VII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN
Vigo, 20 y 21 de febrero de 2025

Tumores Genitourinarios

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Vigo 21 Febrero 2025

Disclosures

- **Consultant or Advisory Role**: Astellas Pharma, Pfizer, Bristol-Myers-Squibb, Ipsen, Merck, Eisai
- **Speaking honoraria**: Novartis, Bristol-Myers-Squibb, Ipsen, Roche, Astellas Pharma, Bayer
- **Travel/Accommodations**: Bristol-Myers-Squibb, Ipsen, Astellas

Keynote 564

KEYNOTE-564 Study (NCT03142334)

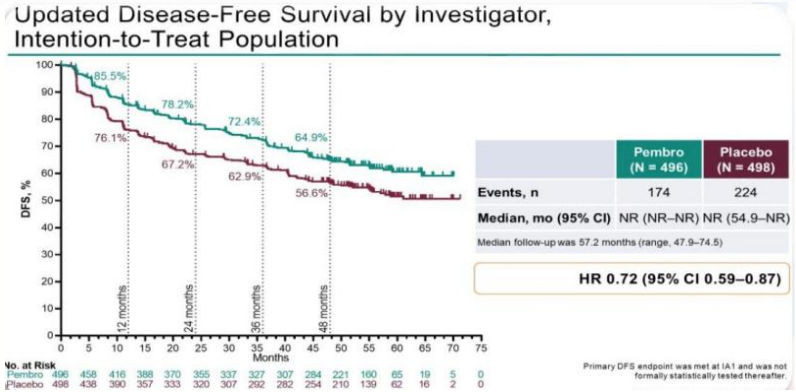
Key Eligibility Criteria

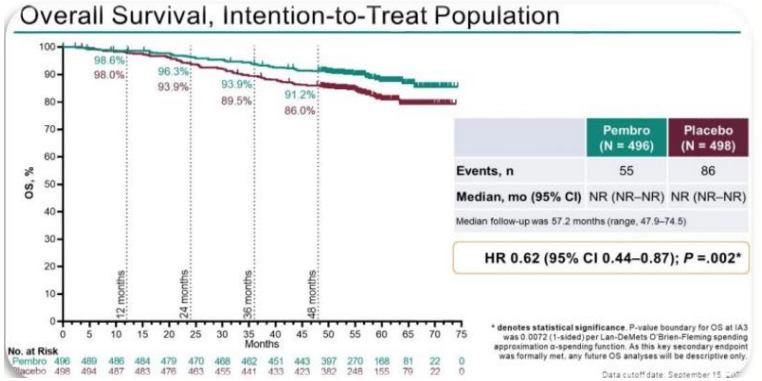
- Histologically confirmed clear cell RCC with no prior systemic therapy
- Surgery ≤12 weeks prior to randomization
- Postnephrectomy intermediate-high risk of recurrence (M0):
  - pT2, grade 4 or sarcomatoid, N0
  - pT3, any grade, N0
- Postnephrectomy high risk of recurrence (M0):
  - pT4, any grade, N0
  - Any pT, any grade, N+
- Postnephrectomy + complete resection of metastasis (M1 NED)
- ECOG PS 0 or 1

R 1:1

N = 496 → **Pembrolizumab** 200 mg Q3W for ~1 year (≤17 cycles)

N = 498 → **Placebo** Q3W for ~1 year (≤17 cycles)





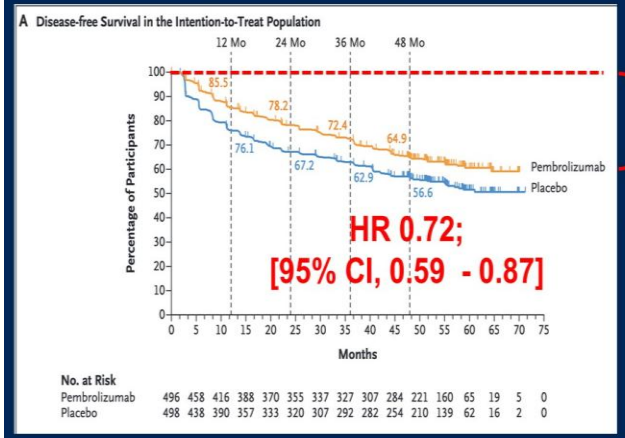
Choueri T, ASCO GU 2025

Keynote 564

Improvement in both **DFS** and **OS** but……..

- Overtreatment
- Toxicity
- We need to select patients based on biomarkers

KEYNOTE-564: Disease-free Survival Outcome



Need biomarkers to identify patients who may not benefit.

Side Effects

- 21% of Pembro group terminated treatment for toxicity (vs 2% placebo).
- Grade 3-4 toxicity: 19% Pembro vs. 1% placebo.

Salami SS, ASCO GU 2025

IMMotion010: Kim-1

Circulating kidney injury molecule-1 (KIM-1) biomarker analysis in IMmotion010, a randomized Phase 3 study of adjuvant atezolizumab vs placebo in patients with renal cell carcinoma at increased risk of recurrence after resection

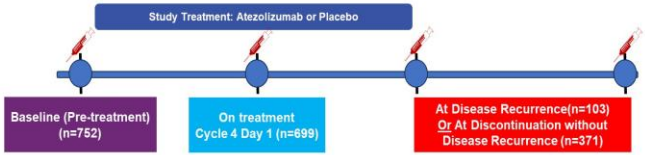
Circulating biomarker analysis scheme

Part 1:
Biomarker identification

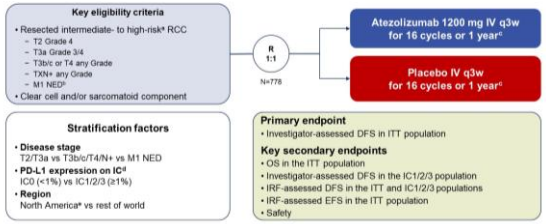
- A high throughput proteomics analysis was performed using an affinity-based proximity extension assay panel of approximately 3000 proteins
- Circulating proteins with differential abundance patterns in matched baseline vs disease recurrence samples (n=73 pairs) were identified

Part 2:
Association of circulating KIM-1 with DFS outcomes

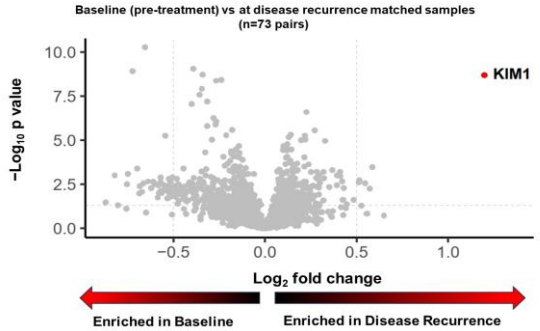
- A high-sensitivity, quantitative, electrochemiluminescence assay was used to evaluate circulating KIM-1 in all available baseline, on-treatment, treatment discontinuation and disease recurrence serum samples
- A serum KIM-1 cutoff was selected based on optimal and stable differentiation of clinical benefit between treatment arms



IMmotion010 Study design (NCT03024996)



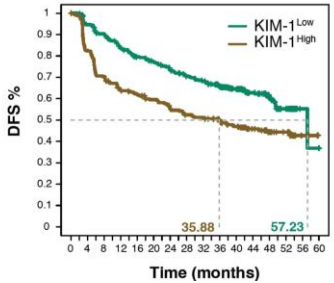
KIM-1 was identified as the most significantly enriched circulating protein in recurrence vs baseline serum samples in IMmotion010



IMMotion010: Kim-1

KIM-1^{High} status at baseline was associated with worse DFS in IMmotion010

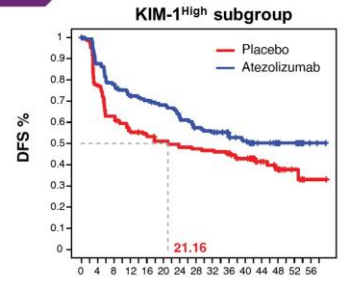
Baseline



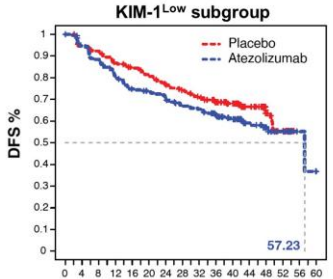
	n	Median DFS (months)	HR[a] (95% CI)
KIM-1^{High}	300	35.88	1.75 (1.40, 2.17)
KIM-1^{Low}	452	57.23	

Atezolizumab improved DFS vs Placebo in the baseline KIM-1^{High} subgroup

Baseline



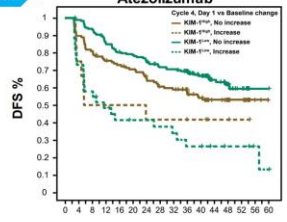
	n	Median DFS	HR[a] (95% CI)
Atezolizumab	151	NE	0.72 (0.52, 0.99)
Placebo	149	21.16	

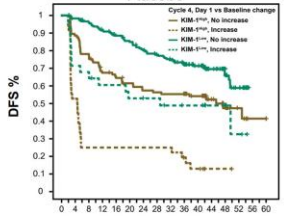


	n	Median DFS	HR[a] (95% CI)
Atezolizumab	229	57.23	1.12 (0.88, 1.63)
Placebo	223	NE	

On-treatment increase in KIM-1 was associated with worse DFS in both KIM-1^{High} and KIM-1^{Low} subgroups

On Treatment





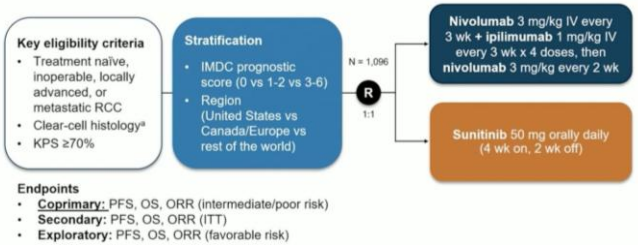
Baseline	On-treatment	n	Median DFS	HR (95% CI)
KIM-1^{High}	Increase[a]	12	14.8	1.68 (0.77, 3.69)
	No increase	126	NE	
KIM-1^{Low}	Increase[a]	34	11.5	3.56 (2.21, 5.75)
	No increase	179	NE	

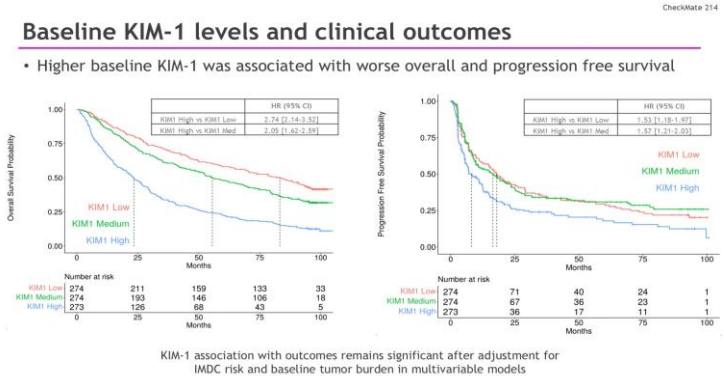
Baseline	On-treatment	n	Median DFS	HR (95% CI)
KIM-1^{High}	Increase[a]	36	4.8	3.53 (2.24, 5.58)
	No increase	105	45.4	
KIM-1^{Low}	Increase[a]	28	29.0	2.51 (1.42, 4.44)
	No increase	179	NE	

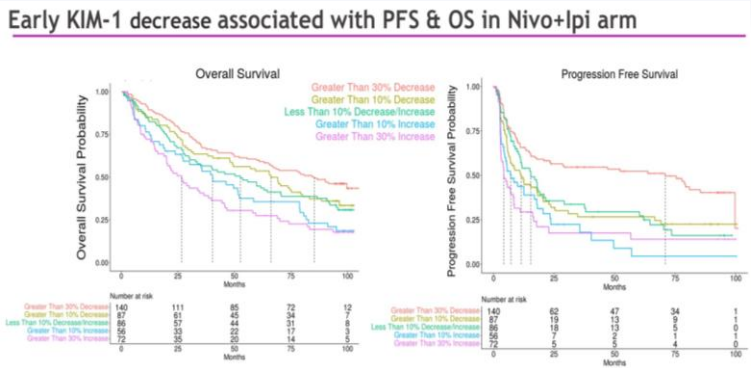
[a]Increase in KIM-1 was defined as a ≥30% increase from baseline to Cycle 4 Day 1 value.

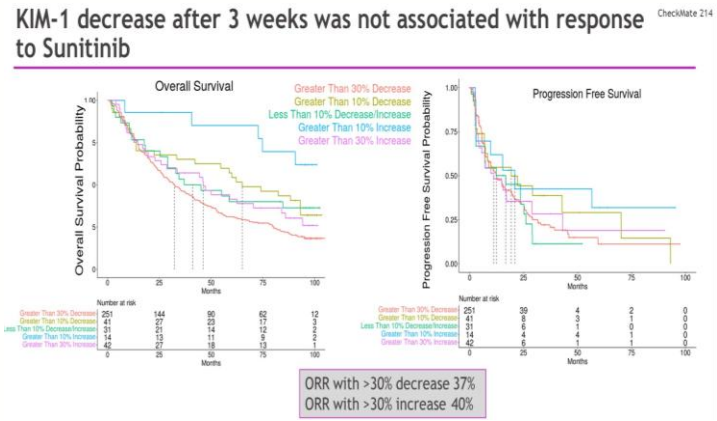
Albiges L, ASCO 2024

Checkmate-214: Kim-1





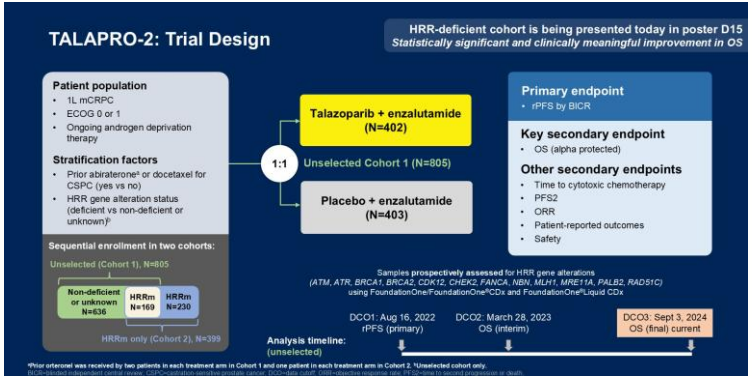




Xu W, ASCO GU 2025

Talapro-2

Prior abiraterone[a] or docetaxel, n (%)		109 (27.1)	110 (27.3)
	Abiraterone	21 (5.2)	25 (6.2)
	Docetaxel	86 (21.4)	93 (23.1)
HRR gene alteration status[b], n (%)	Deficient	85 (21.1)	84 (20.8)
	Non-deficient or unknown	317 (78.9)	319 (79.2)



Tissue source for prospective HRR gene alteration testing, n (%)	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
Tumor tissue	402 (100.0)	403 (100.0)
Tumor tissue and blood (circulating tumor DNA)	57 (14.2)	58 (14.4)

BRCA1/2 gene alterations were detected in 7.3% of patients across both arms

HRR gene alterations by prospective tumor tissue testing, n (%)[1]	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
1 or more alterations in the corresponding gene	85 (21.1)	82 (20.3)
CDK12	23 (5.7)	29 (7.2)
BRCA2	23 (5.7)	28 (6.9)
ATM	23 (5.7)	14 (3.5)
CHEK2	6 (1.5)	5 (1.2)
BRCA1	5 (1.2)	4 (1.0)
Other (*ATR, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*)	14 (3.5)	13 (3.2)

Agarwal N , ASCO GU 2025

Talapro-2

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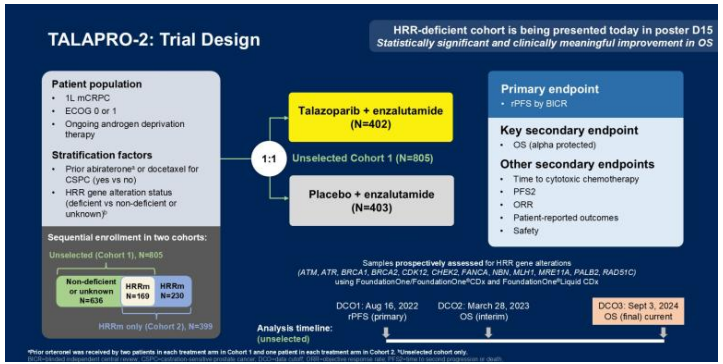

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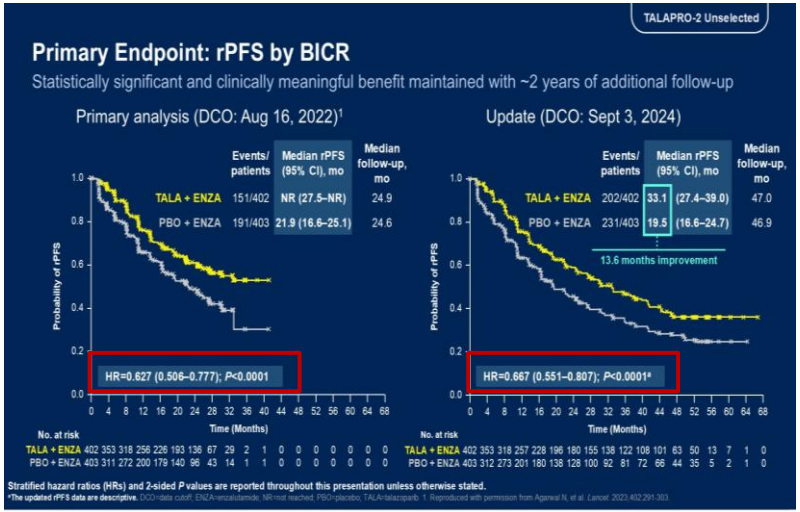
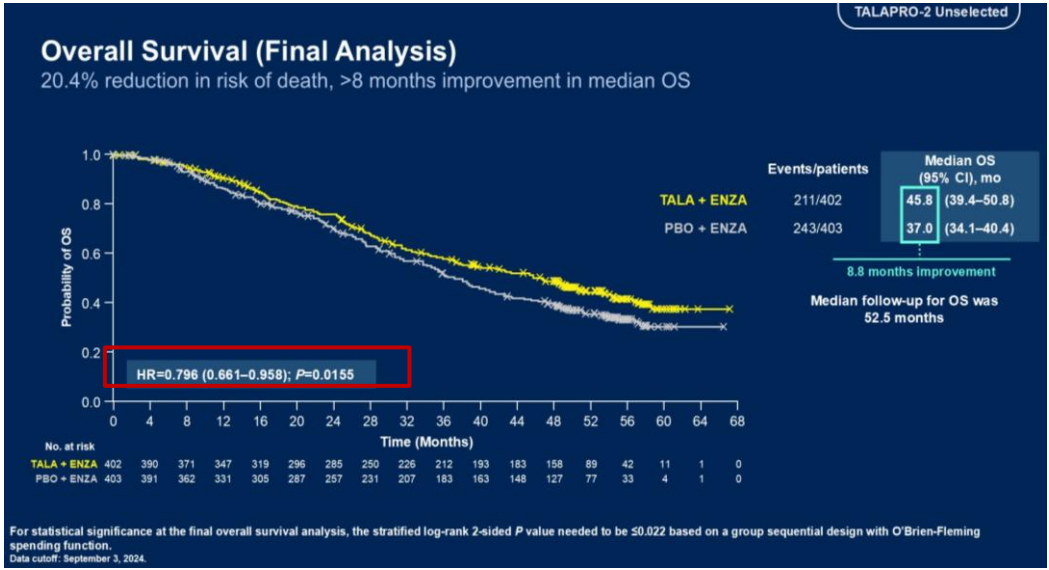
Talapro-2





Agarwal N , ASCO GU 2025

Talapro-2

TEAEs, n (%)	TALA + ENZA (N=398)	PBO + ENZA (N=401)
Any TEAE	394 (99.0)	384 (95.8)
Treatment-related	360 (90.5)	286 (71.3)
SAEs	182 (45.7)	126 (31.4)
Treatment-related	85 (21.4)	13 (3.2)
Grade 3–4 TEAEs	302 (75.9)	179 (44.6)
Grade 5 TEAEs	14 (3.5)	20 (5.0)
Treatment-related	1 (0.3)	2 (0.5)
Dose interruption of talazoparib or placebo due to AE	260 (65.3)	99 (24.7)
Dose reduction of talazoparib or placebo due to AE[a]	217 (54.5)	29 (7.2)
Discontinuation of talazoparib or placebo due to AE	86 (21.6)	52 (13.0)

No new safety findings were identified after an additional 2 years of follow-up

- No additional cases of MDS or AML in the talazoparib group; n=1 of each previously reported
- Rate of discontinuation of talazoparib due to AEs was similar to that in the primary analysis
- In exposure-adjusted analyses, rate of venous embolic and thrombotic events was unchanged with longer follow-up (2.4 per 100 participant-years)

TALAPRO-2 Unselected

Subgroup Analysis of Overall Survival

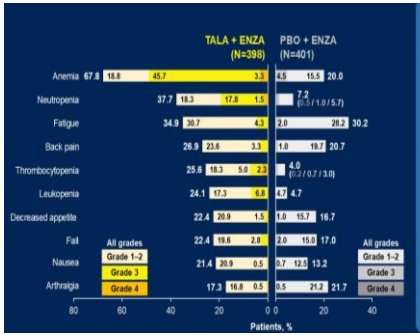
Subgroup		TALA + ENZA Events/patients	PBO + ENZA Events/patients	HR (95% CI)
Overall		211/402	243/403	0.796 (0.661–0.958)
Age, years	≥70	137/240	154/240	0.797 (0.633–1.004)
	<70	74/162	89/163	0.778 (0.571–1.059)
ECOG PS	0	134/259	156/271	0.842 (0.669–1.061)
	1	77/143	87/132	0.700 (0.514–0.952)
Gleason score	<8	56/117	60/113	0.895 (0.622–1.289)
	≥8	153/281	177/283	0.769 (0.619–0.955)
Stage at diagnosis	M0	91/172	111/185	0.828 (0.627–1.093)
	M1	118/226	129/215	0.781 (0.609–1.003)
Site of metastasis	Bone only	81/168	95/155	0.676 (0.502–0.910)
	Soft tissue only	19/48	25/57	0.900 (0.495–1.636)
	Bone and soft tissue	109/181	121/187	0.868 (0.670–1.125)
HRR status[a]	Deficient	40/85	56/84	0.542 (0.361–0.814)
	Non-deficient/unknown	171/317	187/319	0.874 (0.711–1.076)
Prior abiraterone[a] or docetaxel	Yes	55/109	74/110	0.663 (0.467–0.940)
	No	156/293	169/293	0.853 (0.686–1.060)

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8

Favors TALA + ENZA — Favors PBO + ENZA

The HR for the overall ITT population was based on a Cox model stratified by the randomization stratification factors. For all subgroups, the HR was based on an unstratified Cox model with treatment as the only covariate. Data for the HRR-deficient cohort are presented at ASCO GU 2025 in poster D15.

[a]HRR gene alteration status (deficient vs non-deficient or unknown) by randomization stratification. [b]Includes two patients in each treatment arm who received prior orteronel.



In the talazoparib arm:

- 49.0% had grade 1–2 anemia at baseline
- Most common TEAEs leading to a dose reduction of talazoparib were:
  - Anemia (46.2%)
  - Neutropenia (16.3%)
  - Thrombocytopenia (6.2%)
- Grade 3–4 anemia
  - Reported in 49.0% of patients
  - Median time to onset was 3.3 months
  - 42.2% received an RBC transfusion (median of two transfusions)
- 8.5% discontinued talazoparib due to anemia
- Median duration of treatment with talazoparib was 19.7 months

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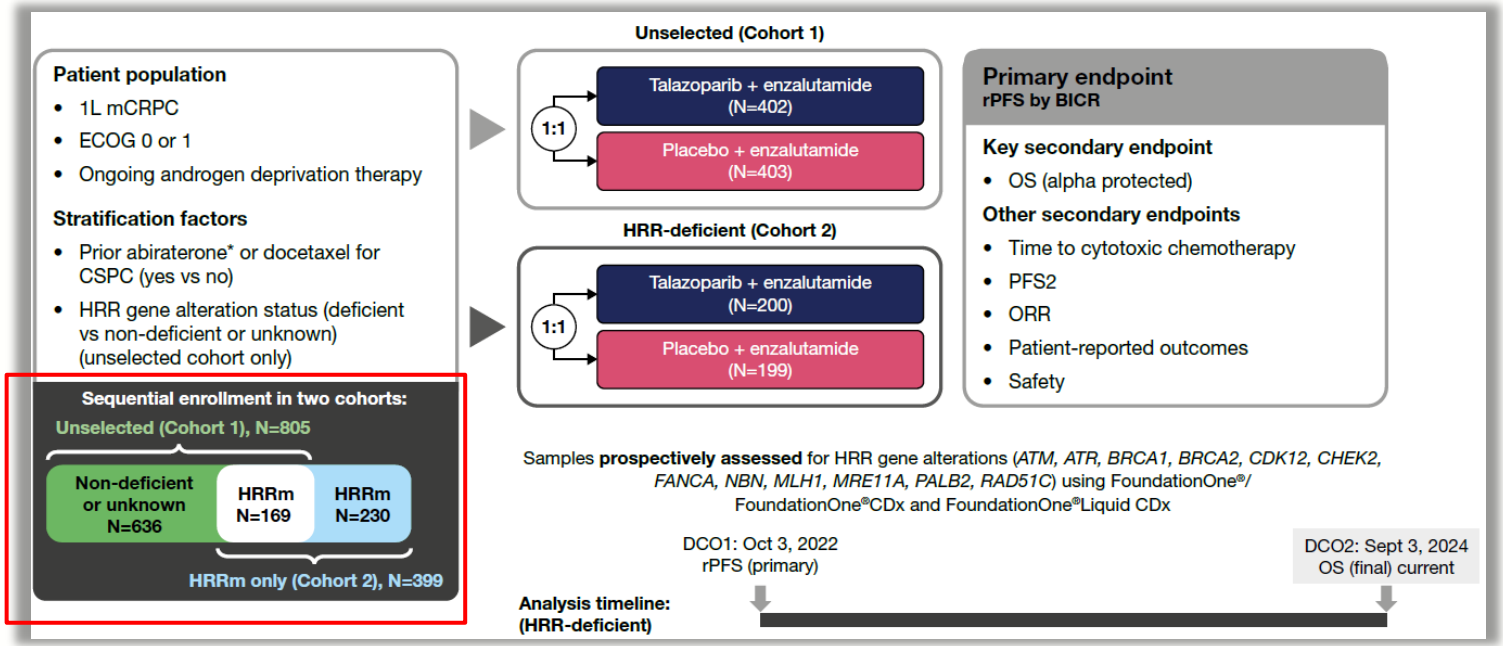
Talapro-2



Fizzazi K, ASCO GU 2025

Talapro-2

rPFS HRR population

Figure 2. (A) Updated and (B) Primary Analysis of BICR-Assessed rPFS (HRR-Deficient Intention-To-Treat Population)

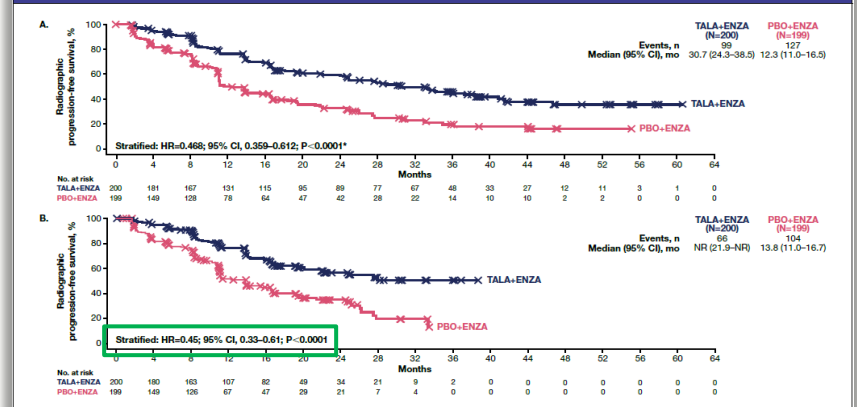
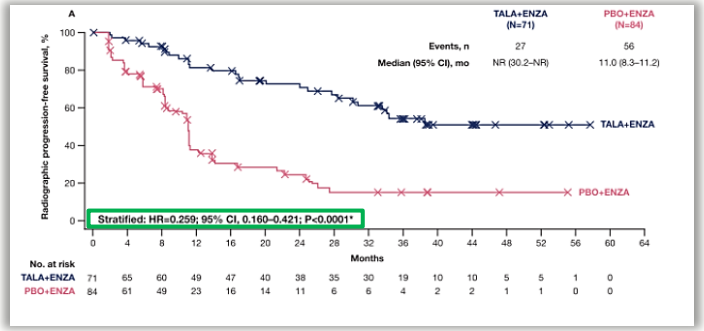
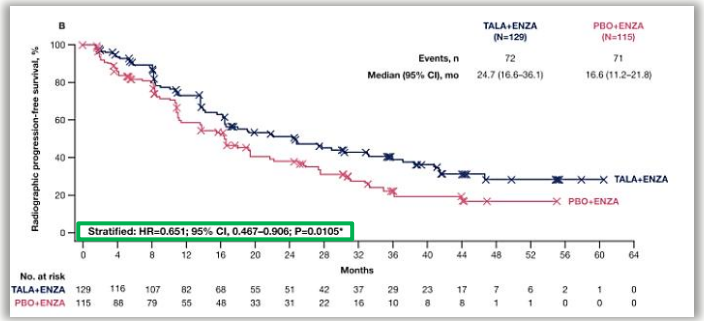


Figure 2B has been reproduced from Fizazi K, et al. First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial. *Nat Med*. 2024;30:257-264, under the terms of the Creative Commons CC BY license Licenses List - Creative Commons.
ENZA=enzalutamide; mo=months; NR=not reached; PBO=placebo; TALA=talazoparib.
*The updated rPFS data are descriptive.

rPFS *BRCA1/2*



rPFS Non-BRCA1/2 HRRm



- **rPFS favored TALA plus ENZA in patients with and without BRCA1/2 alterations**

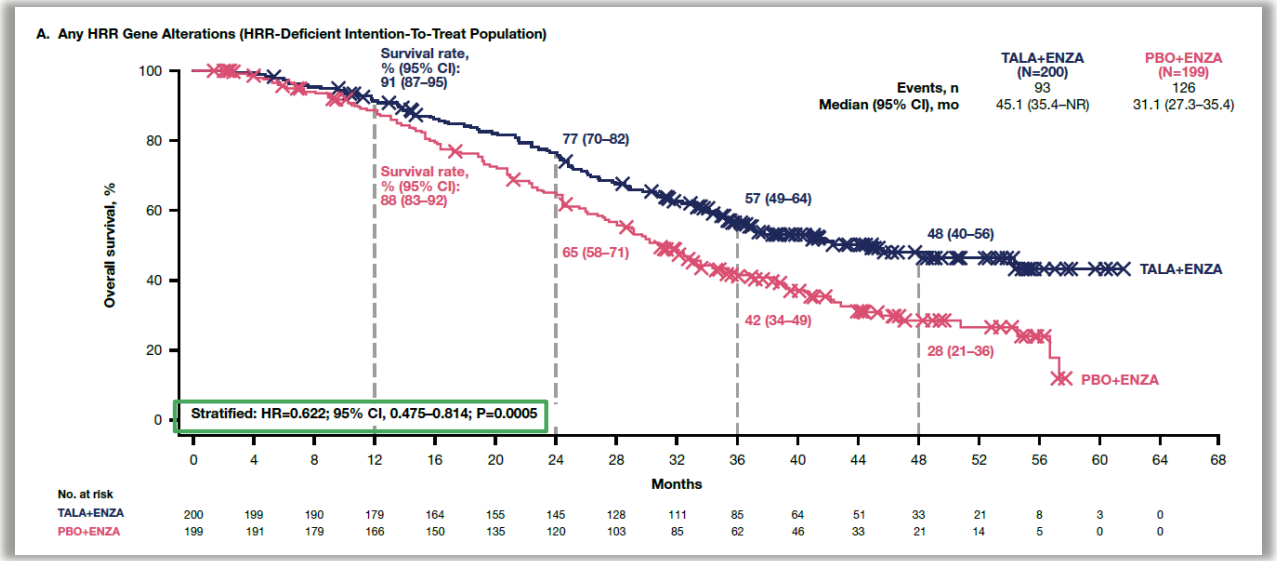
Fizzazi K, ASCO GU 2025

Talapro-2

Overall Survival HRR (Final Analysis)[1]

TALAPRO-2 HRRm

HRRm (ITT)



- At a median follow-up of 44.2 months, treatment with TALA plus ENZA resulted in a 38% reduced risk of death vs ENZA plus PBO for patients with HRR-deficient mCRPC

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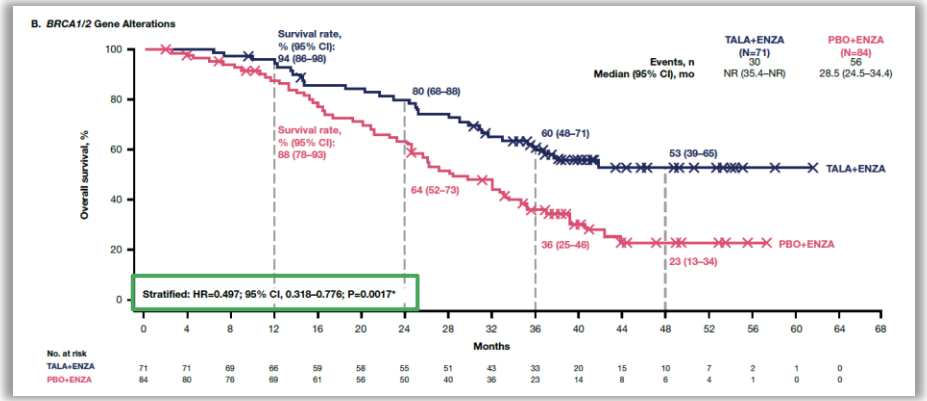
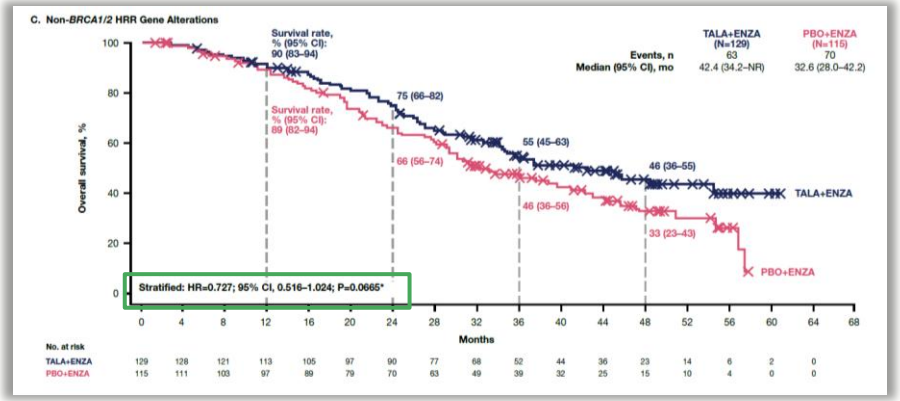
Talapro-2

Overall Survival BRCA1/2 (Final Analysis)[1]

BRCA1/2



Non-BRCA1/2 HRRm

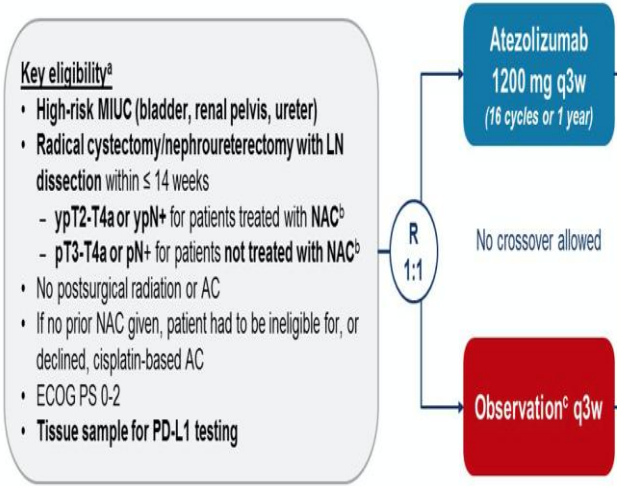


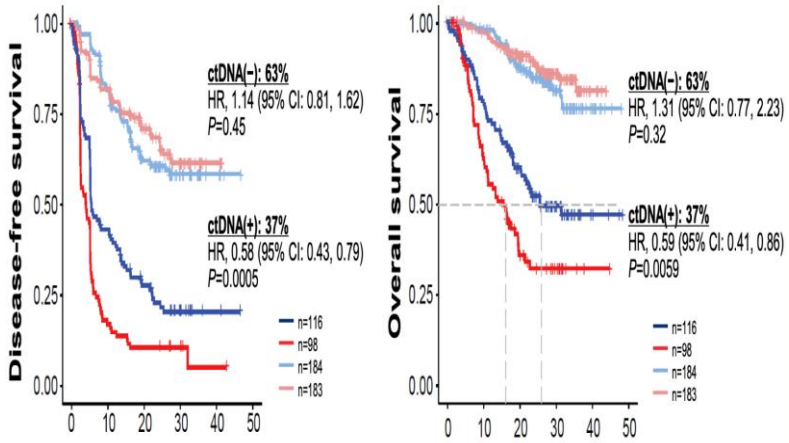
*The P values are nominal and descriptive for the subgroup analyses.

- **Patients with *BRCA1/2* gene alterations had a 50% reduction in risk of death and those with non-*BRCA1/2* HRR gene alterations had a 27% lower risk of death with TALA plus ENZA vs ENZA plus PBO**

Fizzazi K, ASCO GU 2025

Imvigor 010: ctDNA exploratory analysis

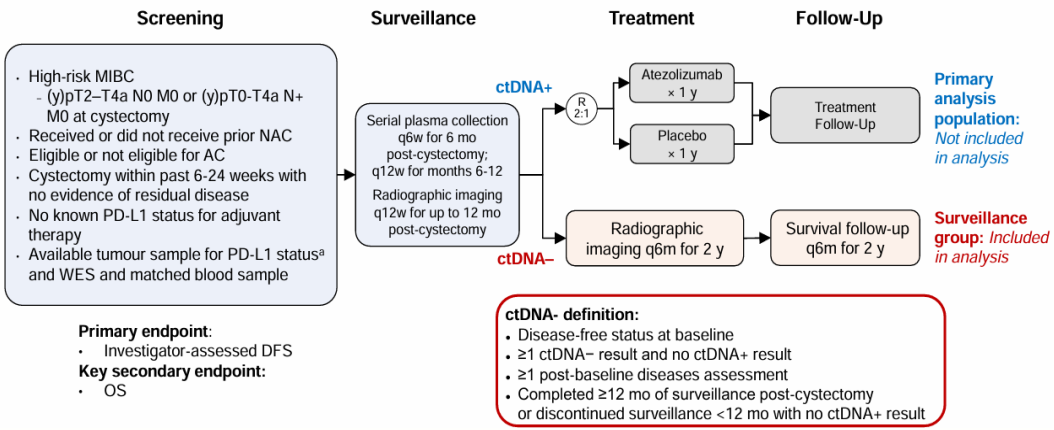




Powles T, et al. Ann Oncol 2020;31(suppl_7):S1417-S1424

Imvigor 011: Surveillance group analysis

Study desing



ctDNA- population

Characteristic		All ctDNA− patients n=171
Median age (range), y		69 (40-90)
Race, n (%)	White	96 (56.1)
	Asian	63 (36.8)
	Other[a]	12 (7.0)
Male, n (%)		135 (78.9)
ECOG PS at screening, n (%)	0	115 (67.3)
	1	49 (28.7)
	2	7 (4.1)
Histology at radical resection, n (%)	UC	142 (83.0)
	UC with mixed histology	29 (17.0)
Tumour stage, n (%)[b]	<T2	18 (10.7)
	T2	59 (34.9)
	T3	74 (43.8)
	T4	18 (10.7)
Nodal stage, n (%)	N0	135 (78.9)
	N+	36 (21.1)
PD-L1 status, n (%)[c]	IC0/1	98 (57.6)
	IC2/3	72 (42.4)
Lymph nodes removed, n (%)[d]	<10	37 (22.2)
	≥10	130 (77.8)
Lymph node density, n (%)[d]	<20	162 (97.0)
	≥20	5 (3.0)
Prior neoadjuvant chemotherapy, n (%)	Yes	83 (48.5)
	No	88 (51.5)

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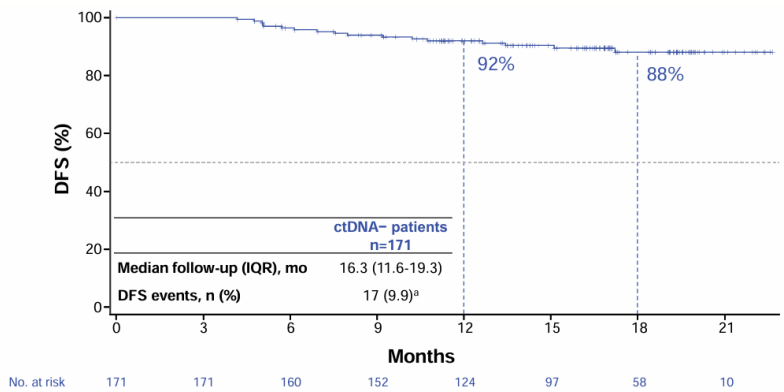
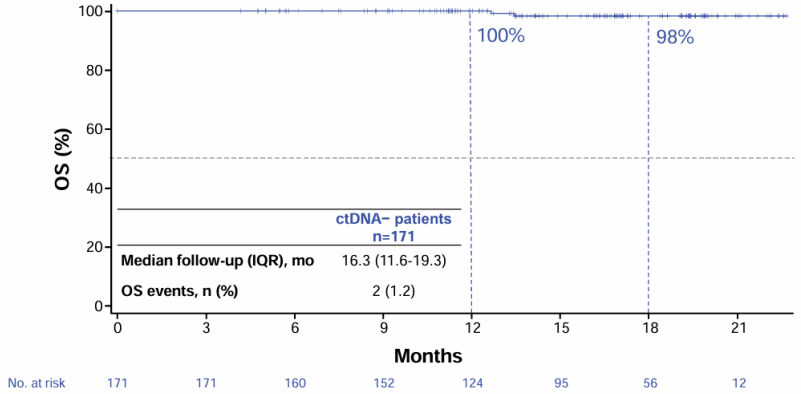
Imvigor 011: Surveillance group analysis

DFS in the ctDNA-population



OS in the ctDNA-population



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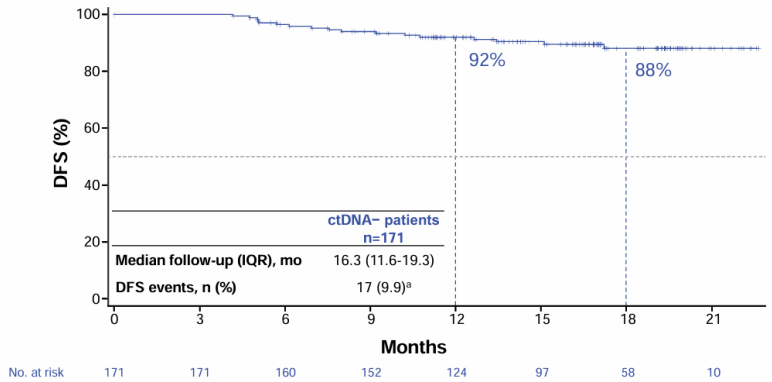
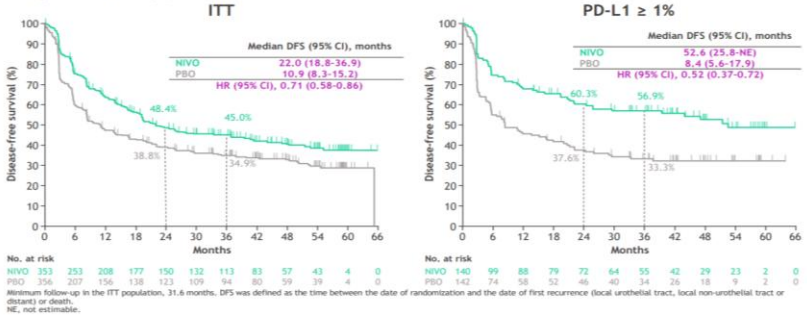
Imvigor 011: Surveillance group analysis

DFS in the ctDNA-population



DFS in Checkmate274

- Continued DFS benefit was observed with NIVO versus PBO both in the ITT and tumor PD-L1 expression ≥ 1% populations



Minimum follow-up in the ITT population, 31.6 months. DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
NE, not estimable.

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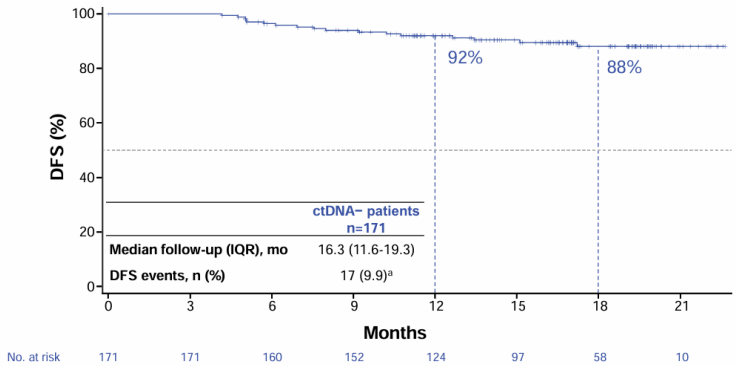
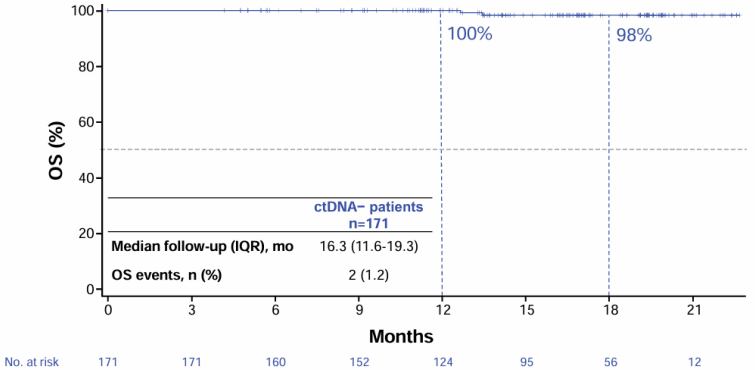
Imvigor 011: Surveillance group analysis

DFS in the ctDNA-population



OS in the ctDNA-population



- We need longer follow-up in both arms
- Has **ctDNA negative** a **negative predictive value?**
- **Serial ctDNA testing may have greater clinical hability than landmark ctDNA as a risk stratification tool using Natera Signature**

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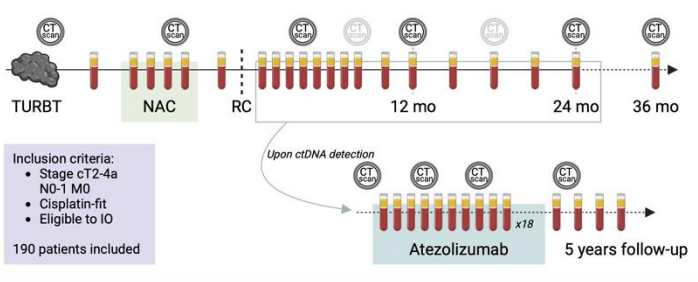
Tombola Trial



Primary objective:

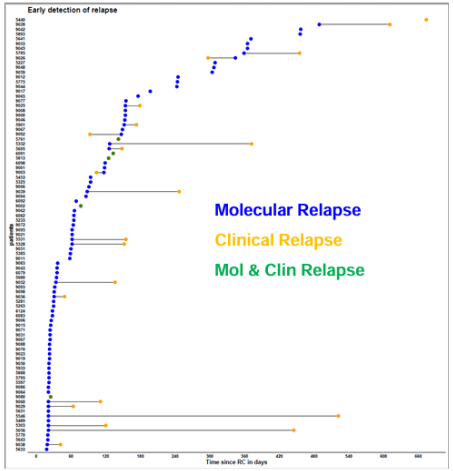
- Complete response (CR) after treatment with investigational agent initiated by ctDNA positive status after radical cystectomy.

CR defined as NED = negative ctDNA and no visible metastasis on CT

Secondary objectives:

- Duration of freedom from clinical relapse
- Overall survival
- Cancer specific survival

Relapse following cystectomy



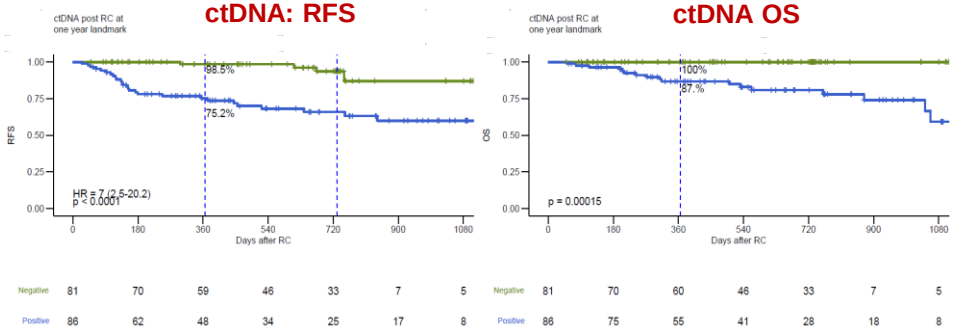
56% were ctDNA+ post-RC

75% were detected < 4 months post RC

Of the ctDNA- patients, only 2 (3%) developed metastases on CT-scan during follow-up

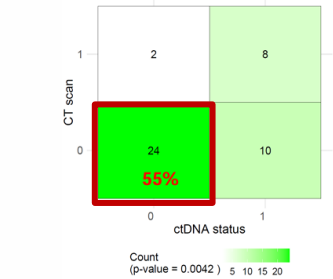
Tombola Trial

Oncological outcome – immunotherapy at the time of molecular relapse



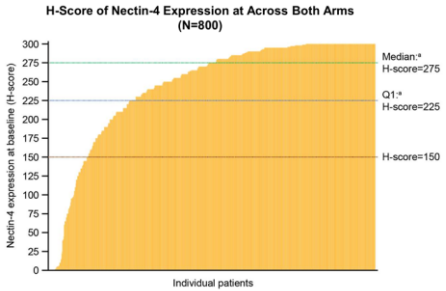
Primary endpoint

NED (No evidense of disease) (CT and ctDNA-) following immunotherapy



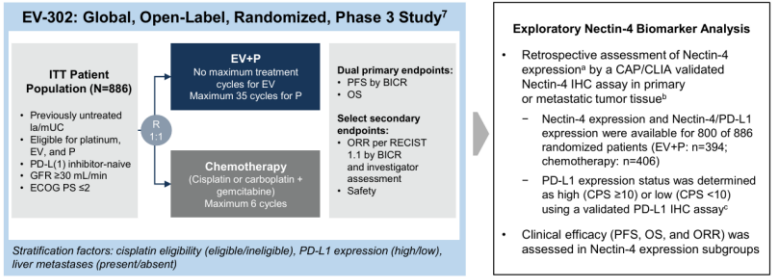
EV-302: Exploratory Analysis Nectin-4 Expression

Distribution of Nectin-4 H-Scores Was Skewed Toward High Expression



Variable	EV+P (n=394)	Chemotherapy (n=406)
H-score, median (IQR)	280 (230-298)	270 (215-297)
Subgroup, H-score, n (%)		
<150	38 (9.6)	50 (12.3)
≥150 to <225	50 (12.7)	56 (13.8)
≥225	306 (77.7)	300 (73.9)
Patients with H-score 0, n (%)	3 (0.8)	6 (1.5)

Study Design and Methods

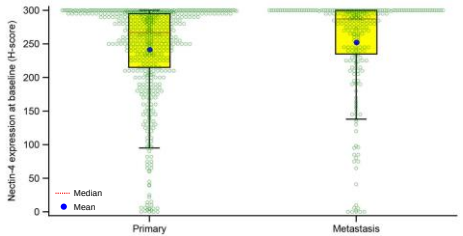


Exploratory Nectin-4 Biomarker Analysis

- Retrospective assessment of Nectin-4 expression[a] by a CAP/CLIA validated Nectin-4 IHC assay in primary or metastatic tumor tissue[b]
  - Nectin-4 expression and Nectin-4/PD-L1 expression were available for 800 of 886 randomized patients (EV+P: n=394; chemotherapy: n=406)
  - PD-L1 expression status was determined as high (CPS ≥10) or low (CPS <10) using a validated PD-L1 IHC assay[c]
- Clinical efficacy (PFS, OS, and ORR) was assessed in Nectin-4 expression subgroups

High Nectin-4 H-Scores Were Observed Regardless of the Biopsy Origin

- The majority (69%) of biopsy samples submitted were of primary origin[a]



Biopsy origin	Primary (n=554)	Metastasis (n=246)
H-score, median (IQR)	267 (215-295)	287 (235-300)

Data cutoff: 8 August 2023.
EV, enfortumab vedotin; IQR, interquartile range; la/mUC, locally advanced or metastatic urothelial cancer; P, pembrolizumab.
[a]These are not matched biopsies; one tumor tissue sample was submitted for each patient.

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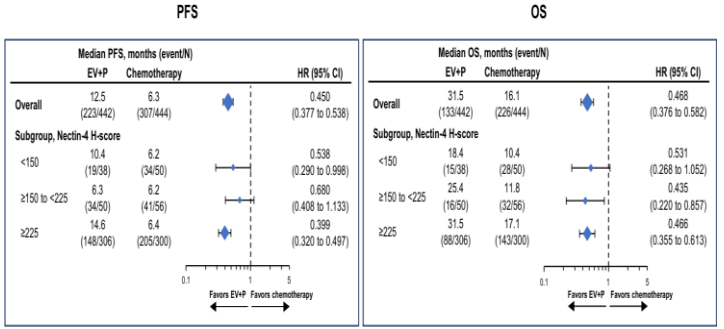
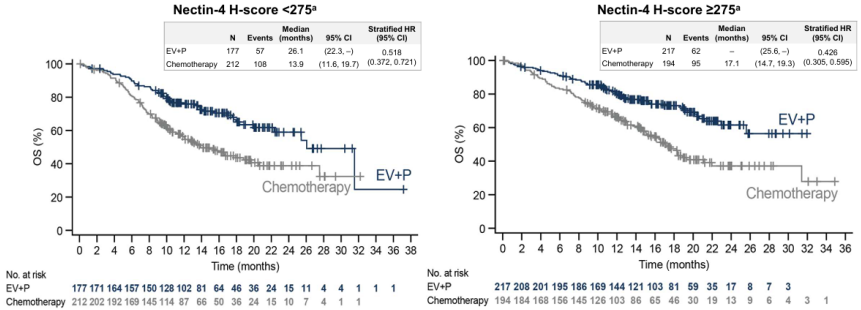
EV-302: Exploratory Analysis Nectin-4 Expression

Consistent PFS and OS Benefit with EV+P Across Nectin-4 H-Score Subgroups

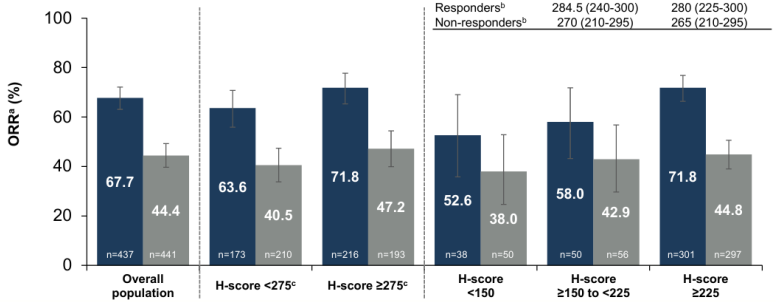


Consistent OS Benefit with EV+P in Both <275 and ≥275 Nectin-4 H-Score Subgroups



Consistent ORR Benefit with EV+P Across All Nectin-4 Subgroups

Nectin-4 H-score, median (IQR)	EV+P n=437	Chemotherapy n=441
Responders[b]	284.5 (240-300)	280 (225-300)
Non-responders[b]	270 (210-295)	265 (210-295)



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Conclusions

Adjuvant Pembrolizumab treatment improves OS in High-Risk RCC patients

Kim-1 could be a biomarker **to select** which patients could benefit from adjuvant **immmunotherapy**

KIM- 1: Preliminary data in patients with advanced disease **treated with IO** show positivy results

Talapro2 (Talazoparib + Enzalutamide) demonstrate an **improvement in OS in mCRP patients**

The question is: what patients? All corners? HRR +? BRCA1/2? And others….

ctDNA is the most promising biomarker in UC (Adjuvant setting) but ……

We can not actually select treatment based on this results

EV +P improve OS independent on Nectin-4 expression

Muchas gracias¡¡¡

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Complexo Hospitalario Universitario de Ourense
Vigo 21 Febrero 2025