Debate:
are we evolving towards a platinum-free future?

Aristotelis Bamias

Maria De Santis

Platinum-based chemotherapy will be gone from first-line mUC by 2025

Yes

No

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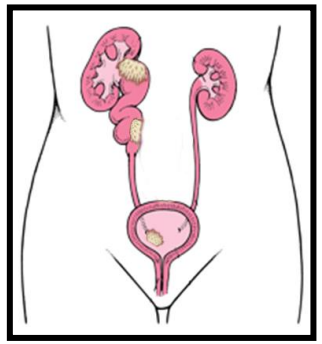

Global Bladder Cancer Conference 2022
Athens, 20.10.2022

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Charité Universitätsmedizin, Berlin
Interdisziplinäre Urologische Onkologie

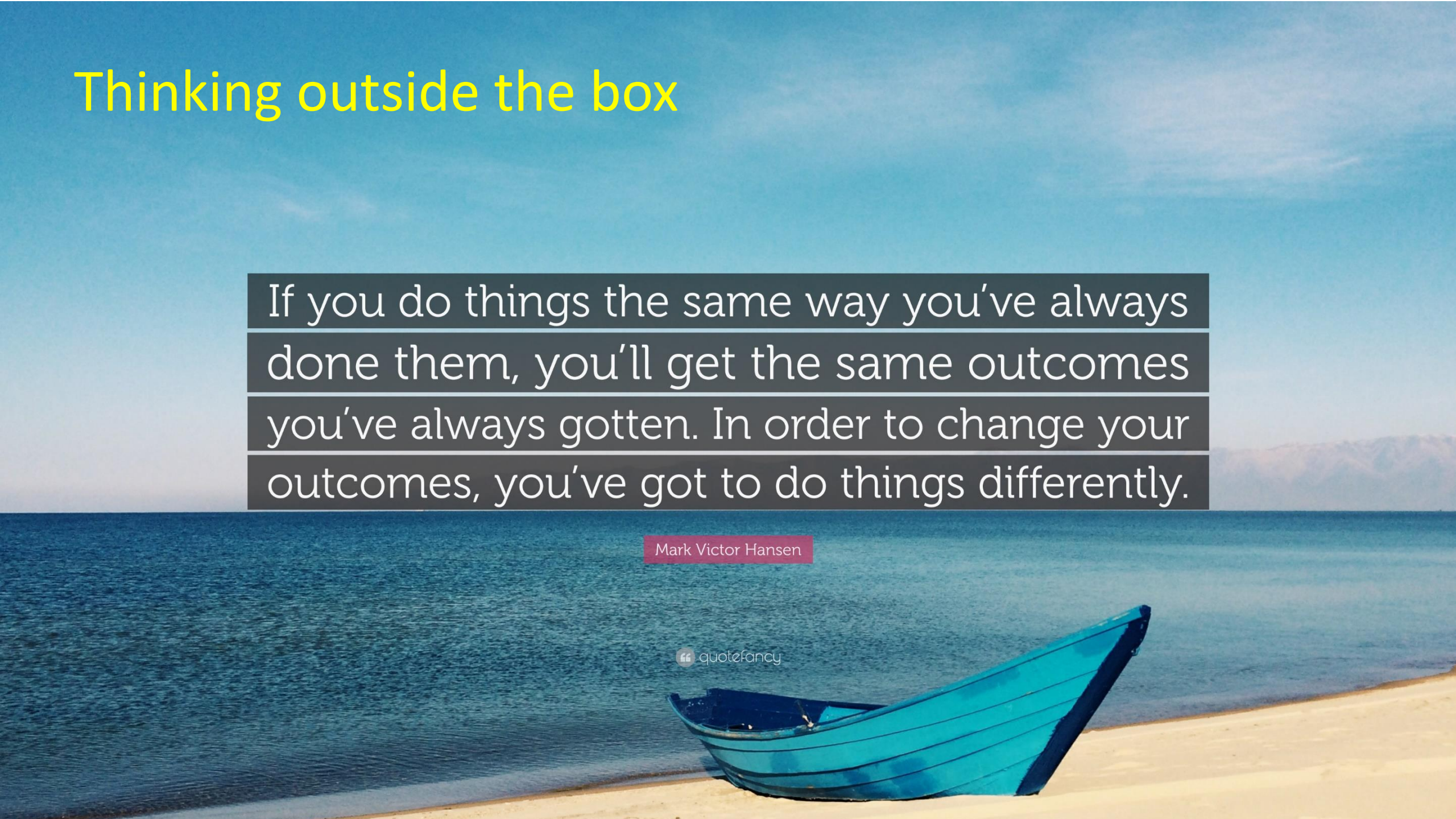
Conflicts of interest - Maria De Santis

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	none
Receipt of honoraria or consultation fees	AAA, Accord, Amgen, Astellas, AstraZeneca, Basilea, Bayer, Bioclin, BMS, EISAI, Exeixis, Ferring, Immunomedics/Gilead, Ipsen, Janssen, MSD, Merck, Novartis, Orion, Pfizer, Pierre Fabre Oncology, Roche, Sandoz, Sanofi, SeaGen
Stock shareholder	none
Other support (please specify):	none

Patinum free future?

What else?

Thinking outside the box



What is the aim?

→ Platinum-free, NOT chemo-free!

Why?

Better and deeper responses → improved long term outcome

How?

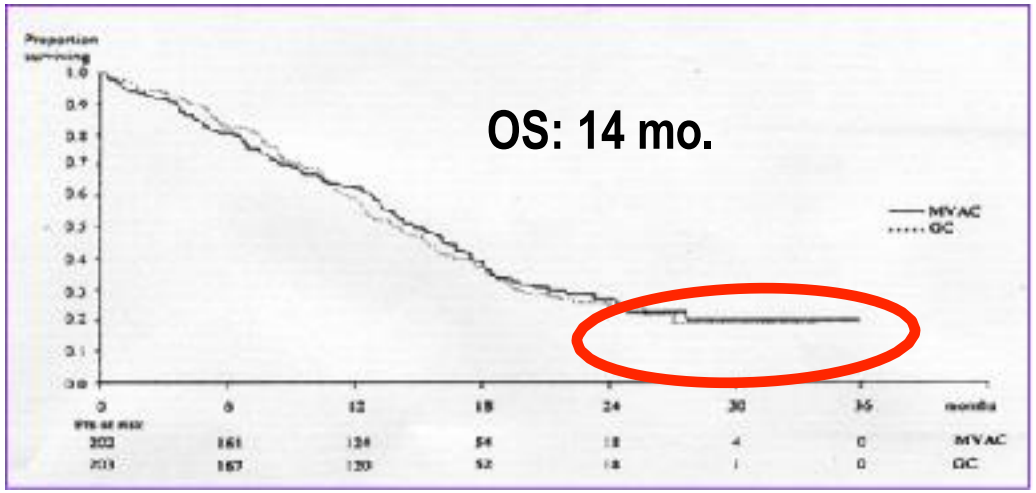
1. Immunecheckpoint inhibitors
2. Novel agents

Until now - platinum based chemotherapy for mUC

But: long-term survivors are rare

(depending on risk factors: ECOG 0 and N+)

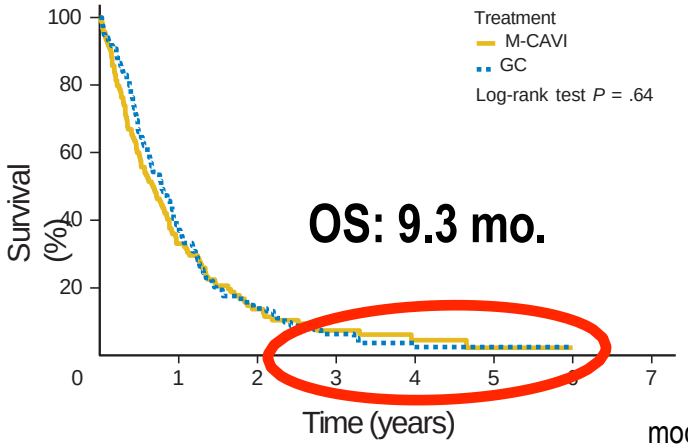
fit pts., eligible for Cisplatin



modified from 1.

Long-term survival with cisplatin: 9-15%

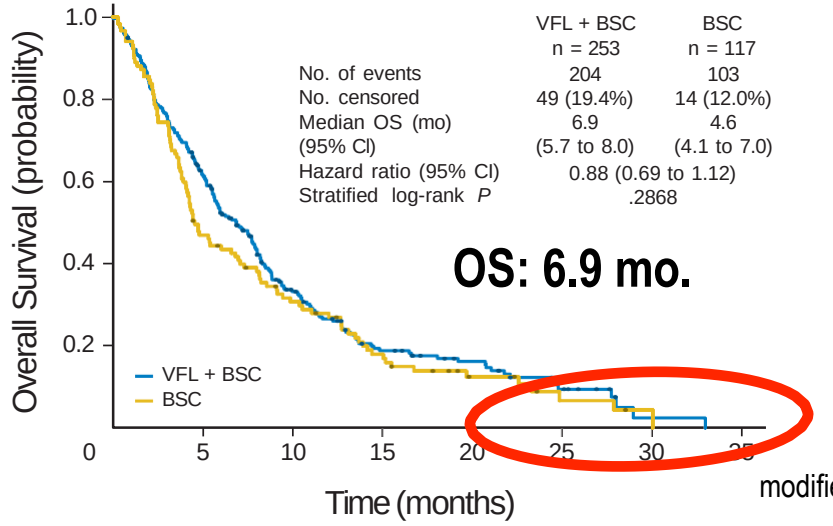
Platin-ineligible



modified from 2.

Treatment	O	N	No. at risk					
M-CAVI	108	119	37	13	7	3	1	1
GC	110	119	44	15	5	2	2	1

2. line



modified from 3.

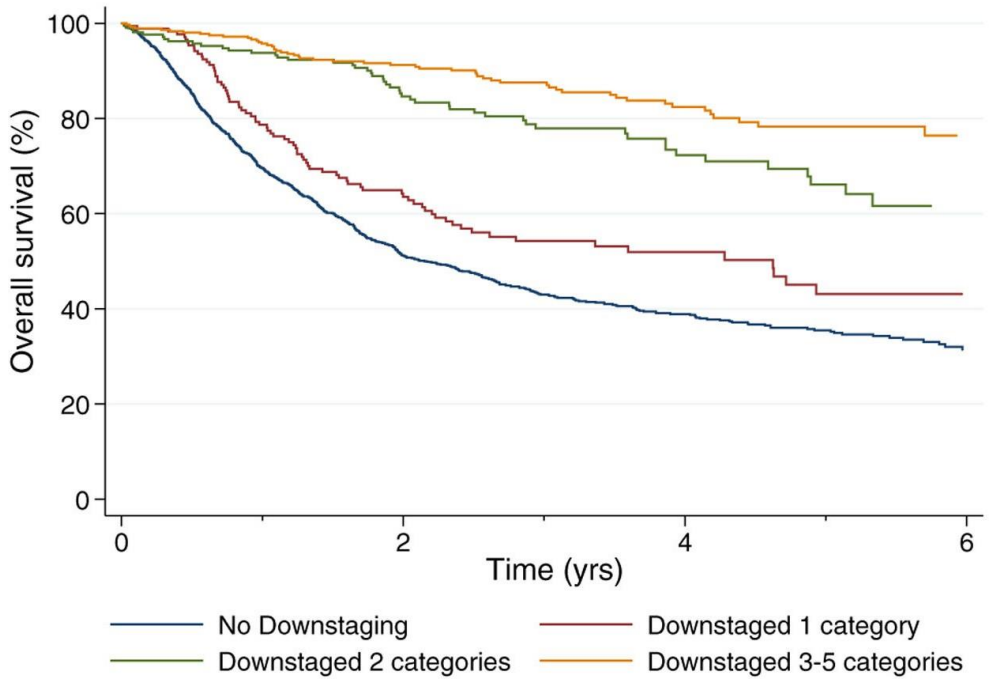
1. Von der Maase H et al. J Clin Oncol 2000;18(17):3068-3077.
2. De Santis M et al. J Clin Oncol 2012;30(2):191-199.
3. Bellmunt et al. J Clin Oncol 2009;27(27):4454-61.

Pathological complete responses are important for MIBC

ypT0 is prognostic in high-risk MIBC

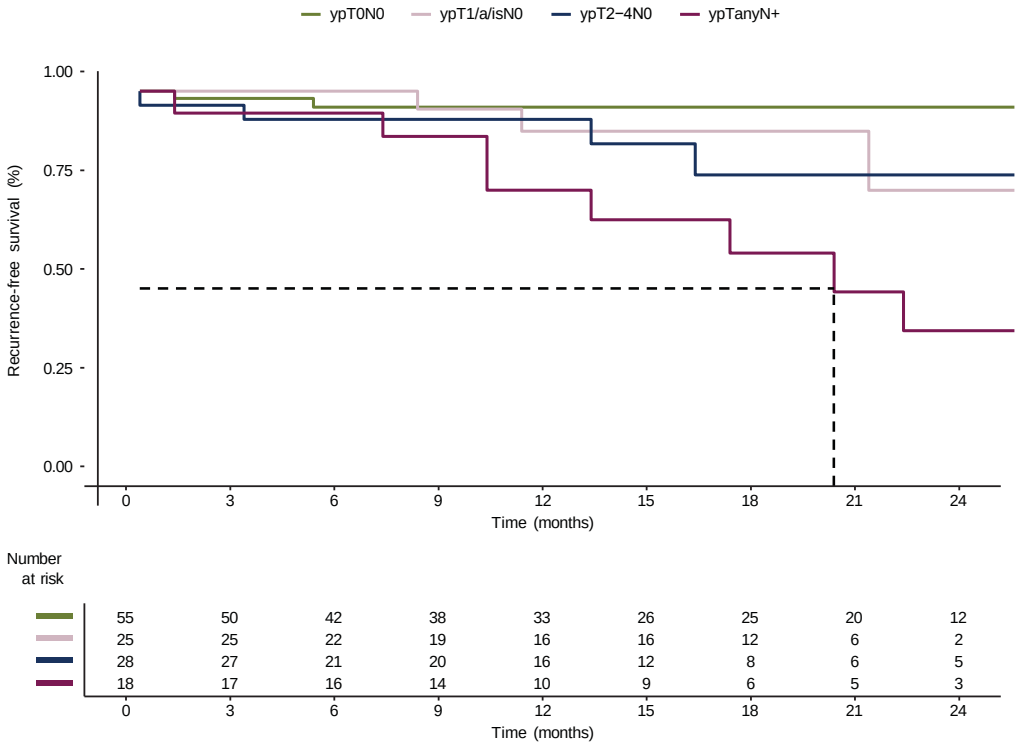
Downstaging and ypT0 are important in localized disease

Chemo



Martini et al. Cancer. 2019 September 15; 125(18): 3155–3163. doi:10.1002/cncr.32169.

Pembrolizumab



Bandini et al. Ann Oncol 2020, 31 (12): 1755-63. https://doi.org/10.1016/j.annonc.2020.09.011

What about depth of response in metastatic disease?

Post hoc pooled analysis of first-line (1L) pembrolizumab (pembro) for advanced urothelial carcinoma (UC): Outcomes by response at week nine in KEYNOTE-052 and KEYNOTE-361.

Pooled outcomes by response at week nine.			
Primary Analysis	**CR/PR n = 160**	**SD n = 154**	**PD n = 234**
Median OS from wk 9, mo (95% CI)	**51.4 (36.9-NR)**	**17.5 (14.5-24.7)**	**5.9 (5.0-7.2)**
36-month OS rate from wk 9, % (95% CI)	62.5 (54.0-69.9)	28.5 (21.1-36.3)	4.8 (2.4-8.4)
Duration of CR/PR/SD, median (range), mo	25.9 (0.0-60.7+)	4.2 (0.0-51.5+)	NA
Sensitivity Analysis	n = 122	n = 125	n = 188
Median OS from wk 9, mo (95% CI)	50.7 (36.2-NR)	17.5 (13.3-24.7)	5.3 (4.0-6.5)
36-month OS rate from wk 9, % (95% CI)	60.7 (51.1-68.9)	29.2 (21.1-37.8)	4.9 (2.3-8.8)
Duration of CR/PR/SD, median (range), mo	26.2 (0.0-60.7+)	4.2 (0.0-51.5+)	NA

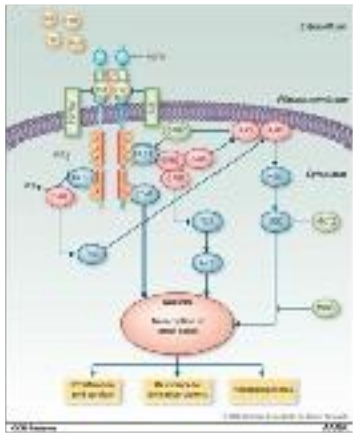
T Powles et al. DOI: 10.1200/JCO.2022.40.6_suppl.519 Journal of Clinical Oncology 40, no. 6_suppl (February 20, 2022) 519-519.

How to move forward with platinum free treatment for UC?
→ Novel agents and combinations

Anti-body-drug conjugates

NECTIN4
TROP2
HER2
…

molecular agents

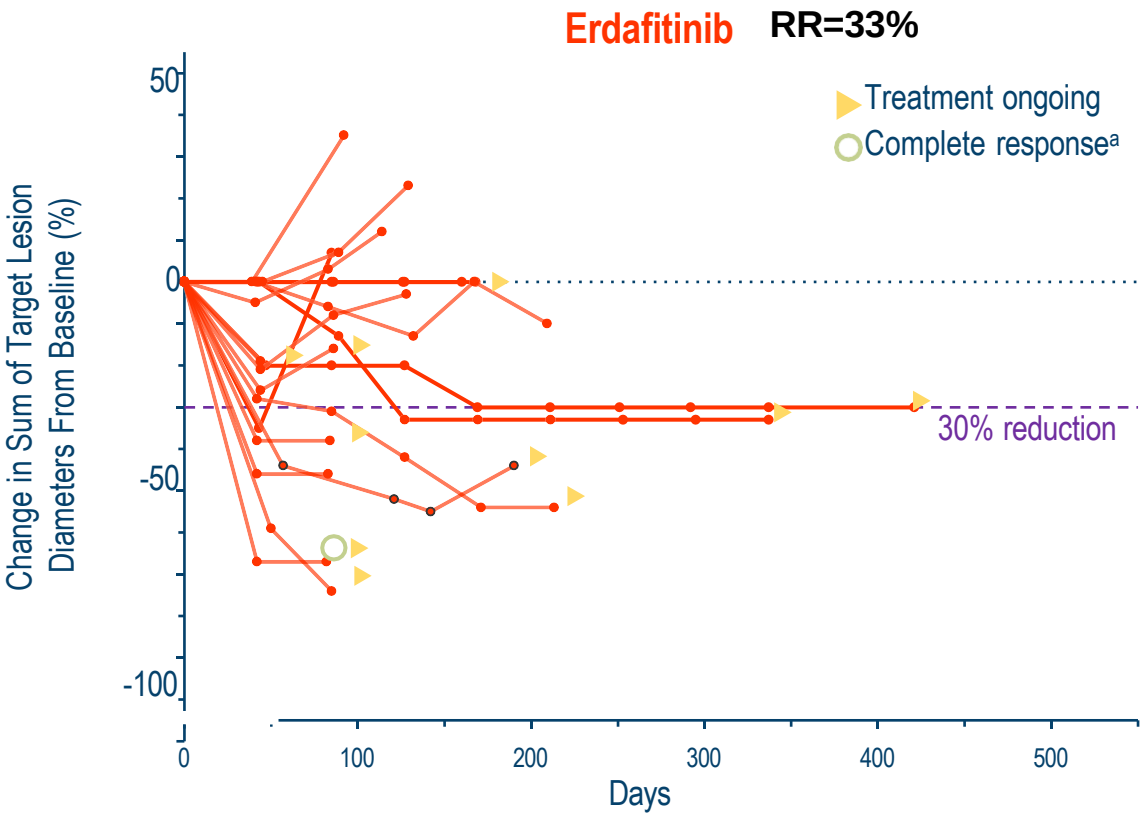


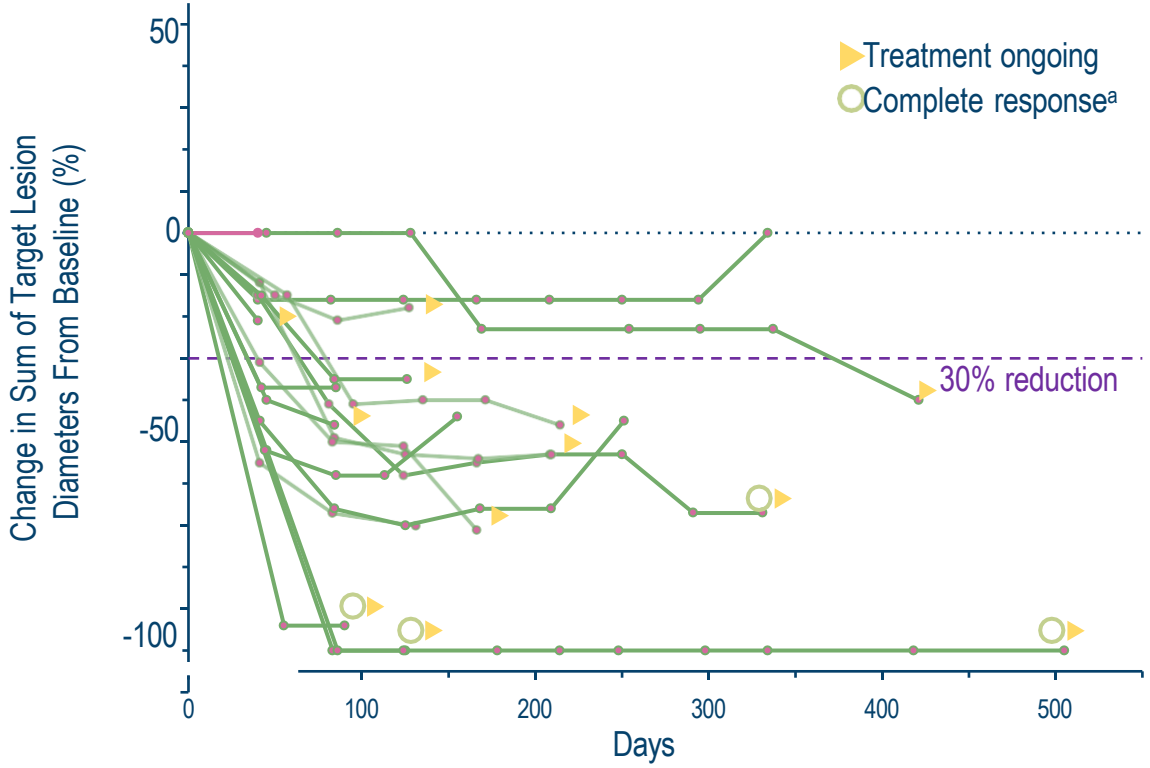
FGFR

Tourt et al. *Clin Cancer Res* (2015) 21 (12): 2684–2694.

FGFR inhibitors
NORSE: Antitumor Activity Over Time

Erdafitinib + Cetrelimab RR=68%

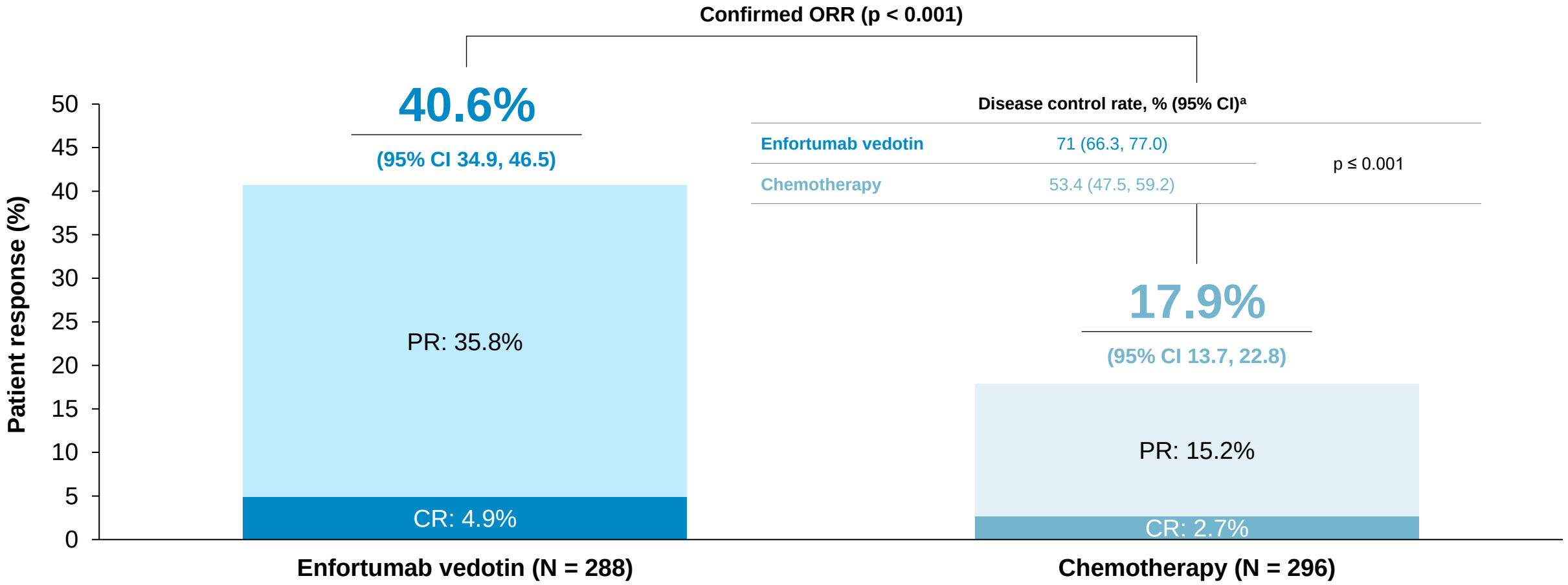




- Patients in both treatment arms had a durable reduction in the sum of target lesion diameters over time
- Median of the maximum reduction in the sum of target lesion diameters was 28% in the erdafitinib arm and 51% in the erdafitinib + cetrelimab arm

[a]Complete responses include patients who had sum of target lesions > 0 mm; in patients with lymph node target lesions, a diameter < 10 mm is required for complete response per RECIST 1.1.

Enfortumab Vedotin
EV-301: investigator-assessed overall response



[a] Indicates the proportion of patients who had a best overall response of confirmed CR, PR, or SD (at least 7 weeks); enfortumab vedotin vs chemotherapy.
Evaluated in the response-evaluable population; response is as assessed by the investigator per RECIST v1.1. Data cut off: July 15 2020.

Powles T, et al. Virtual oral presentation at ASCO GU 2021; abstract 393

First-line - metastatic urothelial cancer, unfit for cisplatin

	Gemcitabine + Carboplatin (n = 119)	Pembro-lizumab (n= 370)	Erdafitinib (n = 18)	Erdafitinib + Cetrelimab (n = 19)	Rogaratinib + Atezolizumab (n = 25)	Enfortumab Vedotin + Pembrolizumab (n= 45)
ORR n (%)	49 **(41)**	106 **(29)**	6 **(33)**	13 **(68)**	11 **(44)**	**33 (73)**
Complete response n (%)	4 (3.4)	33 (9)	1 (6)	4 (21)	4 (16)	7 (16)
Partial response n (%)	45 (38)	73 (20)	5 (28)	9 (47)	7 (28)	26 (58)

Durability of responses low with gem/carbo

ASCO2022 update: median DOR 25.6 months and a DCR 93%

De Santis JCO 2012; Rosenberg J, ASCO 2020; Powles T, ESMO 2021, Friedlander TW 2021, Vuky J JCO 2020; Hoimes CJ, et al. JCO 2022 (In press),

EV-103 Cohort K:
Overall Response Rate and DOR by BICR
EV+P: 64.5% confirmed ORR with median DOR not yet reached

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	**49 (64.5)** (52.7, 75.1)	**33 (45.2)** (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Duration of response, median (95% CI)	NR (10.25, -)	13.2 (6.14, 15.97)

EV+P

- ORR per investigator assessment was consistent with BICR (86.7% concordance)
- cORRs were consistent across all pre-specified subgroups
  - 53.8% cORR observed in patients with liver metastases

EV monotherapy

- Activity is consistent with prior experience in 2L+ la/mUC

Data cutoff: 10 JUN 2022
BICR: Blinded Independent Central Review; cORR: Confirmed Objective Response Rate; NR: Not Reached

EV-103 Cohort K:
Overall Response Rate and DOR by BICR
EV+P: 64.5% confirmed ORR with median DOR not yet reached

	EV+P (N=76)	EV Mono (N=74)
Confirmed ORR, n (%) (95% CI)	**49 (64.5)** (52.7,)	
Best overall response, n (%)		
Complete Response		3 (4.1)
Partial Response	(53.9)	30 (41.1)
Stable D	17 (22.4)	25 (34.2)
	6 (7.9)	7 (9.6)
	3 (3.9)	5 (6.8)
ssment	1 (1.3)	3 (4.1)
Duration of response, median (95% CI)	NR (10.25, -)	13.2 (6.14, 15.97)

Phase III EV-302 first line in cisplatin fit and unfit patients ongoing
EV+pembro vs platinum/gem (→ avelumab maintenance)

stigator assessment consistent with BICR (86.7% concordance)

- cORRs were consistent across all pre-specified subgroups
  - 53.8% cORR observed in patients with liver metastases

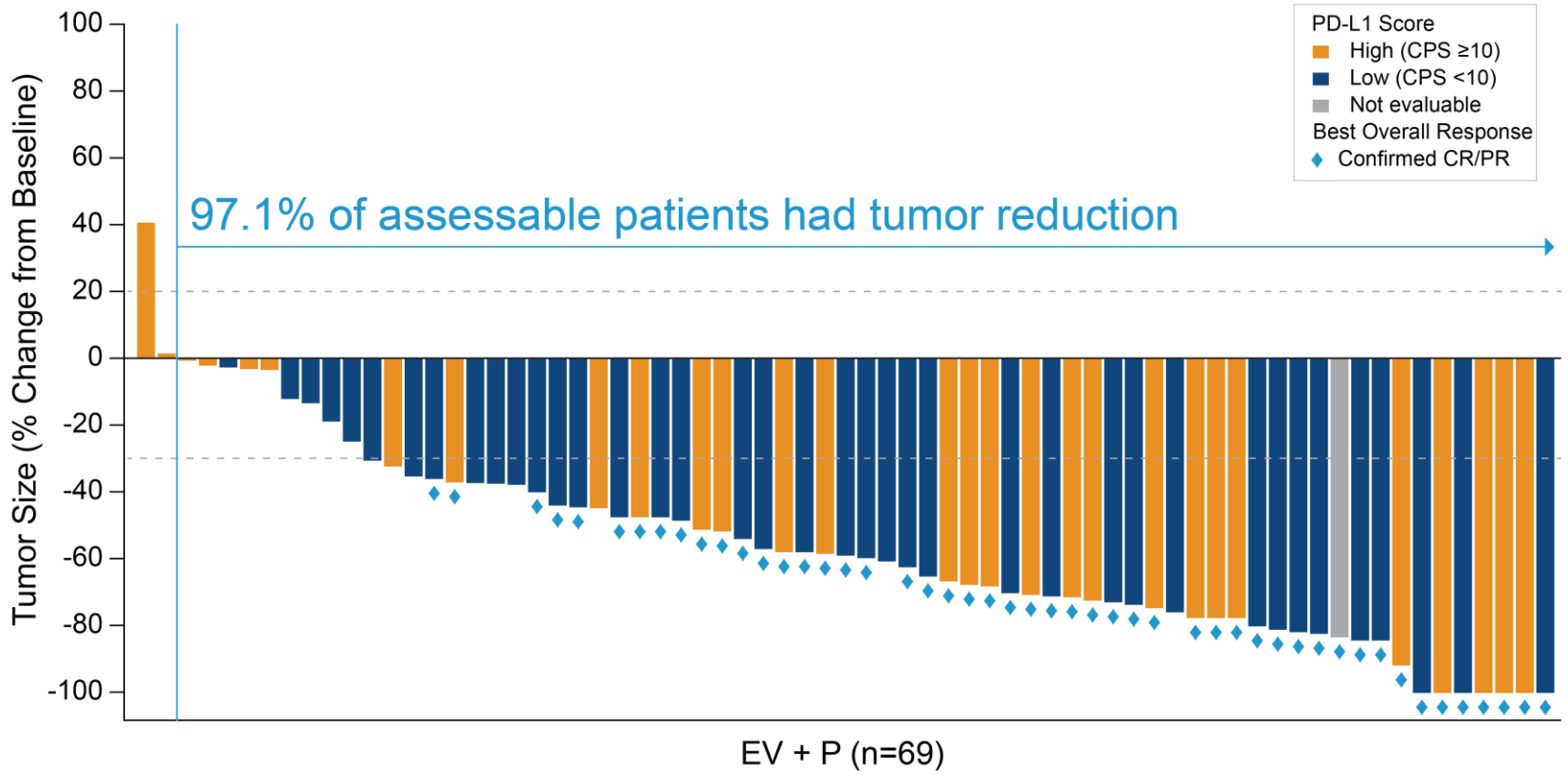
EV monotherapy

- Activity is consistent with prior experience in 2L+ la/mUC

Data cutoff: 10 JUN 2022
BICR: Blinded Independent Central Review; cORR: Confirmed Objective Response Rate; NR: Not Reached

EV+P: Maximum Percent Reduction from Baseline of Target Lesion by BICR

97.1% of assessable patients had tumor reduction or control



- Activity occurred regardless of baseline PD-L1 status

BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

Future Outlook?

No platinum needed!

Look into the right direction:

1. ICI
2. Novel agents
3. Combinations

Are we evolving towards a platinum-free future?

Aristotle Bamias MD PhD MRCP
Professor of Medical Oncology
National & Kapodistrian University of Athens
ATTIKON University Hospital

Are we evolving towards a platinum-free future?

NOOOOOOO!!!!!

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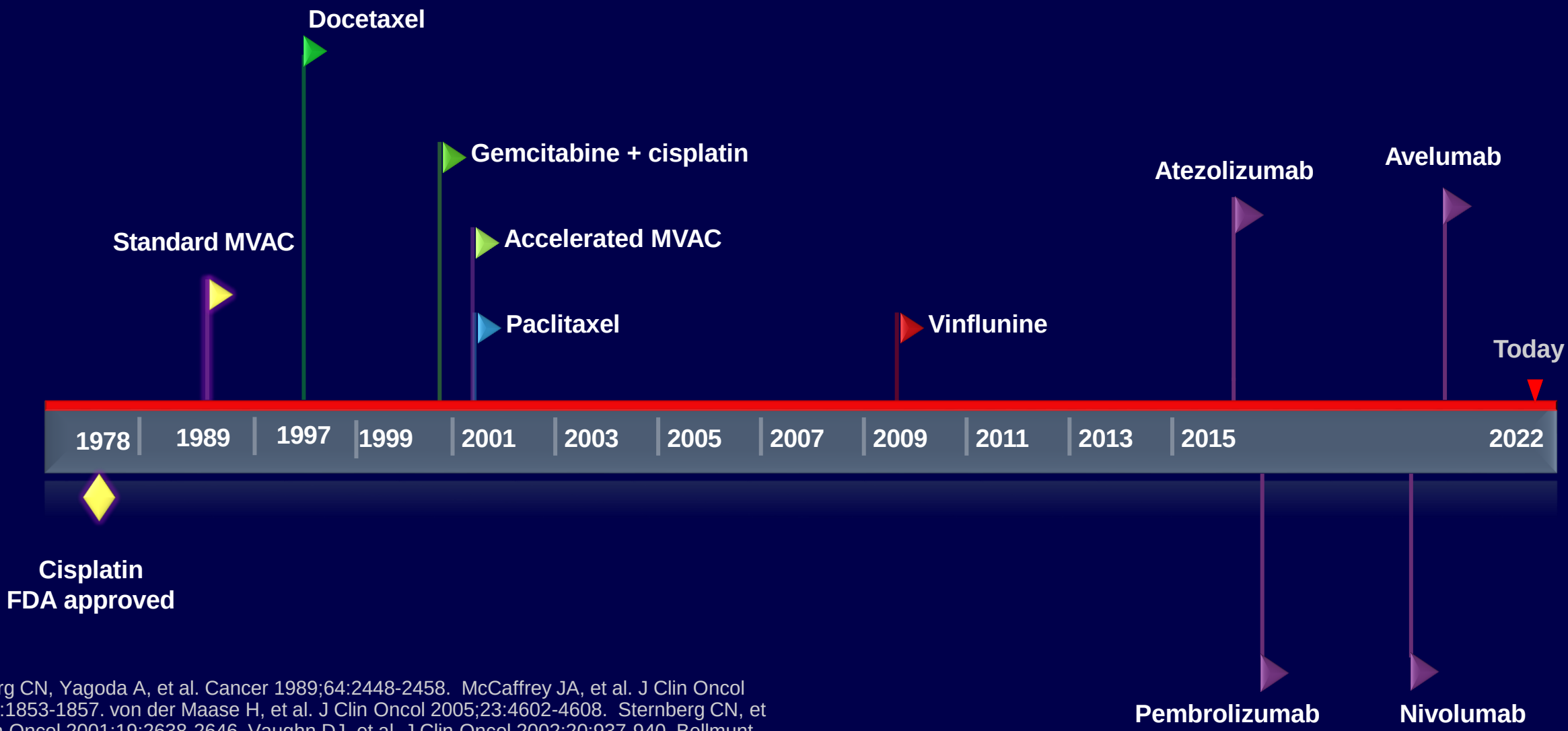
Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	Astra Zeneca, BMS, Pfizer, Ipsen
Receipt of honoraria or consultation fees	BMS, Merck, Astellas, MSD, Ipsen

Evolution of Systemic Therapy for Urothelial Cancer



Sternberg CN, Yagoda A, et al. Cancer 1989;64:2448-2458. McCaffrey JA, et al. J Clin Oncol 1997;15:1853-1857. von der Maase H, et al. J Clin Oncol 2005;23:4602-4608. Sternberg CN, et al. J Clin Oncol 2001;19:2638-2646. Vaughn DJ, et al. J Clin Oncol 2002;20:937-940. Bellmunt J, et al. J Clin Oncol 2009;27:4454-4461. Rosenberg JE, et al. Lancet. 2016;387:1909-1920. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. http://www.ema.europa.eu/ema/

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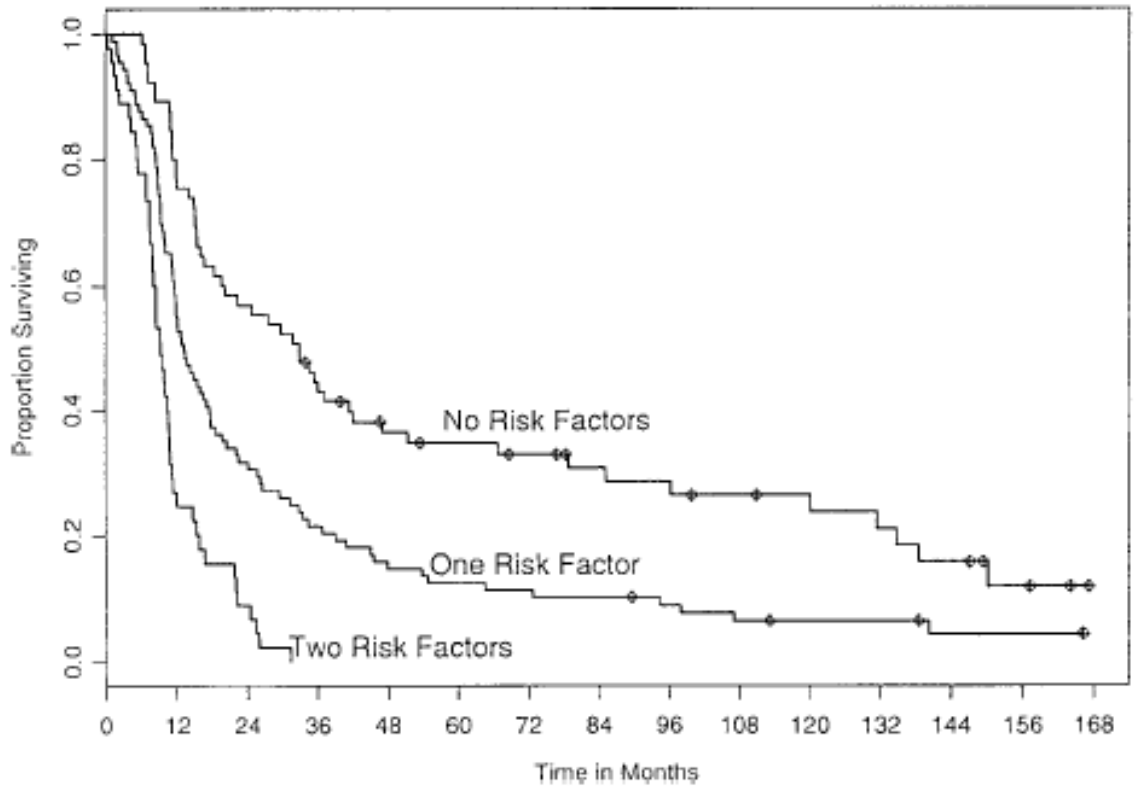
Platinum-based chemotherapy-Standard for more than 30 years

Effective standard



Personalized therapy

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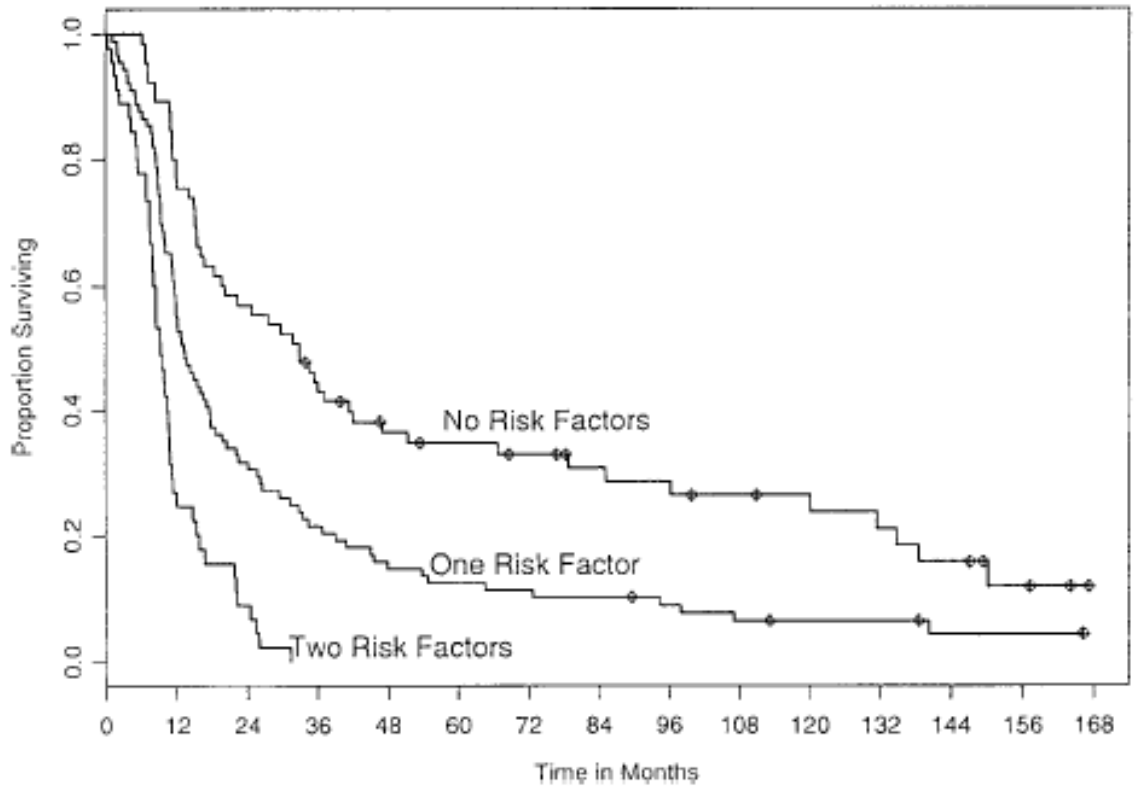
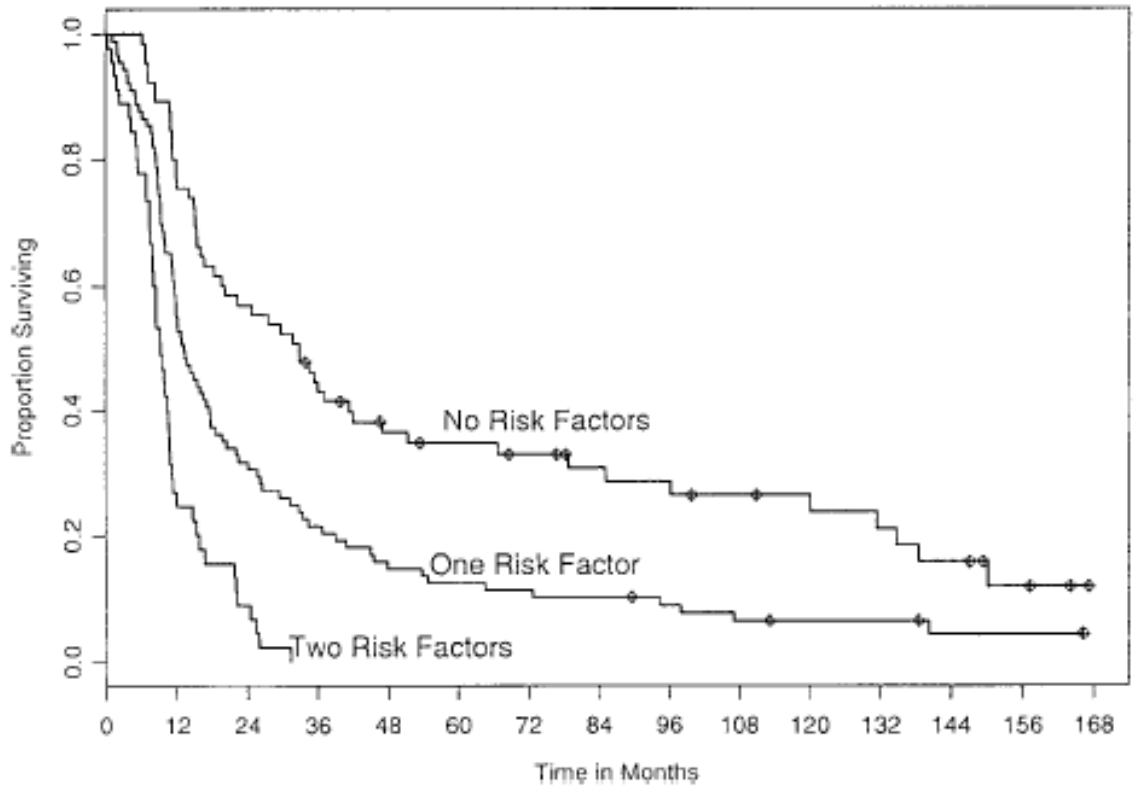


Personalized therapy

- CrCl (calculated C & G formula) ≥ 60 ml/min
- PS 0-1
- No Cardiac failure (NYHAA III, IV)
- No hearing loss ≥ Gr 2
- No peripheral neuropathy ≥ Gr 2

Platinum-based chemotherapy-Standard for more than 30 years

Effective standard



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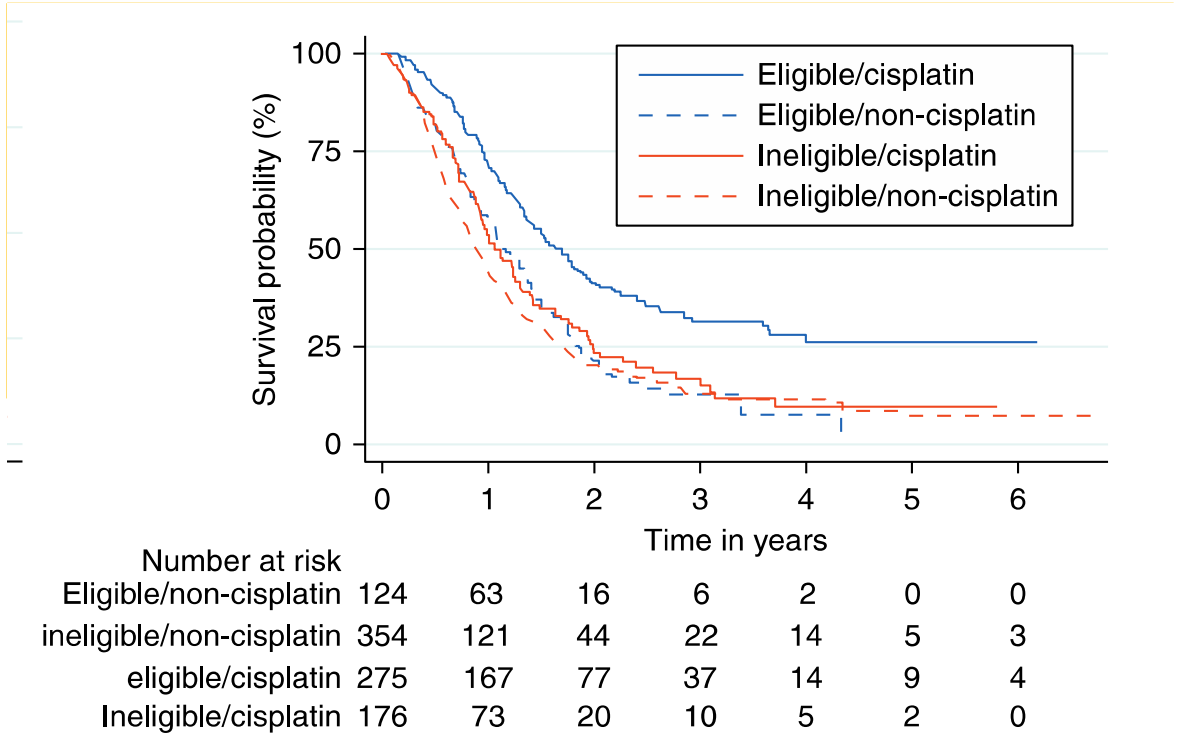

Number at risk							
Eligible/non-cisplatin	124	63	16	6	2	0	0
ineligible/non-cisplatin	354	121	44	22	14	5	3
eligible/cisplatin	275	167	77	37	14	9	4
Ineligible/cisplatin	176	73	20	10	5	2	0

Are we evolving towards a platinum-free future?

- Why do people hate chemotherapy so much?
- Is there any evidence to support this wishful thinking?

Outline

- Why do people hate chemotherapy so much?
- Is there any evidence to support this wishful thinking?

The real reason

- We hate success if it’s not ours
- Little experience

The quoted reasons

- Toxicity
- “Old” therapy

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“Old but good”

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ALL EVIDENCE POINT OUT THAT PLATINUM CHEMOTHERAPY IS THE BACKBONE OF SUCCESSFUL MANAGEMENT IN mUC

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1. 1st-line platinum-chemotherapy results are still improving (with the help of novel agents)
2. No evidence that IO monotherapy can replace current standard in 1st-line

1st-line platinum-chemotherapy results are still improving (with the help of novel agents)

Study	Treatment	OS (m)	HR (95% CI)
JAVELIN 100	Platinum-based chemotherapy → Avelumab Platinum-based chemotherapy	21.4 14.6	0.69 (0.56, 0.86)
IMvigor130	Platinum-based chemotherapy + Atezolizumab Platinum-based chemotherapy Atezolizumab	16·0 13·4/13.1 15.2	0·83 (0·69–1·00) 0.99 (0.83, 1.19)
IMvigor130 No PD	Platinum-based chemotherapy + Atezolizumab Platinum-based chemotherapy	20.5 18.8	0.86 (0.64, 1.16)
KEYNOTE361	Platinum-based chemotherapy + Pembrolizumab Platinum-based chemotherapy Pembrolizumab	17.0 14.3 15.6	0·86 (0·72-1·02) 0·92 (0·77-1·11)
DANUBE	Durvalumab + Tremelimumab Platinum-based chemotherapy	15.1 12.1	0·85 (0·72-1·02)

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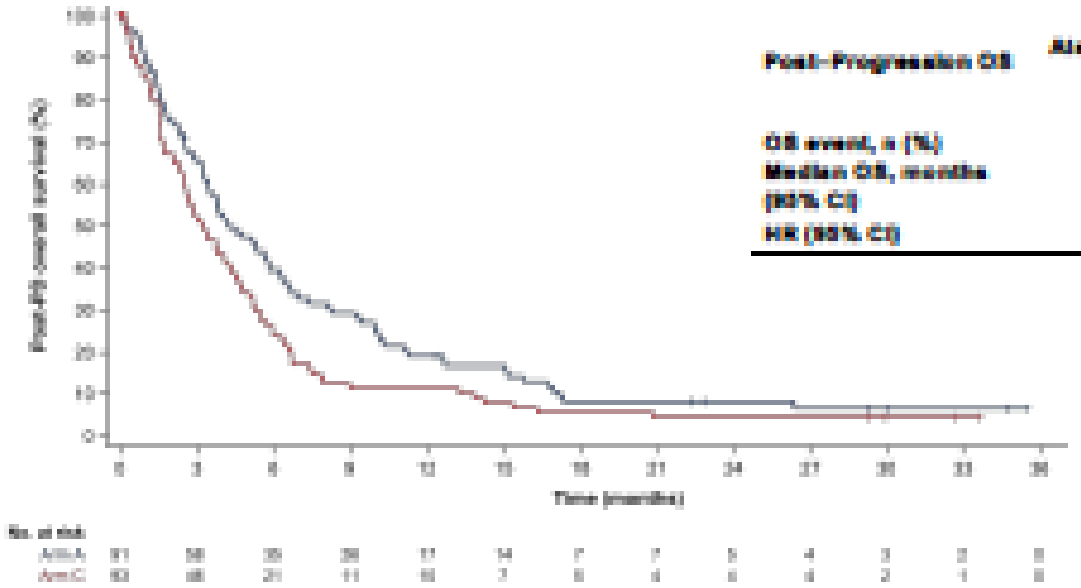
Can other therapies salvage those with PD?

Best results in chemotherapy-treated, no PD

Figure 2. Post-progression OS in patients with PD during induction

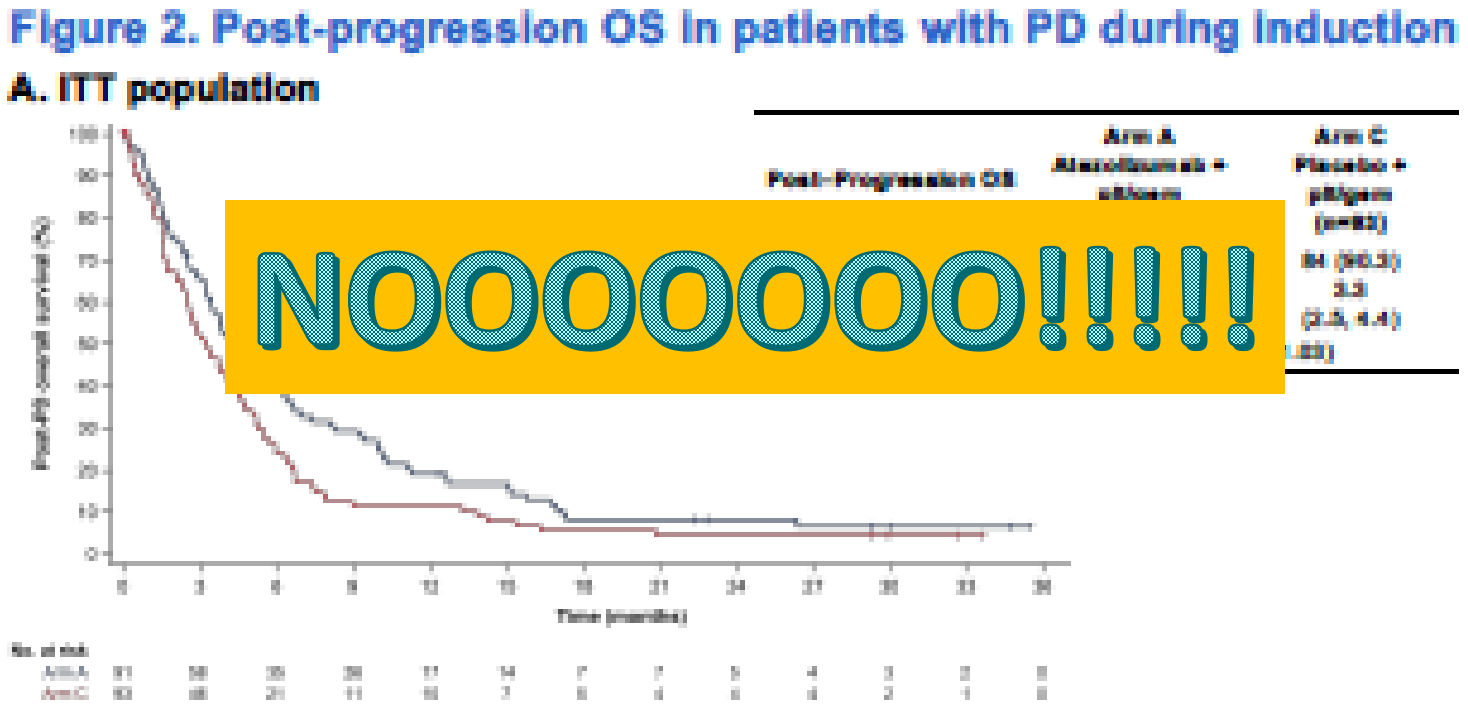
A. ITT population



Post-Progression OS	Arm A Atezolizumab + pBCgem (n=81)	Arm C Placebo + pBCgem (n=82)
OS event, n (%)	82 (90.1)	84 (90.3)
Median OS, months (95% CI)	4.3 (3.5, 5.8)	3.3 (2.5, 4.4)
HR (95% CI)	0.74 (0.53, 1.03)	

Can other therapies salvage those with PD?

Best results in chemotherapy-treated, no PD



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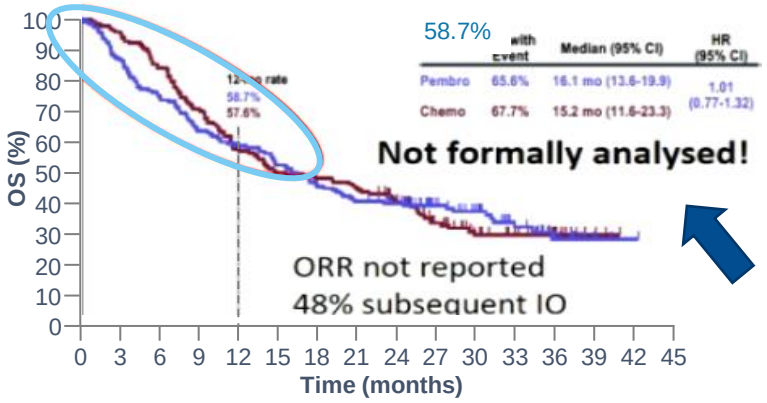
What about PD-L1 positive populations?

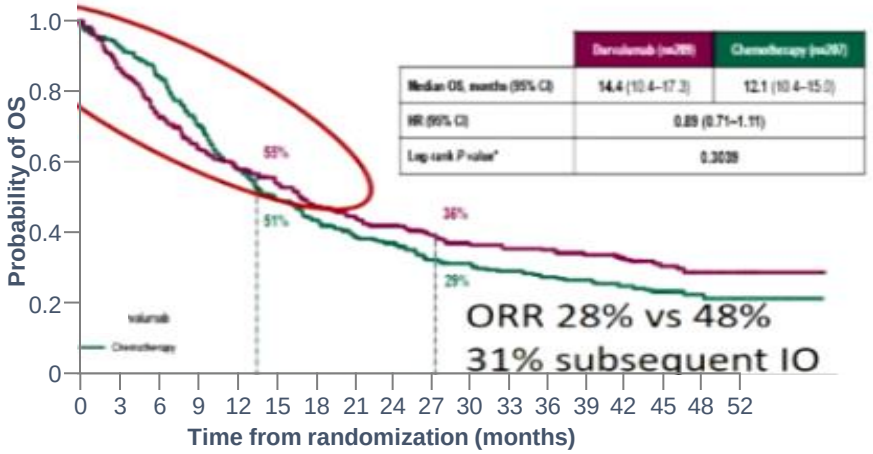
Which high PD-L1 expression?

Astra Zeneca:
Ventana SP 263 ≥ 25% IC or TC pos
MSD:
Dako 22c3 CPS ≥ 10
Roche:
Ventana SP142 ≥ 5% IC

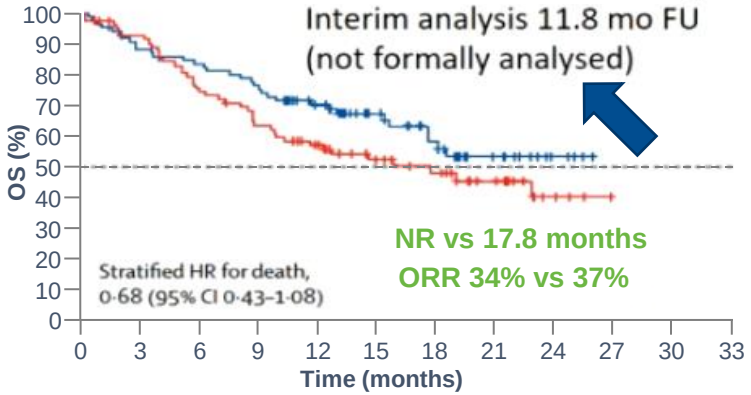
Keynote 361- IO vs chemo



DANUBE- IO vs chemo (1°EP)



IMvigor130- IO vs chemo



Mono, monotherapy.

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CONCLUSIONS

- For more than 30 years platinum-based chemotherapy has been the standard 1st-line therapy for mUC because it is very effective, well tolerated and widely used in everyday practice.
- In spite of the amazing progress in systemic therapy of mUC, success of platinum-based chemotherapy in 1st-line is driving practice and outcome.
- There is no data suggesting that novel agents can replace chemotherapy in 1st-line in the foreseeable future (not in my lifetime anyway)
- Therefore, in 2025, chemotherapy will still be the 1st-line standard in mUC