

1st line advanced disease .

Thomas Powles

Director of Barts Cancer Center.

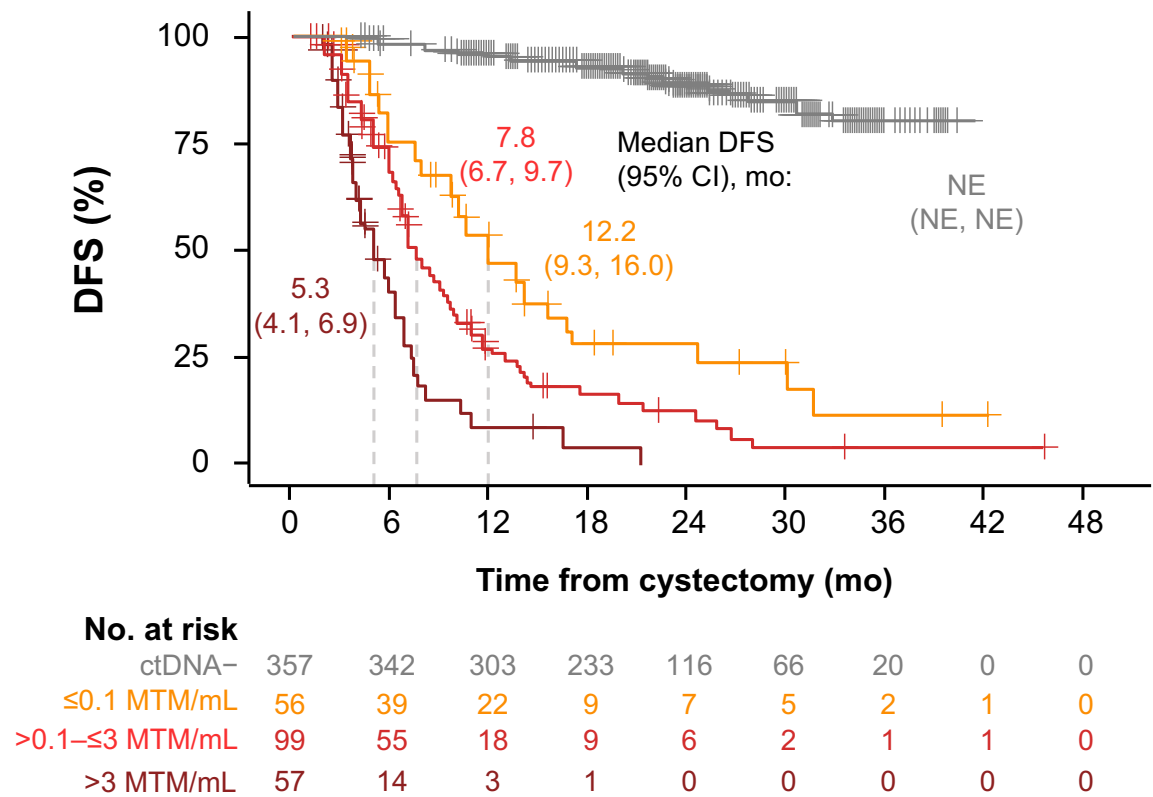
Professor of Urology Cancer, Barts Cancer Institute.



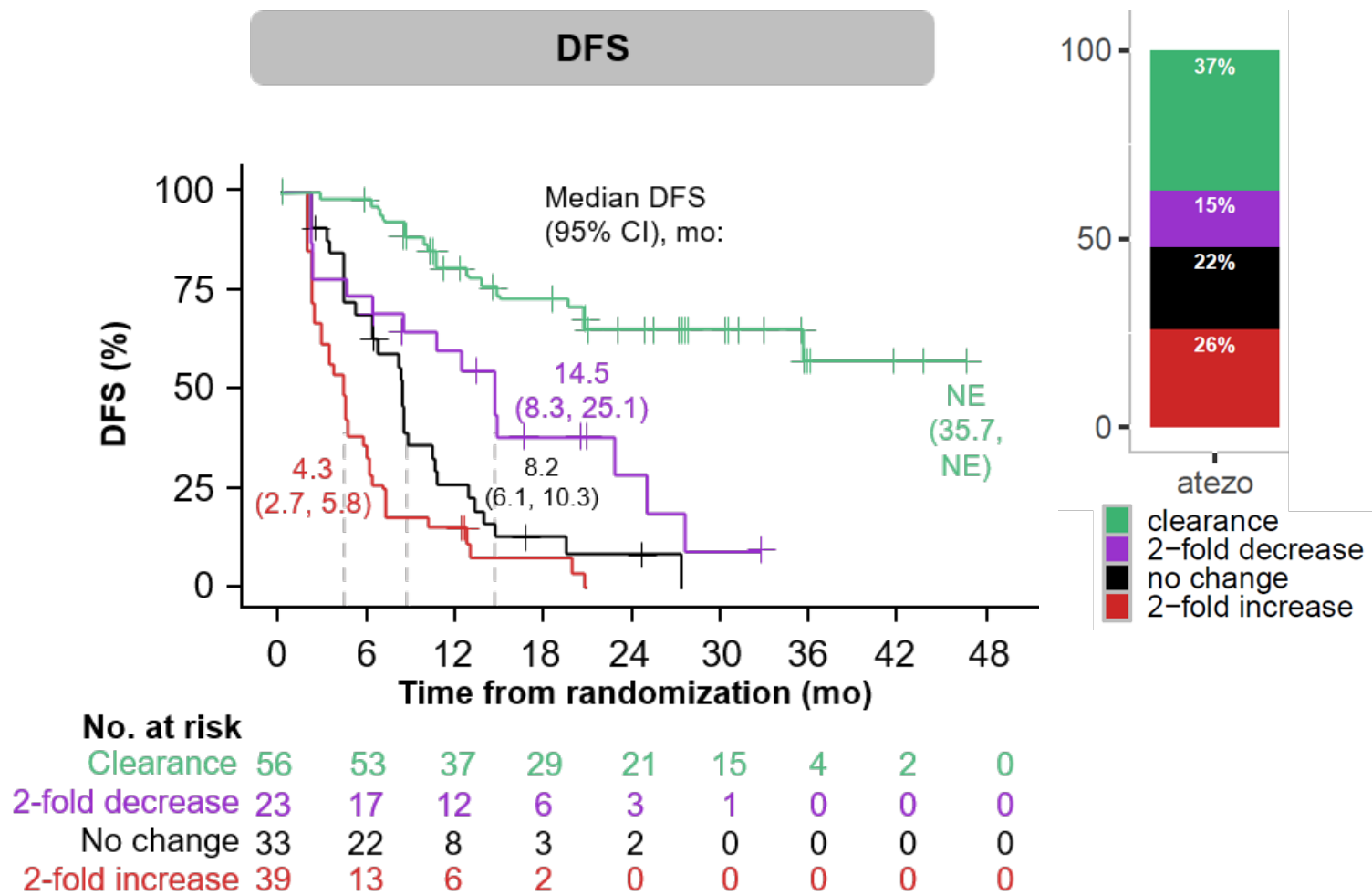
When do we define advanced disease?



ctDNA levels post surgery in the adjuvant setting

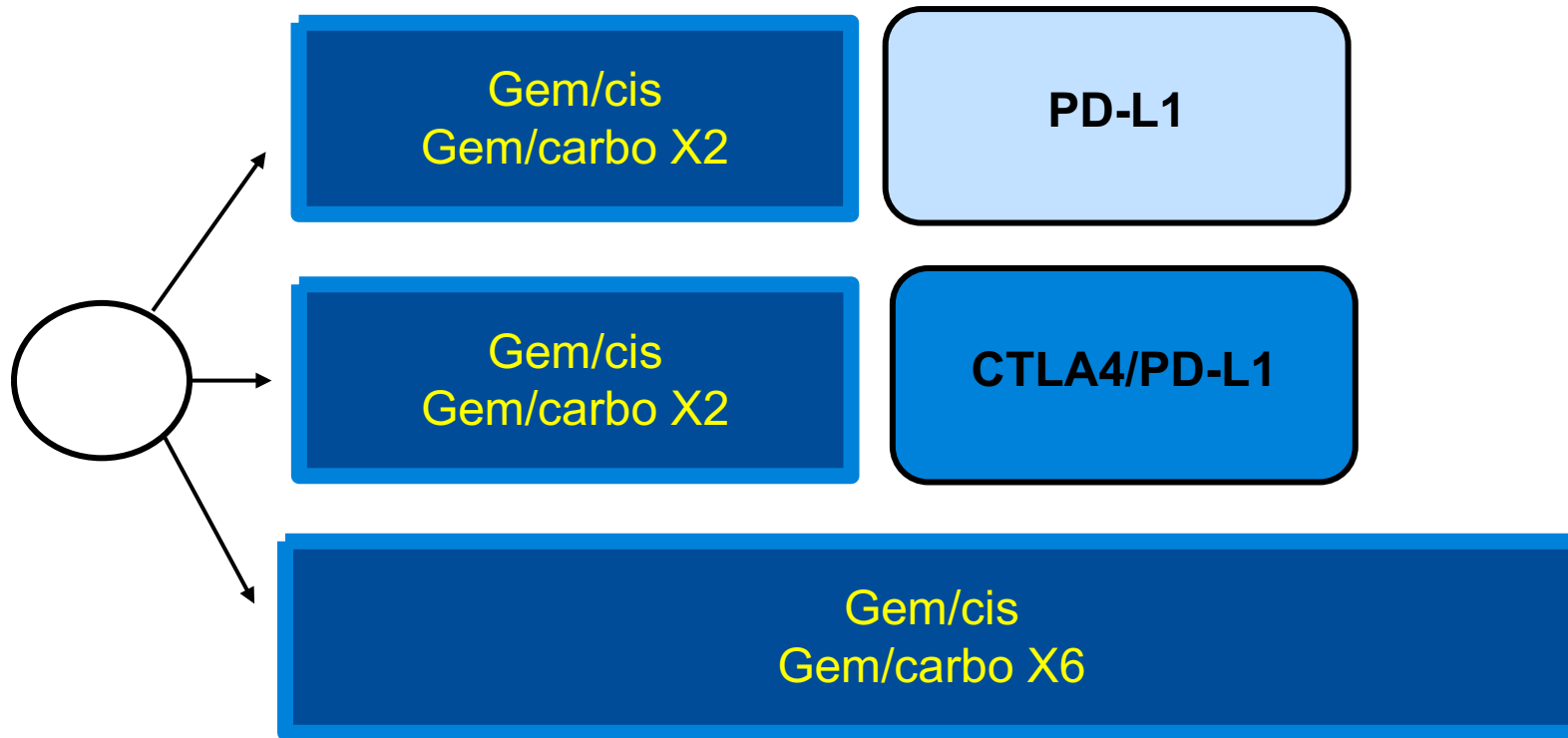


Dynamic changes to ctDNA will be more sensitive than radiology

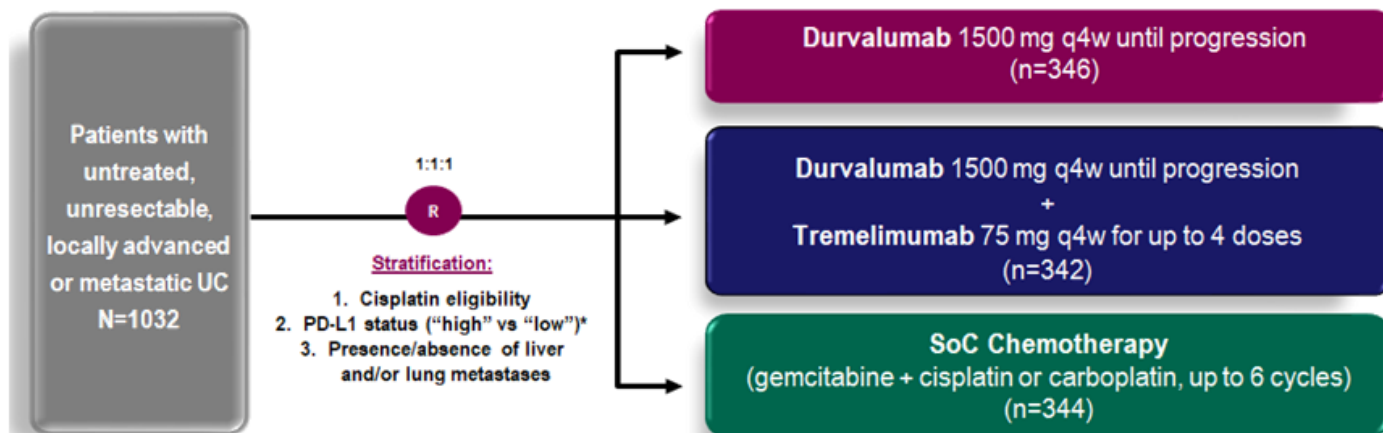


Dynamic changes as 6 weeks

Which 1st line metastatic study was this this?



Overview of DANUBE trial



CO-PRIMARY ENDPOINTS

- OS (D vs SoC in PD-L1 high)
- OS (D+T vs SoC in all comers)

SELECT SECONDARY ENDPOINTS

- OS (D vs SoC in all comers)
- OS (D+T vs SoC in PD-L1 high)
- PFS, ORR, and DoR

Data cutoff date (final analysis):
January 27, 2020

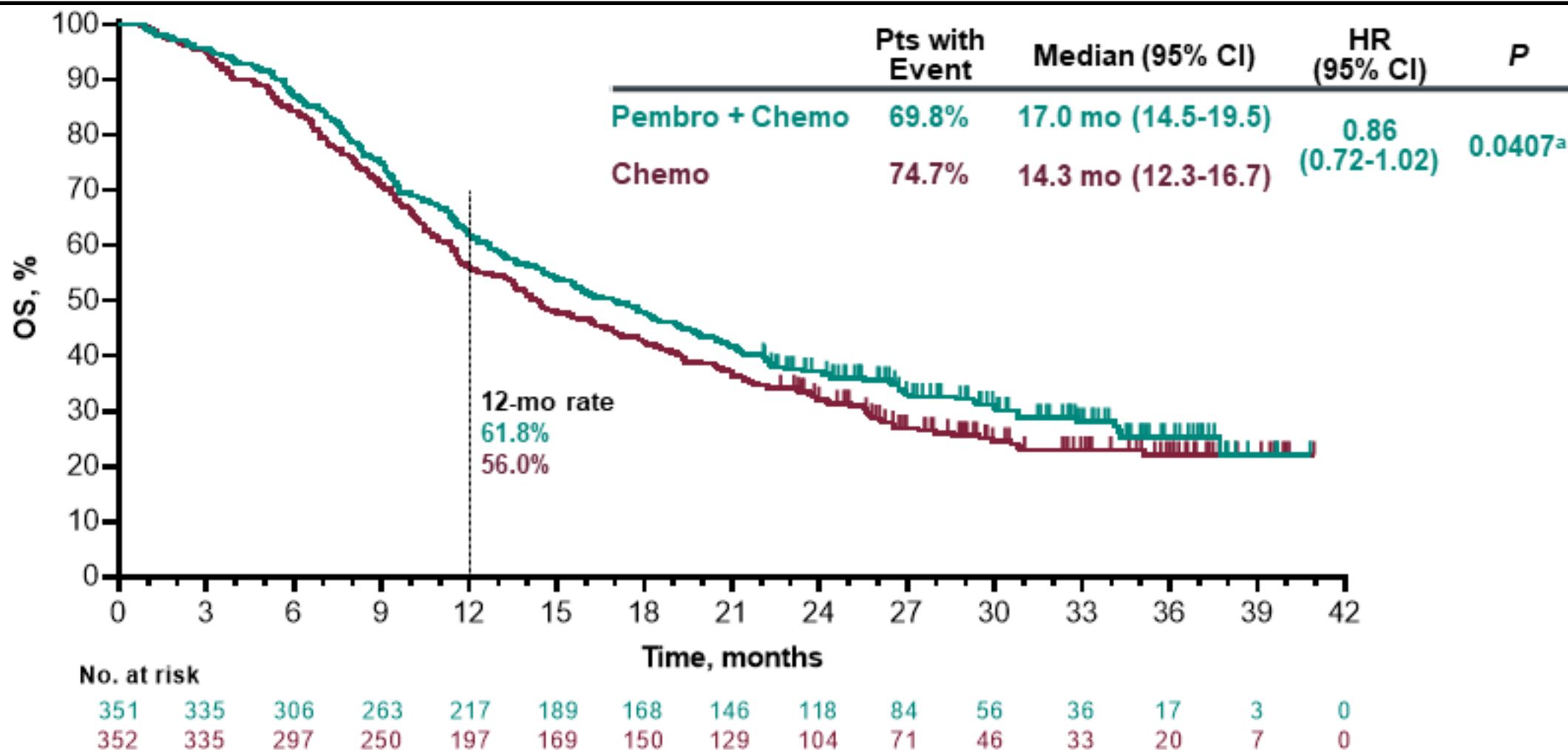
Minimum follow-up from date last patient randomised:
34 months

Median follow-up for survival:
41.2 months for all patients

	CO-PRIMARY ENDPOINTS				SECONDARY ENDPOINTS			
	D vs SoC, PD-L1 High		D + T vs SoC, ITT		D vs SoC, ITT		D + T vs SoC, PD-L1 High	
	Durvalumab (n=209)	Chemotherapy (n=207)	Durvalumab + Tremelimumab (n=342)	Chemotherapy (n=344)	Durvalumab (n=346)	Chemotherapy (n=344)	Durvalumab + Tremelimumab (n=205)	Chemotherapy (n=207)
Median OS, mos. (95% CI)	14.4 (10.4–17.3)	12.1 (10.4–15.0)	15.1 (13.1–18.0)	12.1 (10.9–14.0)	13.2 (10.3–15.0)	12.1 (10.9–14.0)	17.9 (14.8–24.2)	12.1 (10.4–15.0)
HR (95% CI)	0.89 (0.71–1.11)		0.85 (0.72–1.02)		0.99 (0.83–1.17)		0.74 (0.59–0.93)	
Log-rank P value*	0.3039		0.0751					

Powles T, et al. *Lancet Oncol.* 2020; 21: 1574-1588.

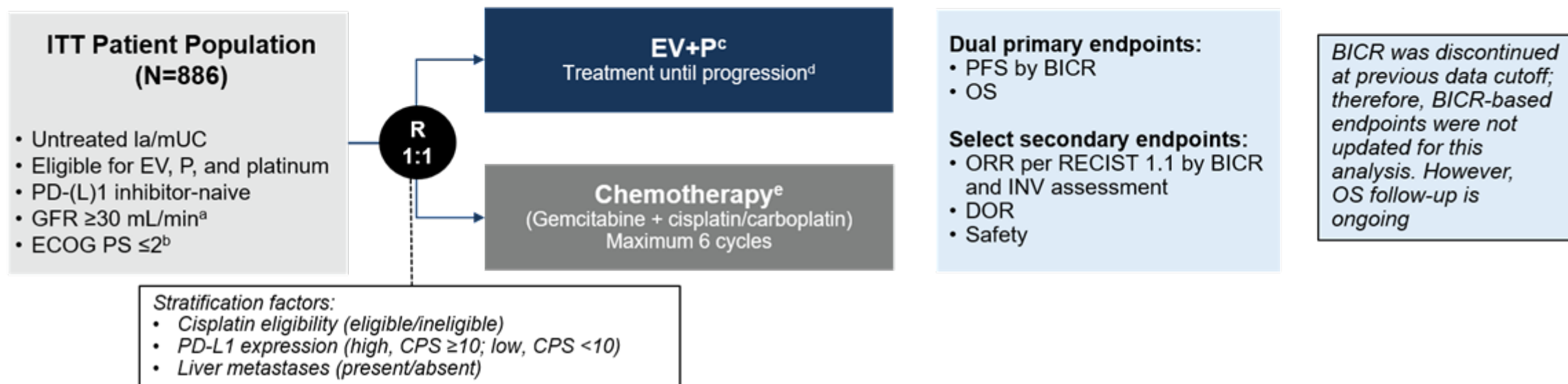
Platinum based chemotherapy +/- pembrolizumab in front line UC



^aP-value boundary of significance at final analysis ≤ 0.0142 . Per the statistical analysis plan, no further formal statistical testing was performed.

Data cutoff date: April 29, 2020.

EV-302/KEYNOTE-A39 Design¹



- This analysis evaluated efficacy and safety outcomes in the ITT population (median follow-up of 42.8 months)
 - Additionally, exploratory subgroup analyses evaluated outcomes in patients who achieved CR (directly or after PR) as well as in patients treated with EV+P for a DOT > 1 or 2 years

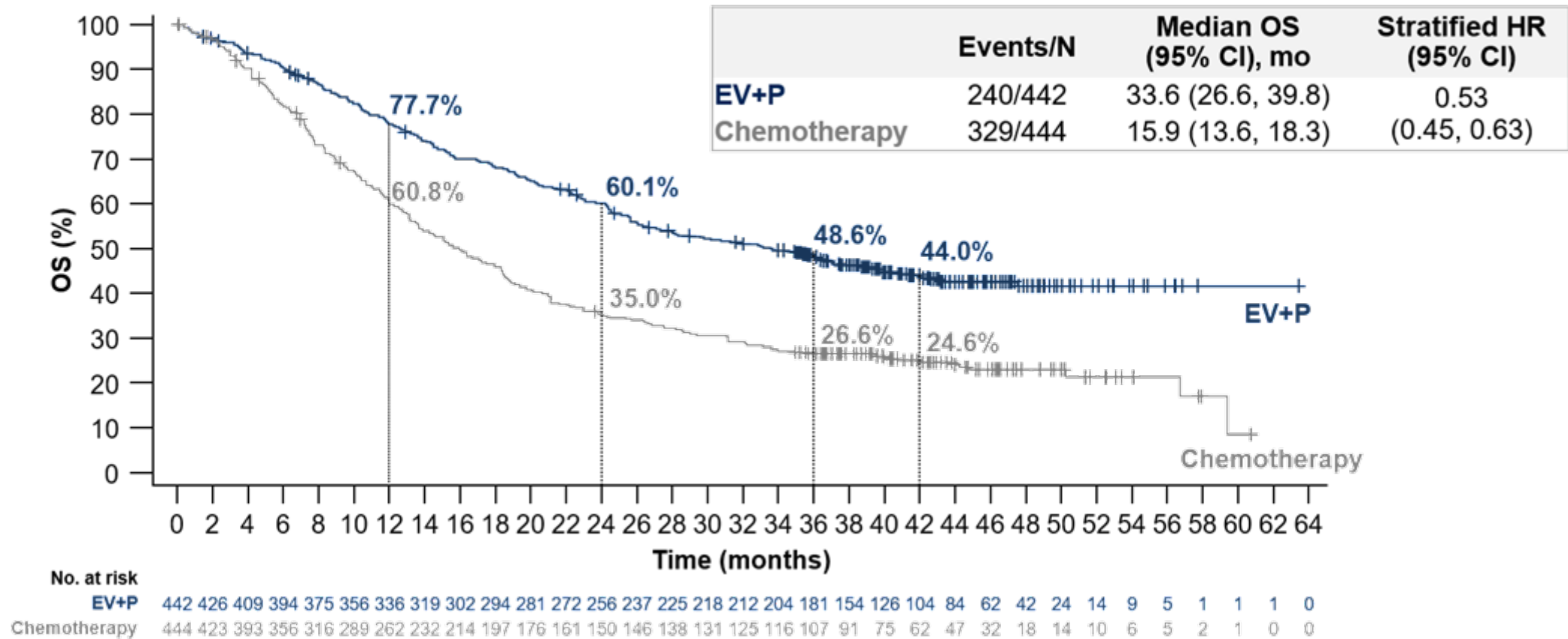
Data cutoff: October 6, 2025. NCT04223856.

BICR, blinded independent central review; CPS, combined positive score; DOR, duration of response; DOT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; GFR, glomerular filtration rate; INV, investigator; IV, intravenously; ITT, intention-to-treat; NYHA, New York Heart Association; ORR, objective response rate; PS, overall survival; P, pembrolizumab; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors. ^aMeasured by Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine; ^bPatients with ECOG PS of 2 were required to also meet additional criteria: hemoglobin ≥ 10 g/dL and GFR ≥ 50 mL/min but may not have NYHA class III heart failure. ^cPatients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1. No maximum number of treatment cycles for EV; maximum of 35 cycles for P. ^dTreatment until progression by BICR, clinical progression, unacceptable toxicity, or if applicable, maximum cycles. ^eCisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol defined.

1. Powles T, et al. N Engl J Med. 2024;390(10):875-88.

Updated OS (ITT Population)

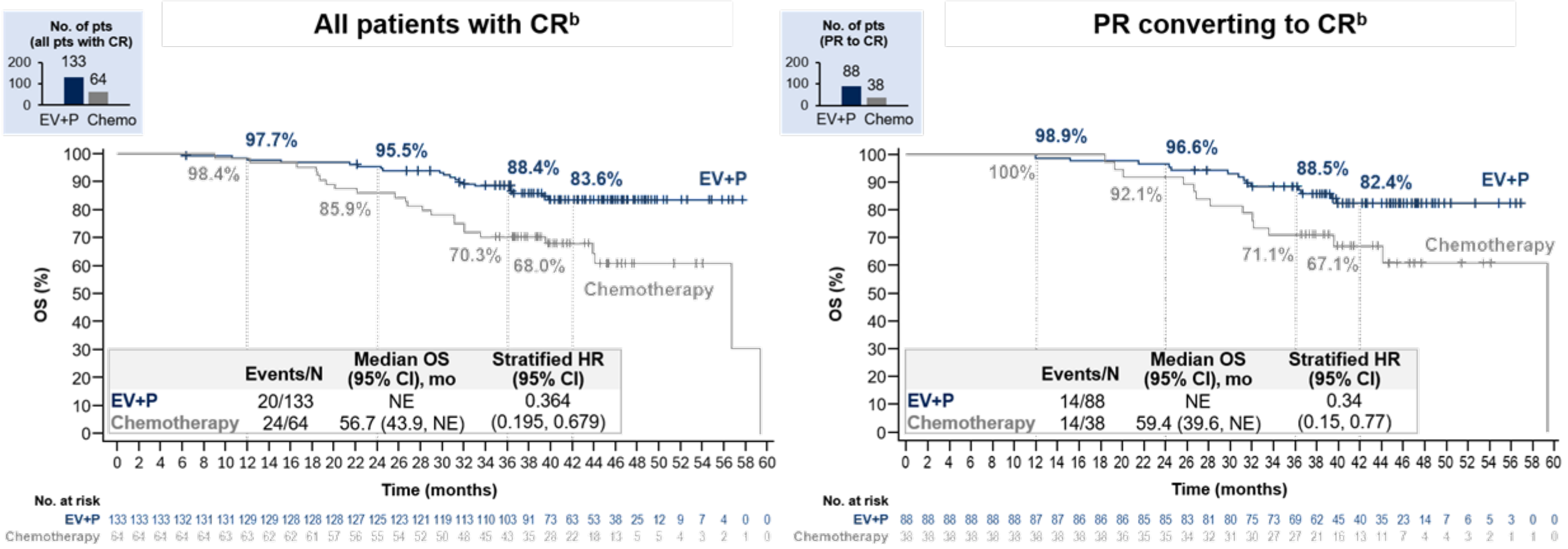
At 3.5 years, an estimated 44.0% of patients in the EV+P arm were alive vs 24.6% in the chemotherapy arm^a



Data cutoff: October 6, 2025. Median follow-up, 42.8 mo.
EV, enfortumab vedotin; ITT, intention-to-treat; OS, overall survival; P, pembrolizumab.
^aBased on Kaplan-Meier estimates.

OS Among Patients with CR^a

Among patients who achieved CR, those whose response deepened from PR to CR had similar 3.5-year survival to the overall CR group (82.4% vs 83.6%)^a

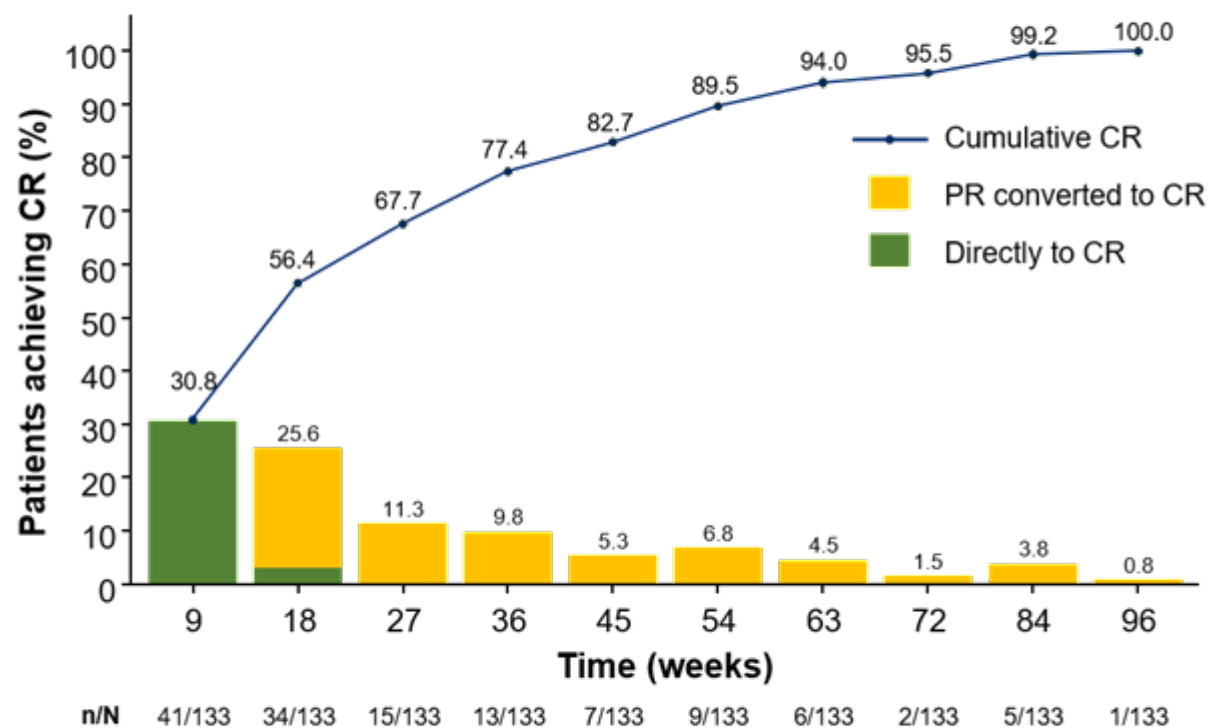


Data cutoff: October 6, 2025.
CR, complete response; EV, enfortumab vedotin; NE, not estimable; OS, overall survival; P, pembrolizumab; PR, partial response. ^aBased on Kaplan-Meier estimates. ^bIn the response evaluable set by BICR; data cutoff August 8, 2024.
1. Powles T, et al. Ann Oncol 2025;36:1212-19. 2. Gupta S, et al. ASCO 2025. Abstract 4502 (Oral).

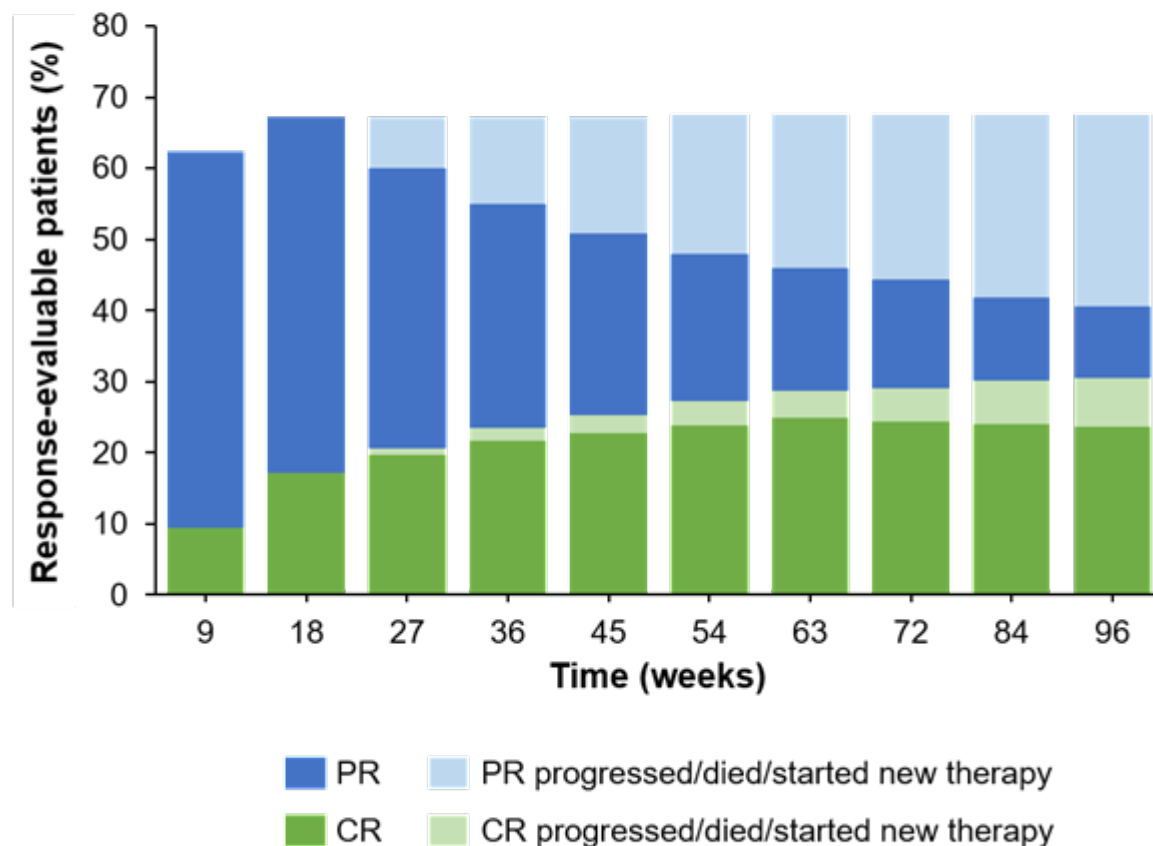
Cumulative Response Rates in the EV+P Arm

Patients continue to achieve CRs over time and CRs show long-term durability

Cumulative CR over time^a



Cumulative ORR over time^a



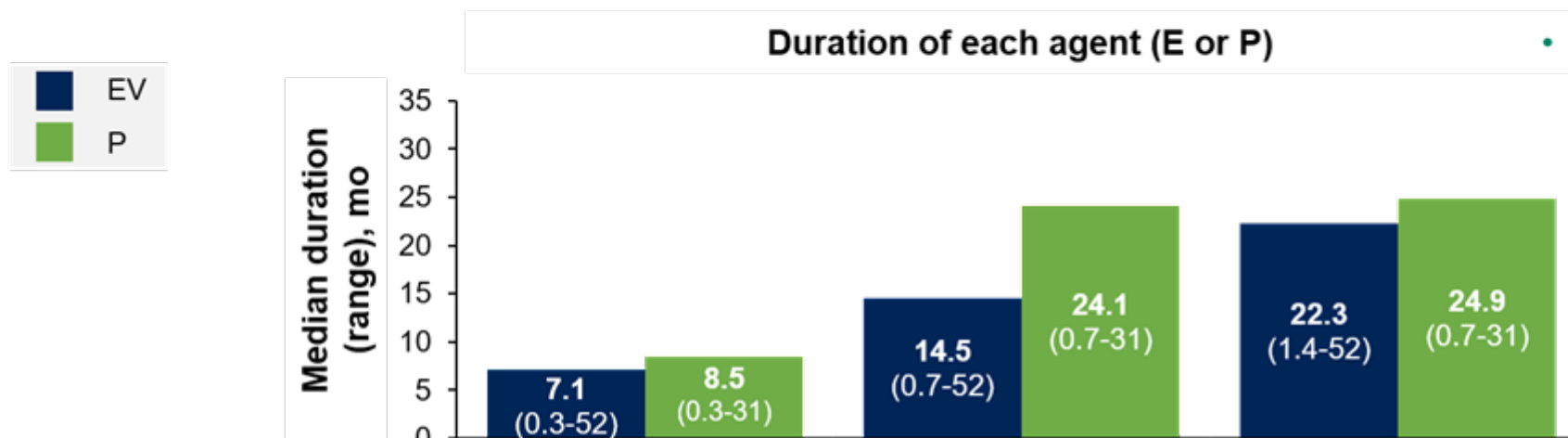
Data cutoff: October 6, 2025.

CR, complete response; EV, enfortumab vedotin; P, pembrolizumab; PR, partial response.

^aIn the response evaluable set by blinded independent central review; data cutoff August 8, 2024.

Safety and Treatment Exposure (EV+P arm)

Safety in patients able to stay on EV+P with DOT >1 or >2 years was similar to the overall population despite longer treatment



Median EV+P duration (both agents):

- Overall^a: 12 cycles (range, 1-73)^b and 9.6 months (range, 0.3-52)
- EV+P DOT >1 year: 34 cycles (range, 9-73)^b and 24.3 months (range, 12.2-52)
- EV+P DOT >2 years: 41 cycles (range, 30-73)^{b,c} and 26.4 months (range, 24.1-52)

Patients, n (%)	Overall population ^a (n=440)	EV+P DOT >1 year (n=184)	EV+P DOT >2 year (n=102)
Patients with TRAEs			
All Grades	428 (97.3)	183 (99.5)	102 (100)
Grade ≥3	251 (57.0)	108 (58.7)	59 (57.8)

Data cutoff: October 6, 2025.

DOT, duration of treatment; EV, enfortumab vedotin; P, pembrolizumab; TRAE, treatment-related adverse event.

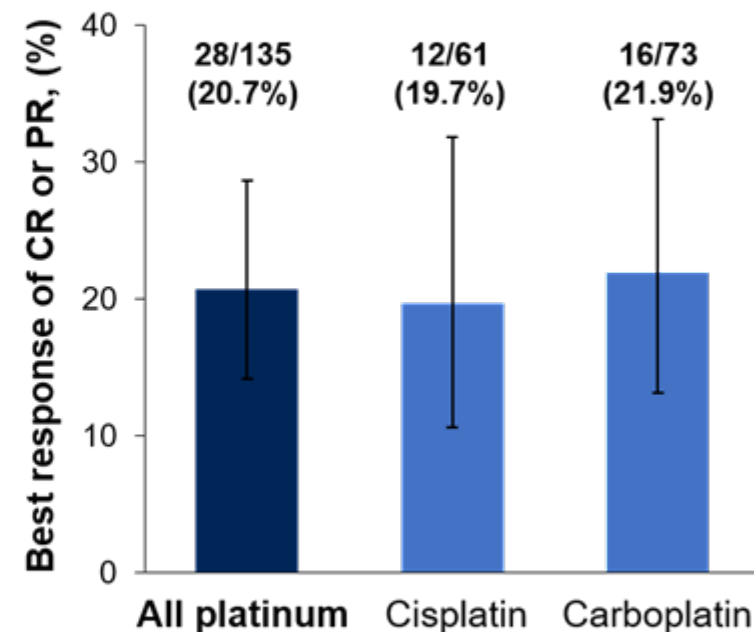
^aSafety analysis set. ^bCycle with any amount (>0) of study drug. ^cMaximum number of 35 treatment cycles for P per protocol.

Subsequent Therapy (ITT population)

In the EV+P arm, the most common first subsequent treatment was platinum-based chemotherapy, which resulted in an ORR of 21% and a median OS of 10.9 months

	EV+P (n=442)
Patients who received subsequent anticancer therapies, n (%)	192 (43.4)
Systemic therapy	173 (39.1)
First subsequent systemic therapy, n (%)	
Platinum-containing chemotherapy^a	135 (30.5)
Carboplatin-based therapy	73 (16.5)
Cisplatin-based therapy	61 (13.8)
PD-(L)1 inhibitor therapy^b	17 (3.8)
Maintenance	0
EV+P-based therapy	2 (0.5)
Other PD-(L)1 inhibitor therapy	15 (3.4)
Atezolizumab	1 (0.2)
Pembrolizumab	14 (3.2)
Other	21 (4.8)

ORR in evaluable patients receiving subsequent platinum-based chemotherapy^{a,c}



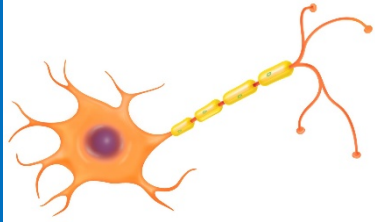
- Median OS from start of platinum-based chemotherapy was 10.9 months (95% CI 8.3, 12.8)

Data cutoff: October 6, 2025.

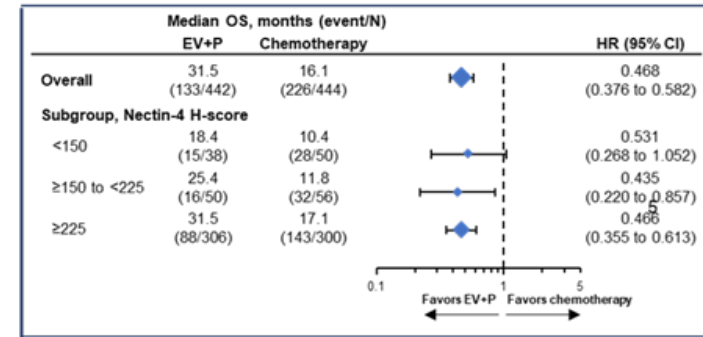
DOT, duration of treatment; EV, enfortumab vedotin; P, pembrolizumab; PD-(L)1, programmed death (ligand) 1. ^aWhen platinum-based therapy and a PD-(L)1 inhibitor were given in the same line of therapy, the therapy was categorized as platinum-containing therapy; one patient received a platinum agent other than carboplatin or cisplatin. ^bPatients could receive more than one PD-(L)1 agent in the same line of therapy; only agents used in >1% of patients in at least one arm are listed. ^cSubsequent response data were reported by the study sites and were not collected systematically across patients.

What are the next steps for EV and pembrolizumab in urothelial cancer ?

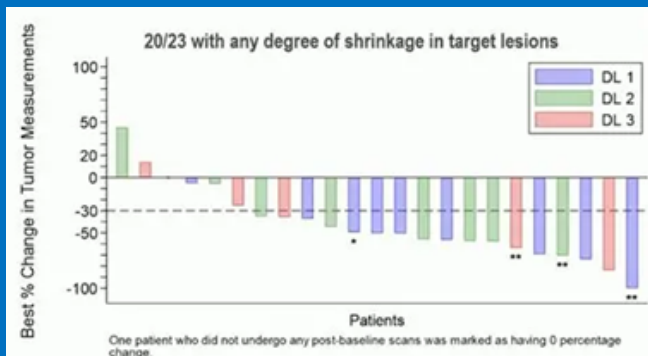
When to stop therapy?



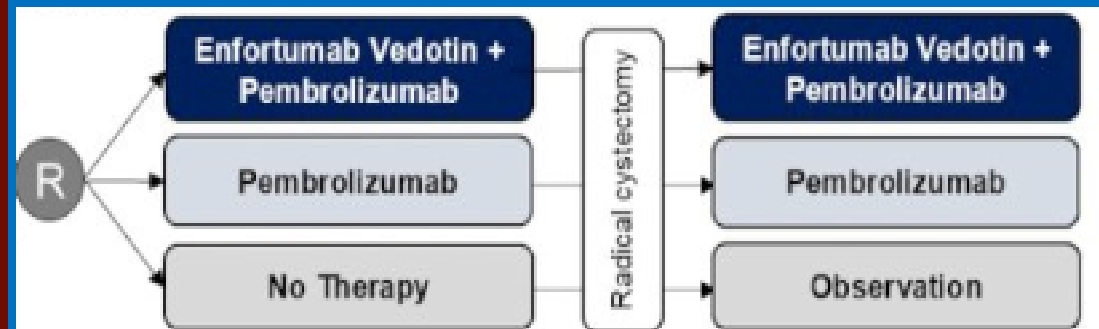
Should we use the Nectin 4 biomarker



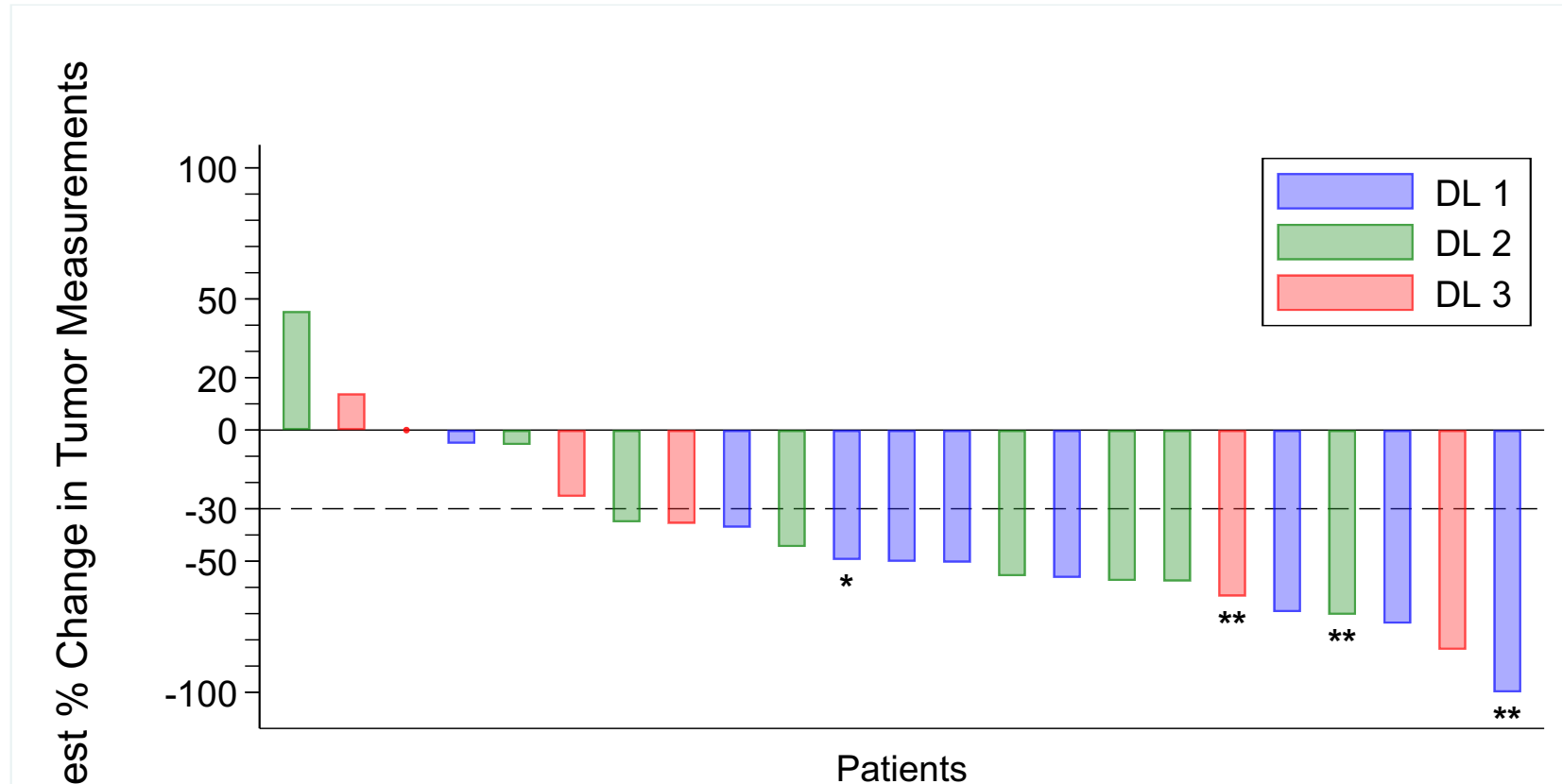
Can we combine with other ADCs for triplets?



What do we do for patients who have had EVP in MIBC



Enforumab vedotin with Sacituzimab vedotin in pretreated advanced urothelial cancer



One patient who did not undergo any post-baseline scans was marked as having 0 percentage change.

* One patient experienced progressive disease due to the emergence of a new non-target lesion, despite the reduction in a target lesion.

** Among three patients with complete response, two had lymph node lesions and the sum of lesions was not zero for those achieving a complete response.

**Add PD-1
Or PD1/VEFD**

FORAGER-3 Randomised phase III EVP +/- Vepugratinib

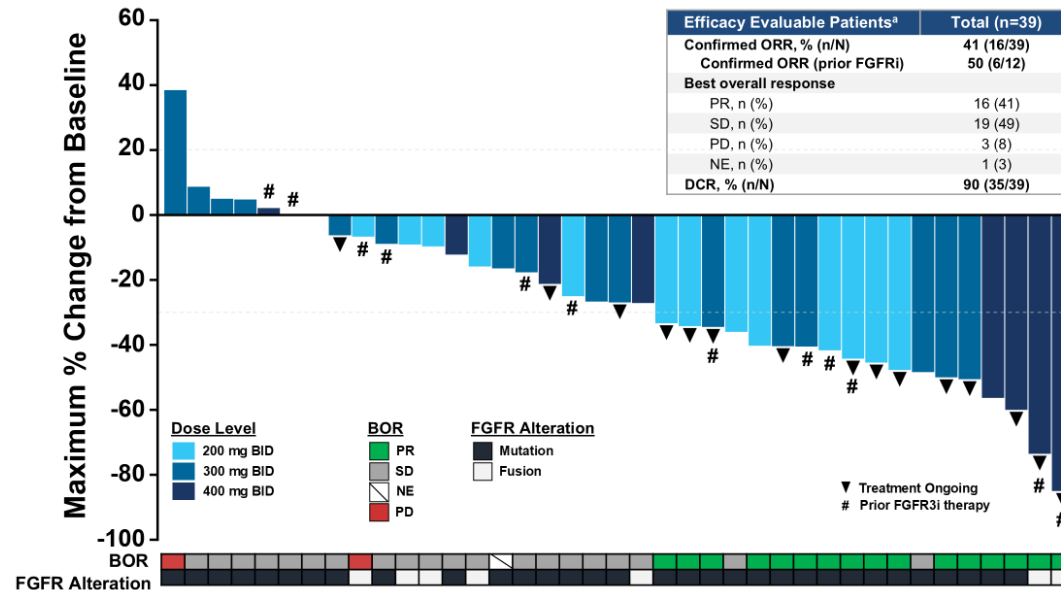
EVP

EVP+vepugratinib

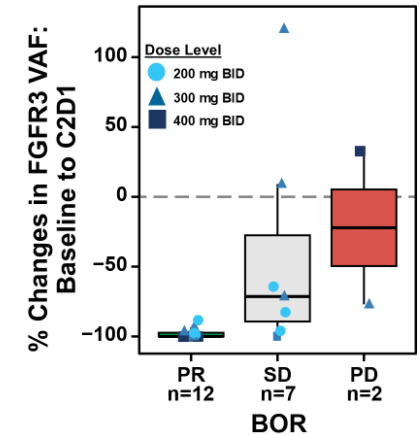
Eligibility Criteria

M1 disease
FGFR3 alterations
Fit for EVP

Radiographic Response and *FGFR3* Variant Allele Frequency: mUC mutation/fusion VEPUGRATINIB ≥200 mg BID



FGFR3 Variant Allele Frequency

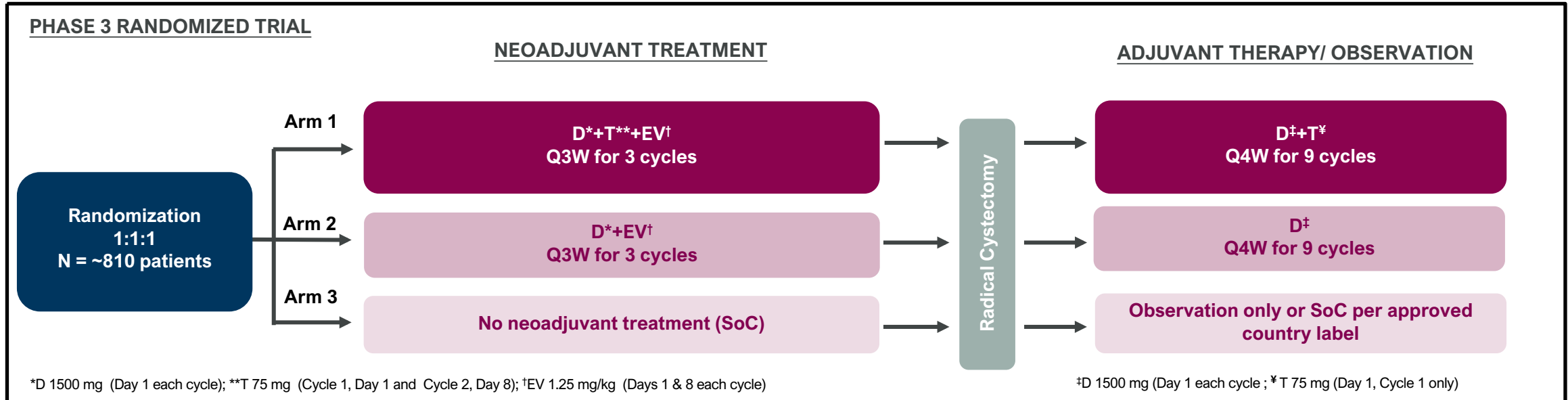


- Decreases in *FGFR3* Variant Allele Frequency (VAF) at C2D1 correlate with BOR

- Responses were also observed in non mUC patients: intrahepatic cholangiocarcinoma and ovarian cancer (n=1 each).

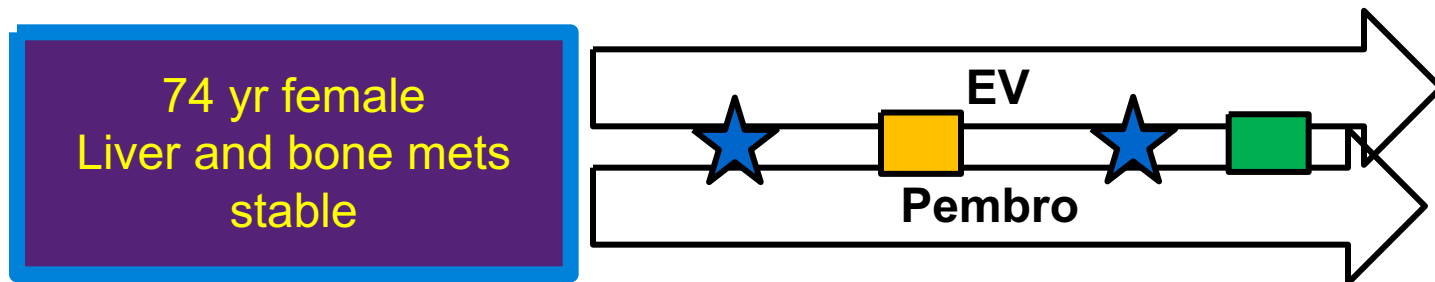
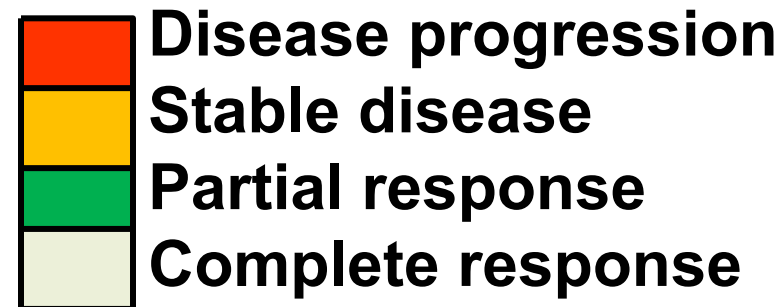
Data cutoff date of 02 Dec 2024. ^aEfficacy evaluable patients are those with measurable disease who had at least 1 post-baseline response assessment or had discontinued treatment before the first post-baseline response assessment. ^bChanges in cDNA between baseline and C2D1 were assessed using Guardant 360 from patients' plasma samples with detectable *FGFR3* VAF at baseline (N=21/39).

Volga Study Design



Is there an optimal duration of ADC and ICI therapy?
Is it the same for all tumors?
Does rechallenge, combination or sequencing work?
Which biomarkers and trial designs are needed to answer these questions?

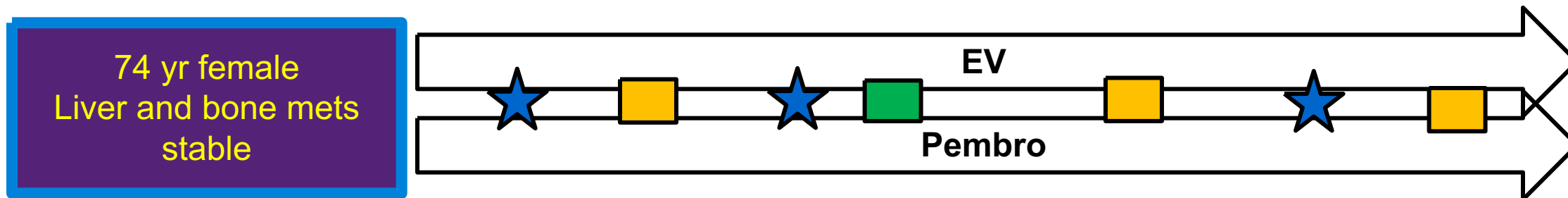
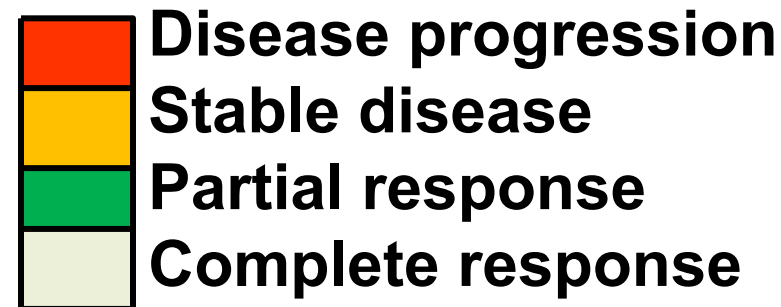
★ Symptomatic toxicity



55 yr T3N2M0 UC

70 yr male PS2
Prior EVP

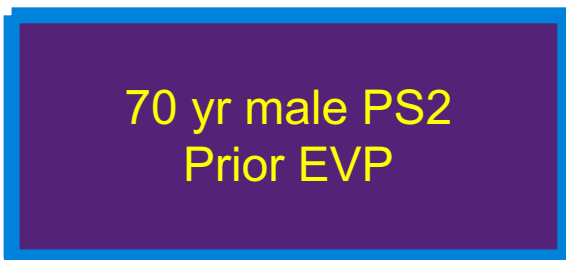
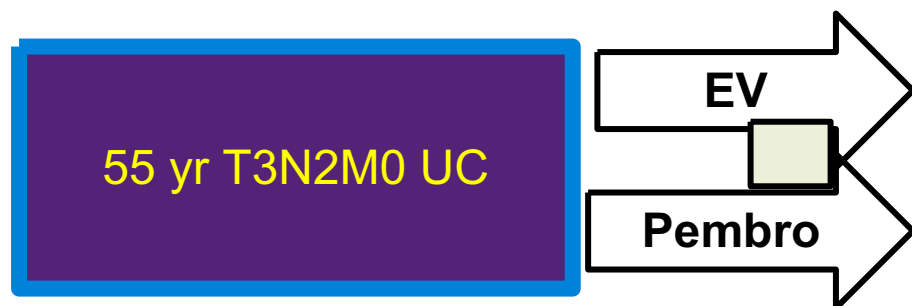
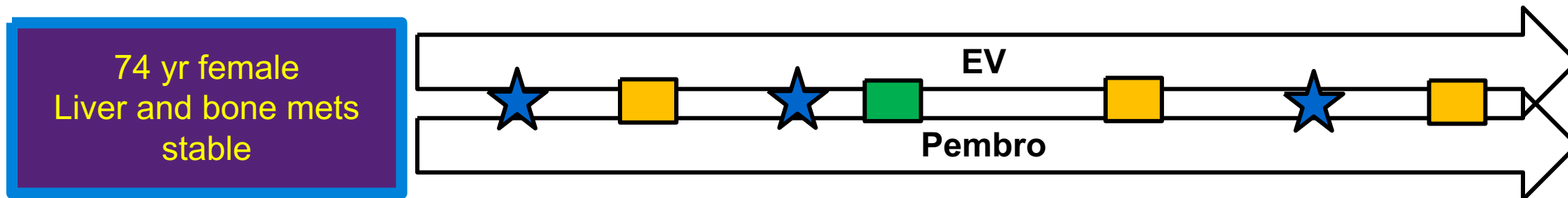
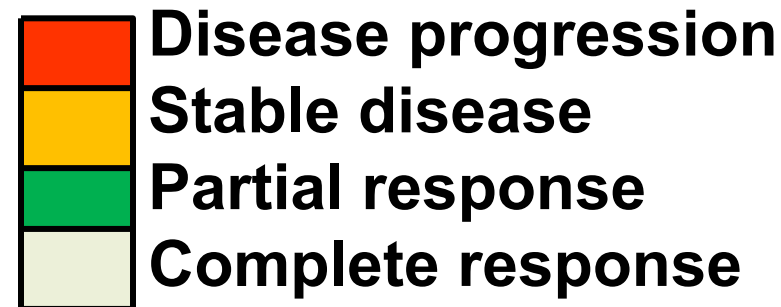
★ Symptomatic toxicity



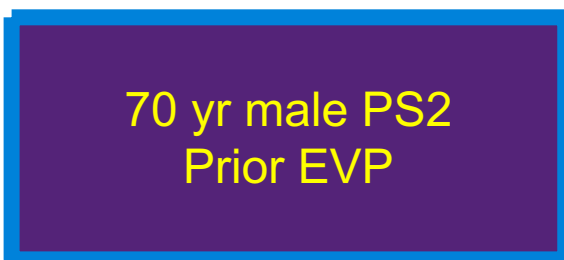
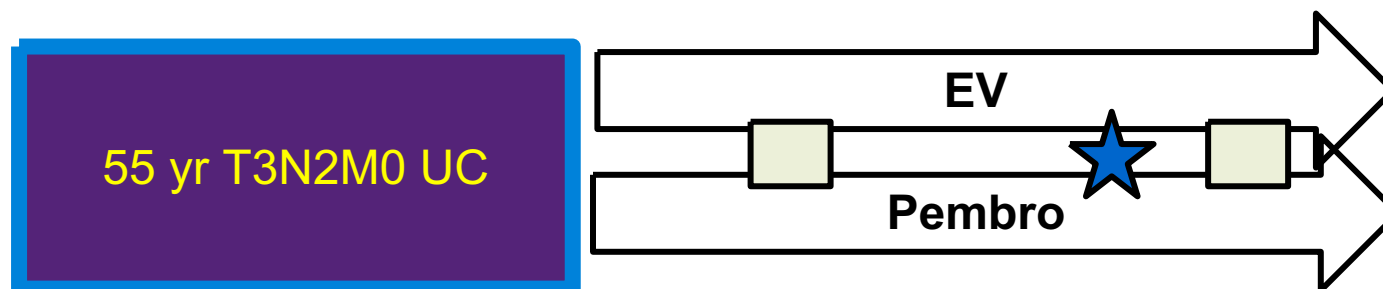
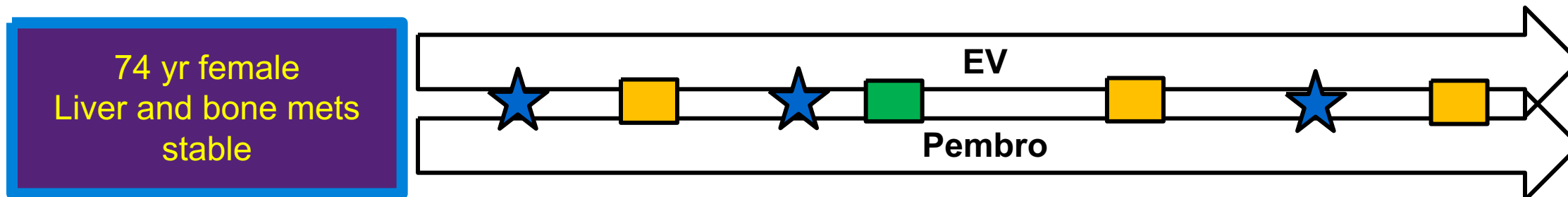
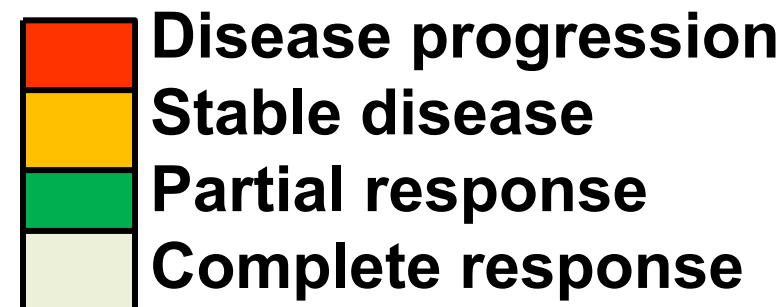
55 yr T3N2M0 UC

70 yr male PS2
Prior EVP

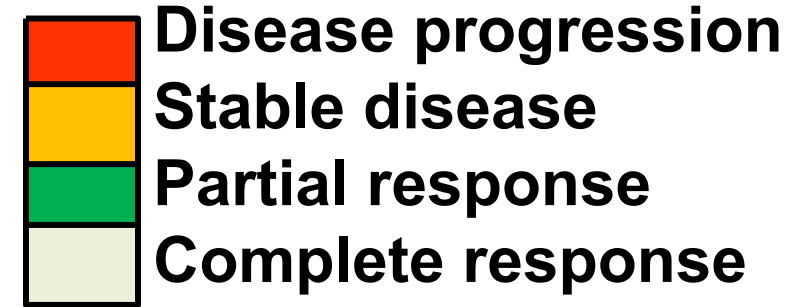
★ Symptomatic toxicity



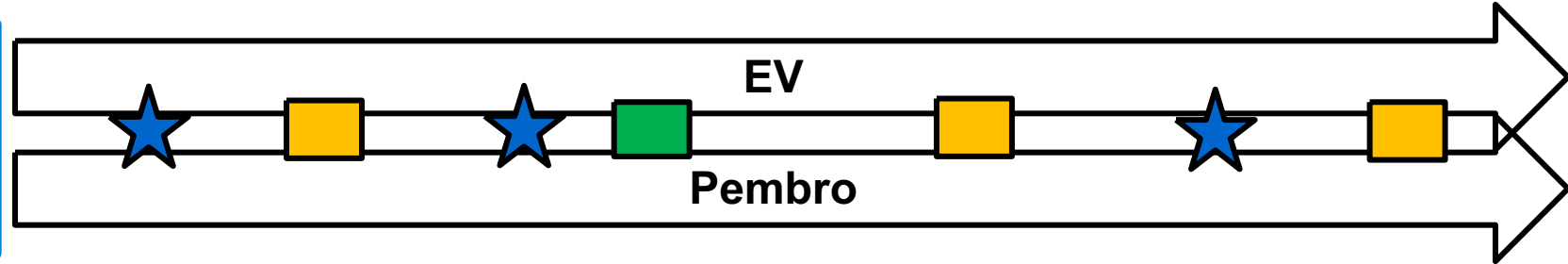
★ Symptomatic toxicity



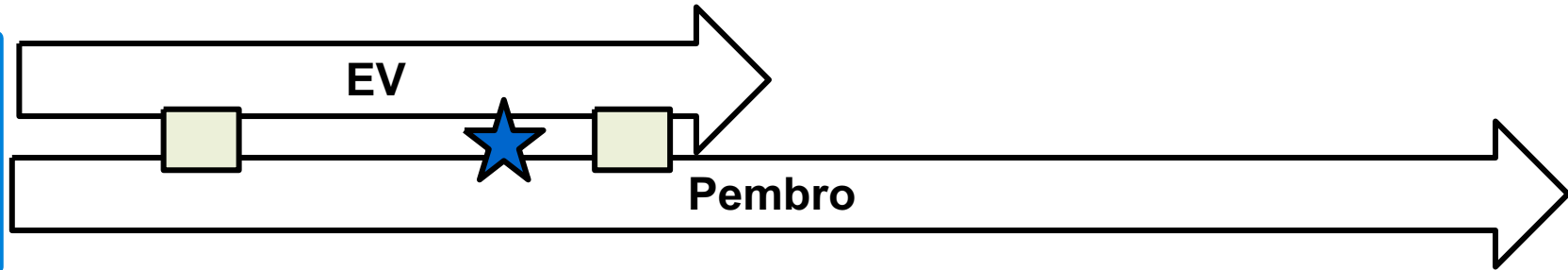
★ Symptomatic toxicity



74 yr female
Liver and bone mets
stable

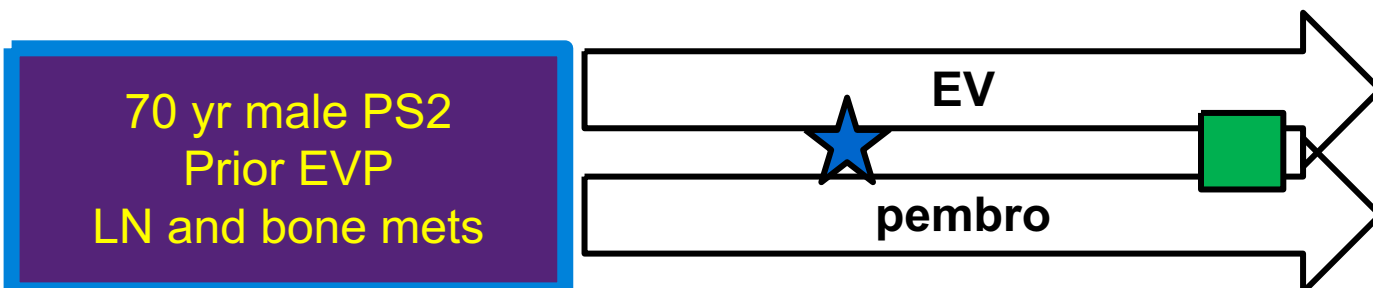
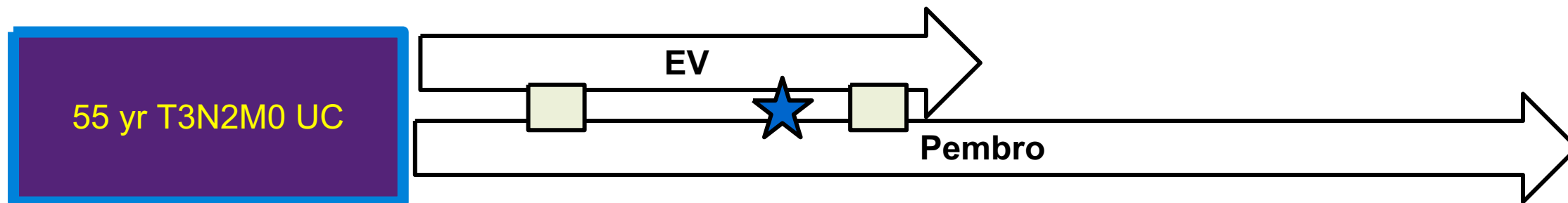
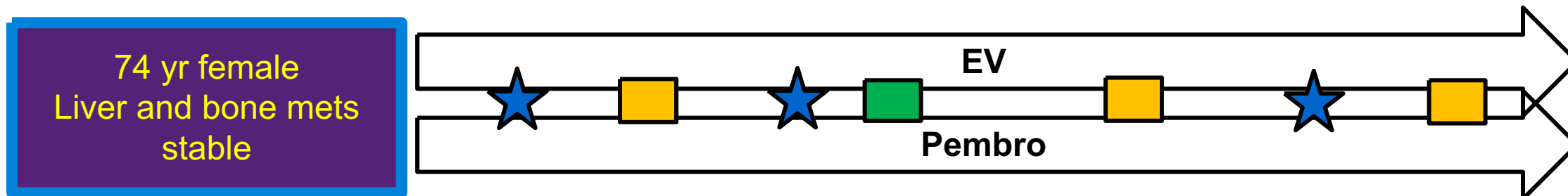
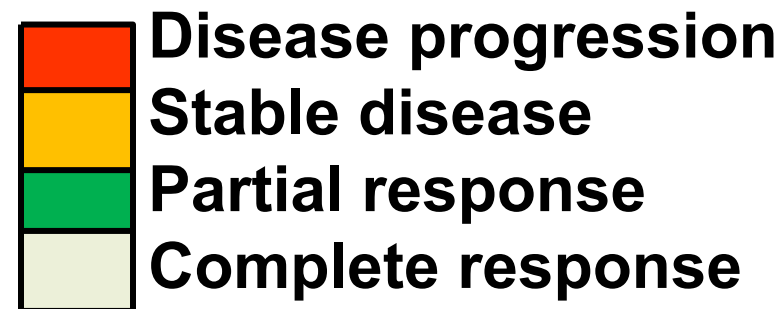


55 yr T3N2M0 UC

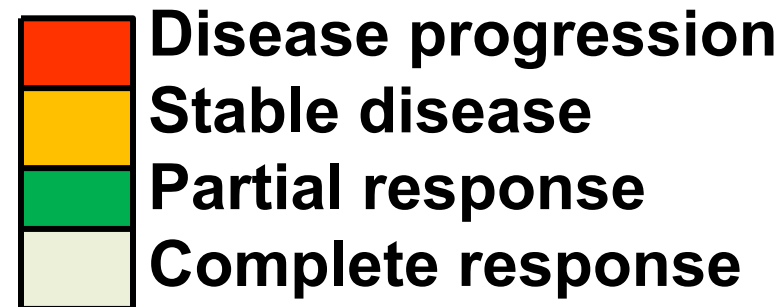


70 yr male PS2
Prior EVP
LN and bone mets

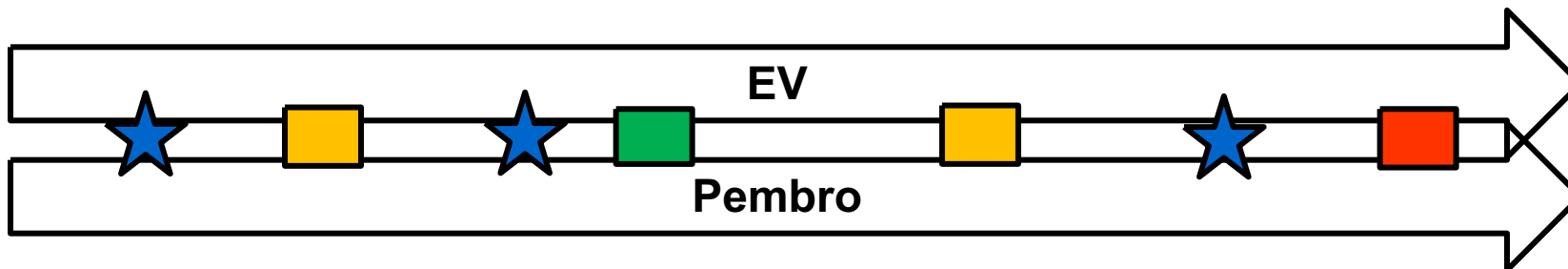
★ Symptomatic toxicity



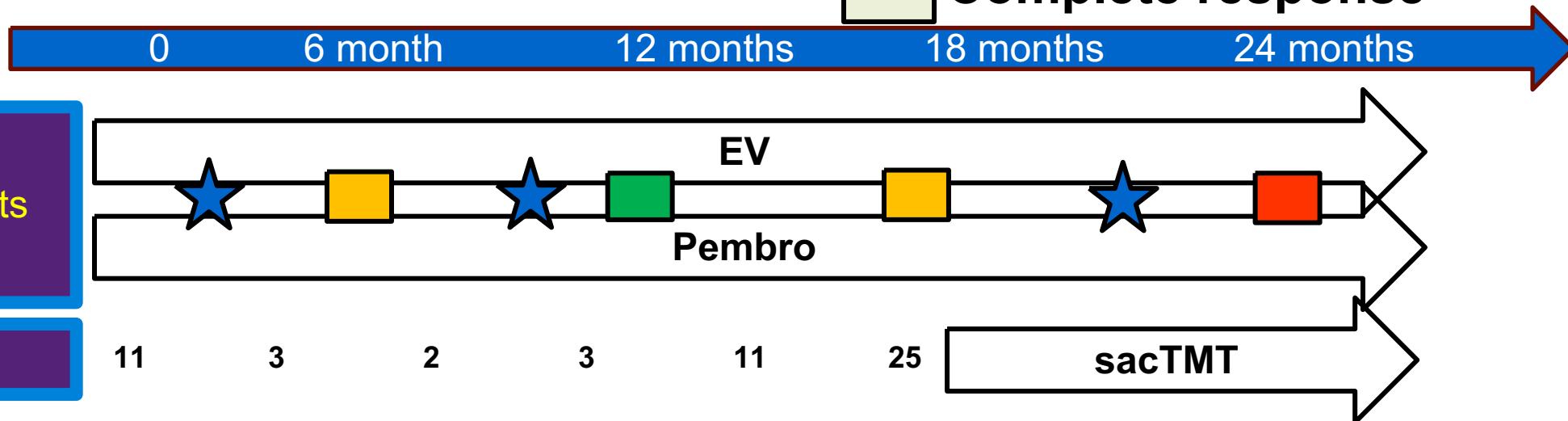
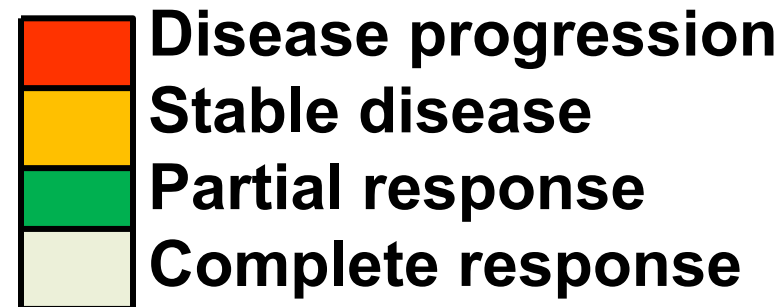
★ Symptomatic toxicity



74 yr female
Liver and bone mets
stable



★ Symptomatic toxicity

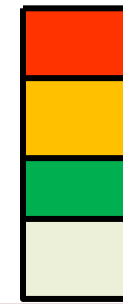


74 yr female
Liver and bone mets
stable

ctDNA (MTM)



Symptomatic toxicity



Disease progression

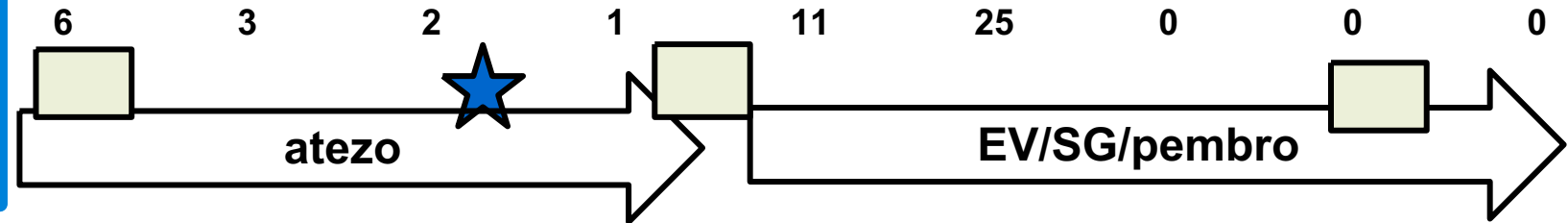
Stable disease

Partial response

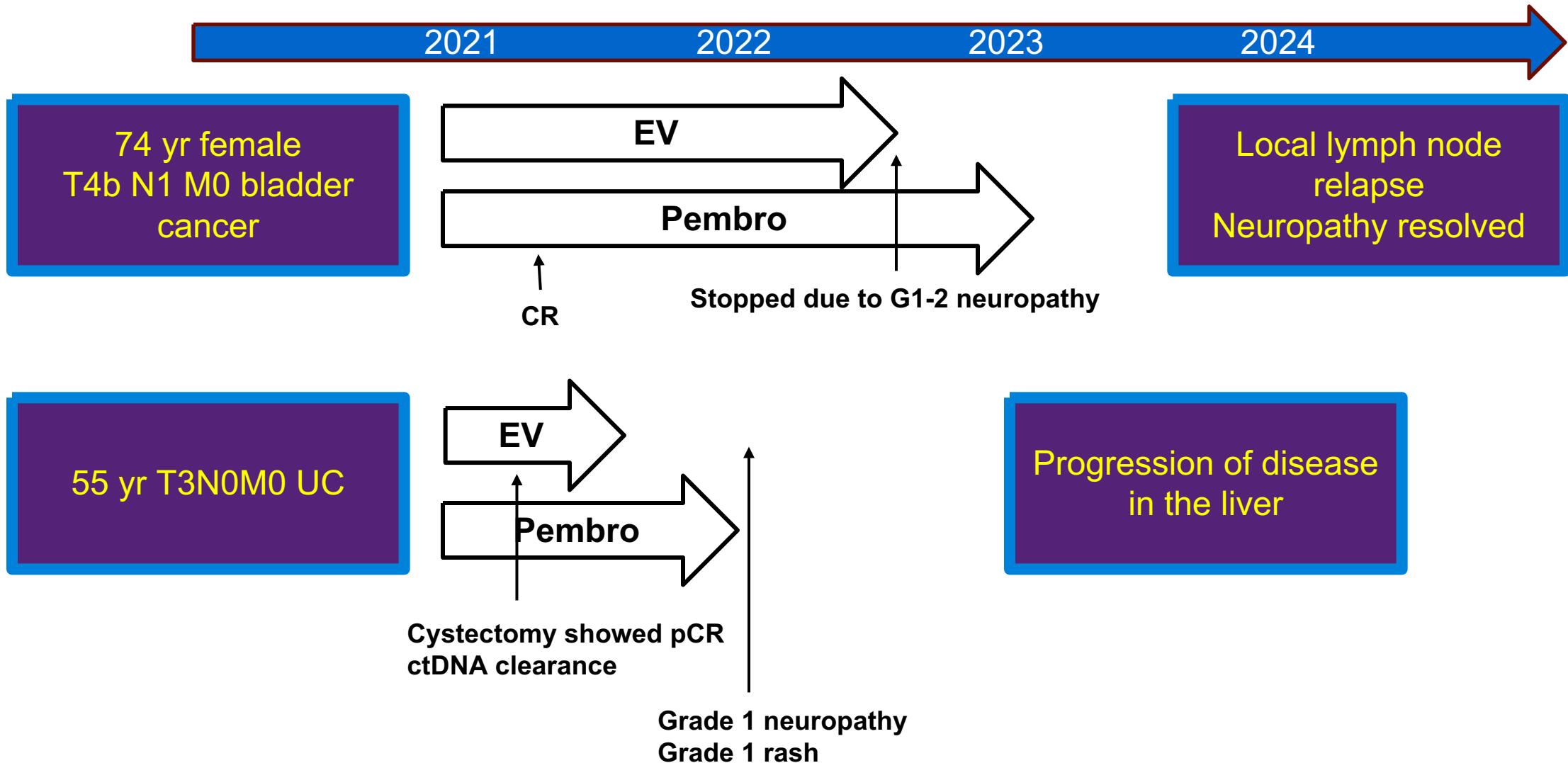
Complete response



75 male ctDNA +ve
radiologically negative
disease.



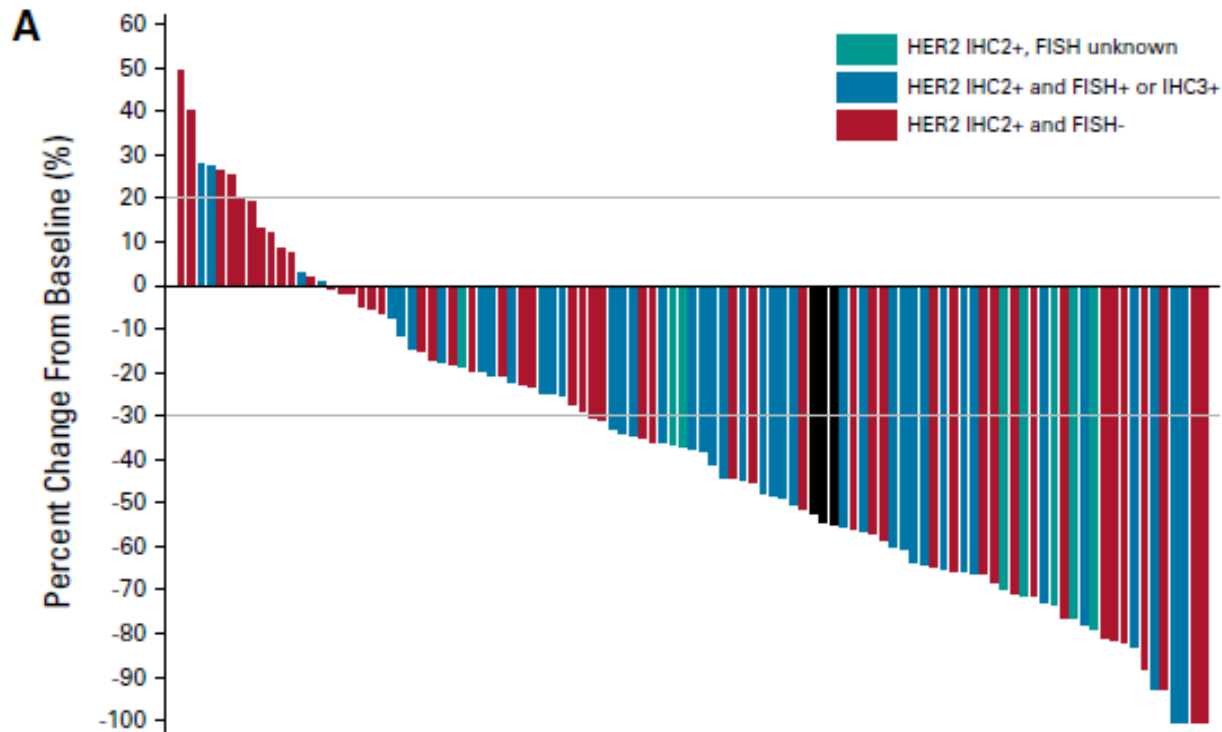
Who gets EVP today and tomorrow?



⑥ **Efficacy and Safety of Disitamab Vedotin in Patients With Human Epidermal Growth Factor Receptor 2–Positive Locally Advanced or Metastatic Urothelial Carcinoma: A Combined Analysis of Two Phase II Clinical Trials**

Xinan Sheng, MD¹ ; Lin Wang, MD²; Zhisong He, MD³; Yanxia Shi, MD⁴; Hong Luo, MD⁵; Weiqing Han, MD⁶; Xin Yao, MD⁷; Benkang Shi, MD⁸; Jiyan Liu, MD⁹ ; Changlu Hu, MD¹⁰; Ziling Liu, MD¹¹; Hongqian Guo, MD¹² ; Guohua Yu, MD¹³; Zhigang Ji, MD¹⁴; Jianming Ying, MD¹⁵ ; Yun Ling, MD¹⁵; Shiyong Yu, MD¹⁶; Yi Hu, MD¹⁷; Jianming Guo, MD¹⁸; Jianmin Fang, PhD^{19,20} ; Aiping Zhou, MD²; and Jun Guo, MD¹ 

DOI <https://doi.org/10.1200/JCO.22.02912>



	C005 (N=43)	C009 (N=64)	Pooled (N=107)
HER2-Positive IHC3+ or 2+/FISH+	60%	64%	62.2%
HER2 Low IHC2+/FISH- IHC2+/FISH Unknown	40% 66%	39.4% 50%	39.6% 55.6%

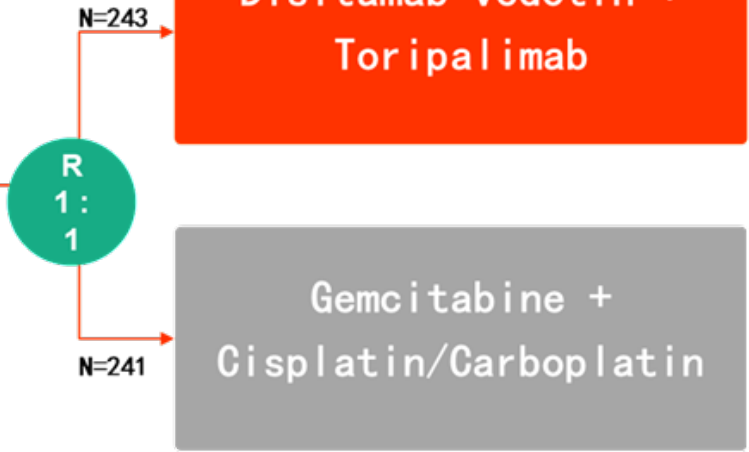
Most frequent TRAE All grades (≥30%)

Any event	100%
Peripheral sensory neuropathy	68%
Leukopenia	51%
AST increase	42%
Neutropenia	42%
Alopecia	40%
Asthenia	39%
ALT increase	36%
Decreased appetite	32%

DISITIMAB VEDOTIN AND TORIPALIMAB IN HER-2 positive UC

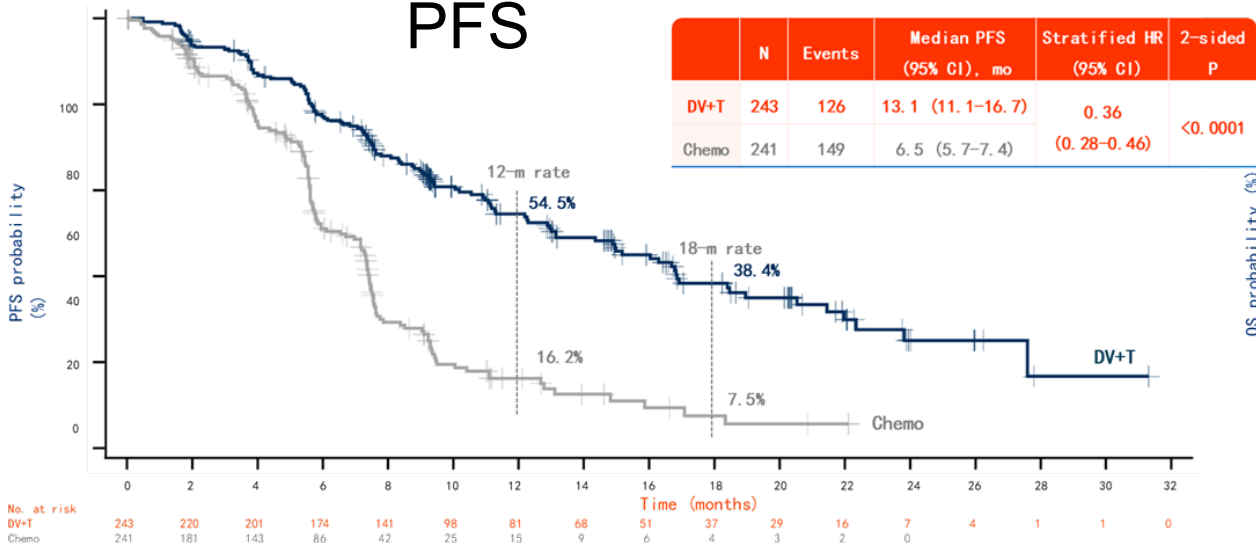
Key Inclusion criteria

- No prior systemic treatment for unresectable locally advanced or metastatic UC
- Central lab-confirmed HER2 IHC 1+, 2+, or 3+
- Measurable disease per RECIST v1.1
- Eligible for cisplatin or carboplatin
- ECOG PS 0 or 1

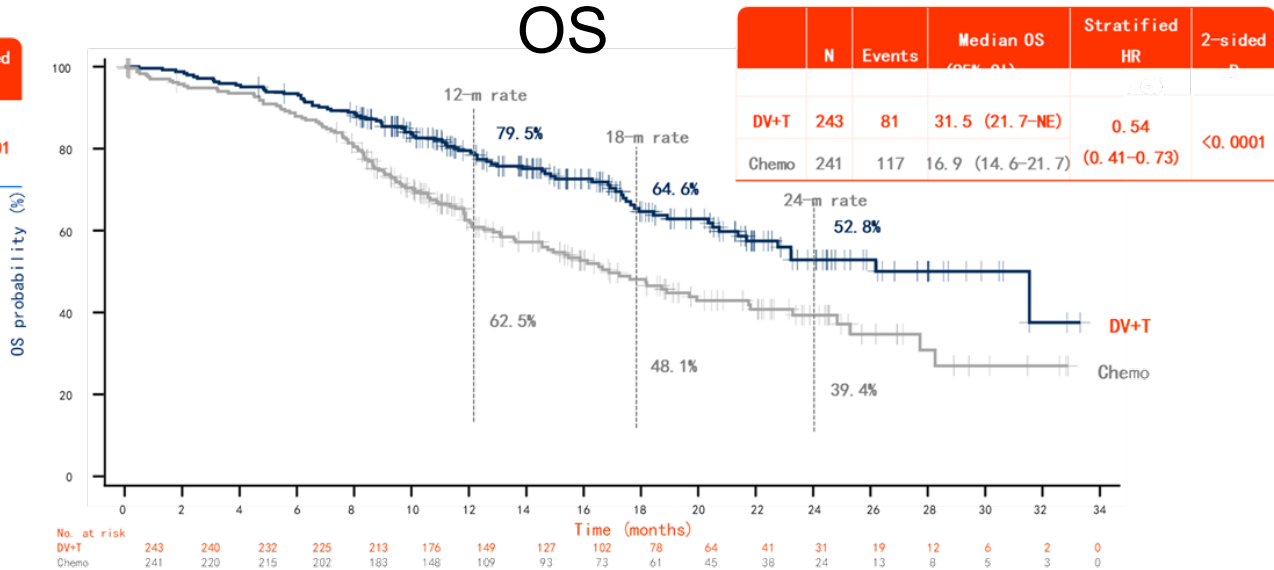


80% were HER 2 positive
No enrichment for efficacy in the HER-2 high
Distinct toxicity profile to EV
Responses over 70% but CR rate was lower
Follow up is relatively short

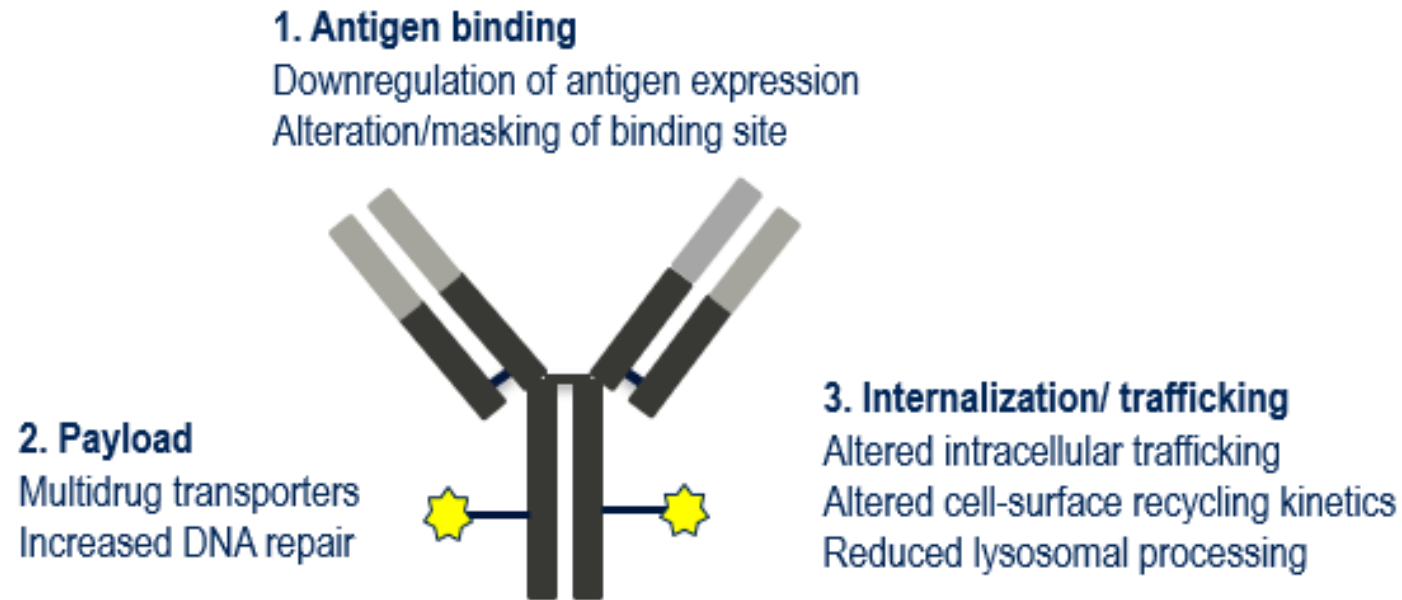
PFS



OS



Mechanisms of resistance to EV



Acquired resistance to EV

Unknown and likely to be multifactorial

Dynamic changes to NECTIN4 maybe partially responsible but PGP efflux pumps will play an important role

Inherent resistance to EV

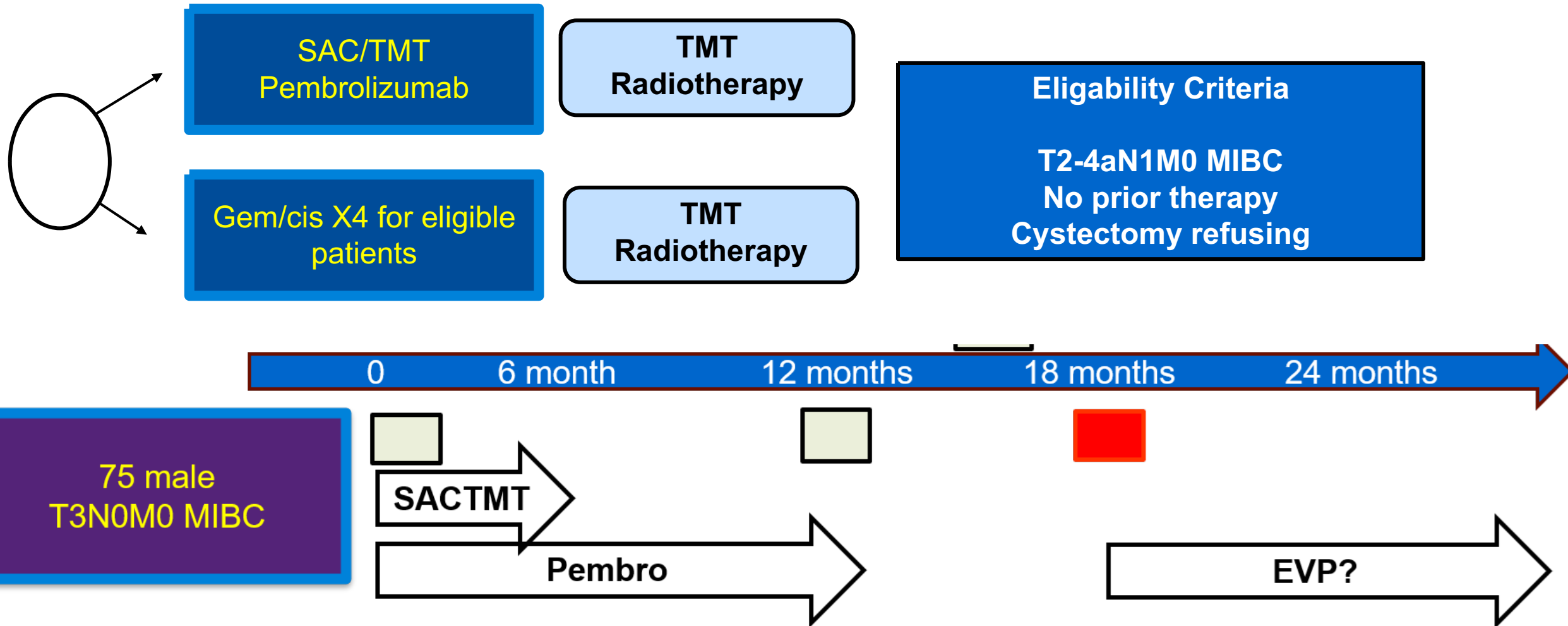
Unknown and likely to be multifactorial

Biomarker expression as well as underlying PGP efflux pumps maybe relevant

Status of global bladder cancer ADCs trials

	Target	Payload	Biomarker Selected	Single agent RIII	Combination RIII	FDA approval
Enfortumab vedotin	Nectin-4	MMAE	No	OS +ve	OS +ve	M1 and MIBC
Zelenectin Pevedotin	Nectin-4	MMAE	No	No	discontinued	No
Disitimab vedotin	HER-2	MMAE	HER2 1-3+	No	OS +ve	No
T-DXD	HER-2	TOPO-1	HER2 3+	No	No	HER 3+
Sacituzumab Govitcan	TROP2	TOPO1	No	OS -ve	No	No
D-DXD	TROP2	TOPO1	No	No	Ongoing	No
SAC-TMT	TROP2	TOPO1	No	Ongoing	No	No
IZA-BREN	HER-1&3	TOPO1	No	Ongoing	No	No

SACTMT + pembrolizumab in MIBC (bladder sparing trial)



What are the key questions for treatment after EVP

EVP first ask questions later

Toxicity management and duration of therapy is the main challenge

Other ADC/IO combinations are probably equally active .

Triplet therapy would need to have great results and more may not always be better

We are moving into a new era of diagnosing and monitoring advances disease

Advanced disease (ctDNA+ve or measurable M1)

1st line therapy

EVP.

NAC
(GEM/CIS/DURVA).

Adjuvant IO

DVP

2nd line therapy

Platinum chemo.

EVP or just EV.

EVP or platinum
chemo.

Platinum chemo.

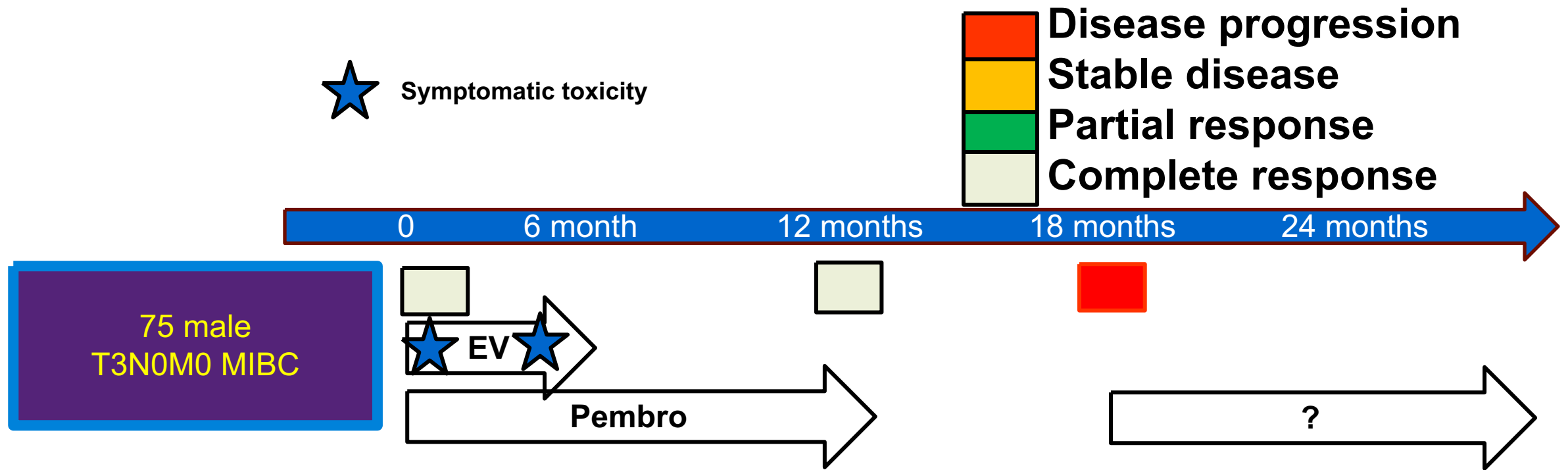
3rd line therapy

Targeted therapy

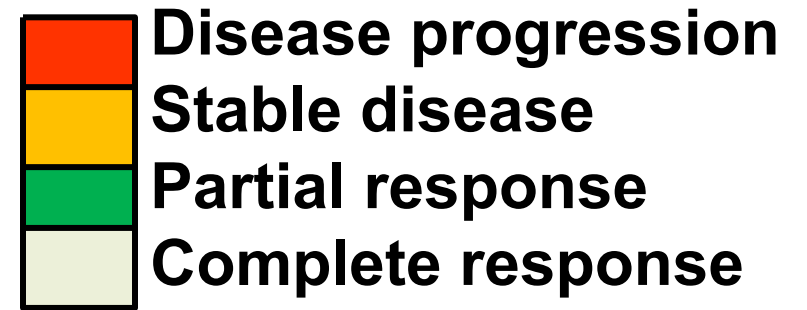
Targeted therapy.

EV or Platinum
chemotherapy.

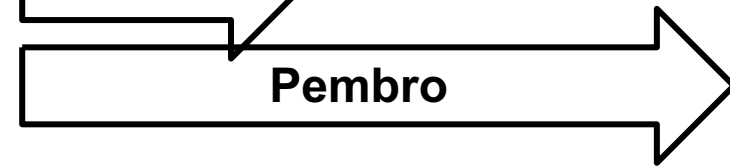
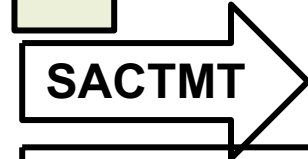
Targeted therapy.



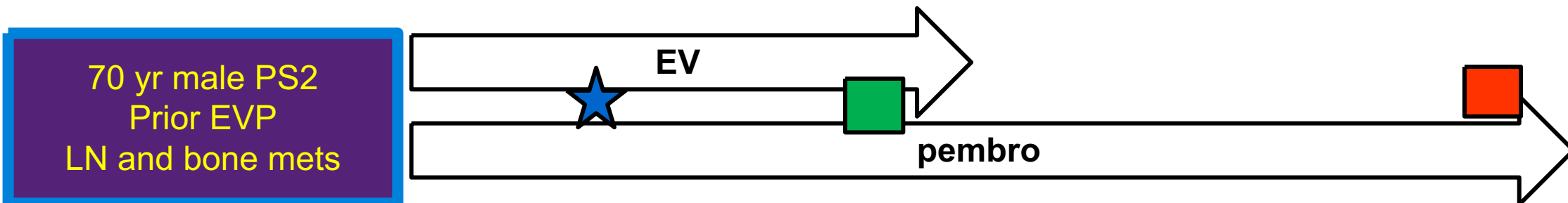
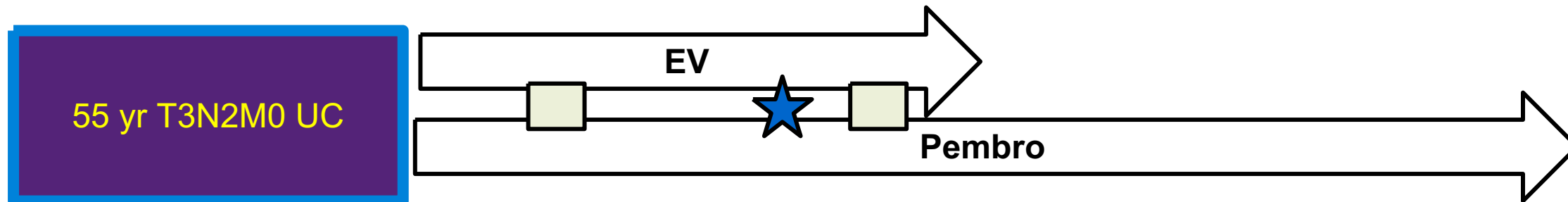
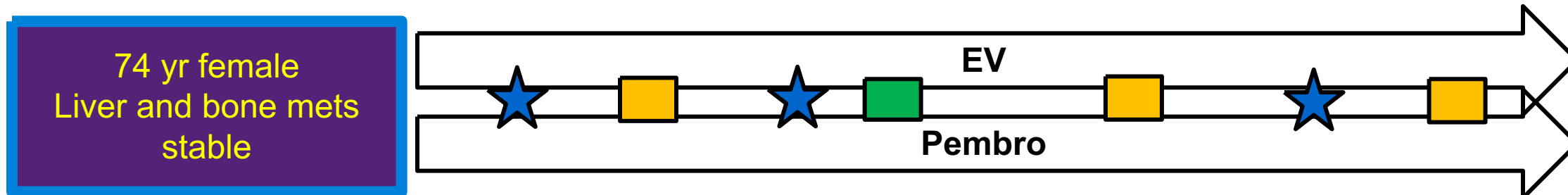
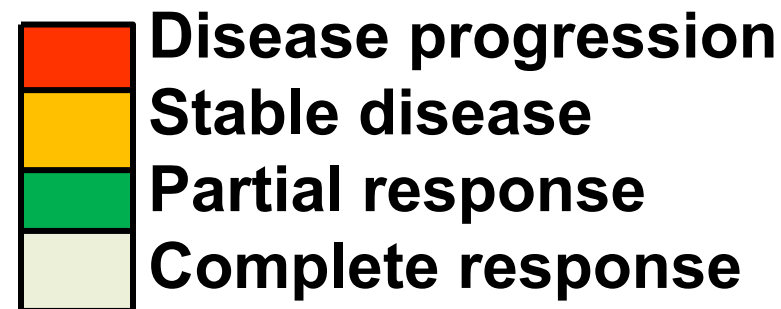
Can we rechallenge with EVP?



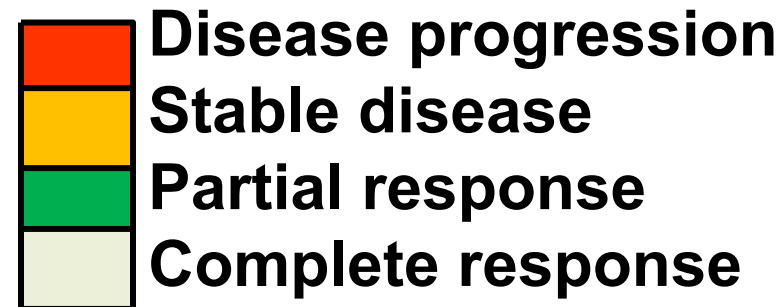
75 male
T3N0M0 MIBC



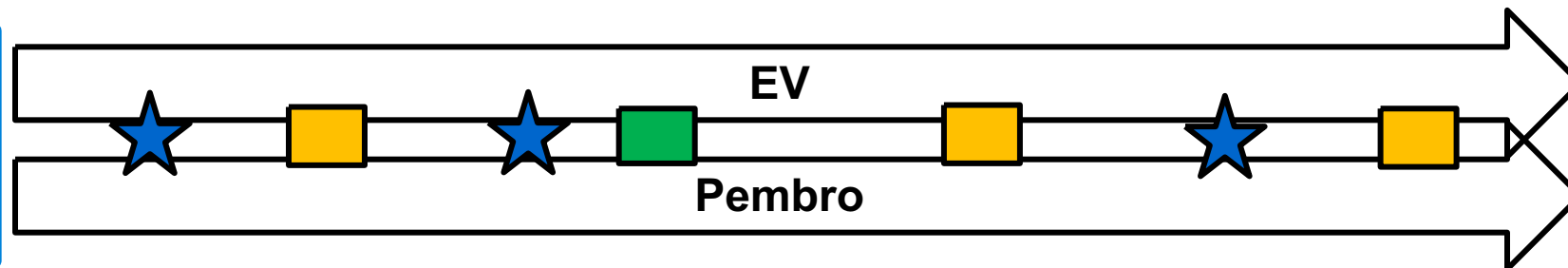
★ Symptomatic toxicity



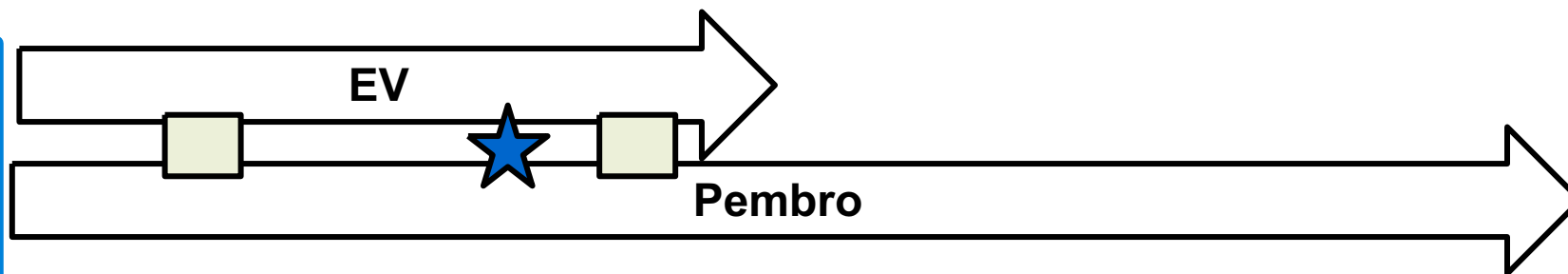
★ Symptomatic toxicity



74 yr female
Liver and bone mets
stable



55 yr T3N2M0 UC



70 yr male PS2
Prior EVP
LN and bone mets

