Ürogenital Kanserlerde Güncel Moleküler Tedaviler

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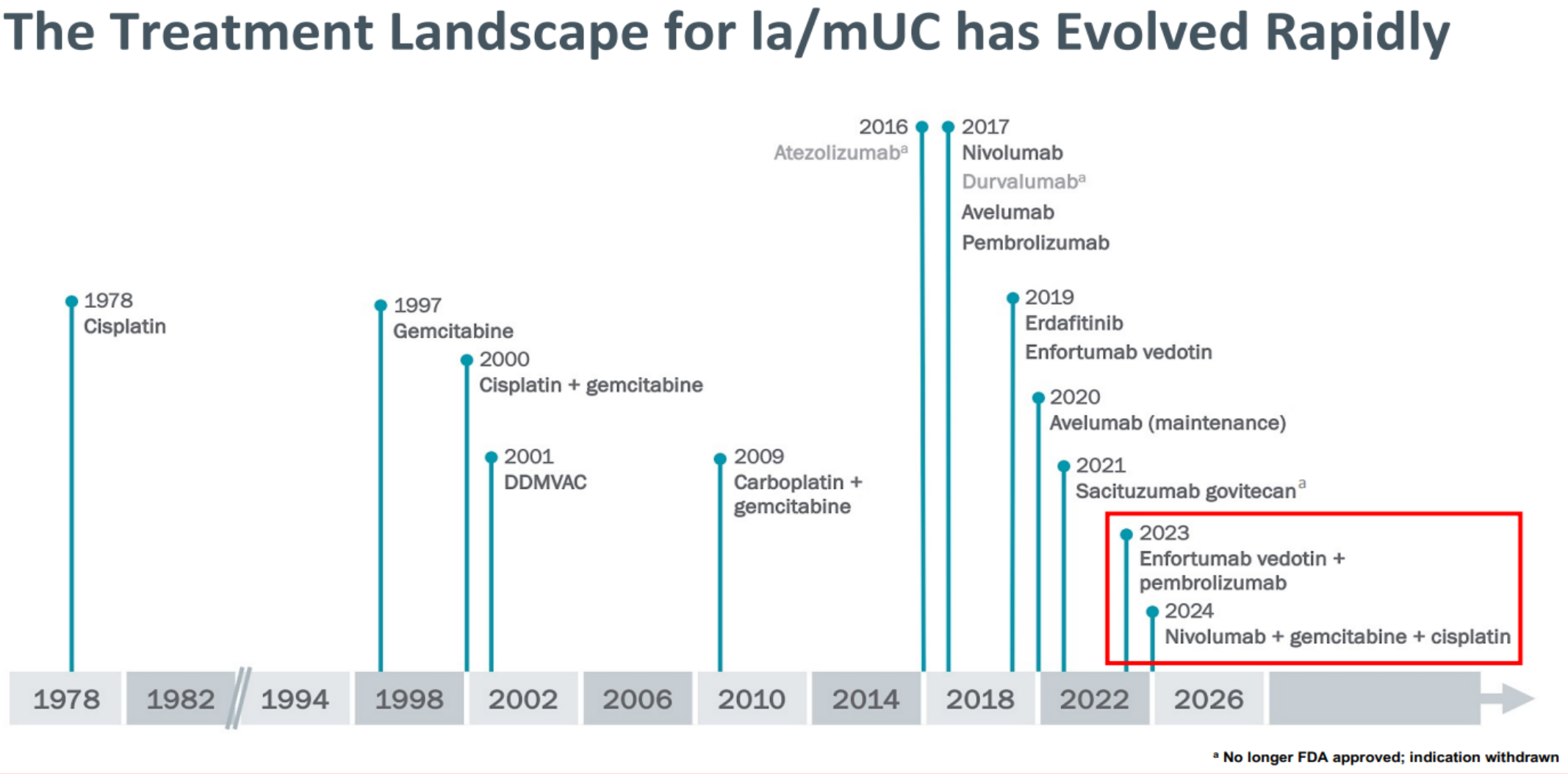
Ders planı

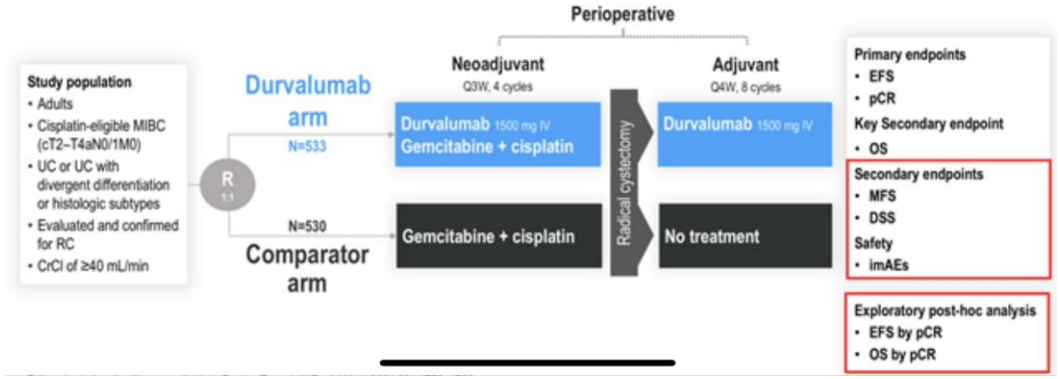
- Üroteliyal kanserlerde neoadjuvan/adjuvan/metastatik güncel tedaviler
- Prostat kanserin PSA nüksü, metastatik evrede yeni tedavi seçenekleri
- Berrak hücreli RCC adjuvan ve sistemik tedaviler
- Berrak hücreli RCC dışı kanserlerde tedavi seçenekleri
- Testis seminom tedavisinde yeni seçenek
- Penil kanserde yeni tedavi seçeneği

Üroteliyal kanserlerde tedavi seçenekleri



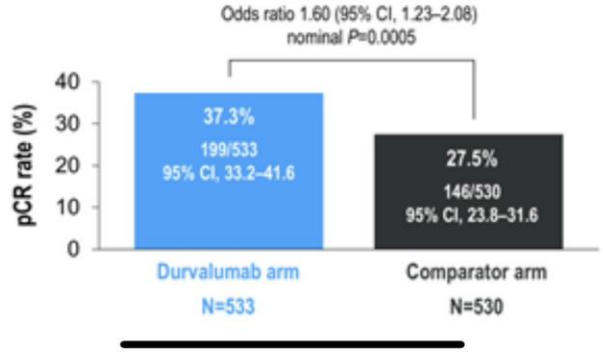
Neoadjuvan Sisplatin+Gemsitabin+İmünoterapi

NIAGARA Study Design



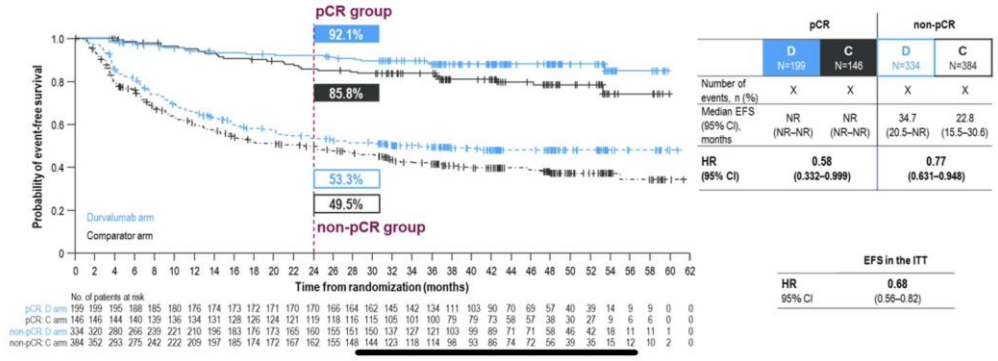
Pathological Complete Response by Central Review (ITT)

10% improvement in pathological complete response rate in favor of the durvalumab arm



Event-free Survival by Pathologic Staging

Perioperative D + NAC improved EFS in both groups

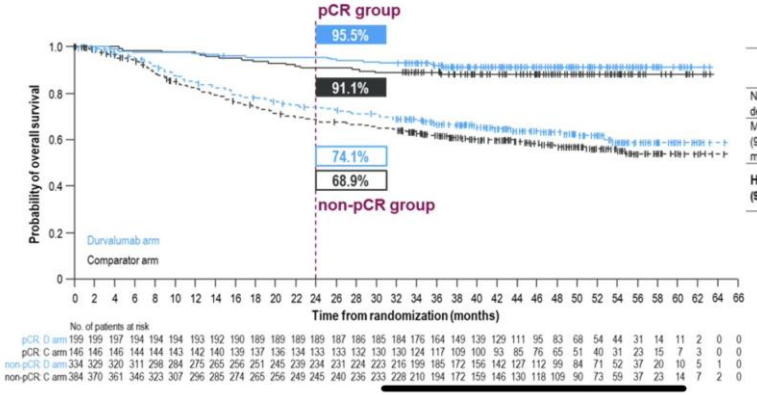


	pCR		non-pCR	
	D N=199	C N=146	D N=334	C N=384
Number of events, n (%)	X	X	X	X
Median EFS (95% CI), months	NR (NR–NR)	NR (NR–NR)	34.7 (20.5–NR)	22.8 (15.5–30.6)
HR (95% CI)	0.58 (0.332–0.999)		0.77 (0.631–0.948)	

EFS in the ITT	
HR	0.68
95% CI	(0.56–0.82)

Overall Survival in pCR and Non-pCR Groups

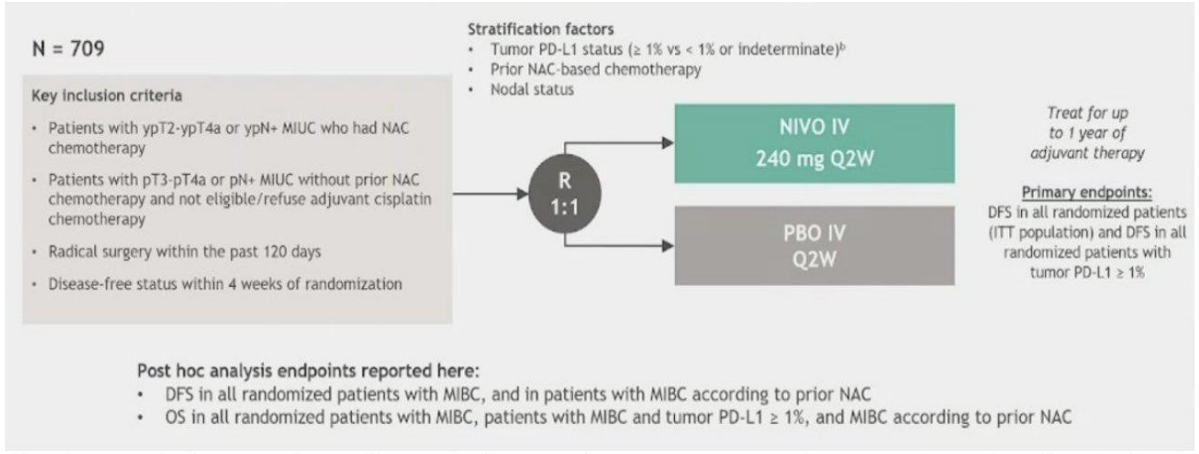
Perioperative D + NAC improved OS in both groups

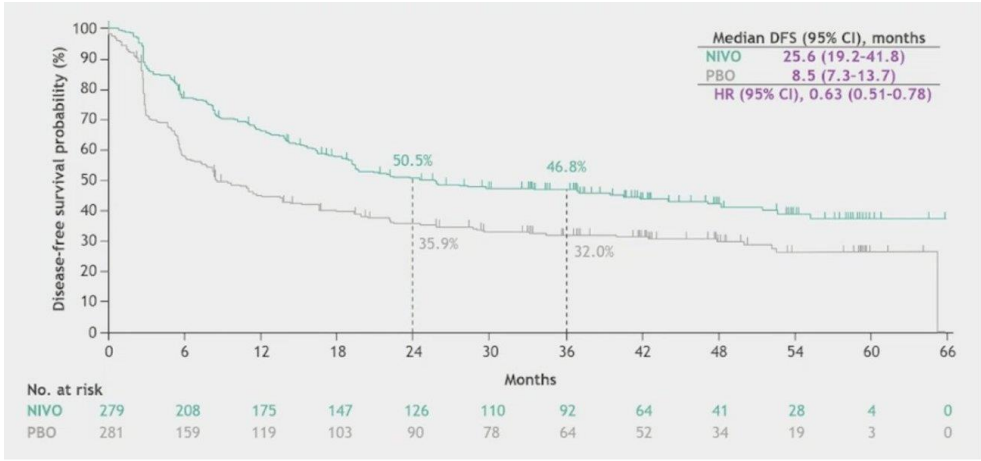


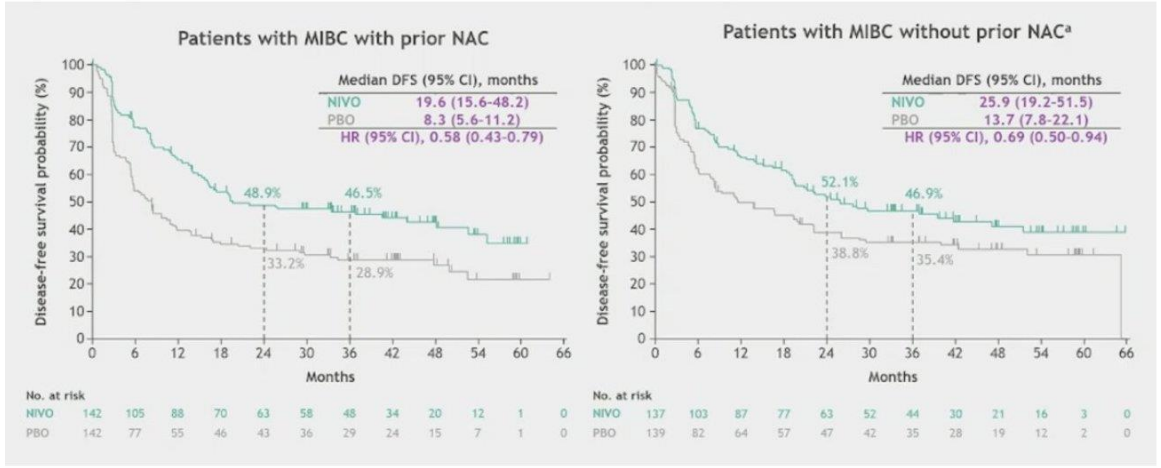
	pCR		non-pCR	
	D N=199	C N=146	D N=334	C N=384
Number of deaths, n (%)	X	X	X	X
Median OS (95% CI), months	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)	NR (53.9–NR)
HR (95% CI)	0.72 (0.367–1.426)		0.84 (0.660–1.068)	

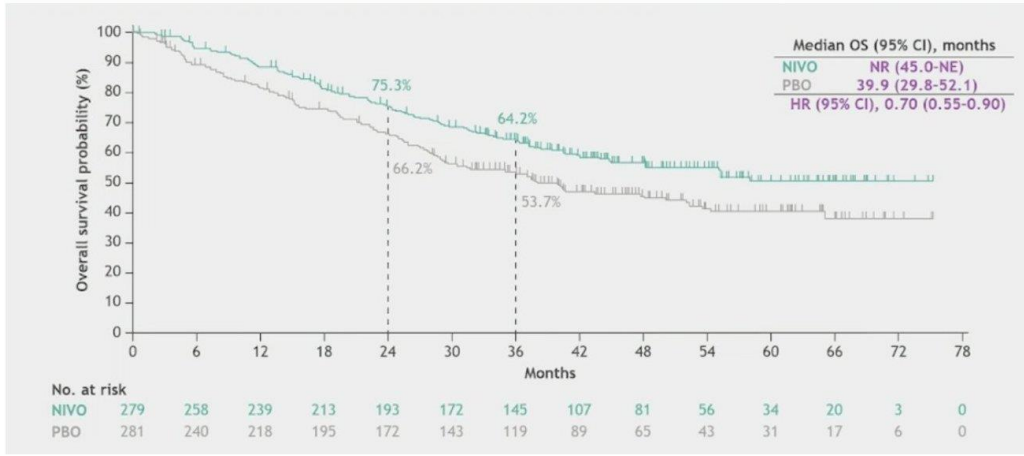
OS in the ITT	
HR	0.75
95% CI	(0.59–0.93)

Adjuvan Nivolumab Uzun Dönem Sonuçları



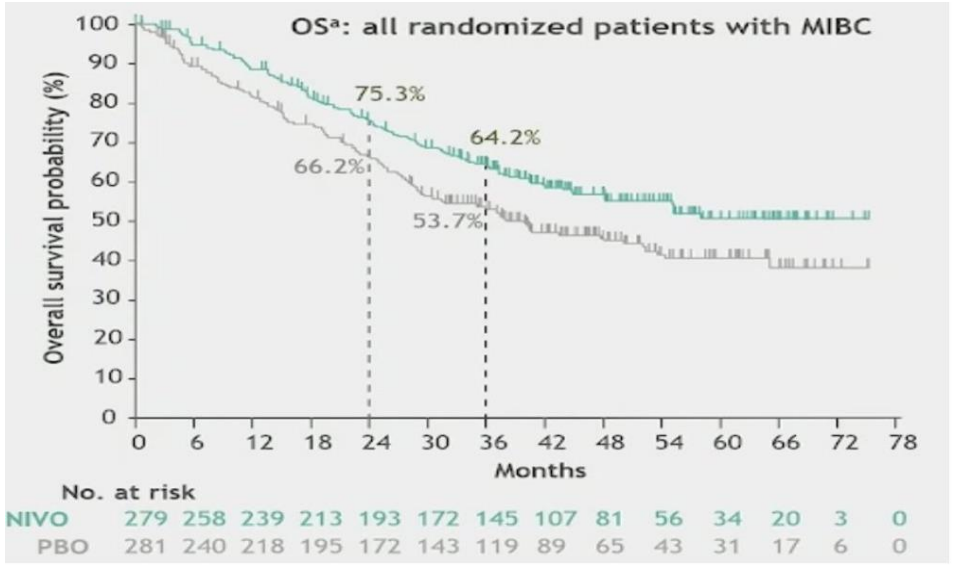




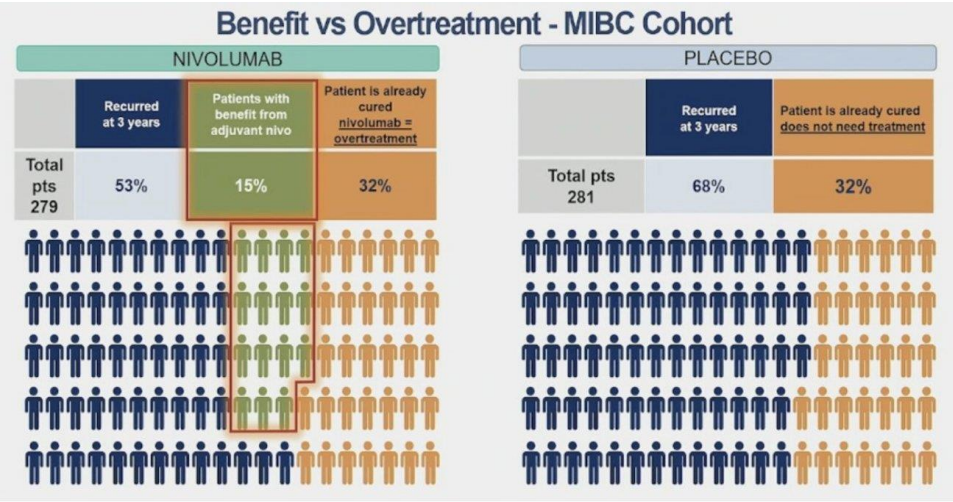


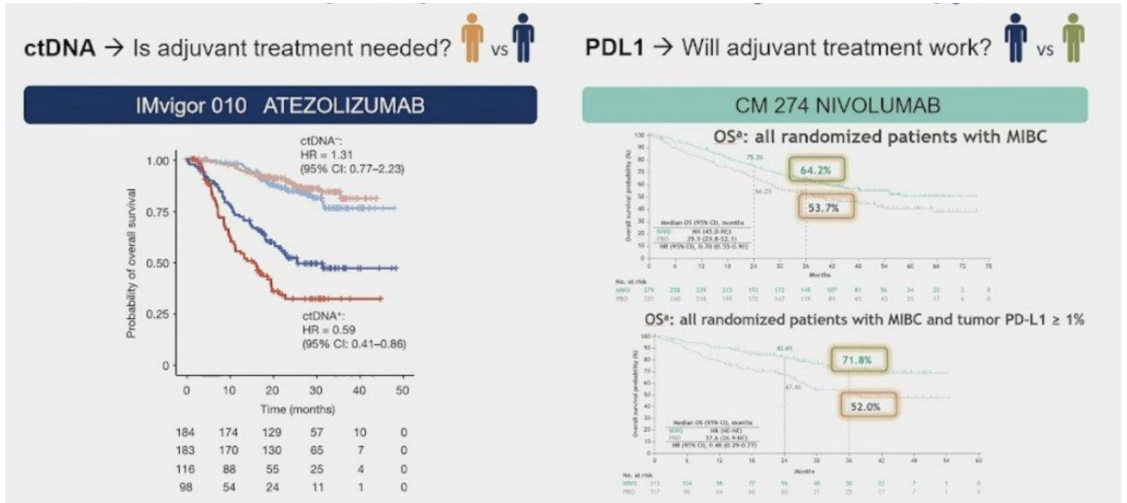
Galsky MD, ASCO GU 2025

Adjuvan Nivolumab Uzun Dönem Sonuçları



	Absolute DFS Benefit	Absolute OS Benefit	Trial
NSCLC (EGFRmut)	41%	12%	ADAURA https://ascopubs.org/doi/pdf/10.1200/JCO.22.02186 https://www.nejm.org/doi/full/10.1056/NEJMoa2304594
Bladder Cancer	**15%**	**11%**	**CHECKMATE 274** Milowsky et al. ASCO GU 2025
Breast (TN)	9%	8%	KEYNOTE-522 https://www.nejm.org/doi/full/10.1056/NEJMoa2409932
Breast (HER2+)	14%	5%	KATHERINE https://www.nejm.org/doi/full/10.1056/NEJMoa2406070
RCC	8%	5%	KEYNOTE-564 https://doi.org/10.1056/NEJMoa2312695
Melanoma	14%	Awaiting events Expected at year 10	KEYNOTE-054 https://pubmed.ncbi.nlm.nih.gov/39288737/
Colorectal Cancer	6%	3%	MOSAIC https://doi.org/10.1200/JCO.2008.20.6771
NSCLC	8%	2%	KEYNOTE 091 https://doi.org/10.1016/S1470-2045(22)00518-6
NSCLC	6%	1%	IMPower010 https://ascopubs.org/doi/10.1200/JCO.2024.42.17_suppl.LBA8035
Breast (HR+)	7%	1%	MonarchE https://doi.org/10.1200/JCO.23.01994





Elizabeth R, ASCO GU 2025

Nectin-4 Üroteliyal kanserler için hedef molekül

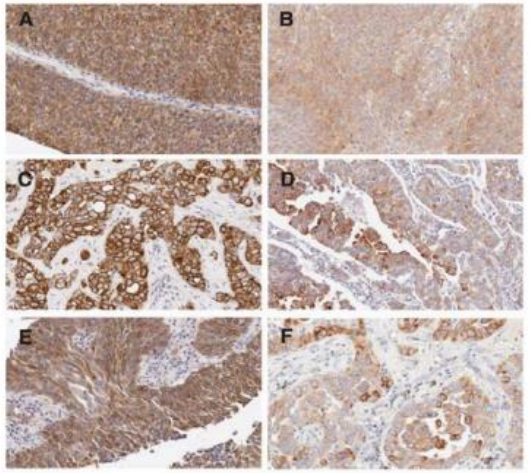
Why target Nectin-4?

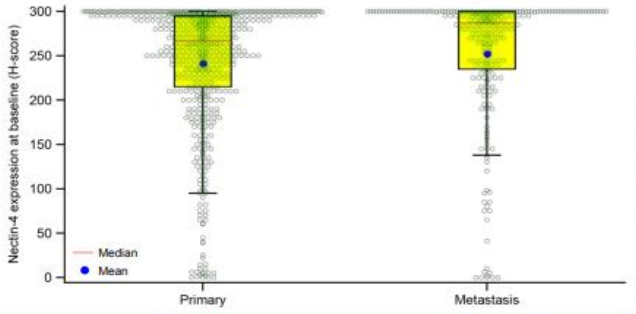
- Nectins are transmembrane cell-adhesion molecules
  - Over-expressed in multiple cancers
  - Highly expressed in **both** localized and mUC

Bladder Cancer

Breast Cancer

Lung Cancer





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

H-score of Nectin-4 expression in EV-302 (n=800)

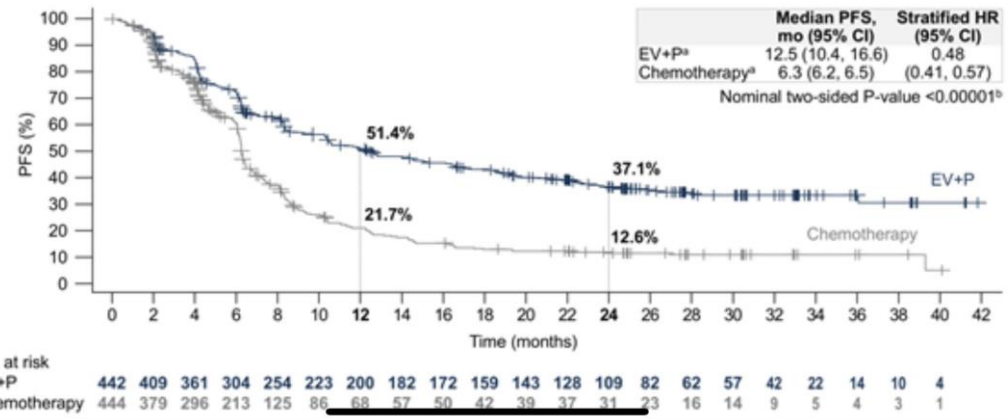
Variable	EV+P (n=394)	Chemotherapy (n=406)
H-score, median (IQR)	280 (230-298)	270 (215-297)
Subgroup, H-score, n (%)		
<150	38 (9.6)	50 (12.3)
≥150 to <225	50 (12.7)	56 (13.8)
≥225	306 (77.7)	300 (73.9)
Patients with H-score 0, n (%)	3 (0.8)	6 (1.5)

Challita-Eid, P et al. Can Res 2016, Powles et al ESMO 2024

Enfortumab ve pembrolizumab kombinasyonu uzun dönem sonuçları

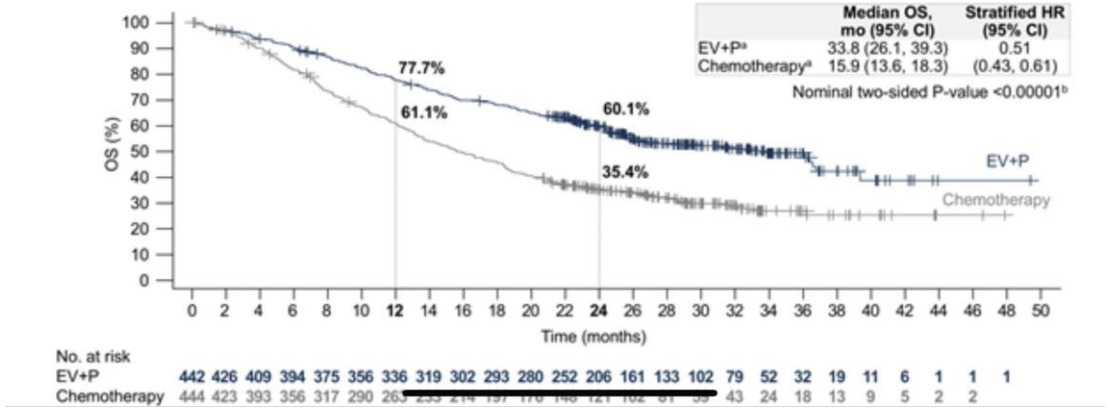
PFS by BICR in the Overall Population

PFS benefit with EV+P was maintained with 1 additional year of follow-up



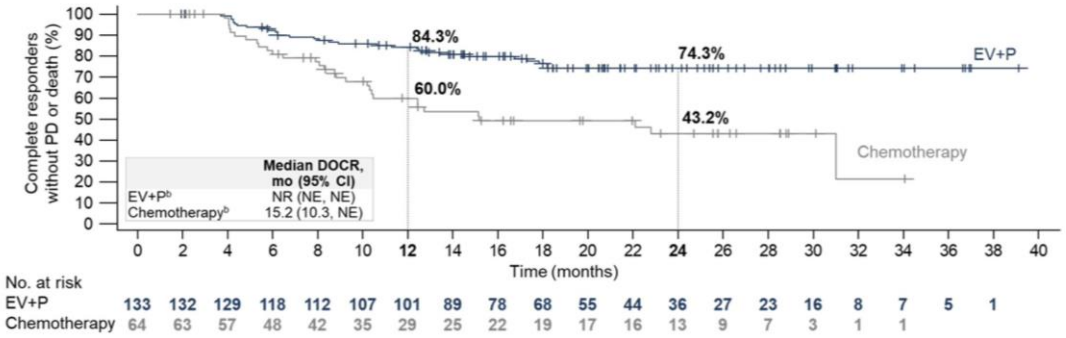
OS in the Overall Population

Risk of death was reduced by almost 50%



Duration of Confirmed Completed Response (cCR)[a] by BICR

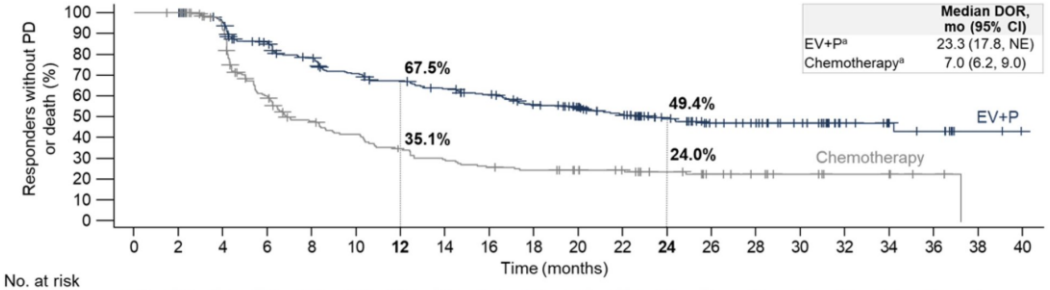
Probability of maintained CR at 24 months was 74% with EV+P



- For patients with cCR:
  - PFS HR=0.36; 95% CI: 0.21, 0.61; estimated 24-month PFS rate: 78.2% for EV+P vs 53.7% for chemotherapy
  - OS HR=0.37; 95% CI: 0.17, 0.80; estimated 24-month OS rate: 95.4% for EV+P vs 85.8% for chemotherapy

Duration of Response (CR or PR) by BICR

Among responders, the probability of maintained response at 24 months was ~50% with EV+P



	EV+P (n=437)	Chemotherapy (n=441)	Nominal two-sided P-value
Confirmed ORR (CR or PR), n (%) [95% CI]	295 (67.5) [62.9, 71.9]	195 (44.2) [39.5, 49.0]	<0.00001[b]
Best overall response, n (%)			
CR	133 (30.4)	64 (14.5)	
PR	162 (37.1)	131 (29.7)	
SD	83 (19.0)	149 (33.8)	

Data cutoff: August 8, 2024.

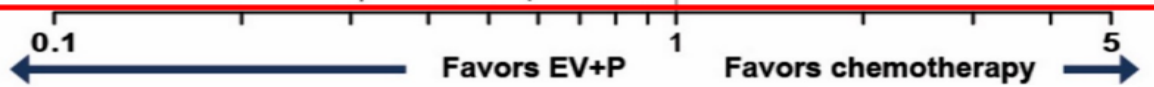
Powles T, ASCO GU 2025

Enfortumab ve pembrolizumab kombinasyonu alt grup etkinliği

Subgroup Analysis of OS

OS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	133/442	226/444	0.47 (0.38-0.58)
Age			
<65 years	39/144	58/135	0.46 (0.30-0.71)
≥65 years	94/298	168/309	0.48 (0.38-0.63)
Sex			
Female	32/98	54/108	0.51 (0.32-0.80)
Male	101/344	172/336	0.47 (0.36-0.60)
ECOG PS			
0	44/223	94/215	0.36 (0.25-0.53)
1-2	89/219	131/227	0.54 (0.41-0.72)
Primary disease site of origin			
Upper tract	38/135	45/104	0.53 (0.34-0.83)
Lower tract	94/305	180/339	0.46 (0.36-0.59)
Liver metastases			
Present	43/100	67/99	0.47 (0.32-0.71)
Absent	90/342	159/345	0.47 (0.36-0.61)
PD-L1 expression			
Low (CPS <10)	53/184	99/185	0.44 (0.31-0.61)
High (CPS ≥10)	79/254	125/254	0.49 (0.37-0.66)
Cisplatin eligibility			
Eligible	69/244	106/234	0.53 (0.39-0.72)
Ineligible	64/198	120/210	0.43 (0.31-0.59)



CPS, Combined Positive Score; **ECOG PS**, Eastern Cooperative Oncology Group Performance Status; **EV+P**, enfortumab vedotin + pembrolizumab; **OS**, overall survival; **PD-L1**, Programmed death-ligand 1.

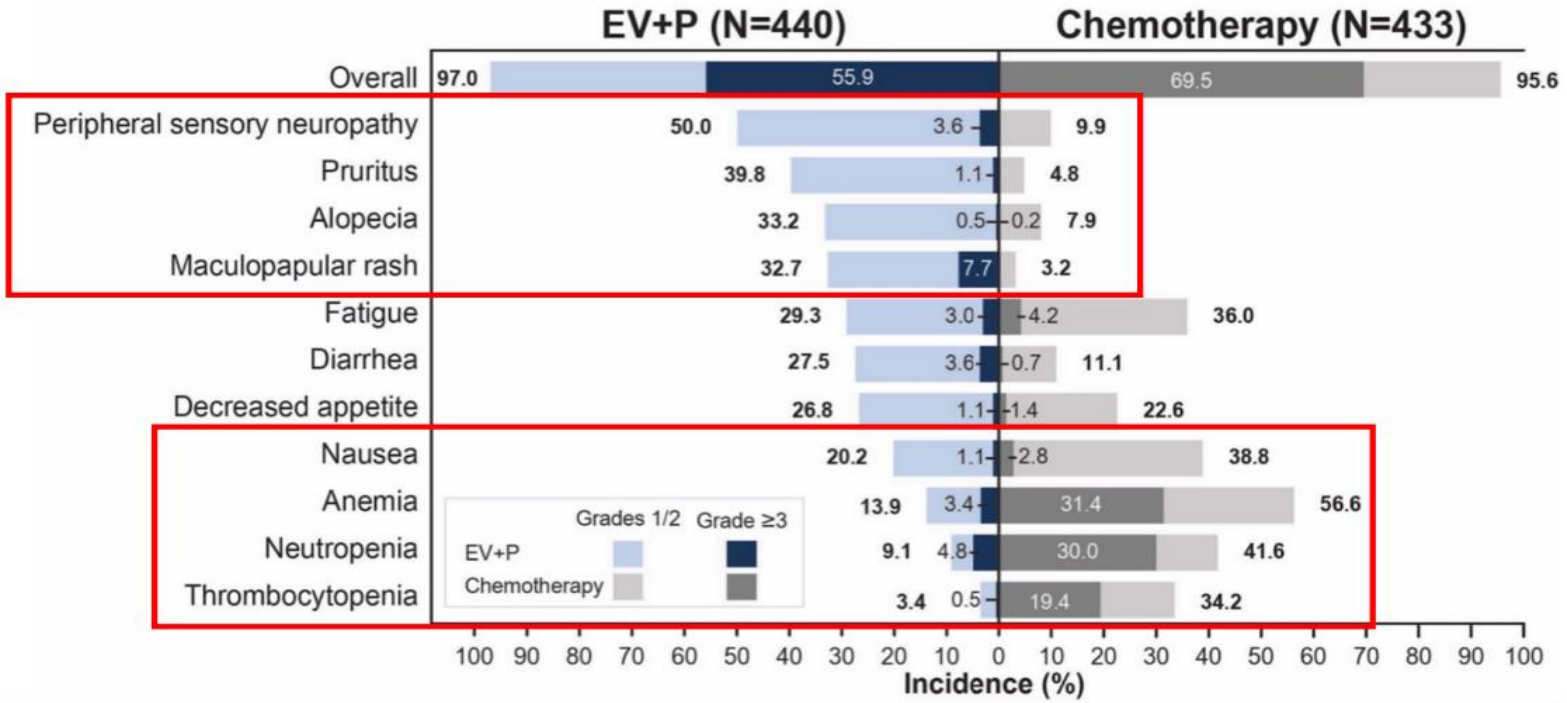
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation) Powles et al. NEJM, 2024.

Data cutoff: 08 Aug 2023

Enfortumab ve pembrolizumab kombinasyonu toksisite yönetimi

Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:
- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):
EV+P: 4 (0.9%)
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

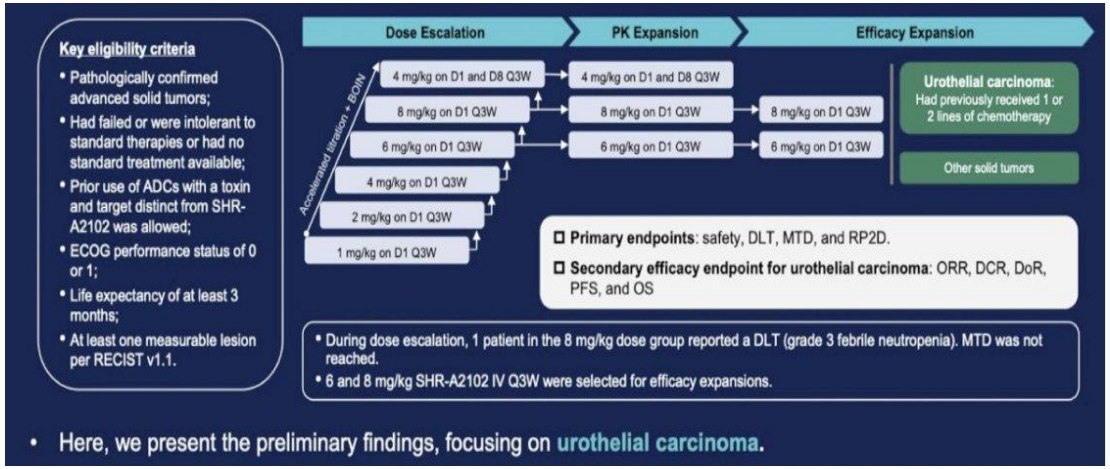
Chemotherapy: 4 (0.9%)
- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

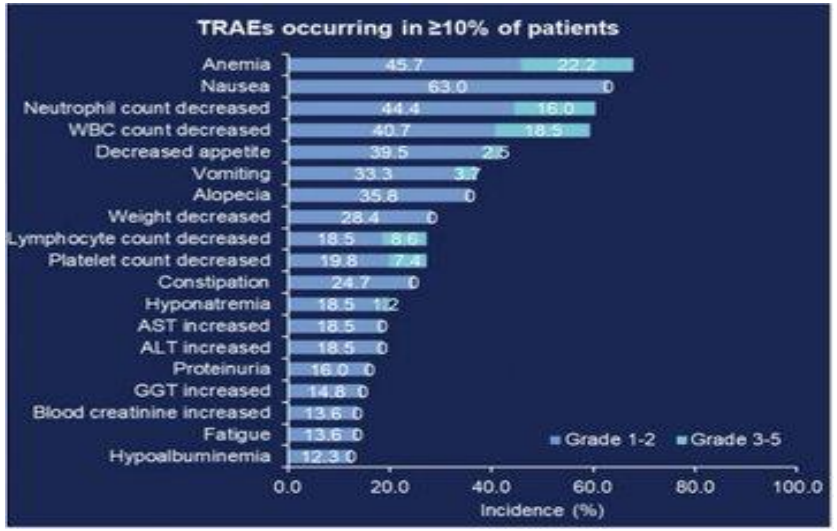
Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

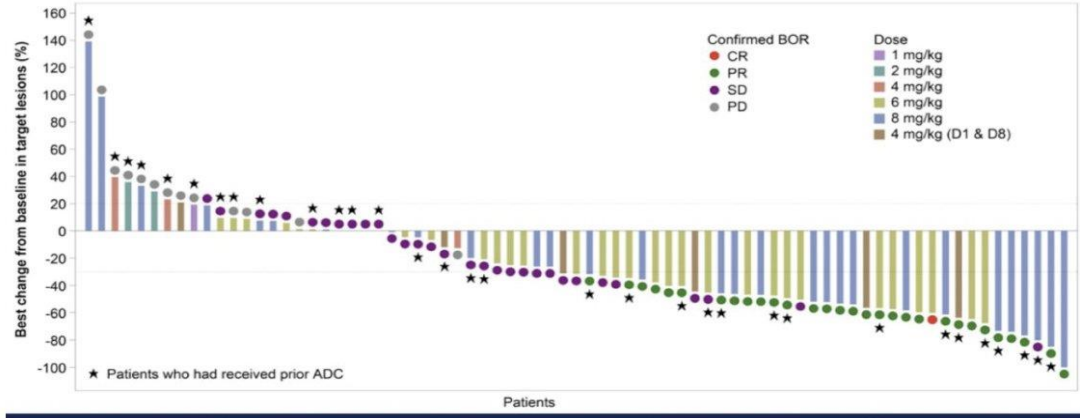
EV+P, enfortumab vedotin + pembrolizumab; **TRAEs,** treatment-related adverse events.
TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm.
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation) Powles et al. NEJM, 2024.

Data cutoff: 08 Aug 2023

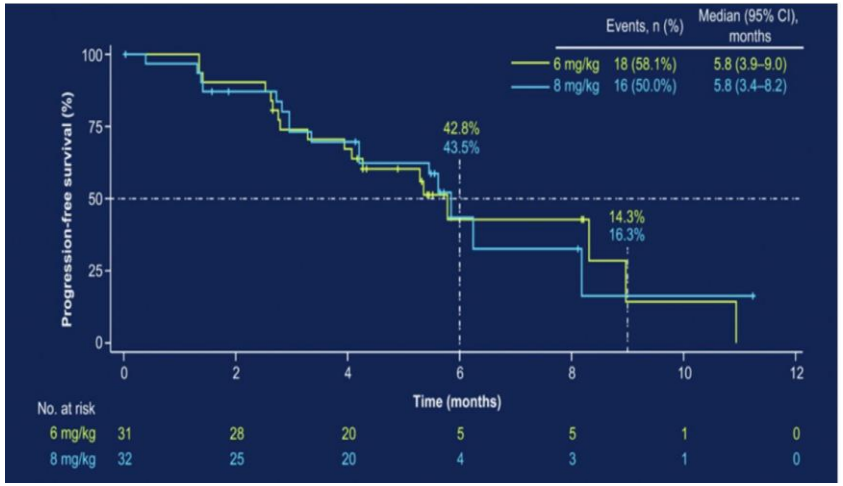
Yeni Nectin-4(SHR-A2102) Tedavi Seçenekleri







	6 mg/kg (N=31)	8 mg/kg (N=32)	4 mg/kg (D1 & D8) (N=11)	All (N=81)
ORR, % (95% CI)	41.9% (24.5–60.9)	50.0% (31.9–68.1)	18.2% (2.3–51.8)	38.3% (27.7–49.7)
DCR, % (95% CI)	90.3% (74.3–98.0)	84.4% (67.2–94.7)	54.5% (23.4–83.3)	76.5% (65.8–85.3)



Bixia Tang, MD, ASCO GU 2025

Yeni Potent FGFR3 İnhibitörleri

FORAGER-1 Study Design, Eligibility, Objectives

Phase 1a Dose Escalation

- **Cohort A1: All Solid Tumors** — Dose Escalation (N=107)
  - Alteration in FGFR3 or its ligands deemed clinical or potentially clinically relevant
  - Renal Insufficiency Sub-study (eGFR 30-49 cc/min)
- **Cohort A2: mUC** — Randomized Dose Optimization
  - Activating FGFR3 mutation/fusion[a]
  - Prior FGFRi permitted

Phase 1b Dose Expansion

- **Cohort B: mUC**
  - B1: 2L+ (erdafitinib and EV experienced)
  - B2[a]: 2L+ (erdafitinib naïve)
  - B3[a]: 2L+ in combination with pembro
  - B4: 2L+ (erdafitinib experienced, EV naïve)
  - B5[a]: 1L in combo with pembro + EV
- **Cohort C: non-UC solid tumors**
  - C1[a]: 2L+ Advanced/Metastatic

Key Eligibility Criteria

- ECOG PS 0-1
- Measurable or non-measurable (cohort A1 only) disease per RECIST v1.1
- Eligible FGFR3 alteration on local testing
- Prior FGFR inhibitor treatment permitted

Phase 1a Design

- Single-patient accelerated design followed by mTPI-2 method
- 21-day cycle (DLT evaluation period)

- Cohort A1 evaluated 10 dose levels (6 mg QD to 400 mg BID)
- Cohort A2 is evaluating 200 mg, 300 mg and 400 mg BID
- Data cutoff of 02 December 2024

Key Objectives Phase 1a/b

- Safety and Tolerability
- Determine Optimal Dose
- Pharmacokinetics
- Preliminary Efficacy per RECIST v1.1

[a]Oncogenic/likely oncogenic/driver alteration, equivalent activating alterations in non-canonical/alternative isoforms of FGFR3 are permitted in consultation with Sponsor. EV, enfortumab vedotin; mTPI-2, modified toxicity probability interval; pembro, pembrolizumab. NCT05614739.

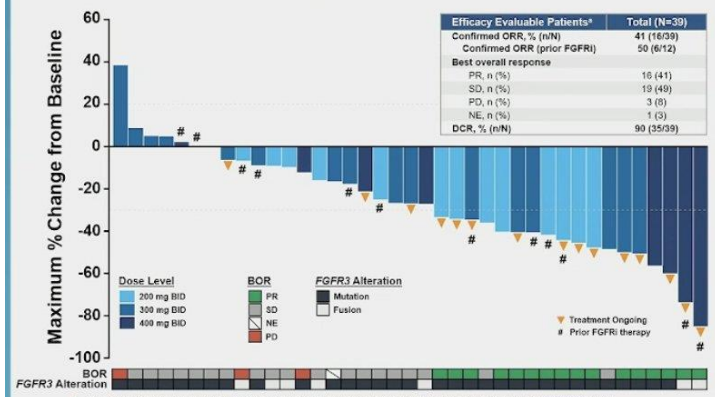
Safety

Treatment-Emergent AEs ≥20%	All Patients (N=107)		200 mg, 300 mg, 400 mg BID (n=70)	
All TEAEs, %	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3[e]**
Any	98	45	100	46
Diarrhea	63	3	76	4
Fatigue	26	<1	29	1
ALT increased	22	7	29	9
AST increased	22	7	29	9
Decreased appetite	21	3	24	1
AEs of interest, %				
Skin disorders[a]	42	3	46	4
Hand-foot (PPE)	6	2	9	3
Hyperphosphatemia[b]	26	<1	36	1
Eye disorders[c]	19	-	21	-
Retinopathy	4	-	4	-
Stomatitis	18	<1	23	1
Nail disorders[d]	16	-	19	-
Dry mouth	14	-	17	-
Dose modifications, %				
Dose reductions due to TEAEs	10		14	
Discontinuations due to TEAEs	5		6	

- Median follow-up time: 5.0 (0.4-19.9+) months
- 10 dose levels evaluated (6 mg QD – 400 mg BID)
- No DLTs observed during dose escalation
- At the higher dose levels (200, 300, 400 mg BID)
  - 25 (36%) remain on treatment at data cutoff
  - Most TEAEs were grade 1-2
  - High-grade FGFR-1, 2, and 4 related AEs typical for erdafitinib[f] were very rare
  - Dose reductions/discontinuations were uncommon[g]

Data cutoff date of 02 Dec 2024. Safety was evaluated across all patients dosed, regardless of dose or tumor type. [a]Includes rash, dry skin, PPE, mouth inflammation/pruritus, alopecia, pruritus, dysgeusia, ulcer, nail/skin seeds, skin fissures, blister, dermatitis acneiform/allergic, hyperkeratosis, hyperkeratosis, neurodermatitis, seborrheic dermatitis, and skin ulcer. [b]10 patients received pharmacologic intervention (7 at 200 mg, 3 at 300 mg, 0 at 400 mg). [c]Includes vision blurred, dry eye, blepharitis, eye pruritus, lacrimation increased, ocular hyperemia, retinal hemorrhage, subretinal fluid, swelling of eyelid, visual acuity reduced, and vitreous floaters. [d]Includes nail edging, discoloration, onycholysis, onychalgia, and onycholysis. [e]4 patients had grade 4 events – ALT/AST increased, hyponatremia, hypotension, and neutrophil count decreased; 2 unrelated grade 5 events occurred – septic shock and cardiac failure. [f]Includes retinopathy, onycholysis, and PPE. ALT/AST increased (n=2), diarrhea (n=2), and stomatitis (n=2) were most common reasons for dose reduction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia.

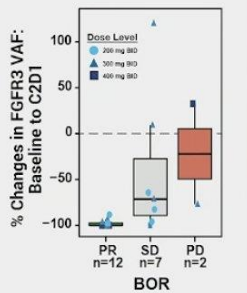
Radiographic Response and *FGFR3* Variant Allele Frequency in *FGFR3*-Altered Efficacy Evaluable mUC Patients Receiving ≥200 mg BID (n=39)



Efficacy Evaluable Patients[a]	Total (N=39)
Confirmed ORR, % (n/N)	41 (16/39)
Confirmed ORR (prior FGFRi)	50 (6/12)
Best overall response	
PR, n (%)	16 (41)
SD, n (%)	19 (49)
PD, n (%)	3 (8)
NE, n (%)	1 (3)
DCR, % (n/N)	90 (35/39)

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

FGFR3 Variant Allele Frequency[b]



- Decreases in FGFR3 Variant Allele Frequency (VAF) at C2D1 correlate with BOR
- 21/39 patients had detectable FGFR3 VAF at baseline

Data cutoff date of 02 Dec 2024. [a]Efficacy 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. [b]Changes in ctDNA were assessed using Guardant 360 from patients' plasma samples.

Conclusions

- LY3866288 (LOXO-435) demonstrates
  - Promising preliminary efficacy in patients with *FGFR3*-altered metastatic urothelial carcinoma treated with ≥200 mg BID
    - ➢ 41% (16/39) of patients with an activating *FGFR3* mutation or fusion had a confirmed response with a 90% DCR
    - ➢ 50% (6/12) of patients who previously received an FGFR inhibitor had a confirmed response
  - Favorable safety profile
    - ➢ Diarrhea was the most common TEAE and was predominantly low grade and manageable
    - ➢ High-grade FGFR-1, 2, and 4 mediated AEs (e.g. nail/skin disorders and ocular toxicity) typical of pan-FGFR inhibitors were very rare
- Randomized dose finding is currently enrolling patients to 200 mg, 300 mg, and 400 mg BID to select an optimal dose for further development
- Select expansion cohorts, including enfortumab vedotin + pembrolizumab + LY3866288 (LOXO-435) in 1L *FGFR3*-altered mUC patients will open in Q1 2025

Datopotamad-Deruxtecan(DXd) çoklu tedavi almış hastalarda kısmi yanıt

ASCO Genitourinary Cancers Symposium

Datopotamab deruxtecan (Dato-DXd) in locally advanced/metastatic urothelial cancer: updated results from the phase 1 TROPION PanTumor01 study

Funda Meric-Bernstam,[1] Omar Alhalabi,[2] Aaron Lisberg,[3] Alexandra Drakaki,[3] Benjamin Garmezy,[4] Takahiro Kogawa,[5] Alexander Spira,[6] Mohamad Salkeni,[6] Xin Gao,[7] Anthony Tolcher,[8] Manali Bhave,[9] Deborah Doroshow,[10] Jeannie Hoffman-Censits,[11] Gunnar Klauss,[12] Yoshiaki Kaga,[13] Yasuyuki Kakurai,[14] Takahiro Kojima[15]

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Study Design

- Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed ADC composed of an anti-TROP2 mAb covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- TROPION-PanTumor01 is an ongoing, phase 1, multi-cohort, multicenter, open-label, dose-escalation and dose-expansion study evaluating Dato-DXd in patients with several types of previously treated advanced solid tumors, including urothelial cancer

Key eligibility criteria
- Unresectable locally advanced/metastatic (stage III or IV) urothelial carcinoma (included renal pelvis, ureter, urinary bladder, and urethra)
- Previous treatment with ≥1 line of therapy including an immune checkpoint inhibitor
- ECOG PS 0–1
- Unselected for TROP2 expression
- No prior treatment with DXd-ADCs or TROP2-directed therapies

→ **Dato-DXd** 6 mg/kg Q3W (N=40)

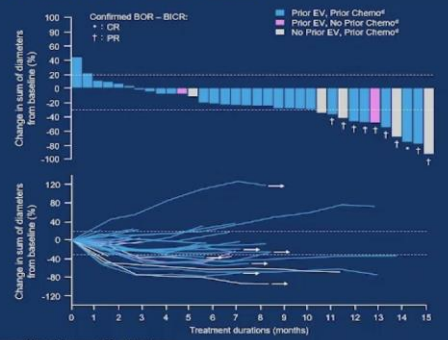
Primary endpoints
- Safety and tolerability

Secondary endpoints (by BICR[a])
- ORR
- DOR
- DCR
- PFS

BICR, blinded independent review committee; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, objective response rate; Q3W, every 3 weeks. Data cut off: April 22, 2024. Median follow-up was 10.0 months (range, 5.0–28.2). [a]Evaluated per RECIST v1.1. 1. Okajima D, et al. Mol Cancer Ther. 2021;20:2329–40.

Response and Change in Tumor Burden

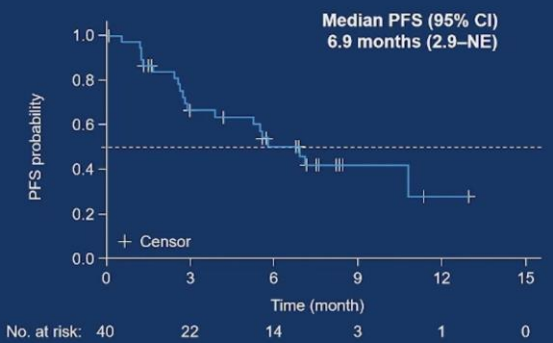
Response by BICR[a]	Dato-DXd (N=40)
ORR[b], n (%) [95% CI]	**10 (25.0)** [12.7–41.2]
DCR[c], n (%) [95% CI]	**31 (77.5)** [61.5–89.2]
BOR, n (%)	
CR	1 (2.5)
PR	9 (22.5)
SD	20 (50.0)
Non-CR/non-PD	1 (2.5)
PD	5 (12.5)
NE	4 (10.0)
DOR, median (95% CI), **months**	NE (2.6–NE)
6-month DOR rate, % (95% CI)	76.2 (33.2–93.5)



ORR by investigator was 30.0% (n=12); all were PR

BOR, best overall response; CI, confidence interval; CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease. [a]Evaluated by BICR per RECIST v1.1. [b]Responses with confirmation of CR/PR. [c]CR + PR + SD + non-CR/non-PD. [d]All patients received prior immunotherapy.

Progression-Free Survival



HER2 Mesane kanserinde Yeni Hedef Molekül

Is HER2 a good target for ADCs in UC?

Location	Her 2 IHC*		
	≥1+	2+	3+
Primary (n = 114)	84 (74%)	36 (32%)	5 (4%)
Lymph node (n = 38)	35 (92%)	17 (45%)	4 (11%)

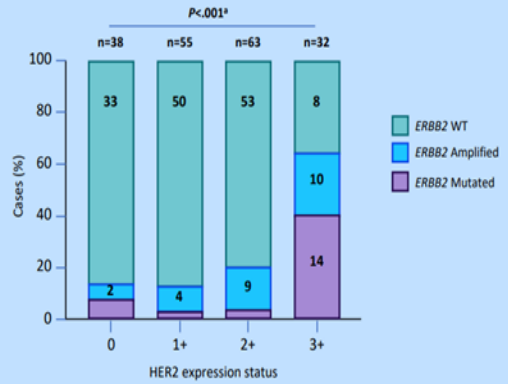
*Dako HercepTest system

Press, ASCO, 2013

Relationship Between *HER2* Alteration by NGS and HER2 Expression by IHC

HER2 IHC

0 = 18.8%
1+ = 29.7%
2+ = 33.7%
3+ = 17.8%



ERBB2 alterations (mutations and/or amplifications) were identified by MSK IMPACT in ≈20% of urothelial cancers

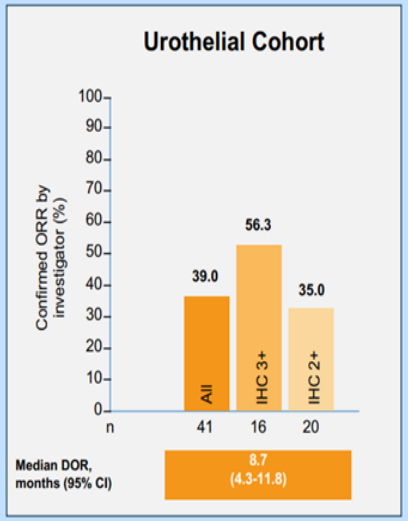
Aggen et al, ASCO GU 2023

HER2 Mesane kanserinde Yeni Hedef Molekül

Anti-HER2 Antibody-Drug Conjugates

	Antibody	Payload	Linker
Trastuzumab emtansine (T-DM1)	Trastuzumab	DM1	Lysine-SMCC
Trastuzumab deruxtecan	Trastuzumab	DXd	Cleavable
Disitamab vedotin (RC48)	Disitamab	MMAE	Cleavable
MRG002	Humanized anti-HER2	MMAE	Cleavable
SYD985	Trastuzumab	Seco-duocarmycin	Cleavable

Phase II DESTINY-PanTumor02 Trastuzumab Deruxtecan



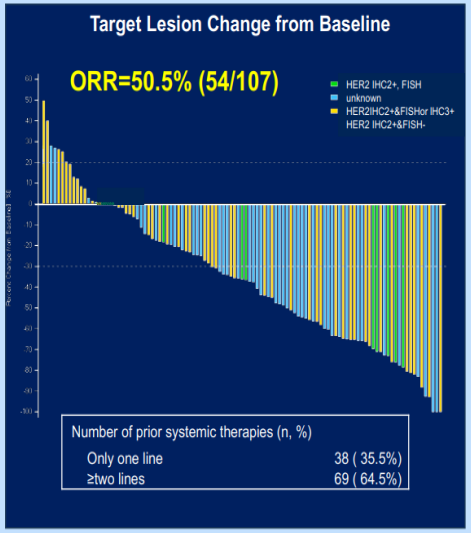
All Patients

	All patients (N=267)	IHC 3+ (n=75)	IHC 2+ (n=125)
ORR, % (95% CI)	37.1 (31.3, 43.2)	61.3 (49.4, 72.4)	27.2 (19.6, 35.9)
Median DOR, months (95% CI)[b]	11.3 (9.6, 17.8)	22.1 (9.6, NR)	9.8 (4.3, 12.6)

Meric-Bernstam et al, ESMO,2023; Meric-Bernstam et al, JCO 2024.

HER2 Mesane kanserinde Yeni Hedef Molekül

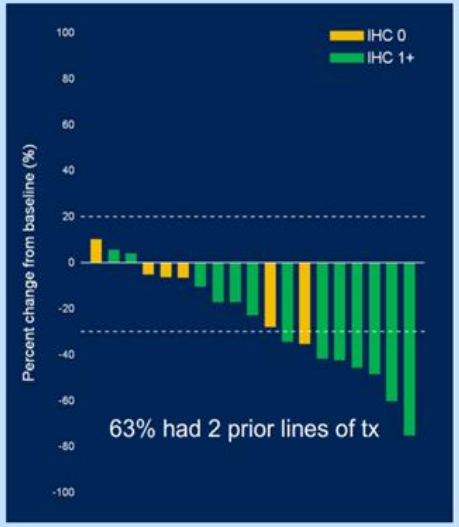
RC48 (Disitamab Vedotin) in HER2 2-3+ mUC



Subgroups	cORR (%, 95% CI)
HER2 status	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
Metastasis site	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
Prior therapies	
Post PD1/PDL1 Treatments (n=27)	55.6% (35.3%, 74.5%)
Post 1 line of Chemotherapy (n=38)	50.0% (33.4%, 66.6%)
Post ≥2 Lines of Chemotherapy (n=69)	50.7% (38.4%, 63.0%)

Sheng et al, ASCO, 2022. Sheng et al, JCO, 2023.

RC48 (Disitamab Vedotin) in HER2 1+ mUC



Confirmed ORR	
n (%)	5 (26.3%)
95%CI	9.1%, 51.2%

Subgroups	cORR (%, 95% CI)
IHC 0 (n=6)	0
IHC 1+ (n=13)	38.5 (13.9, 68.4)

Xu et al, ASCO, 2022

HER2 Mesane kanserinde Yeni Hedef Molekül

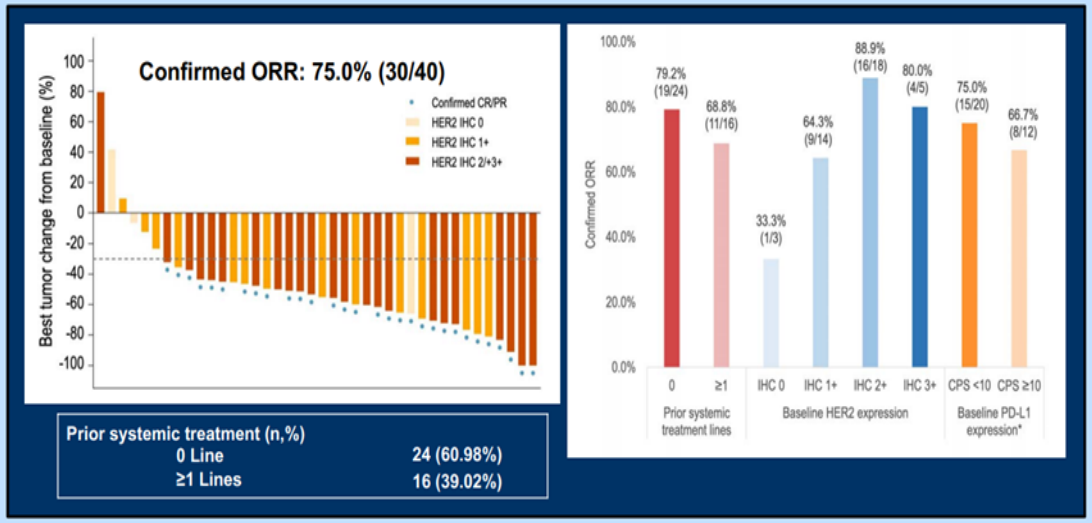
Trastuzumab Deruxtecan + Nivolumab

	Cohort 3: HER2-high n=30	Cohort 4: HER2-low n=4
cORR (CR + PR), n (%) [95% CI]	11 (36.7) [19.9-56.1]	–
Best overall response, n (%)		
CR	4 (13.3)	0
PR	7 (23.3)	2 (50.0)
SD	12 (40.0)	1 (25.0)
PD	5 (16.7)	1 (25.0)
NE	2 (6.7)	0
DoR, median (95% CI), months	13.1 (4.1-NE)	NE
TTR, median (range), months	1.9 (1.2-6.9)	–
PFS, median (95% CI), months	6.9 (2.7-14.4)	NE
OS, median (95% CI), months	11.0 (7.2-NE)	NE
Treatment duration, median (range), months		
T-DXd	3.9 (1-21)	–
Nivolumab	4.1 (1-20)	–

- **36.7%** cORR
- **HER2 IHC 3+: 62.5% (5/8)** patients had a confirmed objective response, including 2 CR (25%)
- HER2 IHC 2+: 27.3% (6/22) patients had a confirmed objective response, including 2 CR (9.1%
- **6.9** months, mPFS
- **11** months, mOS

Galsky et al, ASCO GU, 2022. Hamilton et al, Clin Cancer Res, 2024.

RC48 + Toripalimab



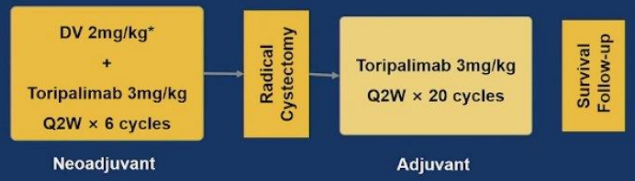
Zhou et al, ESMO, 2024

HER2 Mesane kanserinde Yeni Hedef Molekül

Study design

Key Eligible Criteria:

- Histologically confirmed urothelial carcinoma;
- MIBC at stage of cT2-T4a, N0-1, and M0;
- Eligible for radical cystectomy (RC) + pelvic lymph node dissection (PLND);
- HER2 expression: IHC 1+, 2+, or 3+.



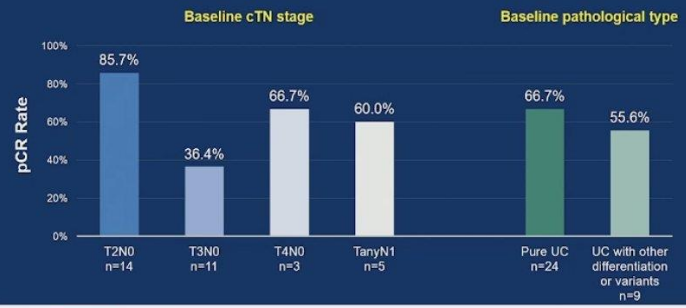
- **Primary endpoint:** Pathologic complete response (pCR, defined as ypT0N0) rate.
- **Secondary endpoints:** Pathological response rate (defined as ≤ypT1N0M0)#; event-free survival (EFS); overall survival (OS)^; adverse events.

The preliminary results of this trial showed promising efficacy and acceptable safety.[1] Herein, we present updated results including the pathological response, event-free survival, safety, and other outcomes with a longer follow-up (data cutoff: Dec 3, 2024).

*Equivalent to dose of 1.5 mg/kg using DV-based extinction coefficient outside of China. #Including complete or partial pathological response. ^OS data was not mature and not reported here. 1. Sheng, et al. J Clin Oncol. 2024; 42(16_suppl):4568.
Abbreviations: IHC=immunohistochemistry; Q2W=every two weeks; RECIST v1=Response Evaluation Criteria in Solid Tumors.

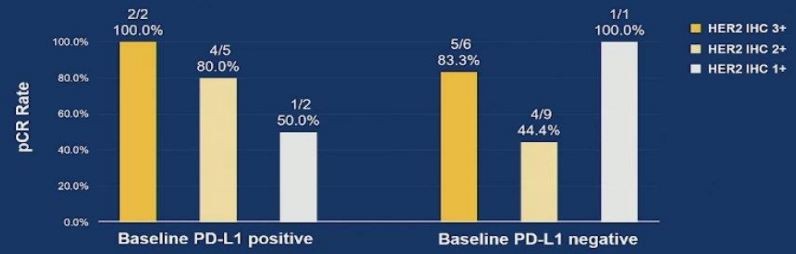
Subgroup analysis

- The pCR rate for the T2N0 patients appeared higher than those for the other subgroups.
- The pCR rates were generally consistent between patients with pure UC and patients with UC with other differentiation or variants.



Subgroup analysis

- The pCR rate for the HER2 IHC 3+ subgroup was numerically higher than those for IHC 1+ and IHC 2+ subgroups regardless of PD-L1 status.



Conclusion

- RC48-017 is the first prospective study showing that ADC in combination with a PD-1 inhibitor as perioperative treatment provided prominent outcomes in operable MIBC.
  - pCR rate: 63.6% (95% CI: 45.1-79.6)
  - 12-month EFS rate: 92.5% (95% CI: 72.8- 98.1)
- Neoadjuvant DV plus toripalimab did not delay RC procedures or impact patients' ability to undergo RC. Safety profile was manageable with no new safety signals.
- The results indicated that neoadjuvant DV plus perioperative toripalimab had promising efficacy and acceptable safety in patients with HER2-expressing MIBC, warranting further investigation.

Kombinasyon Tedavileri

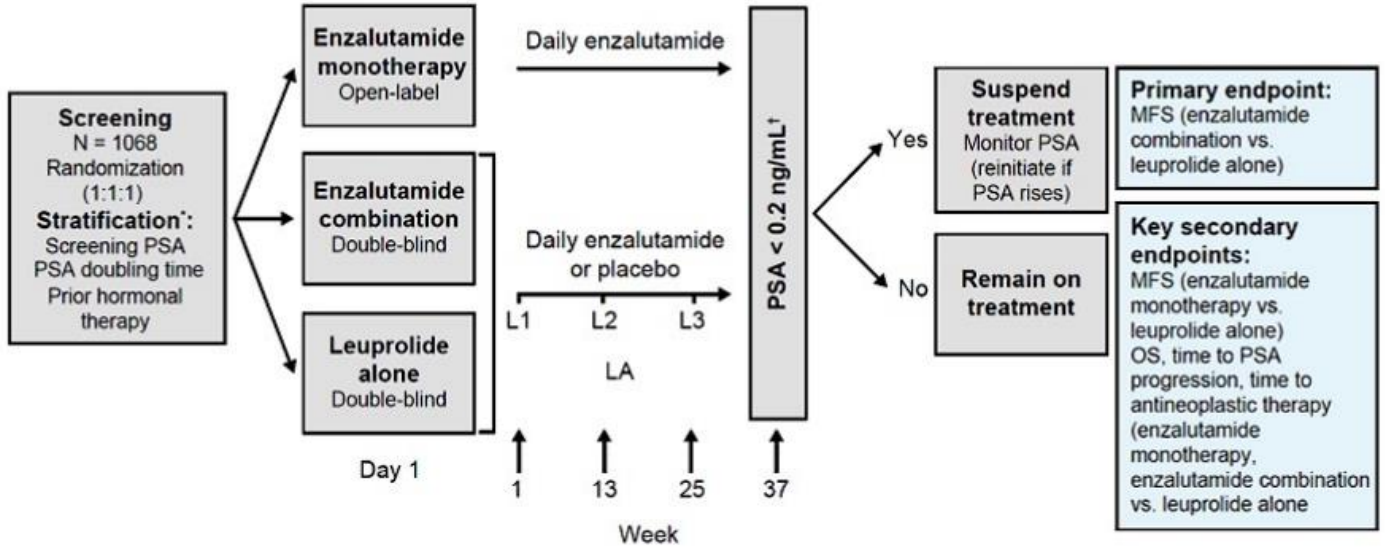
Selected Ongoing Trials of ADCs + Immunotherapy in mUC					
Treatments	**Alias**	**Ph**	**Population**	**Primary Endpoint**	**NCT Number**
Disitamab Vedotin + Pembrolizumab	DV-001	III	1st line HER2+	PFS, OS	NCT05911295
Disitamab Vedotin + Toripalimab		III	1st line HER2+	PFS, OS	NCT05302284
Zelenectide Pevedotin + Pembro	DURAVELO-2	III	1st line	PFS	NCT06225596
EV + SG + Pembrolizumab	DAD-IO	II	1st line	ORR	NCT04724018
Datopotamab-DXd + Volrustomig or Rilvegostomig	TROPION-Pan Tumor 03	II	1st or 2nd line	ORR, AEs	NCT05489211
SG + Avelumab	JAVELIN Bl. Medley	II	1st line	PFS, AEs	NCT05327530
EV + Pembro + Sacituzumab TMT or investigational agents	KEYMAKER-U04	I/II	1st line	ORR, PFS	NCT05845814
EV or SG + Atezolizumab	MORPHEUS-UC	Ib/II	Post-platinum	ORR	NCT03869190
SG + Zimberelimab (aPD-1) + Domvanalimab (aTIGIT)	TROPHY-U01 Cohort 7	I/II	1st line	ORR	NCT03547973
BGB-C354 (B7-H3 ADC) + Tislelizumab		I	Later line	AEs, ORR	NCT06422520

EV: Enfortumab Vedotin. SG: Sacituzumab Govitecan

Prostat Kanseri izole PSA nüksü

Biochemically recurrent prostate cancer: EMBARK

High-risk PSA recurrence:
PSADT<9 mo
No PSMA PET imaging, but N0
M0 on CT/MRI/BS



*Stratification by screening PSA (≤10 ng per milliliter vs. >10 ng per milliliter), PSA doubling time (≤3 months vs. >3 to ≤9 months), and prior hormonal therapy (yes vs. no).

†Study treatment was suspended once if the PSA was less than 0.2 ng per milliliter at week 36 and restarted when PSA was greater than or equal to 5.0 ng per milliliter for those without prior radical prostatectomy and greater than or equal to 2 ng per milliliter for those with prior radical prostatectomy.

Freedland SJ, de Almeida Luz M, De Giorgi U, et al. *N Engl J Med*. 2023;389(16):1453-1465.

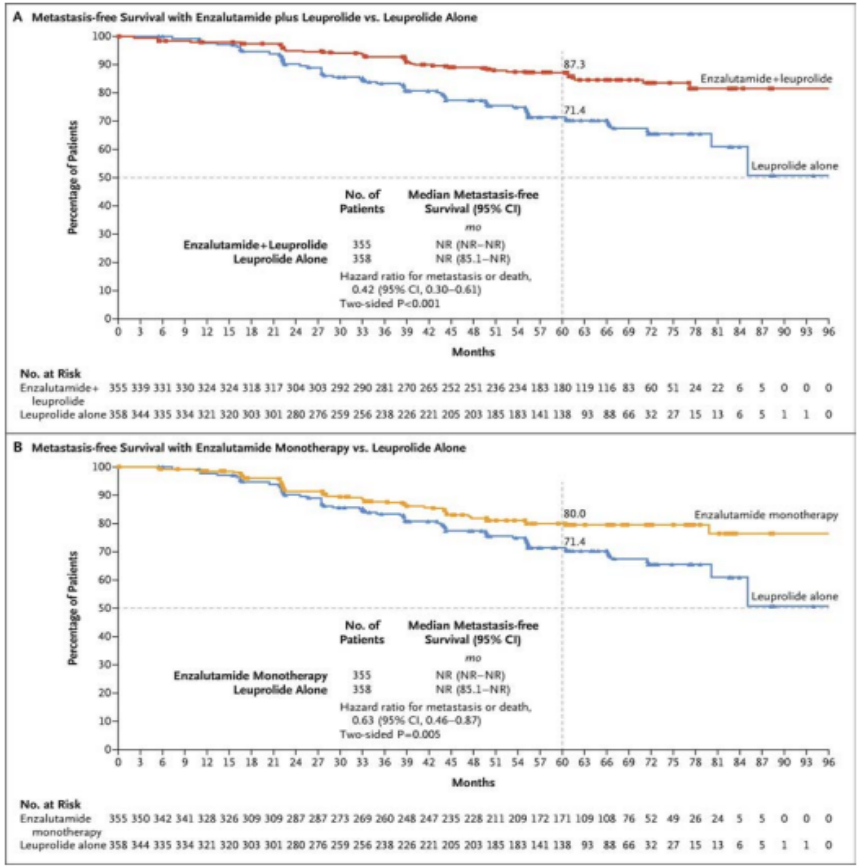
Prostat Kanseri izole PSA nüksü

Biochemically recurrent prostate cancer: EMBARK

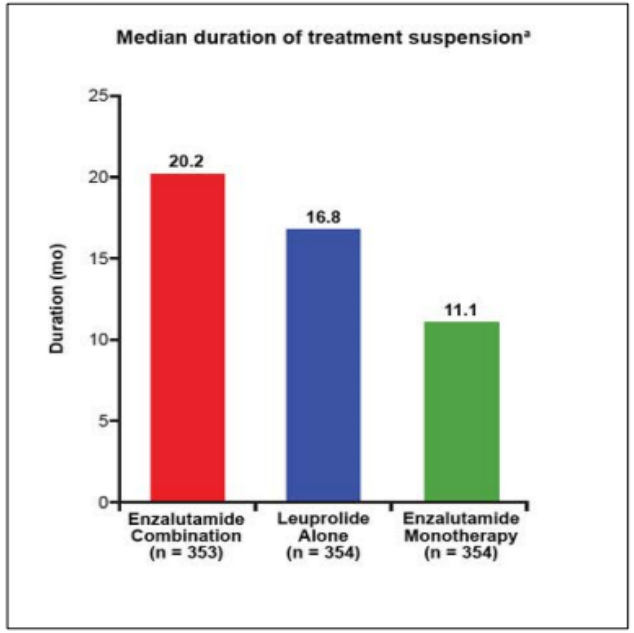
87 v 71% MFS at 5 years

If PSA undetectable (<0.2 ng/mL) at week 36, treatment was held – resumed when PSA >5 (RT) or >2 (surgery)

80 v 71% MFS at 5 years



ADT alone – 50% without metastasis at 8 years



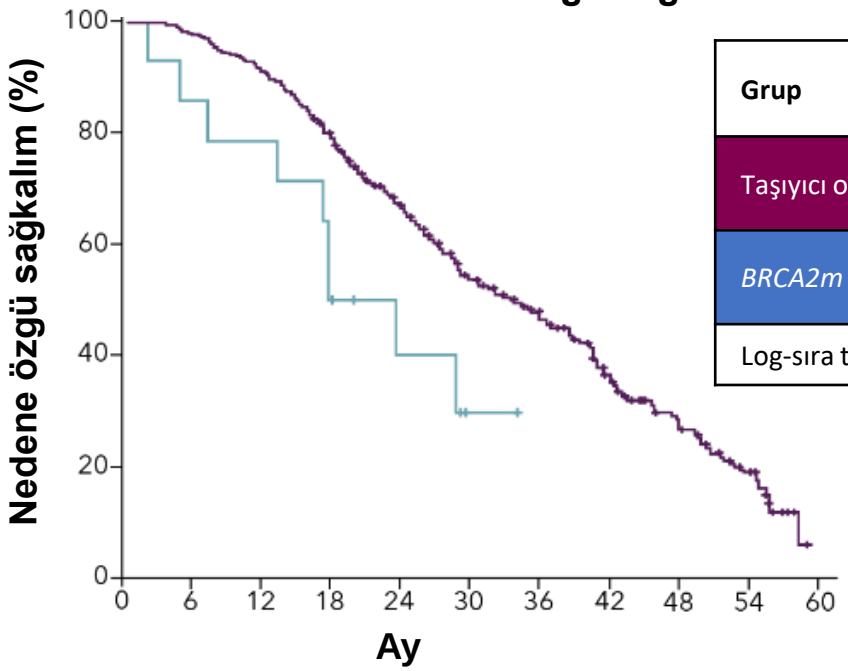
Freedland SJ, de Almeida Luz M, De Giorgi U, et al. *N Engl J Med*. 2023;389(16):1453-1465.

BRCA2 mutasyonu dahil HRR mutasyonu izlenen hastalarda standart tedavilerle Cevap daha kötü

BRCA2**m dahil** germ hattı HRRm *izlenen hastalarda standart tedavilerle* olumsuz sonuç **olasılığı daha yüksektir**[1,2]

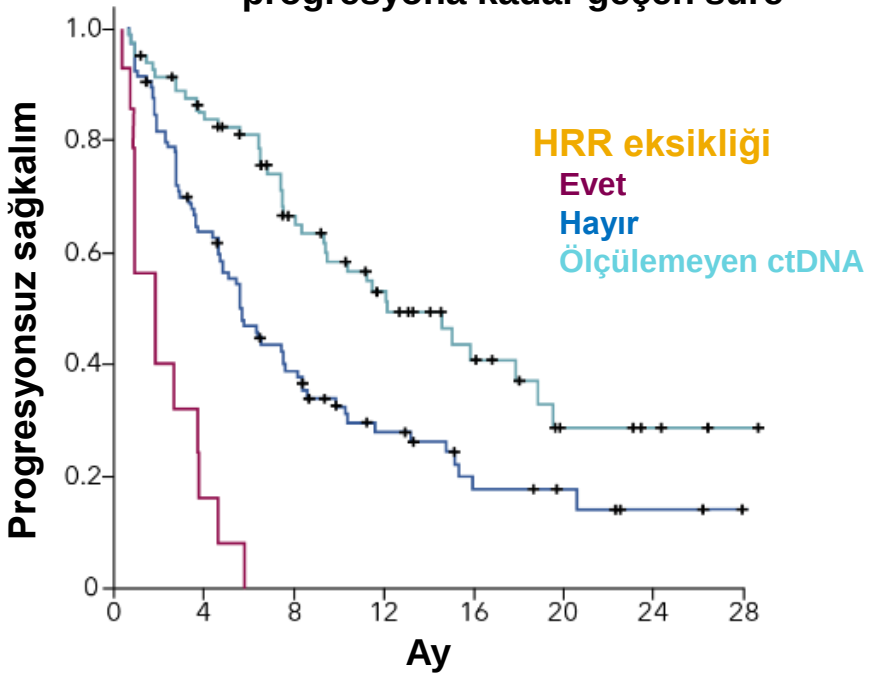
Tümör HRRm için de standart tedaviye **olumsuz yanıt** görülmüştür[3]

gBRCA2m izlenen mKDPK hastalarında kansere özgü sağkalım[1]



Grup	Medyan CSS (%95 GA)
Taşıyıcı olmayanlar	33.2 ay (29.0-37.4)
BRCA2m	17.4 ay (10.7-24.2)
Log-sıra testi p=0.0266	

HRRm izlenen mKDPK hastalarında progresyona kadar geçen süre[3]

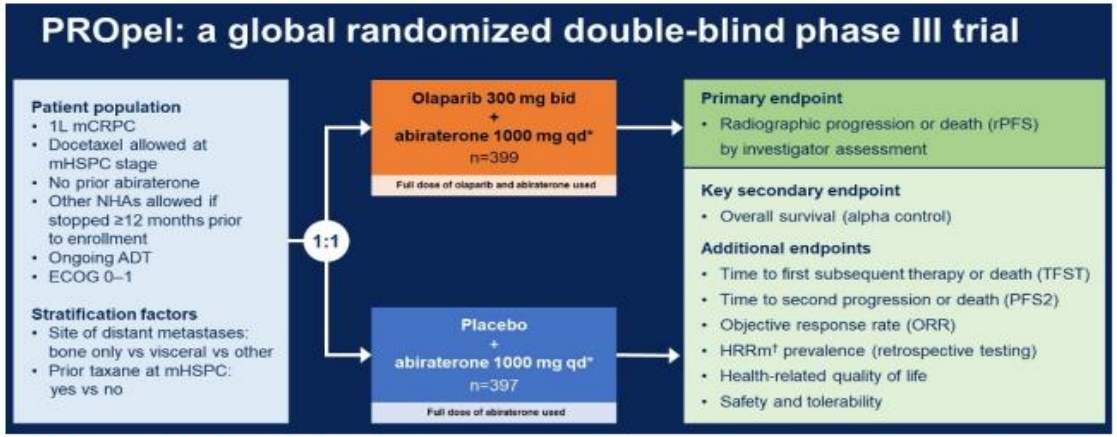


ATM=ataksi telenjiektazi mutasyonlu; *BRCA1/2*=meme kanseri geni 1/2; *BRCA2m*=meme kanseri geni 2 mutasyonu; CSS=nedene özgü sağkalım; *gBRCA*m=germ hattı *BRCA2* mutasyonu; *gHRRm*=germ hattı homolog rekombinasyon onarım mutasyonu

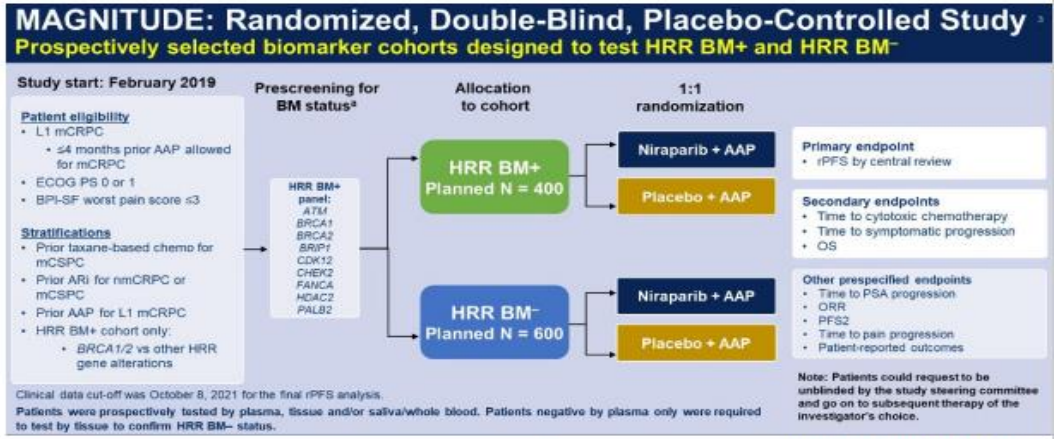
1. Castro E, et al. *J Clin Oncol.* 2019;6:490–503; 2. Annala M, et al. *Eur Urol.* 2017;72:34–42; 3. Annala M, et al. *Cancer Discovery.* 2018;doi:10.1158/2159-8290.CD-17-0937

Kastrasyona Dirençli Prostat Kanserinde PARP inhibitörler ve Yeni nesil androjen reseptör blokörleri

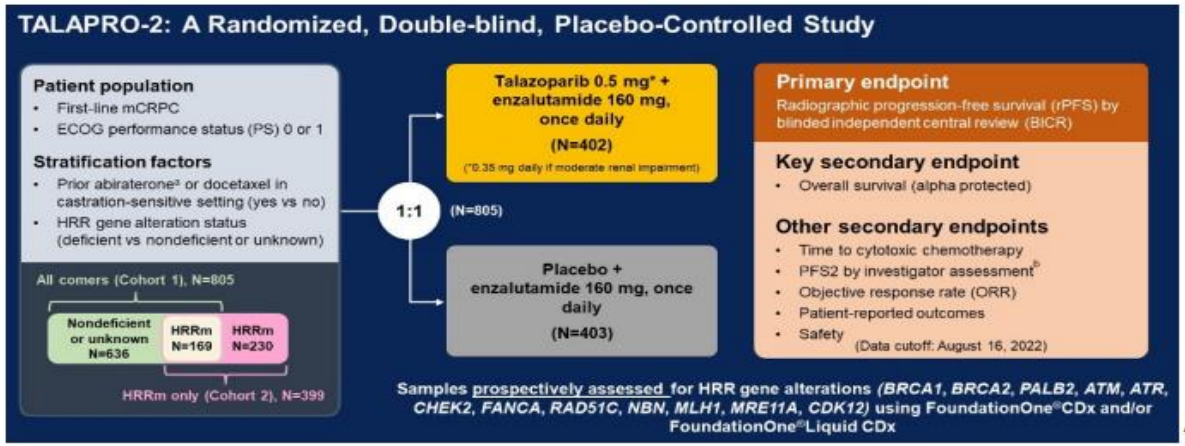
Phase 3 PARPi + ARPI Trials Design



Clarke, NW. *et al.* ***NEJM Evidence,*** 2022

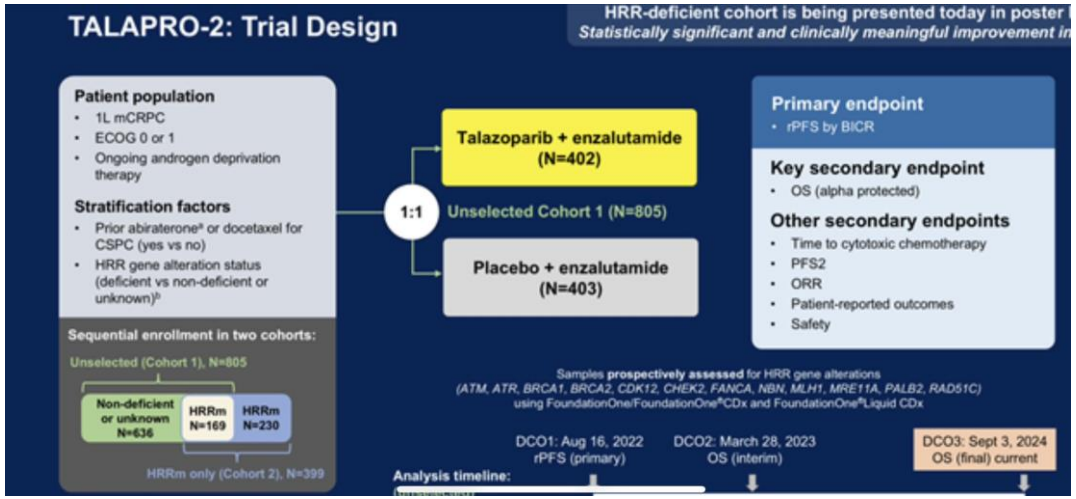


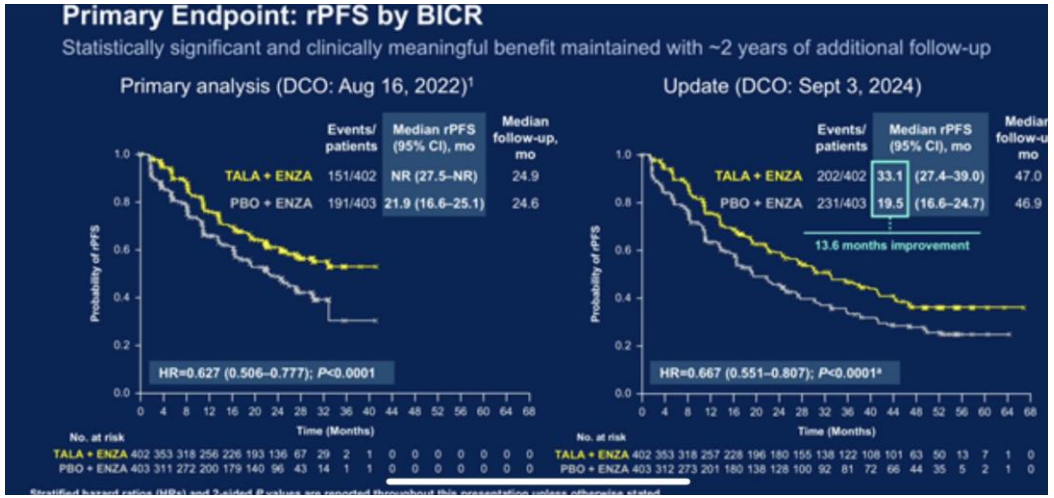
Chi, KN. *et al.* ***JCO,*** 2022

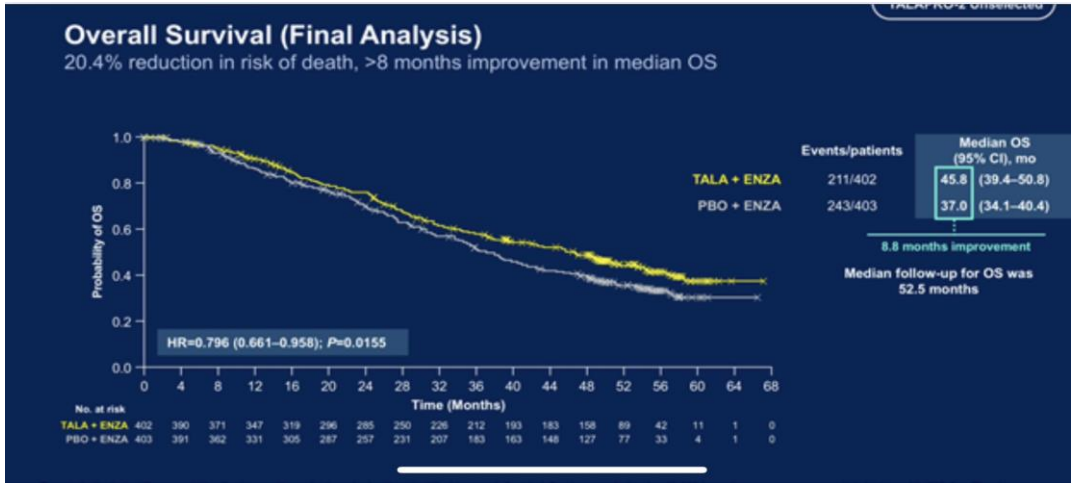


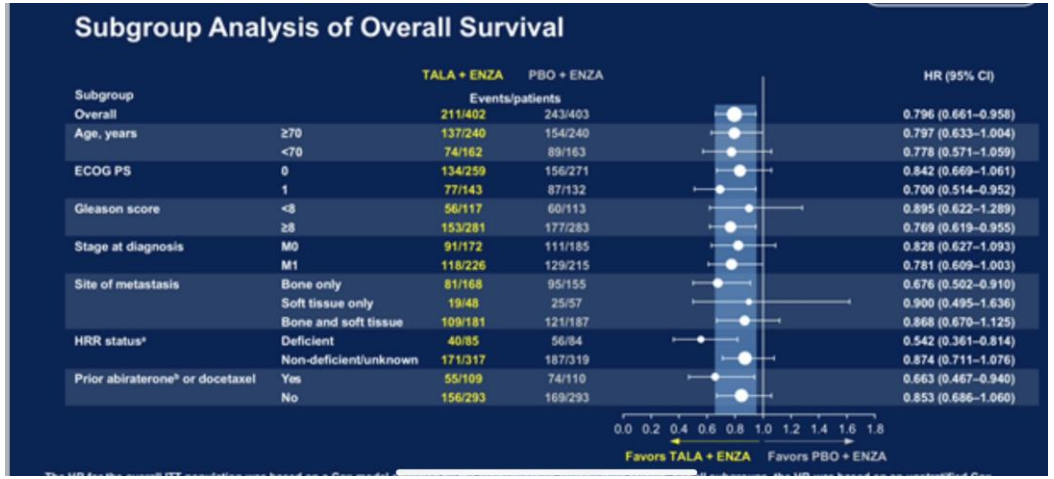
Agarwal, N. *et al.* ***Lancet,*** 2023.

TALAPRO-2 Uzun Dönem Sonuçları









PARP inhibitörü+ ARPİ kombinasyonu

The rationale for combining PARPi with ARPI

ARPIs induce a phenotype resembling HRR deficiency

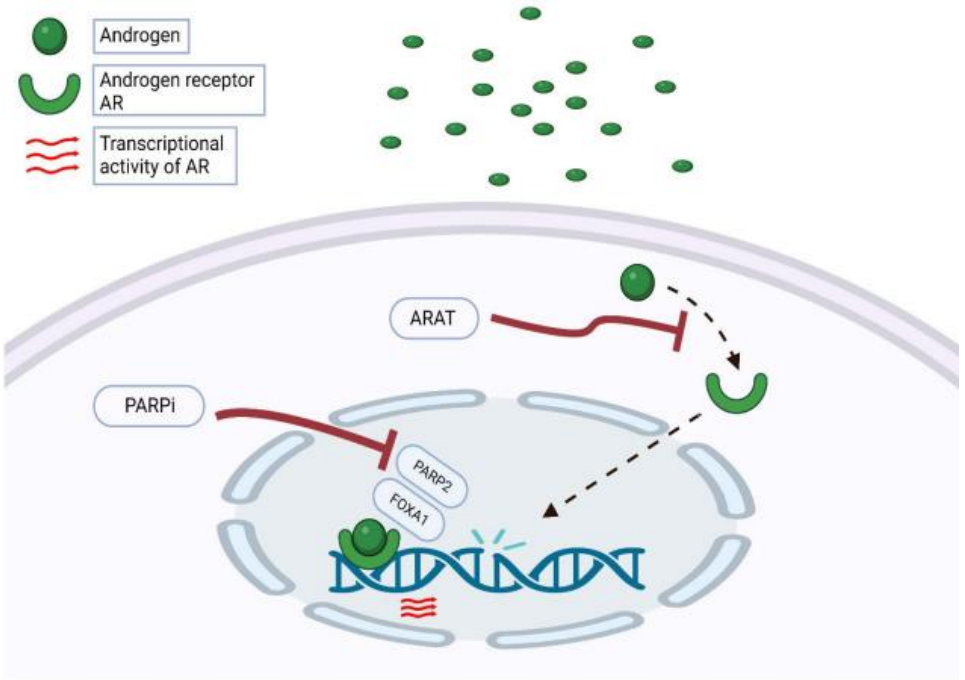
Suppressed AR function causes an upregulation of PARP

ARPIs prime tumor cells for PARP inhibition

PARP augments AR activity

PARP inhibitors may attenuate resistance to ARPIs

PARP inhibitors extend the benefits of ARPIs



1. Adapted from Bin Gui et al., *PNAS* 2019 June, DOI https://doi.org/10.1073/pnas.1908547116
2. **Agarwal N**, et al European Journal of Cancer, 2023.

Enzalutamid +Lutesyum-177 Kombinasyonu

ENZA-p Schema

Eligibility
mCRPC with PSA rising and >5ng/mL
No chemotherapy for mCRPC
≥2 risk features for early enzalutamide failure
Positive ^{68}Ga PSMA PET/CT

R 1:1

- Enzalutamide 160 mg
- Enzalutamide 160 mg + [^{177}Lu]Lu- PSMA-617 7.5 GBq 2-4 doses

Stratification
Study Site
Volume of disease (>20 vs ≤20)
Early docetaxel for hormone-sensitive disease
Prior treatment with abiraterone

Objectives
PSA-PFS (primary endpoint)
Overall survival
Health-related Quality of Life
Radiographic PFS
PSA response rate
Pain response and PFS
Clinical PFS
Adverse events
Health economic analyses
Translational/correlative

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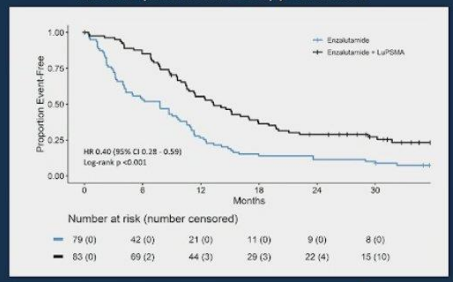
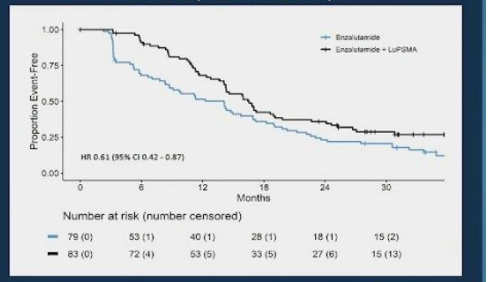
Progression Free Survival

PSA-PFS
HR 0.40 (95%CI 0.28-0.59) p=0.000001



PSA-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	73	6	7.8
Enzalutamide+[^{177}Lu]LuPSMA617	83	60	23	13

R-PFS
HR 0.61 (95% CI 0.42-0.87)



R-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	69	10	14
Enzalutamide+[^{177}Lu]LuPSMA617	83	56	27	17

Lancet Oncol. 2024 May;25(5):563-571

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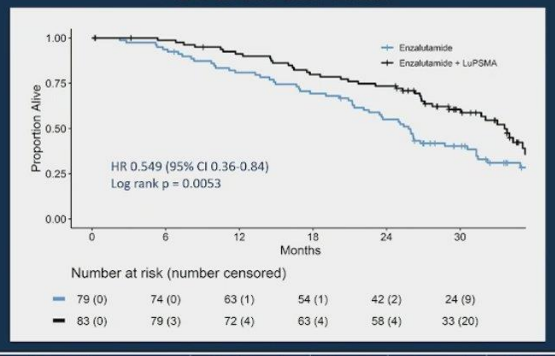
Overall Survival



Overall Survival	Participants	Events	Censored	Median Months
Enzalutamide	79	53	26	26 (C195% 23-31)
Enzalutamide + Lu-PSMA 617	83	43	40	34 (CI95% 30-37)

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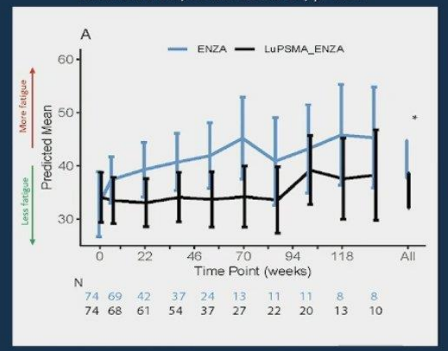
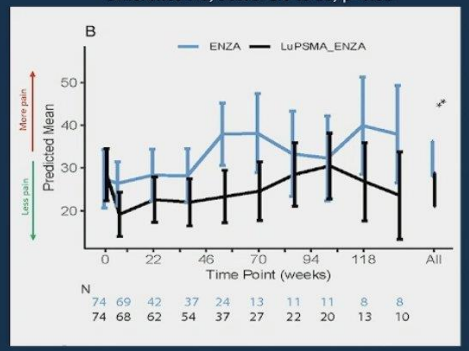
Health-Related Quality of Life

Fatigue
Difference 5.9, 95%CI 1.1 to 11; p=0.02



Pain
Difference 7.3, 95%CI 1.6 to 13; p=0.01



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Mevrometostat(EZH2 İnhibitörü) +Enzalutamide Kombinasyonu

Methods: Study design

Patient population:
- mCRPC
- Prior abiraterone
- ≤1 regimen of prior chemotherapy in any setting
- Evidence of progression per modified PCWG3 criteria
- Ongoing ADT

R 1:1 N=81

Mevrometostat 1250 mg orally BID empty stomach + Enzalutamide 160 mg orally QD n=41

Enzalutamide 160 mg orally QD n=40

Primary endpoints:
- rPFS per investigator assessment
- Safety

Secondary endpoints:
- OR†
- PSA_{50}
- Pharmacokinetics‡

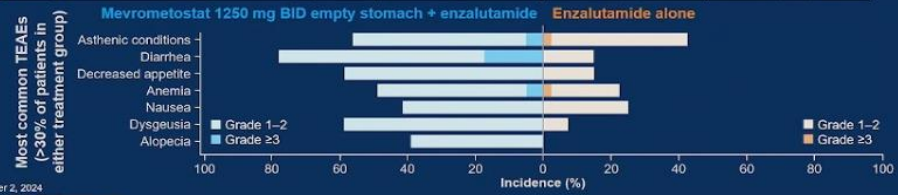
Stratification factor:
- Prior chemotherapy

†Measured by RECIST 1.1 in patients with measurable disease at baseline
‡Including evaluation of the effect of food on the pharmacokinetics and safety profile of mevrometostat
ADT, androgen deprivation therapy; BID, twice daily; mCRPC, metastatic castration-resistant prostate cancer; OR, objective response; PCWG, Prostate Cancer Working Group; PSA_{50}, decline in prostate-specific antigen of ≥50% from baseline; QD, once daily; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiographic progression-free survival

Safety summary

Mevrometostat 1250 mg BID empty stomach + enzalutamide has a manageable safety profile

Event, n (%)	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41) All grades	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41) Grade ≥3	Enzalutamide alone (n=40) All grades	Enzalutamide alone (n=40) Grade ≥3
Any TEAE	40 (97.6)	22 (53.7)	37 (92.5)	17 (42.5)
Treatment-related TEAE	39 (95.1)	20 (48.8)	33 (82.5)	9 (22.5)
Serious AE	14 (34.1)	13 (31.7)	11 (27.5)	10 (25.0)
Treatment-related serious TEAE†	10 (24.4)	10 (24.4)	1 (2.5)	1 (2.5)
TEAE leading to dose reduction	15 (36.6)	7 (17.1)	3 (7.5)	0
TEAE leading to study discontinuation	1 (2.4)	0	2 (5.0)	1 (2.5)



Data cutoff: September 2, 2024
†No treatment-related serious TEAEs led to death
AE, adverse event; BID, twice daily; TEAE, treatment-emergent adverse event

Key findings

Slide deck and MOA

Plain Language Summary

- Mevrometostat in combination with enzalutamide showed promising antitumor activity/oncological outcomes compared with enzalutamide alone in patients with mCRPC (rPFS: HR 0.51 [90% CI: 0.28, 0.95])
- Mevrometostat 1250 mg BID empty stomach in combination with enzalutamide has a manageable safety profile
- Plasma exposure with mevrometostat 875 mg with food was similar to 1250 mg empty stomach, with an improved safety profile
  - Mevrometostat 875 mg with food is the recommended phase 3 dose
- Pivotal phase 3 studies are in progress in patients with mCRPC previously treated with abiraterone (MEVPRO-1; NCT06551324) or who are ARPI-naïve (MEVPRO-2; NCT06629779)

ARPI, androgen receptor pathway inhibitor; BID, twice daily; CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; rPFS, radiographic progression-free survival
Additional findings from this study presented by Dr. Schweizer during Poster Session A: Prostate Cancer on Thursday, February 13, from 11:25 AM–2:45 PM and 5:45–6:45 PM (Poster D20)

Primary endpoint: rPFS by investigator

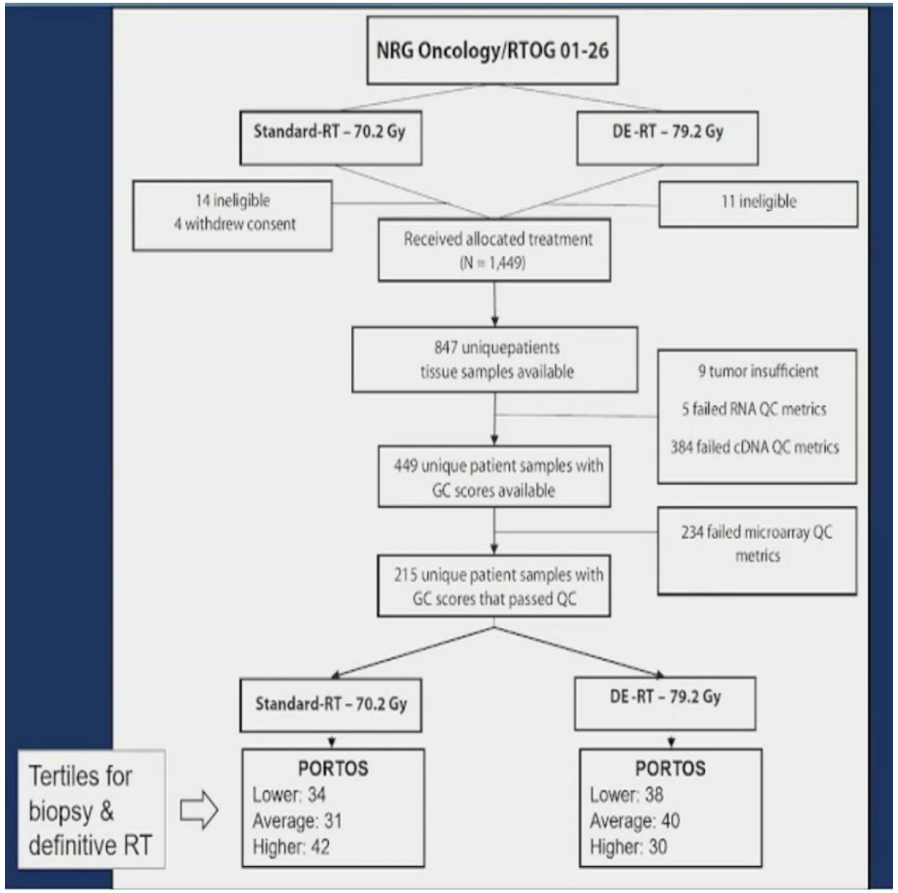
49% reduction in the risk of progression or death and ~8-month improvement in median rPFS

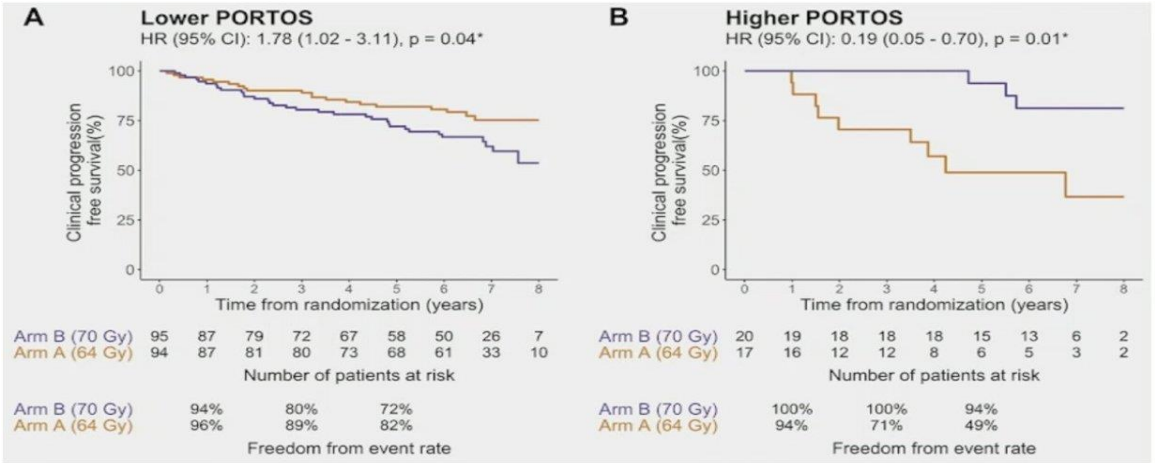
	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41)	Enzalutamide alone (n=40)
Events, n (%)	15 (36.6)	19 (47.5)
Median rPFS (95% CI), months	14.3 (7.5, NE)	6.2 (4.1, 13.9)

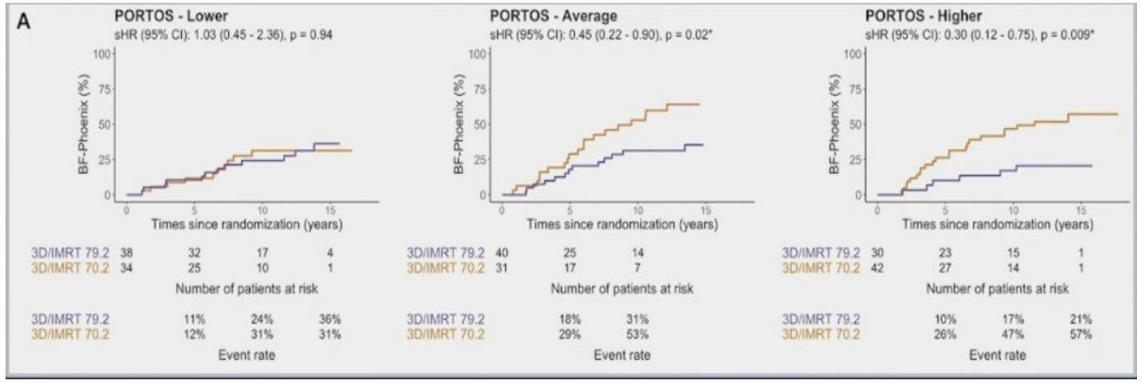
HR 0.51 (90% CI: 0.28, 0.95)

Median (IQR) duration of follow-up for rPFS was 9.6 (3.1–14.5) months. Data cutoff: September 2, 2024
BID, twice daily; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NE, not estimable; rPFS, radiographic progression-free survival

Gene Skoruna Göre Prostat Kanserinde Tedavi Modifikasyonu







RCC Adjuvan Tedavi

What benefit to expect from adjuvant pembrolizumab?

	Pts w/ Event	Median, mo (95% CI)
Pembro	87	NR (NR–NR)
Placebo	127	NR (40.5–NR)

	Pts w/ Event	Median, mo (95% CI)
Pembro	20	22.4 (11.1–NR)
Placebo	23	11.4 (2.9–NR)

	Pts w/ Event	Median, mo (95% CI)
Pembro	7	NR (25.7–NR)
Placebo	19	11.6 (5.6–NR)

Intermediate-high risk: pT2, grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0;
High risk: pT4, any grade, N0, M0; or pT any stage, any grade, N+, M0;
M1 NED: No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy.
DFS, disease free survival. NR, not reached. Data cutoff date: June 14, 2021.

Choueiri et al. ASCOGU 2022; Powles T, et al. Lancet Oncol. 2022 Sep;23(9):1133-1144.

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How to inform the patients? Potential risk of TRAES

Pooled analysis of Pembrolizumab adjuvant trials

While Immune Mediated high grade toxicities are rare (<1-2%)
- Some are life threatening
- Some are life long lasting
- Require prompt diagnosis and management = trained team

European Journal of Cancer

Safety of pembrolizumab as adjuvant therapy in a pooled analysis of phase 3 clinical trials of melanoma, non-small cell lung cancer, and renal cell carcinoma

Summary of immune-mediated adverse events.

	Pembrolizumab n = 2060		Placebo n = 2065	
All immune-mediated AEs	Any grade	Grade 3–5	Any grade	Grade 3–5
Hypothyroidism	382 (18.5)	2 (0.1)	76 (3.7)	0 (0)
Hyperthyroidism	227 (11.0)	3 (0.1)	27 (1.3)	0 (0)
Pneumonitis	52 (4.0)	17 (0.8)	29 (1.4)	4 (0.2)
Colitis	62 (3.0)	29 (1.4)	14 (0.7)	2 (0.1)
Severe skin reactions	44 (2.1)	38 (1.8)	9 (0.4)	7 (0.3)
Adrenal insufficiency	38 (1.8)	16 (0.8)	5 (0.2)	1 (<0.1)
Thyroiditis	34 (1.7)	2 (0.1)	6 (0.3)	0
Hepatitis	35 (1.7)	29 (1.4)	8 (0.4)	5 (0.2)
Hypophysitis	32 (1.6)	11 (0.5)	1 (<0.1)	0 (0)
Type 1 diabetes mellitus	17 (0.8)	17 (0.8)	0 (0)	0 (0)
Sarcoidosis	17 (0.8)	1 (<0.1)	0 (0)	0 (0)
Nephritis	16 (0.8)	6 (0.3)	1 (<0.1)	0 (0)
Myositis	10 (0.5)	4 (0.2)	3 (0.1)	0 (0)
Pancreatitis	6 (0.3)	3 (0.1)	3 (0.1)	2 (0.1)
Myocarditis	7 (0.3)	6 (0.3)	2 (0.1)	2 (0.1)
Myasthenic syndrome	6 (0.3)	2 (0.1)	0 (0)	0 (0)
Vasculitis	3 (0.1)	2 (0.1)	0 (0)	0 (0)
Uveitis	3 (0.1)	0 (0)	1 (<0.1)	0 (0)
Encephalitis	1 (<0.1)	1 (<0.1)	0 (0)	0 (0)
Myelitis	1 (<0.1)	1 (<0.1)	0 (0)	0 (0)

Luke JJ, , et al. . Eur J Cancer. 2024 Aug;207:114146.

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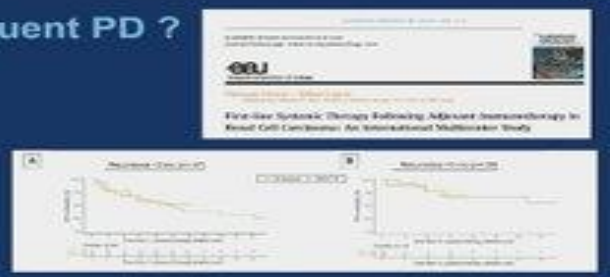
How to treat subsequent PD ?

- Retrospective study
- Patients with recurrent RCC following adjuvant IO
- N= 95 pts from 29 institutions
- 1L Treatment strategy:
  - VEGF-TT: 39%,
  - IO + VEGF-TT 28%,
  - IO + IO: 13%
  - local therapy



How to treat patients post adjuvant pembrolizumab?
Does time to relapse matter?
Randomised trial and new MoA are needed!

Conclusion

- ADJUVANT is SOC !
- Discussing adjuvant in eligible patients is needed with both the information on the estimated risk of relapse and the potential toxicity related to the treatment
- Further developments are ongoing
  - To increase the benefit of adjuvant strategy
  - To optimize the patient selection

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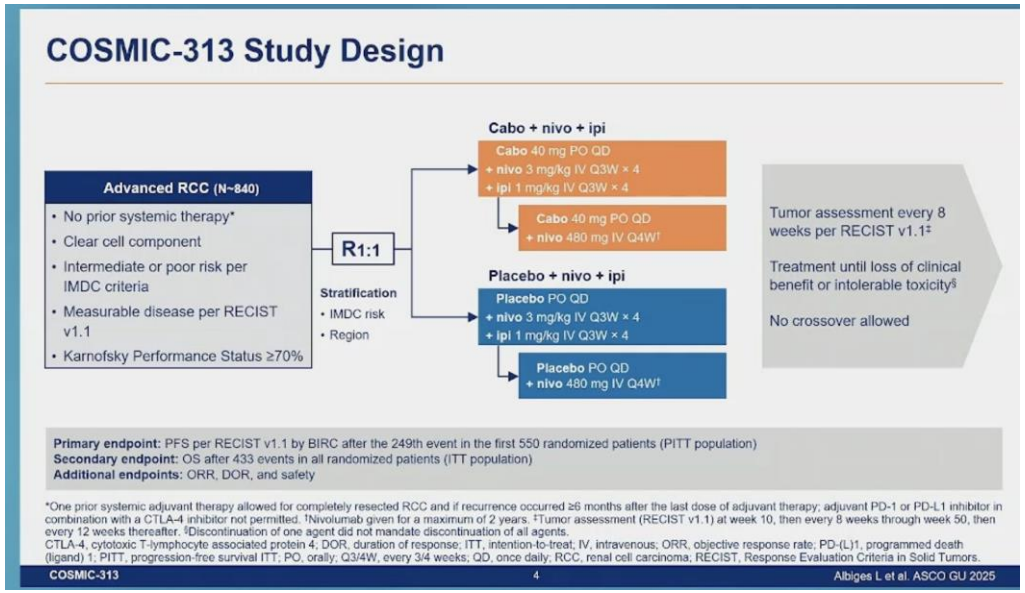
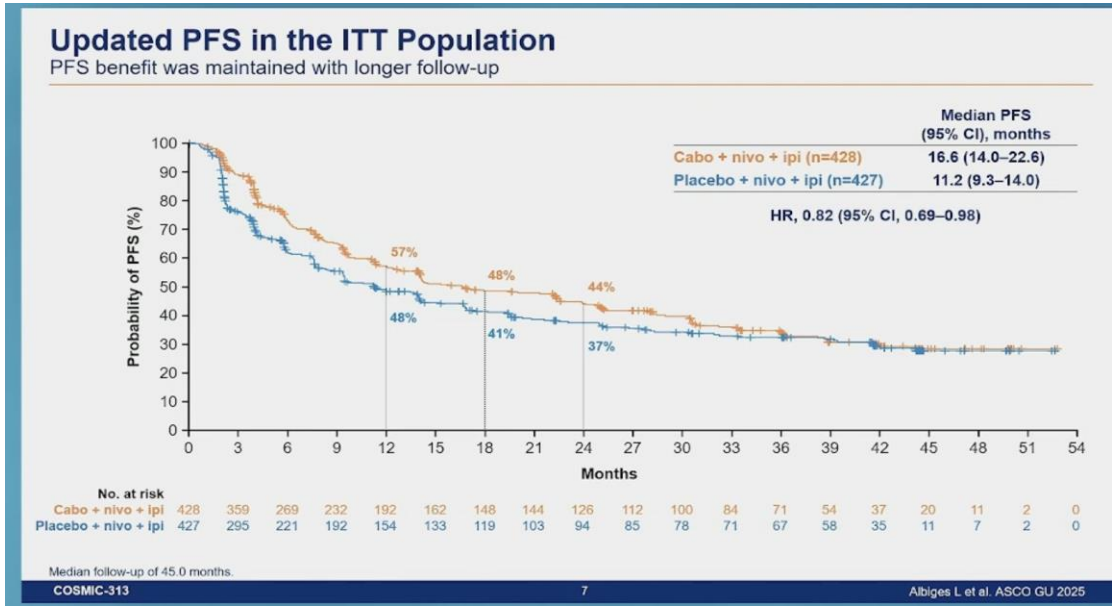
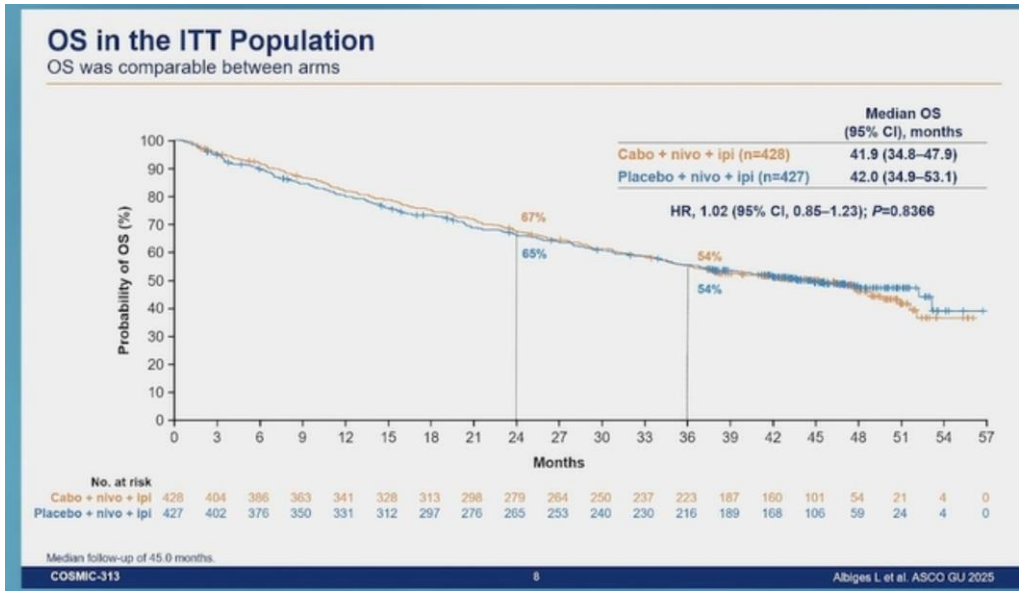
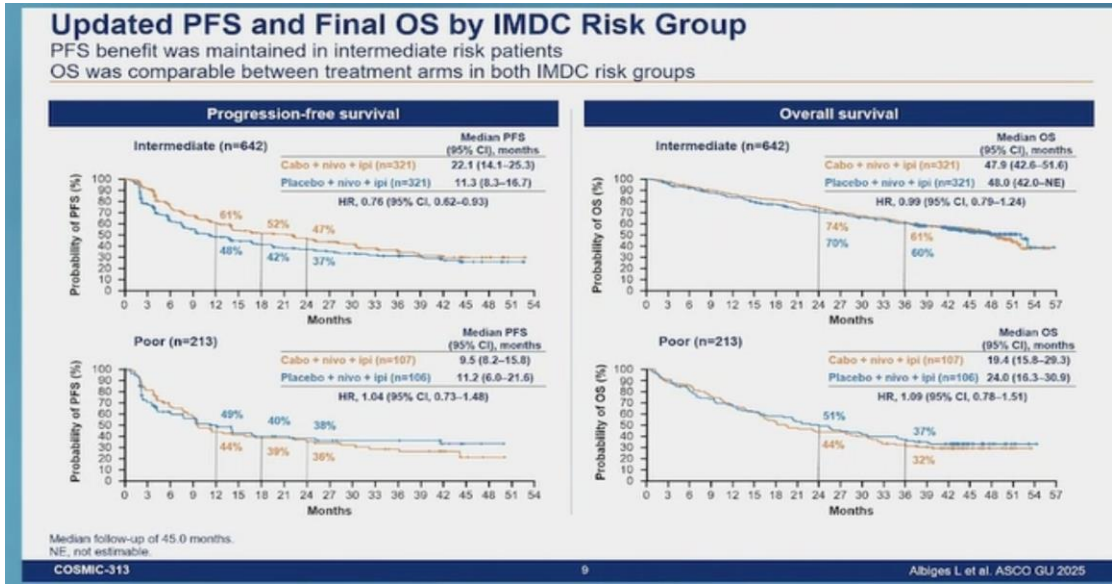
RCC Berrak Hücreli Kanserde Üçlü kombinasyon Uzun dönem sonuçları



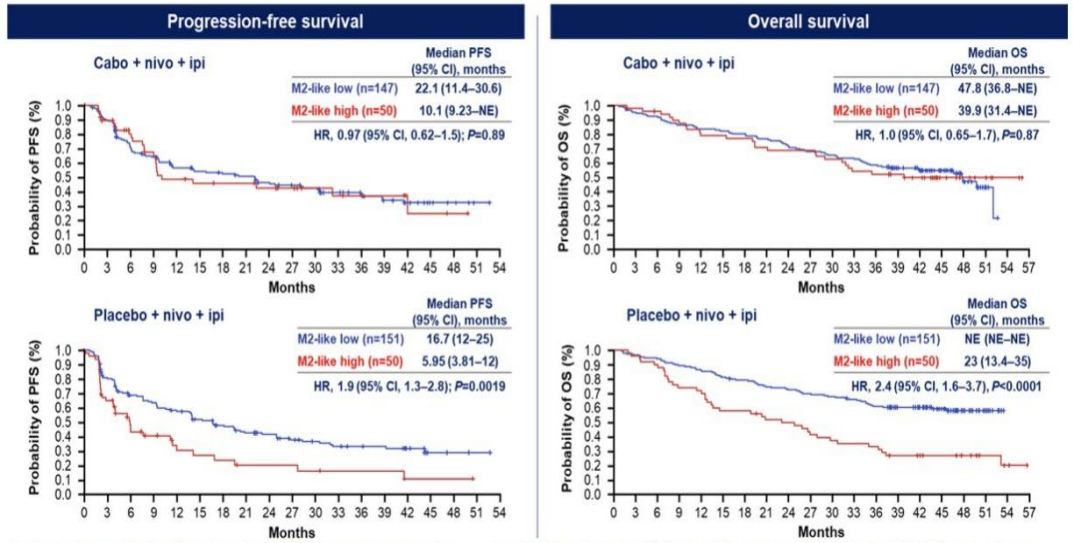






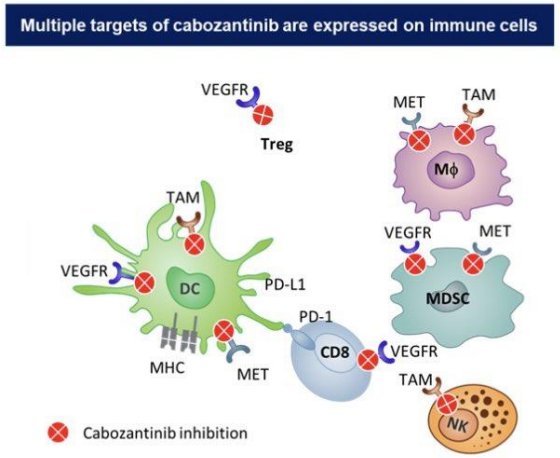
RCC Berrak Hücreli Kanserde Üçlü kombinasyon Uzun dönem sonuçları

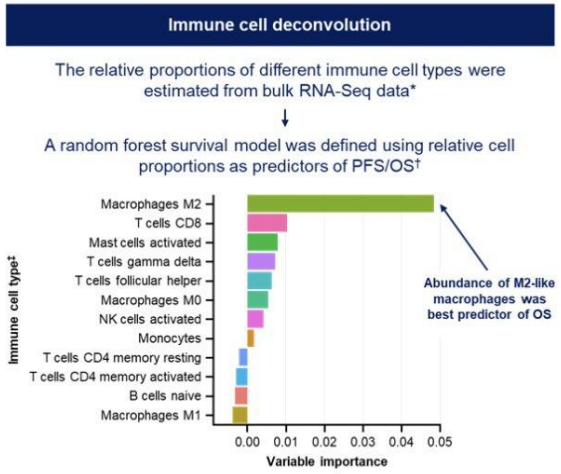
The Addition of Cabo to Nivo + Ipi Overcomes M2-like Macrophage-Mediated Immune Suppression



A cox univariate model with different quantiles of M2-like macrophage abundance was used to determine the cutoff with the minimum hazard ratio. Patients with M2-like macrophage abundance in the top 25% were classified as M2-like high. Median follow-up of 45 months for PFS. Median follow-up of 37.5 (cabo + nivo + ipi) and 36.8 (placebo + nivo + ipi) months for OS.

Deconvolution Was Used to Investigate the Effects of Cabozantinib on Immune Cell Types





*Immune deconvolution was performed using CIBERSORT (LM22 signature). †A random forest survival model was built using relative abundance of immune cell subsets from patients across both treatment arms as predictors of PFS/OS. Hyperparameters were optimized to select the model with the best prediction accuracy. ‡Variable importance with regards to OS showing immune subsets with >0 cells in at least 10% of patients. DC, dendritic cell; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; MΦ, macrophage; NK, natural killer; Treg, regulatory T cell; VEGFR, vascular endothelial growth factor receptor.

RCC Berrak Hücreli Kanserde Birinci Basamak Nivolumab+Kabozantinib Uzun dönem sonuçları

Study design: CheckMate 9ER

N = 651

Key inclusion criteria[1]
- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

Stratification factors
- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region

R 1:1

- **Nivolumab** 240 mg IV Q2W + **Cabozantinib** 40 mg PO QD[b]
- **Sunitinib** 50 mg PO QD, cycle of 4 weeks on/ 2 weeks off[b]

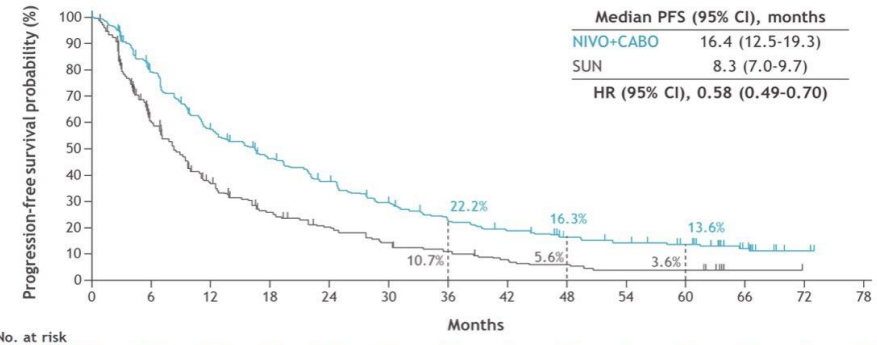
Median (range) follow-up for OS[c] in the ITT population, 67.6 (60.2-80.2) months
Database lock, June 21, 2024

Primary endpoint: PFS per BICR (RECIST v1.1)
Key secondary endpoints: OS, ORR per BICR (RECIST v1.1), safety

- All analyses presented are descriptive and exploratory

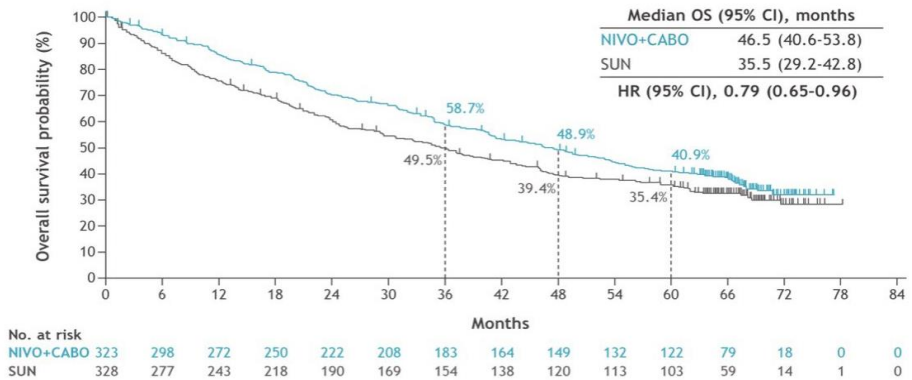
[a]Defined as the percentage of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC 28-8 pharmDx immunohistochemistry assay. [b]Patients were treated until RECIST v1.1-defined progression or unacceptable toxicity. NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression. [c]Follow-up was defined as the time from patient's randomization date to last patient last visit date; median follow-up represents the median of individual follow-up periods of all randomized patients. Minimum follow-up was defined as the time from the last patient randomization date to the last patient last visit date. Maximum follow-up was defined as the time from first patient randomization date to last patient last visit date.
1. Choueiri TK, et al. *N Engl J Med* 2021;384:829-841.

PFS per BICR in the *ITT population*



Median follow-up, 67.6 (range, 60.2-80.2) months (ITT population).
Stratified Cox proportional hazards model used for HR.

OS in the *ITT population*



Median follow-up, 67.6 (range, 60.2-80.2) months (ITT population).
Stratified Cox proportional hazards model used for HR.

Efficacy by baseline organ sites of metastases

- PFS, OS, and ORR favored NIVO+CABO vs SUN in subgroups by baseline organ sites of metastases shown here

Outcome	Liver[a,b]		Bone[a,b]		Lung[a,b]	
	NIVO+CABO (n = 73)	SUN (n = 56)	NIVO+CABO (n = 79)	SUN (n = 75)	NIVO+CABO (n = 241)	SUN (n = 251)
Median PFS (95% CI), mo	10.9 (7.0-15.2)	6.2 (2.9-8.3)	13.8 (8.3-20.1)	5.3 (3.9-8.2)	16.4 (12.3-21.4)	8.3 (6.9-9.7)
HR (95% CI)[c]	0.55 (0.37-0.82)		0.43 (0.30-0.64)		0.56 (0.46-0.69)	
Median OS (95% CI), mo	37.6 (23.5-49.9)	22.1 (9.9-29.3)	34.8 (21.4-58.9)	20.7 (12.7-29.2)	47.5 (40.6-55.8)	32.4 (24.6-38.0)
HR (95% CI)[c]	0.65 (0.43-0.97)		0.66 (0.45-0.95)		0.75 (0.60-0.94)	
ORR (95% CI), %	52.1 (40.0-63.9)	21.4 (11.6-34.4)	49.4 (37.9-60.9)	9.3 (3.8-18.3)	57.3 (50.8-63.6)	27.9 (22.4-33.9)

[a]An exploratory analysis of efficacy outcomes by baseline organ sites of metastases was conducted in the ITT population (prespecified for bone; post hoc for liver and lung). [b]Within each subgroup, all patients had metastasis within the specified site but may have had lesions in more than 1 site. [c]Unstratified Cox proportional hazards model used for HR.

RCC Tedavi Yanıtını öngören biyomarkerlar

ASCO Genitourinary Cancers Symposium

Evaluation of circulating kidney injury molecule-1 (KIM-1) as a prognostic and predictive biomarker in advanced renal cell carcinoma (aRCC): Post-hoc analysis of CheckMate 214

Wenxin Xu,[1,2,3] Sai Vikram Vemula,[4] Robert J. Motzer,[5] Aparna Chhibber,[4] Deepthi Chowbene,[6] Nahuel Perrot,[6] Xiaowen Liu,[6] Joseph V. Bonventre,[2,3] Toni K. Choueiri,[1,2,3] David F. McDermott,[3,6] Saurabh Gupta,[4] Rupal S. Bhatt[4]

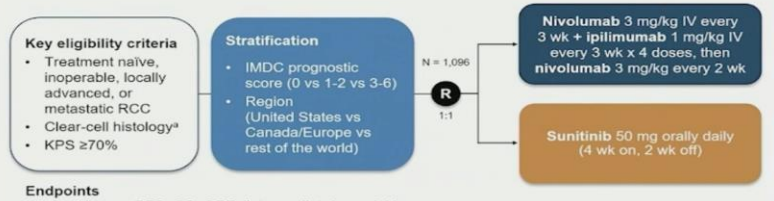
[1]Dana-Farber Cancer Institute, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Harvard Medical School, Boston, MA; [4]Bristol Myers Squibb, Princeton, NJ; [5]Memorial Sloan Kettering Cancer Center, New York, NY; [6]Beth Israel Deaconess Medical Center, Boston, MA;

Abstract number 437

CheckMate 214

CheckMate 214 Background and Study design

- CheckMate 214 demonstrated that Nivo+Ipi has superior OS and durable response compared to Sunitinib with 8 years of follow-up in first line treatment of aRCC[1]
  - These results continue to support Nivo+Ipi as a first-line standard of care for intermediate/poor risk aRCC
- There are currently no RCC specific biomarkers to help prognosticate patients or to identify those who are likely to respond to Nivo+Ipi



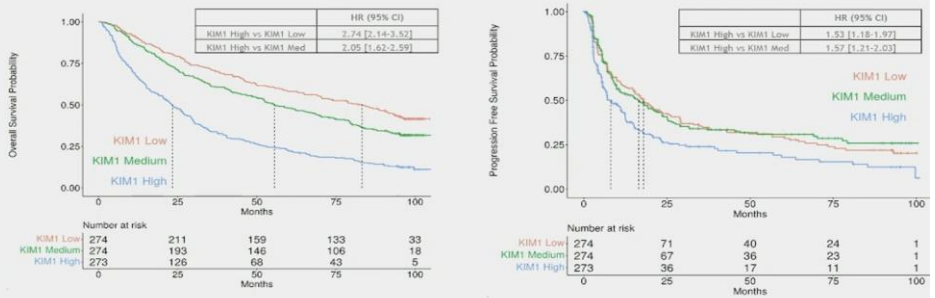
Endpoints
- **Coprimary:** PFS, OS, ORR (intermediate/poor risk)
- **Secondary:** PFS, OS, ORR (ITT)
- **Exploratory:** PFS, OS, ORR (favorable risk)

1. Tannir NM, et al. *Ann Oncol* 2024

CheckMate 214

Baseline KIM-1 levels and clinical outcomes

- Higher baseline KIM-1 was associated with worse overall and progression free survival

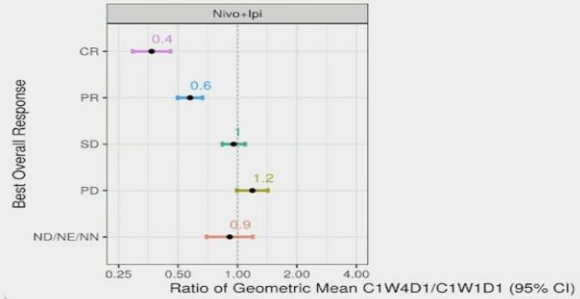


KIM-1 association with outcomes remains significant after adjustment for IMDC risk and baseline tumor burden in multivariable models

CheckMate 214

Early KIM-1 decrease post treatment predicts overall radiographic response in Nivo+Ipi arm

- Decrease in KIM-1 at 3 weeks post treatment was strongly associated with subsequent radiographic response in Nivo+Ipi but not Sunitinib arm



Evre IV RCC Birinci Basamak Tedavi Seçenekleri

Summary of first-line combinations in RCC (at Feb 2025)*

	CHECKMATE 214[1]		KEYNOTE 426[2]		CHECKMATE 9ER[3]		CLEAR[4]		COSMIC-313[5]	
	Ipi / Nivo	Sunitinib	Axi / Pembro	Sunitinib	Cabo / Nivo	Sunitinib	Len / Pembro	Sunitinib	Ipi / Nivo / Cabo	Ipi / Nivo
Prognostic groups	Fav 23% / Int 61% / Poor 17% **Intermediate/Poor risk**		Fav 32% / Int 55% / Poor 13% **All risk**		Fav 23% / Int 58% / Poor 19% **All risk**		Fav 31% / Int 60% / Poor 9% **All risk**		Int 75% / Poor 25% **Intermediate/Poor risk**	
Follow-up, mos	99.1		67		67.6		49.8		45	
Nephrectomy (%)	82	80	83	83	69	71	74	77	65	65
ORR (%)	42	27	61	40	56	28	71	37	46	37
CR	11	2	12	4	14	5	18	4	4	3
PR	31	25	49	36	42	23	53	33	42	33
SD	31	44	23	36	32	41	19	38	40	36
PD	19	17	12	17	6	14	5	14	8	20
Median OS, mos	46.7 (35.0-55.7)	26.0 (21.8-32.6)	47.2 (43.6-54.8)	40.8 (34.3-47.5)	46.5 (40.6-53.8)	35.5 (29.2-42.8)	53.7 (48.7-NE)	54.3 (40.9-NE)	41.9 (34.8-47.9)	42.0 (34.9-53.1)
OS HR (95%CI)	**0.69 (0.59-0.81)**		**0.84 (0.71-0.99)**		**0.79 (0.65-0.96)**		**0.79 (0.63-0.99)**		**1.02 (0.85-1.23)**	
Median PFS, mos	12.4	8.5	15.7	11.1	16.4	8.3	23.9	9.2	16.6	11.2
PFS HR (95%CI)	0.73 (0.61-0.87)		0.69 (0.59-0.81)		0.58 (0.49-0.70)		0.47 (0.38-0.57)		**0.82 (0.69-0.98)**	

***Includes first line doublets positive for OS and emerging triplets. Not intended for cross trial comparisons.**

1. Tannir et al. GU ASCO 2024. 2. Rini et al. ASCO 2023. 3. Motzer et al. GU ASCO 2025. 4. Motzer et al. ASCO 2023. 5. Albiges et al. GU ASCO 2025.

@LalaniMD

Berrak hücreli dışı RCC Tedavi Seçenekleri

ASCO Genitourinary Cancers Symposium

Abstract ID: 443

Lenvatinib plus tislelizumab as first-line therapy for advanced fumarate hydratase-deficient renal cell carcinoma (FH-RCC): A single-center, single-arm, phase II study

Wen Kong[1], Guangyu Wu[2], Yunze Xu[1], Zaoyu Wang[3], Jin Zhang[1]

1. Department of Urology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
2. Department of Radiology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
3. Department of Pathology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Study Design

Key Eligibility Criteria
- Age ≥ 18y, < 80y
- ECOG 0-2
- Confirmed diagnosis of FH-deficient RCC (Histology or molecular sequencing)
- Unresectable recurrent or metastatic Stage IV disease
- No previous systemic treatment
- Measurable lesions per RECIST v1.1
- Adequate organ function

Treatment
Tislelizumab 200mg IV Q3W
+
Lenvatinib 20mg PO QD

Assessment
- During first 24 weeks: Clinical and laboratory assessment every 3 weeks Imaging assessment every 6 weeks
- After first 24 weeks: Efficacy and safety follow-up every 3 months

End of treatment
- Progressive disease
- Intolerable toxicity
- Death or loss of follow-up
- Consent withdraw

(NCT05877820)

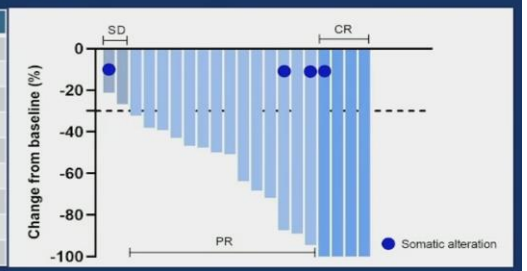
- **Primary Endpoint:** ORR per RECIST 1.1
- **Secondary Endpoint:** PFS, DCR, DOR, 1/2-year OS rate, safety
- **Exploring Endpoint:** circulating succinate-modifying metabolites, characteristics of immune infiltration

ECOG, Eastern Cooperative Oncology Group; FH, Fumarate Hydratase; RECIST, Response Evaluation Criteria In Solid Tumors; Q3W, once every 3 weeks; QD, once daily; ORR, objective response rate; PFS, progression free survival; DCR, disease control rate; DOR, duration of response; OS, overall survival

Results: efficacy

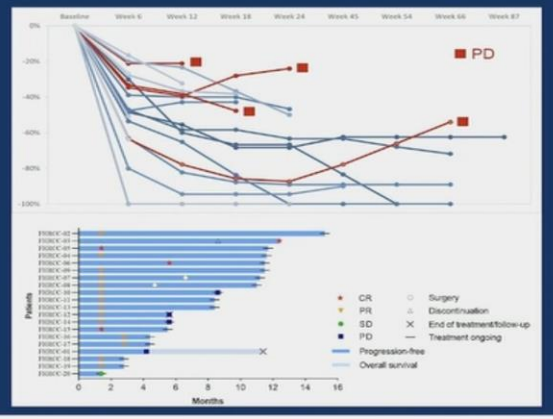
- The median follow up was 9.7 (1.4-15.2) months.
- ORR：90% (18/20)；DCR: 100%.
- Both hereditary and sporadic FH-RCC benefited from the treatment.

Response	Cohort (n=20)
ORR, % (95% CI)	90 (66.9-98.3)
Best response, No. (%)	
CR	4 (20)
PR	14 (70)
SD	2 (10)
PD	0 (0)
Disease control rate, % (95% CI)	100 (80.0-100)
Clinical benefit rate, % (95% CI)	85 (61.1-96.0)
Median PFS, months	NR



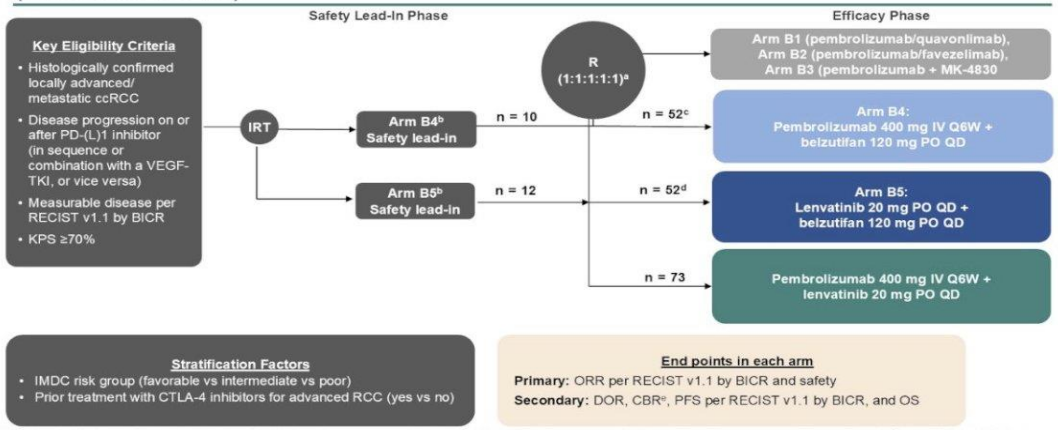
Results: efficacy

- The median time to response was 6 weeks.
- We did not observe primary progression on this regimen, for all patients achieved at least SD at 12 weeks, and all patients achieved some shrinkage in tumor burden.
- Four patients got PD at the latest assessment.
- Overall, four PFS and one OS events occurred. Median PFS and OS were not reached, while 6-month PFS and OS rate were 85% and 100% respectively.
- Three patients underwent definitive surgery with/without radiotherapy in the cohort.
- At the last follow-up, there are 17/20 patients still kept in the treatment.



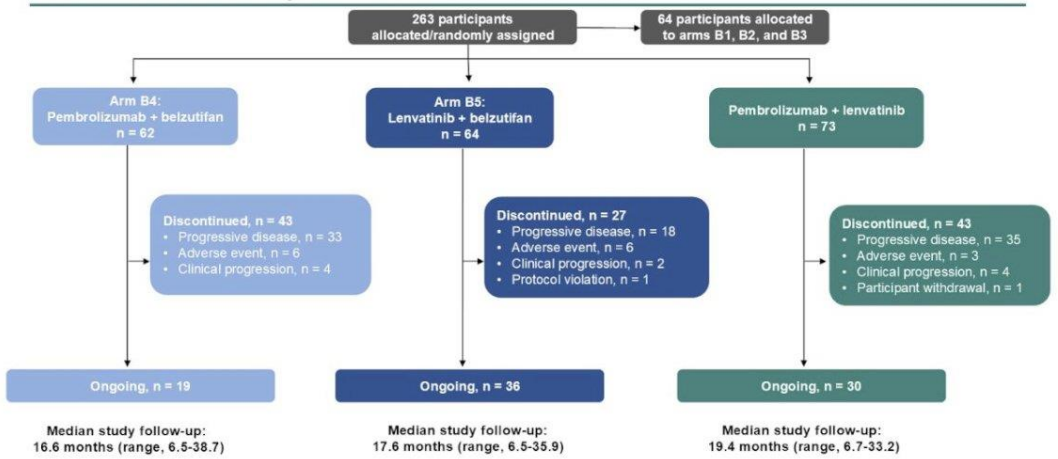
Berrak Hücreli RCC 2.Basamak ve Sonrası

KEYMAKER-U03 Substudy 03B Study Design (NCT04626518)

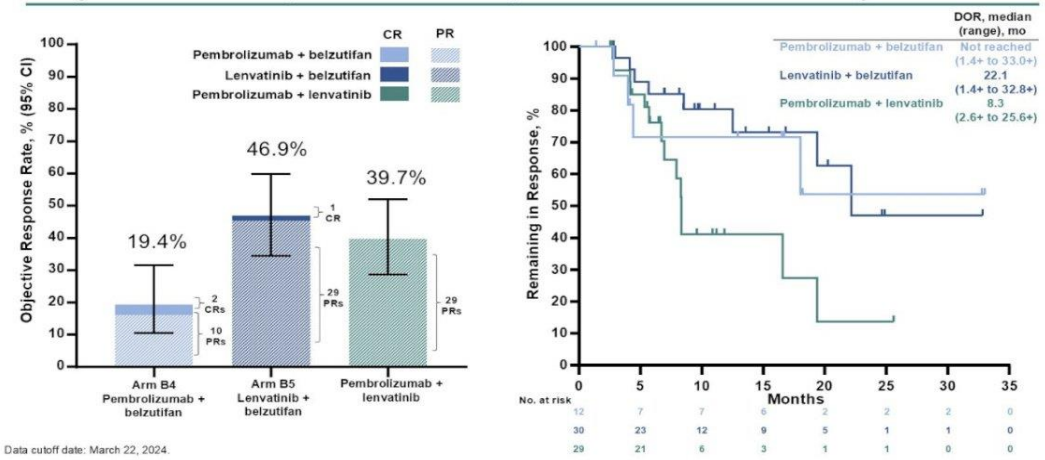


BICR, blinded independent central review; IRT, interactive response technology. [a]Participants were randomly assigned to arms open for enrollment. [b]Arms B4 and B5 had a safety lead-in phase where 10 and 12 patients, respectively, were initially enrolled before randomization. [c]62 participants were evaluated in arm B4 in the efficacy phase. [d]64 participants were evaluated in arm B5 in the efficacy phase. [e]CBR is defined as CR + PR + SD ≥6 months.

Treatment Disposition

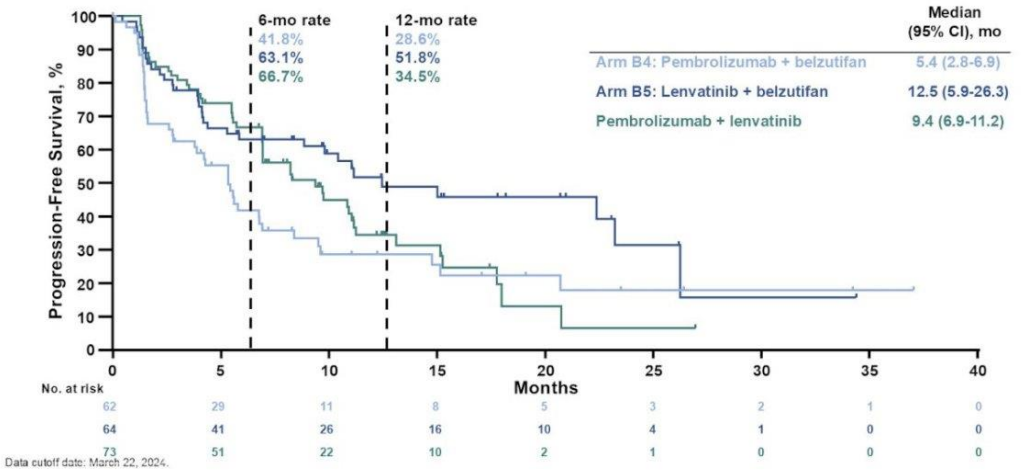


Objective Response Rate per RECIST v1.1 by BICR



Data cutoff date: March 22, 2024.

Progression-Free Survival per RECIST v1.1 by BICR



Data cutoff date: March 22, 2024.

Berrak Hücreli RCC 2.Basamak ve Sonrası

Phase 3 Study Evaluating Cas + Cabo in Advanced or Metastatic ccRCC, Following Prior PD-1 Therapy

Anticipated first half 2025 **PEAK-1**

PATIENT POPULATION:
- Unresectable, locally advanced or metastatic ccRCC
- Measurable disease per RECIST v1.1
- Have had prior anti–PD-1/PD-L1
- Have not received cabozantinib
- HIF-2α–inhibitor naive

N = ~700

R 2:1

- 100 mg QD casdatifan + 60 mg cabozantinib
- Placebo + 60 mg cabozantinib

PRIMARY ENDPOINT:
- PFS

KEY SECONDARY ENDPOINTS:
- OS
- ORR, DOR, DCR

Cabo, cabozantinib; cas, casdatifan; HIF, hypoxia-inducible factor; R, randomized.

ASCO Genitourinary Cancers Symposium #GU25 PRESENTED BY: Toni K Choueiri, MD

ARC-20 is a Phase 1 Dose-Escalation and Dose-Expansion Study of Casdatifan

KEY INCLUSION CRITERIA
- At least 1 measurable lesion per RECIST v1.1
- Adequate organ and marrow function

Dose Escalation

PATIENTS WITH ADVANCED SOLID TUMORS
Casdatifan monotherapy

200 mg QD
150 mg QD
50 mg BID
50 mg QD
20 mg QD

Dose Expansion
N = ~30 per cohort

- 2L+ ccRCC Casdatifan mono 50 mg BID capsule
- 2L+ ccRCC Casdatifan mono 50 mg QD capsule
- 2L+ ccRCC Casdatifan mono 100 mg QD tablet

- 2L+ ccRCC Casdatifan mono 150 mg QD
- Post-IO ccRCC Casdatifan 100 mg QD + Cabozantinib 60 mg QD
- Favorable-risk 1L ccRCC Casdatifan mono 100 mg QD
- 1L ccRCC Casdatifan 100 mg QD + Zimberelimab 360 mg Q3W
- Post-IO ccRCC Casdatifan mono 100 mg QD

PRIMARY OUTCOMES: AEs, DLTs

SECONDARY OUTCOMES: ORR[a], PK/PD

EXPLORATORY OUTCOMES: PFS, OS, Biomarkers

1L, first-line treatment setting; 2L+, second-line treatment setting or greater; DLT, dose-limiting toxicity; IO, immunotherapy.
[a]Assessed by the investigator according to RECIST v1.1.

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Treatment With Casdatifan Showed Meaningful Clinical Activity and Disease Control Across Doses

Efficacy-Evaluable Population[a]	50 mg BID (n = 32)	50 mg QD (n = 28)	100 mg QD (n = 27)
Median follow-up, mo (range)	15 (7–19+)	12 (9–14+)	5 (2–6+)
Confirmed ORR, % (n) (95% CI)	**25% (8) (11.5, 43.4)**	**29% (8) (13.2, 48.7)**	**33% (9) (16.5, 54.0)**
Best Overall Response[b], n (%)	10 (31%)	9 (32%)	9 (33%)
CR	0	1 (4%)	0
PR	10 (31%)	8 (29%)	9 (33%)
SD	16 (50%)	15 (54%)	14 (52%)
PD	6 (19%)	4 (14%)	2[c] (7%)

Data cutoff date: 03 January 2025.
[a]All eligible patients who received any study treatment and have at least one post-baseline efficacy assessment or discontinued study treatment due to progressive disease or death.
[b]Unconfirmed best overall response.
[c]In addition to the two patients with radiological progressive disease, 2 patients had clinical progression before first scan.

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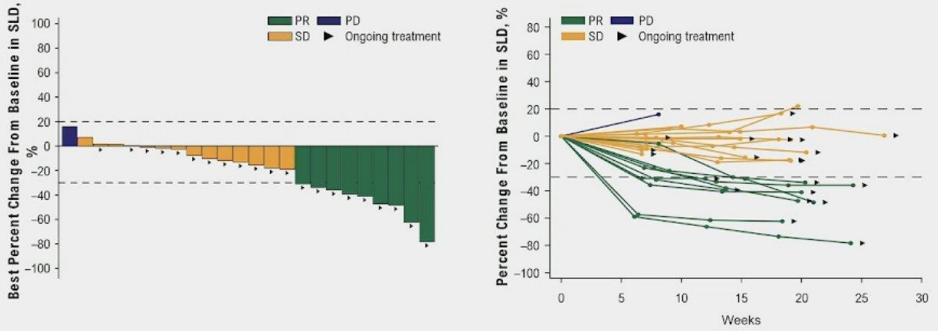
Casdatifan 100 mg QD Showed Rapid Response and a Trend of Decreasing Sum of Target Lesion Diameters



Median (range) follow-up for the 100 mg QD cohort is 5 (2–6+) months (ongoing)

Data cutoff date: 03 January 2025.

ASCO Genitourinary Cancers Symposium #GU25 PRESENTED BY: Toni K Choueiri, MD

Evre IIA/IIB Seminom Tedavisinde RPLND

ASCO Genitourinary Cancers Symposium

Prospective COTRIMS (Cologne Trial of Retroperitoneal Lymphadenectomy in Metastatic Seminoma): final results

Axel Heidenreich, MD, PhD
Professor of Urology
University Hospital Cologne, Germany

Guideline recommended treatment options

.....are associated with significant long-term toxicity

	Radiation	chemotherapy
Solid cancer	RR 2.9 – 5.9	RR 3.4 – 7.5
Leukemia	RR 3.0	RR 3.2 - 5.1
cardiovascular	RR 2.3	RR 5.7
Diabetes mellitus	RR 2.3	RR 2.6

Mortality

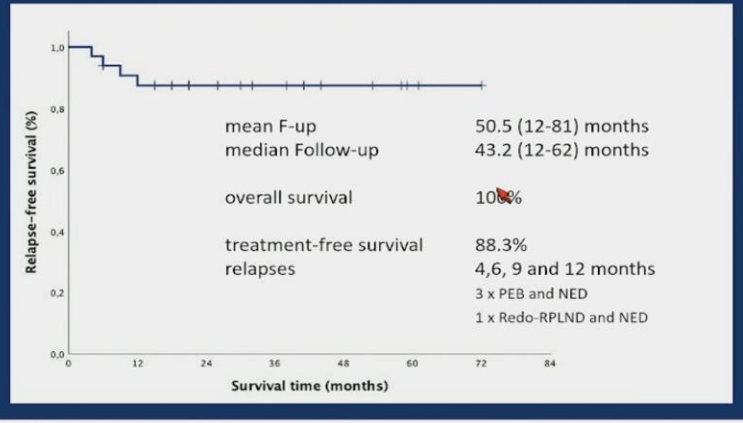
especially in seminomas beyond 15 years

Fung et al., 2018; Kvammen et al., 2016

Results I

Patient characteristics	number (n = 34)
age (years), median (IQR)	34.2 (21-54)
Primary orchiectomy, n (%)	
right	11 (32)
left	23 (68)
pT1	22 (65)
pT2	12 (35)
Rete testis Invasion	6/22 (28)
Tumo diameter (cm), median (IQR)	4.3 (2.1 – 5.1)
Clinical stage at diagnosis, n (%)	
CS I	16 (47)
CS IIA	14 (41)
CS IIB	4 (12)
Clinical stage at RPLND, n (%)	
CS IIA	22 (65)
CS IIB	12 (35)
number lymph nodes on preop. CT, median (IQR)	1.6 (1-3)
Size of lymph nodes (cm), median (IQR)	2.2 (1.3-4.5)

Oncological Outcome



mean F-up	50.5 (12-81) months
median Follow-up	43.2 (12-62) months
overall survival	100%
treatment-free survival	88.3%
relapses	4,6, 9 and 12 months
	3 x PEB and NED
	1 x Redo-RPLND and NED

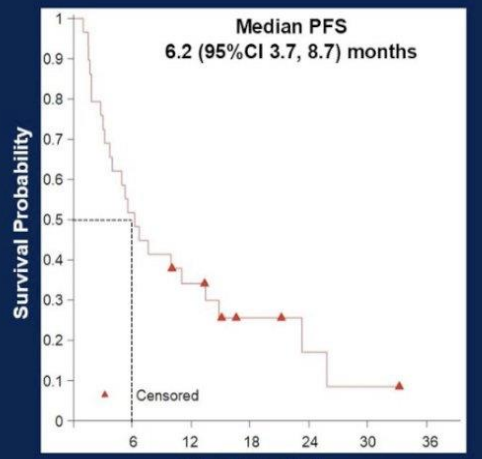
Penil kanserde Kemoterapi ve İmmünoterapi Kombinasyonu

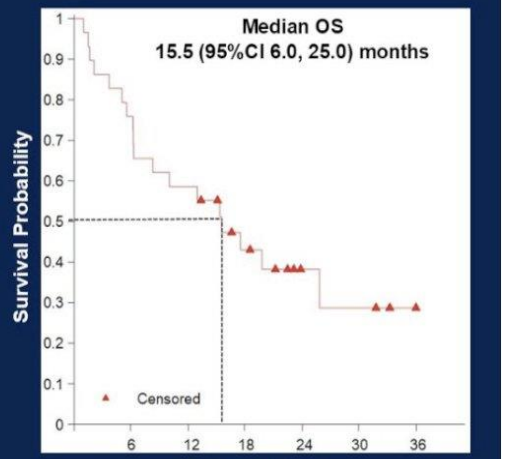
ASCO Genitourinary Cancers Symposium

EPIC-A: Phase II trial of cemiplimab plus standard of care chemotherapy followed by maintenance cemiplimab in locally advanced or metastatic penile carcinoma.

Amit Bahl[1], Amarnath Challapalli[2], Balaji Venugopal[3], Mehran Afshar[3], Constantine Alifrangis[4], Alastair Thomson[5], Anna Tran[6], Andrew Hudson[6], Christopher Kent[7], Jim Barber[8], Helen Dearden[9], Rachel Pearson[10], Vivekanandan Kumar[11], Robert Wade[11], Alicia Bravo[1], Emily Foulstone[1], Paul White[12]

Survival outcomes: PFS and OS





Efficacy: Clinical Benefit Rate (CBR)

Efficacy outcome	N=29
12 weeks	
Clinical benefit rate (CBR)	62.1% (95%CI 44.4%, 79.7%)
CR	0
PR	15 (51.7%)
SD	3 (10.3%)
Objective response rate (ORR)	51.7% (95%CI 34.4%, 68.6%)
21 (12+9) weeks	
Clinical benefit rate (CBR)	48.3% (95%CI 31.4%, 65.6%)
CR	1 (3.4%)
PR	12 (41.4%)
SD	1 (3.4%)
Objective response rate (ORR)	44.8% (95%CI 28.4%, 62.4%)

95%CI lower limit for both ORR and CBR is higher than the null hypothesis limit of 25%

Table: List of AEs ≥ Grade 3 related to chemotherapy or cemiplimab.

AE CTC Cat 0	Chemotherapy Related		Cemiplimab Related	
	N	%	N	%
Gastrointestinal disorders	3	13.6	1	11.1
Blood and lymphatic system	2	9.1	---	
Infections and infestations	2	9.1	2	22.2
Cardiac disorders	1	4.5	---	
Ear and labyrinth disorders	1	4.5	---	
Immune system disorders	1	4.5	1	11.1
Musculoskeletal & connective tis	1	4.5	1	11.1
Respiratory, thoracic and medias	1	4.5	---	
Vascular disorders	---		1	11.1
Total	22	100	9	100

Sonuç

Üroteliyal kanserlerde neoadjuvan ve adjuvan immünoterapi verileri olgunlaşıyor

Üroteliyal kanserde FGRF3 daha potent moleküler

RCC berrak hücreli kanserde TKİ+İmmünoterapi/Nivolumab/İpilimumab kombinasyonu standart

RCC berrak hücreli hastalarda 2. ve sonrası Belfuzan+Lenvatinib verileri dikkat çekici

Prostat kanseri izole PSA nüksü yüksek riskli hastalarda yoğun tedavi seçeneği

Kastrasyona dirençli hastalarda özelikle PARP inhibitörleri ve lütesyum kombinasyonları öne çıkıyor

Testis seminom evre IIA/IIB RPLND bir seçenek

Penil kanserde standart kemoterapiye immünoterapi eklemek sağkalımı artırabilir