate 901: Cis + gem +/- nivo shows OS benefit

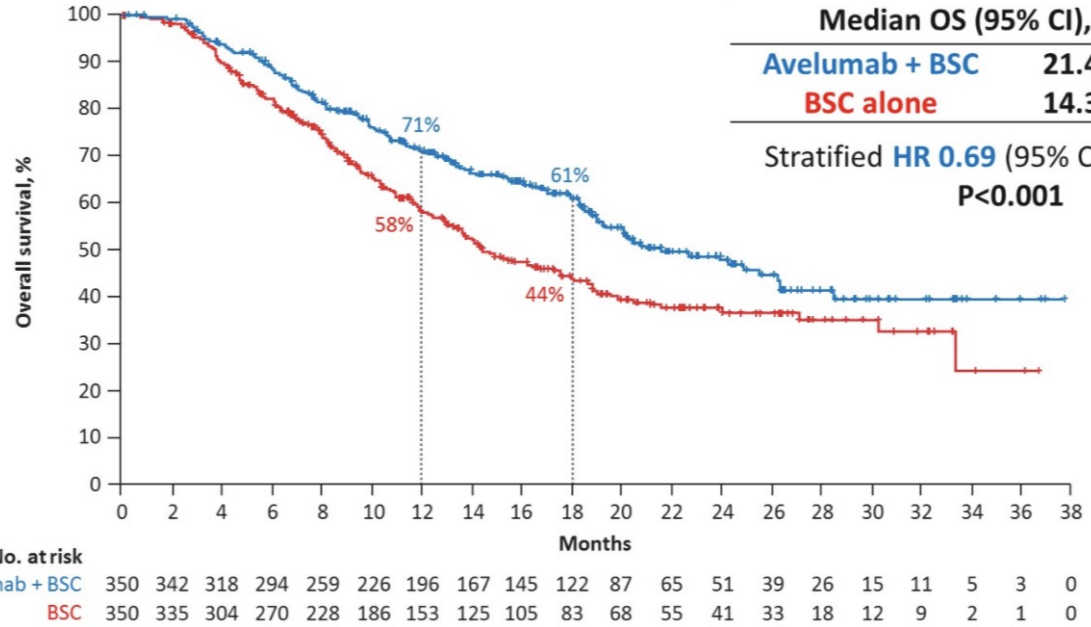
JAVELIN Bladder 100 study design (NCT02603432)



PD-L1+ status was defined as PD-L1 expression in ≥1% of tumor cells or in ≥1% or ≥10% of tumor-associated immune cells, the percentage of immune cells was >1% or ≥1%, respectively, using the VENTANA SP263 assay. 218 patients (16%) had a PD-L1–positive tumor.

JAVELIN-100 OS results

OS in the overall population

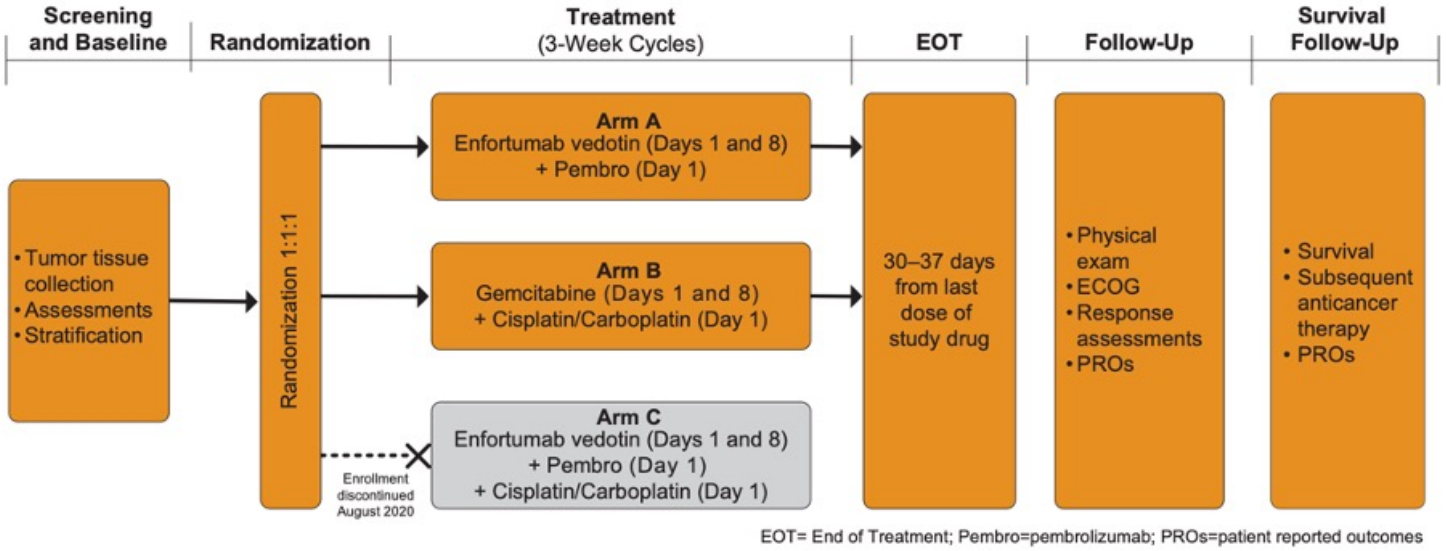


Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

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)

EV-302 Enfortumab vs Platinum Based Chemo



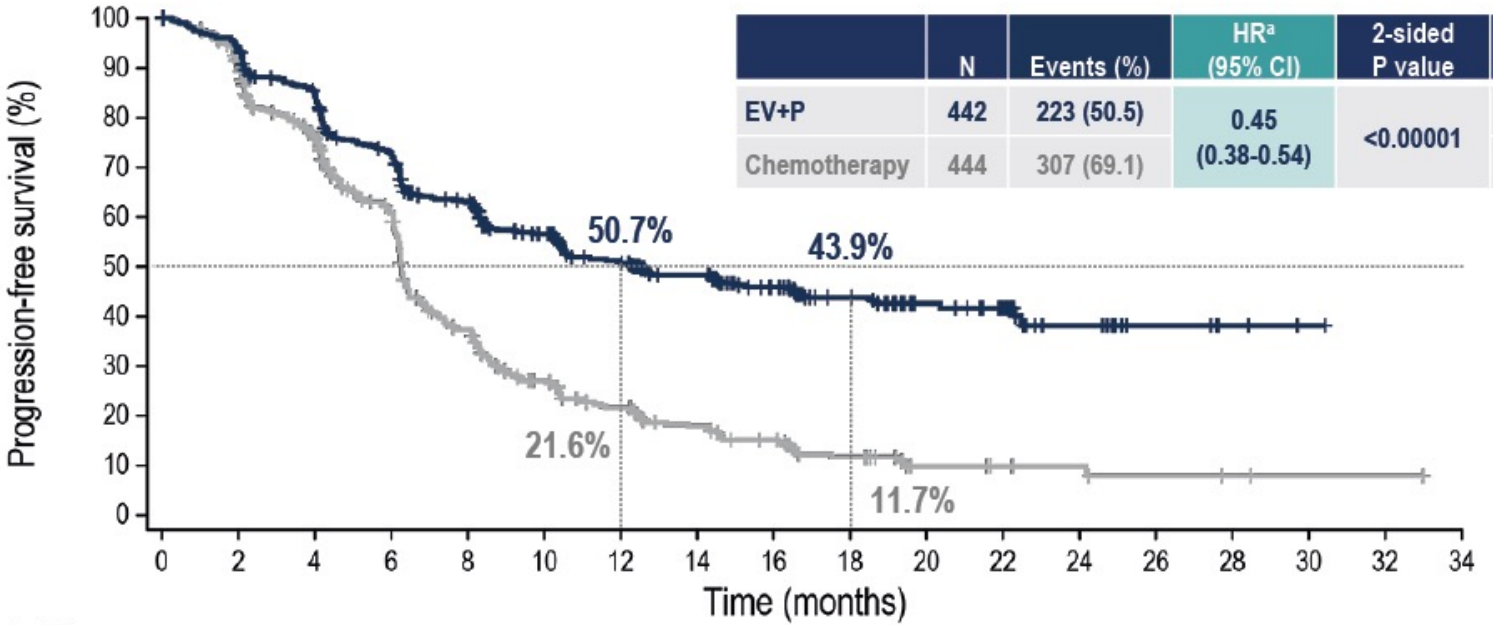
EOT= End of Treatment; Pembro=pembrolizumab; PROs=patient reported outcomes

- Stratification Factors for Randomization: cisplatin eligibility (eligible/ineligible), liver metastases (present/absent), PD-L1 expression (high/low)
- Follow-up until disease progression, death, consent withdrawal, or study closure

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



N at risk

EV+P	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

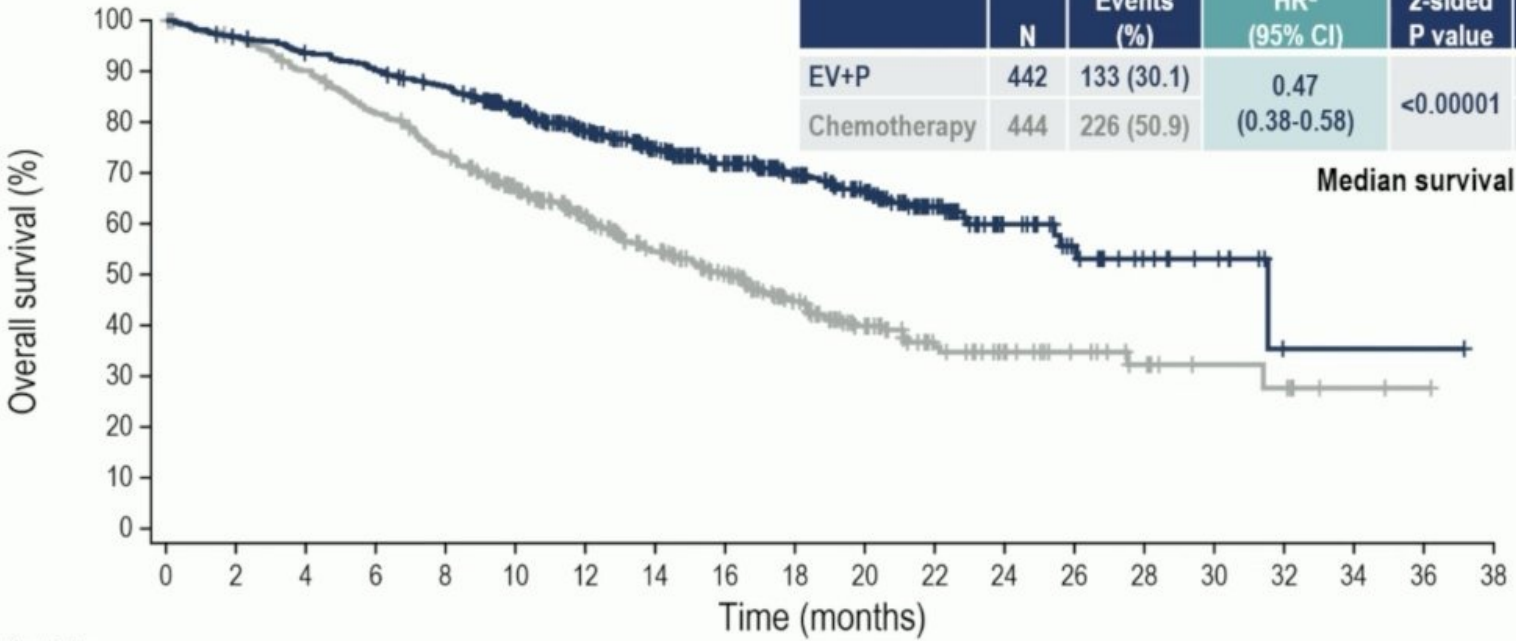
mPFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months

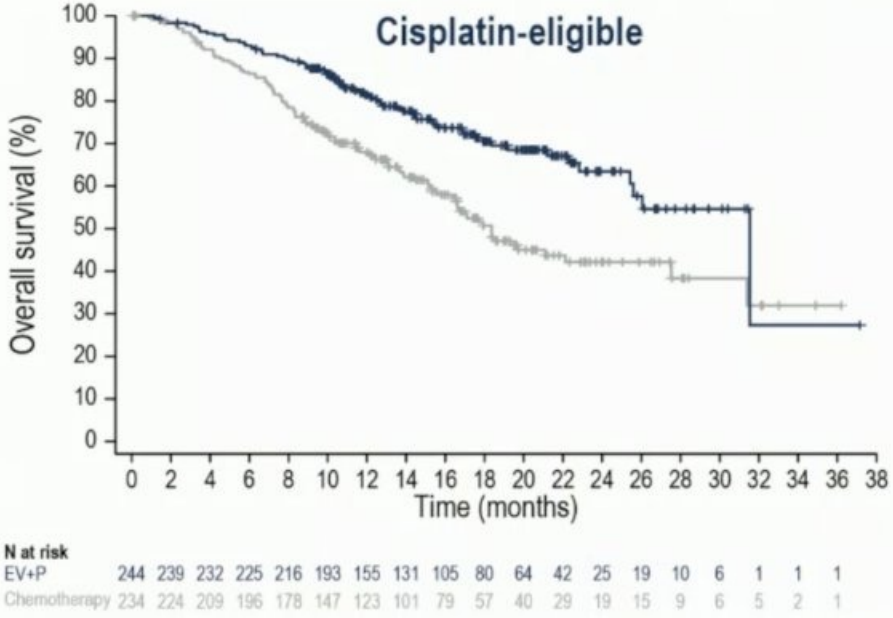


N at risk

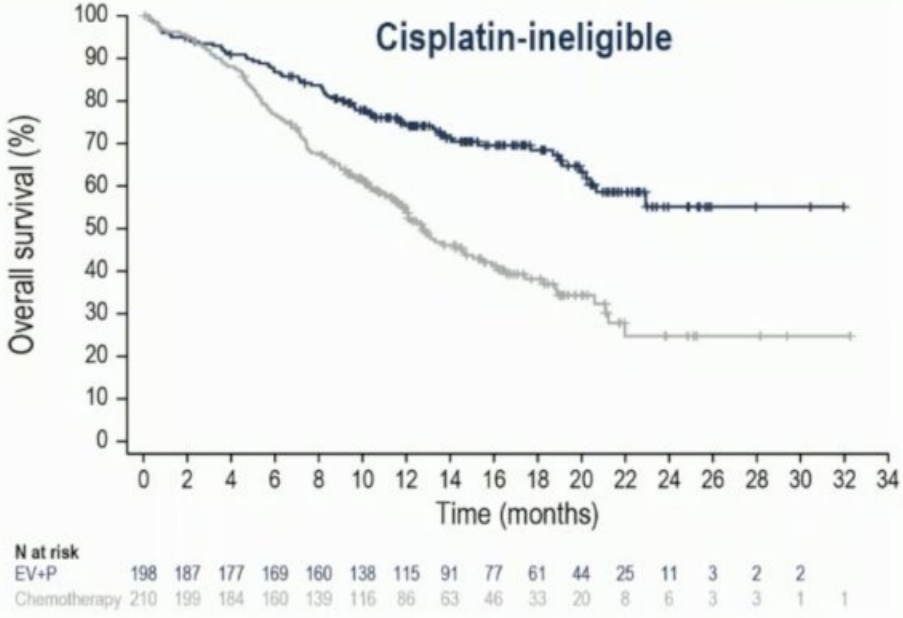
EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

OS Subgroup Analysis: Cisplatin Eligibility

OS benefit was consistent with overall population regardless of cisplatin eligibility

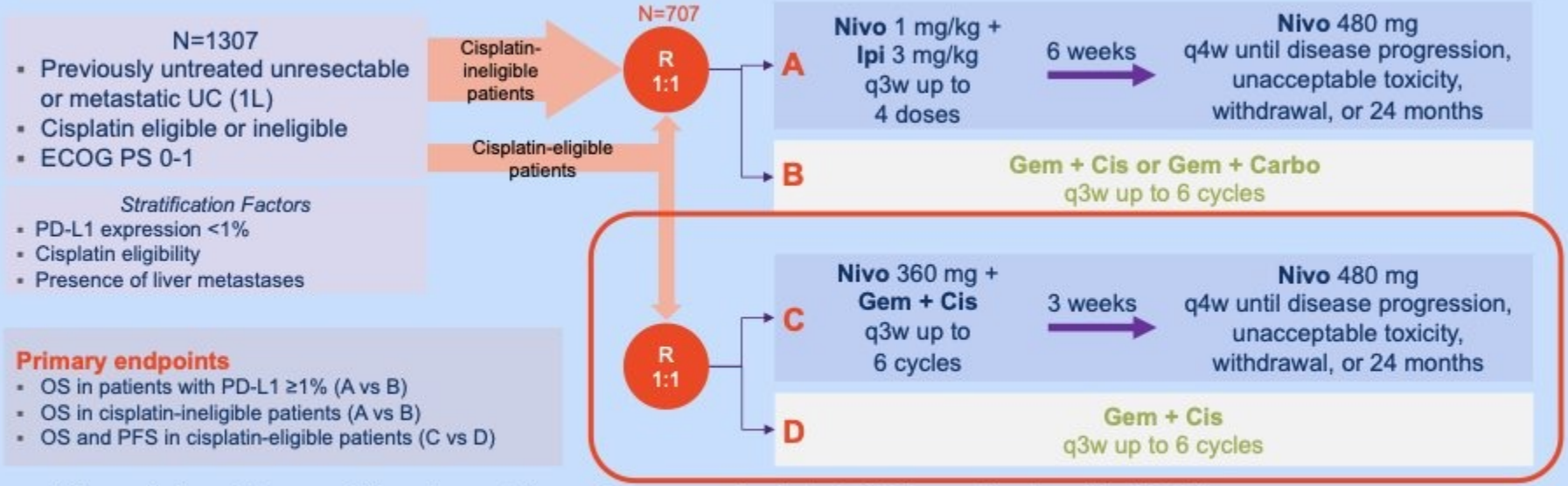


	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	69	0.53 (0.39-0.72)	31.5 (25.4-NR)
Chemotherapy	106		18.4 (16.4-27.5)



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	64	0.43 (0.31-0.59)	NR (20.7-NR)
Chemotherapy	120		12.7 (11.4-15.5)

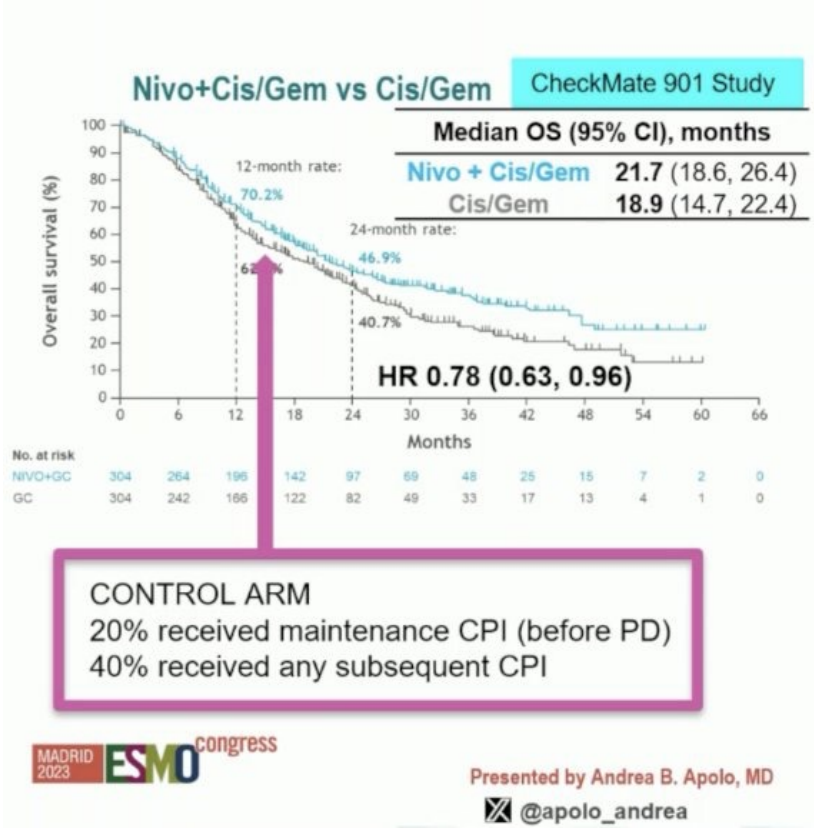
CheckMate 901: Phase 3 Trial of Nivolumab in Combination

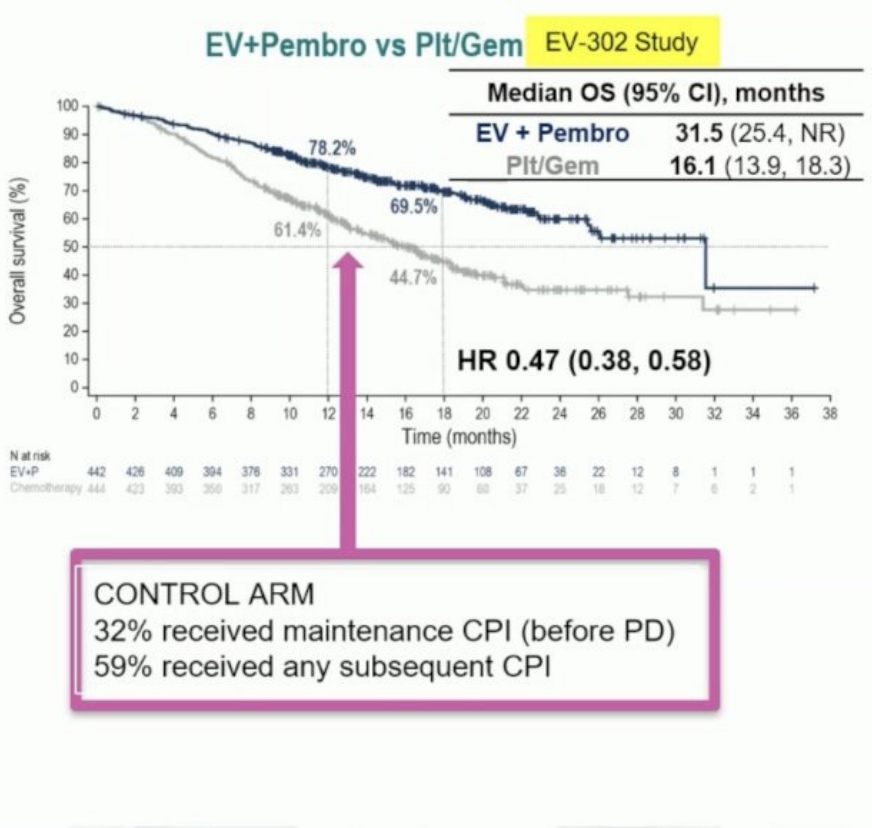


- Nivo + Ipi vs Chemo did not meet the primary endpoint of OS in patients with PD-L1 ≥1%
- Ongoing assessment of Nivo + Ipi vs Carbo + Gem in cisplatin-ineligible patients
- Ongoing substudy of Nivo + Cis + Gem vs Cis + Gem

Galsky MD. ASCO 2018. Abstract TPS4588.

EV302 and Checkmate 901

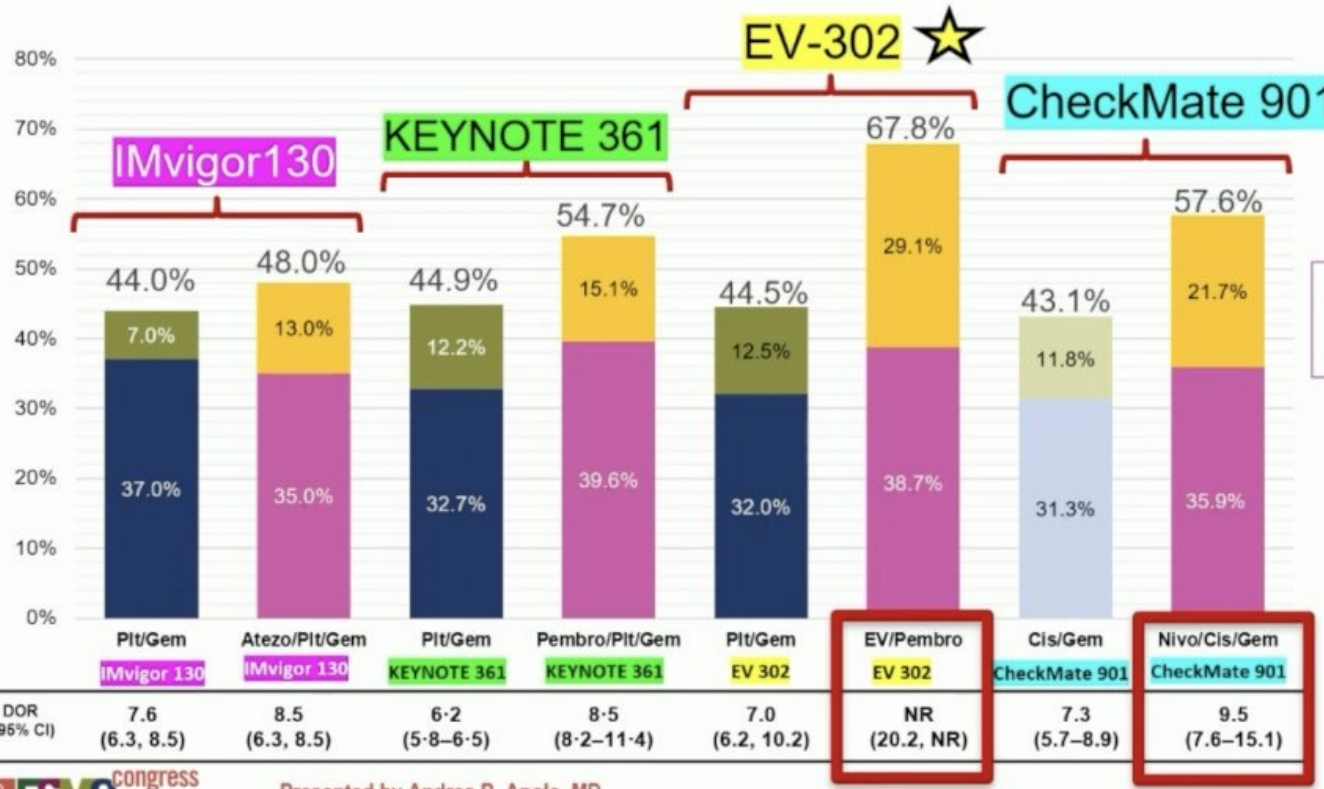




Cross-trial comparison on display

WARNING

EV + Pembro's Duration of Response is longer



	Plt/Gem IMvigor 130	Atezo/Plt/Gem IMvigor 130	Plt/Gem KEYNOTE 361	Pembro/Plt/Gem KEYNOTE 361	Plt/Gem EV 302	EV/Pembro EV 302	Cis/Gem CheckMate 901	Nivo/Cis/Gem CheckMate 901
Median DOR Months, (95% CI)	7.6 (6.3, 8.5)	8.5 (6.3, 8.5)	6·2 (5·8–6·5)	8·5 (8·2–11·4)	7.0 (6.2, 10.2)	NR (20.2, NR)	7.3 (5.7–8.9)	9.5 (7.6–15.1)

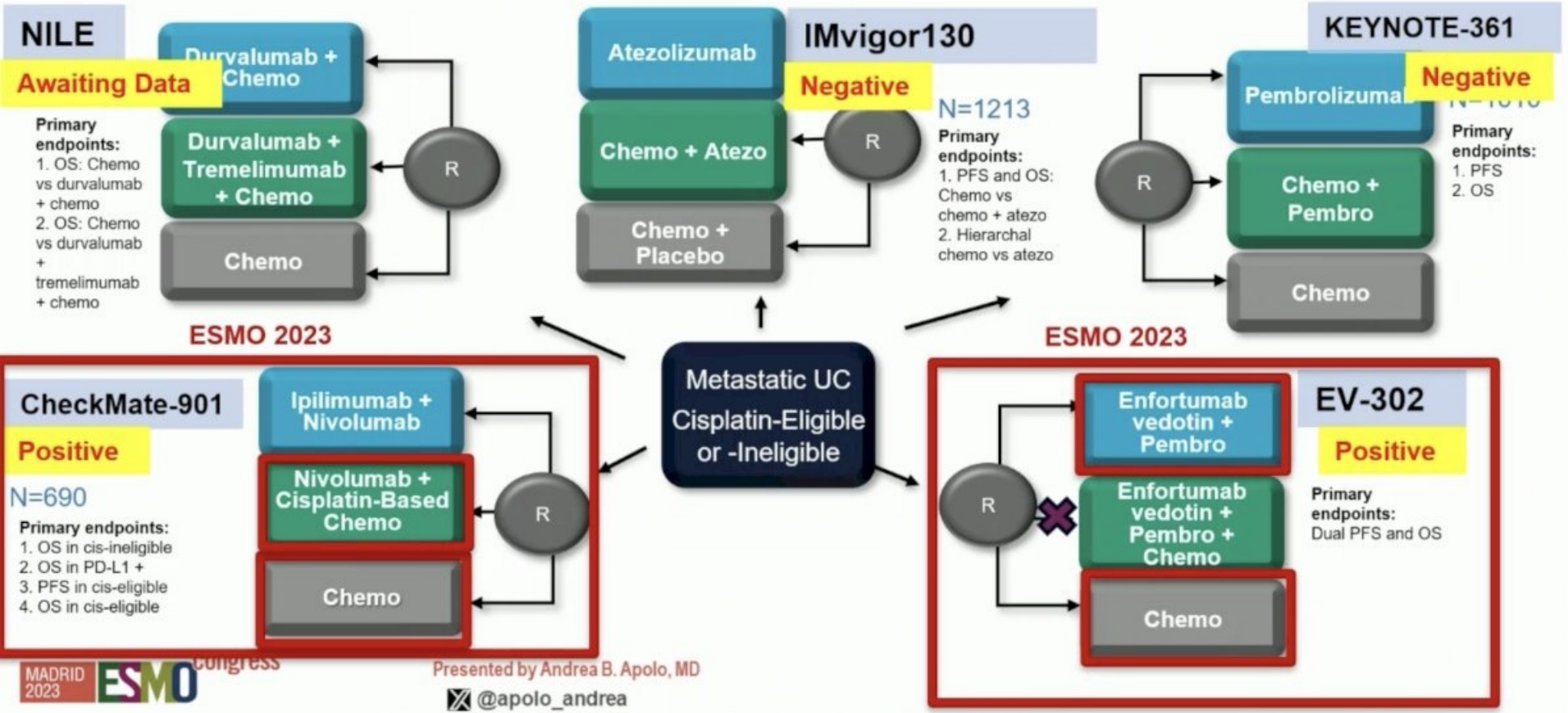
EV302 and CM901:
Time to response was ~2 months or first restaging scan

MADRID 2023 ESMO congress

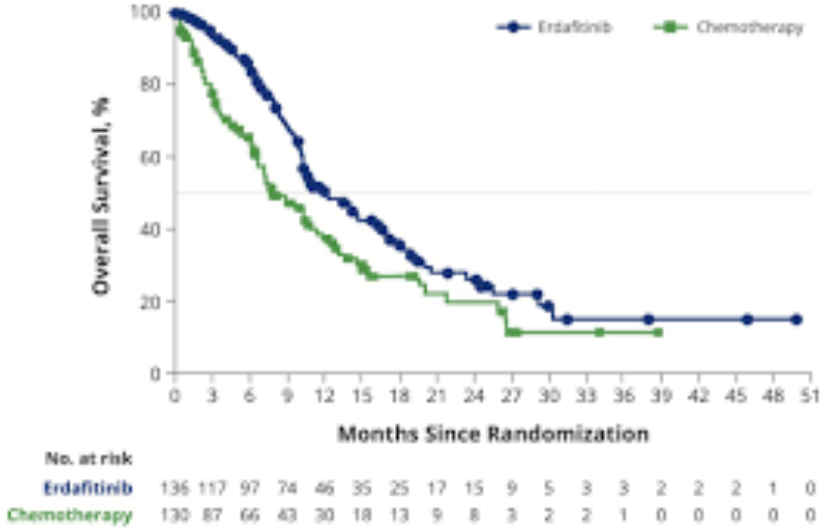
Presented by Andrea B. Apolo, MD

@apolo_andrea

First-line Phase 3 Trials with Checkpoint-Inhibitor Combinations vs Platinum-based Chemo for Metastatic Urothelial Carcinoma



THOR trial: Erdafitinib vs Taxane Chemo post Platinum therapy in met Urothelial cancer



	Erdafitinib (136 patients)	Chemotherapy (130 patients)
OS, median (95% CI), mo	12.1	7.8
HR (95% CI)	0.64 [0.47, 0.88]; *P* = .005	
PFS, median (95% CI), mo	5.6	2.7
HR (95% CI)	0.58 [0.44, 0.78]; *P* = .0002	
ORR, %	45.6	11.5
RR (95% CI)	3.94 [2.37, 6.57]; *P* < .001	

Comparison of Patient Characteristics: THOR, EV-301 and TROPHY-U-1

	UT Primary	Bladder Primary	Visceral disease	Liver Metastases	PDL-1 Low	Prior CT 1-2	Prior CT
THOR	30.1	69.9	74.3	22.8	92.7	100	0
EV-301	32	67	77.7	30.9	NR	87	13
TROPHY-U-01	NR	NR	66.0	34.0	NR	47	50

Loriot Y LBA 4619 Proc ASCO 2023; Powles T et al NEJM 2021;Tagawa S et al JCO 2021

Efficacy: THOR, EV-301 and TROPHY-U-1

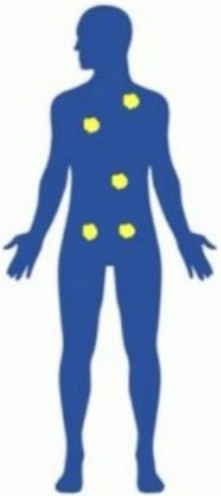
	Median Survival (Months)	Progression Free Survival (Months)	Complete Response (%)	Partial Response (%)
THOR	12.1	5.6	6.6	39.0
EV-301	12.9	5.5	4.9	35.7
TROPHY-U-01	10.9	5.4	5.3	22.1

Loriot Y LBA 4619 Proc ASCO 2023; Powles T et al NEJM 2021;Tagawa S et al JCO 2021

Toxicity: THOR, EV-103 and TROPHY-U-1

	All Grades (%)	Grade 3 or 4 (%)
Erdafitinib	78.5	5.2
Hyperphosphatemia	54.8	3.0
Diarrhea	17.2	2.2
Central Serous Retinopathy		
Enfortumab Vedotin		
Peripheral Sensory Neuropathy	33.8	3.0
Rash	16.2	7.4
Neutropenia	6.8	4.7
Sacituzumab Govitecan		
Neutropenia	46.0	34
Diarrhea	65.0	4

What would be the best 2nd line therapy?



First-Line

- Enfortumab vedotin + Pembrolizumab

Second-Line?

Cisplatin-eligible

- Cisplatin + gemcitabine
- Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (ddMVAC)

Cisplatin-ineligible

- Carboplatin + gemcitabine

Beyond-Second -Line

- Erdafitinib (if tumor + FGFR 2/3 genetic alterations)
- Sacituzumab govitecan
- Clinical trial
- Paclitaxel, docetaxel, or vinflunine

New Paradigm of Bladder Cancer Therapy

Front Line Therapy:
Enfortumab + Pembro
No reason to consider platinum eligibility

Second Line:
FGFR3 mutation:
Erdafitinib

Sacituzumab?
or
Platinum + Gem?

Third Line:

Clinical Trial

Her-2 ADC?

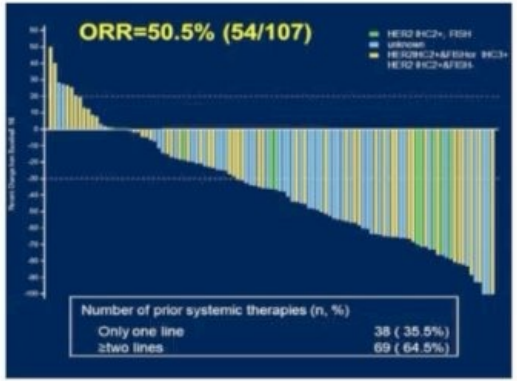
Sacituzumab

Does CPI combine best with ADCs with MMAE payloads?

Disitamab vedotin in HER2 2/3+ Metastatic Urothelial Carcinoma

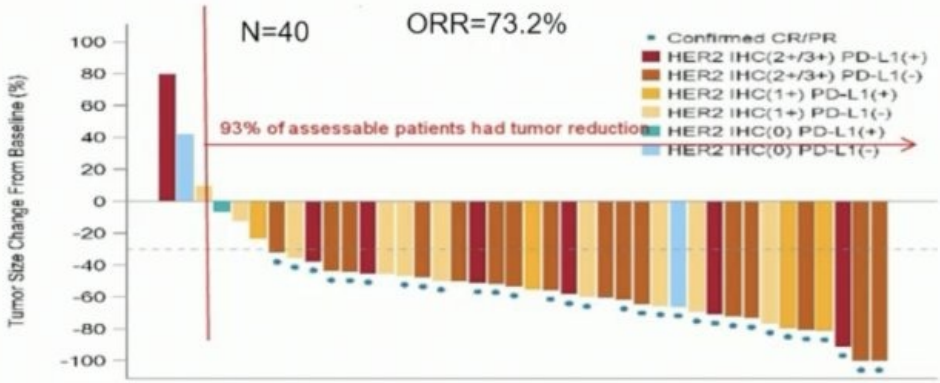
Disitamab vedotin

N=107 In the Second or Third-line setting



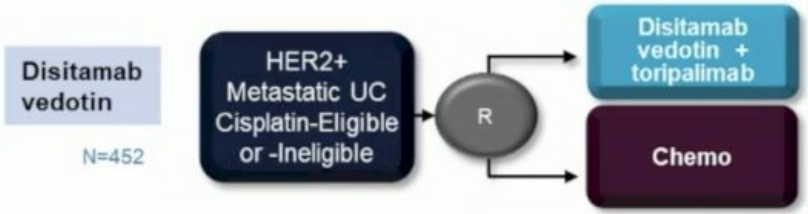
Sheng, et al. ASCO 2022 abstract 4518

Disitamab vedotin + toripalimab

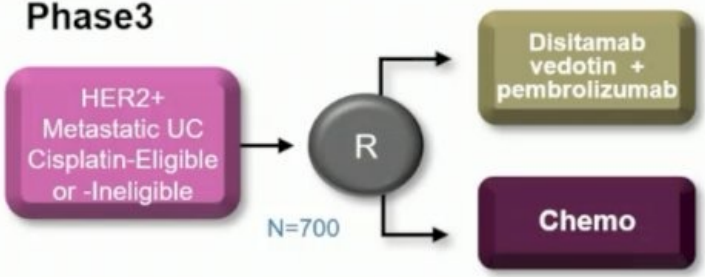


Sheng, X., et al. ASCO 2023

Phase 3



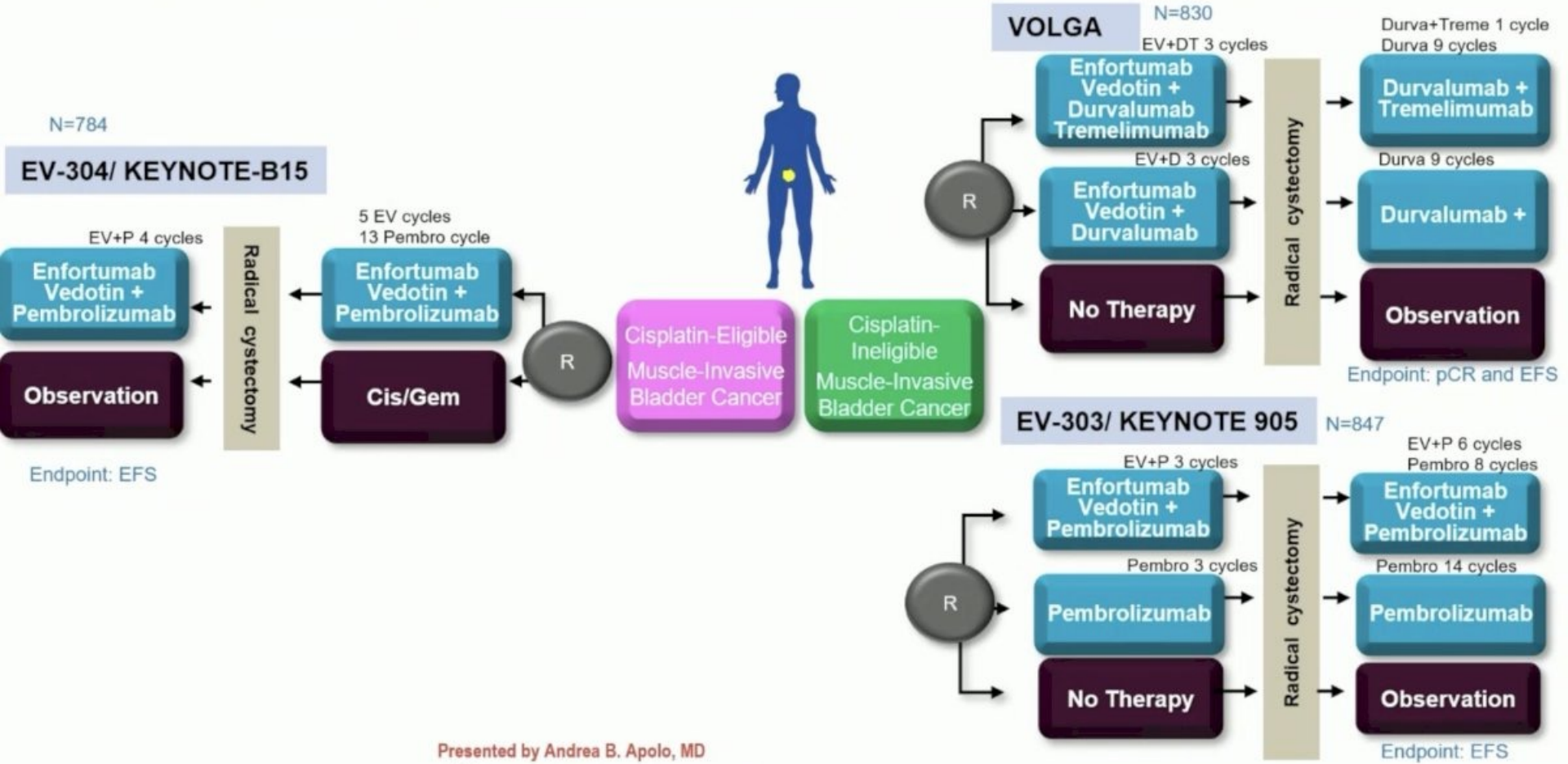
Phase3



Presented by Andrea B. Apolo, MD

@apolo_andrea

What is the efficacy of EV+CPI as Neoadjuvant or Adjuvant Therapy for MIBC?



Presented by Andrea B. Apolo, MD
@apolo_andrea

How do you decide on Therapy Choice?

- Toxicity/efficacy balance
- Optimize therapy
- Sites of mets
- Judicious AE management
- QOL
- Cost/access

Urothelial Cancer Therapy is now a MARATHON!