

Ürogenital Kanserlerde Güncel Moleküler Tedaviler

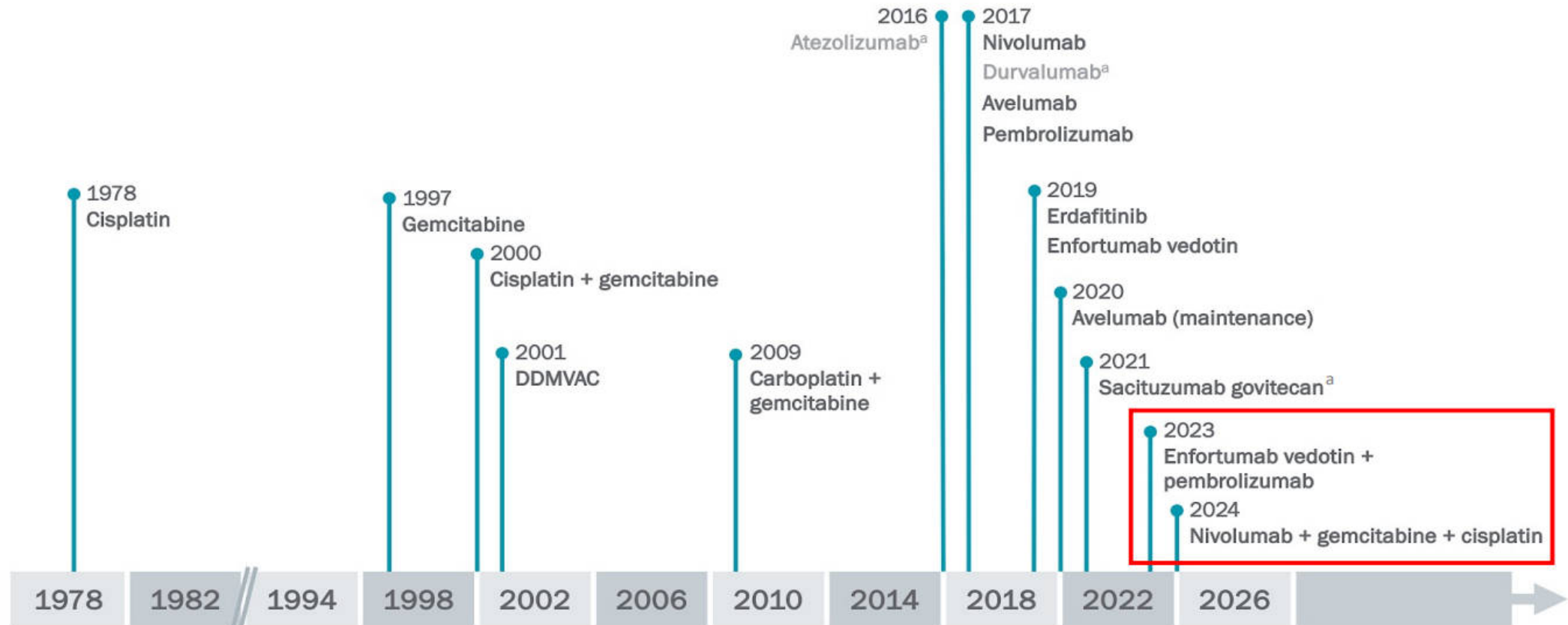
Dr. Deniz Tural
Koç Üniversitesi Hastanesi Medikal Onkoloji

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

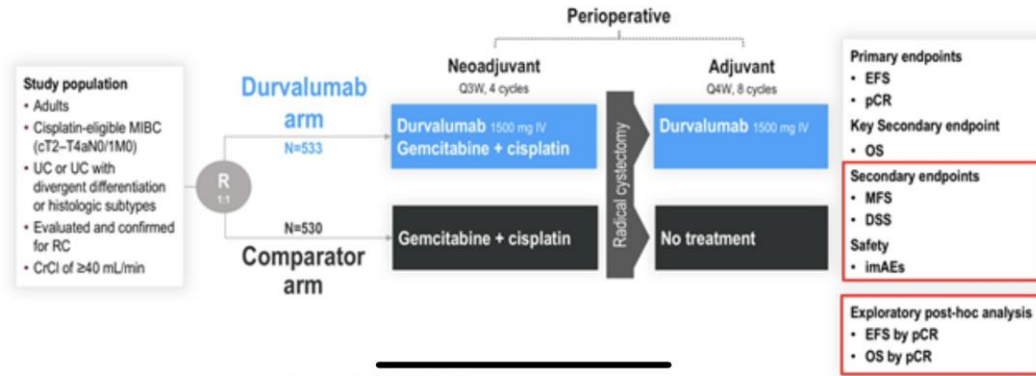
The Treatment Landscape for Ia/mUC has Evolved Rapidly



^a No longer FDA approved; indication withdrawn

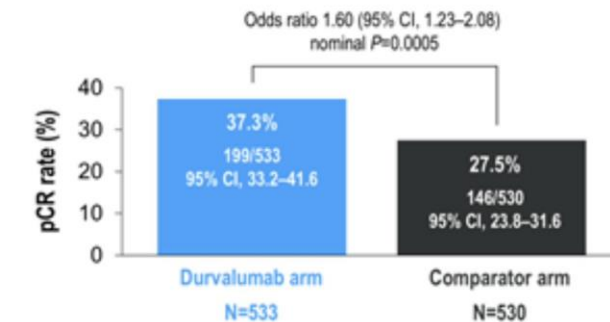
Neoadjuvant Cisplatin+Gemcitabin+İmünoterapi

NIAGARA Study Design



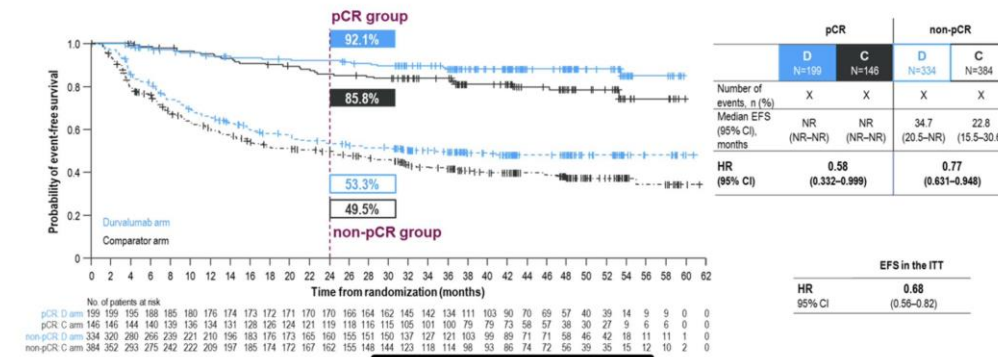
Pathological Complete Response by Central Review (ITT)

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



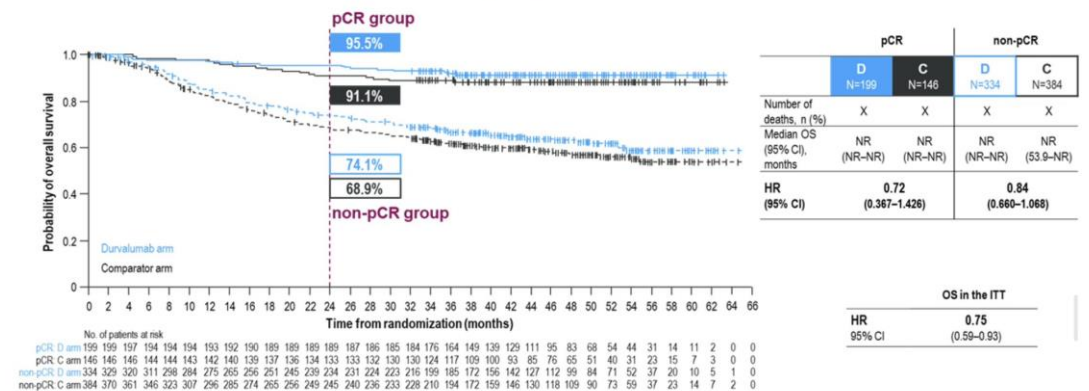
Event-free Survival by Pathologic Staging

Perioperative D + NAC improved EFS in both groups

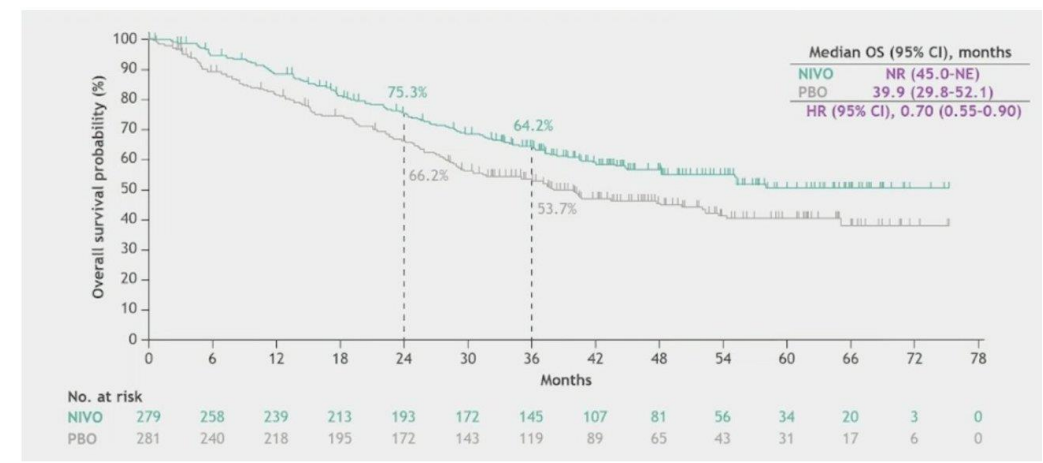
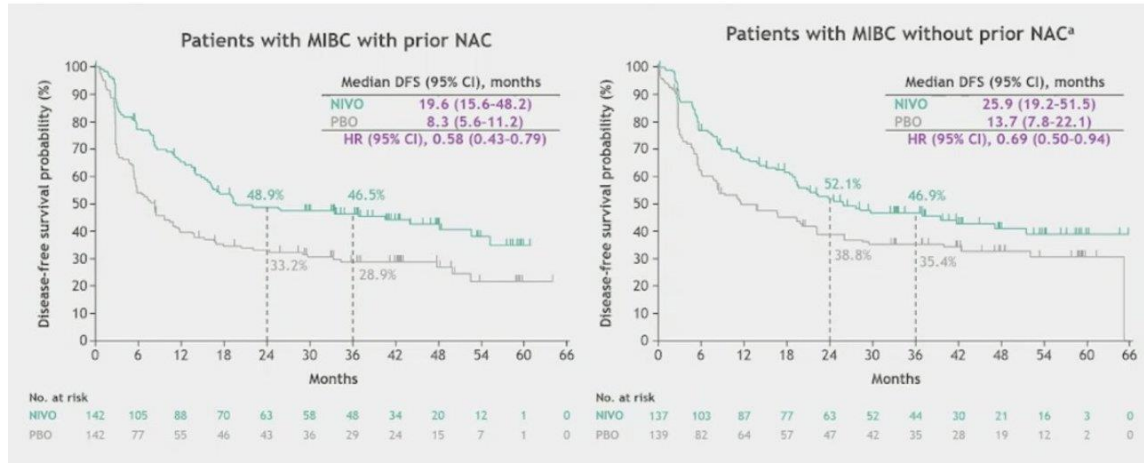
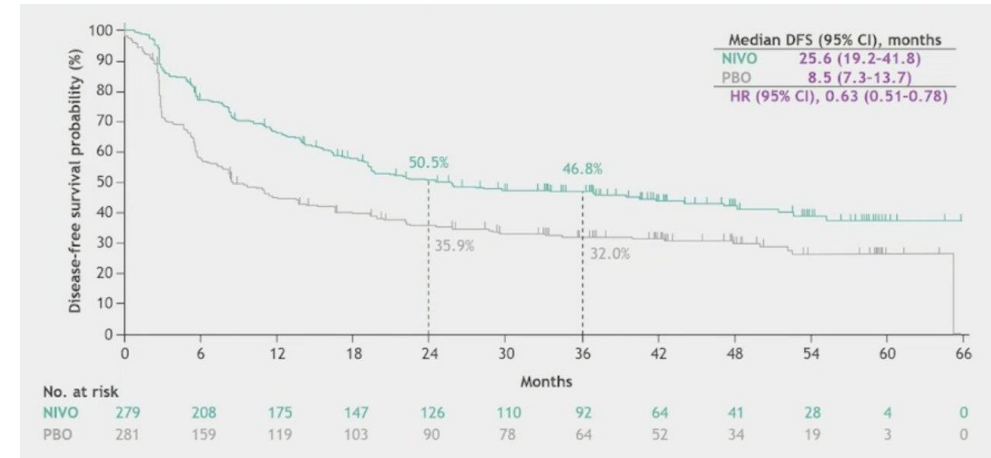
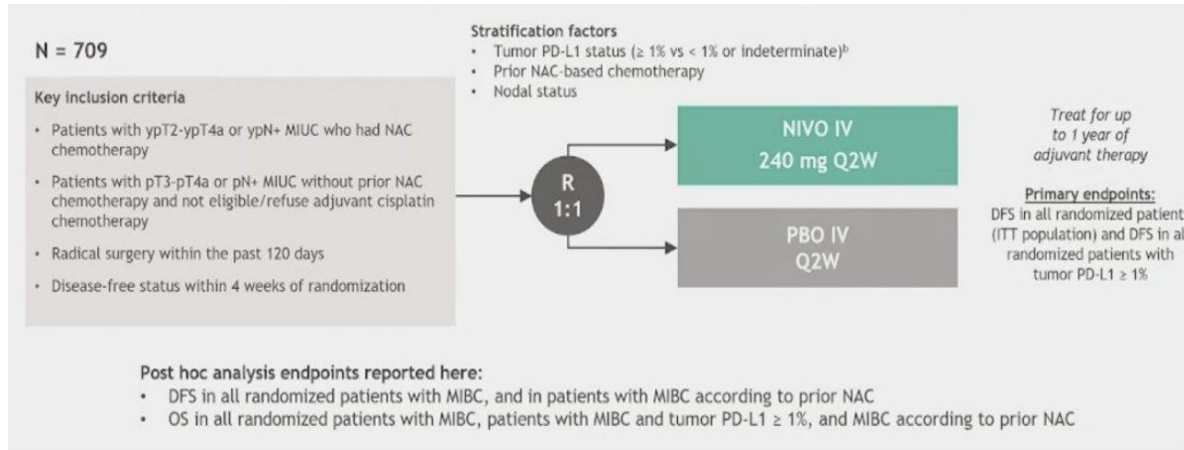


Overall Survival in pCR and Non-pCR Groups

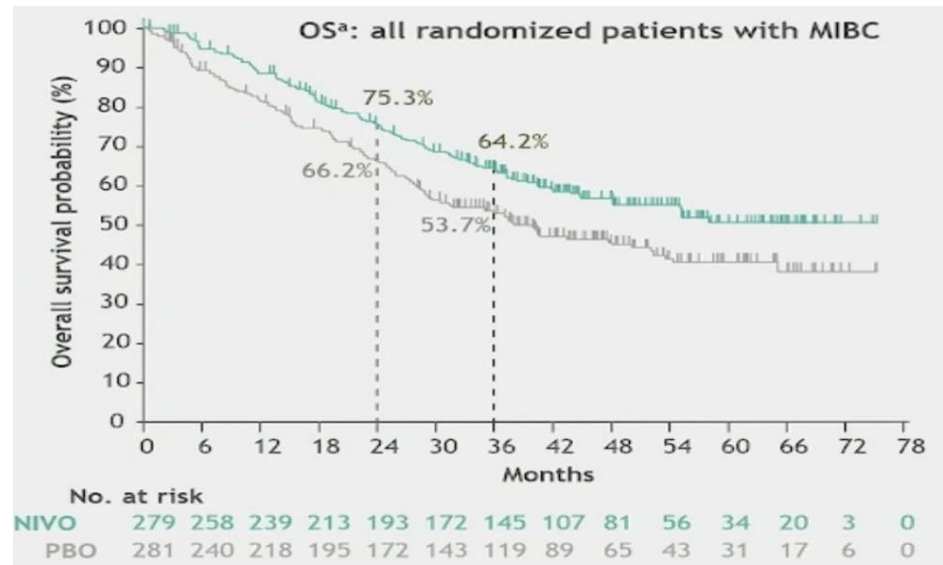
Perioperative D + NAC improved OS in both groups



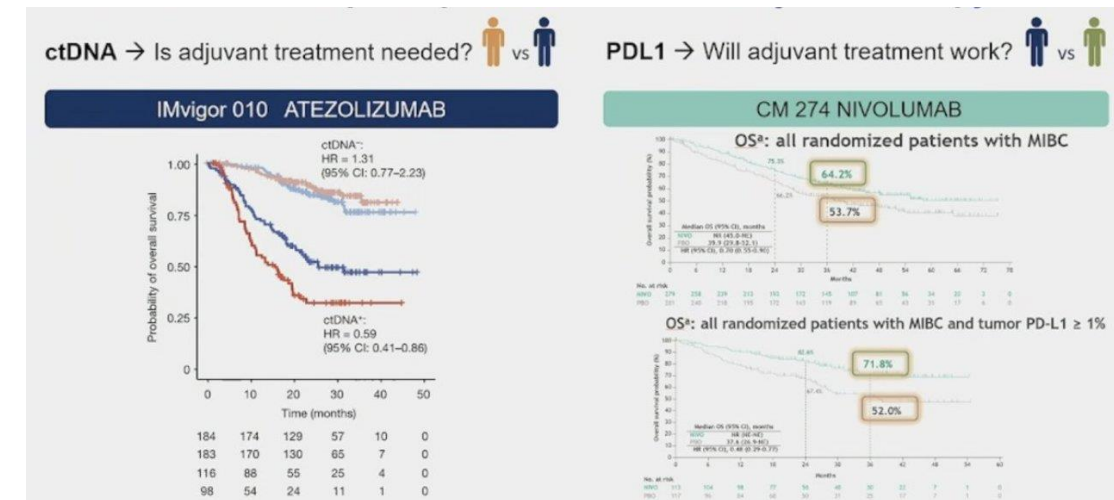
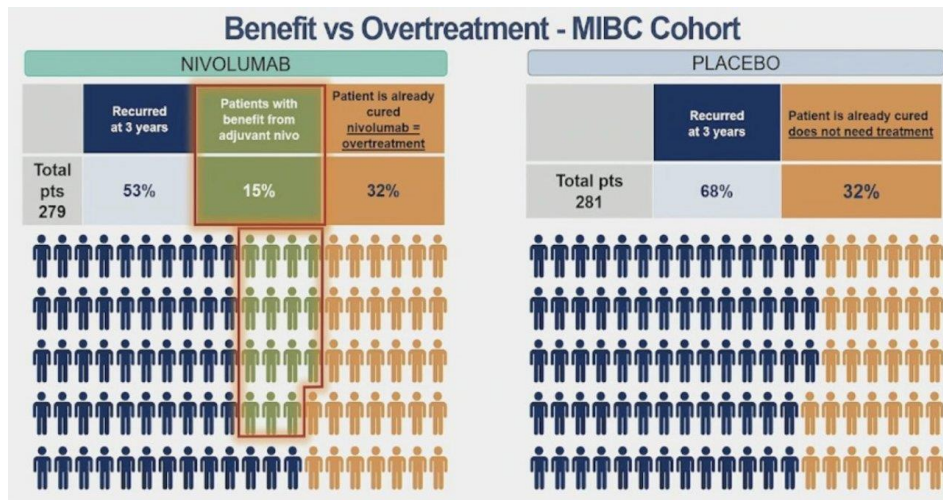
Adjuvan Nivolumab Uzun Dönem Sonuçları



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 2021
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



Nectin-4 Üroteliyal kanserler için hedef molekül

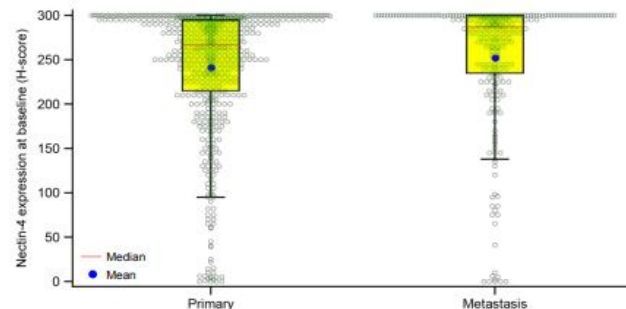
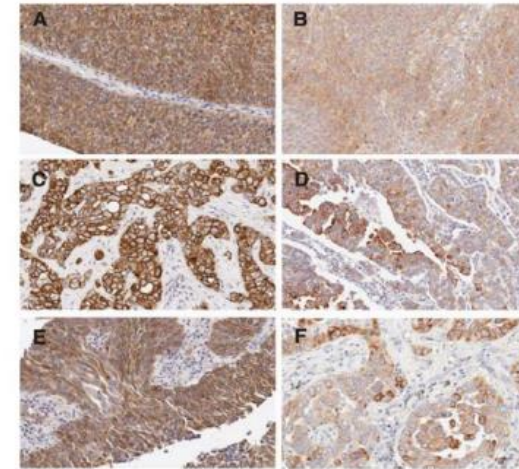
Why target Nectin-4?

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

Bladder Cancer

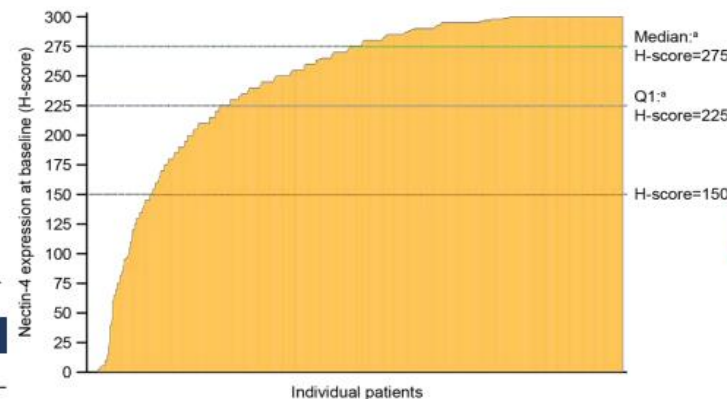
Breast Cancer

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)

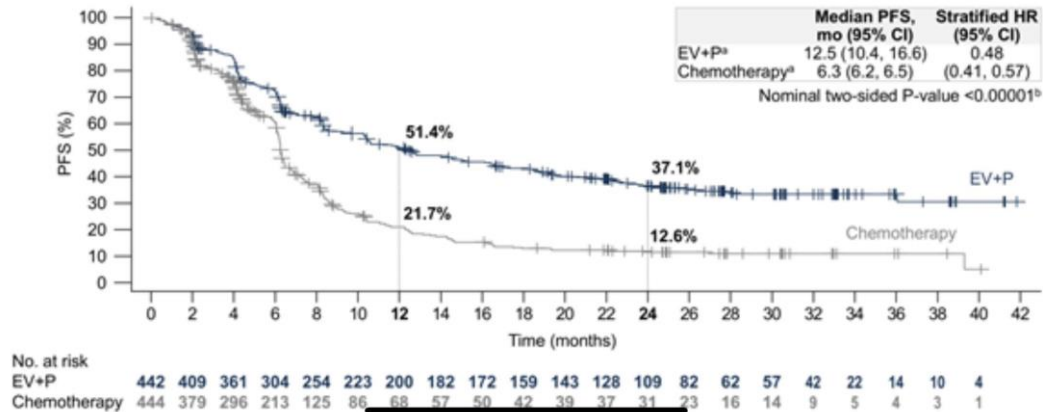


Variable	EV+P (n=394)	Chemotherapy (n=406)
H-score, median (IQR)	280 (230-298)	270 (215-297)
Subgroup, H-score, n (%)		
<150	38 (9.6)	50 (12.3)
≥150 to <225	50 (12.7)	56 (13.8)
≥225	306 (77.7)	300 (73.9)
Patients with H-score 0, n (%)	3 (0.8)	6 (1.5)

Enfortumab ve pembrolizumab kombinasyonu uzun dönem sonuçları

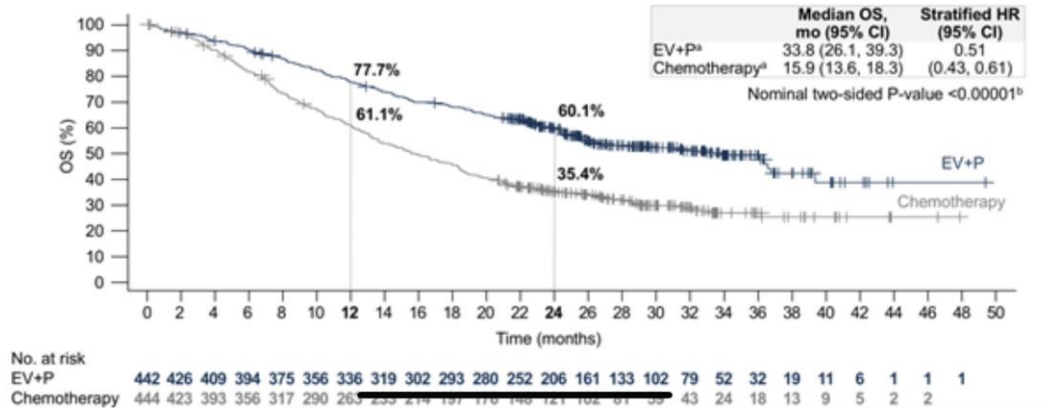
PFS by BICR in the Overall Population

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



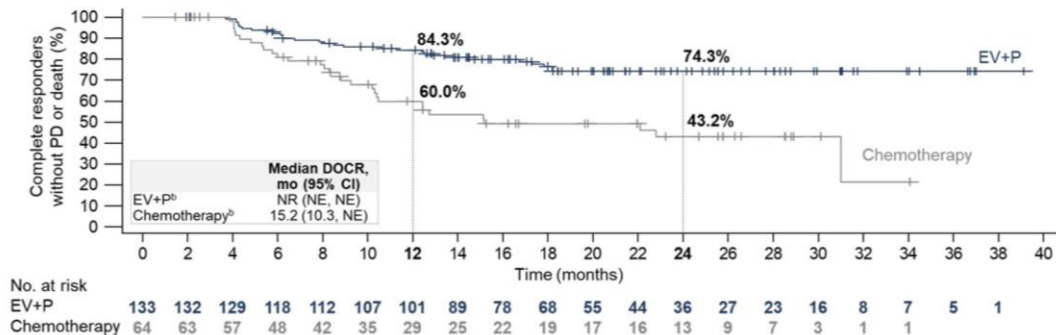
OS in the Overall Population

Risk of death was reduced by almost 50%



Duration of Confirmed Completed Response (cCR)^a by BICR

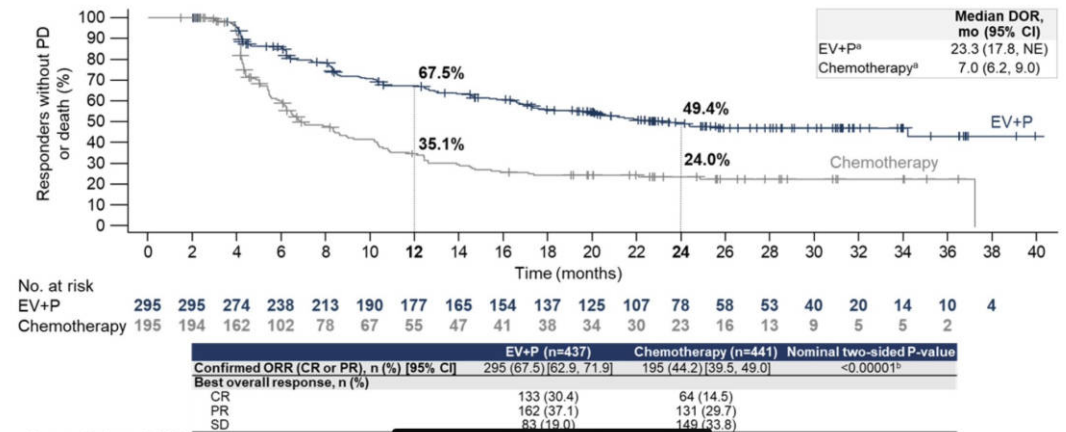
Probability of maintained CR at 24 months was 74% with EV+P



- 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

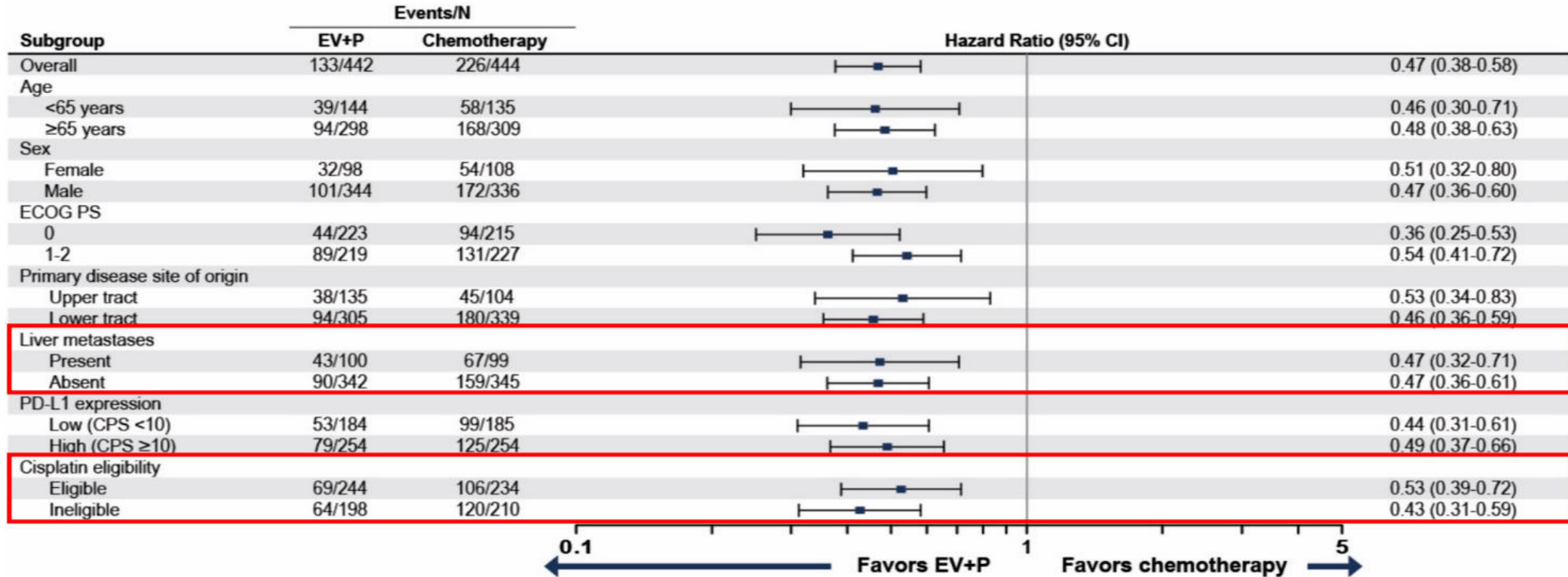
Among responders, the probability of maintained response at 24 months was ~50% with EV+P



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



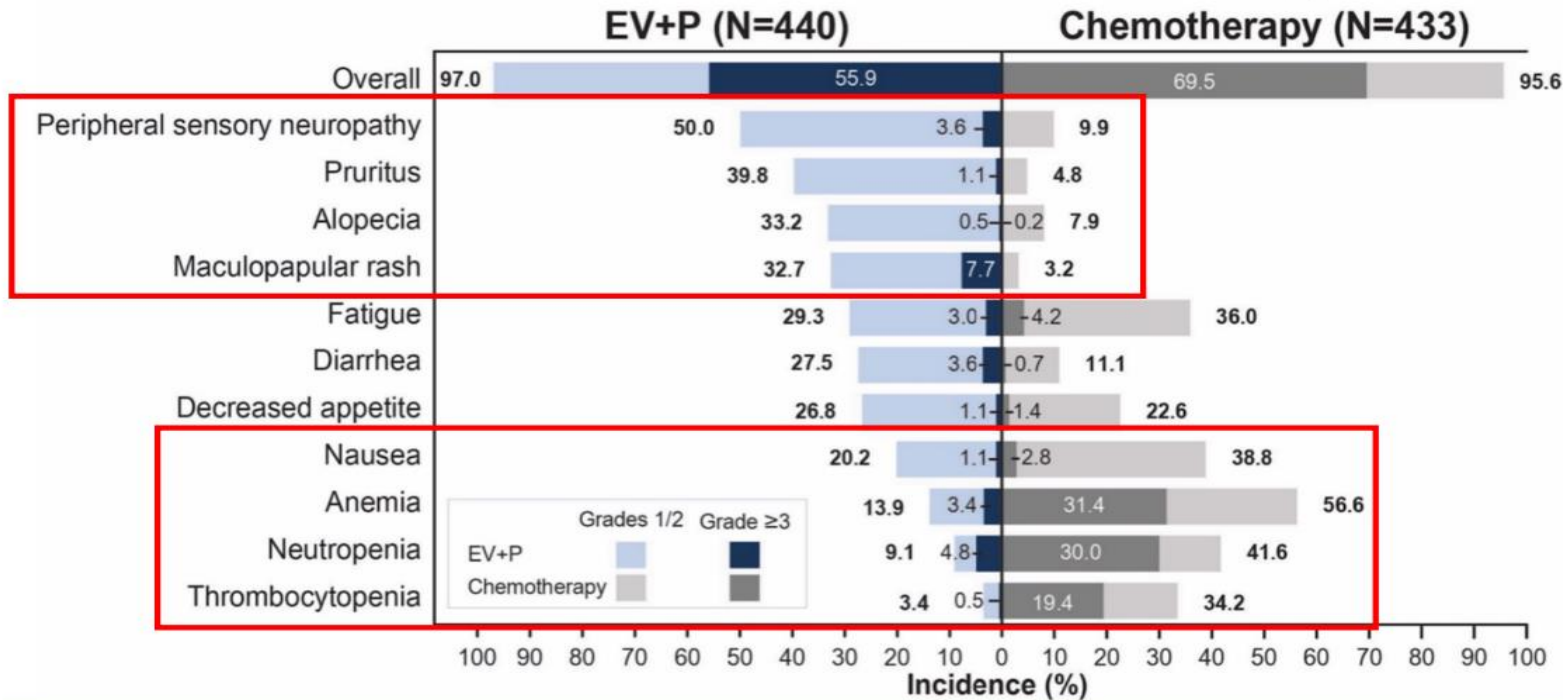
CPS, Combined Positive Score; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EV+P, enfortumab vedotin + pembrolizumab; OS, overall survival; PD-L1, Programmed death-ligand 1. Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential 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

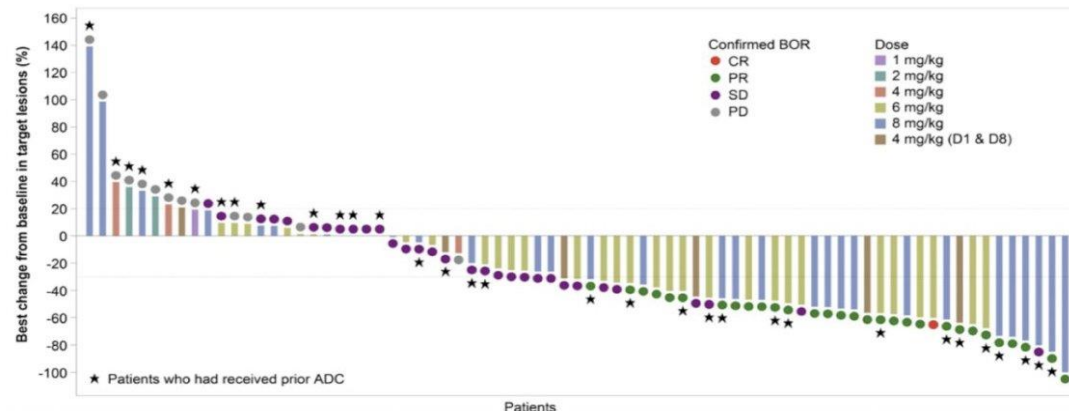
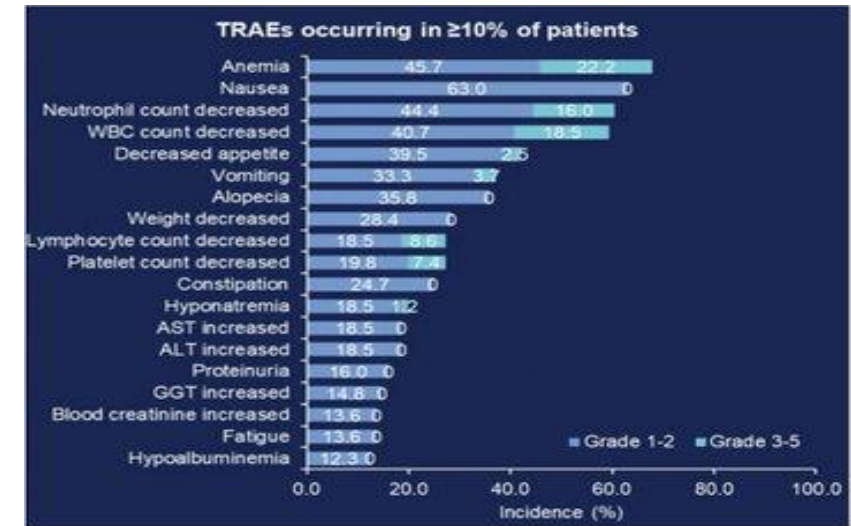
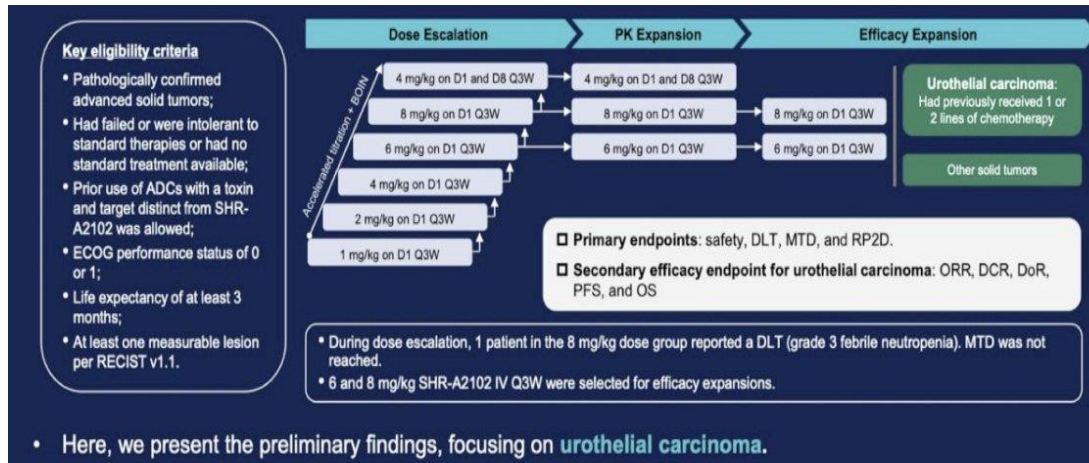
EV+P, enfortumab vedotin + pembrolizumab; TRAEs, treatment-related adverse events.

TRAEs shown in figure are any grade by preferred term in $\geq 20\%$ of patients for any grade in either arm.

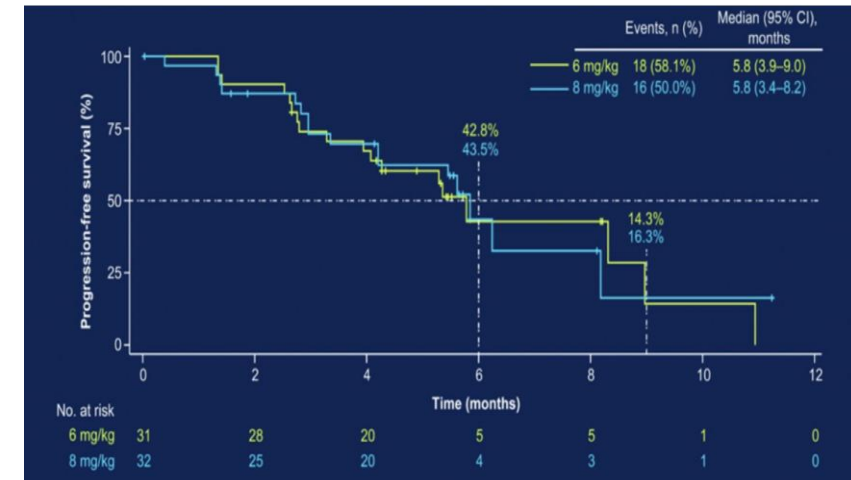
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation) Powles et al. NEJM, 2024.

Data cutoff: 08 Aug 2023

Yeni Nectin-4(SHR-A2102) Tedavi Seçenekleri

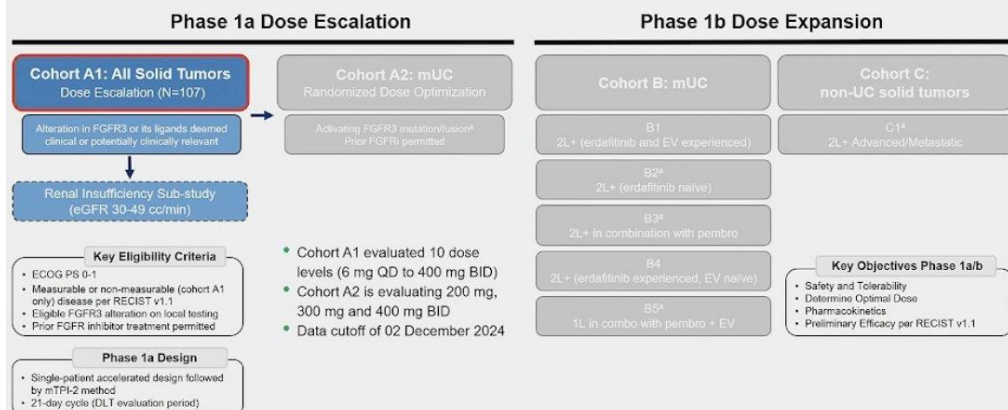


	6 mg/kg (N=31)	8 mg/kg (N=32)	4 mg/kg (D1 & D8) (N=11)	All (N=81)
ORR, % (95% CI)	41.9% (24.5–60.9)	50.0% (31.9–68.1)	18.2% (2.3–51.8)	38.3% (27.7–49.7)
DCR, % (95% CI)	90.3% (74.3–98.0)	84.4% (67.2–94.7)	54.5% (23.4–83.3)	76.5% (65.8–85.3)



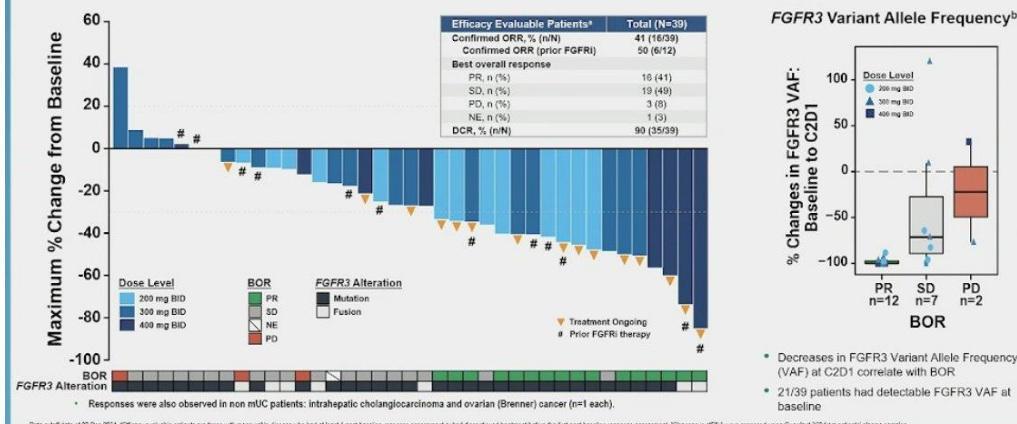
Yeni Potent FGFR3 İnhibitörleri

FORAGER-1 Study Design, Eligibility, Objectives



*Oncogenically reconstituted (over expression) equivalent activating alterations in non-canonical alternative isoforms of EGFR are omitted in consultation with factor IV, as follows within nTP-2: modified tyrosine antibody internal control, peribulbular, NCT05614739

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



Safety

Treatment-Emergent AEs ≥20%				
	All Patients (N=107)		200 mg, 300 mg, 400 mg B (n=70)	
All TEAEs, %	Any Grade	Grade ≥3	Any Grade	Grade ≥3
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	

Data cutoff date of 12 Dec 2004. Safety was evaluated across all patients treated, regardless of dose or tumor type. Includes rash, dry skin, PPE, sinus nasopharyngitis, alopecia, pruritus, dehydration, skin night sweats, skin fissures, blister, dermatitis, acneiform dermatitis, hyperhidrosis, hyperkeratosis, neurodermatitis, subconjunctival dermatitis, and skin disc. ¹¹ Patients received pharmacologic intervention. ¹² at 200 mg, ¹³ at 300 mg, ¹⁴ at 400 mg. Includes sinus flared, dry eye, blepharitis, eye pain, blepharitis, lacrimation increased, ocular hyperemia, retinal hemorrhage, abnormal tearage, abnormal dry eye, swelling of eyelid, vision blurry decreased, and vision focus altered. ¹⁵ 4 patients had grade 4 events. ¹⁶ ALT/AST increased, hypotension, hypokalemia, hypophosphatemia, and neutrophil count decreased. ² unexplained weight events occurred – weight loss and weight gain. Includes laboratory abnormalities, and events. ¹⁷ ALT/AST increased in 2, diarrhea in 2, and constipation in 2. Most common reasons for dose reduction: ALT, alkaline phosphatase, AST, acetaminophen toxicity, sinus disease, and cytarabine toxicity.

- 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 erdafitinib¹ were very rare
 - Dose reductions/discontinuations were uncommon²

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

Datopotamab-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 Garnezy,⁴ Takahiro Kogawa,⁵ Alexander Spira,⁶ Mohamad Salkeni,⁶ Xin Gao,⁷ Anthony Tolcher,⁸ Manali Bhawe,⁹ Deborah Doroshow,¹⁰ Jeannie Hoffman-Censits,¹¹ Gunnar Klauß,¹² Yoshiaki Kaga,¹³ Yasuyuki Kakurai,¹⁴ Takahiro Kojima¹⁵

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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 linker¹
- 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*)

- 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, 0.0-29.2). *Evaluated per RECIST v1.1.1. Ochiai D, et al. Mol Cancer Ther. 2021;20:2329-40.

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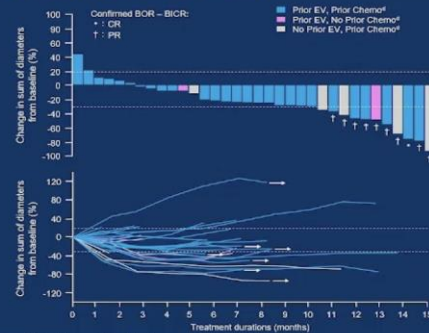
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Response and Change in Tumor Burden

Response by BICR*	Dato-DXd (N=40)
ORR ^a , n (%) [95% CI]	10 (25.0) [12.7-41.2]
DCR ^a , 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

BICR, best overall response; CI, confidence interval; CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease. *Evaluated by BICR per RECIST v1.1.1. ^aResponses with confirmation of CR/PR. ^bCR + PR + SD + non-CR/non-PD. ^cAll patients received prior immunotherapy.



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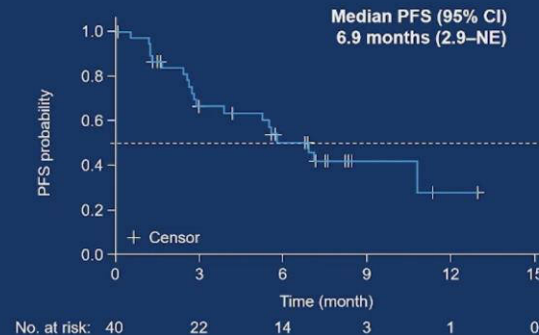
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Progression-Free Survival



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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%)

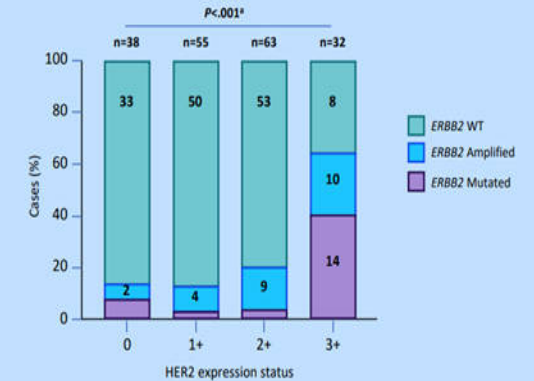
*Dako HercepTest system

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

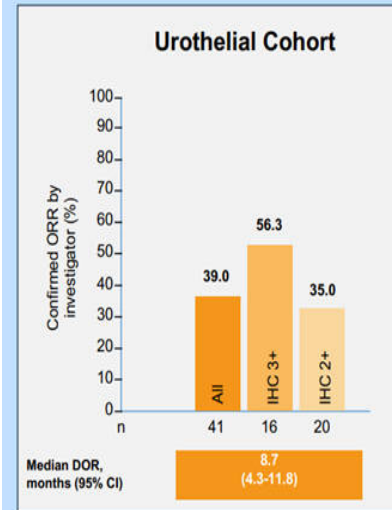
Aggen et al, ASCO GU 2023

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



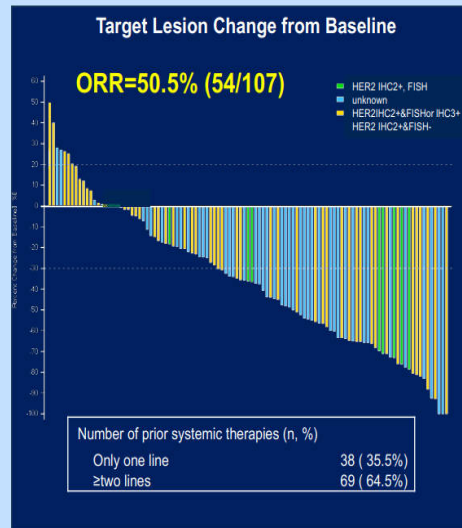
All Patients

	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

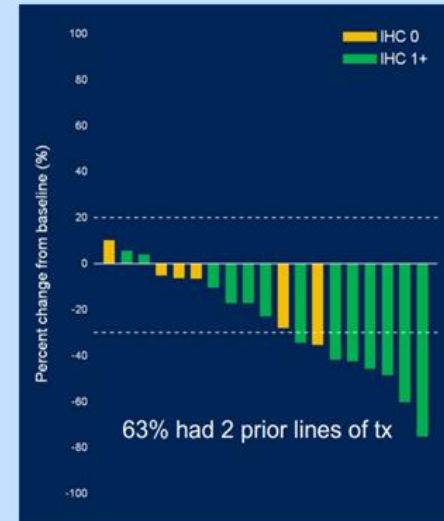
RC48 (Disitamab Vedotin) in HER2 2-3+ mUC



Subgroups	cORR (% , 95% CI)
<i>HER2 status</i>	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
<i>Metastasis site</i>	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
<i>Prior therapies</i>	
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

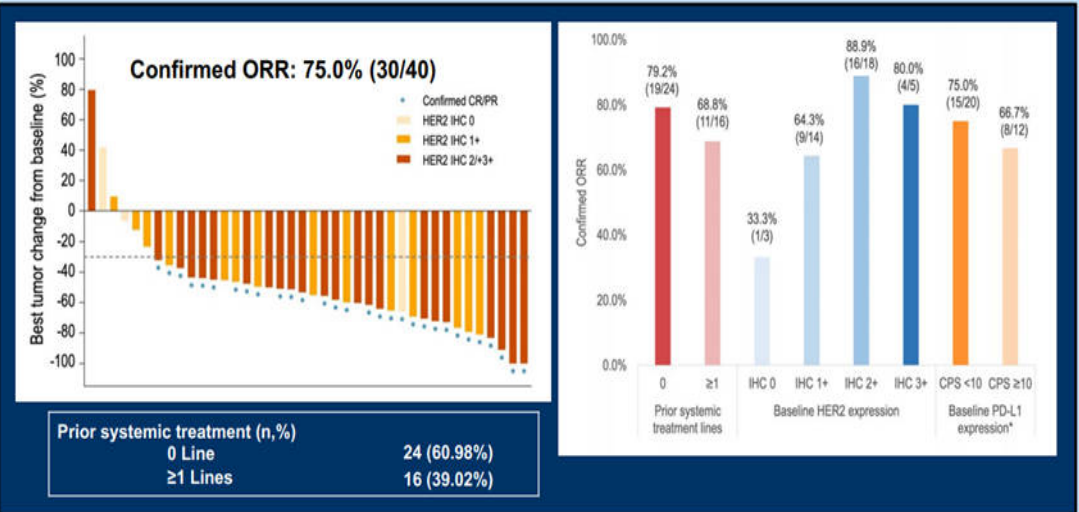
Trastuzumab Deruxtecan + Nivolumab

	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	3.9 (1-21)	–
T-DXd	4.1 (1-20)	–
Nivolumab		

- **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



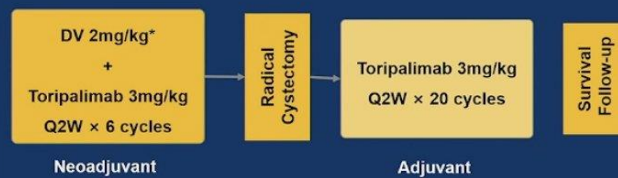
Zhou et al, ESMO, 2024

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 $\geq$ 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).

Pathological tumor response was assessed by the local pathologists and investigators based on the postoperative pathology. Radiological assessment was performed by the investigators per RECIST v1.1. [#]Operative status of T3/T4a using the local urologist's assessment. [^]OS data was not mature and not reported here. 1. Sheng, et al. J Clin Oncol. 2024. 42(11_suppl):4588.

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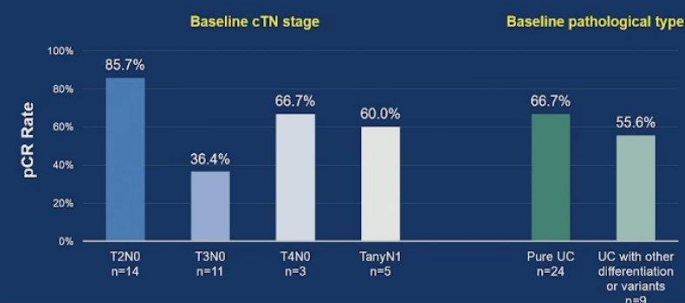
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Subgroup analysis

- 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.



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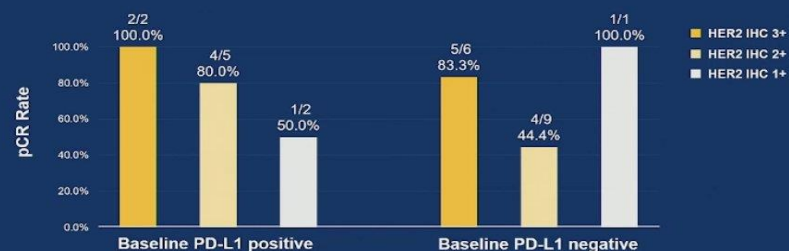
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Subgroup analysis

- 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.



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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.

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Kombinasyon Tedavileri

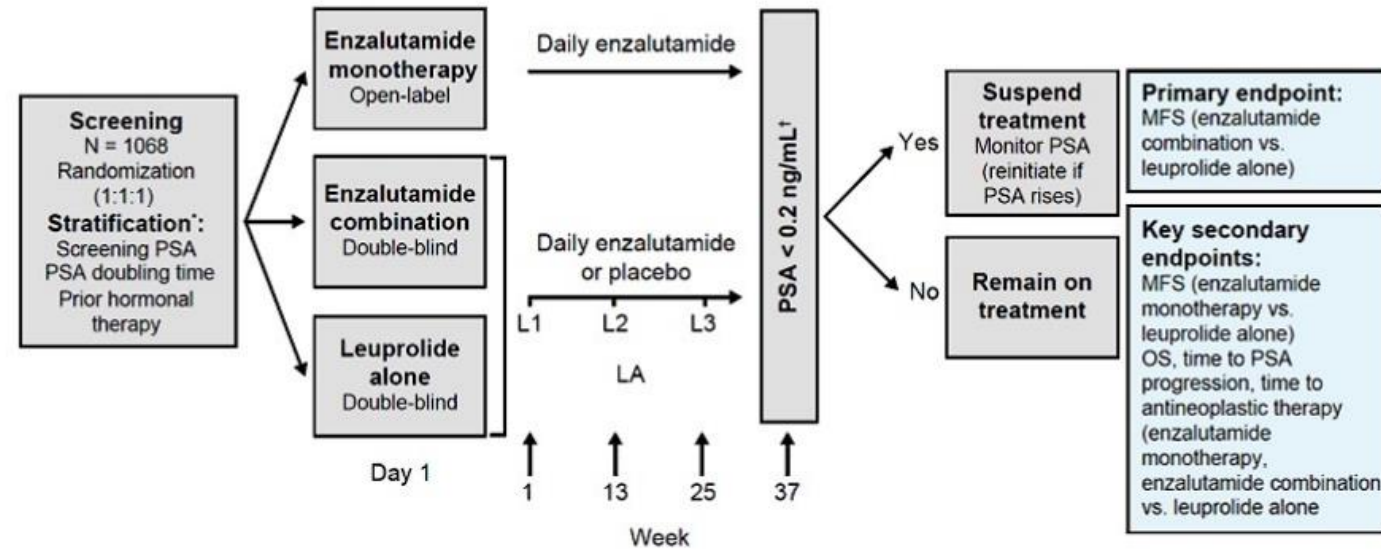
Selected Ongoing Trials of ADCs + Immunotherapy in mUC					
Treatments	Alias	Ph	Population	Primary Endpoint	NCT Number
Disitamab Vedotin + Pembrolizumab	DV-001	III	1 st line HER2+	PFS, OS	NCT05911295
Disitamab Vedotin + Toripalimab		III	1 st line HER2+	PFS, OS	NCT05302284
Zelenectide Pevedotin + Pembro	DURAVELO-2	III	1 st line	PFS	NCT06225596
EV + SG + Pembrolizumab	DAD-IO	II	1 st line	ORR	NCT04724018
Datopotamab-DXd + Volrustomig or Rilvegostomig	TROPION-Pan Tumor 03	II	1 st or 2 nd line	ORR, AEs	NCT05489211
SG + Avelumab	JAVELIN Bl. Medley	II	1 st line	PFS, AEs	NCT05327530
EV + Pembro + Sacituzumab TMT or investigational agents	KEYMAKER-U04	I/II	1 st 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	1 st 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 NO
MO 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.

Prostat Kanseri izole PSA nüksü

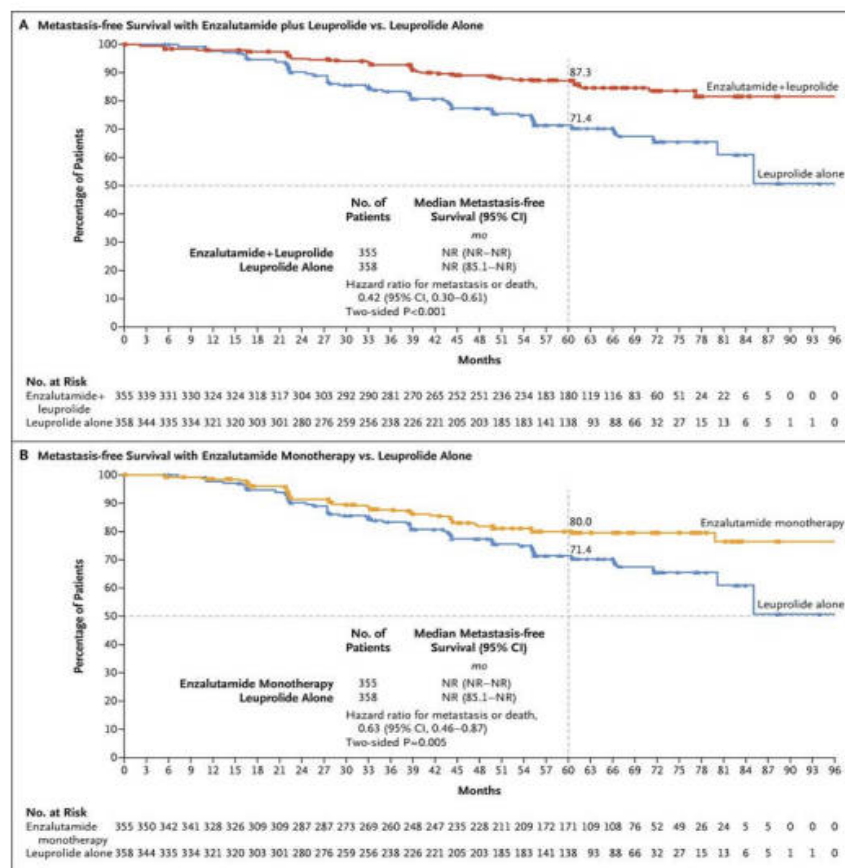
Biochemically recurrent prostate cancer: EMBARK

87 v 71% MFS at 5 years

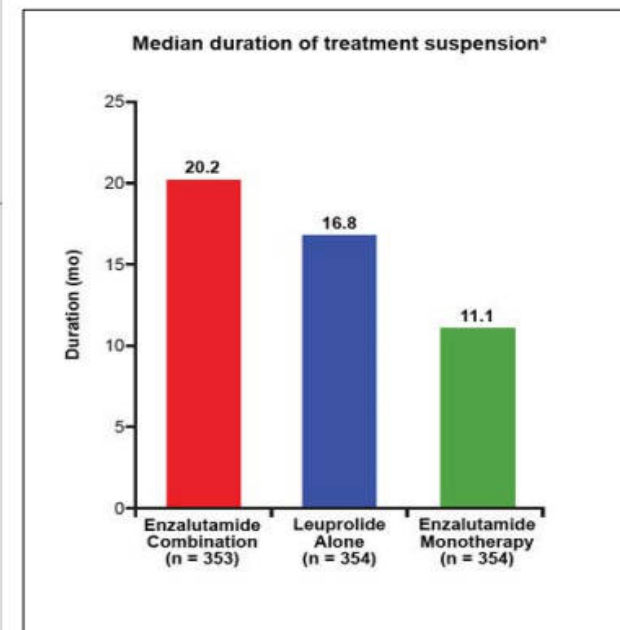
If PSA undetectable
(<0.2 ng/mL) at week 36,
treatment was held – resumed
when PSA >5 (RT)
or >2 (surgery)

80 v 71% MFS at 5 years

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



ADT alone – 50% without metastasis at 8 years

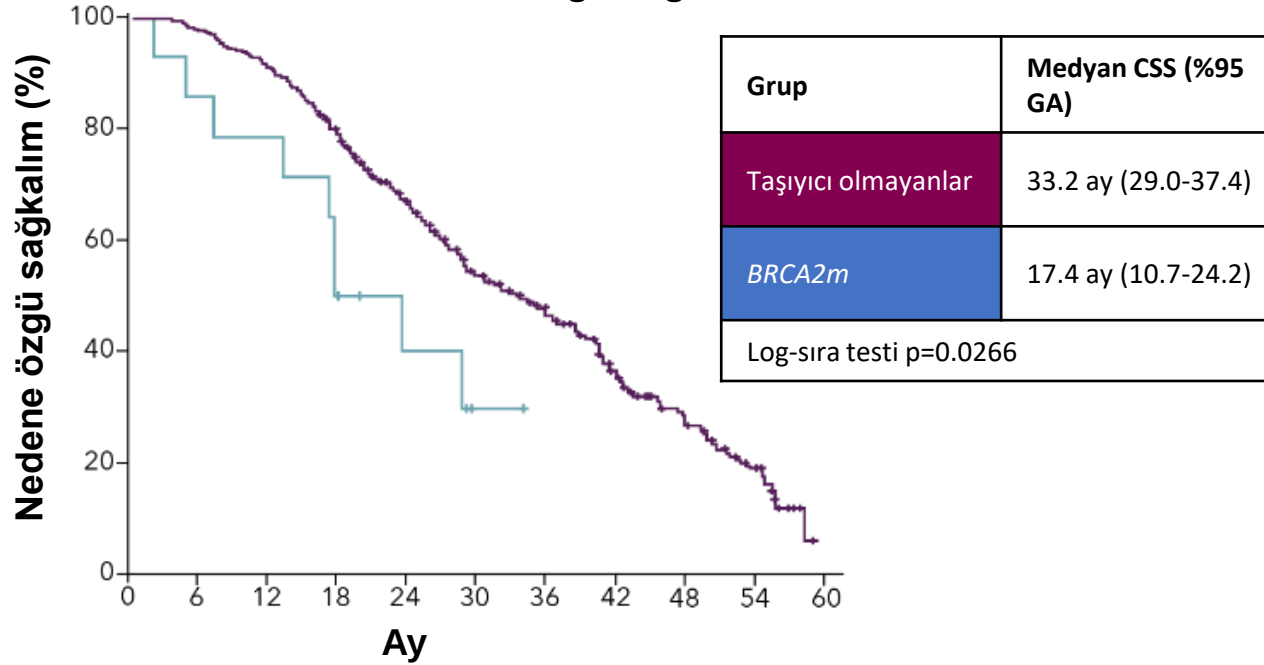


BRCA2 mutasyonu dahil HRR mutasyonu izlenen hastalarda standart tedavilerle Cevap daha kötü

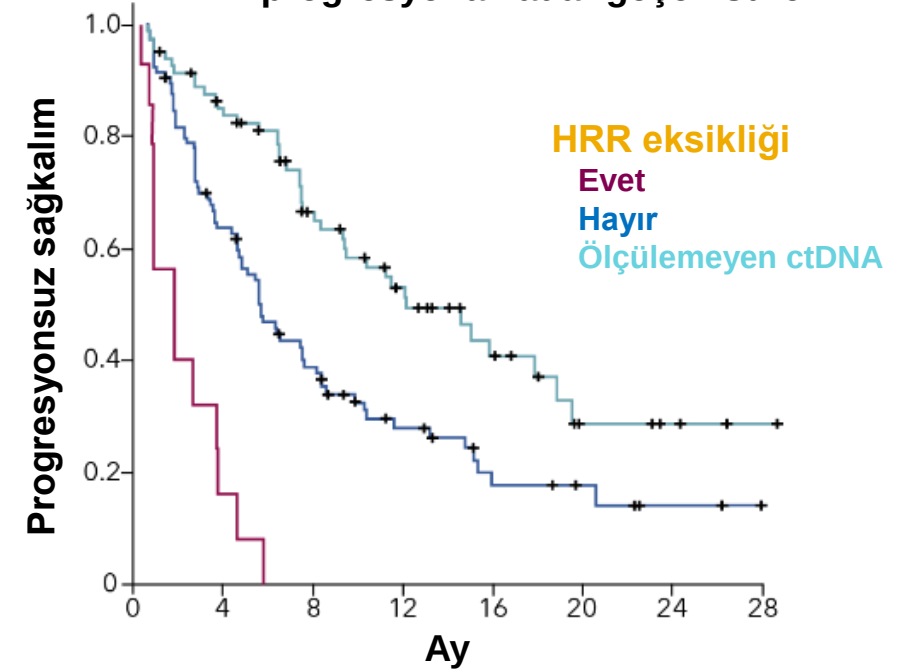
BRCA2m dahil germ hattı HRRm izlenen hastalarda standart tedavilerle olumsuz sonuç olasılığı daha yüksektir^{1,2}

Tümör HRRm için de standart tedaviye olumsuz yanıt görülmüştür³

gBRCA2m izlenen mKDPK hastalarında kansere özgü sağkalım¹



HRRm izlenen mKDPK hastalarında progresyona kadar geçen süre³



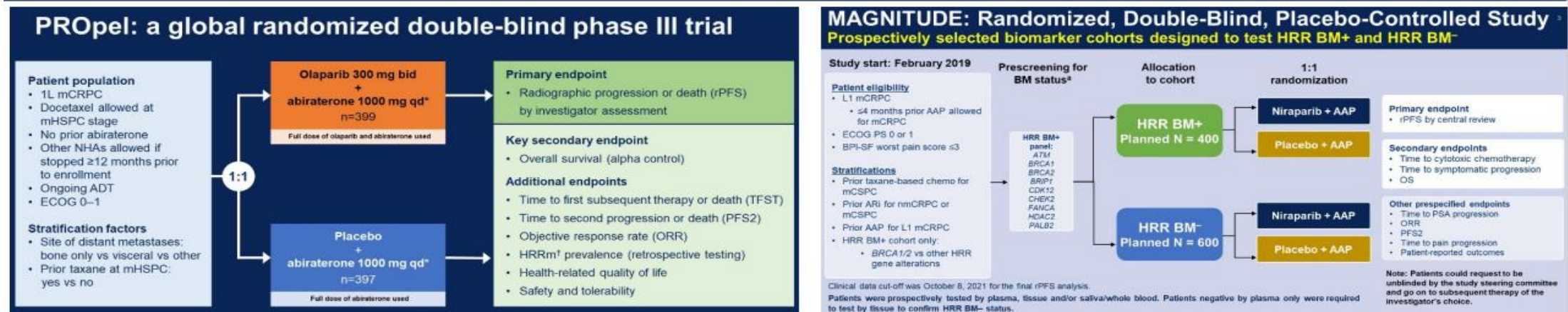
ATM=ataksi telenjektazi mutasyonlu; BRCA1/2=meme kanseri geni 1/2; BRCA2m=meme kanseri geni 2 mutasyonu; CSS=nedene özgü sağkalım;

gBRCAm=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

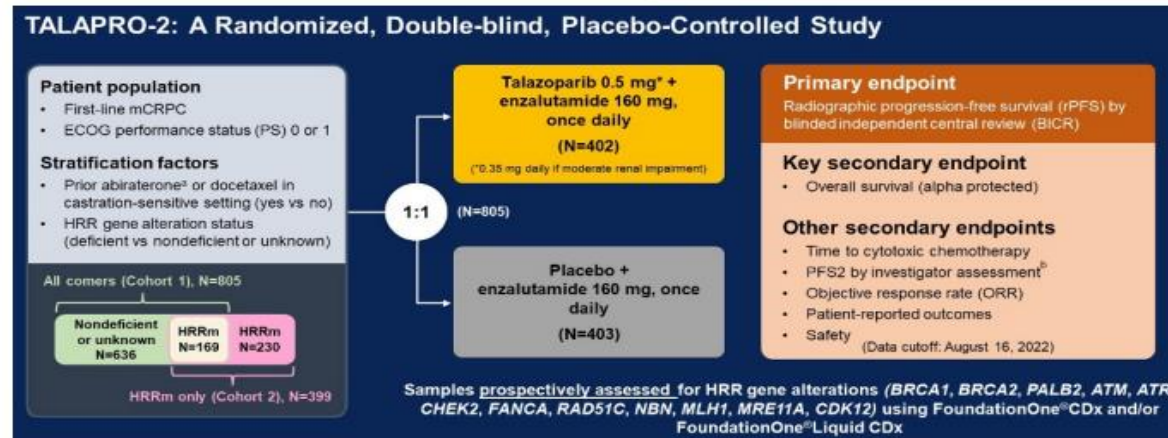
Kastrasyona Dirençli Prostat Kanserinde PARP inhibitörler ve Yeni nesil androjen reseptör blokörleri

Phase 3 PARPi + ARPI Trials Design



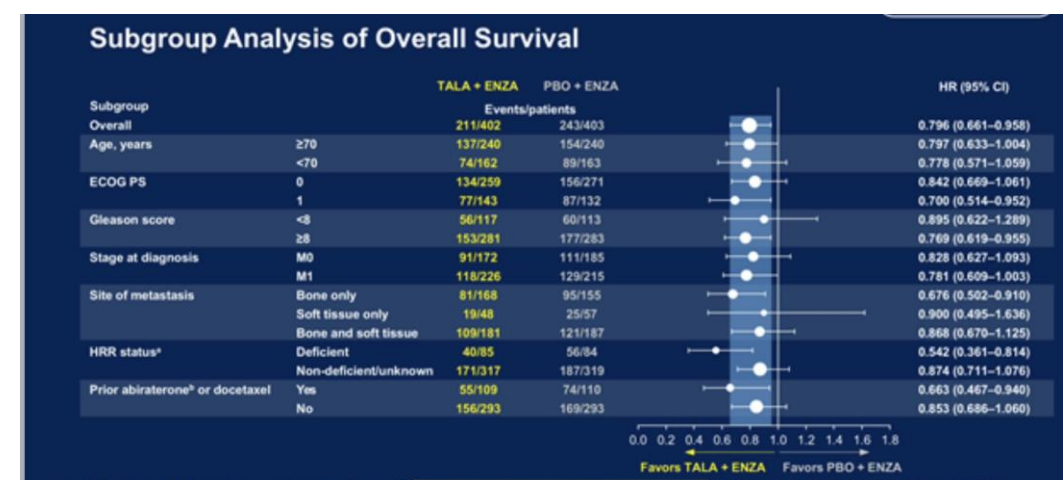
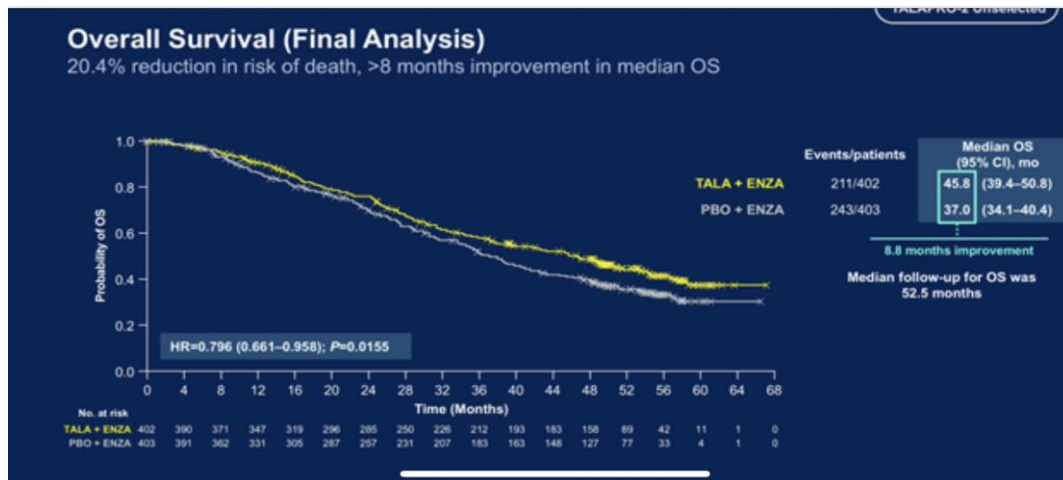
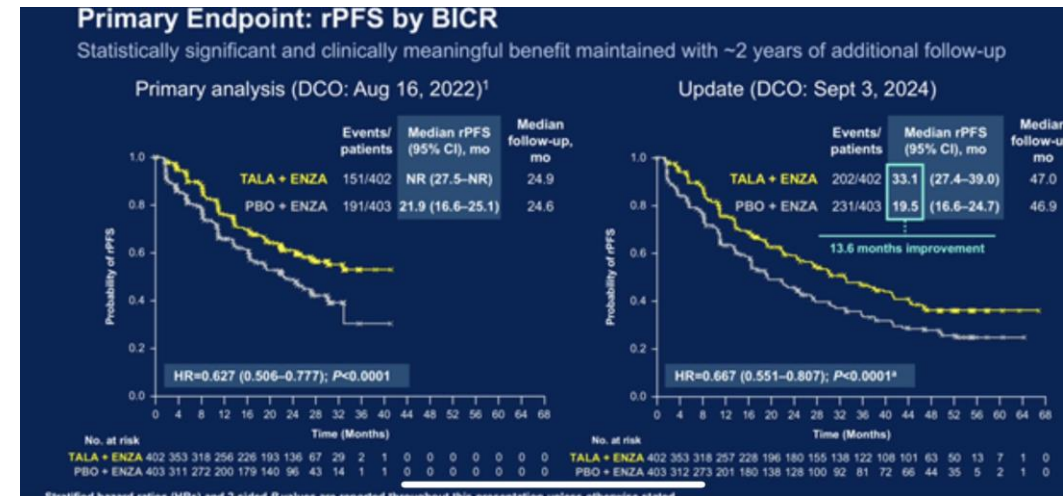
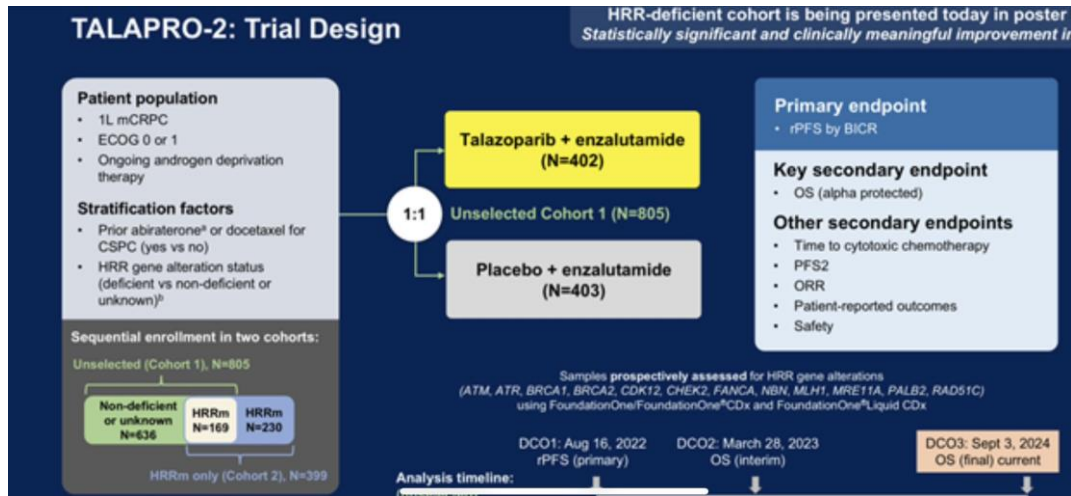
Clarke, NW. et al. *NEJM Evidence*, 2022

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



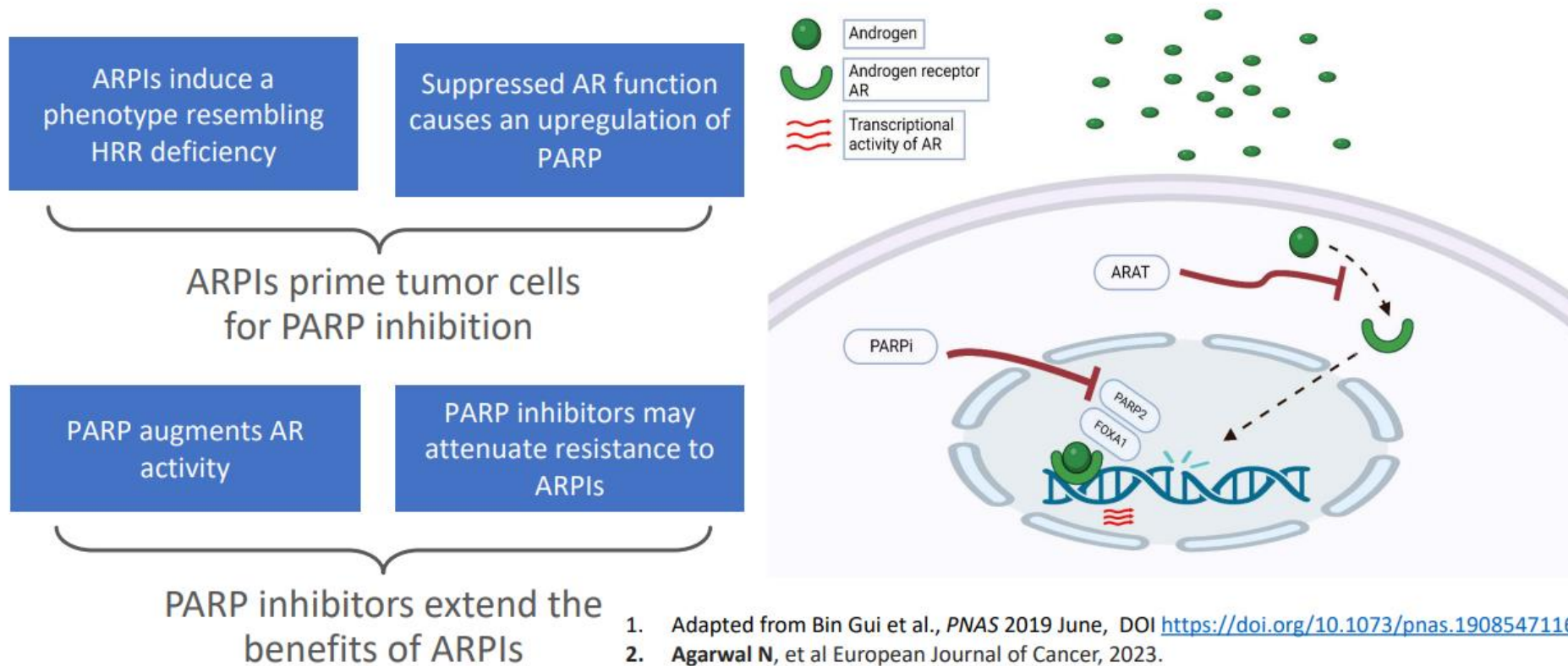
Agarwal, N. et al. *Lancet*, 2023.

TALAPRO-2 Uzun Dönem Sonuçları



PARP inhibitörü+ ARPi kombinasyonu

The rationale for combining PARPi with ARPi



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 ⁶⁸Ga PSMA PET/CT

Stratification

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

R 1:1

Enzalutamide 160 mg

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

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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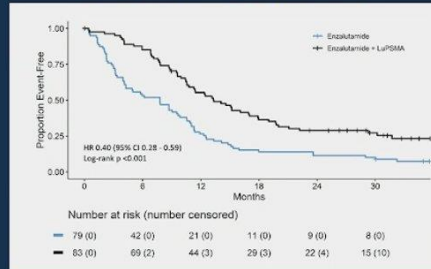
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Progression Free Survival

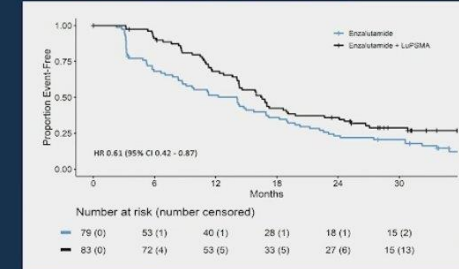
PSA-PFS

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



R-PFS

HR 0.61 (95% CI 0.42-0.87)



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

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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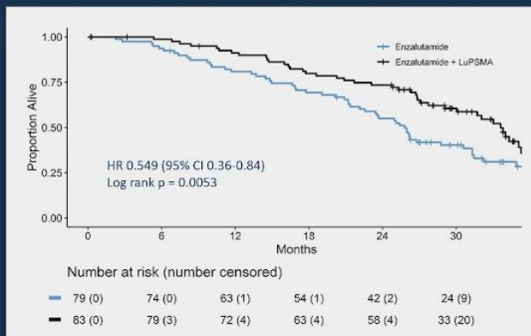
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Overall Survival



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

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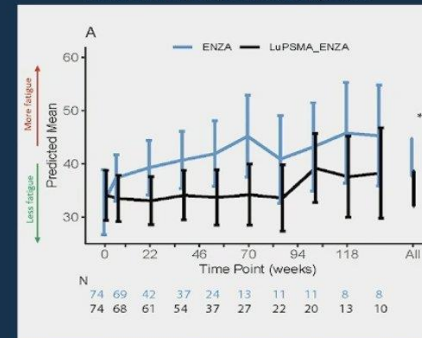
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Health-Related Quality of Life

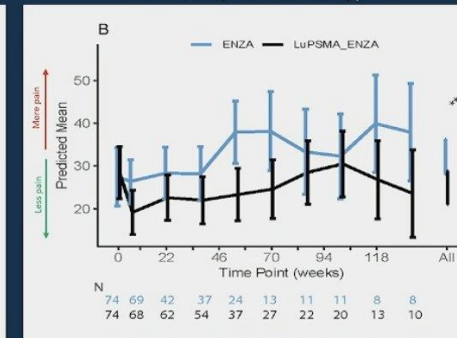
Fatigue

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 inhibitörü) +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[†]
- PSA₅₀
- 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; PSA₅₀, 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

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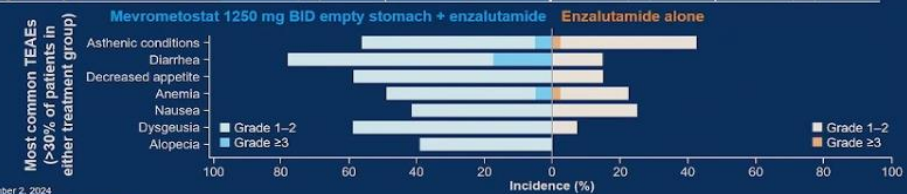
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Safety summary

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

Event, n (%)	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41)		Enzalutamide alone (n=40)	
	All grades	Grade ≥3	All grades	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

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Key findings



Slide
deck
and MOA



Plain
Language
Summary

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- 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 11:26 AM–2:45 PM and 5:45–6:45 PM (Poster D20)

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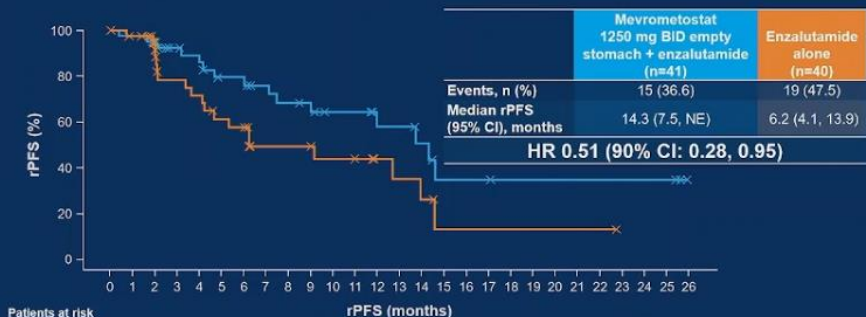
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Primary endpoint: rPFS by investigator

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



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

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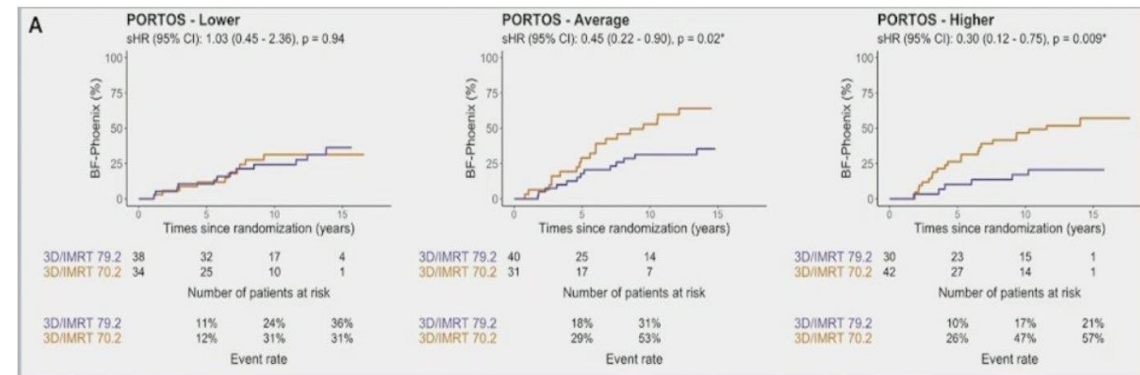
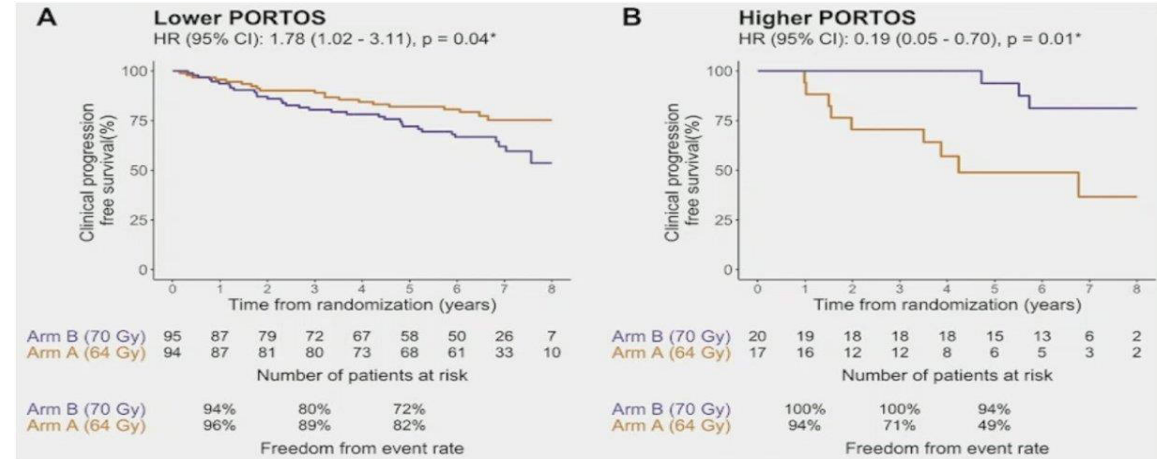
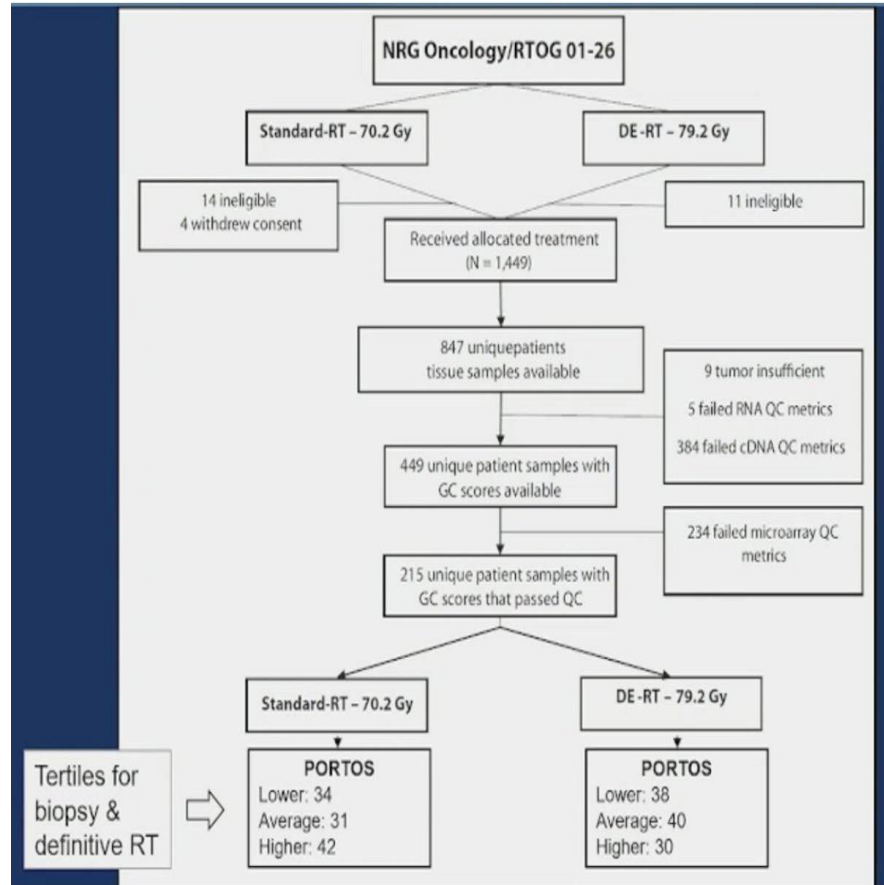
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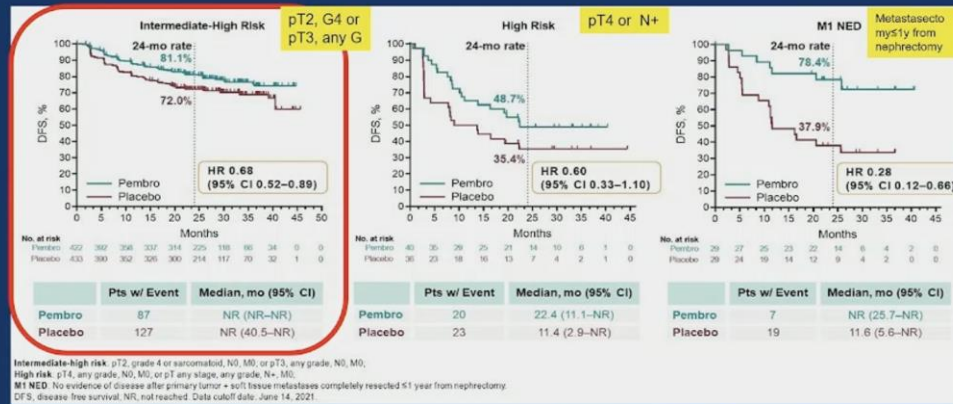
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Gene Skoruna Göre Prostat Kanserinde Tedavi Modifikasyonu



RCC Adjuvan Tedavi

What benefit to expect from adjuvant pembrolizumab?



Choueiri et al. ASCO 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

Original research
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	
	Any grade	Grade 3-5	Any grade	Grade 3-5
All immune-mediated AEs	352 (16.9)	2 (0.1)	76 (3.7)	0 (0)
Hypothyroidism	227 (11.0)	3 (0.1)	27 (1.3)	0 (0)
Hyperthyroidism	52 (2.5)	17 (0.8)	29 (1.4)	4 (0.2)
Pneumonitis	62 (3.0)	29 (1.4)	14 (0.7)	2 (0.1)
Colitis	44 (2.1)	35 (1.6)	9 (0.4)	7 (0.3)
Severe skin reactions	35 (1.6)	16 (0.8)	5 (0.2)	1 (<0.1)
Adrenal insufficiency	34 (1.7)	2 (0.1)	6 (0.3)	0
Thyroiditis	35 (1.7)	29 (1.4)	6 (0.4)	5 (0.2)
Hepatitis	32 (1.6)	11 (0.5)	1 (<0.1)	0 (0)
Hypophysitis	17 (0.8)	17 (0.8)	0 (0)	0 (0)
Type 1 diabetes mellitus	17 (0.8)	1 (<0.1)	0 (0)	0 (0)
Sarcoidosis	16 (0.8)	6 (0.3)	1 (<0.1)	0 (0)
Nephritis	10 (0.5)	4 (0.2)	3 (0.1)	0 (0)
Myositis	6 (0.3)	3 (0.1)	3 (0.1)	2 (0.1)
Pancreatitis	7 (0.3)	6 (0.3)	2 (0.1)	2 (0.1)
Myocarditis	6 (0.3)	2 (0.1)	0 (0)	0 (0)
Myasthenic syndrome	3 (0.1)	2 (0.1)	0 (0)	0 (0)
Vasculitis	3 (0.1)	0 (0)	1 (<0.1)	0 (0)
Uveitis	1 (<0.1)	1 (<0.1)	0 (0)	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.

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

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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



© Zaid T. et al. Eur Urol. 2024 Oct;86(5):552-512

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

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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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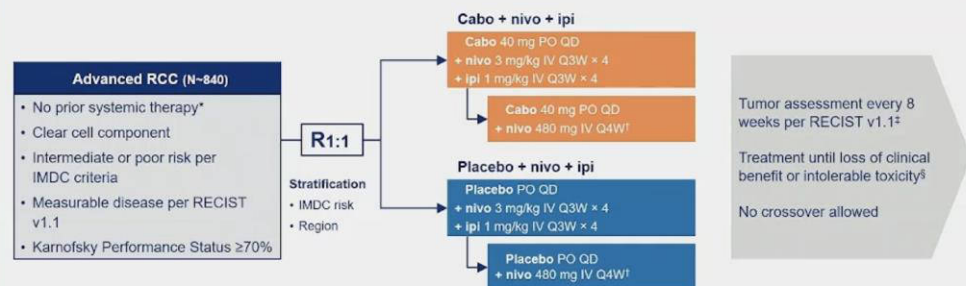
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RCC Berrak Hücreli Kanserde Üçlü kombinasyon Uzun dönem sonuçları

COSMIC-313 Study Design



Primary endpoint: PFS per RECIST v1.1 by BIRC after the 249th event in the first 550 randomized patients (PITT population)

Secondary endpoint: OS after 433 events in all randomized patients (ITT population)

Additional endpoints: ORR, DOR, and safety

*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥ 6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. [†]Nivolumab given for a maximum of 2 years. [‡]Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. [§]Discontinuation of one agent did not mandate discontinuation of all agents.

CTLA-4, cytotoxic T-lymphocyte associated protein 4; DOR, duration of response; ITT, intention-to-treat; IV, intravenous; ORR, objective response rate; PD-(L)1, programmed death (ligand) 1; PITT, progression-free survival ITT; PO, orally; Q3/4W, every 3/4 weeks; QD, once daily; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.

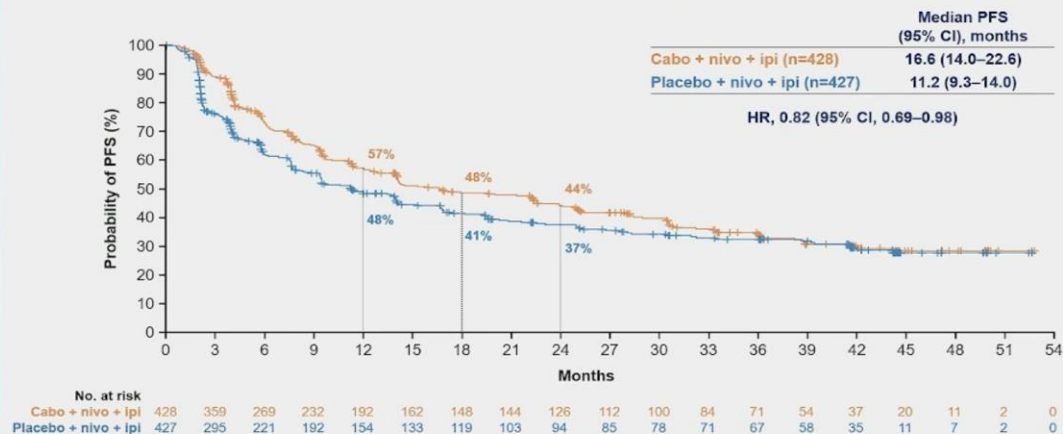
COSMIC-313

4

Albiges L et al. ASCO GU 2025

Updated PFS in the ITT Population

PFS benefit was maintained with longer follow-up



Median follow-up of 45.0 months.

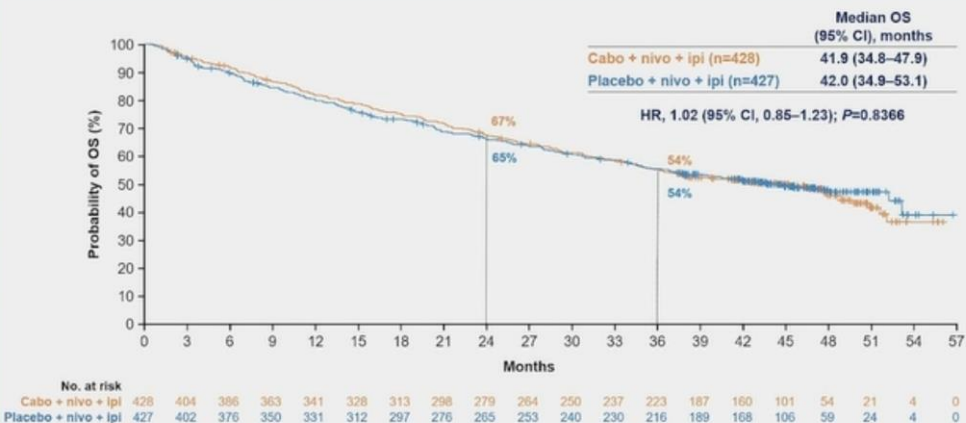
COSMIC-313

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Albiges L et al. ASCO GU 2025

OS in the ITT Population

OS was comparable between arms



Median follow-up of 45.0 months.

COSMIC-313

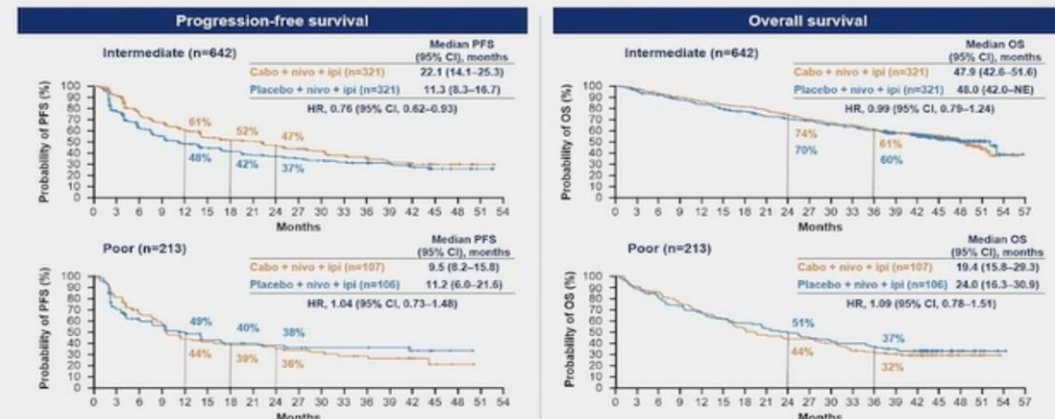
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Albiges L et al. ASCO GU 2025

Updated PFS and Final OS by IMDC Risk Group

PFS benefit was maintained in intermediate risk patients

OS was comparable between treatment arms in both IMDC risk groups



Median follow-up of 45.0 months.

NE, not estimable.

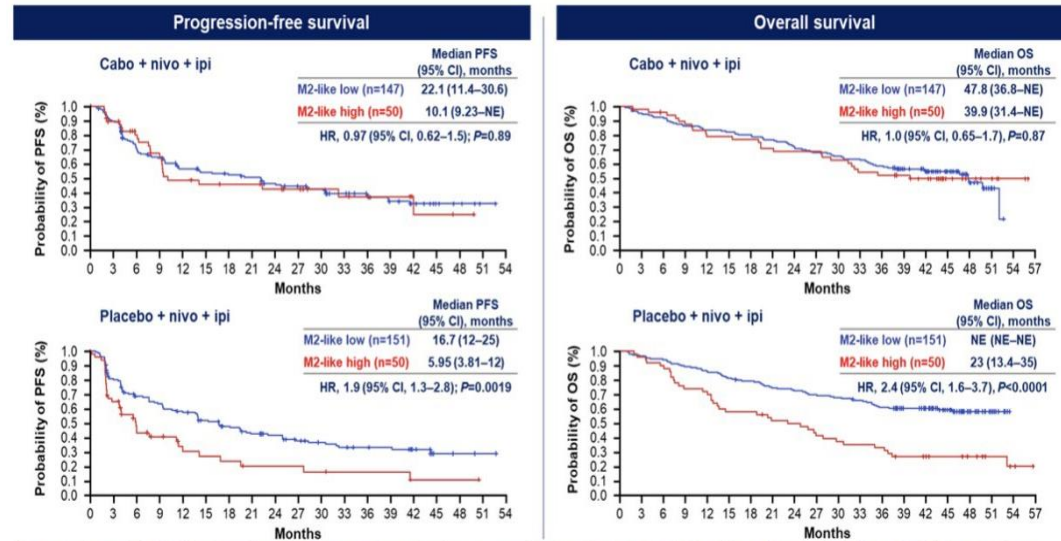
COSMIC-313

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Albiges L et al. ASCO GU 2025

RCC Berrak Hücreli Kanserde Üçlü kombinasyon Uzun dönem sonuçları

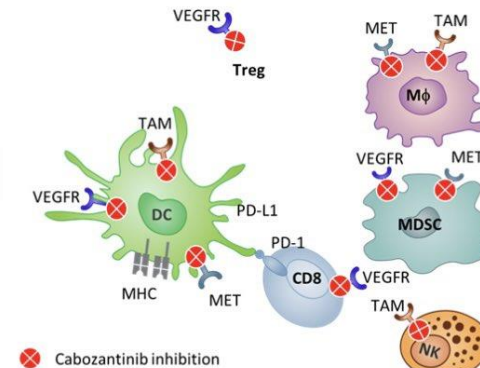
The Addition of Cabo to Nivo + Ipi Overcomes M2-like Macrophage-Mediated Immune Suppression



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

Multiple targets of cabozantinib are expressed on immune cells

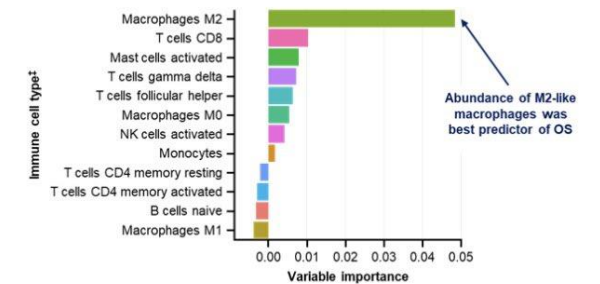


*Immune deconvolution was performed using CIBERSORT (LM22 signature). [†]A random forest survival model was built using relative abundance of immune cell subsets from patients across both treatment arms as predictors of PFS/OS. Hyperparameters were optimized to select the model with the best prediction 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.

Immune cell deconvolution

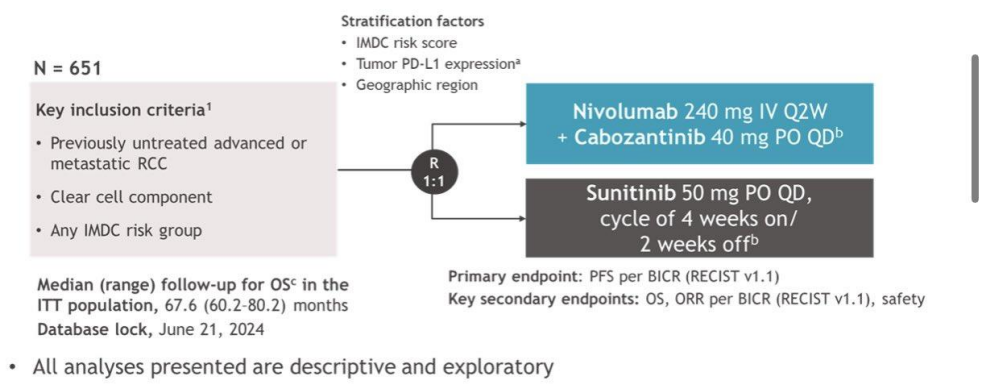
The relative proportions of different immune cell types were estimated from bulk RNA-Seq data*

A random forest survival model was defined using relative cell proportions as predictors of PFS/OS[†]



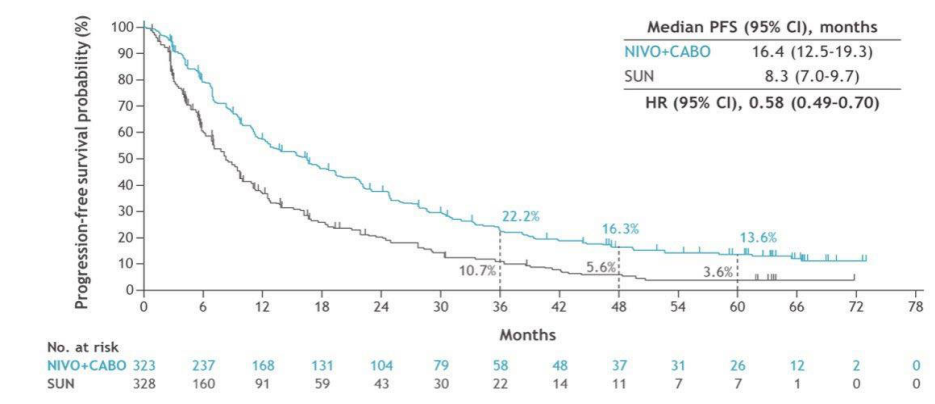
RCC Berrak Hücreli Kanserde Birinci Basamak Nivolumab+Kabozantinib Uzun dönem sonuçları

Study design: CheckMate 9ER



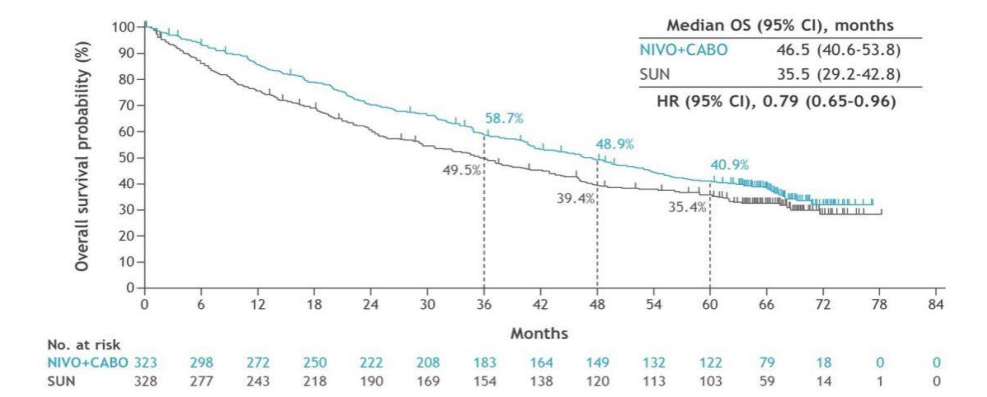
^aDefined as the percentage of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC 28-8 pharmDx immunohistochemistry assay.
^bPatients were treated until RECIST v1.1-defined progression or unacceptable toxicity. NIVO dosing may not exceed a total 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. ^cFollow-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)

^aAn 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). ^bWithin each subgroup, all patients had metastasis within the specified site but may have had lesions in more than 1 site. ^cUnstratified Cox proportional hazards model used for HR.

RCC Tedavi Yanıtını Öngören biyomarkerlar

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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

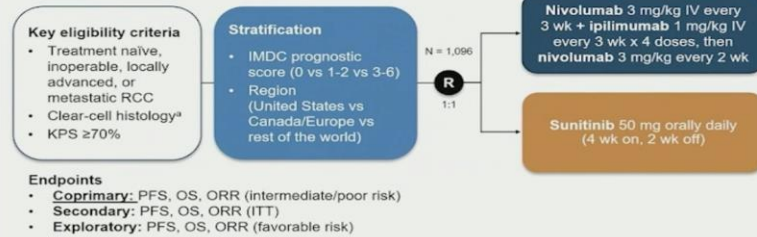
Wenzin Xu,^{1,2,3} Sai Vikram Vemula,⁴ Robert J. Motzer,⁵ Aparna Chhibber,⁶ Deepthi Chowbene,⁸ Nahuel Perrot,⁸ Xiaowen Liu,⁸ Joseph V. Bonventre,^{2,3} Toni K. Choueiri,^{1,2,3} David F. McDermott,^{7,8} Saurabh Gupta,⁴ Rupal S. Bhatt⁴

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

Abstract number 437

CheckMate 214 Background and Study design

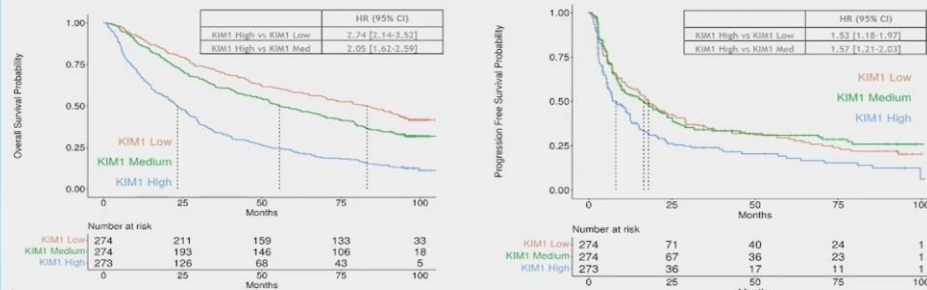
- CheckMate 214 demonstrated that Nivo+Ipi has superior OS and durable response compared to Sunitinib with 8 years of follow-up in first line treatment of aRCC¹
 - These results continue to support Nivo+Ipi as a first-line standard of care for intermediate/poor risk aRCC
- There are currently no RCC specific biomarkers to help prognosticate patients or to identify those who are likely to respond to Nivo+Ipi



1. Tannir NM, et al. Ann Oncol 2024

Baseline KIM-1 levels and clinical outcomes

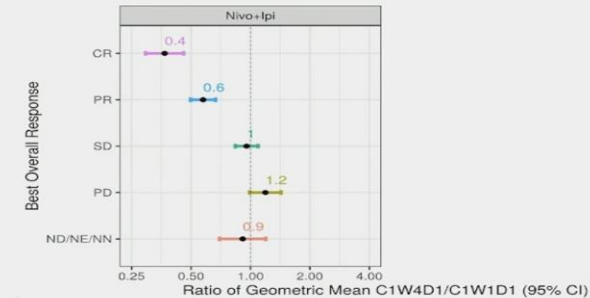
- Higher baseline KIM-1 was associated with worse overall and progression free survival



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

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%		Fav 32% / Int 55% / Poor 13%		Fav 23% / Int 58% / Poor 19%		Fav 31% / Int 60% / Poor 9%		Int 75% / Poor 25%	
	Intermediate/Poor risk		All risk		All risk		All risk		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.

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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 Kong¹, Guangyu Wu², Yunze Xu¹, Zaoyu Wang³, Jin Zhang¹

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

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Study Design

Key Eligibility Criteria

- Age ≥ 18 y, < 80 y
- 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

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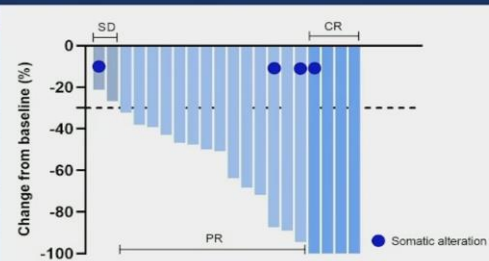
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Results: efficacy

- 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



ASCO Genitourinary Cancers Symposium

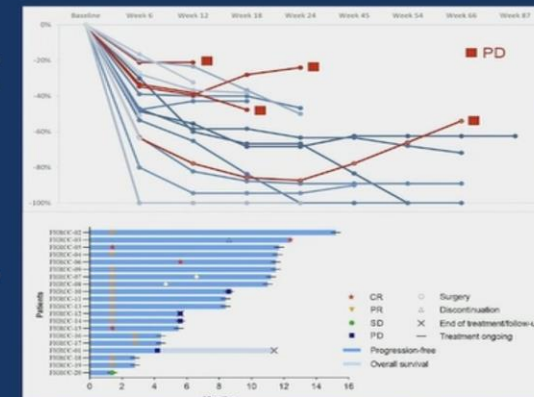
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Results: efficacy

- 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.



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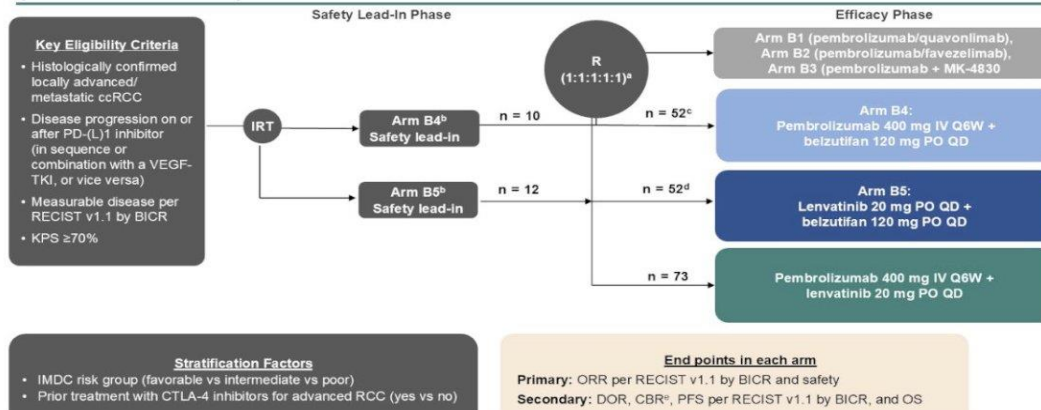
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Berrak Hücreli RCC 2.Basamak ve Sonrası

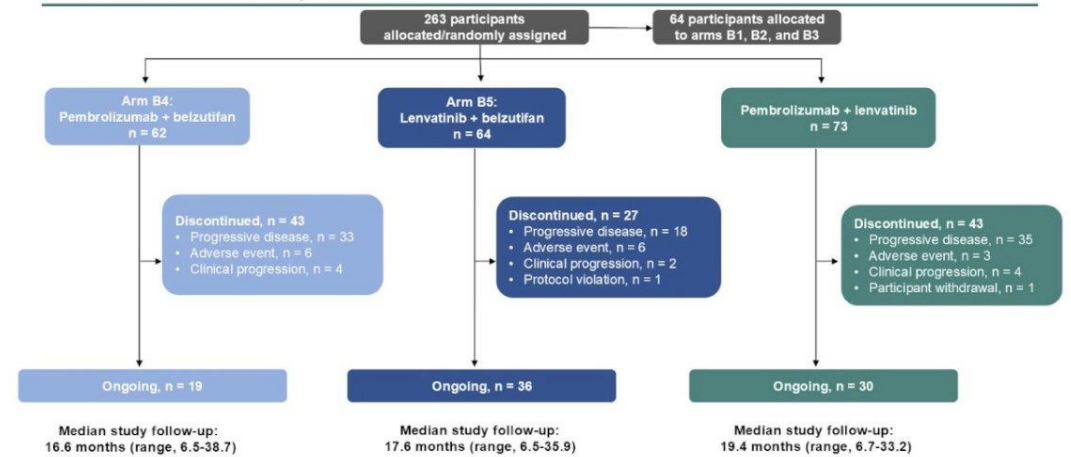
KEYMAKER-U03 Substudy 03B Study Design (NCT04626518)



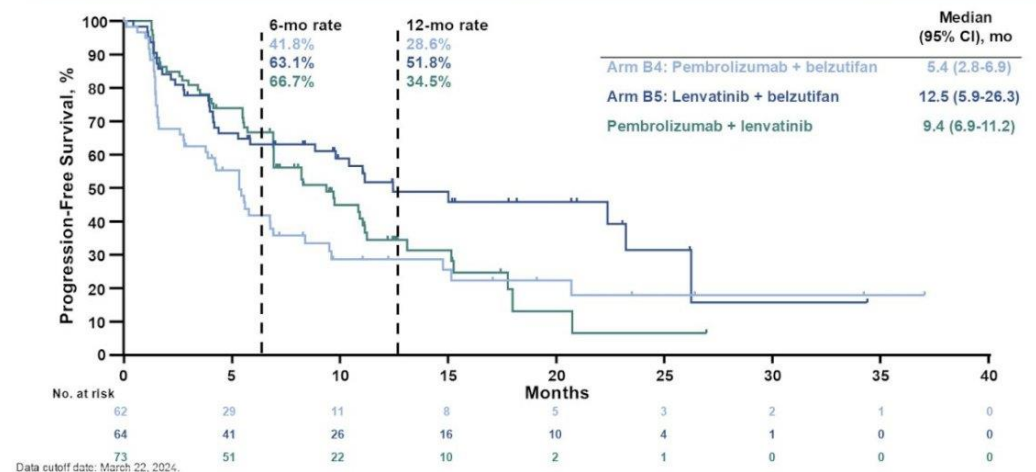
BICR, blinded independent central review; IRT, interactive response technology. ^aParticipants were randomly assigned to arms open for enrollment. ^bArms B4 and B5 had a safety lead-in phase where 10 and 12 patients, respectively, were initially enrolled before randomization. ^c62 participants were evaluated in arm B4 in the efficacy phase. ^d64 participants were evaluated in arm B5 in the efficacy phase. ^eCBR is defined as CR + PR + SD ≥ 6 months.

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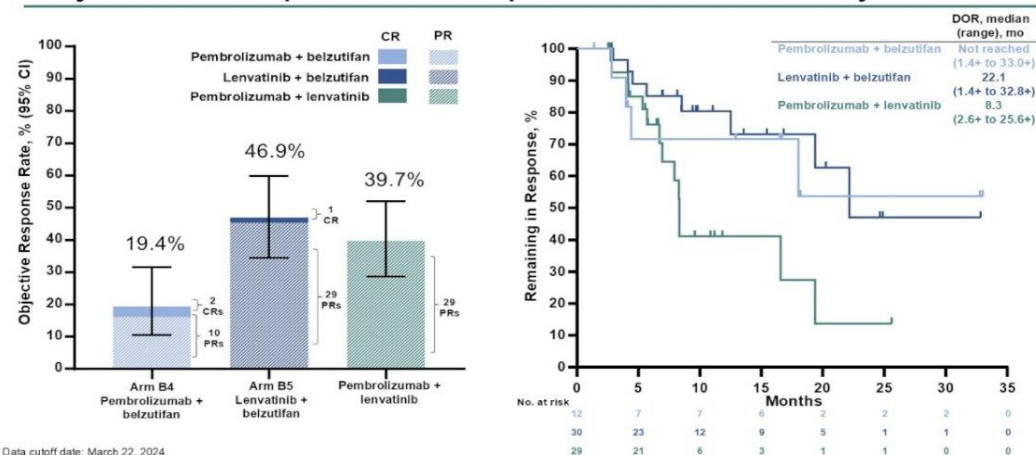
Treatment Disposition



Progression-Free Survival per RECIST v1.1 by BICR



Objective Response Rate per RECIST v1.1 by BICR



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



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 naïve

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

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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.
*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.

^aAll 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.

^bUnconfirmed best overall response.

^cIn addition to the two patients with radiological progressive disease, 2 patients had clinical progression before first scan.

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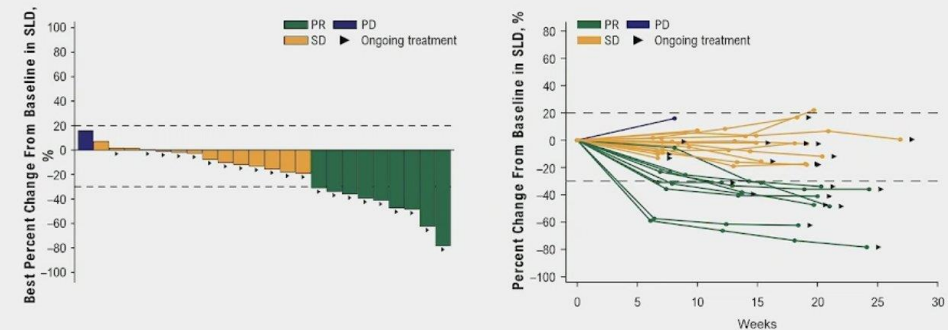
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Casdatifan 100 mg QD Showed Rapid Response and a Trend of Decreasing Sum of Target Lesion Diameters



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

Data cutoff date: 03 January 2025.

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Evre IIA/IIB Seminom Tedavisinde RPLND

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

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

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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

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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)

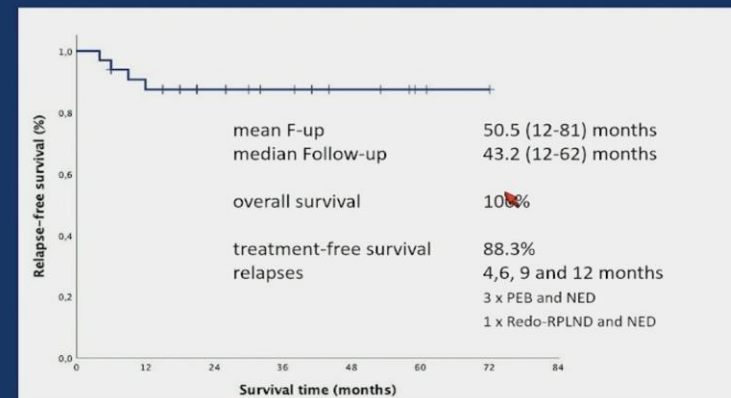
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Oncological Outcome



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Penil kanserde Kemoterapi ve İmmünoterapi Kombinasyonu

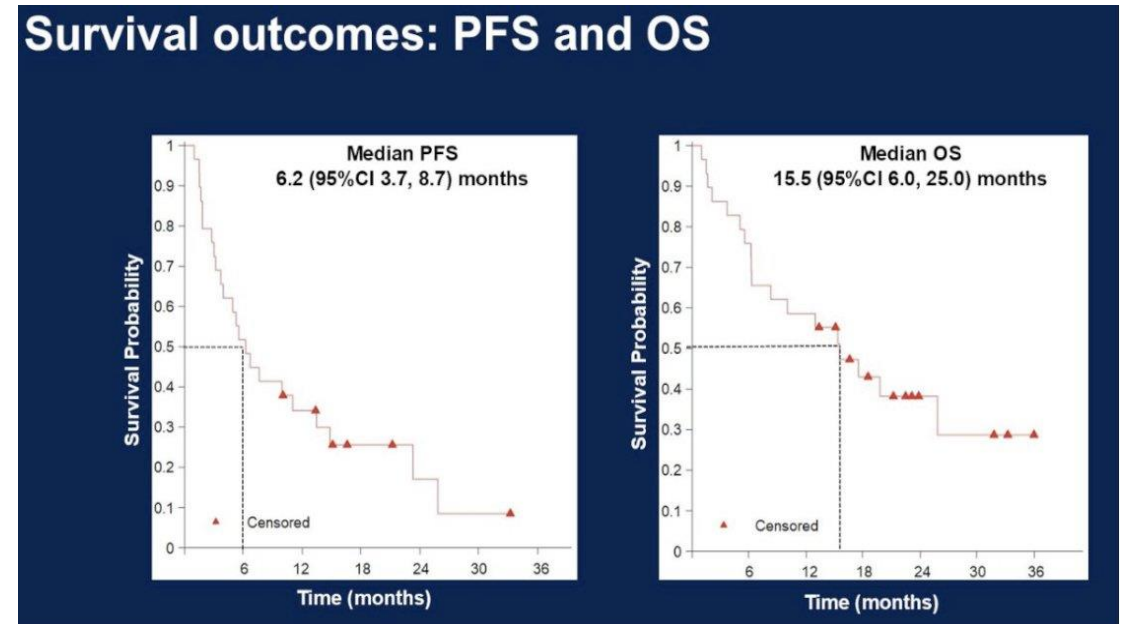
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EPIC-A: Phase II trial of cemiplimab plus standard of care chemotherapy followed by maintenance cemiplimab in locally advanced or metastatic penile carcinoma.

Amit Behl¹, Amamath Challapalli¹, Balaji Venugopal², Mehran Afshar³, Constantine Alifrangis⁴, Alastair Thomson⁵, Anna Tran⁶, Andrew Hudson⁷, Christopher Kent⁸, Jim Barber⁹, Helen Dearden⁹, Rachel Pearson¹⁰, Vivekanandan Kumar¹¹, Robert Wade¹¹, Alicia Bravo¹², Emily Foulstone¹, Paul White¹³

1. Beales Haematology and Oncology Centre, St. James's Hospital, Dublin, Ireland; 2. Royal Free London NHS Foundation Trust, London, United Kingdom; 3. St. James's Hospital, Dublin, Ireland; 4. University College London Hospitals NHS Foundation Trust, London, United Kingdom; 5. Royal Free London NHS Foundation Trust, London, United Kingdom; 6. The Christie NHS Foundation Trust, Manchester, United Kingdom; 7. Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; 8. Yorkshire Cancer Centre, Leeds, United Kingdom; 9. University of Leicester, United Kingdom; 10. University of Leicester, United Kingdom; 11. University of Leicester, United Kingdom; 12. University of Leicester, United Kingdom; 13. University of Leicester, United Kingdom

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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%

Response over time

12 weeks 21 weeks

■ SD ■ PR ■ CR

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 FGFR3 daha potent moleküler

RCC berrak hücreli kanserde TKI+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 özellikle PARP inhibitörleri ve lütesyum kombinasyonları öne çıkıyor

Testis seminom evre IIA/IIB RPLND bir seçenek

Penil kanserde standart kemoterapiye immünoterapi eklemek sağkalımı artırabilir