Neues aus der Uroonkologie
ASCO 2021

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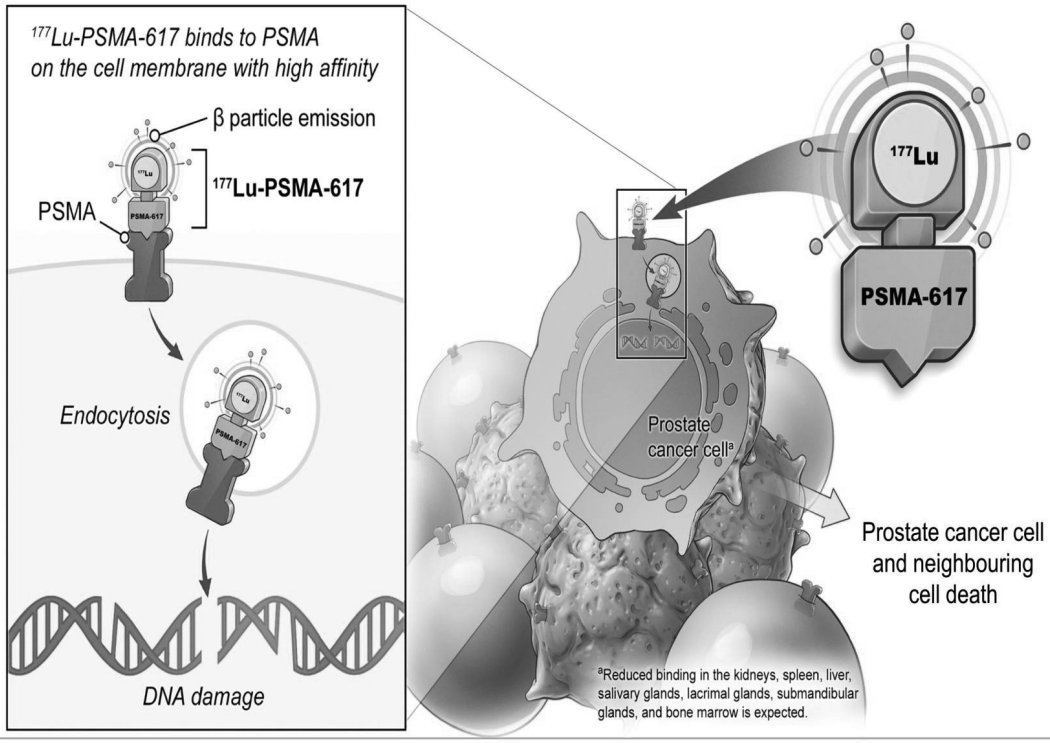
Übersicht

1. Prostatakarzinom
2. Nierenzellkarzinom
3. Urothelkarzinom

LBA4: Phase 3 study of 177Lu-PSMA in patients with metastatic castration-resistant prostate cancer (VISION)

Michael J Morris,et al.

^{177}Lu-PSMA-617 targeted radioligand therapy



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Open-label study of protocol-permitted standard of care ± ^{177}Lu-PSMA-617 in adults with PSMA-positive mCRPC

Eligible patients

- Previous treatment with both
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

2:1

Protocol-permitted SOC + ^{177}Lu-PSMA-617
7.4 GBq (200 mCi) every 6 weeks
4 cycles, increasable to 6

Protocol-permitted SOC alone

Treatment → Follow-up → Final analysis

- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

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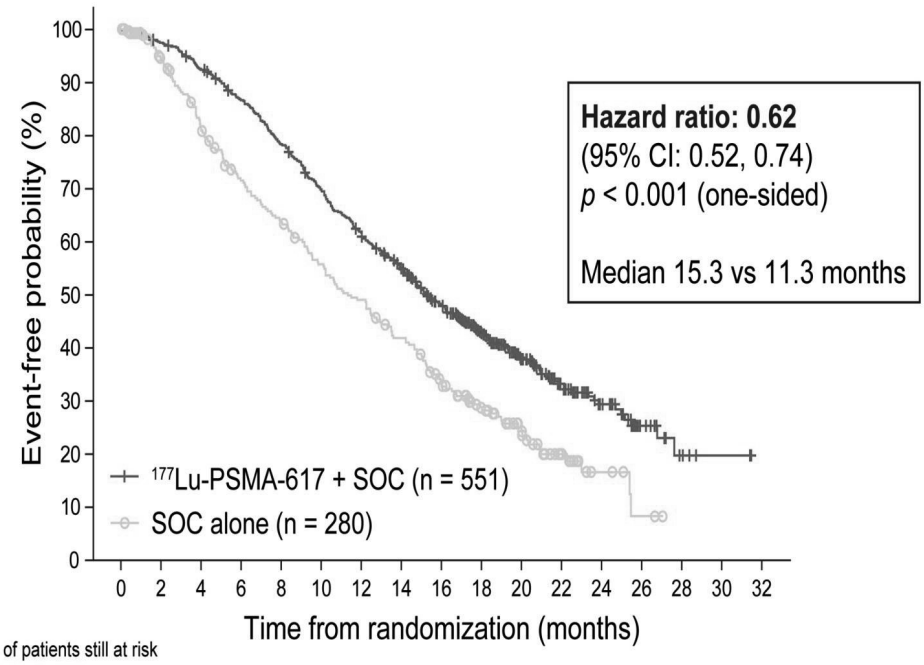
Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients
(N = 831)



Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
SOC alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

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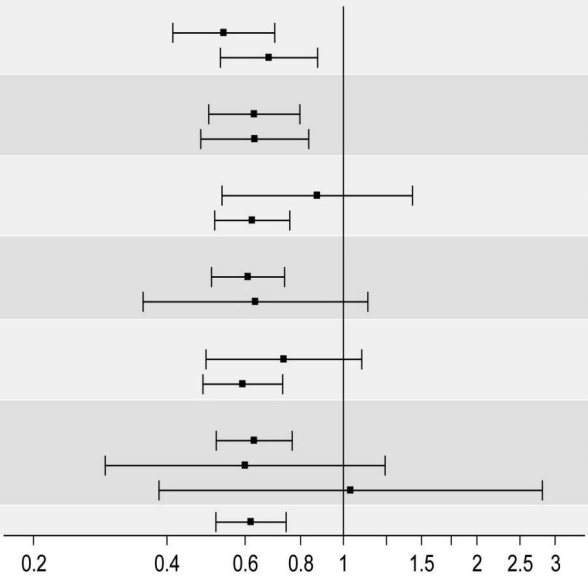
Overall survival was generally consistent across prespecified stratification factor subgroups

Subgroup	^{177}Lu-PSMA-617 + SOC (n = 551)	SOC alone (n = 280)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned SOC			
Yes	243	146	0.54 (0.41, 0.70)
No	308	134	0.68 (0.53, 0.87)
LDH			
≤ 260 IU/L	368	182	0.63 (0.50, 0.80)
> 260 IU/L	182	97	0.63 (0.48, 0.84)
Liver metastases			
Yes	48	34	0.87 (0.53, 1.43)
No	503	246	0.62 (0.51, 0.76)
ECOG score			
0 or 1	510	258	0.61 (0.50, 0.74)
2	41	22	0.63 (0.35, 1.13)
Age			
< 65 years	145	60	0.73 (0.49, 1.10)
≥ 65 years	406	220	0.59 (0.48, 0.73)
Race			
White	486	235	0.63 (0.52, 0.77)
African American or Black	34	21	0.60 (0.29, 1.24)
Asian	9	11	1.04 (0.38, 2.81)
All patients	551	280	0.62 (0.52, 0.74)



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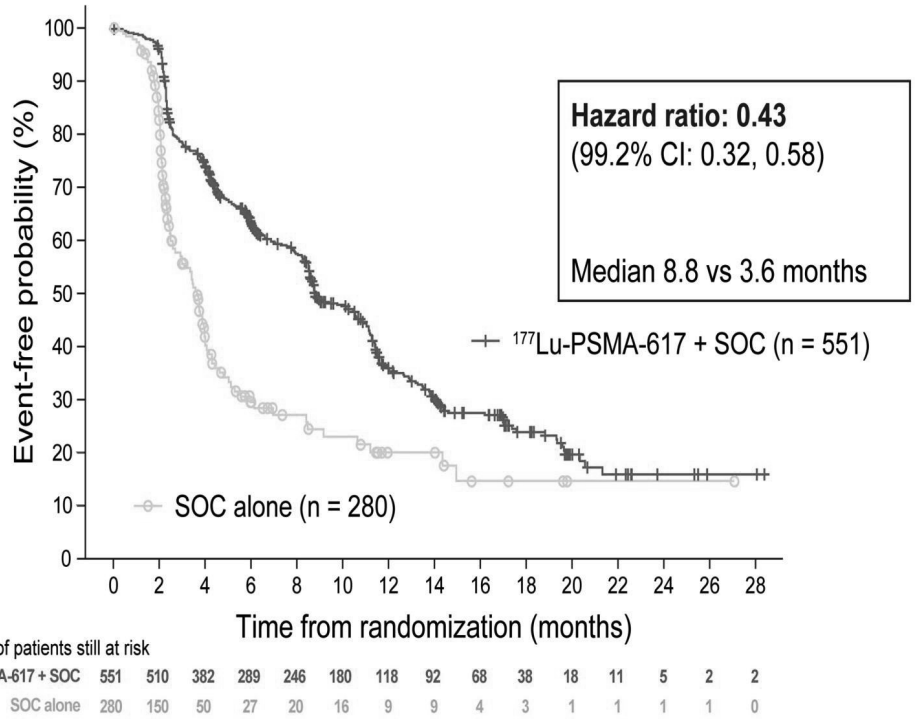
^{177}Lu-PSMA-617 improved rPFS in the OS analysis set

Additional analysis

All randomized patients
(N = 831)



Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	551	510	382	289	246	180	118	92	68	38	18	11	5	2	2
SOC alone	280	150	50	27	20	16	9	9	4	3	1	1	1	1	0

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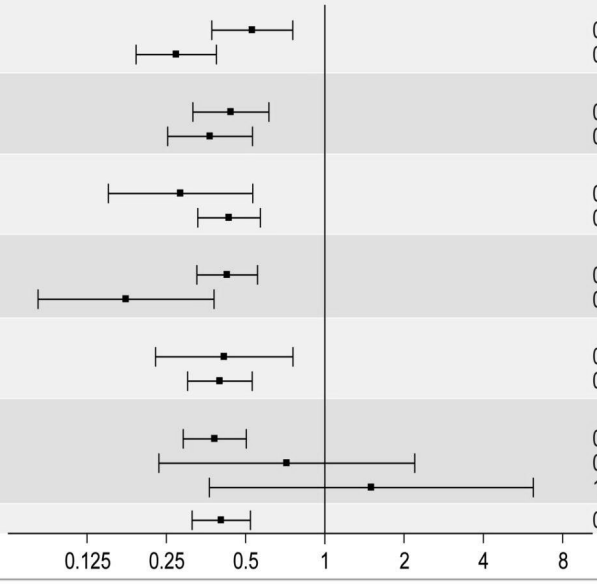
rPFS was generally consistent across prespecified stratification factor subgroups

Subgroup	^{177}Lu-PSMA-617 + SOC (n = 385)	SOC alone (n = 196)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned SOC			
Yes	170	107	0.53 (0.37, 0.76)
No	215	89	0.27 (0.19, 0.39)
LDH			
≤ 260 IU/L	244	120	0.44 (0.32, 0.61)
> 260 IU/L	140	75	0.37 (0.25, 0.53)
Liver metastases			
Yes	37	22	0.28 (0.15, 0.53)
No	348	174	0.43 (0.33, 0.57)
ECOG score			
0 or 1	352	179	0.43 (0.33, 0.56)
2	33	17	0.18 (0.08, 0.38)
Age			
< 65 years	96	39	0.42 (0.23, 0.76)
≥ 65 years	289	157	0.40 (0.30, 0.53)
Race			
White	336	166	0.38 (0.29, 0.50)
African American or Black	29	14	0.72 (0.23, 2.20)
Asian	6	9	1.50 (0.36, 6.19)
All patients	385	196	0.40 (0.31, 0.52)



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Higher rate of drug-related treatment-emergent adverse events with addition of ^{177}Lu-PSMA-617 to SOC

Patients, n (%)	All grades		Grade 3–5	
	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Any TEAE	451 (85.3)	59 (28.8)	150 (28.4)	8 (3.9)
Serious	49 (9.3)	5 (2.4)	43 (8.1)	5 (2.4)
Grade 5	–	–	5 (0.9)	0 (0.0)

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Treatment-emergent adverse events grouped as topics of interest: no unexpected or concerning safety signals

Patients, n (%)	All grades		Grade 3–5	
	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

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VISION study conclusions

- Adding ^{177}Lu-PSMA-617 to safely combinable standard of care in patients with mCRPC after androgen receptor pathway inhibition and chemotherapy
  - Extended overall survival
  - Delayed radiographic disease progression
- ^{177}Lu-PSMA-617 was well tolerated
- These findings warrant adoption of ^{177}Lu-PSMA-617 as a new treatment option in patients with mCRPC

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#5000: A Phase 3 Trial ith a 2x2 Factorial Design of Abiraterone Acetate plus Prednisone and/or local Radiotherapy in men with de novo metastatic castration-sensitive cancer (mCSPC): First results of PEACE-1

Karim Fizazi,et al.

Design of PEACE-1

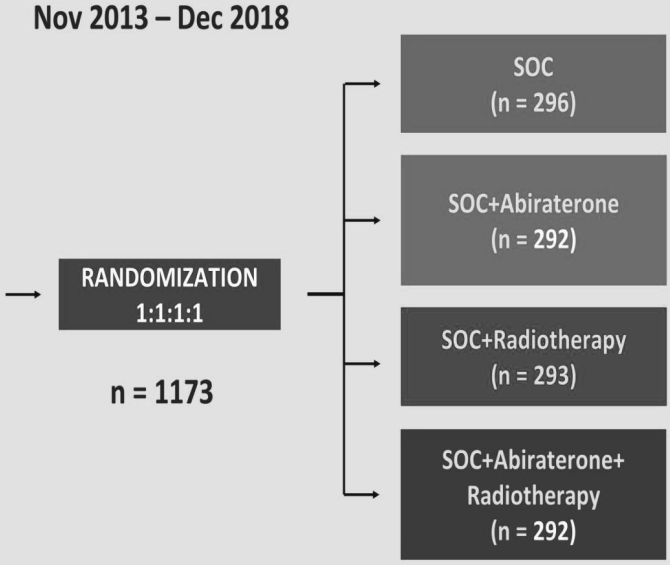
Endpoints: OS, rPFS

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

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No interaction detected between the effect of local radiotherapy and that of Abiraterone on rPFS (p=0.64)

Allows pooling of the 2 Abiraterone arms for analysis

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Patient characteristics

Median follow-up: 42 months

		SOC (+/- RXT) (n = 589)	SOC (+/- RXT) + Abiraterone (n = 583)
Median age, year (IQR)		66 (59–72)	67 (61–72)
ECOG PS score, n (%)	0 1-2	412 (70) 177 (30)	412 (71) 171 (29)
Gleason score at initial diagnosis, n (%)	≤ 7 ≥ 8	132 (23) 440 (77)	144 (25) 427 (75)
Median time from diagnosis, month (IQR)		2.3 (1.5-3.1)	2.3 (1.6-3.2)
Metastatic sites, n (%)	Lymph nodes only Bone without visceral Visceral	52 (9) 475 (81) 62 (11)	47 (8) 472 (81) 64 (11)
Disease burden, n (%)	Low High	252 (43) 334 (57)	250 (43) 330 (57)
Median baseline PSA, ng/mL (IQR)		11.4 (3.1-55.3)	14.2 (3.2-62.1)
Docetaxel, n (%)	Yes No	355 (60) 234 (40)	355 (61) 228 (39)

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Follow-up and duration of treatment (ADT+Docetaxel population)

	ADT+Docetaxel (+/- RXT) (n=355)	ADT+Docetaxel (+/- RXT) + Abiraterone (n=355)
Median follow-up time for OS, month	36.0	35.7
Median number of docetaxel cycles (Q1-Q3)	6 (6-6)	6 (6-6)
Median time to Abiraterone discontinuation (Q1-Q3), month	-	31.4 (12.3-NE)

Cut-off date: September 1, 2020

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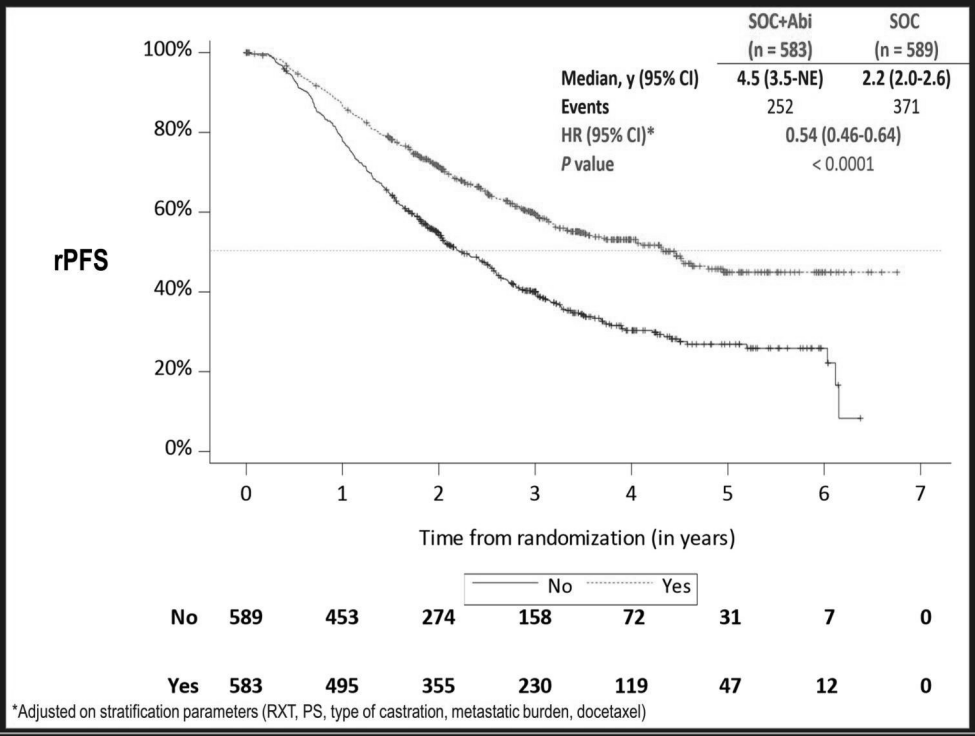
Radiographic Progression-Free Survival (rPFS) Overall population: SOC=ADT+/- Docetaxel (+/- RXT)



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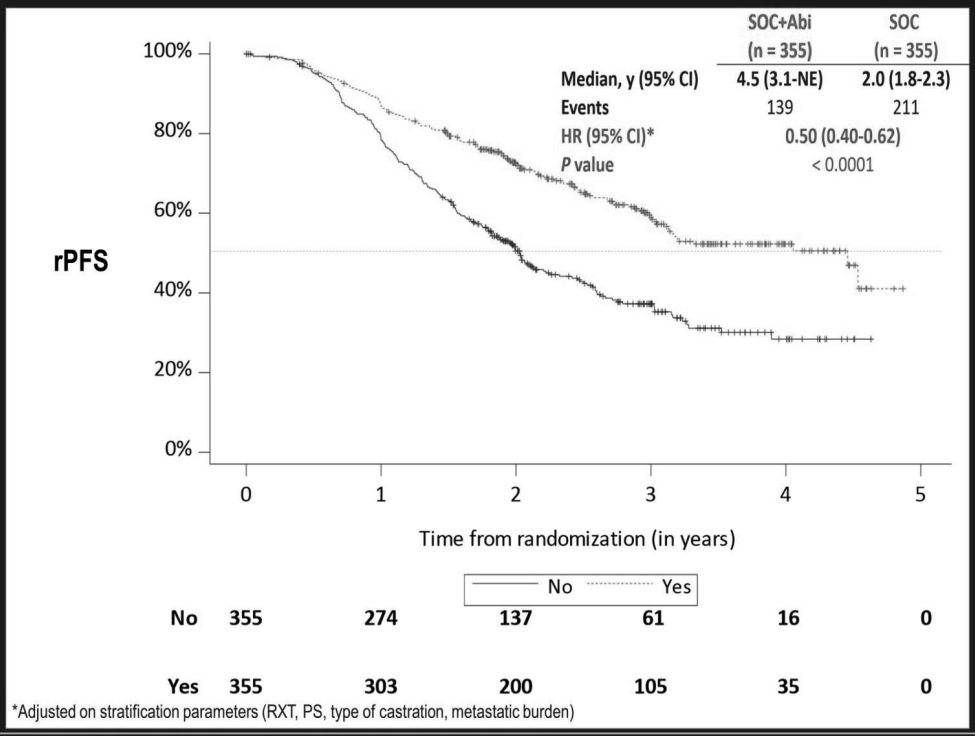
Radiographic Progression-Free Survival (rPFS) ADT+Docetaxel population: SOC=ADT+Docetaxel (+/- RXT)



*Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden)

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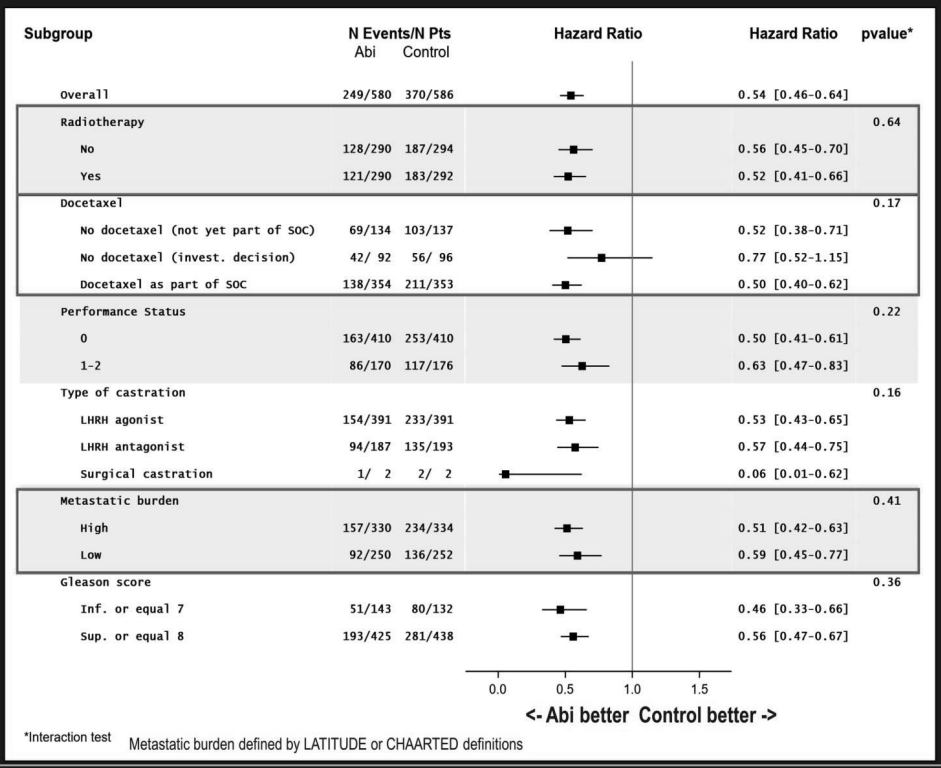
Subgroup analysis of rPFS: Abiraterone effect



*Interaction test

Metastatic burden defined by LATITUDE or CHAARTED definitions

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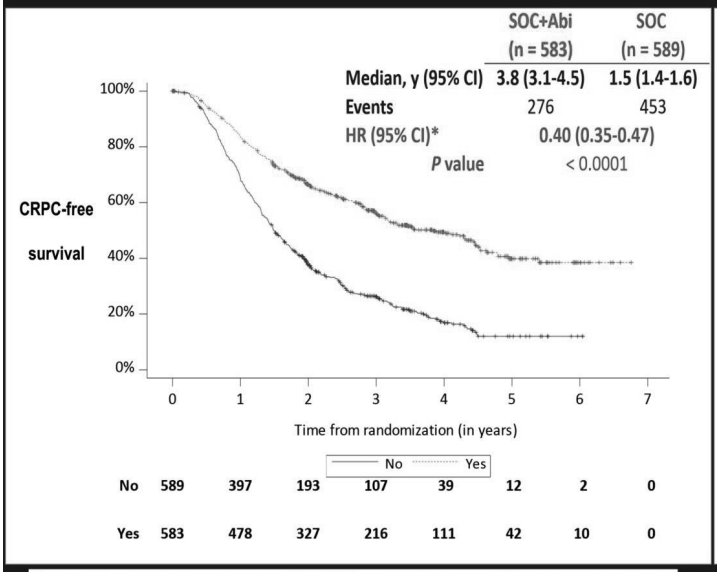
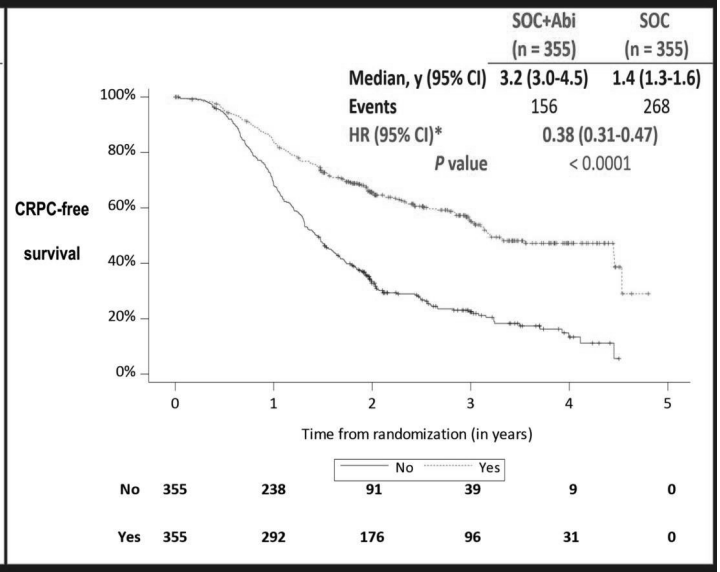
CRPC-free Survival

Overall population
SOC=ADT+/- Docetaxel (+/- RXT)



Docetaxel population
SOC=ADT+Docetaxel (+/- RXT)



*Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden, docetaxel)

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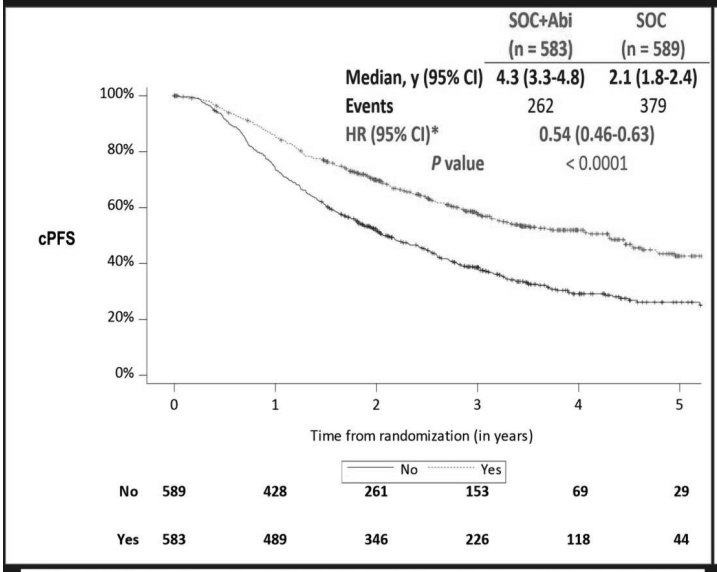
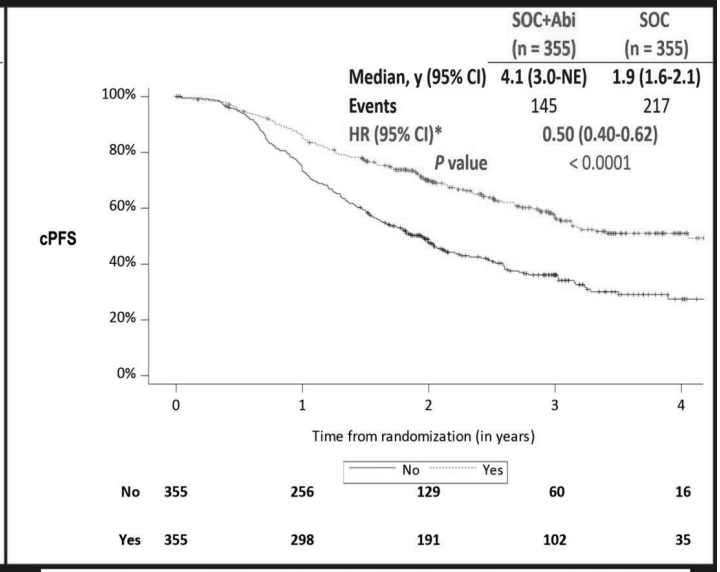
Clinical PFS (cPFS): exploratory endpoint

Overall population
SOC=ADT+/- Docetaxel (+/- RXT)



Docetaxel population
SOC=ADT+Docetaxel (+/- RXT)



cPFS events: Symptomatic progression by investigator's judgement, radiographic progression, death

*Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden, docetaxel)

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Grade 3-5 Toxicity (6 first months, Docetaxel pop.)

	SOC (+/- RXT) + Abiraterone (n=335)	SOC (+/- RXT) (n=336)
	n (%)	n (%)
Hematological	50 (14)	52 (15)
Neutropenia	33 (10)	31 (9)
Febrile neutropenia	16 (5)	16 (5)
Liver	20 (6)	1 (0)
Cardiac	3 (1)	3 (1)
Hypertension	43 (12)	28 (8)
Gastro-intestinal	8 (2)	15 (4)
Fatigue	6 (2)	13 (4)
Grade 5	3 (0.9)	2 (0.6)

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Conclusion

- Adding abiraterone to ADT + docetaxel significantly improves rPFS in men with *de novo* metastatic prostate cancer.
- All secondary endpoints of PFS (CRPC-free survival, symptom-defined PFS) were also clearly improved. OS data maturing.
- No meaningful additional short-term toxicity.
- Regardless of OS results, should we deny patients approximately 2.5 years of absolute benefit in median rPFS or do we have a new standard of care?

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1. Prostatakarzinom

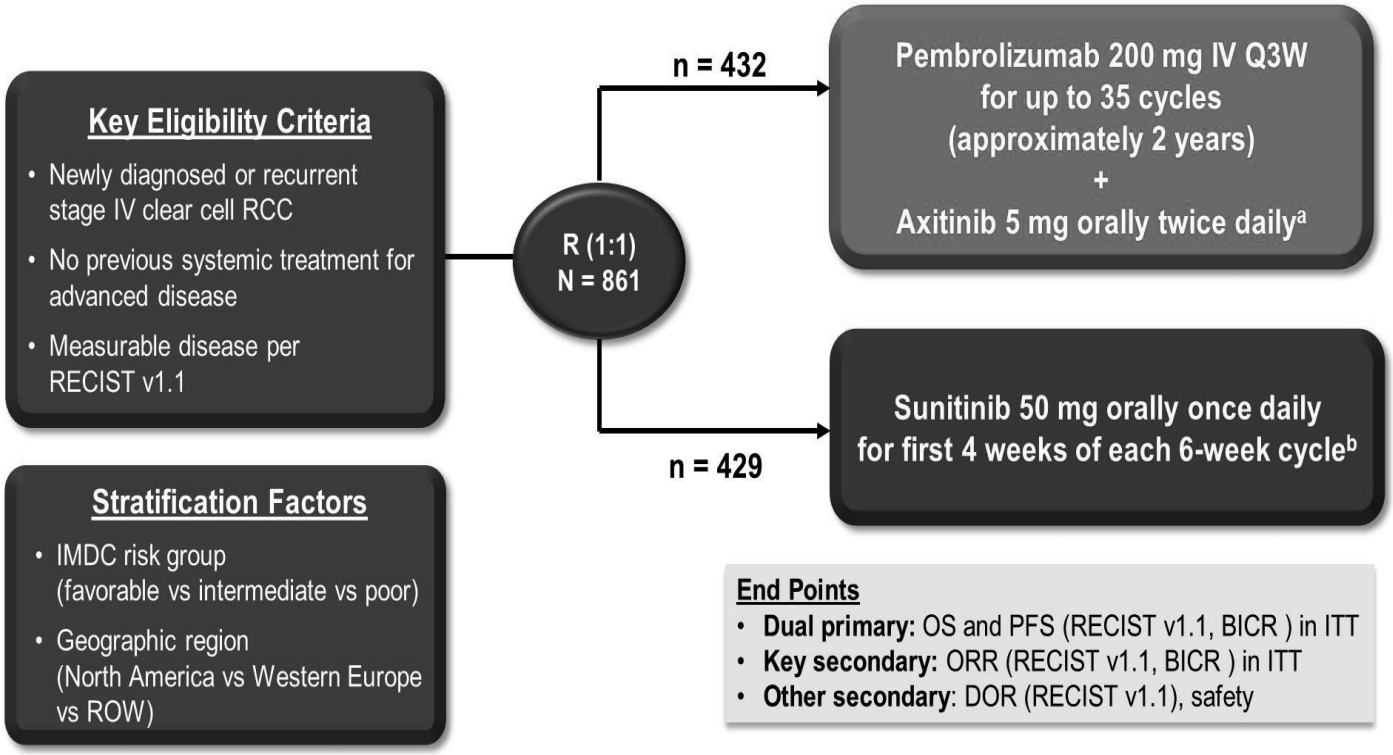
2. Nierenzellkarzinom

3. Urothelkarzinom

#4500: Pembrolizumab plus Axitinib vs. Sunitinib as First-Line Therapy for Advanced Cler Cell Renal Cell Carcinoma: Results from 42-Month Follow-UP of Keynote-426

B. I. Rini,et al.

KEYNOTE-426 Study Design



[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 11, 2021.

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Subsequent Anticancer Therapy

n (%)	Pembrolizumab + Axitinib	Sunitinib
Discontinued treatment	**N = 432** 349 (81.4)	**N = 429** 385 (90.6)
Received any subsequent therapy	**n = 349** 204 (58.4)	**n = 385** 281 (73.0)
By type of treatment	**n = 204**	**n = 281**
Any PD-1/PD-L1 inhibitor	44 (21.6)	209 (74.4)
Any VEGF/VEGFR inhibitor	180 (88.2)	193 (68.7)
Other[a]	66 (32.4)	64 (22.8)

[a]Doxorubicin, everolimus, glutaminase inhibitor (unspecified), ibrutinib, interferon (unspecified), interferon alfa 2a, interferon gamma, investigational drug (unspecified), ipilimumab, savolitinib, temsirolimus, vinblastine. Data cutoff: January 11, 2021.

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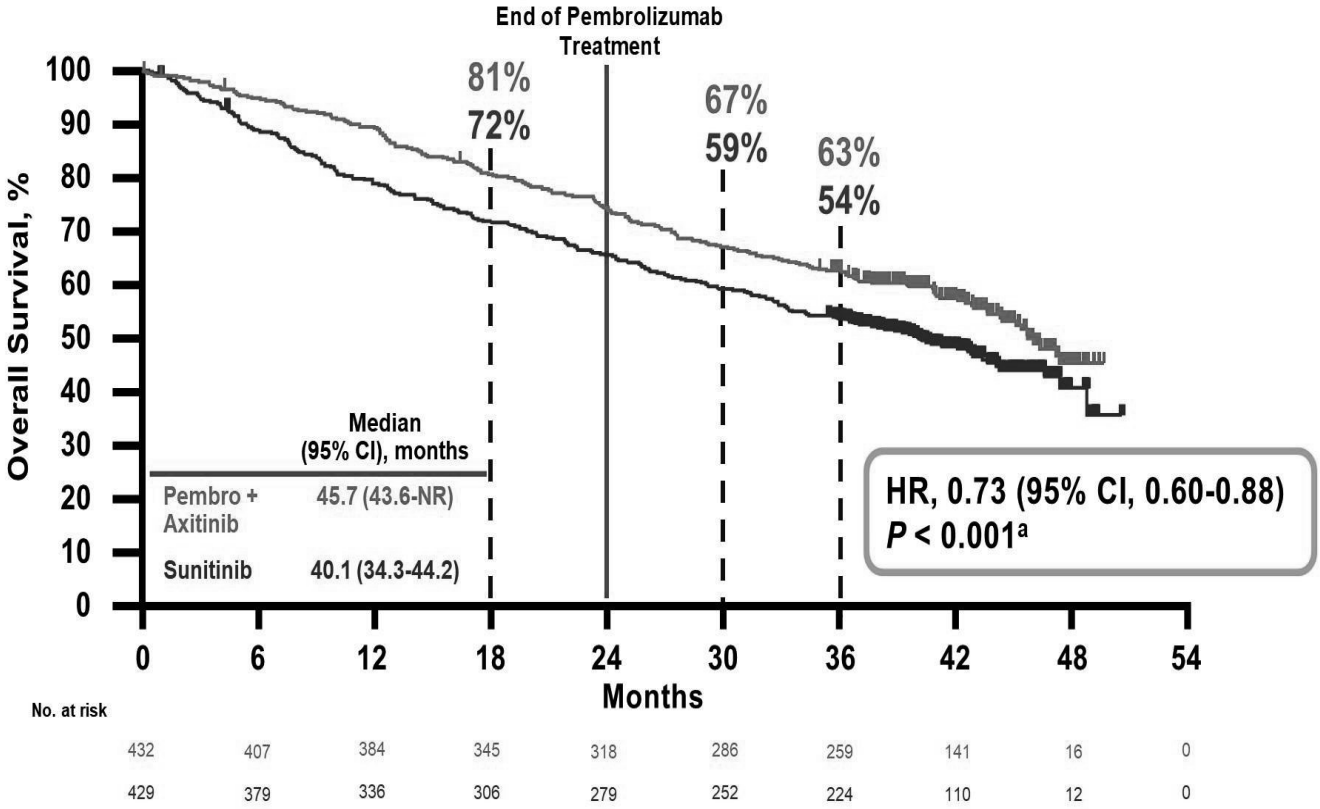
OS in the ITT Population



[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 11, 2021.

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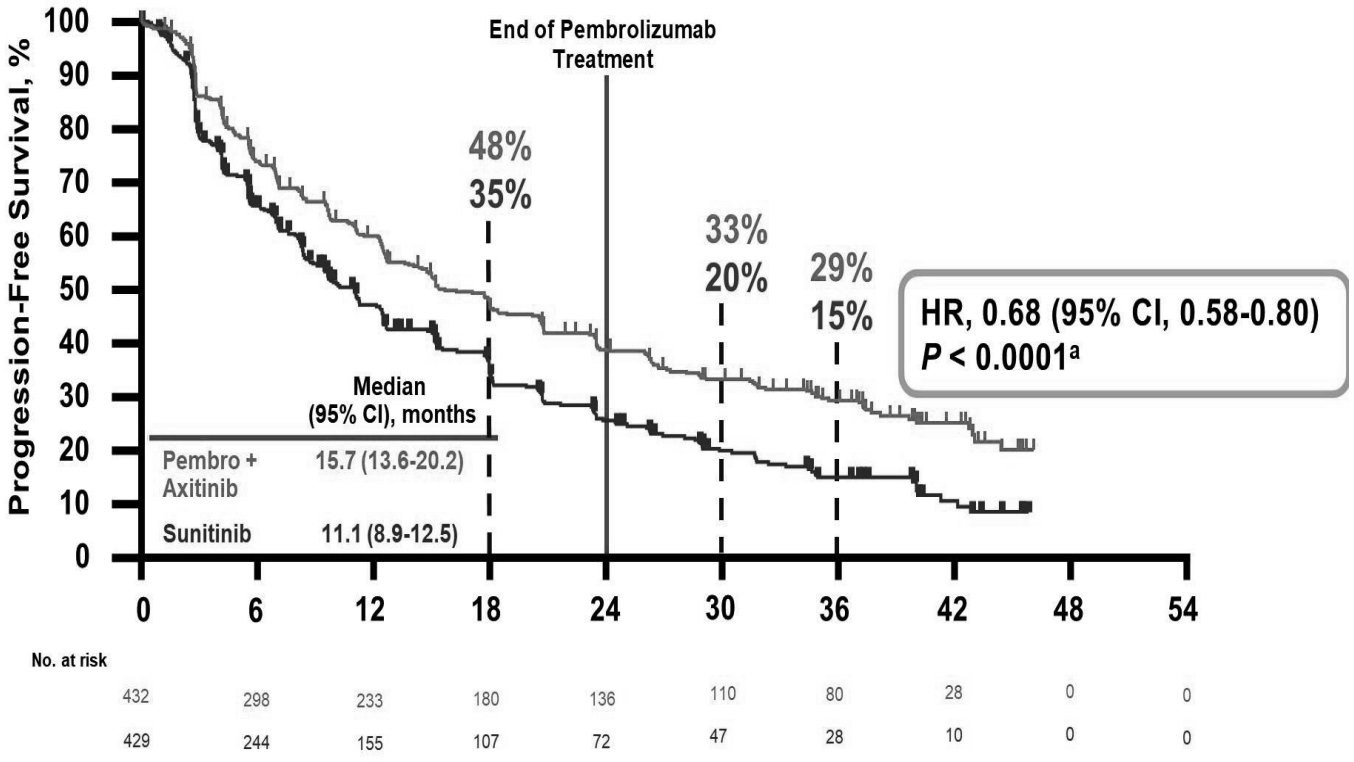
PFS in the ITT Population



[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to PFS; only nominal *P* values are reported. Data cutoff: January 11, 2021.

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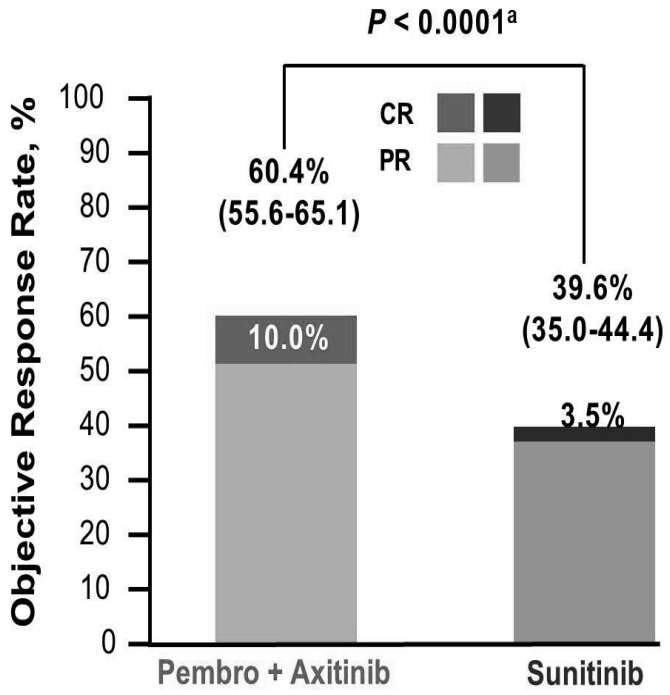
Confirmed Objective Response Rate

ITT Population



	Pembro + Axitinib n = 432	Sunitinib n = 429
Best response, n (%)		
CR	43 (10.0)	15 (3.5)
PR	218 (50.5)	155 (36.1)
SD	99 (22.9)	152 (35.4)
PD	49 (11.3)	73 (17.0)
NE[b]	7 (1.6)	6 (1.4)
NA[c]	16 (3.7)	28 (6.5)

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to confirmed objective response; only nominal *P* values are reported. [b]Postbaseline assessment available but not evaluable (ie, all postbaseline assessments with insufficient data for assessment of response per RECIST v1.1 or CR/PR/SD <6 weeks from randomization). [c]No postbaseline assessment available for response evaluation; + indicates an ongoing response at time of last disease assessment. Data cutoff: January 11, 2021.

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Duration of Response

	Pembro + Axitinib n = 261	Sunitinib n = 170
Time to response, median (range), months	**2.8 (1.5-34.8)**	**3.0 (2.1-26.3)**
DOR, median (range), months	**23.6 (1.4+ to 43.4+)**	**15.3 (2.3 to 42.8+)**
Response duration, n (%[a])		
≥6 months	215 (87.4)	126 (80.3)
≥12 months	171 (71.1)	92 (62.2)
≥18 months	138 (58.5)	60 (45.5)
≥24 months (end of pembrolizumab treatment)	102 (48.9)	42 (37.1)
≥30 months	87 (44.5)	29 (32.1)

[a]Percentage based on Kaplan-Meier method for censored data. + indicates an ongoing response at time of last disease assessment. Data cutoff: January 11, 2021.

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Efficacy in IMDC Subgroups

Parameter	ITT		Favorable Risk		Intermediate/Poor Risk	
	Pembro + Axitinib n = 432	Sunitinib n = 429	Pembro + Axitinib n = 138	Sunitinib n = 131	Pembro + Axitinib n = 294	Sunitinib n = 298
OS, HR (95% CI)	0.73 (0.60-0.88)		1.17 (0.76-1.80)		0.64 (0.52-0.80)	
42-month rate, %	57.5	48.5	72.3	73.0	50.6	37.6
PFS, HR (95% CI)	0.68 (0.58-0.80)		0.76 (0.56-1.03)		0.67 (0.55-0.81)	
Median, months	15.7	11.1	20.7	17.8	13.8	8.2
ORR, %	**60.4**	**39.6**	**68.8**	**50.4**	**56.5**	**34.9**
CR, %	10.0	3.5	11.6	6.1	9.2	2.3
PR, %	50.5	36.1	57.2	44.3	47.3	32.6

Data cutoff: January 11, 2021.

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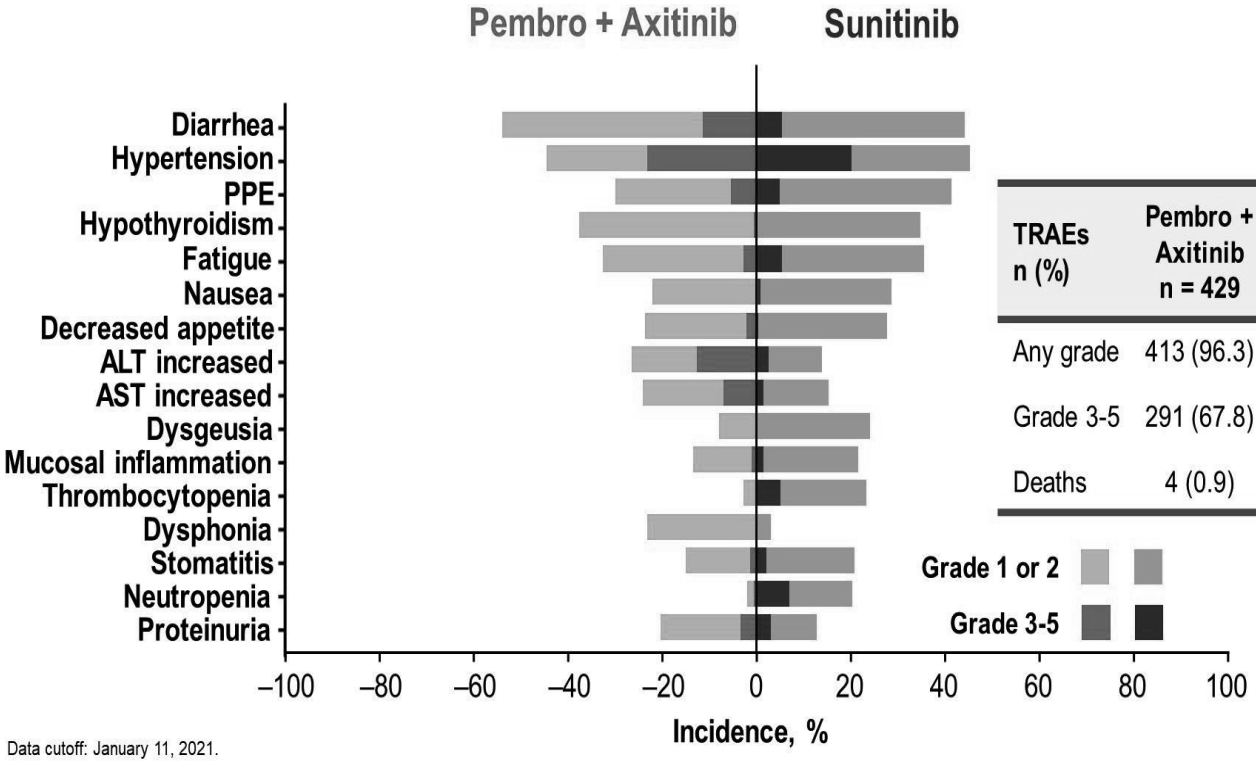
Treatment-Related Adverse Events

Incidence ≥20% Within Either Treatment Arm



TRAEs n (%)	Pembro + Axitinib n = 429	Sunitinib n = 425
Any grade	413 (96.3)	415 (97.6)
Grade 3-5	291 (67.8)	271 (63.8)
Deaths	4 (0.9)	7 (1.6)

Data cutoff: January 11, 2021.

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#4583: Effect of High-Dose Corticosteroid Use of Immune Checkpoint Inhibitors in Patients with Renal Cell Carcinoma (RCC)

Chris Labaki, et al.

Background

Corticosteroids in patients with cancer

- Immunosuppressive properties (inactivation of effector T-cells, increased regulatory T-cells)[1,2]
- Treatment of cancer-related symptoms (dyspnea, brain metastases) and other non-oncologic indications (rheumatologic diseases)
- Primary therapeutic modality for immune-related adverse events (irAEs)

Efficacy of immune checkpoint inhibitors (ICIs) in patients receiving corticosteroids

- Corticosteroids (>10mg/day prednisone) in patients with NSCLC: decreased overall response rate, shorter progression-free survival (PFS) and overall survival (OS)[3,4]
- Urothelial carcinoma (UC) and melanoma patients: shorter OS[5]

Hypothesis: Corticosteroids may be associated with worse outcomes in patients with renal cell carcinoma (RCC) treated with ICIs

1. Bianchi M. et al., *Proc Natl Acad Sci* , 2000
2. Chen X. et al., *Eur. J. Immunol*., 2006
3. Scott S.C. et al., *J Thorac Oncol*, 2018
4. Arbour K.C. et al., *J Clin Oncol*., 2018
5. Drakaki A. et al., *Ann. Onc*., 2019

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Methods

- **Patients with metastatic renal cell carcinoma (mRCC) treated with immune checkpoint inhibitors (ICIs) in the first- or second-line setting**

Two groups:

Group A: High-dose corticosteroids (≥10 mg/day for ≥ 1 week)

Group B: No (or low-dose) corticosteroids

Primary Outcomes – Time-to-Treatment-Failure (TTF) and Overall Survival (OS)

Confounding factors – Multivariate Analysis (Cox Regression):

- IMDC risk group
- RCC histology (clear-cell vs. non-clear cell)
- ICI regimen type (ICI monotherapy, ICI + ICI, ICI + VEGF inhibitor)
- Line of therapy

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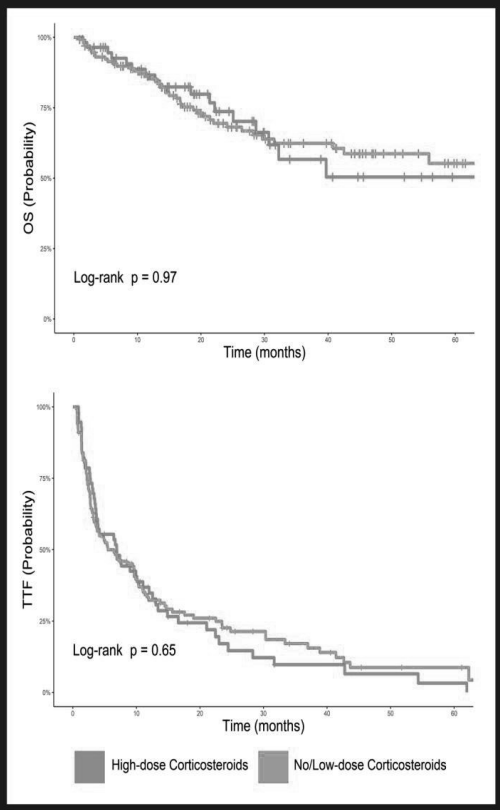
Results

		Group A High-dose corticosteroids	Group B No/low-dose corticosteroids	P-value*
Number of patients, n		56	134	-
Median age, years (IQR)		57 (50-63)	60 (54-65)	0.18
Male sex, n(%)		42 (75)	103 (77)	0.78
IMDC risk group, n(%)	Intermediate	24 (43)	89 (66)	Ref.
	Favorable	19 (34)	24 (18)	0.005
	Poor	13 (23)	21 (16)	0.04
Histology, n(%)	Clear-cell	48 (86)	107 (80)	Ref.
	Non clear-cell	8 (14)	27 (20)	0.34
Line of therapy, n(%)	1st line	46 (82)	94 (70)	Ref.
	2nd line	10 (18)	40 (30)	0.09
Regimen type, n(%)	ICI + anti-VEGF	25 (45)	58 (43)	Ref.
	ICI monotherapy	14 (25)	43 (32)	0.47
	ICI dual therapy	17 (30)	33 (25)	0.64
Corticosteroid indication, n(%)	Cancer-related**	8 (14)	N/A	-
	Non-cancer related	8 (14)		
	irAEs	40 (72)		
Survival, %[95%CI]	**12-month TTF rate**	**34.8 [24.1-50.1]**	**32.3 [24.9-41.9]**	**0.65**
	36-month OS rate	**56.7 [41.2-78.0]**	**62.4 [53.2-73.1]**	**0.97**

*: Logistic regression for clinical variables, log-rank test for survival outcomes
**: Other than irAEs



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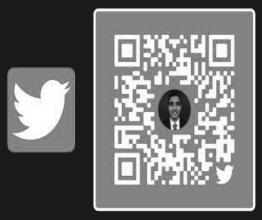
Conclusions

No association between high-dose corticosteroid use and TTF or OS in patients with renal cell carcinoma

- Moderate sample size: larger studies needed to evaluate the impact of corticosteroids in patients with RCC
- Timing of corticosteroid administration in relation to ICI regimens



Dana-Farber Cancer Institute

@Chrislabaki1

Presented By: Dr Chris Labaki
Dana Farber Cancer Institute

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Erstlinientherapie des fortgeschrittenen RCC: EAU Guidelines Update 2021

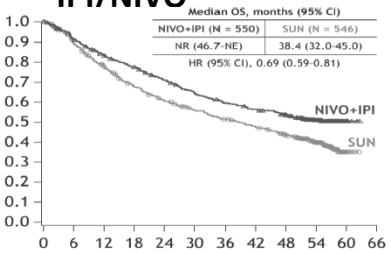
	Standard of Care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b]	sunitinib* [1b] pazopanib* [1b]
IMDC intermediate and poor risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b] nivolumab/ipilimumab [1b]	cabozantinib* [2a] sunitinib*[1b] pazopanib* [1b]

IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium
**pazopanib for intermediate-risk disease only.*
[1b] = based on one randomised controlled phase III trial.
[2a] = based on a well-designed study without randomisation, or a subgroup analysis of a randomised controlled trial.

Ljungberg et al, EAU guidelines 2021

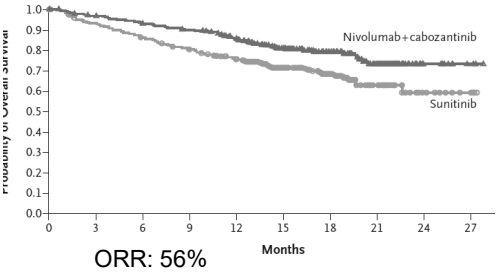
Vergleich des Ansprechens der unterschiedlichen Phase 3 Studien

IPI/NIVO



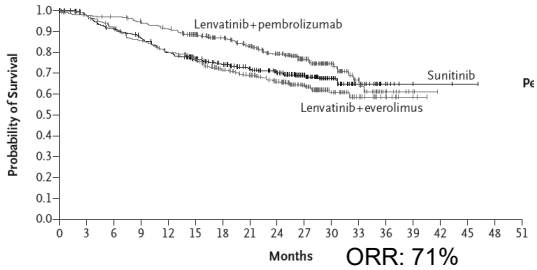
ORR: 39%
CR: 11%
PR: 28%
SD: 36%
PD: 18%
AEs≥3: 65%

NIVO/CABO



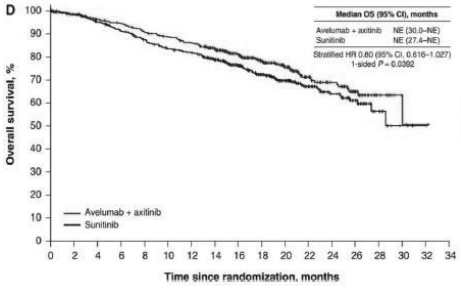
ORR: 56%
CR: 8%
PR: 48%
SD: 32%
PD: 6%
AEs≥3: 75%

PEMBRO/LENVA



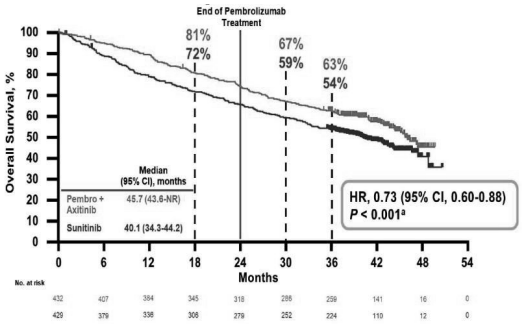
ORR: 71%
CR: 16%
PR: 55%
SD: 19%
PD: 5%
AEs≥3: 82%

Avelu/AXI



ORR: 53%
CR: 4%
PR: 49%
SD: 28%
PD: 12%
AEs≥3: 71%

PEMBRO/AXI



ORR: 60%
CR: 9%
PR: 51%
SD: 23%
PD: 11%
AEs≥3: 76%

1. Motzer et al, ESMO 2020 2. Choueiri et al, NEJM 2021; 3. Motzer et al, NEJM 2021; 4. Plimack et al, ASCO 2020 5. Choeiri et al, ASCO 2021

#LBA5: Pembrolizumab vs. Placebo as Post Nephrectomv Adjuvant Therapy for Patients with Renal Cell Carcinoma: Radomized, Double-Blind Phase 3 Keynote-564-Study

Toni K. Choueiri,et al.

Adjuvant Therapy for Renal Cell Carcinoma

- 2018: Kidney cancer was responsible for 175,000 deaths worldwide[1]
- Nephrectomy is the standard of care treatment for locoregional RCC[2,3]
  - No globally accepted standard adjuvant therapy supported by high levels of evidence
  - Studies of adjuvant immunotherapy with cytokines have yielded negative results[4]
  - VEGF-targeted therapy has not shown a consistent benefit in the adjuvant setting[5]
- Nearly half of patients eventually experience disease recurrence after surgery[4-6]
  - Risk factors include tumor stage/size, nodal involvement, and nuclear grade
  - Patients with M1 stage and no evidence of disease (NED) after resection of oligometastatic sites are also at high risk of relapse[7]
- **KEYNOTE-564** (NCT03142334) is a phase 3, double-blind, multicenter trial of pembrolizumab vs placebo following nephrectomy in participants with clear cell RCC

1. Bray et al. *CA Cancer J Clin* 2018;68:394-424; 2. NCCN. Kidney cancer (version 6.2021); 3. Escudier et al. *Ann Oncol* 2019;30:706-20; 4. Smaldone et al. *Hematol Oncol Clin North Am* 2011;25:765-91; 5. Sun et al. *Eur Urol* 2018;74:611-20; 6. Correa et al. *J Clin Oncol* 2019;37:2062-2071; 7. Appleman et al. *J Clin Oncol* 37, 2019 (suppl; abstr 4502).

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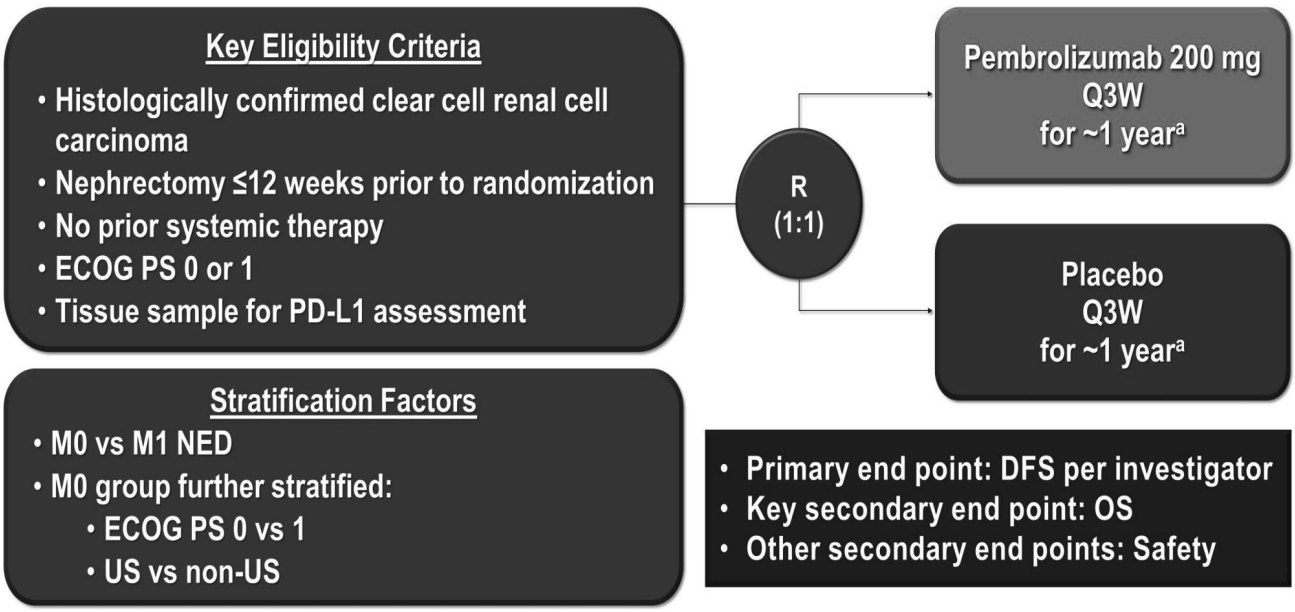
KEYNOTE-564 Study Design



DFS, disease-free survival; Q3W, every 3 weeks.
[a]≤17 cycles of treatment were equivalent to ~1 year.

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Baseline Characteristics

Characteristic, n (%)	Pembro N = 496	Placebo N = 498
Age, median (range), yrs	60 (27–81)	60 (25–84)
Male	347 (70.0)	359 (72.1)
ECOG PS		
0	421 (84.9)	426 (85.5)
1	75 (15.1)	72 (14.5)
Disease risk category		
M0 intermediate-high risk	427 (86.1)[a]	433 (86.9)
M0 high risk	40 (8.1)	36 (7.2)
M1 NED	29 (5.8)	29 (5.8)

Characteristic, n (%)	Pembro N = 496	Placebo N = 498
Geographic location		
North America	113 (26.8)	125 (25.1)
European Union	188 (37.9)	187 (37.6)
Rest of the world	175 (35.3)	186 (37.3)
PD-L1 status[b]		
CPS <1	124 (25.0)	113 (22.7)
CPS ≥1	365 (73.6)	383 (76.9)
Missing	7 (1.4)	2 (0.4)
Sarcomatoid features		
Present	52 (10.5)	59 (11.8)
Absent	417 (84.1)	415 (83.3)
Unknown	27 (5.4)	24 (4.8)

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
[a]Included 5 participants with T2, grade ≤3, N0 M0 or T1 N0 M0. [b]Assessed using the PD-L1 IHC 22C3 pharmDx assay. CPS (combined positive score) is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. Data cutoff date: December 14, 2020.

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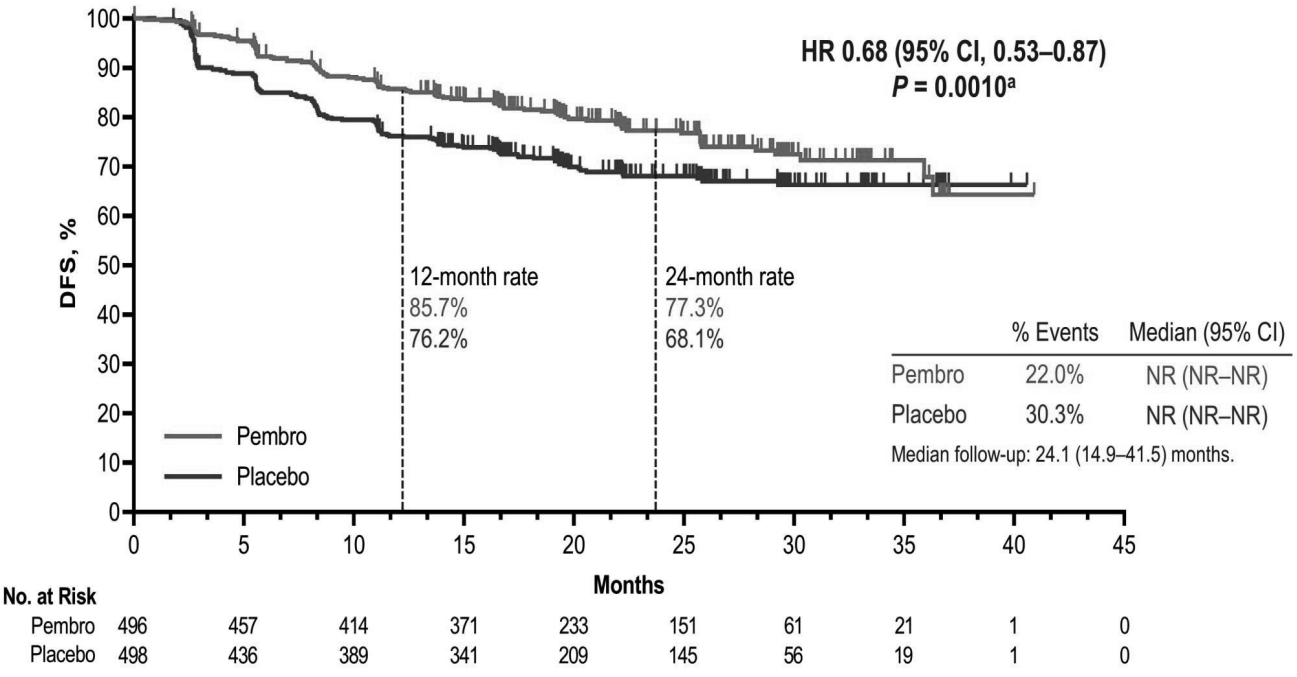
DFS by Investigator, ITT Population



[a]Crossed prespecified p-value boundary for statistical significance of 0.0114.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

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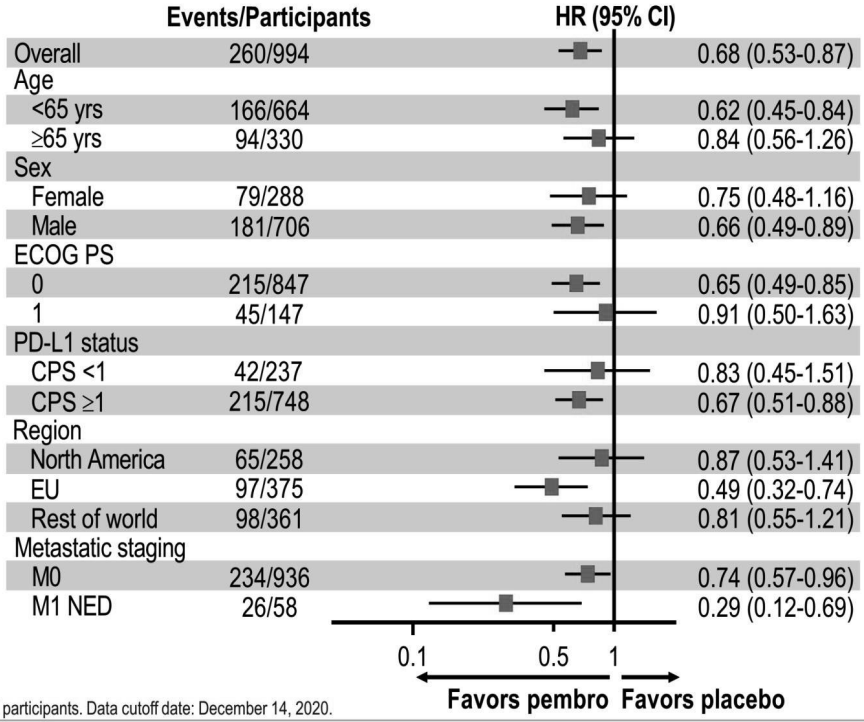
DFS by Investigator in Subgroups, ITT Population



ITT population included all randomized participants. Data cutoff date: December 14, 2020.

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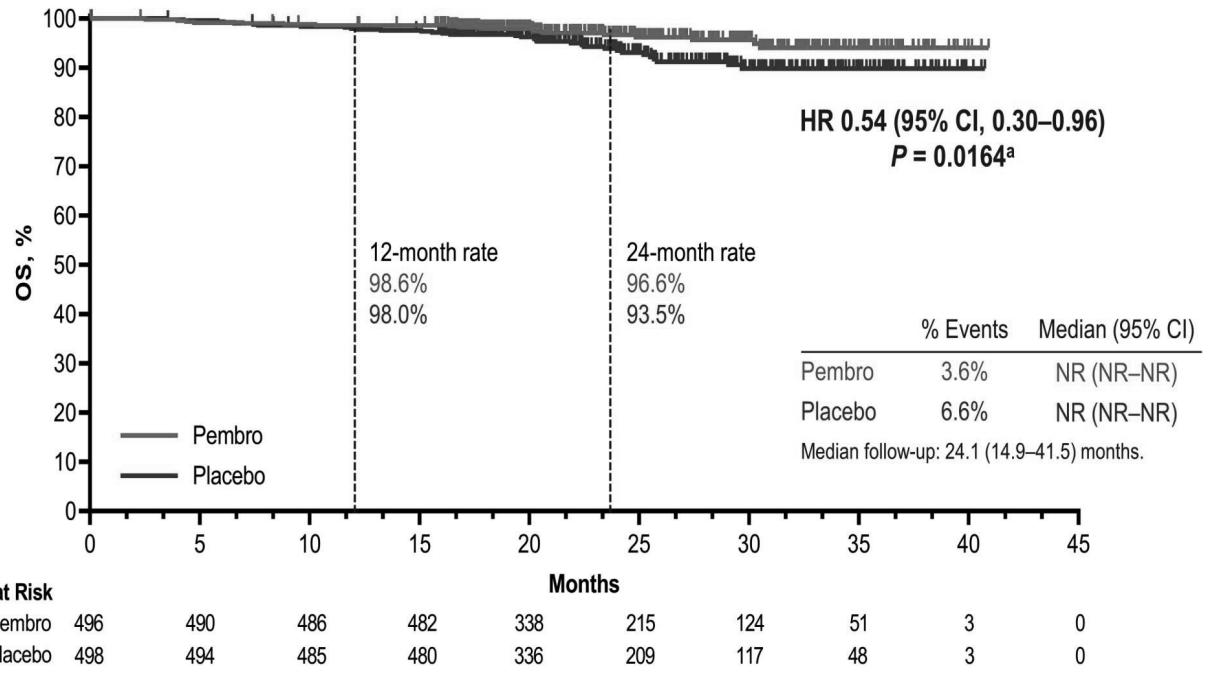
Interim OS Results, ITT Population



[a]Did not cross prespecified p-value boundary for statistical significance of 0.0000093 for 51 events. Final analysis for OS to occur after approximately 200 OS events.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

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Summary of Safety Results, As-Treated Population

Participants with ≥1 AE, n (%)	Pembro N = 488	Placebo N = 496
All-cause AEs	470 (96.3)	452 (91.1)
Grade 3–5	158 (32.4)	88 (17.7)
Led to treatment discontinuation	101 (20.7)	10 (2.0)
Led to death	2 (0.4)	1 (0.2)
Serious all-cause AEs[a]	100 (20.5)	56 (11.3)
Led to treatment discontinuation	49 (10.0)	5 (1.0)
Treatment-related AEs	386 (79.1)	265 (53.4)
Grade 3–5	92 (18.9)	6 (1.2)
Led to treatment discontinuation	86 (17.6)	3 (0.6)
Led to death	0	0

[a]Serious AEs were AEs that were life-threatening, required hospitalization, resulted in death or persistent/significant disability/incapacity, or were judged as serious per investigator.
As-treated population included all participants who received ≥1 dose of study treatment. Median duration (range) of treatment was 11.1 (0.0–14.3) months with pembro and 11.1 (0.0–15.4) months with placebo.
Data cutoff date: December 14, 2020.

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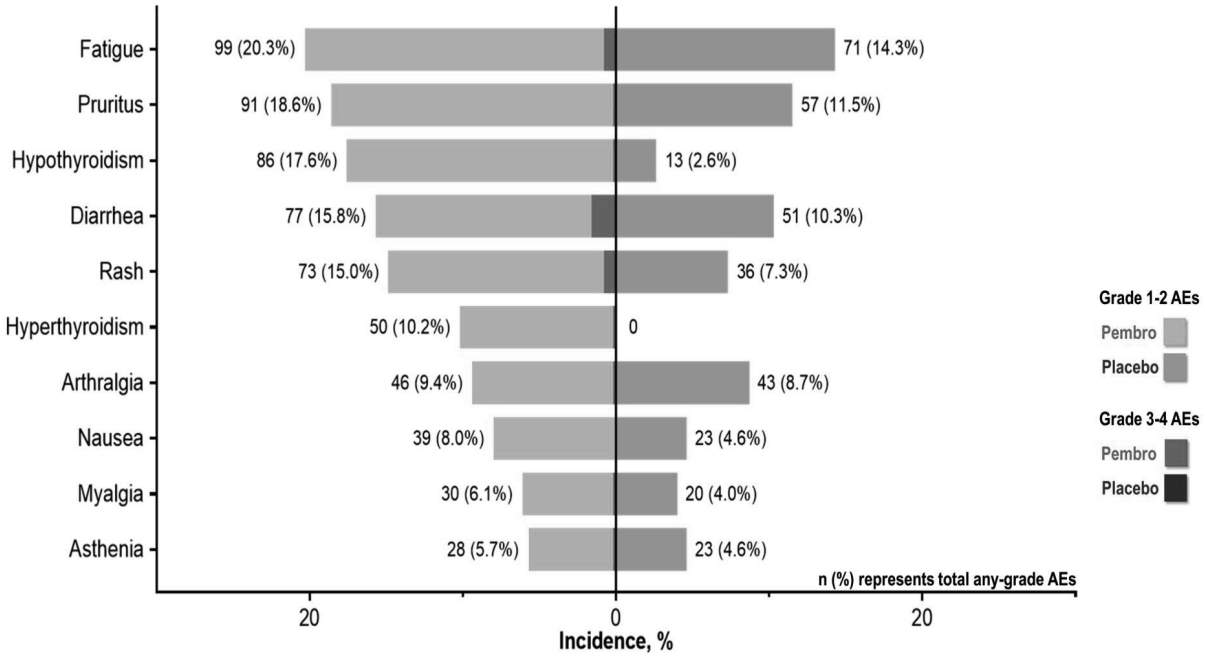
Treatment-Related AEs with Incidence ≥5%, As-Treated Population



As-treated population included all participants who received ≥1 dose of study treatment. No treatment-related deaths occurred. Data cutoff date: December 14, 2020.

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Summary and Conclusions

- Adjuvant pembrolizumab post nephrectomy demonstrated a statistically significant and clinically meaningful improvement in DFS vs placebo
  - Additional follow-up is planned for the key secondary endpoint of OS
- Benefit was consistent across subgroups, including the M1 NED population, potentially extending the use of pembrolizumab to these patients
- Safety results were in line with expectations and no new safety signals were observed
  - Low incidence of high-dose corticosteroid treatment for immune-mediated AEs
- KEYNOTE-564 is the first positive phase 3 study of an adjuvant immunotherapy in RCC
- Pembrolizumab is a potential new standard of care for patients with RCC in the adjuvant setting

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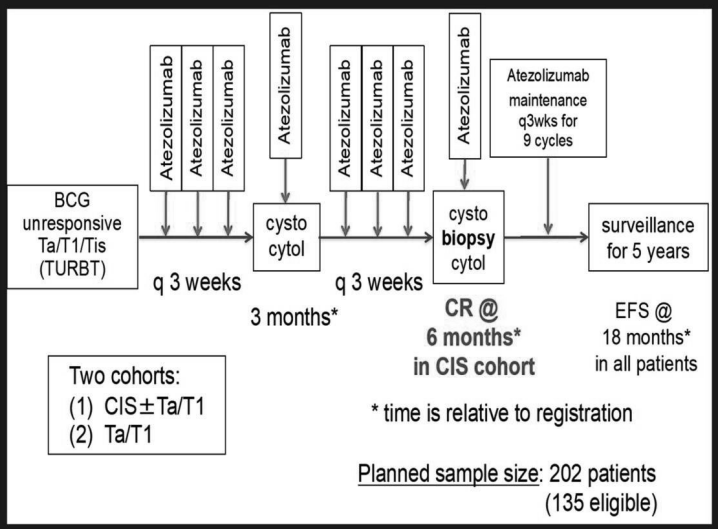
1. Prostatakarzinom
2. Nierenzellkarzinom
3. Urothelkarzinom

#4541: Phase II Trial of Atezolizumab in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer: SWOG S1605

Peter C. Black,et al.

S1605 Trial Design



Previously reported @ ASCO 2020:

- Primary endpoint at 6 months in CIS +/- Ta/T1

Update @ ASCO 2020:

- Co-primary endpoint EFS @18 months in patients with Ta/T1 (no CIS)
- Duration of CR 12 months after primary endpoint (i.e. @18 months after registration) in patients with CIS

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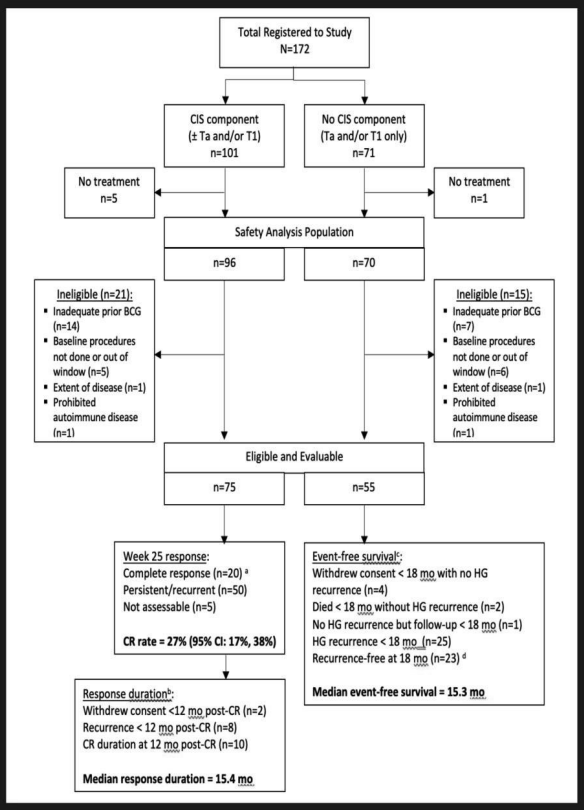

a 20/75 = 27% (95% CI 17%, 38%)
b Calculated from date of week 25 biopsy
c Calculated from date of registration
d n=5 had subsequent HG event post 18 mo

	CIS (± Ta/T1) N=75	Ta/T1 only N=55
Sex – Male (N, %)	63 (84%)	46 (84%)
Age (median, range)	73.7 (47.4, 90.8)	74.1 (38.3, 97.7)
Race (N, %)		
White	71 (95%)	49 (89%)
Other/Unknown	4 (5%)	6 (11%)
Zubrod Performance Status (N, %)		
0	58 (77%)	36 (65%)
1	17 (23%)	17 (31%)
2	0 (0%)	2 (4%)
Histology		
CIS only	44 (59%)	--
CIS/Ta	14 (19%)	--
CIS/T1	13 (17%)	--
CIS/Ta/T1	4 (5%)	--
Ta only	--	30 (55%)
T1 only	--	22 (40%)
Ta/T1	--	3 (5%)
# prior BCG instillations (median, range)	12 (6, 29)	12 (6, 31)
Days since last BCG (median, range)	155 (5, 564)	127 (67, 273)

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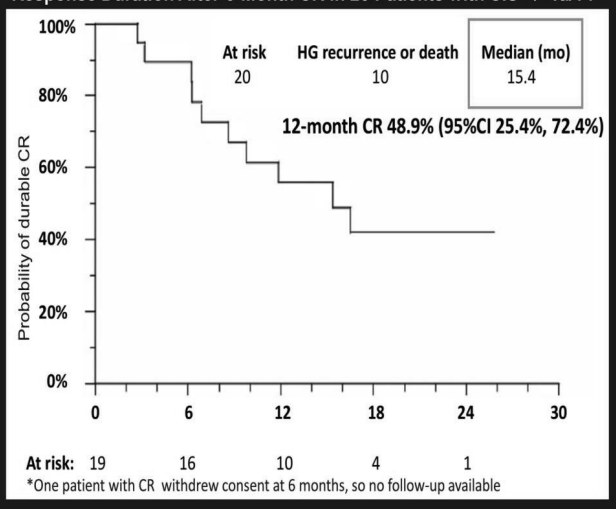
Treatment Outcomes

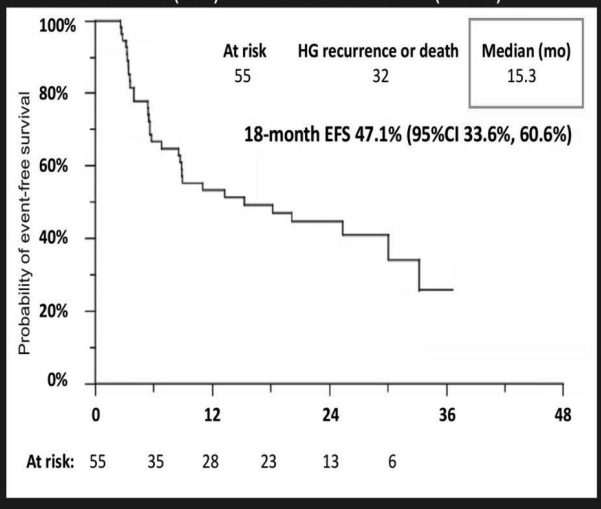
	EFS in CIS (± Ta/T1) % (95% CI)	EFS in Ta/T1 % (95% CI)
6 months	32% (22%, 43%)	65% (52%, 78%)
12 months	25% (15%, 35%)	51% (38%, 65%)
18 months	14% (6%, 23%)	47% (34%, 61%)

Response Duration After 6-Month CR in 20 Patients with CIS +/- Ta/T1



*One patient with CR withdrew consent at 6 months, so no follow-up available

Event-free Survival (EFS) in 55 Patients with Ta/T1 (no CIS)



EFS: event is first high grade recurrence or death; patients censored at last disease assessment

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Adverse Events *(n=166)*

Worst Grade Reported	Any Adverse Event N (%)	Treatment-related* Adverse Event N (%)
None reported	4 (2%)	24 (14%)
Grade 1-2	100 (60%)	114 (69%)
Grade 3-4	60 (36%)	26 (16%)
Grade 5	2 (1%)	2 (1%)**
Treatment discontinued due to AE	14 (8%)	--

* attribution: possible, probable, definite
** death due to (1) sepsis resulting from respiratory failure secondary to myasthenia gravis; (2) E coli sepsis

Conclusions

- The observed CR to atezolizumab at 6 months and the 12-month durability of CR in patients with BCG-unresponsive CIS were similar to that of recently reported trials.
- The 18-month EFS in patients with BCG-unresponsive Ta/T1 also compared favorably to recently reported results in similar patient populations.
- This trial provided no new safety concerns.
- Atezolizumab demonstrates clinically meaningful activity in patients with BCG-unresponsive CIS, Ta and T1 tumors who are ineligible for or have declined cystectomy.

Thank you to all 172 patients, their families and their caregivers for their trust and participation!

Presented By: **Peter Black & Parminder Singh**

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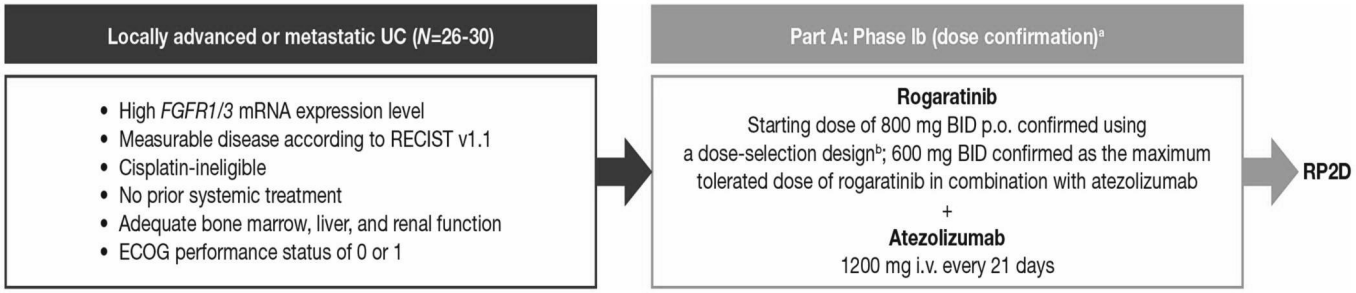
#4532: Safety and Efficacyof Rogaratinib in Combination with Atezolizumab in Patients with Cisplatin-Inelegible, Locally advanced or metastatic Urothelial Cancer and FGFR mRNA Overexpression in Phase IB/II Fort-2-study

Jonathan E. Rosenberg,et al.

Methods



- *FGFR1* or *3* mRNA expression levels were detected by RNA *in situ* hybridization in archival or fresh tumor biopsies (RNAscope®; Advanced Cell Diagnostics, Inc., Seattle, WA, USA)
  - *FGFR3* mutation status, presence of *FGFR3* translocations, and activating mutations in *PIK3CA*- and / or *RAS*- encoding genes were evaluated
- Primary objectives of the Phase Ib portion involved determining the safety, tolerability, and RP2D of rogaratinib in combination with atezolizumab

[a]The results of Part A: Phase Ib will gate the start of the Part B: Phase II portion; the study design of Part B is to be confirmed;
[b]Dose reductions from rogaratinib 800 mg to 600 mg and 400 mg were permitted in the event of clinically significant toxicities
BID, twice daily; ECOG, Eastern Cooperative Oncology Group; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended Phase II dose; UC, urothelial cancer

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Patient demographics

- 26 patients were treated with rogaratinib in combination with atezolizumab (data cut-off February 8, 2021)

	Rogaratinib 600 mg BID + atezolizumab 1200 mg (*N*=26)
Male, *n* (%)	23 (88)
Median age, years (range)	76 (47-85)
Stage at study entry,[a] *n* (%)	
III	1 (4)
IV	21 (81)
ECOG performance status, *n* (%)	
0	11 (42)
1	15 (58)

- PD-L1 expression was negative or non-detectable in 20 patients (77%) (combined positive score of <10)

[a]Tumor, node, metastasis classification; stage IV is an independent classification
PD-L1, programmed cell death ligand 1

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Safety

- All patients experienced ≥1 TEAE; serious AEs were reported in **54%** of patients
- TEAEs led to treatment interruptions or reductions in **65%** and **42%** of patients, respectively
- **23%** of patients discontinued treatment due to TEAEs
- Grade 5 TEAEs (*n*=3), were all deemed unrelated to treatment
- Unique AEs related to rogaratinib included detachment of retinal pigment epithelium (1 patient, **4%**) and hyperphosphatemia (15 patients, **58%**); all grade 1 or 2

n (%)	Rogaratinib 600 mg BID + atezolizumab 1200 mg (*N*=26)		
	All grade	Grade 1 or 2	Grade 3 or 4
Diarrhea	17 (65)	16 (62)	1 (4)
Hyperphosphatemia	15 (58)	15 (58)	0
Nausea	11 (42)	10 (38)	1 (4)
Fatigue	10 (38)	10 (38)	0
Urinary tract infection	9 (35)	8 (31)	1 (4)
Increased alanine aminotransferase	8 (31)	8 (31)	0
Decreased appetite	8 (31)	8 (31)	0
Abdominal pain	7 (27)	6 (23)	1 (4)
Asthenia	7 (27)	7 (27)	0
Constipation	7 (27)	6 (23)	1 (4)
Increased aspartate aminotransferase	6 (23)	6 (23)	0
Dry mouth	6 (23)	6 (23)	0
Increased lipase	6 (23)	1 (4)	5 (19)
Pyrexia	6 (23)	5 (19)	1 (4)
Vomiting	6 (23)	6 (23)	0

AEs were reported using Medical Dictionary for Regulatory Activities and graded using Common Terminology Criteria for Adverse Events
AE, adverse event; TEAE, treatment-emergent adverse event

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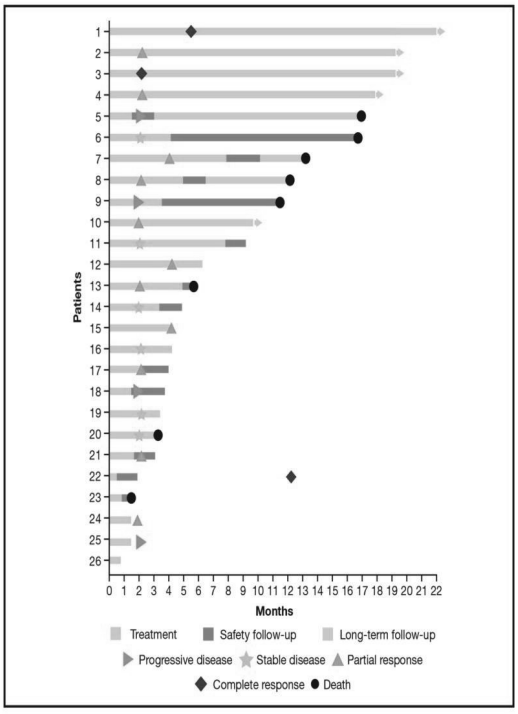
Efficacy

- Of the **14** responders, **11** (**79%**) had low or negative PD-L1 expression

n (%) [95% CI]	Rogaratinib 600 mg BID + atezolizumab 1200 mg (*N*=24)
Best response	
Complete response	3 (13)
Partial response	11 (46)
Stable disease	6 (25)
Progressive disease	4 (17)
Objective response rate	14 (58) [37, 78]
Disease control rate	20 (83) [63, 95]

- Median duration of response was not reached
- Median follow-up was 7.4 months, with **5 responders** remaining on treatment



CI, confidence interval

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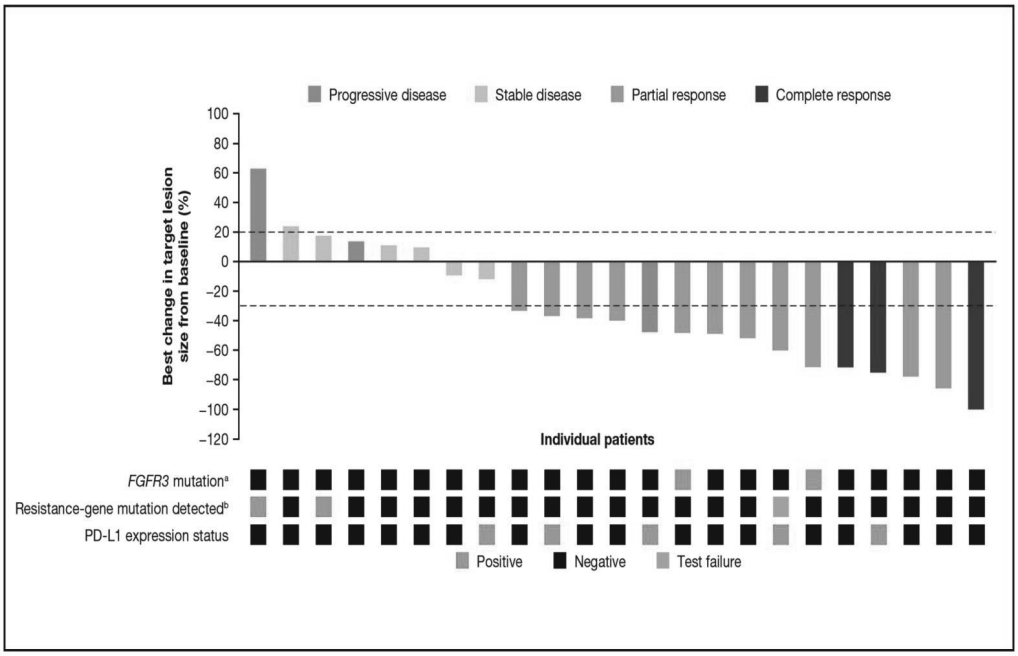
Clinical response



- Promising clinical efficacy was observed, regardless of PD-L1 expression or *FGFR3* mutation or fusion status
- Based on resulting efficacy and safety data, rogaratinib 600 mg BID was determined as the RP2D

[a]No *FGFR3* fusions were detected; [b]Only *PIK3CA* and *KRAS* mutations were detected; no mutations were detected in *HRAS* or *NRAS*
3 patients did not have complete values for tumor size at all post-baseline assessments and were excluded from the analysis. One patient achieved a 48% reduction in target lesion, corresponding to a partial response, but reported progressive disease in non-target lesions on first scan; therefore, best overall response was determined as progressive disease

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