Patrik Palacka

Genitourinárne malignity

Vyhlásenie o konflikte záujmov autora

Deklarujem nasledujúci konflikt záujmov

Forma finančného prepojenia	Spoločnosť
Participácia na klinických štúdiách/firemnom grante	Bayer, Roche, Pfizer
Nepeňažné plnenie (v zmysle zákona)	Janssen, Astellas, Bayer, Pfizer, Roche, Astra Zeneca, Novartis, Teva, Merck
Prednášajúci	Novartis, Janssen, Astellas, Bayer, Pfizer, Roche, Astra Zeneca, Teva, Merck
Akcionár	
Konzultant/odborný poradca	Pierre Fabre
Ostatné príjmy (špecifikovať)	

Podľa UEMS (upravené v zmysle slovenskej legislatívy)

Prednáška je podporená agentúrou
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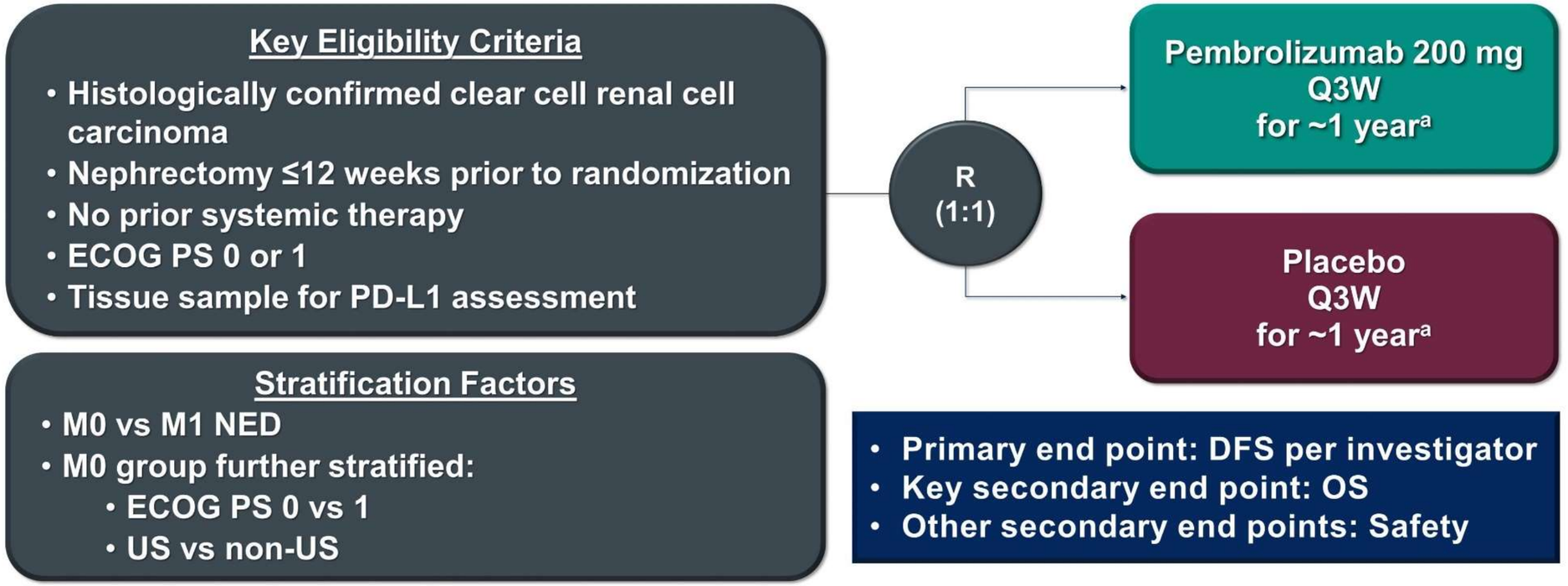
1. Zhubné nádory obličiek

Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

KEYNOTE-564 Study Design



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

Choueiri TK. Abstract LBA5

Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

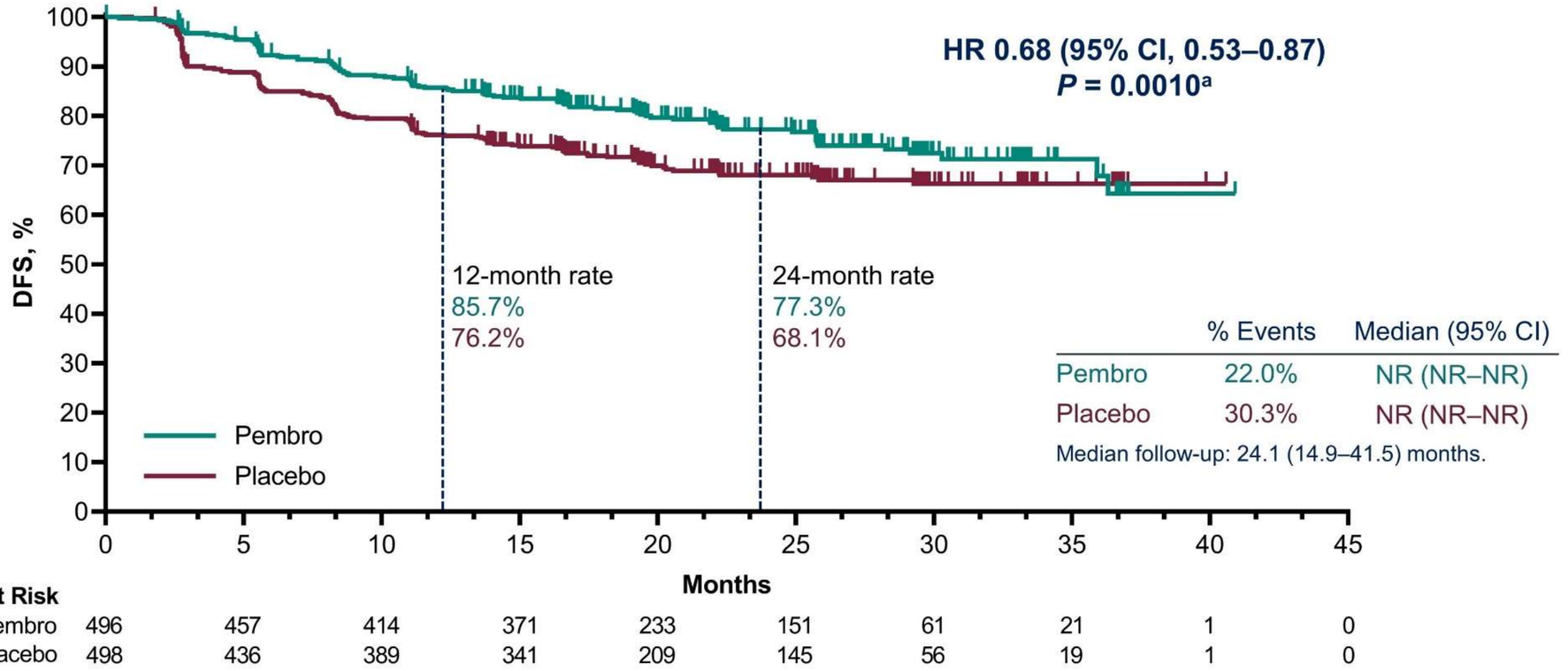
Prespecified Disease Risk Categories

Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	

Choueiri TK. Abstract LBA5

Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

DFS by Investigator, ITT Population

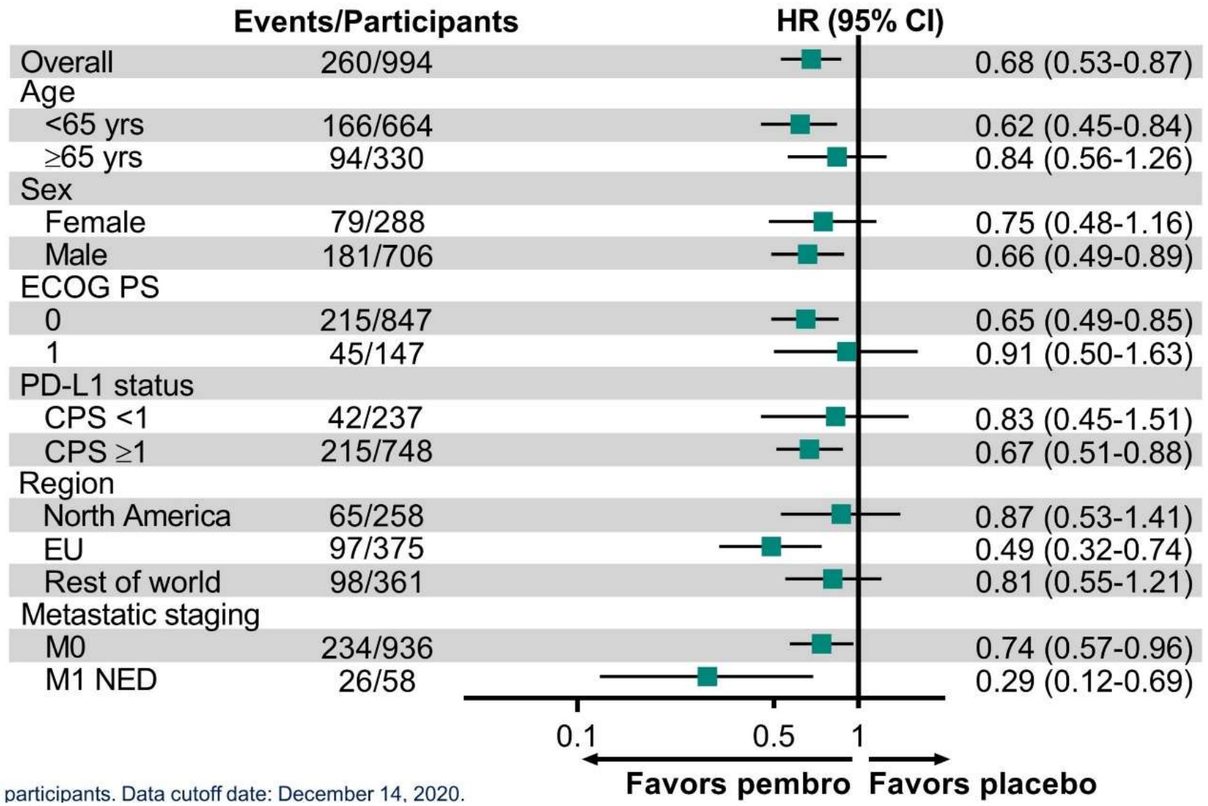


[a]Crossed prespecified p-value boundary for statistical significance of 0.0114.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

Choueiri TK. Abstract LBA5

Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

DFS by Investigator in Subgroups, ITT Population



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

Choueiri TK. Abstract LBA5

Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

Interim OS Results, ITT Population

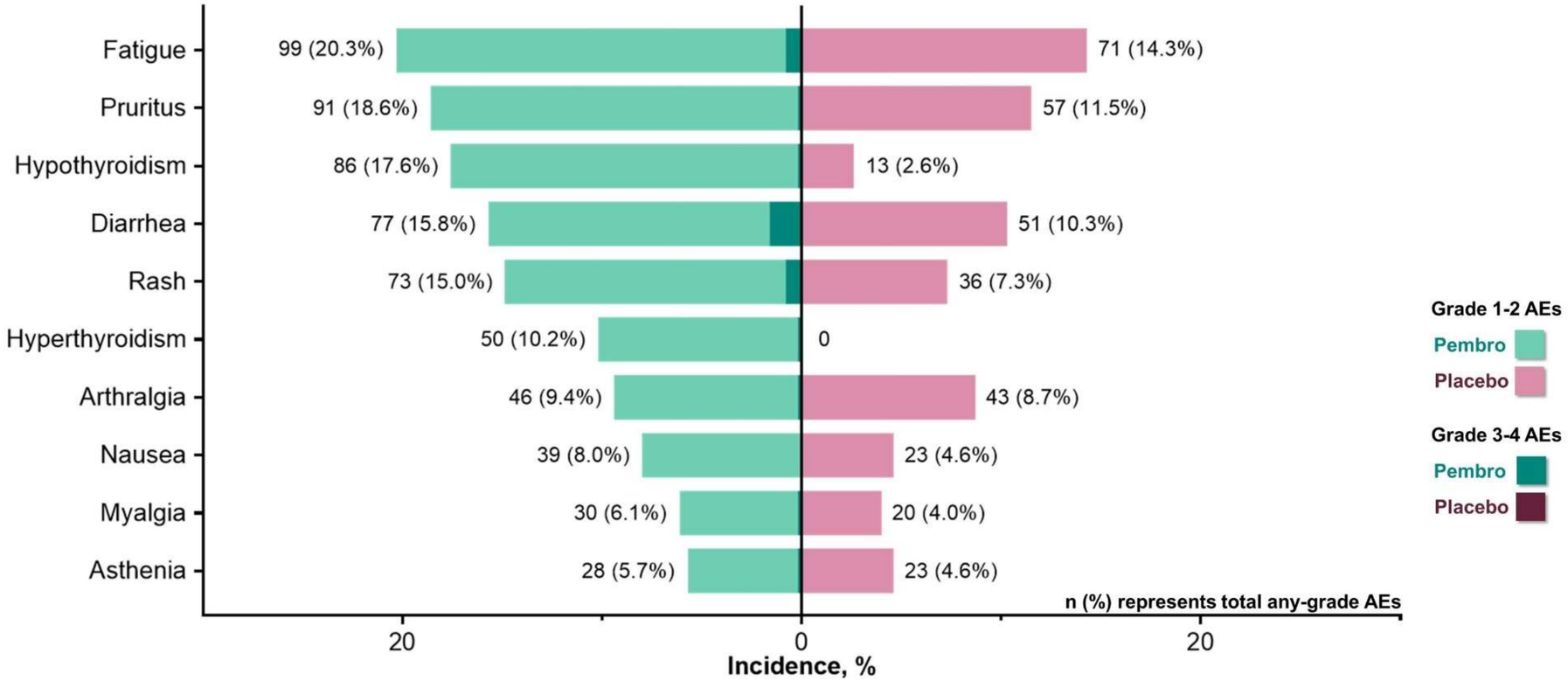
No. at Risk										
Pembro	496	490	486	482	338	215	124	51	3	0
Placebo	498	494	485	480	336	209	117	48	3	0

[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.

Choueiri TK. Abstract LBA5

Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

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

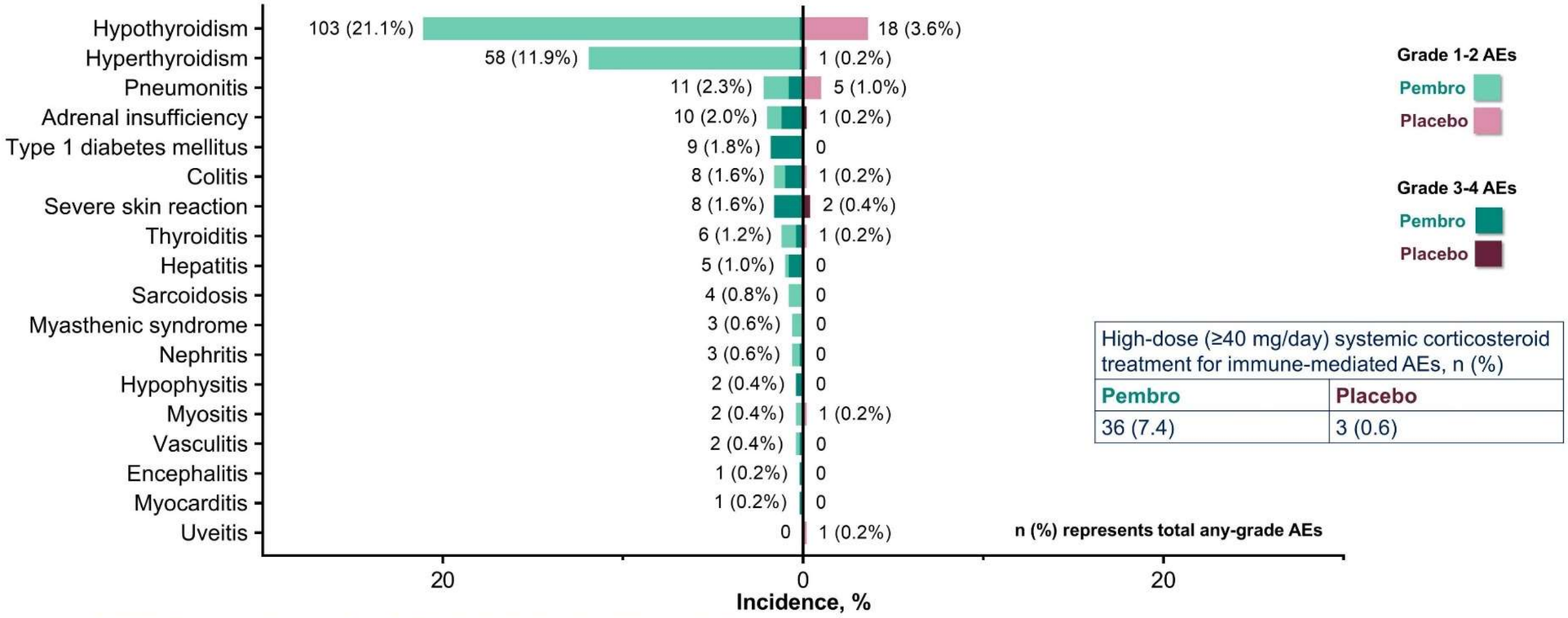


As-treated population included all participants who received ≥1 dose of study treatment. No treatment-related deaths occurred. Data cutoff date: December 14, 2020.

Choueiri TK. Abstract LBA5

Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

Immune-Mediated AEs[a], As-Treated Population



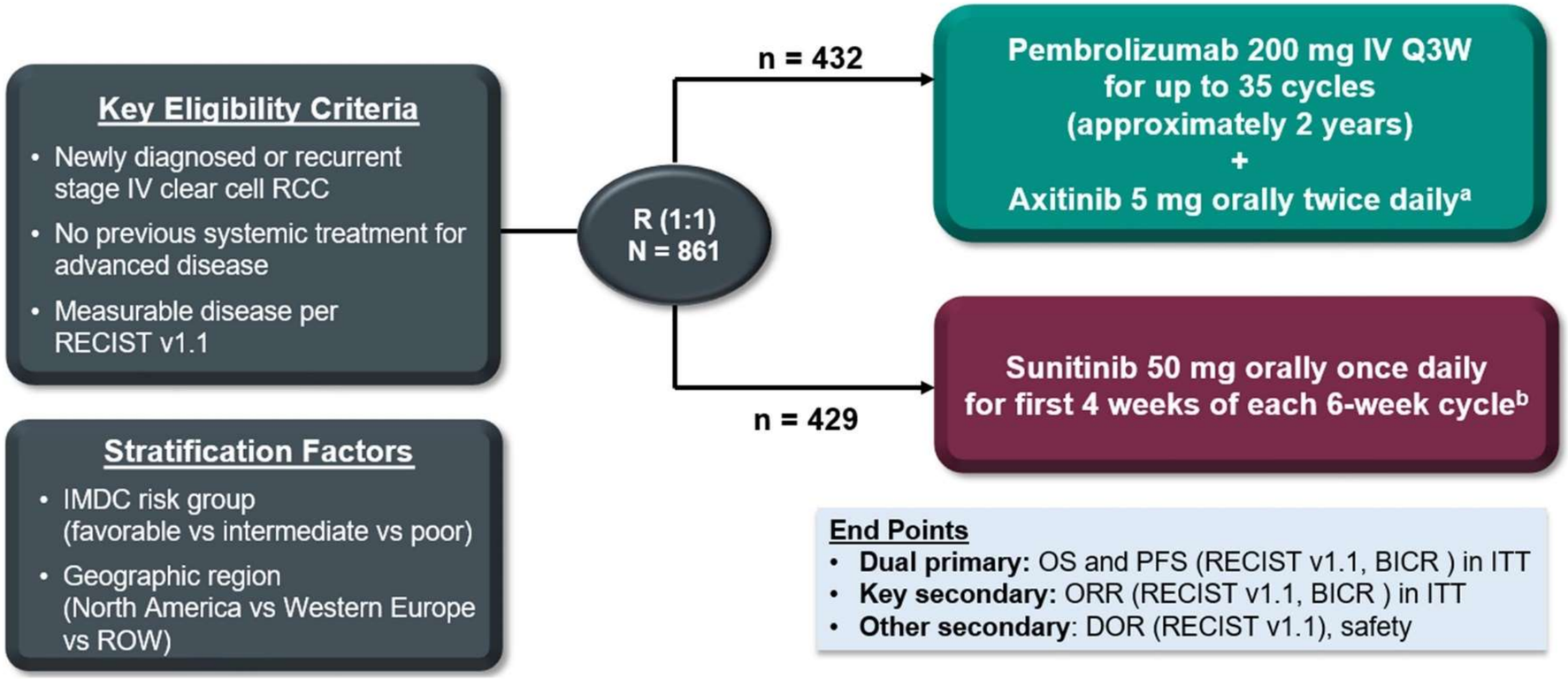
High-dose (≥40 mg/day) systemic corticosteroid treatment for immune-mediated AEs, n (%)	
Pembro	**Placebo**
36 (7.4)	3 (0.6)

[a]Based on a prespecified list of terms included regardless of attribution to study treatment by investigator.
Infusion reactions, pembro: any grade in 7 participants (1.4%), grade 3 in 2 participants (0.4%). Infusion reactions, placebo: any grade in 5 participants (1.0%), grade 3-4 in no participants. No deaths due to immune-mediated events occurred. As-treated population included all participants who received ≥1 dose of study treatment. Data cutoff date: December 14, 2020.

Choueiri TK. Abstract LBA5

- Abstract 4500: Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: Results from 42-month follow-up of KEYNOTE-426

KEYNOTE-426 Study Design

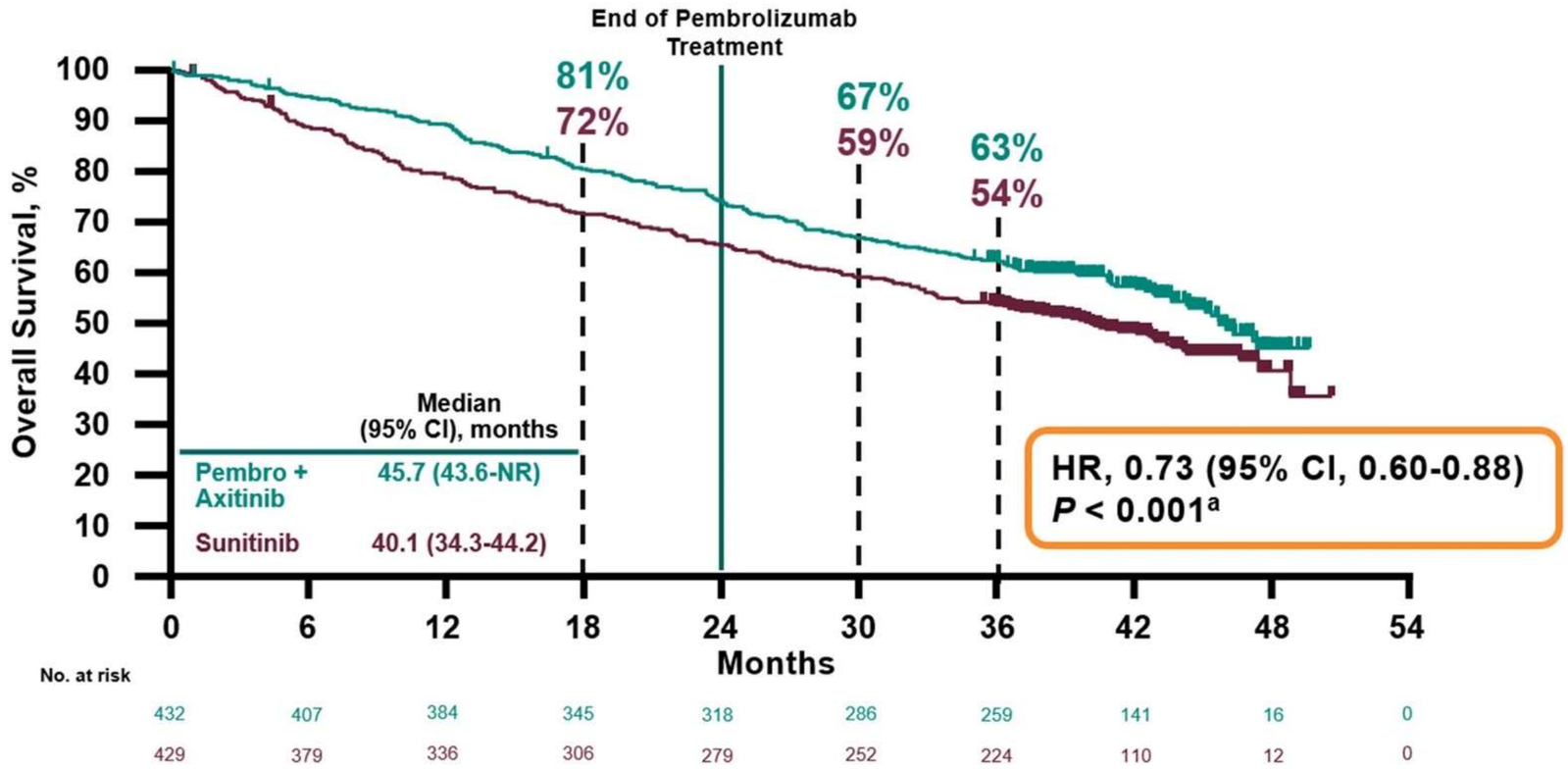


[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity.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

Rini BI. Abstract 4500

- Abstract 4500: Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: Results from 42-month follow-up of KEYNOTE-426

OS in the ITT Population

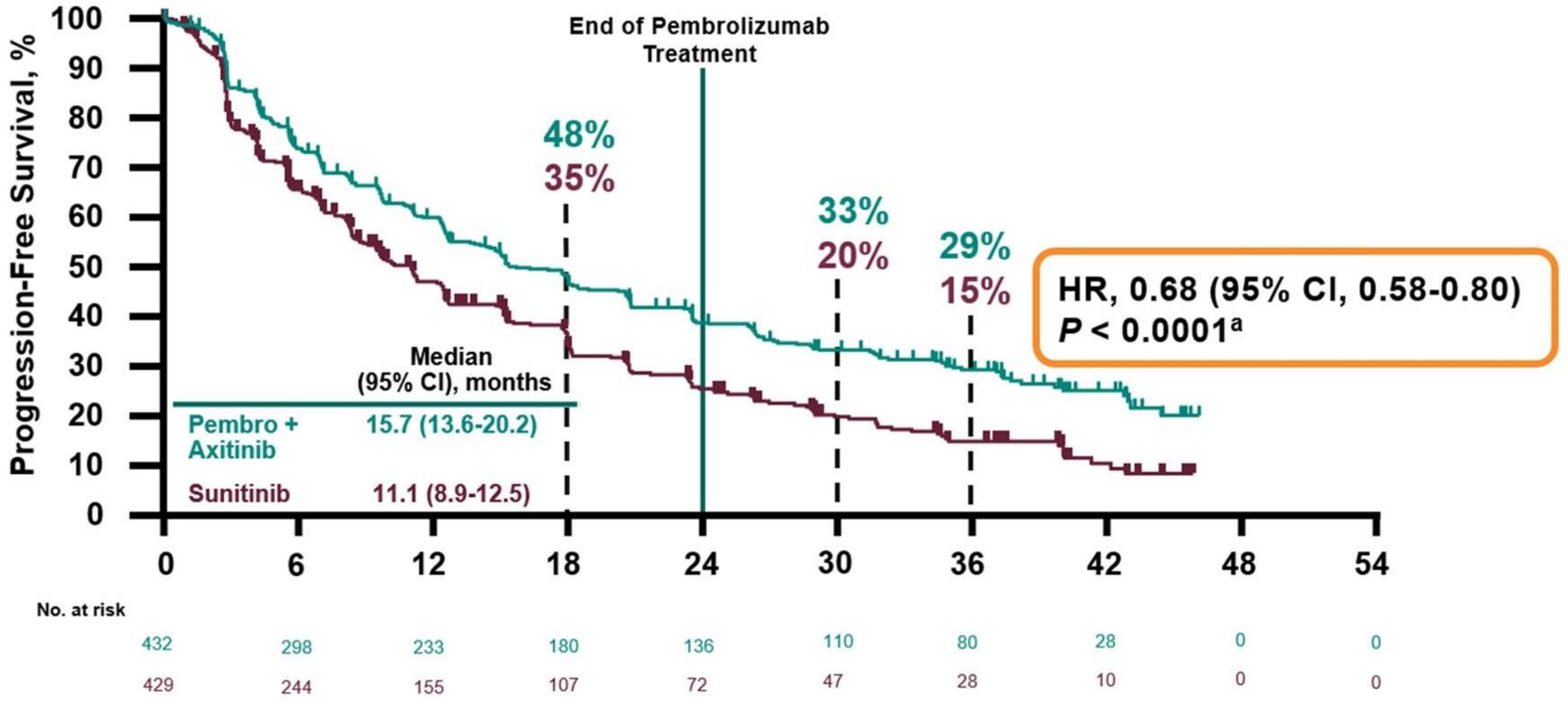


[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 11, 2021.

Rini BI. Abstract 4500

- Abstract 4500: Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: Results from 42-month follow-up of KEYNOTE-426

PFS in the ITT Population

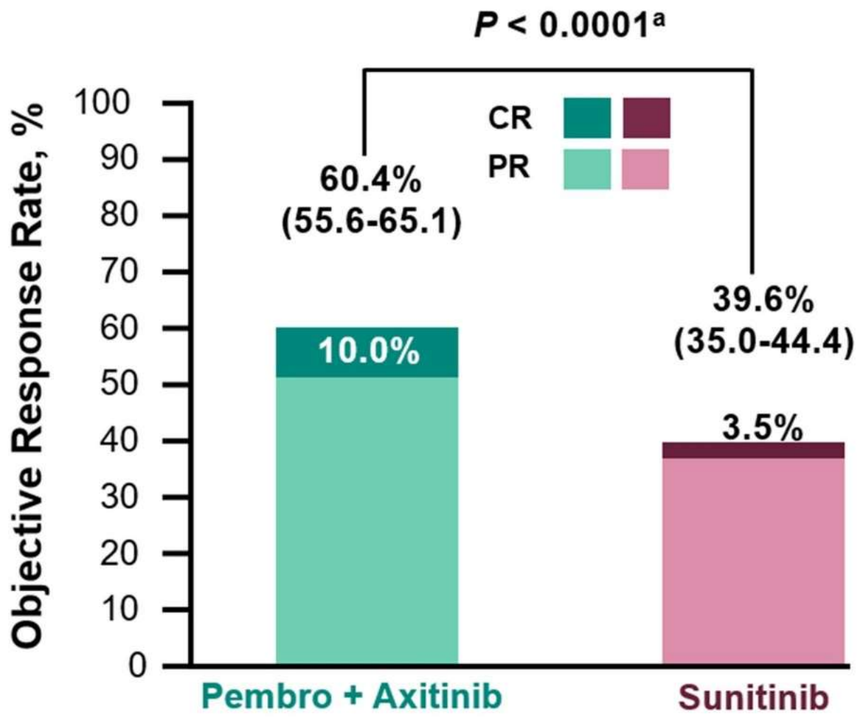


[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to PFS; only nominal *P* values are reported. Data cutoff: January 11, 2021.

Rini BI. Abstract 4500

- Abstract 4500: Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: Results from 42-month follow-up of KEYNOTE-426

Confirmed ORR in the 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.

Rini BI. Abstract 4500

- Abstract 4500: Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: Results from 42-month follow-up of KEYNOTE-426

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.

Rini BI. Abstract 4500

- Abstract 4500: Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: Results from 42-month follow-up of KEYNOTE-426

Improved Outcomes with Pembrolizumab + Axitinib

Median Follow-Up	12.8 months	30.6 months	42.8 months
OS	NR	NR	45.7
HR (95% CI)	0.53 (0.38-0.74)	0.68 (0.55-0.85)	0.73 (0.60-0.88)
PFS, months	15.1	15.4	15.7
HR (95% CI)	0.69 (0.57-0.84)	0.71 (0.60-0.84)	0.68 (0.58-0.80)
ORR	59%	60%	60%
CR	6%	9%	10%

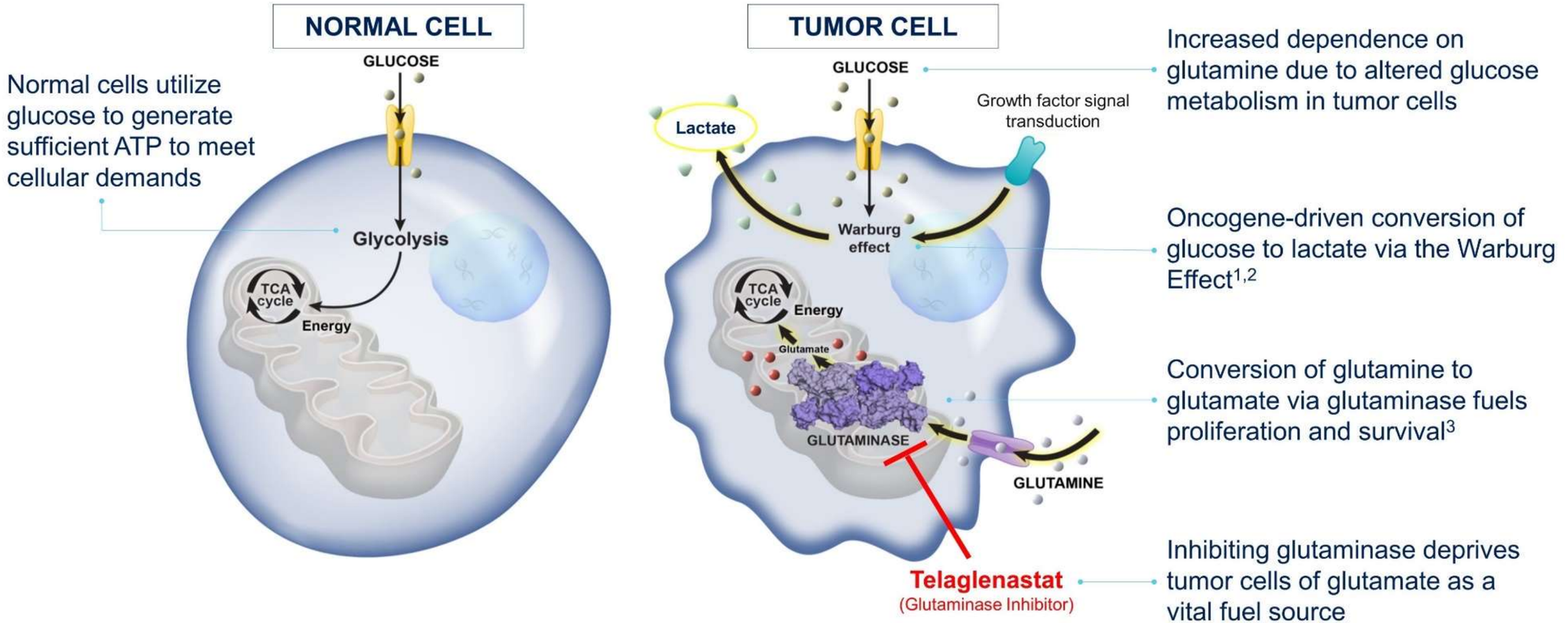
OS=Overall survival; HR=Hazard ratio; CI=Confidence interval; PFS=Progression-free survival; ORR=Objective response rate; CR=Complete response; NR=Not reached.

Rini et al, NEJM, 2019; Powles et al, Lancet Oncol, 2020

Rini BI. Abstract 4500

- Abstract 4501: CANTATA: Primary analysis of a global, randomized, placebo-controlled, double-blind trial of telaglenastat (CB-839) + cabozantinib versus placebo + cabozantinib in advanced/metastatic renal cell carcinoma patients who progressed on immune checkpoint inhibitor or anti-angiogenic therapies

Altered Tumor Metabolism in Tumor Cells



Tannir NM. Abstract 4501

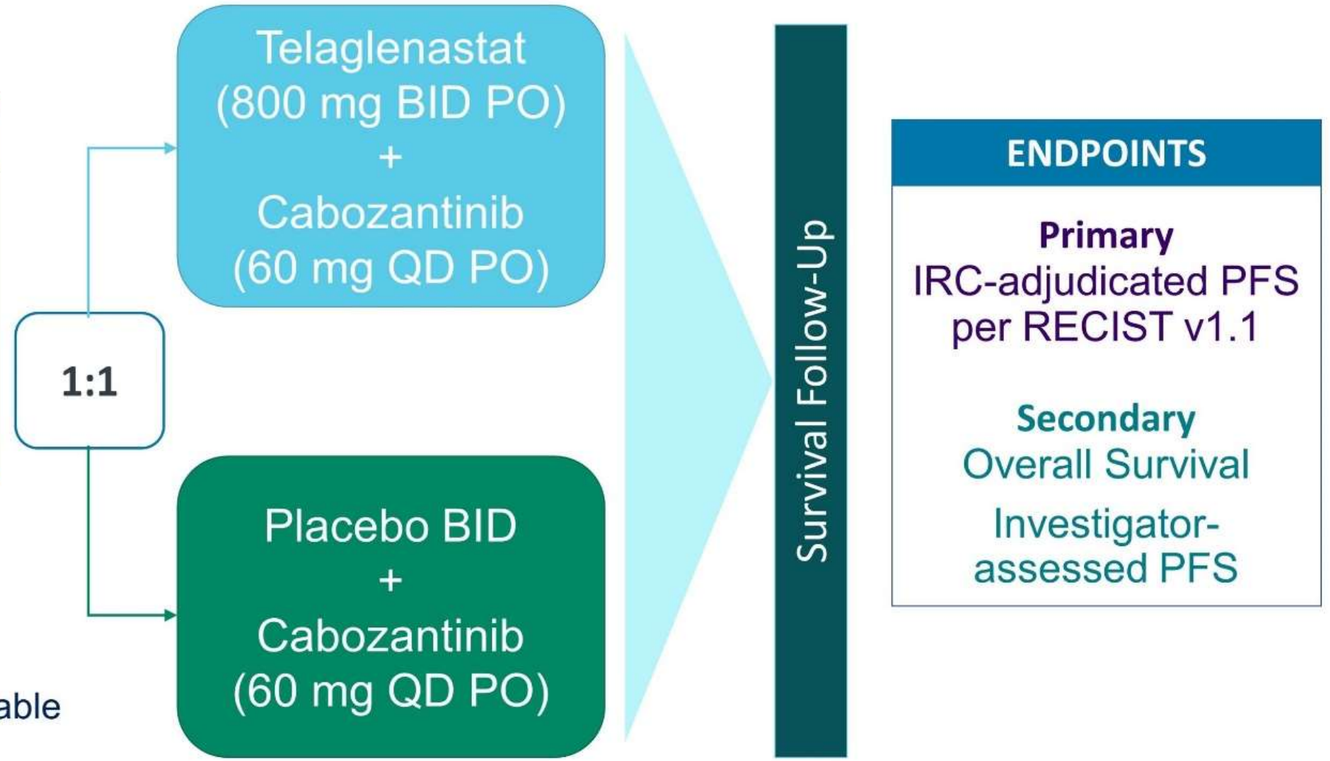
- Abstract 4501: CANTATA: Primary analysis of a global, randomized, placebo-controlled, double-blind trial of telaglenastat (CB-839) + cabozantinib versus placebo + cabozantinib in advanced/metastatic renal cell carcinoma patients who progressed on immune checkpoint inhibitor or anti-angiogenic therapies

CANTATA Study Design

Key Eligibility Criteria

- Advanced/metastatic clear cell RCC
- KPS ≥ 70%
- 1-2 lines of prior therapy including at least 1 antiangiogenic therapy **or** nivolumab + ipilimumab

- N=444
- Stratification factors:
  - Prior ICI therapy (yes vs. no)
  - IMDC Prognostic Risk Group (favorable vs. intermediate vs. poor)



ENDPOINTS

Primary
IRC-adjudicated PFS per RECIST v1.1

Secondary
Overall Survival
Investigator-assessed PFS

NCT03428217

Tannir NM. Abstract 4501

- Abstract 4501: CANTATA: Primary analysis of a global, randomized, placebo-controlled, double-blind trial of telaglenastat (CB-839) + cabozantinib versus placebo + cabozantinib in advanced/metastatic renal cell carcinoma patients who progressed on immune checkpoint inhibitor or anti-angiogenic therapies

Efficacy (IRC-Assessed)

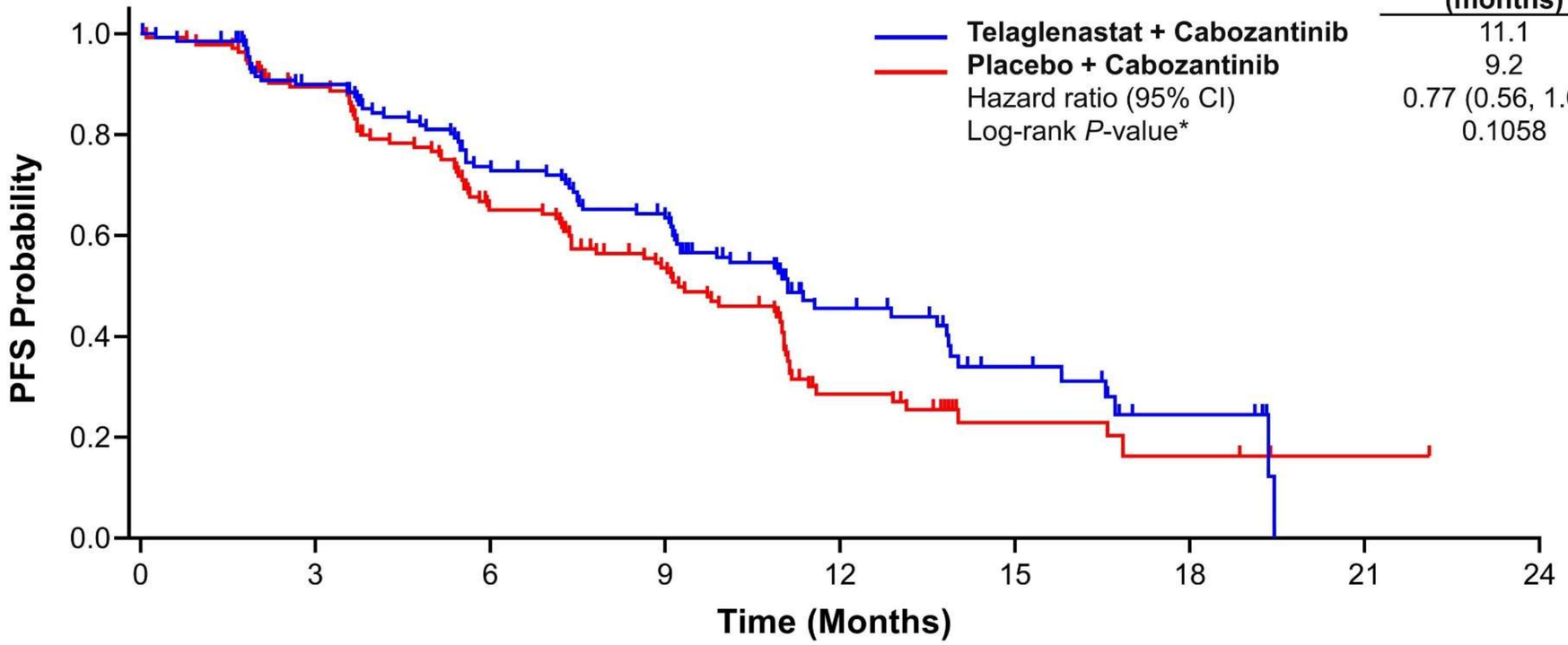
Parameter	Telaglenastat + Cabozantinib (n=221)	Placebo + Cabozantinib (n=223)
Progression-free survival (IRC)		
Median, months (95% CI)	9.2 (7.6, 11.1)	9.3 (7.6, 11.0)
Hazard ratio (95% CI)[a]	0.94 (0.74, 1.21)	
P-value	0.653	
Confirmed best responses, n (%)		
Complete response	2 (0.9)	2 (0.9)
Partial response	67 (30.3)	60 (26.9)
Stable disease	121 (54.8)	134 (60.1)
Progressive disease	19 (8.6)	19 (8.5)
Not evaluable/unknown	12 (5.4)	8 (3.6)
Overall response rate, n (%)	69 (31.2)	62 (27.8)

CI, confidence interval; CR, complete response; IRC, independent-review committee; PR, partial response.
NOTE: Hazard ratios based on stratified analyses for progression-free survival. Overall survival data not mature at data cutoff for primary analysis (August 31, 2020).
[a]Based on stratified analysis according to IMDC prognostic risk group (favorable/intermediate/poor).

Tannir NM. Abstract 4501

- Abstract 4501: CANTATA: Primary analysis of a global, randomized, placebo-controlled, double-blind trial of telaglenastat (CB-839) + cabozantinib versus placebo + cabozantinib in advanced/metastatic renal cell carcinoma patients who progressed on immune checkpoint inhibitor or anti-angiogenic therapies

PFS (IRC): Subgroup of Patients With Prior ICI



Number at risk

Telaglenastat + Cabozantinib:	137	114	88	75	29	13	5	0	0
Placebo + Cabozantinib:	139	113	76	57	19	9	3	1	0

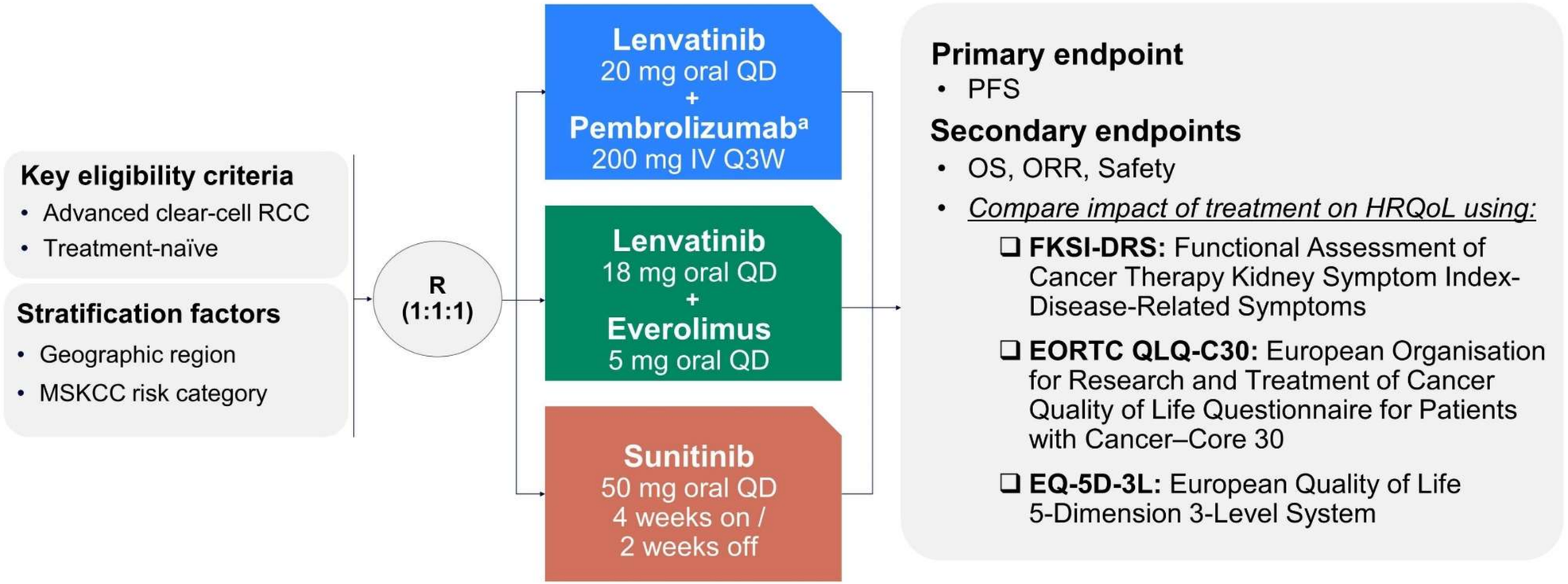
CI, confidence interval; ICI, immune checkpoint inhibitor; IRC, independent review committee; PFS, progression-free survival

*Nominal *P*-value

Tannir NM. Abstract 4501

- Abstract 4502: Health-Related Quality-of-life Analysis From the Phase 3 CLEAR Trial of Lenvatinib Plus Pembrolizumab or Everolimus vs Sunitinib for Patients With Advanced Renal Cell Carcinoma

Study Design



[a]Patients could receive a maximum of 35 pembrolizumab treatments.
HRQoL, Health-related quality of life; MSKCC, Memorial Sloan Kettering Cancer Center; R, randomization.

Motzer RJ. Abstract 4502

- Abstract 4502: Health-Related Quality-of-life Analysis From the Phase 3 CLEAR Trial of Lenvatinib Plus Pembrolizumab or Everolimus vs Sunitinib for Patients With Advanced Renal Cell Carcinoma

Efficacy Summary for the CLEAR Trial

	LEN + PEMBRO n = 355	LEN + EVE n = 357	SUN n = 357
Median PFS, mo (95% CI)	23.9 (20.8–27.7)	14.7 (11.1–16.7)	9.2 (6.0–11.0)
Stratified HR (95% CI) vs SUN *P*-value	**0.39 (0.32–0.49)** < 0.001	**0.65 (0.53–0.80)** < 0.001	-- --
Median OS, mo (95% CI)	NR (33.6–NE)	NR (NE)	NR (NE)
Stratified HR (95% CI) vs SUN *P*-value	**0.66 (0.49–0.88)** 0.005	**1.15 (0.88–1.50)** 0.3	-- --
Objective response rate, %	**71.0**	**53.5**	**36.1**
Complete response, %	16.1	9.8	4.2
Median duration of treatment, mo (range)	17.0 (0.1, 39.1)	11.0 (0.1, 40.0)	7.8 (0.1, 37.0)

Motzer R et al. *N Engl J Med*. 2021;384:1289-1300.
CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reached.

Motzer RJ. Abstract 4502

- Abstract 4502: Health-Related Quality-of-life Analysis From the Phase 3 CLEAR Trial of Lenvatinib Plus Pembrolizumab or Everolimus vs Sunitinib for Patients With Advanced Renal Cell Carcinoma

HRQoL Collection Schedule and Instruments

Study period	Pre-randomization	Randomization (21-day cycles)				
	Baseline	Treatment period				
Day	-3 to -1	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1 to Last Cycle Day 1	Off-treatment
HRQoL	**X**		**X**	**X**	**X**	**X**

FKSI-DRS	EORTC QLQ-C30	EQ-5D-3L
• 9 symptoms deemed important for advanced kidney cancer	• 9 multiple-item scales (5 functional scales, 3 symptom scales, 1 GHS/QoL scale) • 6 single-item symptom scales	• Descriptive system of 5 items • A visual analog scale (VAS)
• Total score ranges from 0 to 36 • Higher scores represent better HRQoL	• Scores for all scales range from 0 to 100 • For the GHS/QoL and functional scales, a higher score corresponds to better HRQoL • For symptom scales, a higher score represents worse symptoms	• Index scores range from 0 (health state equivalent to death) to 1 (perfect health) • Higher VAS scores (0 to 100) represent better current health

GHS, global health status.

Motzer RJ. Abstract 4502

- Abstract 4502: Health-Related Quality-of-life Analysis From the Phase 3 CLEAR Trial of Lenvatinib Plus Pembrolizumab or Everolimus vs Sunitinib for Patients With Advanced Renal Cell Carcinoma

Methodology

- The impact of treatment on HRQoL was assessed using the FKSI-DRS, EORTC QLQ-C30, and EQ-5D-3L scales for each of the following analyses:

Longitudinal change from baseline	Time to deterioration
• Assessed by mixed model analysis • Least squares (LS) mean changes and 95% CI were calculated from baseline	*Time to first deterioration* • The number of weeks between randomization and the first deterioration event[1] *Time until definitive deterioration* • The number of weeks between randomization and the earliest deterioration event with no subsequent recovery above the deterioration threshold or no subsequent HRQoL assessment data[2] • All times to deterioration were calculated and compared using the Kaplan-Meier method, stratified log-rank tests and Cox models

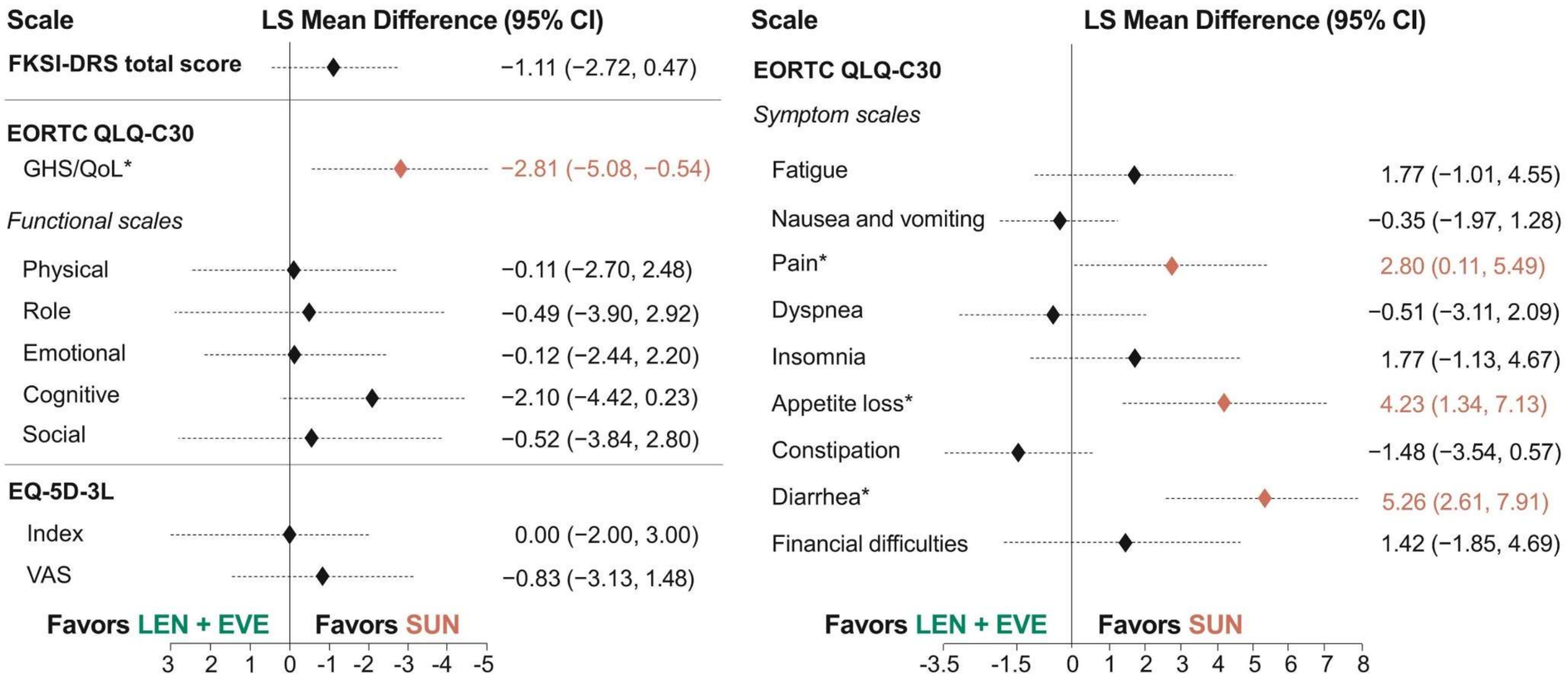
- No adjustments for multiple testing or estimation were used; all *P*-values (two-sided) and CIs are nominal and descriptive

All randomly assigned patients with any HRQoL data who received ≥ 1 dose of study treatment were included in the HRQoL analyses, unless otherwise specified. Among all patients randomly assigned to treatment, completion and compliance rates for HRQoL instruments were > 90% at baseline across groups. The rates for completion of any instrument declined below 50% at cycle 26 for LEN + PEMBRO, cycle 16 for LEN + EVE, and cycle 12 for SUN as patients discontinued treatment. Compliance was ≥ 80% until cycle 51 across groups; compliance at the off-treatment visit for any instrument was > 78% across groups.

1. Hamidou Z et al. *Oncologist*. 2011;16(10):1458-1468; 2. Bonnetain F et al. *Eur J Cancer*. 2010;46(15):2753-2762.

- Abstract 4502: Health-Related Quality-of-life Analysis From the Phase 3 CLEAR Trial of Lenvatinib Plus Pembrolizumab or Everolimus vs Sunitinib for Patients With Advanced Renal Cell Carcinoma

Overall Least Squares Mean Difference: LEN + EVE vs SUN

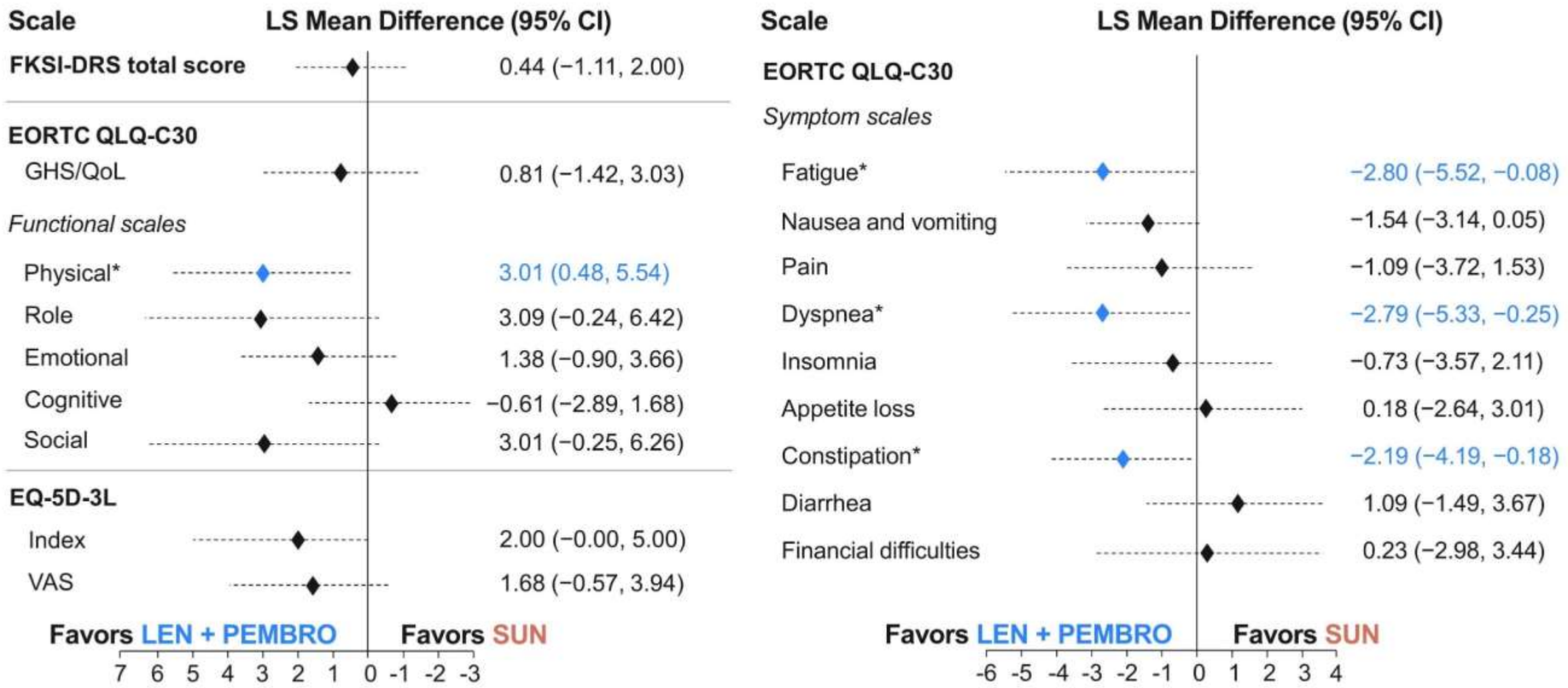


The overall LS mean difference was estimated at mean follow-up (46 weeks, cycle 15). For the FKSI-DRS total score, EORTC QLQ-C30 GHS/QoL and functional scales, and EQ-5D-3L scales, a higher score corresponds to better HRQoL. For EORTC QLQ-C30 symptom scales, a higher score represents worse symptoms *Statistically significant difference ($P < 0.05$).

Motzer RJ. Abstract 4502

- Abstract 4502: Health-Related Quality-of-life Analysis From the Phase 3 CLEAR Trial of Lenvatinib Plus Pembrolizumab or Everolimus vs Sunitinib for Patients With Advanced Renal Cell Carcinoma

Overall Least Squares Mean Difference: LEN + PEMBRO vs SUN



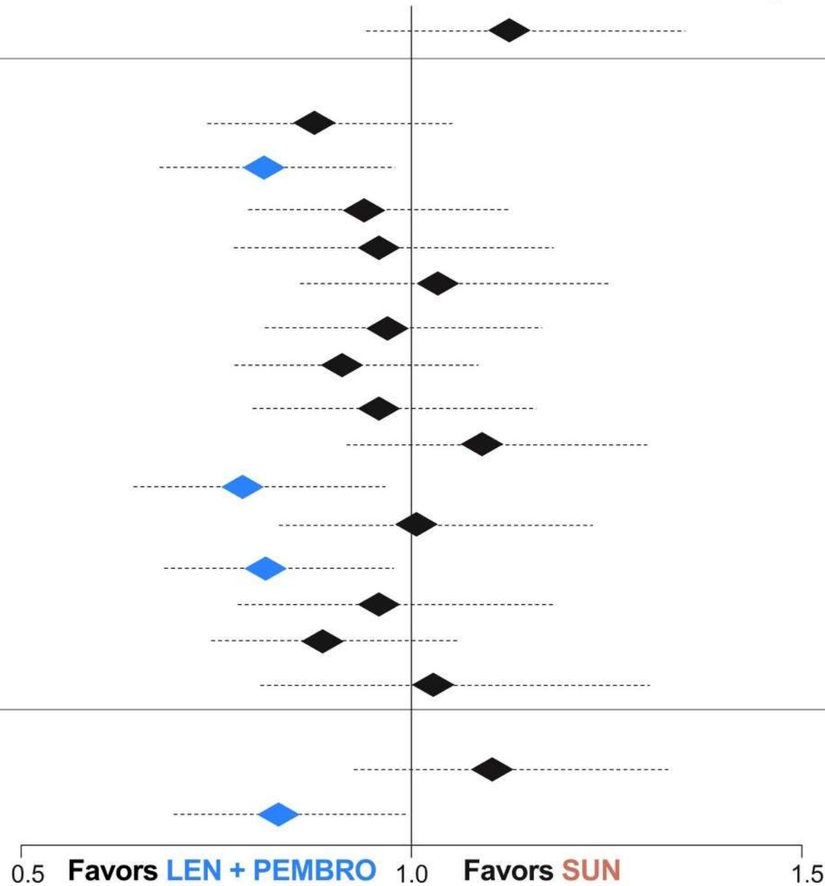
The overall LS mean difference was estimated at mean follow-up (46 weeks, cycle 15). For the FKSI-DRS total score, EORTC QLQ-C30 GHS/QoL and functional scales, and EQ-5D-3L scales, a higher score corresponds to better HRQoL. For EORTC QLQ-C30 symptom scales, a higher score represents worse symptoms *Statistically significant difference ($P < 0.05$).

Motzer RJ. Abstract 4502

- Abstract 4502: Health-Related Quality-of-life Analysis From the Phase 3 CLEAR Trial of Lenvatinib Plus Pembrolizumab or Everolimus vs Sunitinib for Patients With Advanced Renal Cell Carcinoma

Time to First Deterioration[a]: LEN + PEMBRO vs SUN

Scale	# Pts with Events L + P/S	Hazard Ratio (95% CI)
FKSI-DRS total score	265 / 218	1.13 (0.94–1.35)
EORTC QLQ-C30		
GHS/QoL	255 / 242	0.88 (0.74–1.05)
Physical functioning*	236 / 228	0.81 (0.68–0.98)
Role functioning	254 / 245	0.94 (0.79–1.13)
Emotional functioning	189 / 158	0.96 (0.77–1.18)
Cognitive functioning	232 / 199	1.04 (0.86–1.25)
Social functioning	247 / 224	0.97 (0.81–1.17)
Fatigue	279 / 265	0.92 (0.77–1.09)
Nausea and vomiting	241 / 203	0.96 (0.80–1.16)
Pain	271 / 240	1.09 (0.92–1.30)
Dyspnea*	190 / 189	0.79 (0.64–0.97)
Insomnia	217 / 184	1.01 (0.83–1.23)
Appetite loss*	251 / 233	0.82 (0.68–0.98)
Constipation	192 / 166	0.96 (0.78–1.18)
Diarrhea	266 / 232	0.89 (0.74–1.06)
Financial difficulties	158 / 118	1.03 (0.81–1.31)
EQ-5D-3L		
Index	260 / 222	1.11 (0.93–1.33)
EQ-VAS*	246 / 246	0.83 (0.70–0.99)



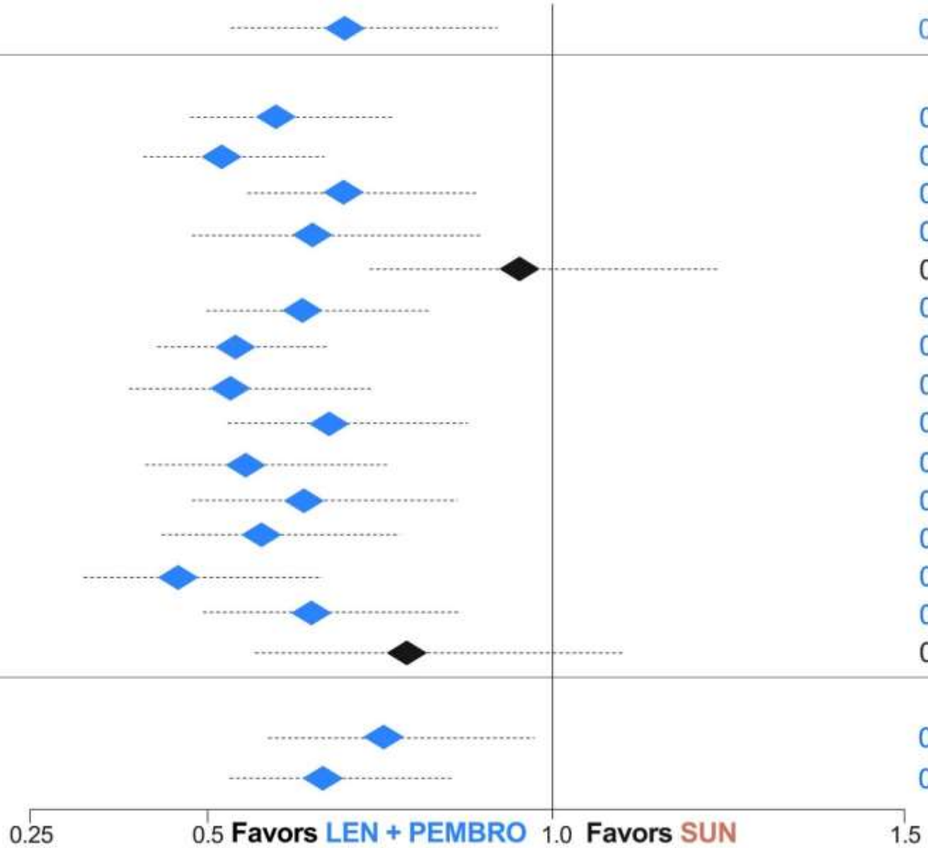
[a]The number of weeks between randomization and the first deterioration event. Thresholds used to determine deterioration: FKSI-DRS: decrease of ≥3 points; EORTC QLQ-C30 functional and GHS/QoL score decrease of ≥10 points; EORTC QLQ-C30 symptom scores: increase of ≥10 points; EQ-5D-3L Index: decrease of ≥0.08 points, VAS: decrease of ≥7 points. *Statistically significant differences for the hazard of time to first deterioration.

Motzer RJ. Abstract 4502

- Abstract 4502: Health-Related Quality-of-life Analysis From the Phase 3 CLEAR Trial of Lenvatinib Plus Pembrolizumab or Everolimus vs Sunitinib for Patients With Advanced Renal Cell Carcinoma

Time Until Definitive Deterioration[a]: LEN + PEMBRO vs SUN

Scale	# Pts with Events L + P/S	Hazard Ratio (95% CI)
FKSI-DRS total score*	110 / 105	0.70 (0.53–0.92)
EORTC QLQ-C30		
GHS/QoL*	132 / 144	0.60 (0.47–0.77)
Physical functioning*	120 / 144	0.52 (0.41–0.67)
Role functioning*	150 / 145	0.70 (0.56–0.89)
Emotional functioning*	82 / 80	0.65 (0.48–0.89)
Cognitive functioning	138 / 99	0.95 (0.73–1.23)
Social functioning*	128 / 129	0.64 (0.50–0.82)
Fatigue*	143 / 170	0.54 (0.43–0.67)
Nausea and vomiting*	74 / 82	0.53 (0.39–0.74)
Pain*	128 / 122	0.68 (0.53–0.87)
Dyspnea*	80 / 90	0.56 (0.41–0.76)
Insomnia*	91 / 91	0.63 (0.47–0.85)
Appetite loss*	89 / 98	0.58 (0.43–0.78)
Constipation*	52 / 71	0.46 (0.32–0.66)
Diarrhea*	106 / 97	0.65 (0.49–0.86)
Financial difficulties	80 / 67	0.79 (0.57–1.10)
EQ-5D-3L		
Index*	135 / 120	0.75 (0.59–0.97)
EQ-VAS*	141 / 144	0.67 (0.53–0.85)

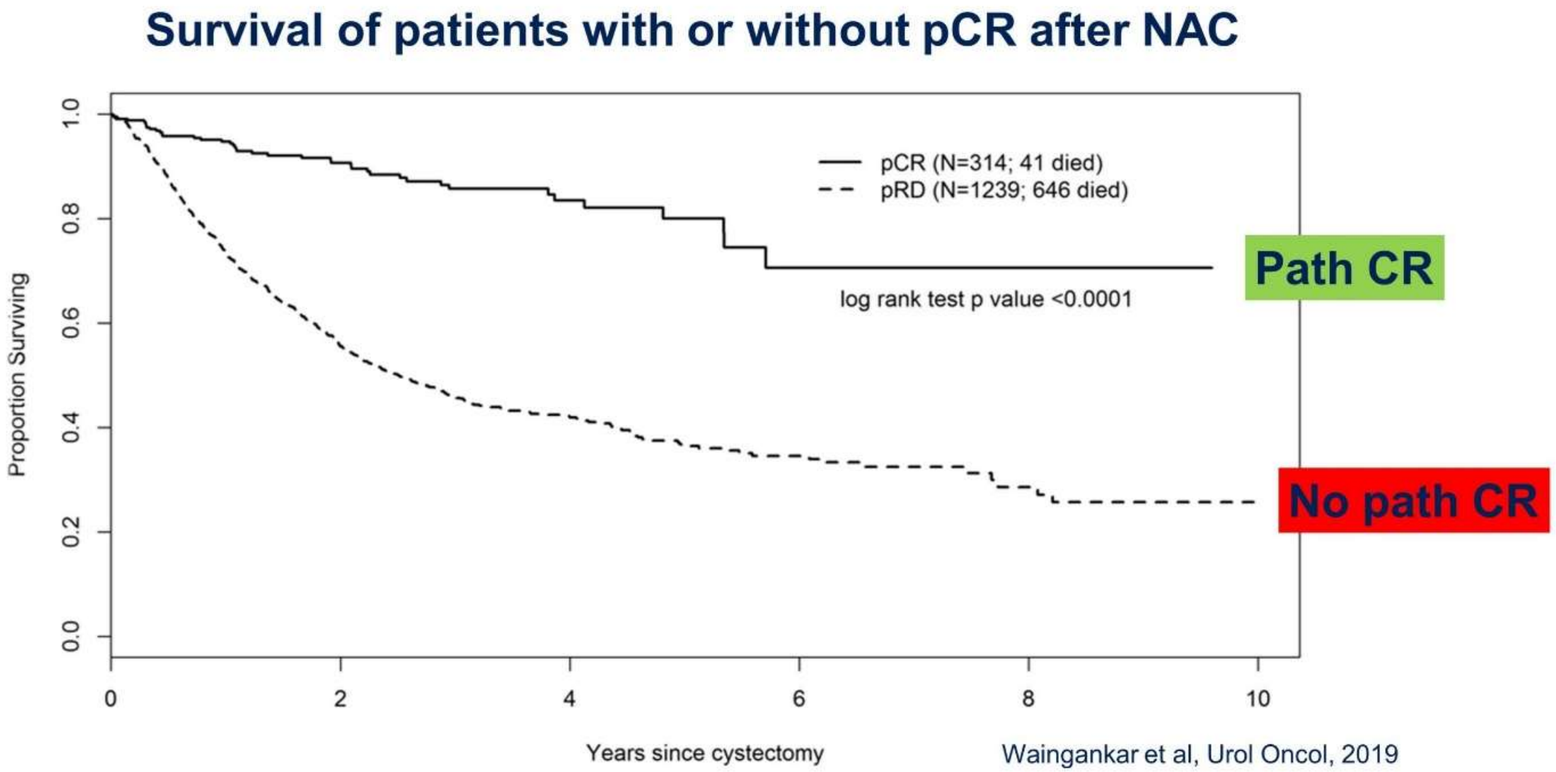


[a]The number of weeks between randomization and the earliest deterioration event with no subsequent recovery above the deterioration threshold or no subsequent HRQoL assessment data. Thresholds used to determine deterioration: FKSI-DRS: decrease of ≥3 points; EORTC QLQ-C30 functional and GHS/QoL score: decrease of ≥10 points; EORTC QLQ-C30 symptom scores: increase of ≥10 points; EQ-5D-3L Index decrease of ≥0.08 points, VAS: decrease of ≥7 points. *Statistically significant differences for the hazard of time to definitive deterioration.

Motzer RJ. Abstract 4502

Zhubné nádory močového mechúra

- Abstract 4503: Phase 2 trial of gemcitabine, cisplatin, plus nivolumab with selective bladder sparing in patients with muscle- invasive bladder cancer: HCRN GU 16-257



A pathological CR is achieved in ~30-40% of patients with cisplatin-based NAC for MIBC and is associated with favorable outcomes

Galsky MD. Abstract 4503

- Abstract 4503: Phase 2 trial of gemcitabine, cisplatin, plus nivolumab with selective bladder sparing in patients with muscle- invasive bladder cancer: HCRN GU 16-257

HCRN GU16-257

Clinical Complete Response Definition:
-No abnormalities on post-cycle #4 imaging
-No abnormalities on post-cycle #4 urine cytology
-≤ low grade Ta on post-cycle #4 bladder biopsies

76 patients

cT2-4aN0M0

Gemcitabine + Cisplatin + Nivolumab X 4 cycles

64 patients

Clinical Restaging

Cysto + biopsies
Urine cytology
MRI

31 patients

Clinical CR

30 patients

No cystectomy → **Nivo x 4 mos**

* Treatment based on patient choice

Cystectomy

1 patient

33 patients

No Clinical CR → **Cystectomy**

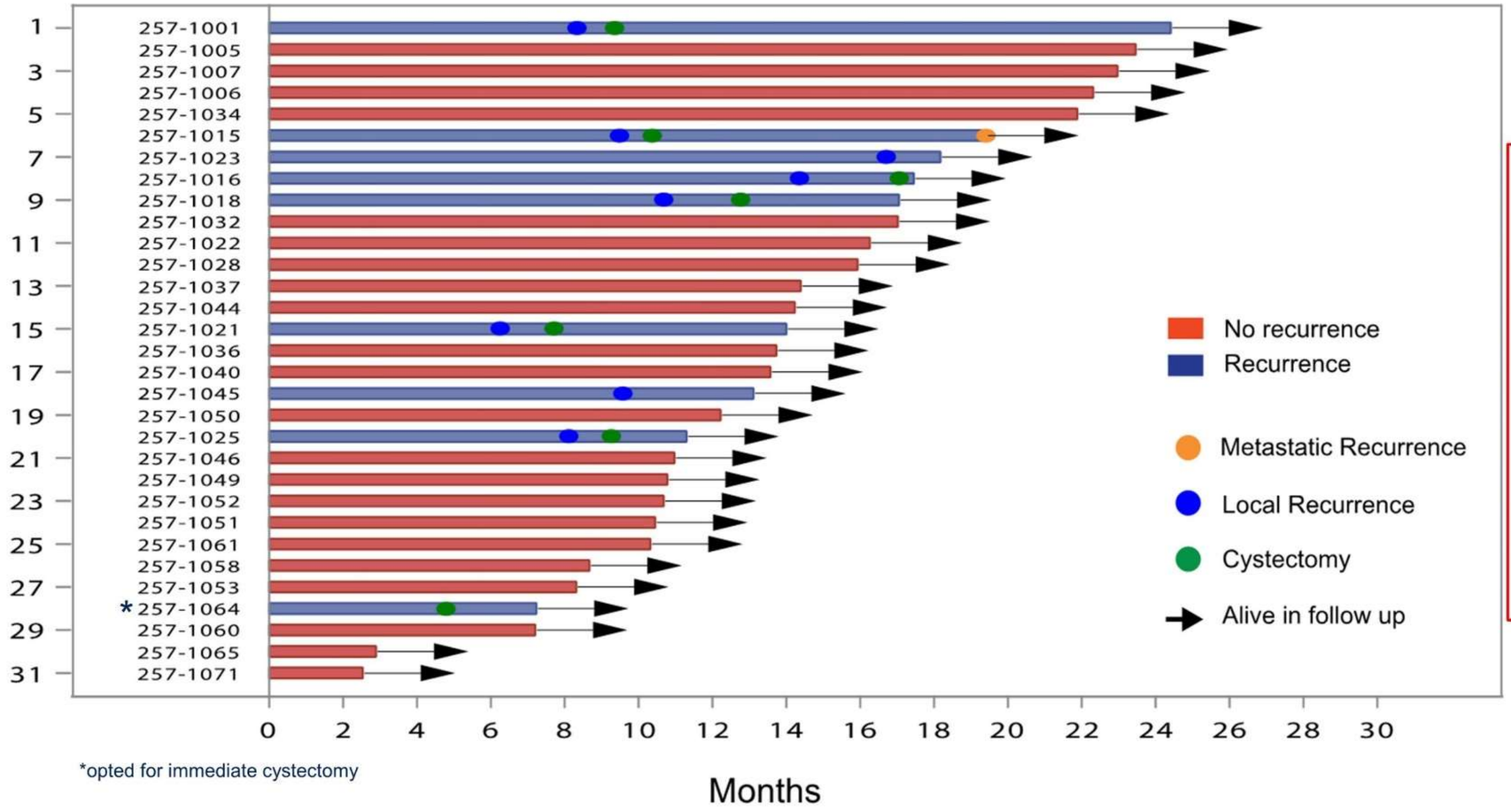
Co-Primary Endpoint:
-2 year MFS in patients pursuing surveillance OR
-Pathologic CR in patients undergoing cystectomy

Clinical complete response rate = 48% (95% CI 36%, 61%)

Galsky MD. Abstract 4503

- Abstract 4503: Phase 2 trial of gemcitabine, cisplatin, plus nivolumab with selective bladder sparing in patients with muscle- invasive bladder cancer: HCRN GU 16-257

Outcomes of patients with clinical CR



31 with Clinical CR
-22 without recurrence (71%)
-8 with local recurrence (26%)
-7 with cystectomy (23%)
-1 with metastasis (3%)

Longer follow-up is needed (range from 2-24 month follow up)

Galsky MD. Abstract 4503

- Abstract 4503: Phase 2 trial of gemcitabine, cisplatin, plus nivolumab with selective bladder sparing in patients with muscle- invasive bladder cancer: HCRN GU 16-257

Pathological stage in patients with cCR undergoing *delayed* cystectomy after local recurrence (n=6)

Pathological stage	N (%)
ypT0N0	1 (17%)
ypTaN0	1 (17%)
ypTisN0	1 (17%)
ypT2N0	2 (32%)
ypT4N1	1 (17%)

50%

Galsky MD. Abstract 4503

- Abstract 4504: Pembrolizumab in combination with gemcitabine and concurrent hypofractionated radiation therapy as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder: A multicenter phase 2 trial

TREATMENT SCHEMA

NYU Langone Health

Phase I Lead In followed by Phase II

KEY ELIGIBILITY CRITERIA
- UC Histology Mixed Allowed
- cT2-T4aN0M0
- ECOG PS 0 or 1
- RC ineligible/ refusing
- No Perioperative ChemoTx

Pembro 200 mg IV → 2-3 Wks → Maximal TURBT → 3-4 Wks

Centrally reviewed radiation therapy plans

4 WEEKS CHEMORADIATION
52 Gy x 20 Fx Bladder Only
w Gemcitabine 27 mg/m2
Twice Weekly

Pembrolizumab
200 mg IV every 3 weeks for 3 doses

12 Wks Post-RT → TUR of Tumor Bed + UCy

Assessment of Response

CT/MR AP w Contrast

5 Years Disease Surveillance on Study beginning post-RT

Imaging:

CT/MR AP Q3 months for 18 months, Q6 months for 18 months, Q12 months for 24 months.

Cystoscopy/Cytology

Q3 months for 12 months, Q4 months for 12 months, Q6 months for 3 years

Primary Endpoint Phase II: 2-year Bladder Intact Disease-Free Survival

Balar AV. Abstract 4504

- Abstract 4504: Pembrolizumab in combination with gemcitabine and concurrent hypofractionated radiation therapy as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder: A multicenter phase 2 trial

NYU Langone Health

Treatment Summary

Phase I Cohort:

- 1 of 3 initial patients had a DLT (Grade 2 irAE (diarrhea) treated with corticosteroids, missed final dose of pembrolizumab)
- 3 additional patients treated with no additional DLT events and all completed protocol therapy

Phase II Cohort:

	N= 48	Comments
Completed All Protocol Therapy	42 (85%)	
Dose Reductions in Gemcitabine	12 (25%)	78% due to hematologic toxicity
Discontinued RT/Gemcitabine	1 (2%)	
Discontinued Gemcitabine only	3 (6%)	2 pts after initial dose reductions (LFTs and diarrhea/fatigue)
Discontinued Pembrolizumab	4 (8%)	immune-related nephritis, protein-losing enteropathy, polyneuropathy, myalgias

2 pts did not start combination therapy due to 1. enrollment in hospice, 2. not meeting treatment parameters on W1D1 of combination therapy

- Abstract 4504: Pembrolizumab in combination with gemcitabine and concurrent hypofractionated radiation therapy as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder: A multicenter phase 2 trial

NYU Langone Health

12 Weeks Post-RT Response – Per Protocol[1]

12 weeks post RT Response	N=6	N=48	N=54
CR	5 (83%)	27(56%)	32 (59%)
PR	0	4 (8.3%)	4 (7.4%)
NR	0	0	0
Progression	0	1 (2.4%)	1 (1.8%)
Not-evaluable[2]	1(17%)	10 (21%)	11 (20%)
Missed	0	3	3
Off-Study	0	3	3

- [2]Not-evaluable for the post-RT response per protocol due to missed cytology or biopsy
- 2 patients who remained on study missed week 12 cystoscopy/biopsy/cytology
- 3 patients were off-study before the 12-weeks post-RT response assessment

[1]Assessment of post-treatment response required:
- TUR/biopsy of tumor bed
- Urine cytology
- CT/MRI AP
  - If all 3 not complete, pts were not evaluable per protocol

CR: Negative cysto/TUR path and cytology
PR: Positive cytology or CIS/non-invasive disease
NR: cT1 or greater
Progression: progression to muscle-invasive or metastatic disease

Balar AV. Abstract 4504

- Abstract 4504: Pembrolizumab in combination with gemcitabine and concurrent hypofractionated radiation therapy as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder: A multicenter phase 2 trial

NYU Langone Health

12 Weeks Post-RT Response – Per Protocol[1]

12 weeks post RT Response	N=6	N=48	N=54
CR	6 (100%)	37(77%)	43 (80%)
PR	0	4 (8.3%)	4 (7.4%)
NR	0	0	0
Progression	0	1 (2.4%)	1 (2.0%)
Missed	0	3	3
Off-Study	0	3	3

11 inevaluable patients were clinically without evidence of disease at the time of the 12-weeks post-RT assessment consistent with clinical CR

How does post RT response augment therapy?

- 3 patients who remained on study missed week 12 cystoscopy/biopsy/cytology
- 3 patients were off-study before the 12-weeks post-RT response assessment

Stringently defined criteria for response assessments warranted

[1]Assessment of post-treatment response required:

- TUR/biopsy of tumor bed
- Urine cytology
- CT/MRI AP
  - If all 3 not complete, pts were not evaluable per protocol

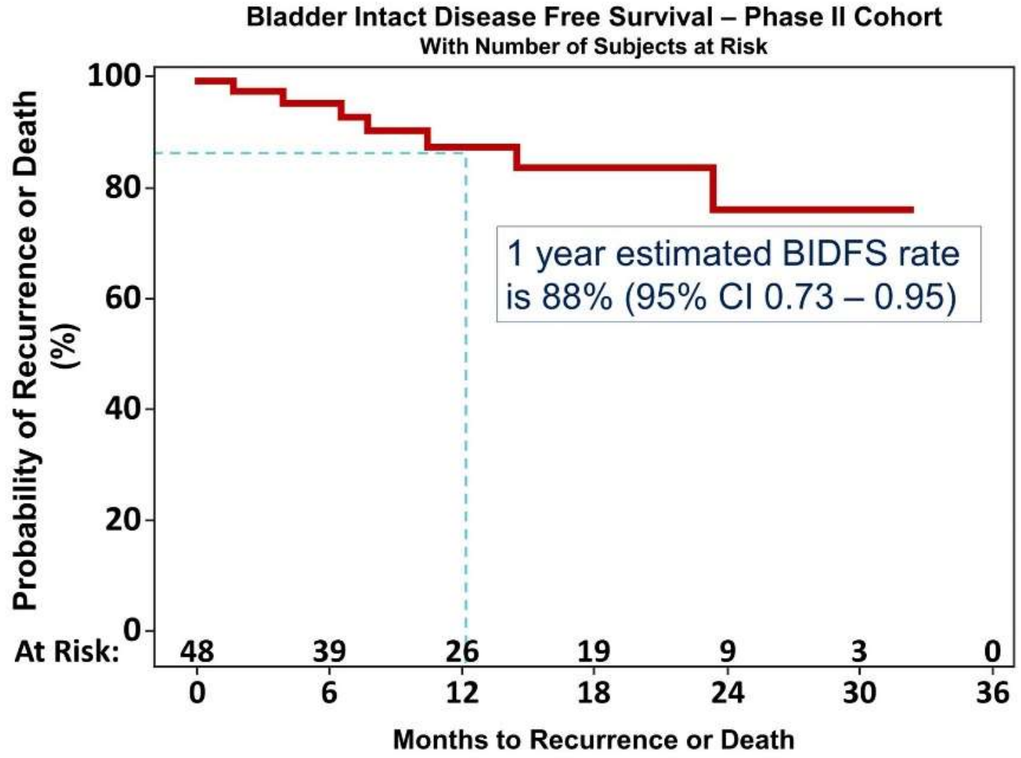
Only Tumor Bed Evaluated

CR: Negative cysto/TUR path and cytology
PR: Positive cytology or CIS/non-invasive disease
NR: cT1 or greater
Progression: progression to muscle-invasive or metastatic disease

Balar AV. Abstract 4504

- Abstract 4504: Pembrolizumab in combination with gemcitabine and concurrent hypofractionated radiation therapy as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder: A multicenter phase 2 trial

Primary Endpoint: Bladder-Intact Disease-Free Survival - Efficacy Cohort (N=48)

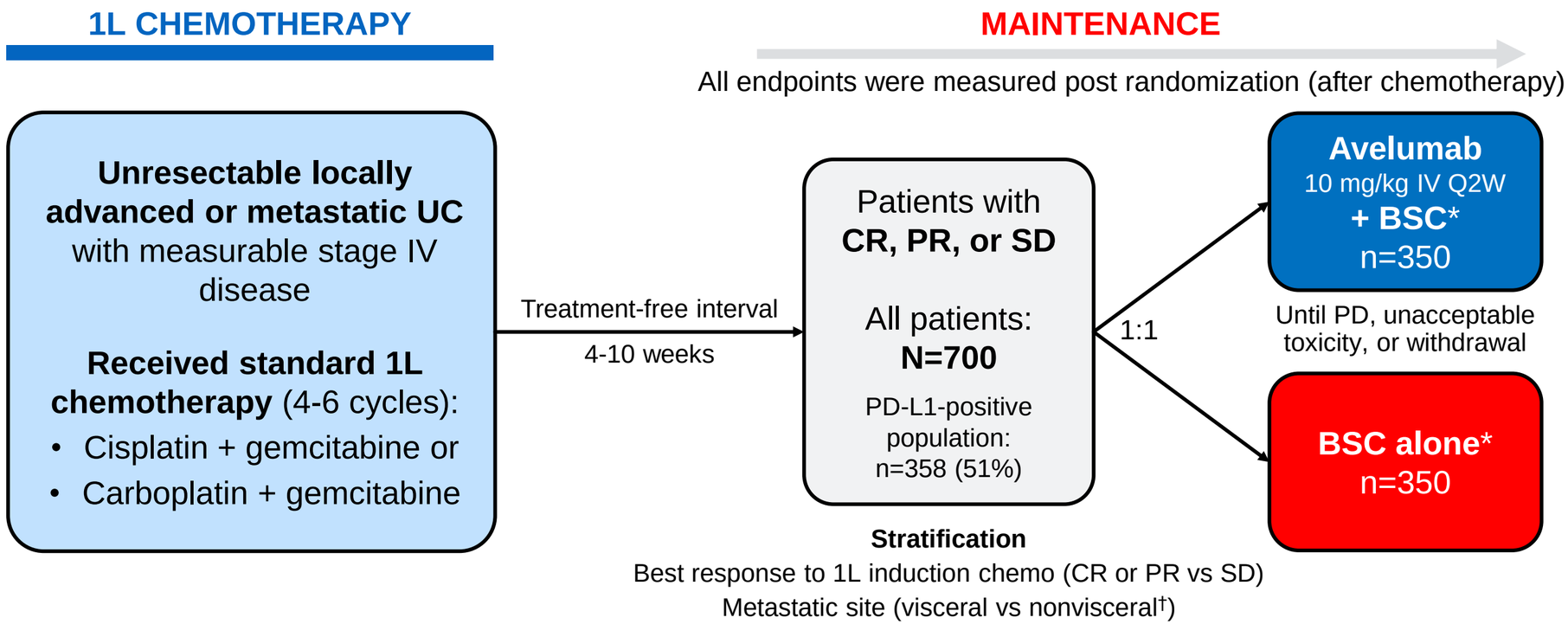


Median Follow up Efficacy Cohort: 14.6 months (1.6 months - 32.3 months)

Longer Follow Up Warranted as Primary Endpoint is 2 year BIDFS

Balar AV. Abstract 4504

JAVELIN Bladder 100 study design (NCT02603432)



- **Primary endpoint**
  - OS in 2 primary analysis populations:
    - All randomized patients
    - PD-L1–positive population
- **Secondary endpoints**
  - PFS and objective response per RECIST 1.1 by BICR
  - TTR, DOR, and disease control‡ by BICR
  - Safety

* BSC (eg, antibiotics, nutritional support, hydration, and pain management) was administered according to local practice on the basis of the clinical judgment and the patient's condition; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable.
† Nonvisceral stratum included patients with unresectable locally advanced disease in addition to those with only nonvisceral disease, including bone metastasis.
‡ Response plus SD for ≥6 weeks.

Powles T, et al. N Engl J Med. 2020

Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): Analysis of clinical and genomic subgroups from the JAVELIN Bladder 100 trial.

	Pts, n		Median OS (95% CI), months		
Subgroup	Avelumab + BSC	BSC	Avelumab + BSC	BSC	HR (95% CI)
Upper tract	106	81	19.9 (15.3, NE)	17.4 (12.8, 33.0)	0.89 (0.578, 1.373)
Lower tract	244	269	22.5 (19.0, 28.3)	14.1 (11.8, 17.9)	0.62 (0.477, 0.802)
Metastatic disease	216	215	18.2 (13.8, 20.3)	14.1 (11.7, 17.3)	0.88 (0.678, 1.147)
LA and unresectable disease	133	133	NE (25.3, NE)	17.9 (13.5, NE)	0.40 (0.265, 0.617)
Lymph node-only disease*	48	39	NE (23.8, NE)	NE (10.7, NE)	0.55 (0.259, 1.152)
1L gemcitabine + carboplatin, PD-L1+ tumor	74	54	24.0 (18.6, NE)	16.1 (9.4, NE)	0.67 (0.393, 1.137)
TCGA: basal squamous	45	44	24.0 (16.0, NE)	17.9 (12.7, NE)	0.62 (0.326, 1.187)
TCGA: luminal	30	25	23.8 (12.5, NE)	NE (14.3, NE)	1.01 (0.403, 2.509)
TCGA: luminal infiltrated	143	143	19.9 (18.2, NE)	14.3 (12.8, 18.6)	0.68 (0.481, 0.968)
TCGA: luminal papillary	61	63	22.5 (18.2, 26.0)	13.4 (10.1, NE)	0.63 (0.370, 1.079)

NE, not estimable *Post-chemotherapy.

Powles T. Abstract 4520

Avelumab first-line (1L) maintenance plus best supportive care (BSC) versus BSC alone for advanced urothelial carcinoma (UC): Analysis of time to end of next-line therapy in JAVELIN Bladder 100.

	Patients, n		Median time to end of next-line therapy (95% CI), months		Hazard ratio
	Avelumab + BSC	BSC alone	Avelumab + BSC	BSC alone	(95% CI)
All randomized pts	350	350	14.8 (12.0, 17.0)	9.2 (8.0, 11.5)	0.67 (0.545, 0.815)
Pts with PD-L1+ tumors	189	169	18.1 (12.5, 19.2)	9.0 (7.9, 12.5)	0.61 (0.451, 0.818)
Pts with PD-L1− tumors	139	131	11.9 (9.1, 15.4)	9.3 (7.6, 12.8)	0.76 (0.560, 1.035)

Grivas P. Abstract 4525

Zhubné nádory prostaty

Phase 3 study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)

Presenter: Michael J. Morris, Memorial Sloan Kettering Cancer Center

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

Morris MJ. Abstract LBA4

Phase 3 study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)

Presenter: Michael J. Morris, Memorial Sloan Kettering Cancer Center

Alternate primary endpoints

- Radiographic progression-free survival (rPFS) per PCWG3
- Overall survival (OS)

Key secondary endpoints

- Time to first symptomatic skeletal event (SSE)
- RECIST v1.1 overall response rate
- RECIST v1.1 disease control rate

Other secondary endpoints

- Safety and tolerability
- Biomarkers including PSA
- Health-related quality of life and pain

Morris MJ. Abstract LBA4

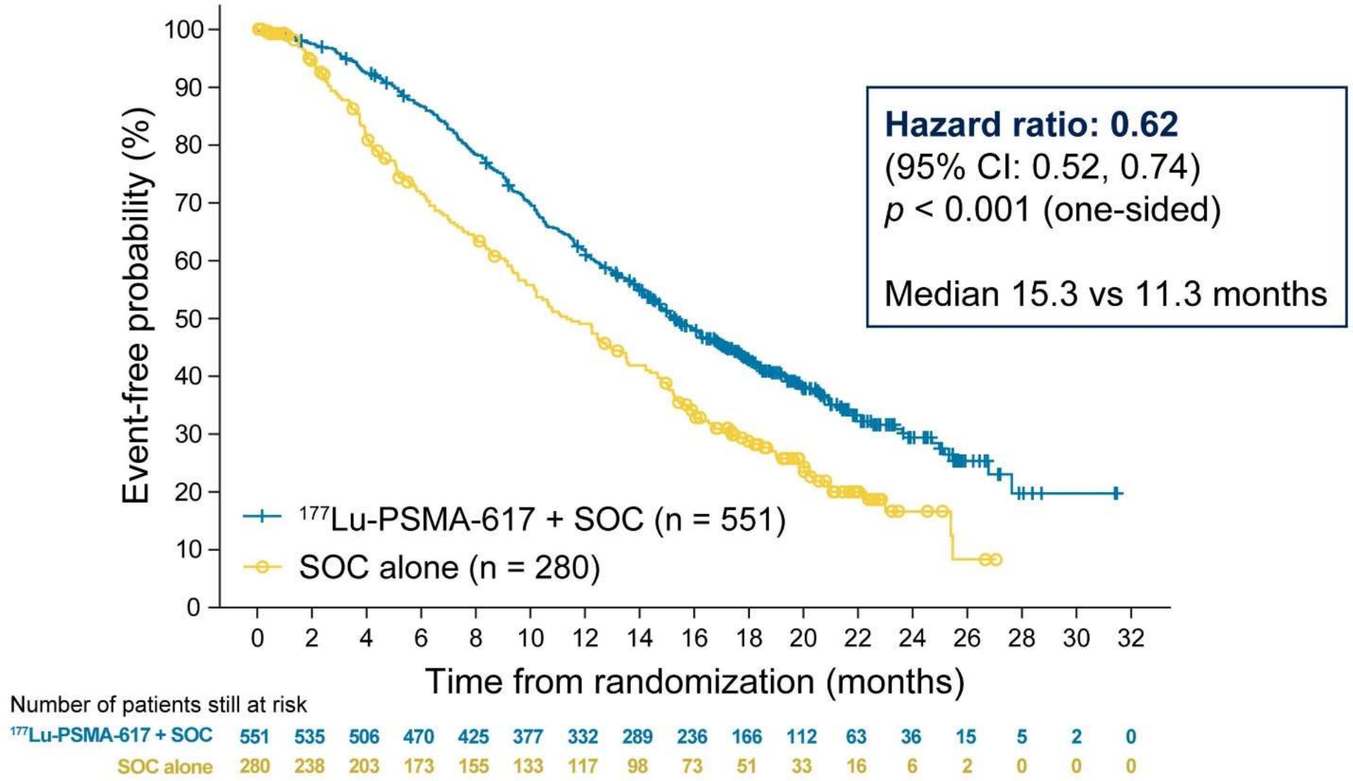
Phase 3 study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)

Presenter: Michael J. Morris, Memorial Sloan Kettering Cancer Center

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

Primary analysis

All randomized patients
(N = 831)



Morris MJ. Abstract LBA4

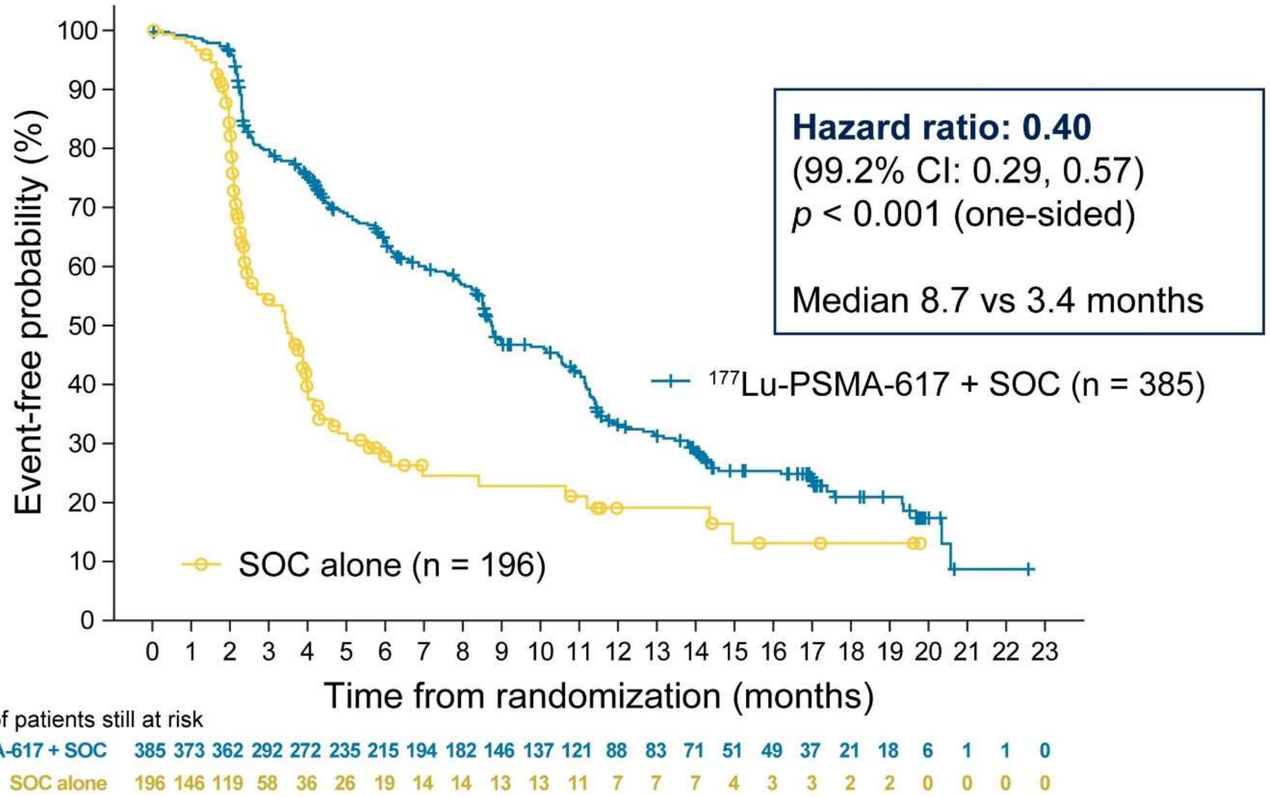
Phase 3 study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)

Presenter: Michael J. Morris, Memorial Sloan Kettering Cancer Center

Primary endpoints: ^{177}Lu-PSMA-617 improved rPFS

Primary analysis

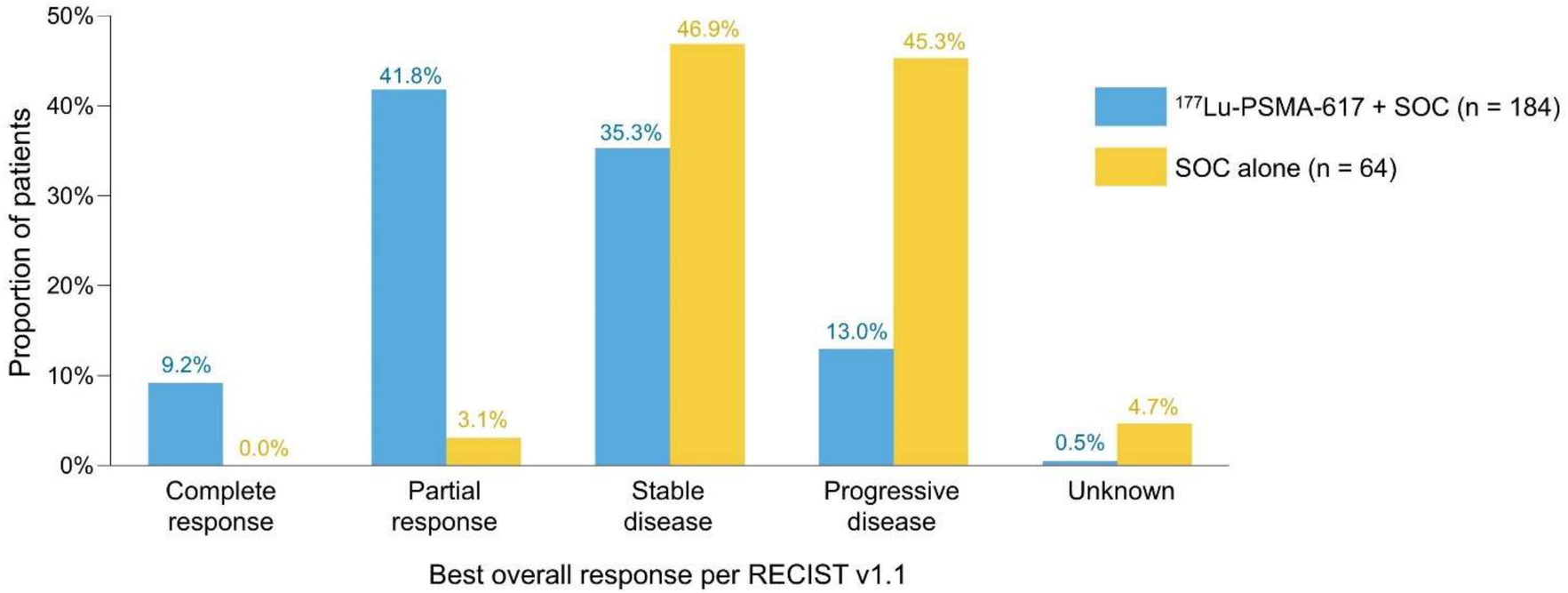
rPFS analysis set (n = 581)



Phase 3 study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)

Presenter: Michael J. Morris, Memorial Sloan Kettering Cancer Center

Secondary endpoint: RECIST v1.1 responses favored the ^{177}Lu-PSMA-617 arm in patients with measurable disease



Morris MJ. Abstract LBA4

Phase 3 study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)

Presenter: Michael J. Morris, Memorial Sloan Kettering Cancer Center

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)

Morris MJ. Abstract LBA4

Phase 3 study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)

Presenter: Michael J. Morris, Memorial Sloan Kettering Cancer Center

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

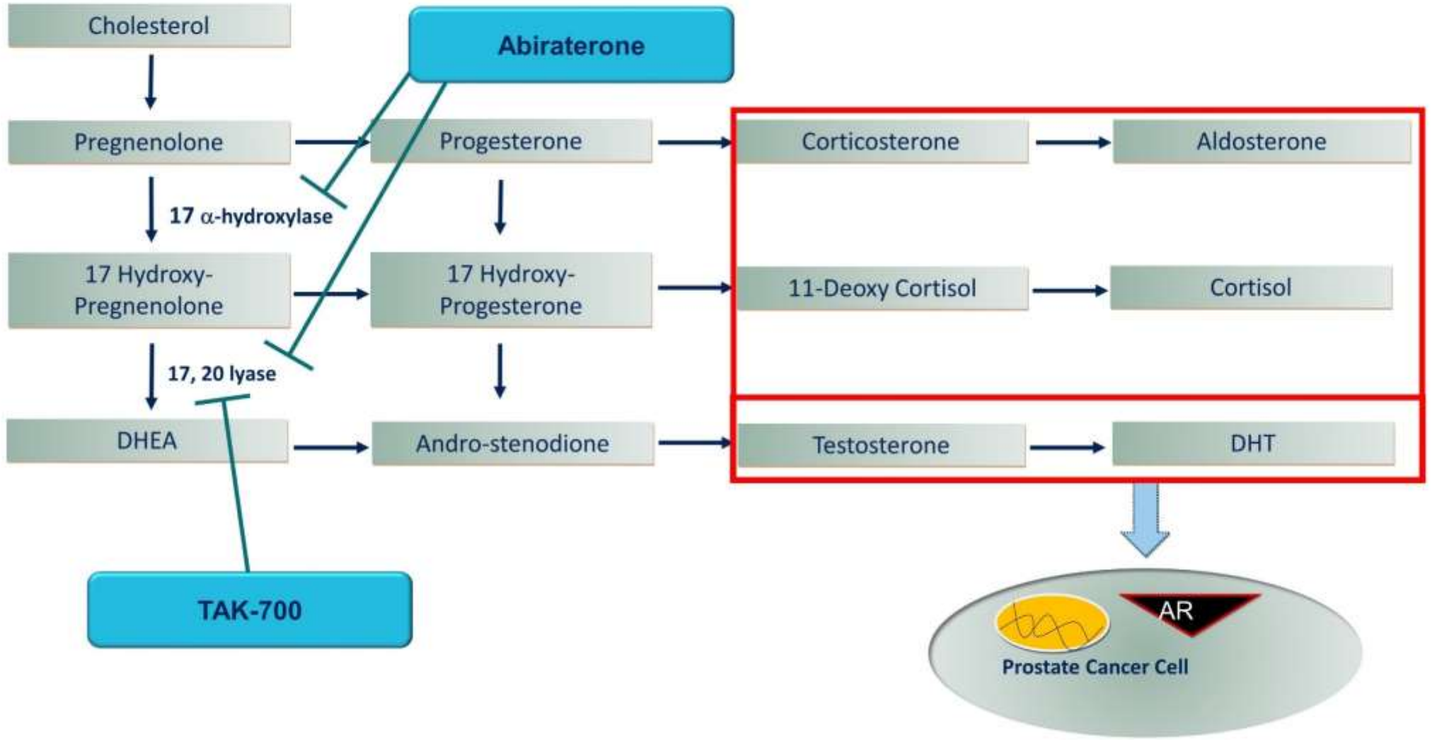
Patients, n (%)	All grades		Grade 3–5	
	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
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)

Morris MJ. Abstract LBA4

SWOG S1216: A PHASE III RANDOMIZED TRIAL COMPARING ANDROGEN DEPRIVATION THERAPY (ADT) PLUS TAK-700 WITH ADT PLUS BICALUTAMIDE IN PATIENTS (PTS) WITH NEWLY DIAGNOSED METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC)

ABSTRACT: 5001

Mechanism of Action of TAK-700



Stanbrough, et al. Cancer Res, 66:2815–2825, 2006. Montgomery, et al. Cancer Res, 68:4447–4454, 2008. Attard, et al. Cancer Cell,16:458–462, 2008. Potter, et al. J Med Chem, 38:2463–2471, 1995.

SWOG S1216: A PHASE III RANDOMIZED TRIAL COMPARING ANDROGEN DEPRIVATION THERAPY (ADT) PLUS TAK-700 WITH ADT PLUS BICALUTAMIDE IN PATIENTS (PTS) WITH NEWLY DIAGNOSED METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC)

ABSTRACT: 5001

Study Design and Endpoints

Key Eligibility Criteria
- Newly diagnosed hormone sensitive prostate cancer
- Distant metastatic disease
- Performance status Zubrod 0-2 (3 allowed only if secondary to bone pain)

On-Study Requirement
- Continuous ADT

Exclusion criteria
- Prior docetaxel or androgen axis inhibitors
- ≥ 6 months since completion of ADT

Patients accrued
- N=1279
- Mar 2013 – Jul 2017

RANDOMIZED 1:1

- LHRH agonist + TAK 700 (Orteronel 300 mg PO twice daily) (N=638)
- LHRH agonist + Bicalutamide** (50 mg PO daily) (N=641)

Efficacy endpoints

Primary:
- Overall survival (OS)

Secondary:
- Progression-free survival (PFS)***
- PSA at 7 months (≤0.2 vs 0.2<PSA; ≤-4 vs. >4 ng/mL)
- Adverse event profile

Stratification
- Performance status Zubrod 0-1 vs. 2-3
- Extensive vs. minimal disease *
- Early vs. late induction (Early: ADT started ≤30 days of registration)

PSA, prostate-specific antigen

* Minimal: Patients with involvement of vertebrae and/or pelvic bones and/or lymph nodes. Extensive: All patients with greater than minimal involvement.

** Combined androgen blockade was used to provide a more rigorous comparator *(Prostate Cancer Trialists Collaborative Group. The Lancet 2000, 9214:1491-8)*

*** From date of randomization to first occurrence of PSA or radiographic progression, symptomatic deterioration, or death due to any cause

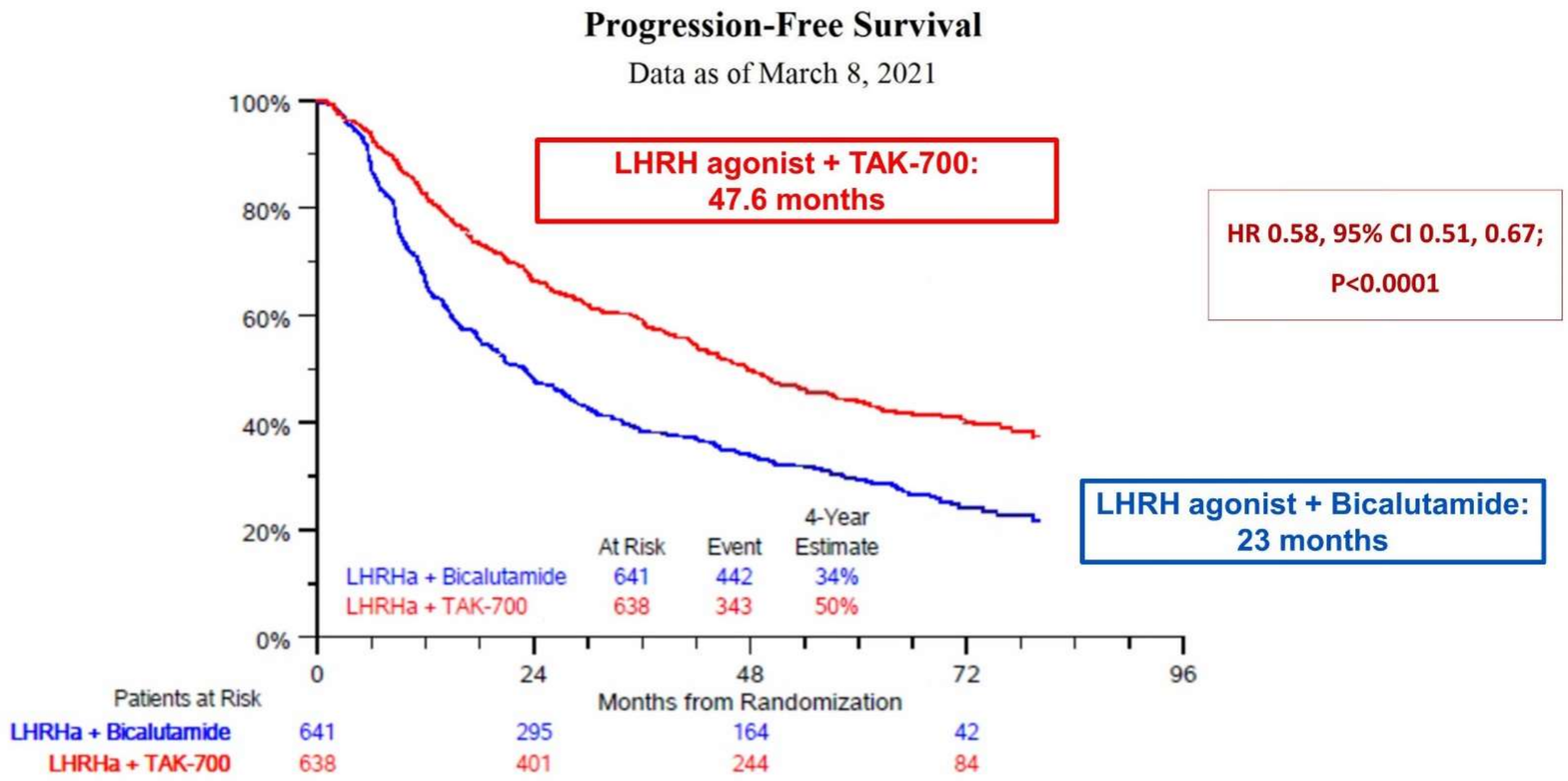
www.ClinicalTrials.gov (NCT01809691)

Agarwal N. Abstract 5001

SWOG S1216: A PHASE III RANDOMIZED TRIAL COMPARING ANDROGEN DEPRIVATION THERAPY (ADT) PLUS TAK-700 WITH ADT PLUS BICALUTAMIDE IN PATIENTS (PTS) WITH NEWLY DIAGNOSED METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC)

ABSTRACT: 5001

PFS: TAK-700 significantly reduced the risk of progression by 42%

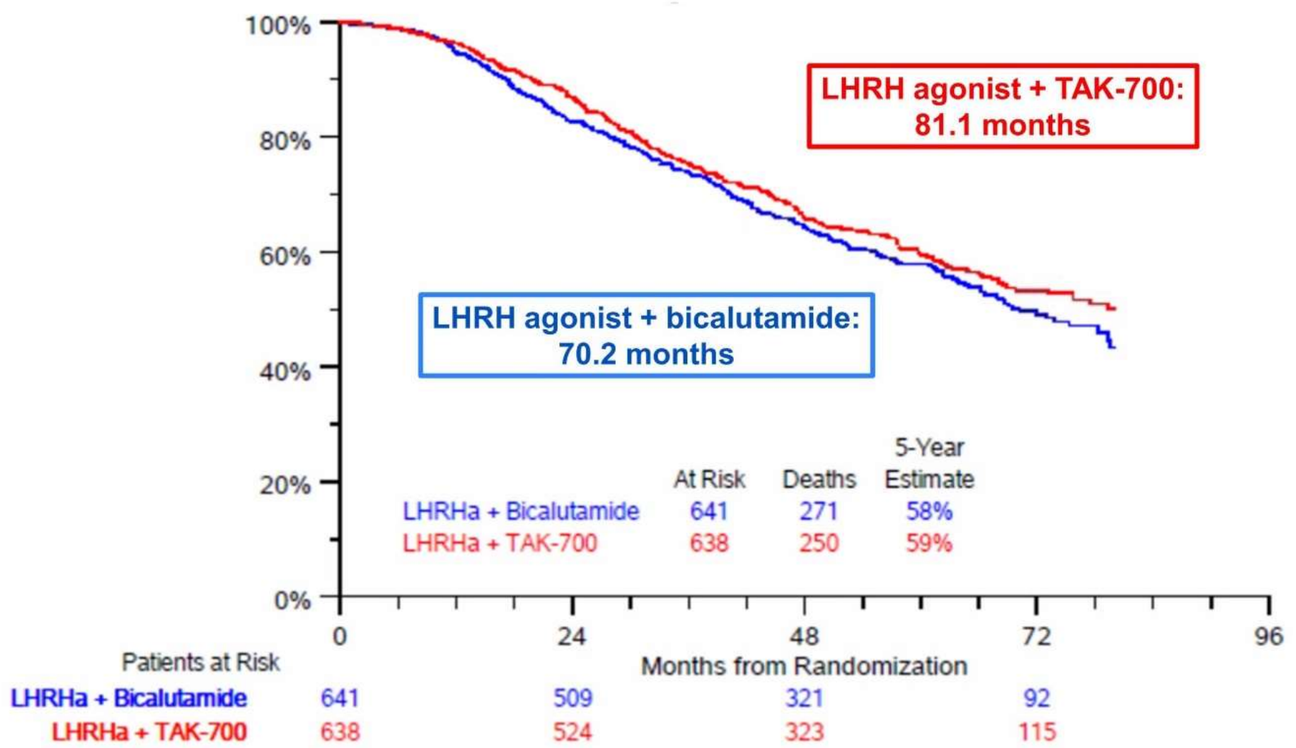


Agarwal N. Abstract 5001

SWOG S1216: A PHASE III RANDOMIZED TRIAL COMPARING ANDROGEN DEPRIVATION THERAPY (ADT) PLUS TAK-700 WITH ADT PLUS BICALUTAMIDE IN PATIENTS (PTS) WITH NEWLY DIAGNOSED METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC)

ABSTRACT: 5001

Primary Analysis ITT Comparison of OS By Arm



HR 0.86, 95% CI 0.72, 1.02;
P=0.040, 1-sided

Median Follow-up: 4.9 years

Agarwal N. Abstract 5001

Ďakujem za pozornosť.

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