Genitourinary Updates

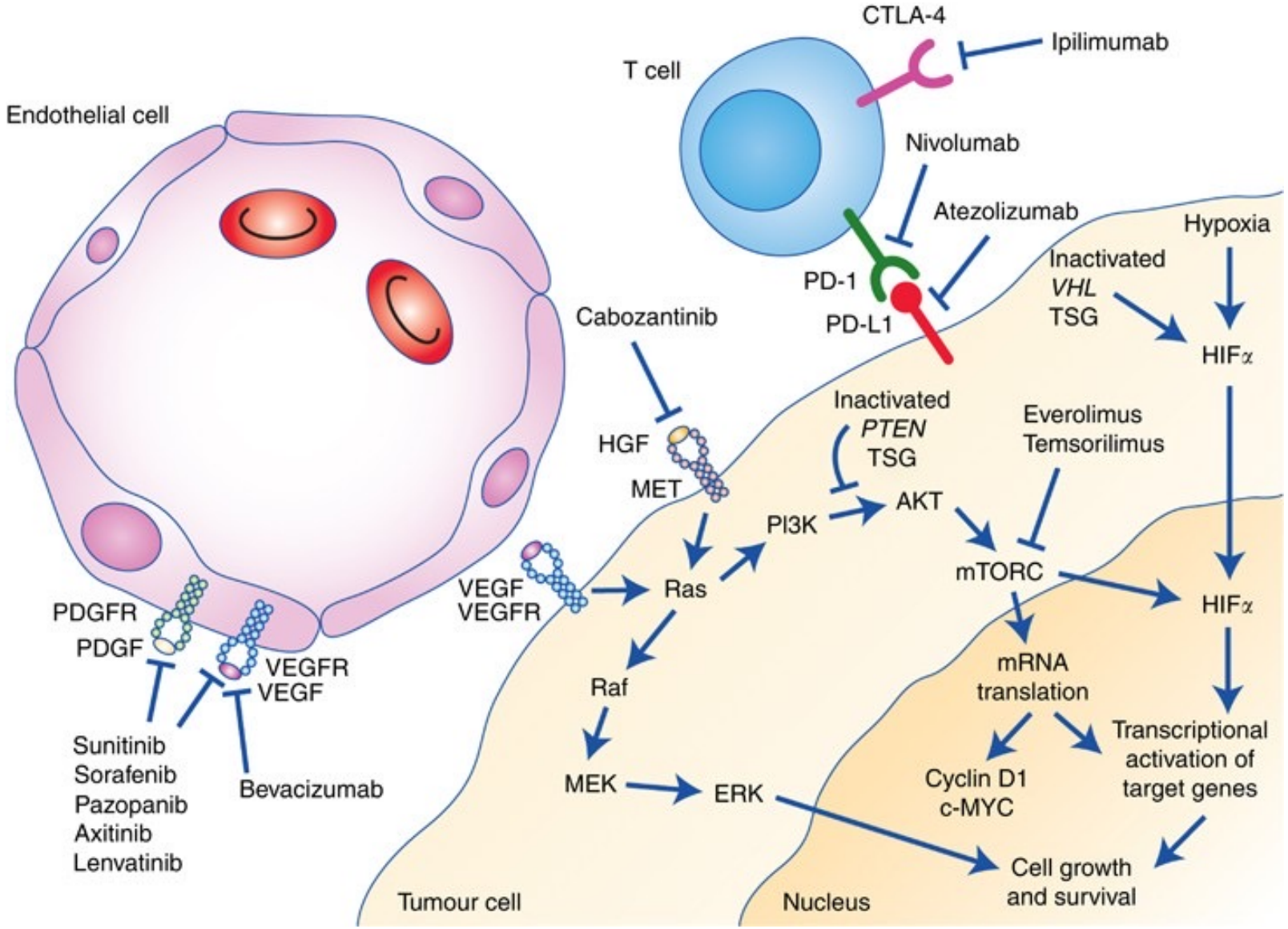
Manoj Bupathi, MD, MS
Rocky Mountain Cancer Center
Sarah Cannon Research Institute
Associate Chair- USON GU Cancer Research

Objectives

- Renal Cell Carcinoma
  - Adjuvant therapy
  - Locally advanced/metastatic disease

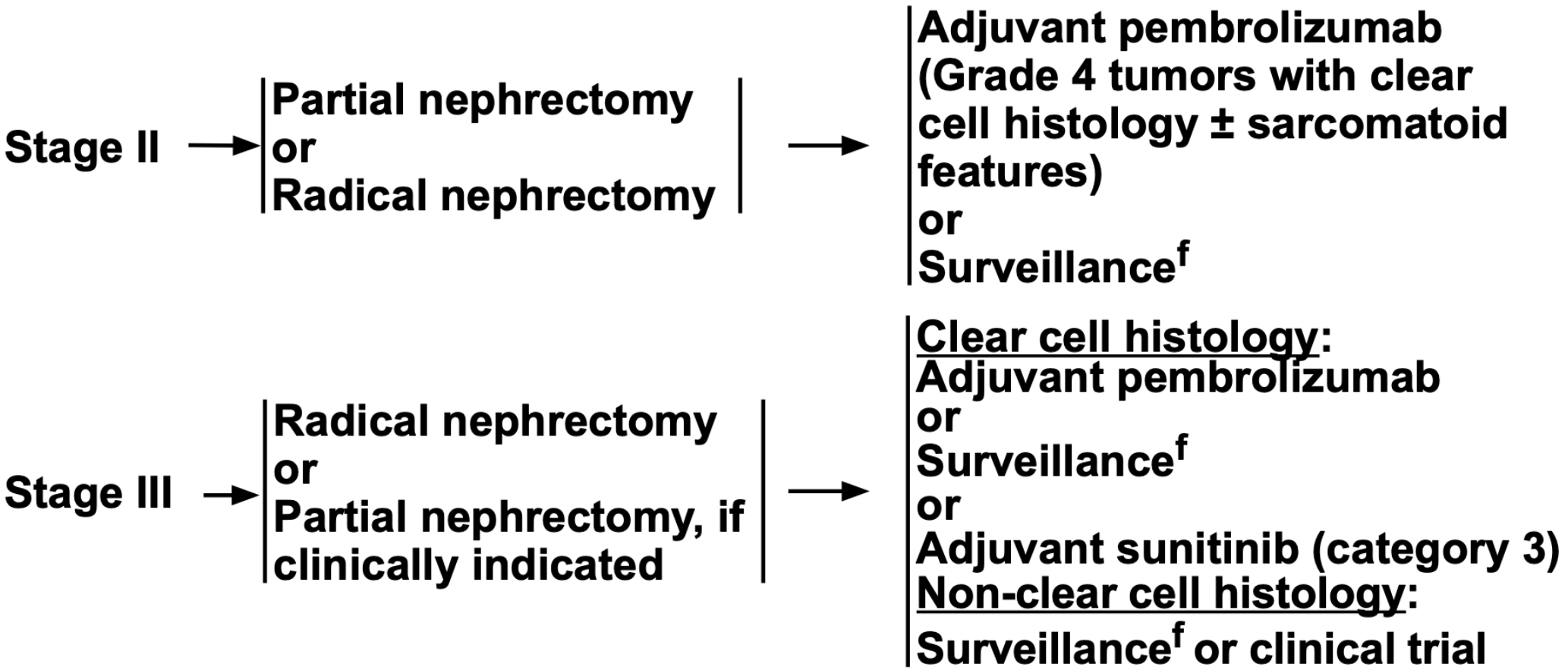
- Bladder Cancer
  - Locally advanced/metastatic disease

Targets in renal cell caner: mTOR, checkpoint, VEGF and transcription factors



Greef, et al. BJC 2016

Guidelines for adjuvant therapy for RCC



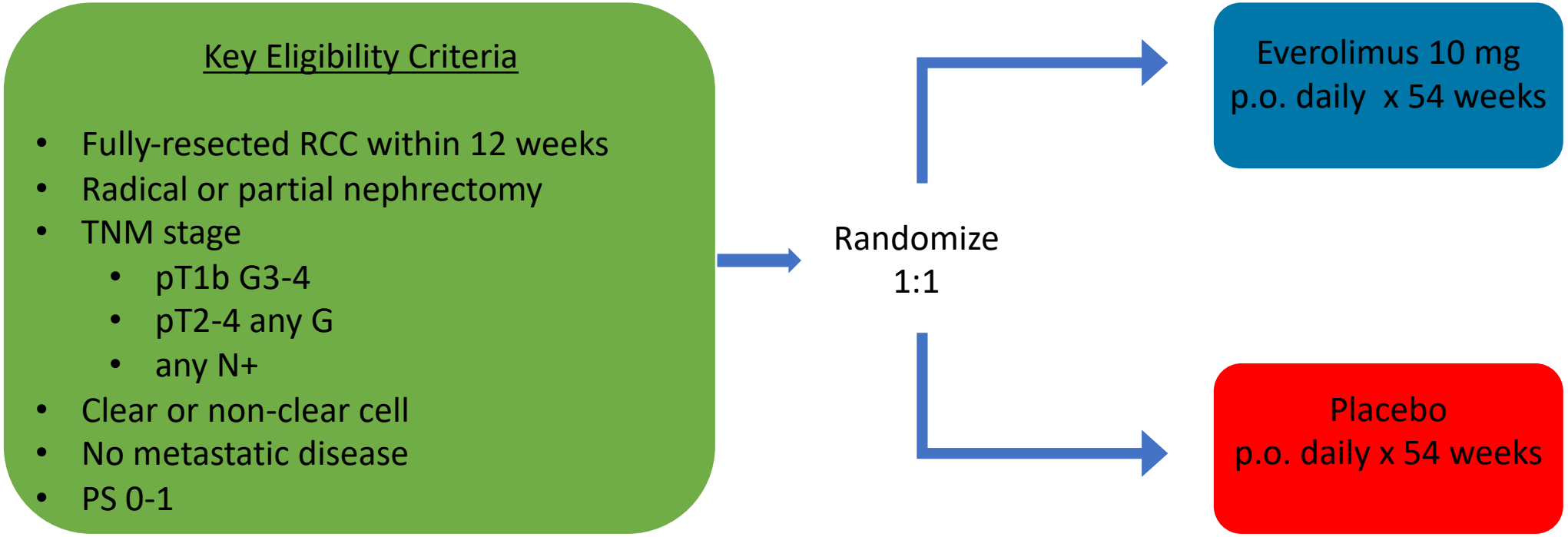
What adjuvant therapy clinical trials in RCC have shown thus far

Trial	Agent	DFS HR	95% CI	P-value	OS
ASSURE	Sunitinib	1.02	0.85 - 1.23	P=0.80	NS
	Sorafenib	0.97	0.80 – 1.17	P=0.72	NS
SORCE	Sorafenib 3 yr	1.01	0.83 – 1.23	P=0.95	NS
	Sorafenib 1 yr	0.94	0.77 – 1.14	P=0.51	NS
PROTECT	Pazopanib	0.86	0.70 – 1.06	P=0.17	NS
ATLAS	Axitinib	0.87	0.66 – 1.15	P=0.32	NR
S-TRAC	Sunitinib	0.76	0.59 – 0.98	P = 0.03	NS
KEYNOTE-564	Pembrolizumab	0.63	0.50 - 0.80	P<0.0001	NS

* All placebo-controlled, DFS primary endpoint

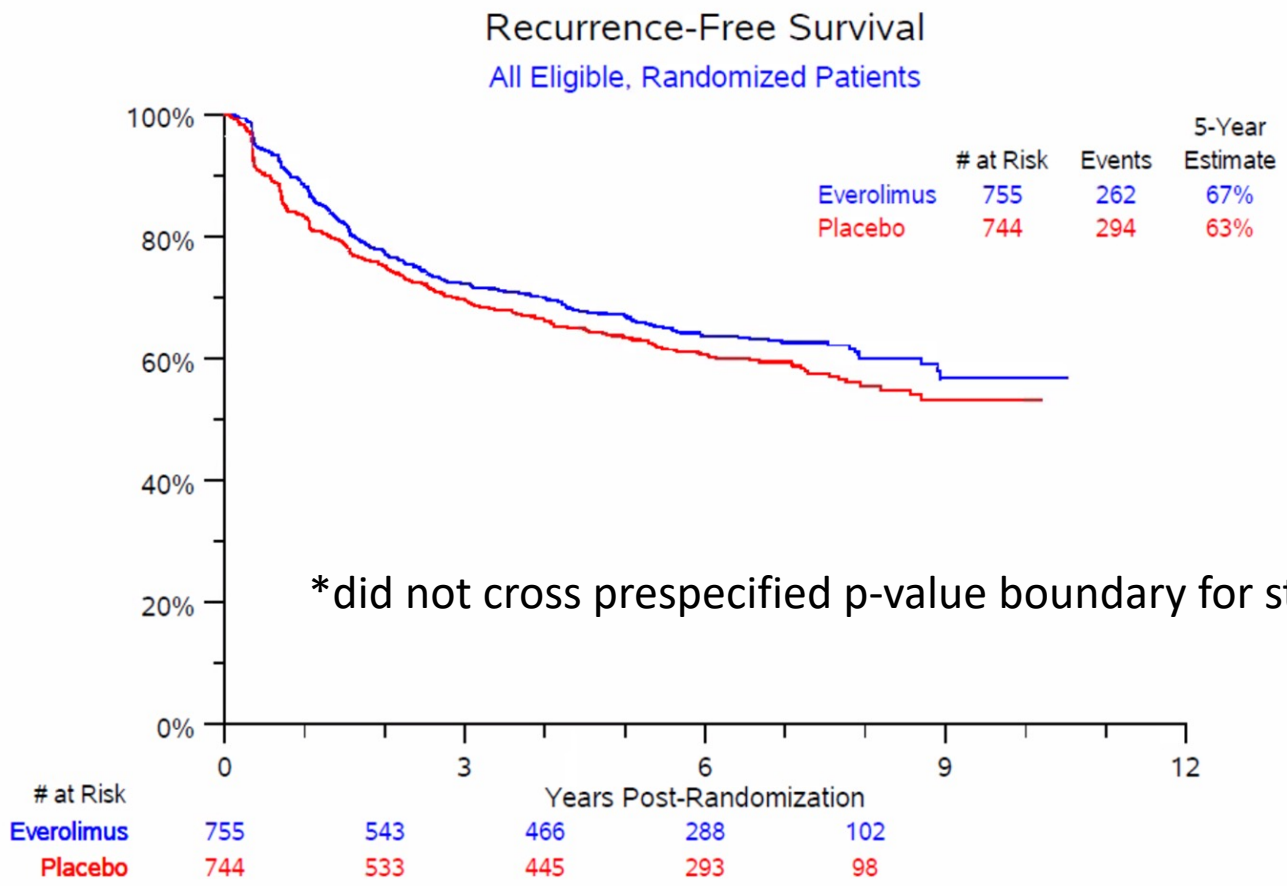
Haas NB *Lancet* 2016; Eisen T *JCO* 2020; Motzer RJ *JCO* 2017 and *Eur Urol 2021 ;* Gross-Goupil M *Ann* Oncol 2018; Rauvad A *N Engl J Med* 2016 and *Eur Urol* 2018; Choueiri TK *N Engl J Med* 2021 and GU ASCO 2022

EVEREST Trial Design



Stratification Factors:
Risk Group (Intermediate-High vs. Very High)
Histology (Clear cell vs. non-Clear Cell)
Performance Status (0 vs. 1)

Recurrence-Free Survival in all patients

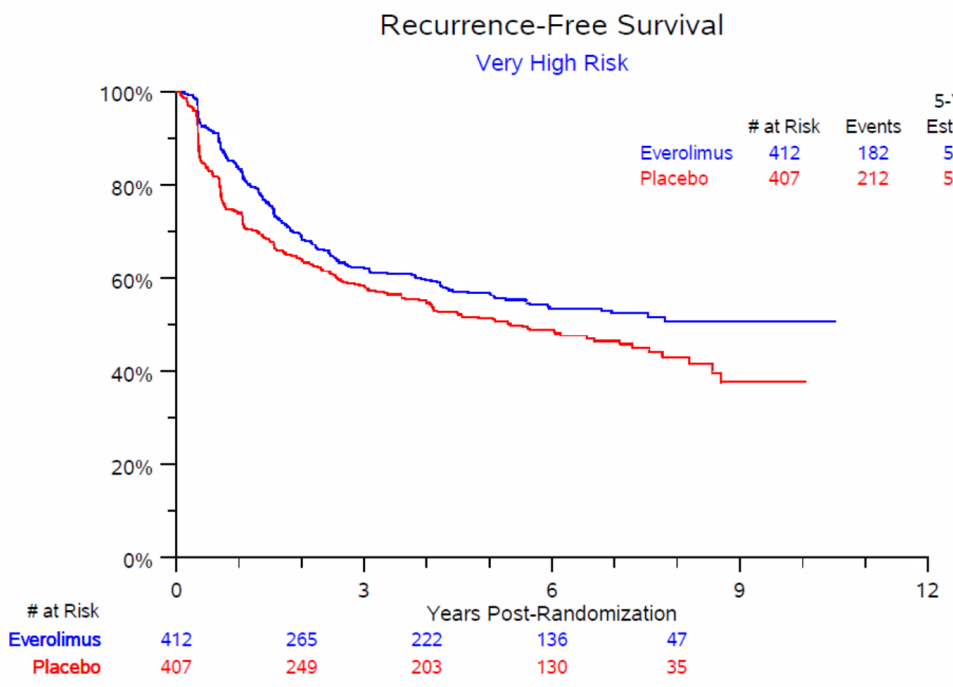


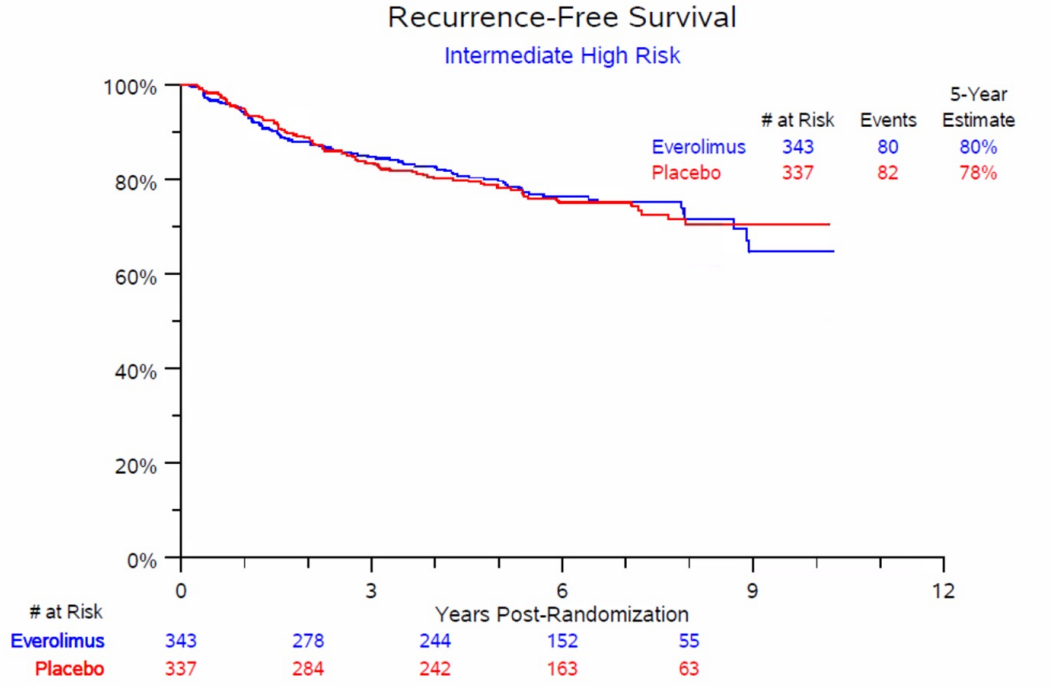
HR 0.85 (95% CI, 0.72, 1.00)

$P_{1\text{-}sided}$ = 0.025*

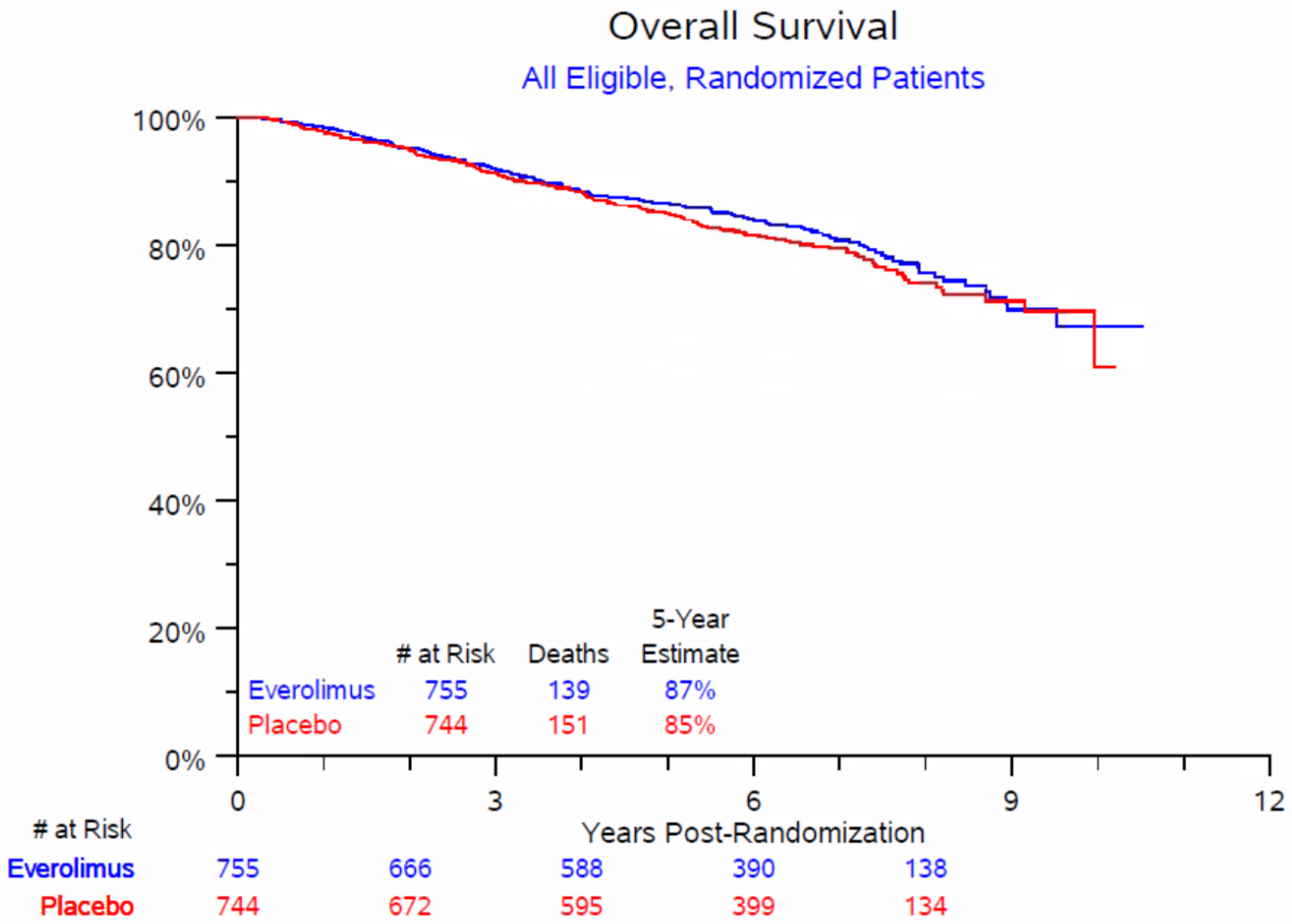
*did not cross prespecified p-value boundary for statistical significance of 0.022

Recurrence-Free Survival based on risk group



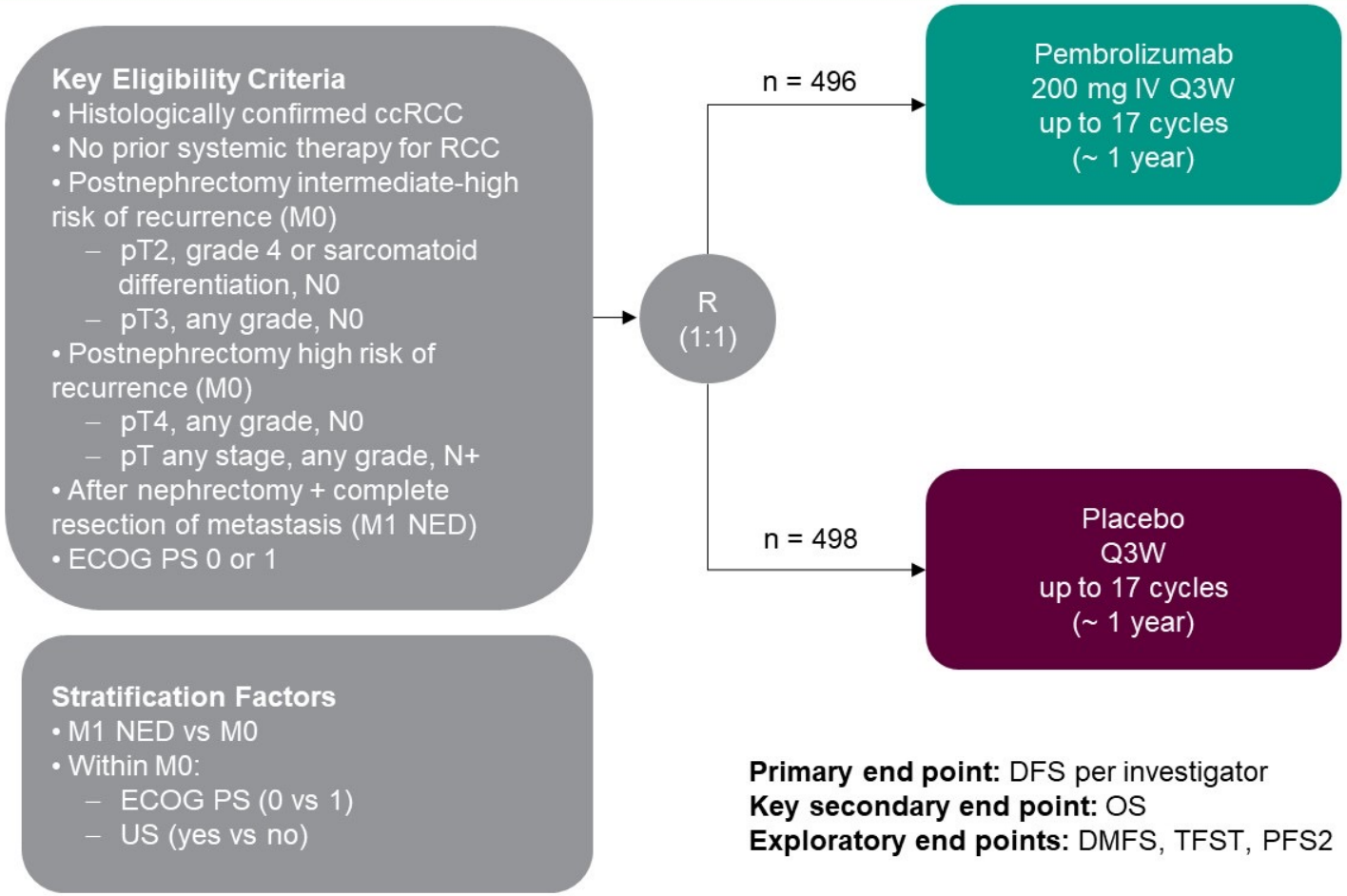


Adjuvant everolimus did not improve overall survival



Background and Study Design

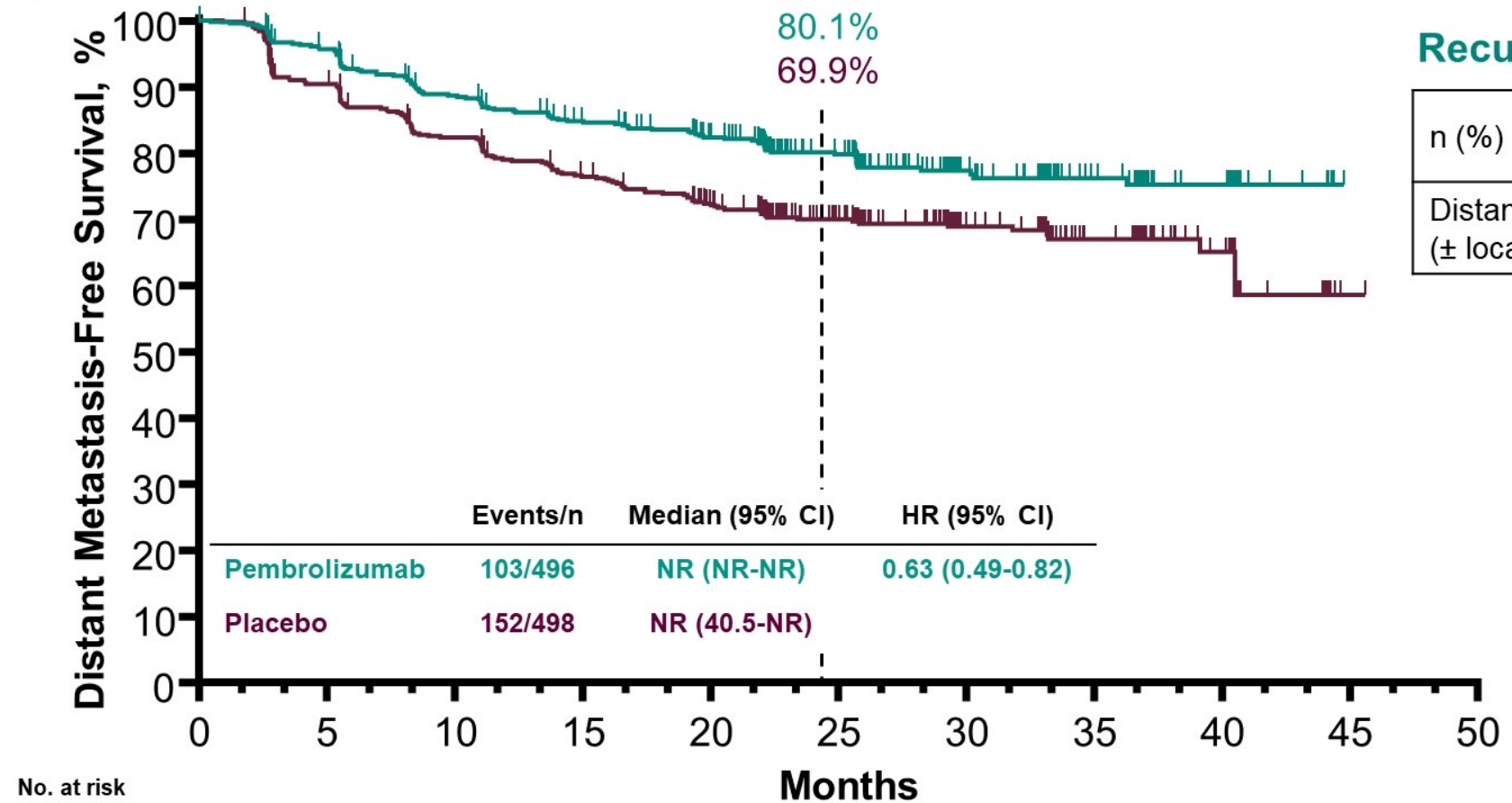
- Results of KEYNOTE-564 showed that adjuvant pembrolizumab improved DFS compared with placebo after a median 30.1 months of follow-up in patients with ccRCC at increased risk for recurrence after nephrectomy[1]
- Post hoc exploratory analyses are presented of
  - Distant metastasis-free survival (DMFS; time to radiographically detectable metastatic disease or any-cause death)
  - Time to first subsequent drug treatment (TFST; time to first subsequent therapy or any-cause death)
  - Time to second progression (PFS2; time from randomization to progression on next-line therapy or any-cause death)
- Median time from randomization to database cutoff was 30.1 months (range, 20.8-47.5 months)



Primary end point: DFS per investigator
Key secondary end point: OS
Exploratory end points: DMFS, TFST, PFS2

1. Choueiri TK et al. *J Clin Oncol*. 2022;40(suppl 6). Abstract 290.

Distant Metastasis-Free Survival (ITT)



No. at risk

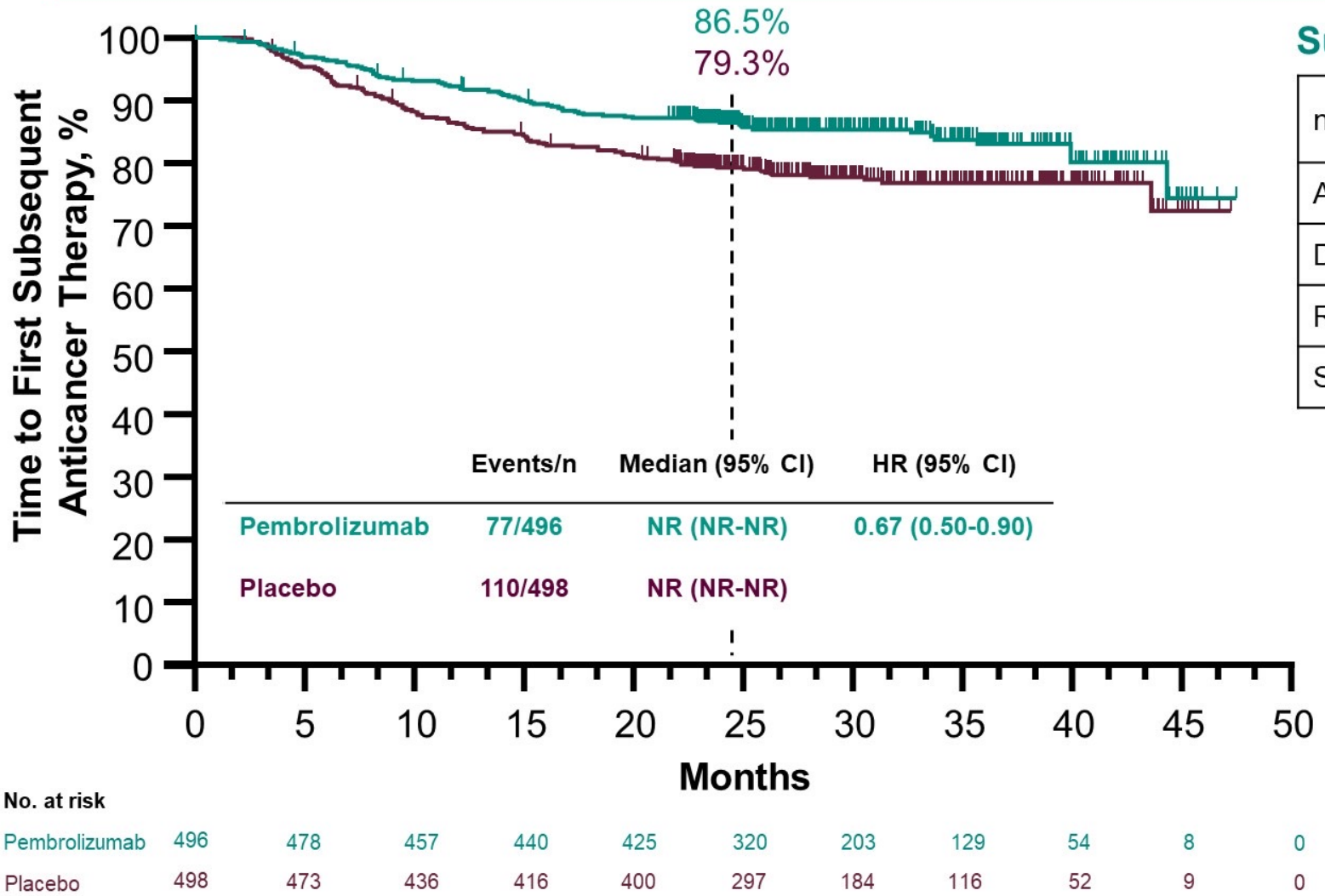
Pembrolizumab	496	457	415	387	361	255	135	76	37	0	0
Placebo	498	439	394	360	327	230	126	74	33	1	0

Database cutoff date: June 14, 2021.

Recurrence events

n (%)	Pembrolizumab n = 496	Placebo n = 498
Distant (± local)	95 (19.2)	140 (28.1)

Time to First Subsequent Anticancer Therapy (ITT)

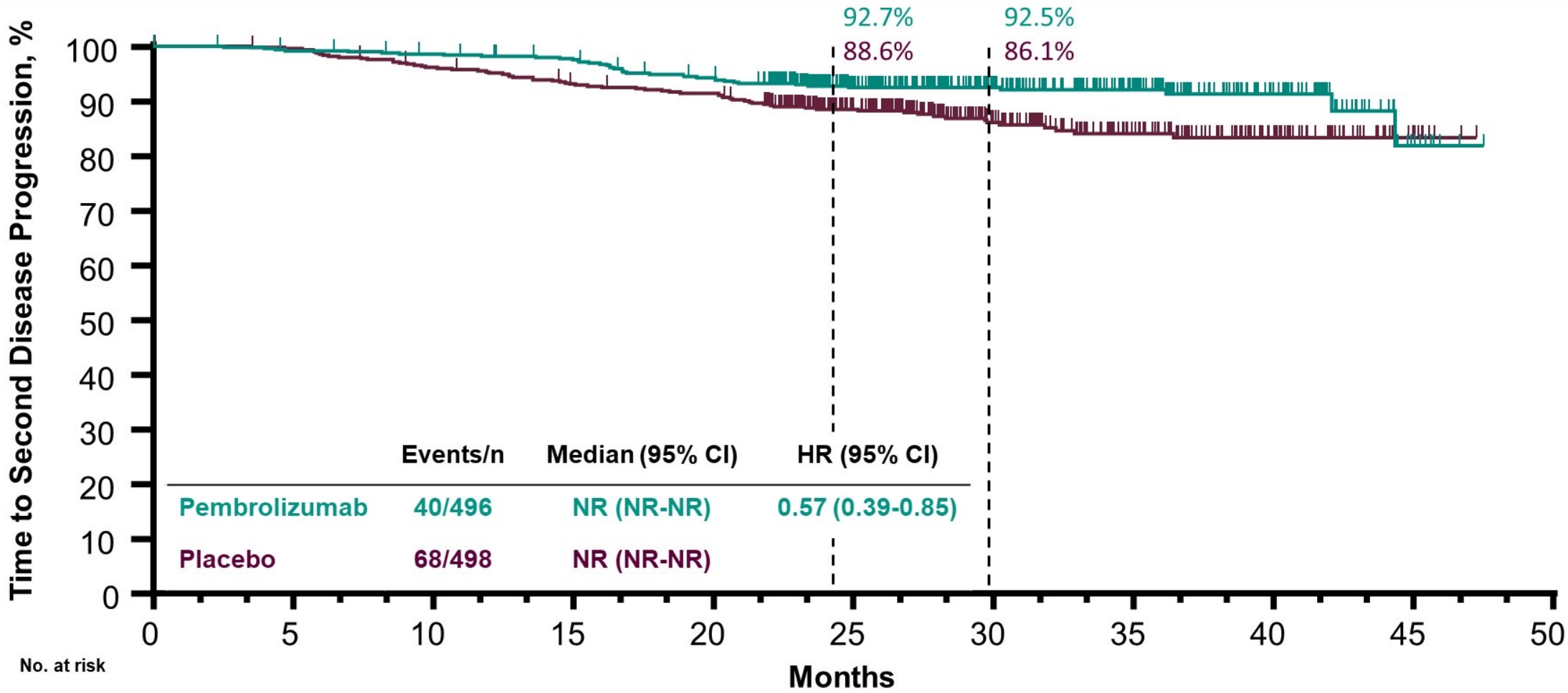


Database cutoff date: June 14, 2021.

Subsequent therapy

n (%)	Pembrolizumab n = 496	Placebo n = 498
Any	84 (17.5)	124 (24.9)
Drug therapy	67 (13.5)	99 (19.9)
Radiation therapy	17 (3.4)	19 (3.8)
Surgery	23 (4.6)	36 (7.2)

Time to Second Disease Progression (ITT)

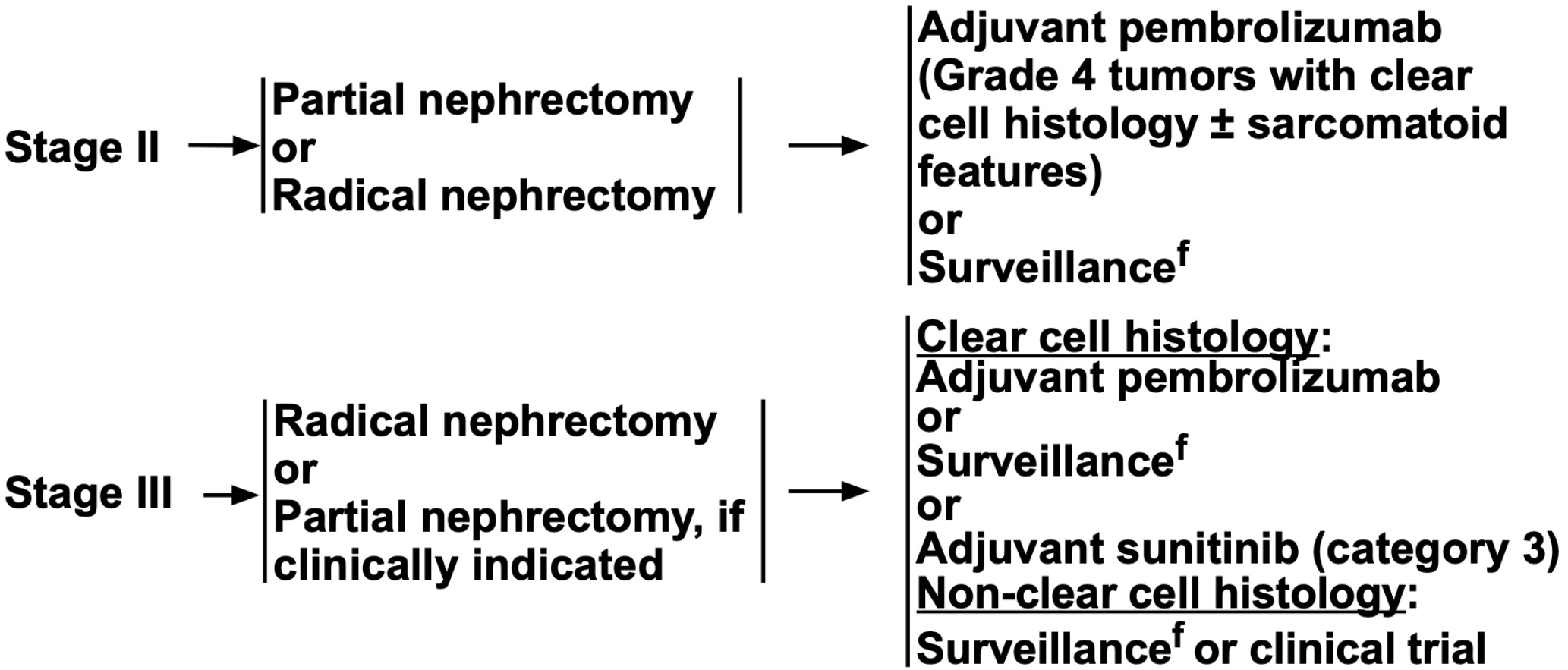


No. at risk

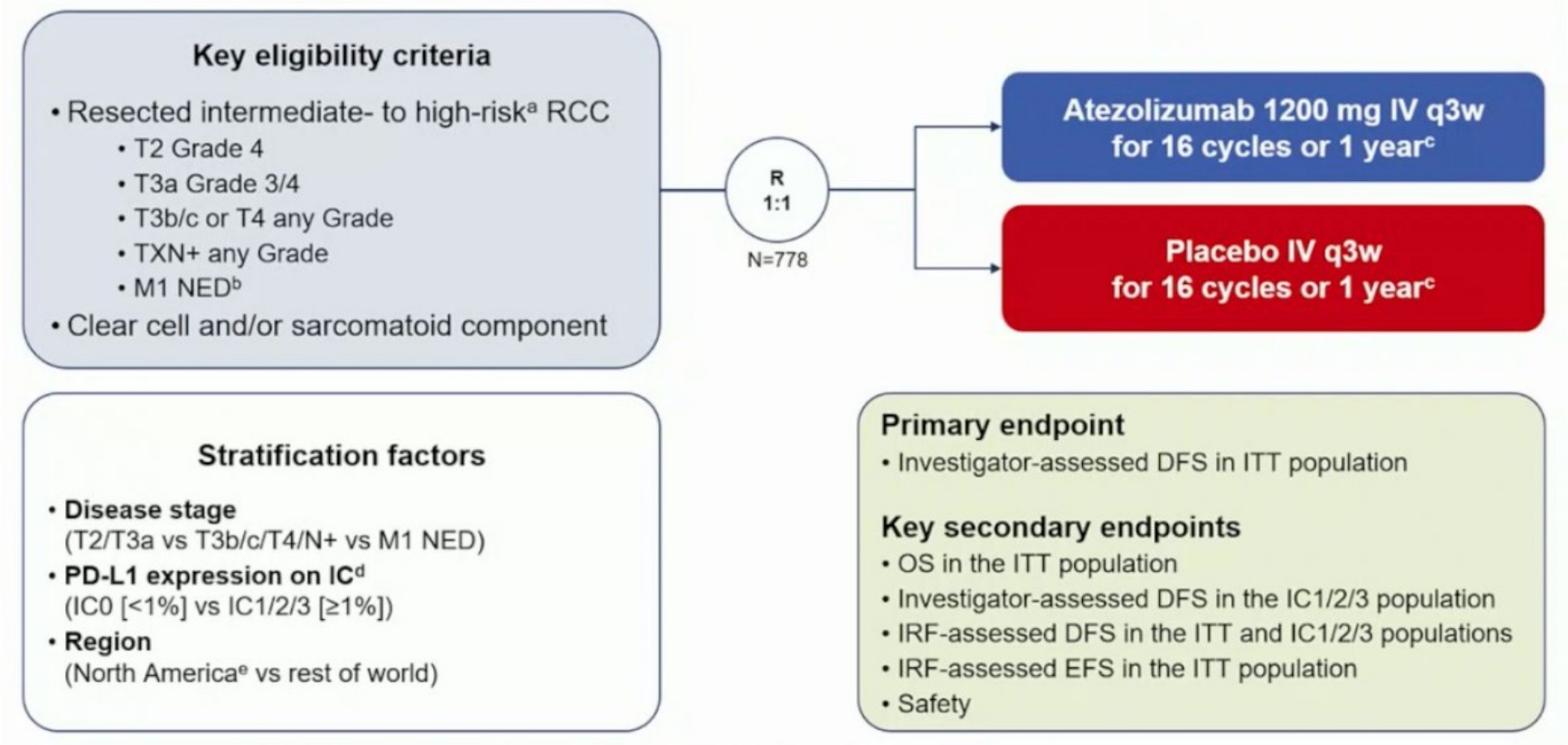
Pembrolizumab	496	489	483	474	454	340	215	138	61	8	0
Placebo	498	494	475	457	448	330	202	126	56	9	0

Database cutoff date: June 14, 2021.

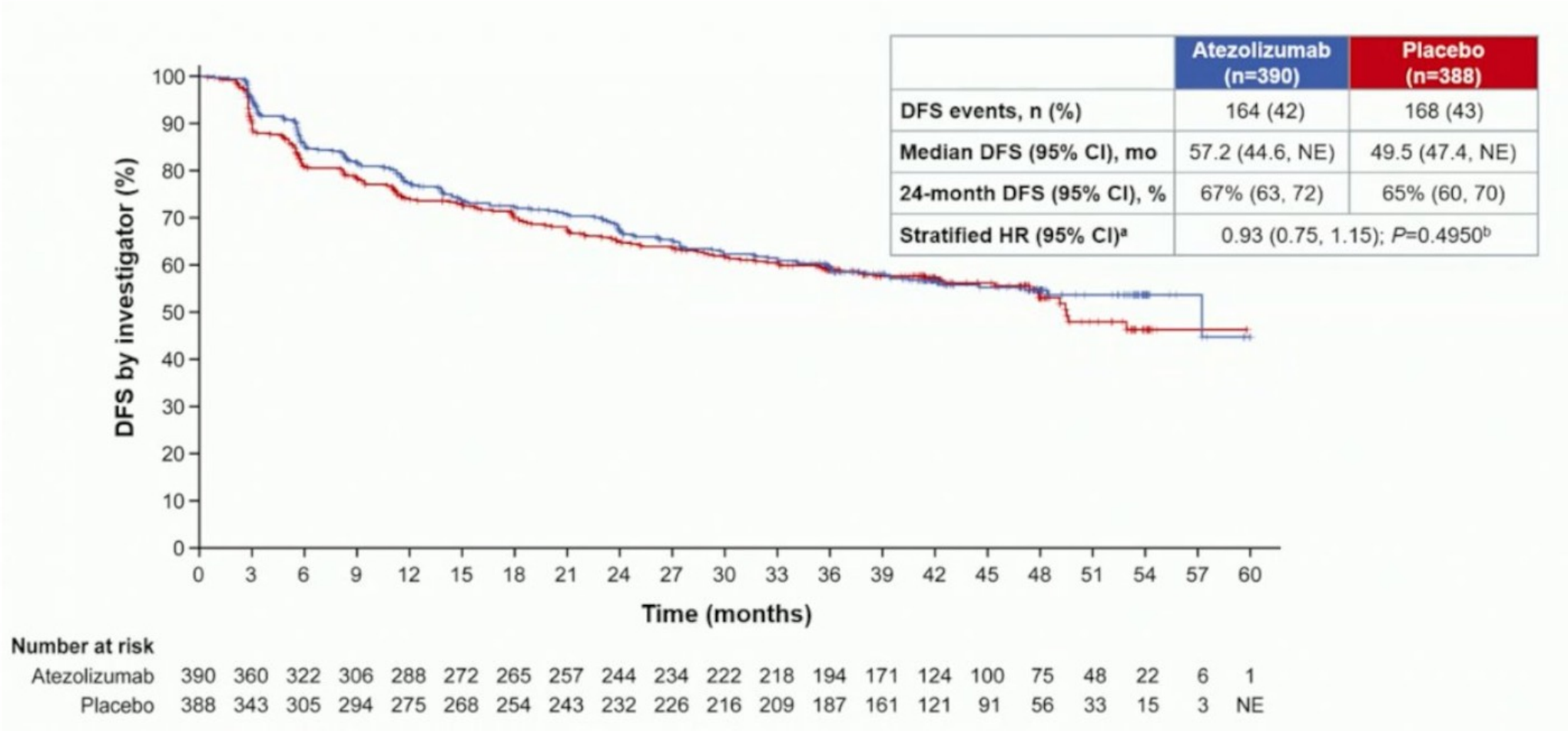
Guidelines for adjuvant therapy for RCC



IMmotion010: efficacy and safety of atezolizumab vs placebo as adjuvant therapy in patients with RCC at increased risk of recurrence after resection



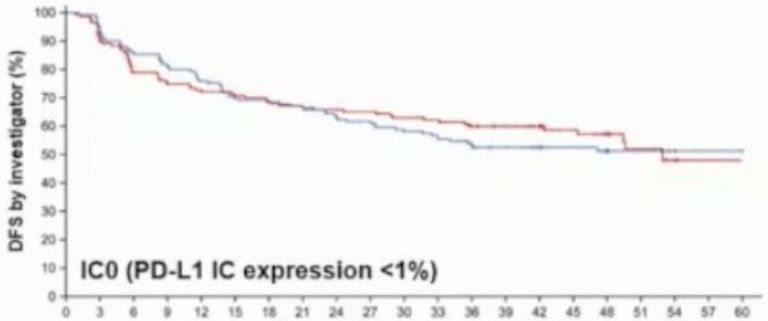
PFS ITT Population



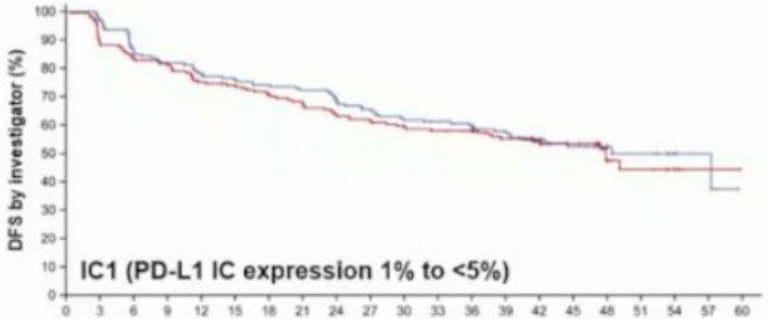
	Atezolizumab (n=390)	Placebo (n=388)
DFS events, n (%)	164 (42)	168 (43)
Median DFS (95% CI), mo	57.2 (44.6, NE)	49.5 (47.4, NE)
24-month DFS (95% CI), %	67% (63, 72)	65% (60, 70)
Stratified HR (95% CI)[a]	0.93 (0.75, 1.15); *P*=0.4950[b]	

Overall Survival

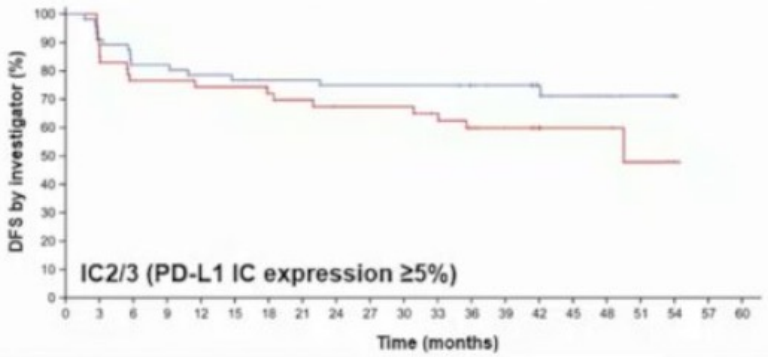
PD-L1 status



	Atezolizumab (n=158)	Placebo (n=153)
DFS events, n (%)	71 (44.9)	63 (41.2)
Median DFS (95% CI), mo	NE (31.7, NE)	52.9 (45.4, NE)
Stratified HR (95% CI)	1.09 (0.77, 1.53)	



	Atezolizumab (n=176)	Placebo (n=188)
DFS events, n (%)	78 (44.3)	86 (45.7)
Median DFS (95% CI), mo	48.4 (39.1, NE)	47.9 (36.5, NE)
Stratified HR (95% CI)	0.92 (0.68, 1.25)	



	Atezolizumab (n=56)	Placebo (n=47)
DFS events, n (%)	15 (26.8)	19 (40.4)
Median DFS (95% CI), mo	NE (NE, NE)	49.5 (33.1, NE)
Stratified HR (95% CI)	0.57 (0.29, 1.15)	

Data cutoff: 3 May 2022.

Bex A et al. IMmotion010 [abstract 4634]
https://bit.ly/3Ai7cQl

Conclusions

- Atezolizumab as adjuvant therapy did not improve clinical outcomes vs placebo in the ITT population
- Atezolizumab was well tolerated, and safety results were consistent with the known safety profile of atezolizumab
- Subgroup analysis suggests further evaluation of sarcomatoid and high-expression PD-L1 populations is warranted

Checkmate914 Adjuvant Nivo + Ipi vs placebo for localized renal cell carcinoma (RCC) at high risk of relapse after nephrectomy

N = 816

Key inclusion criteria[1]

- Radical or partial nephrectomy with negative surgical margins
- Predominant clear cell histology, including sarcomatoid features
- Pathologic TNM staging:
  - pT2a, G3 or G4, N0 M0
  - pT2b, G any, N0 M0
  - pT3, G any, N0 M0
  - pT4, G any, N0 M0
  - pT any, G any, N1 M0
- No clinical/radiological evidence of residual disease or distant metastases after nephrectomy, confirmed by BICR
- ECOG performance status of 0-1

Stratification factors:

- Pathologic TNM staging[a]
- Type of nephrectomy

R 1:1

Randomization > 4 weeks but ≤ 12 weeks after surgery

Expected treatment duration of 24 weeks[b]

NIVO 240 mg IV Q2W (× 12 doses) + **IPI** 1 mg/kg IV Q6W (× 4 doses)
N = 405

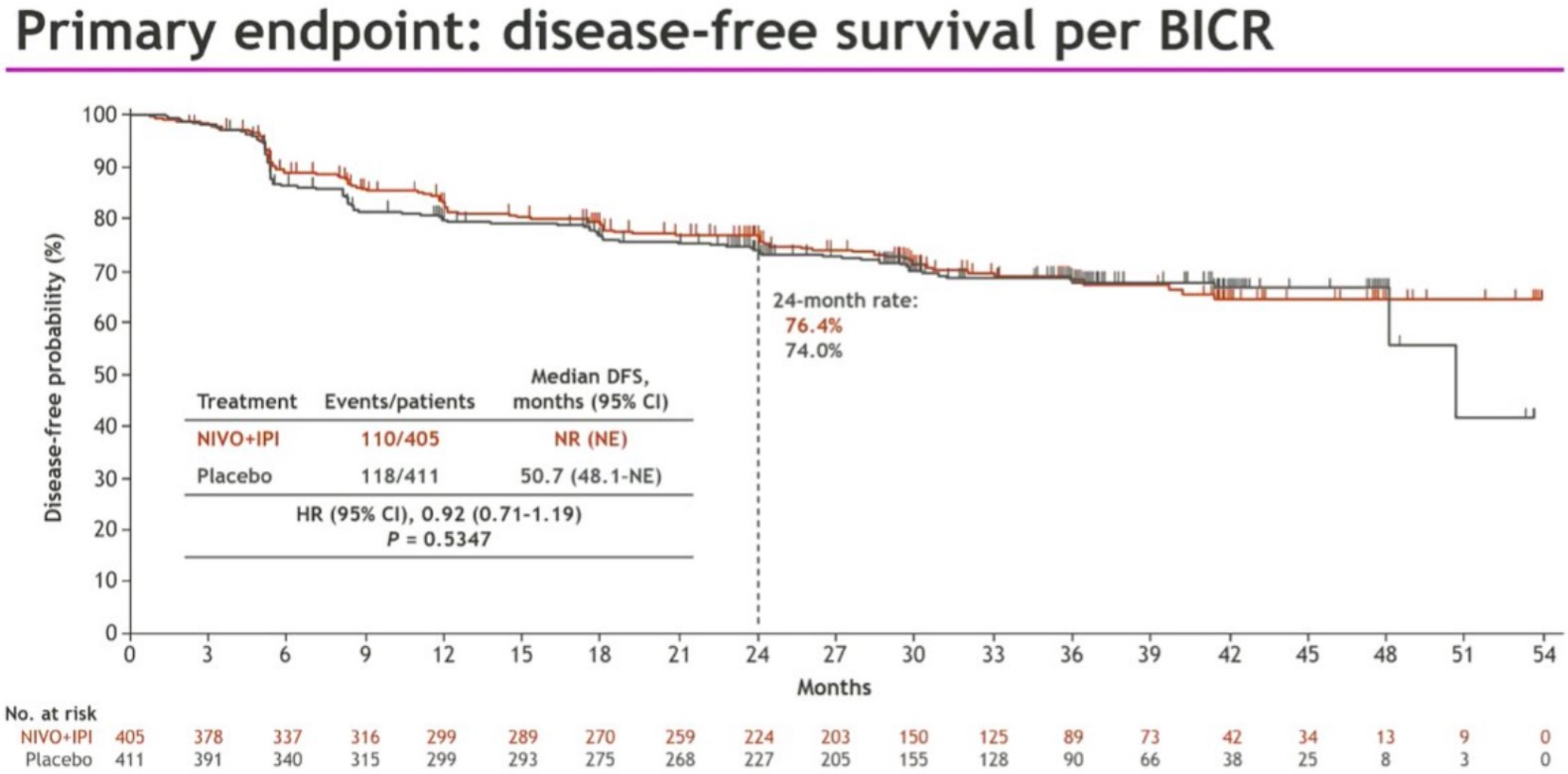
Placebo IV Q2W (× 12 doses) + **Placebo** IV Q6W (× 4 doses)
N = 411

Primary endpoint: DFS by BICR

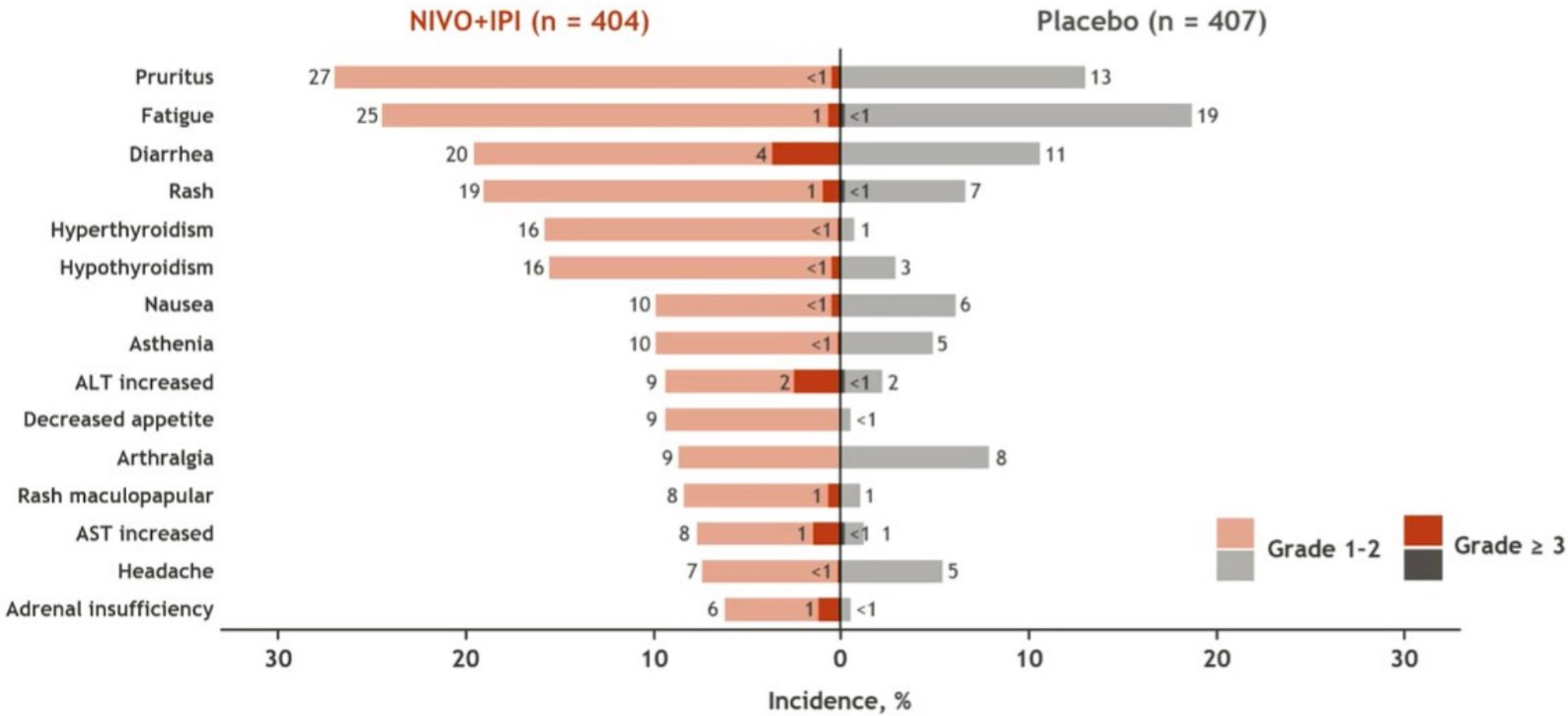
Secondary endpoints: OS and safety

Median (range) study follow-up, 37.0 (15.4-58.0) months

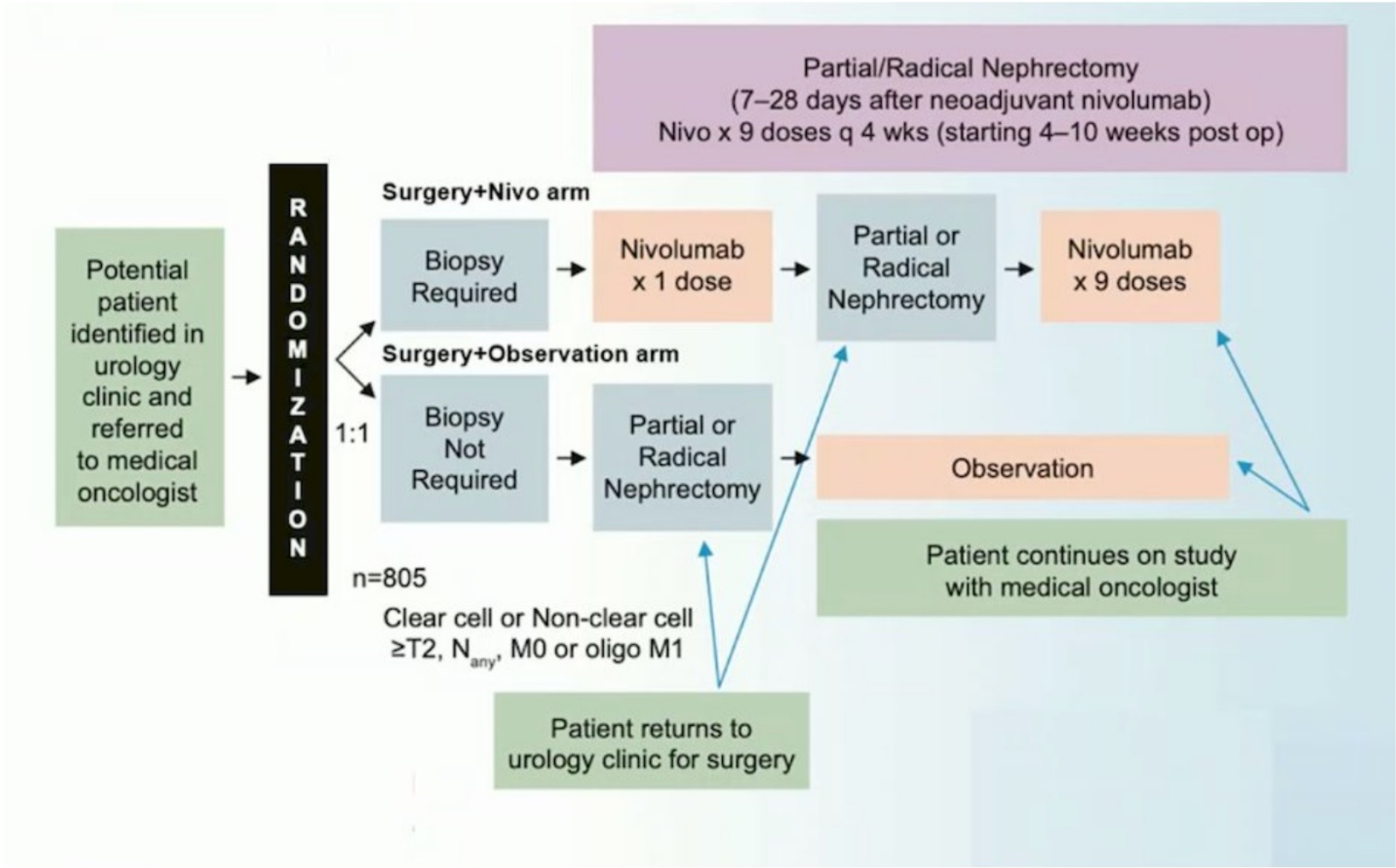
Disease- Free Survival

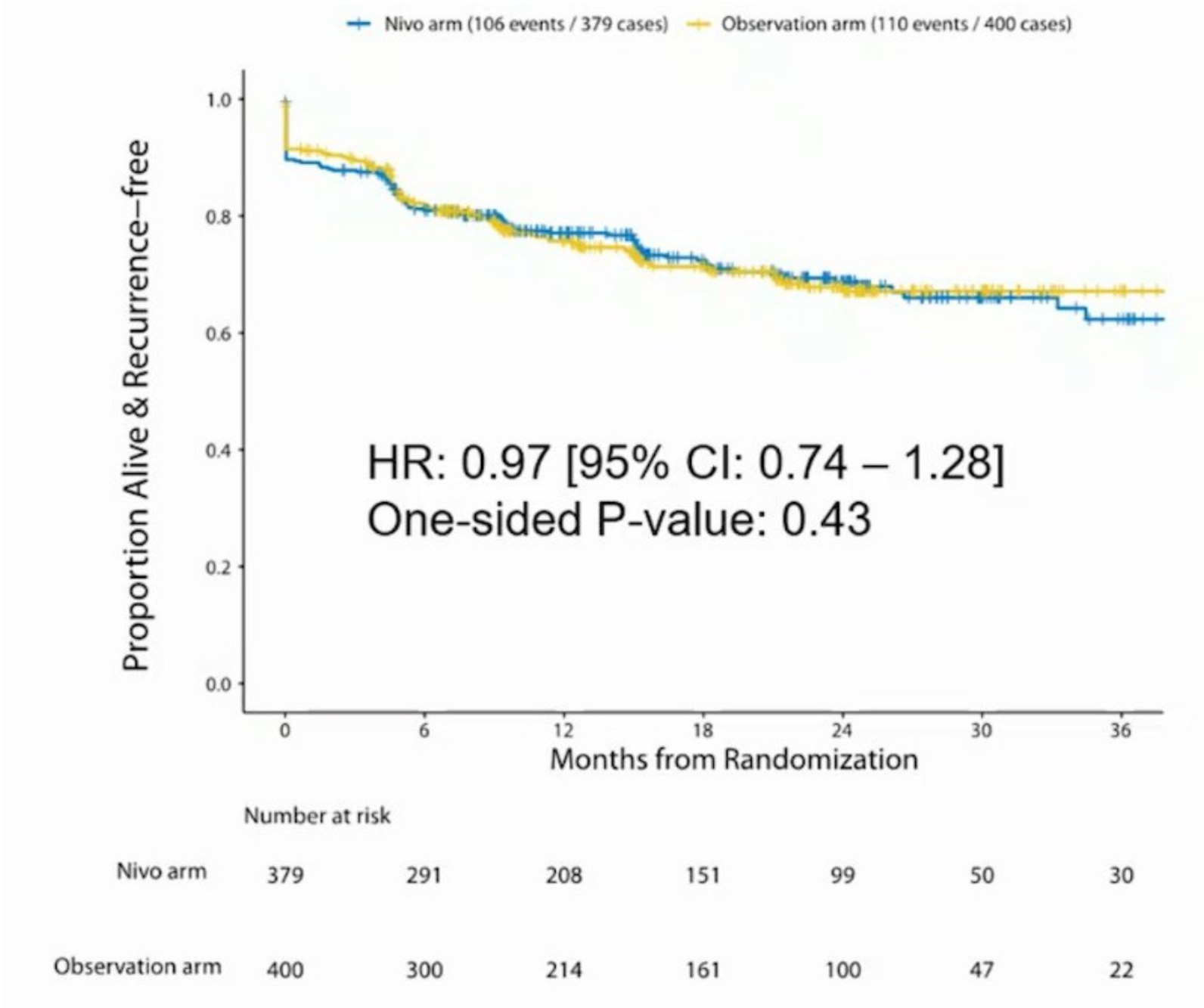


Treatment-related AEs in all treated patients[a]



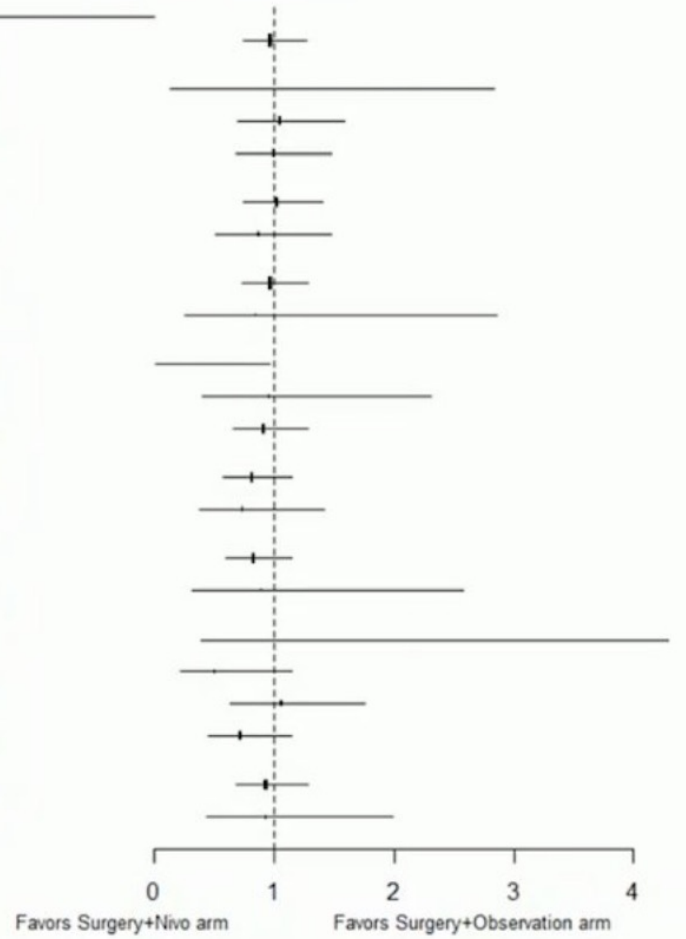
Phase III open-label PROSPER Trial Assessing Perioperative Nivolumab versus Observation in Patients With RCC




Nivo arm (106 events / 379 cases)
Observation arm (110 events / 400 cases)
Proportion Alive & Recurrence–free
1.0
0.8
0.6
0.4
0.2
0.0
HR: 0.97 [95% CI: 0.74 – 1.28]
One-sided P-value: 0.43
0
6
12
18
24
30
36
Months from Randomization
Number at risk
Nivo arm 379 291 208 151 99 50 30
Observation arm 400 300 214 161 100 47 22

RFS in Subgroups – No Clinical Benefit

Sub-group	N	HR	95% CI
All RCC Patients	779	0.97	(0.74, 1.27)
cT1	25	0.61	(0.13, 2.83)
cT2	398	1.05	(0.69, 1.59)
cT3 or cT4	394	1.00	(0.68, 1.47)
cNx or cN0	697	1.02	(0.74, 1.40)
cN1	121	0.87	(0.51, 1.47)
cMx or cM0	790	0.97	(0.73, 1.28)
cM1	27	0.85	(0.25, 2.86)
pTx or pT1	79	0.12	(0.01, 0.96)
pT2	164	0.96	(0.40, 2.31)
pT3 or pT4	494	0.91	(0.65, 1.28)
pNx or pN0	671	0.81	(0.57, 1.14)
pN1	66	0.73	(0.37, 1.41)
pMx or pM0	708	0.83	(0.60, 1.14)
pM1	28	0.89	(0.31, 2.57)
Fuhrman Grade 1	24	3.37	(0.38, 30.18)
Fuhrman Grade 2	185	0.50	(0.21, 1.15)
Fuhrman Grade 3	282	1.06	(0.63, 1.76)
Fuhrman Grade 4	181	0.72	(0.45, 1.14)
Clear-cell	625	0.93	(0.68, 1.28)
Non-clear cell	128	0.93	(0.44, 1.99)

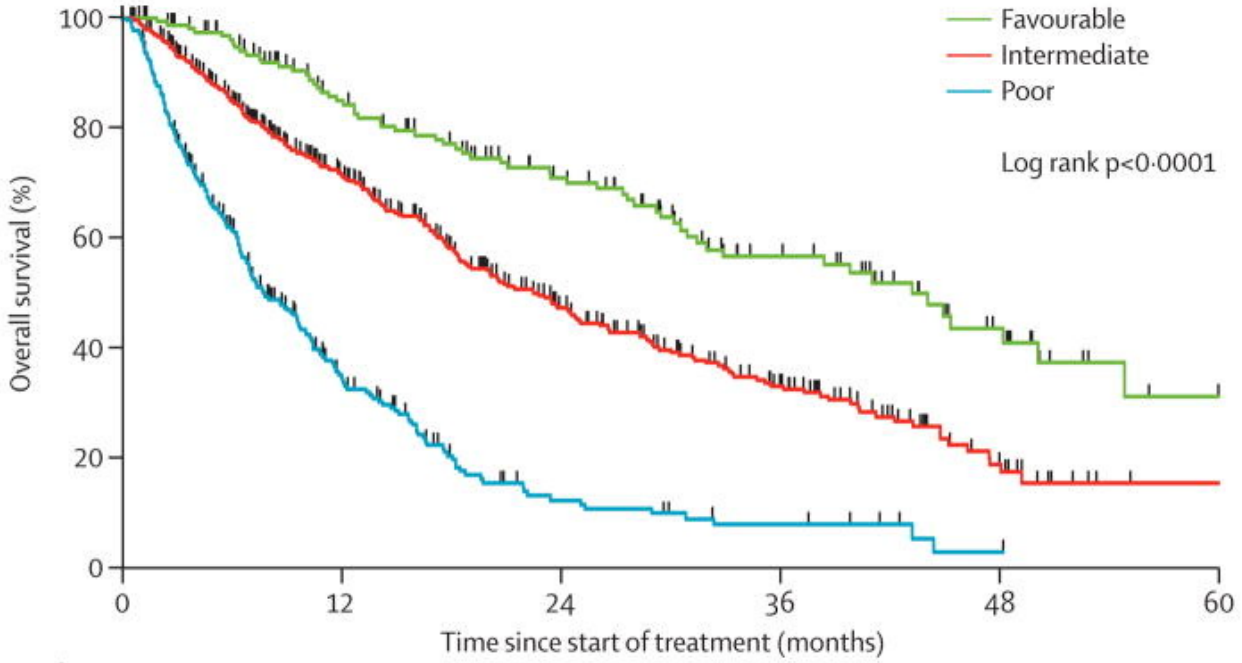


PROSPER Conclusions

- First phase III neoadjuvant trial using IO in RCC
- Perioperative RCC did not improve RFS
- OS is immature but is not statistically different between the two arms
- AE in surgery + nivolumab is similar to previous trials

Risk Stratification in ccRCC- IMDC (International Metastatic RCC Database Consortium)

- Less than one year from time of diagnosis to systemic therapy
- Performance status
- Hemoglobin< lower limit of normal
- Calcium > upper limit of normal
- Neutrophil > upper limit of normal
- Platelets > upper limit of normal



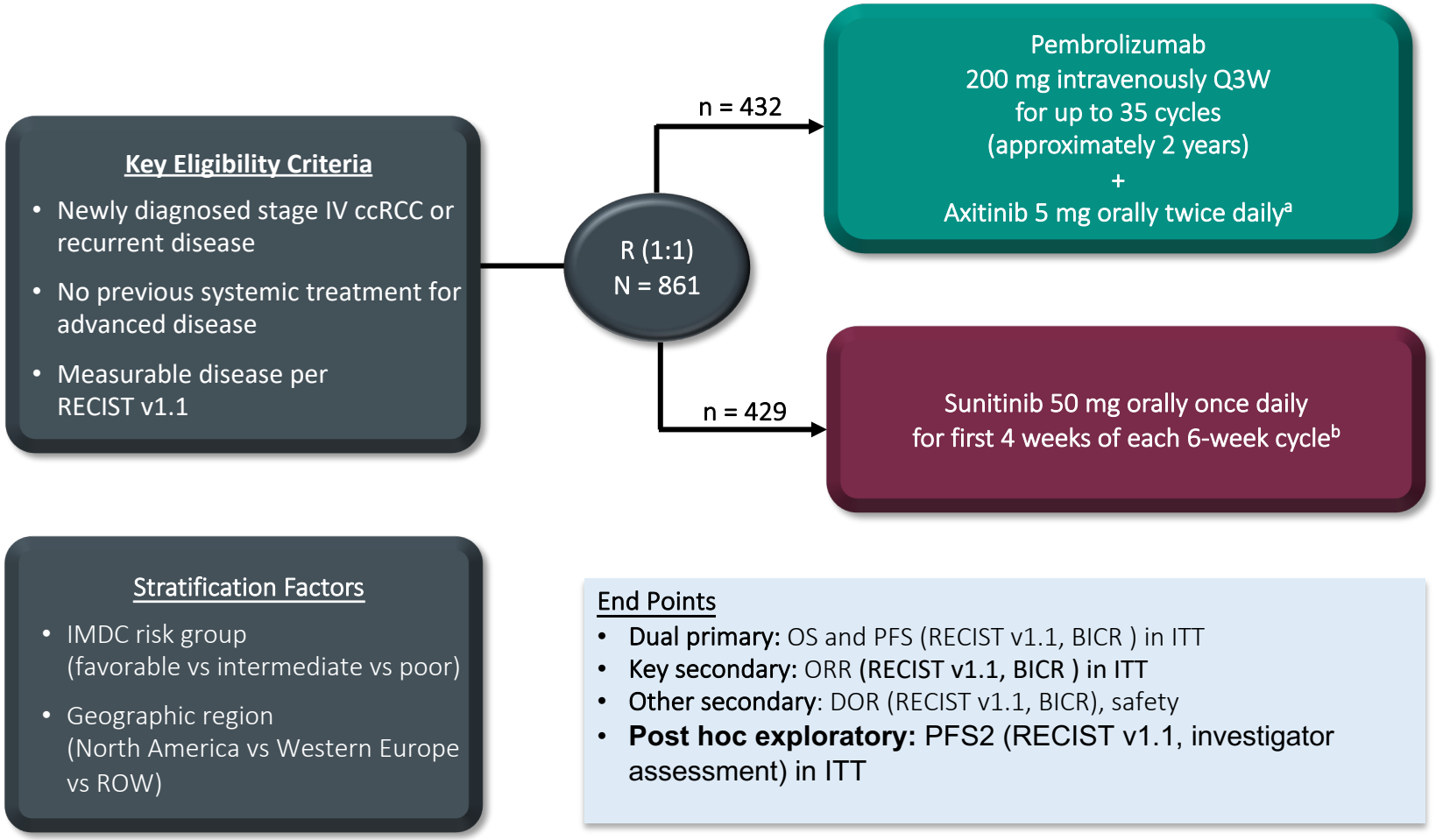
Number at risk						
Favourable	157	109	74	40	17	3
Intermediate	440	247	122	59	15	1
Poor	252	65	15	7	1	0

Frontline therapy in mRCC- four Phase 3 trials

	CM 214 (Ipi/Nivo) [1] (n=550 vs n=546)	KN-426 (Axi/Pembro)[2] (n=432 vs n=429)	CM 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
FDA Approval	2018, 1L for int/poor risk	2019, 1L	2021, 1L	2021, 1L
Fav/Int/Poor, %	23/61/17	32/55/13	23/58/19	31/59/9
Med f/u, mo	55	42.8	23.5	27
mOS (int/poor), mo **HR (CI)**	48.1 vs 26.6 0.65 (0.54-0.78)	50.6 vs 37.6 0.64 (0.52-0.80)	I: 0.74 (0.50–1.08) P: 0.45 (0.27–0.76)	NE vs NE 0.58 (0.42-0.80)
mPFS (int/poor), mo **HR (CI)**	11.2 vs 8.3 0.74 (0.62-0.88)	13.8 vs 8.2 0.67 (0.55-0.81)	I: 0.58 (0.45–0.76) P: 0.36 (0.23–0.56)	22.1 vs 5.9 0.36 (0.26-0.47)
ORR (int/Poor), %	42 v 27	57 vs 35	I: 56 vs 29 / P: 38 vs 10	72 vs 30
CR (int/Poor), %	11 vs 1	9 vs 2	I: 11 vs 3 (I) / P: 5 vs 1	14 vs 4

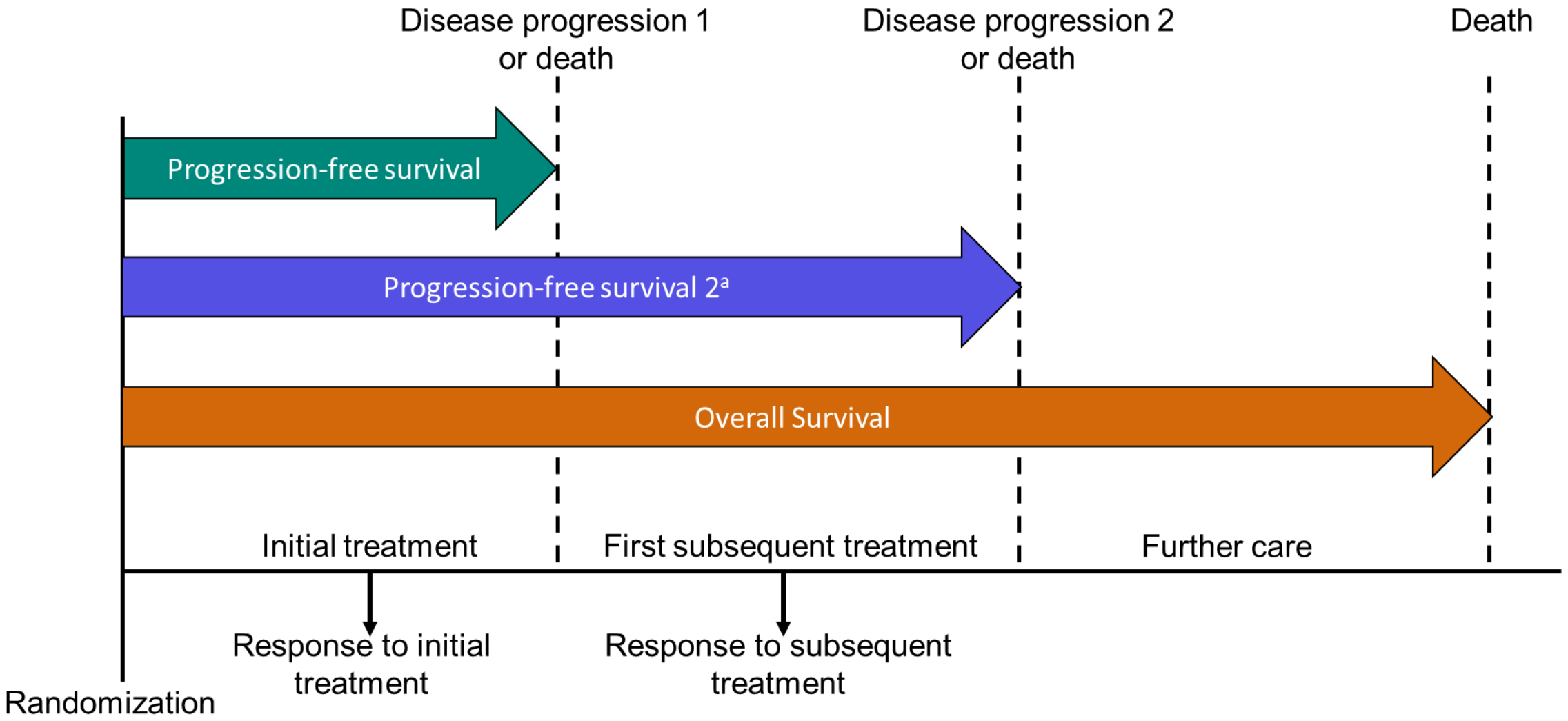
After first line combination therapy- what happens?

- The randomized, open-label, phase 3 KEYNOTE-426 study (NCT02853331) met its primary and key secondary end points of improved OS, PFS, and ORR with pembrolizumab + axitinib versus sunitinib as first-line treatment for patients with advanced ccRCC and pembrolizumab + axitinib showed durable benefit with extended follow-up[1-3]
- **Post hoc exploratory analyses of subsequent therapy use and PFS2 are presented**
- Median time from randomization to database cutoff was 42.8 months (range, 35.6-50.6 months)



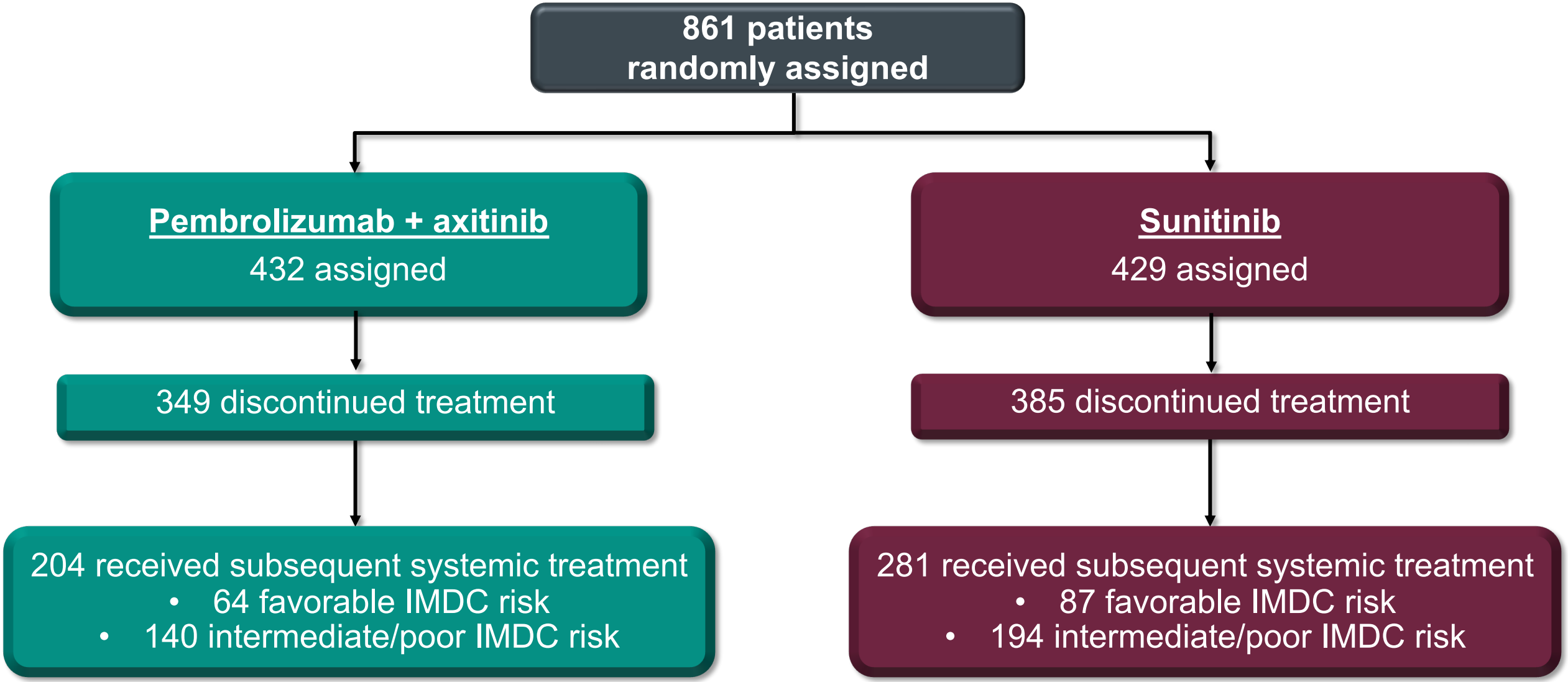
1. Rini BI et al. *N Engl J Med.* 2019;380:1116-1127. 2. Powles T et al. *Lancet Oncol*. 2020;21:1563-1573. 3. Rini BI et al. *J Clin Oncol.* 2021;39:4500.
Database cutoff date: January 11, 2021.

Timeline of Clinical Trial End Points



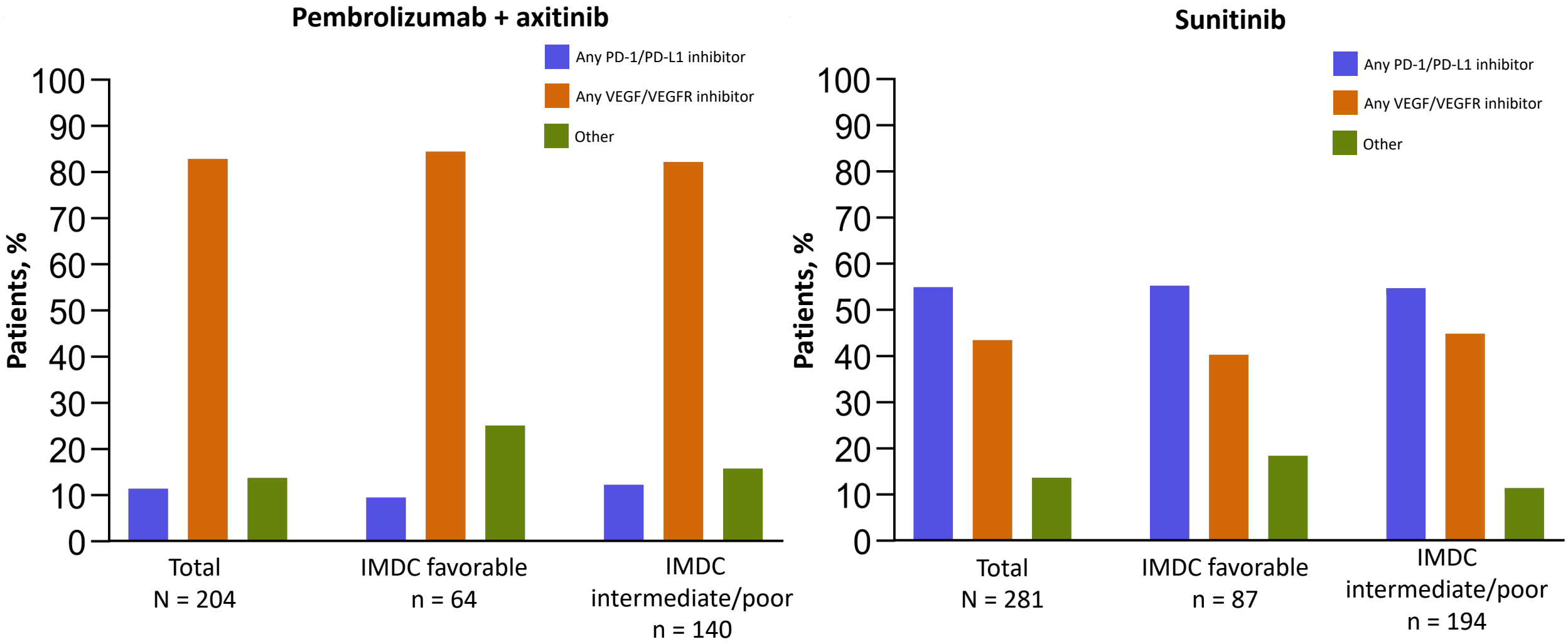
[a]Patients who are alive and did not receive subsequent therapy are censored.

Subsequent Therapy, 1/3 of patients may not receive subsequent therapy



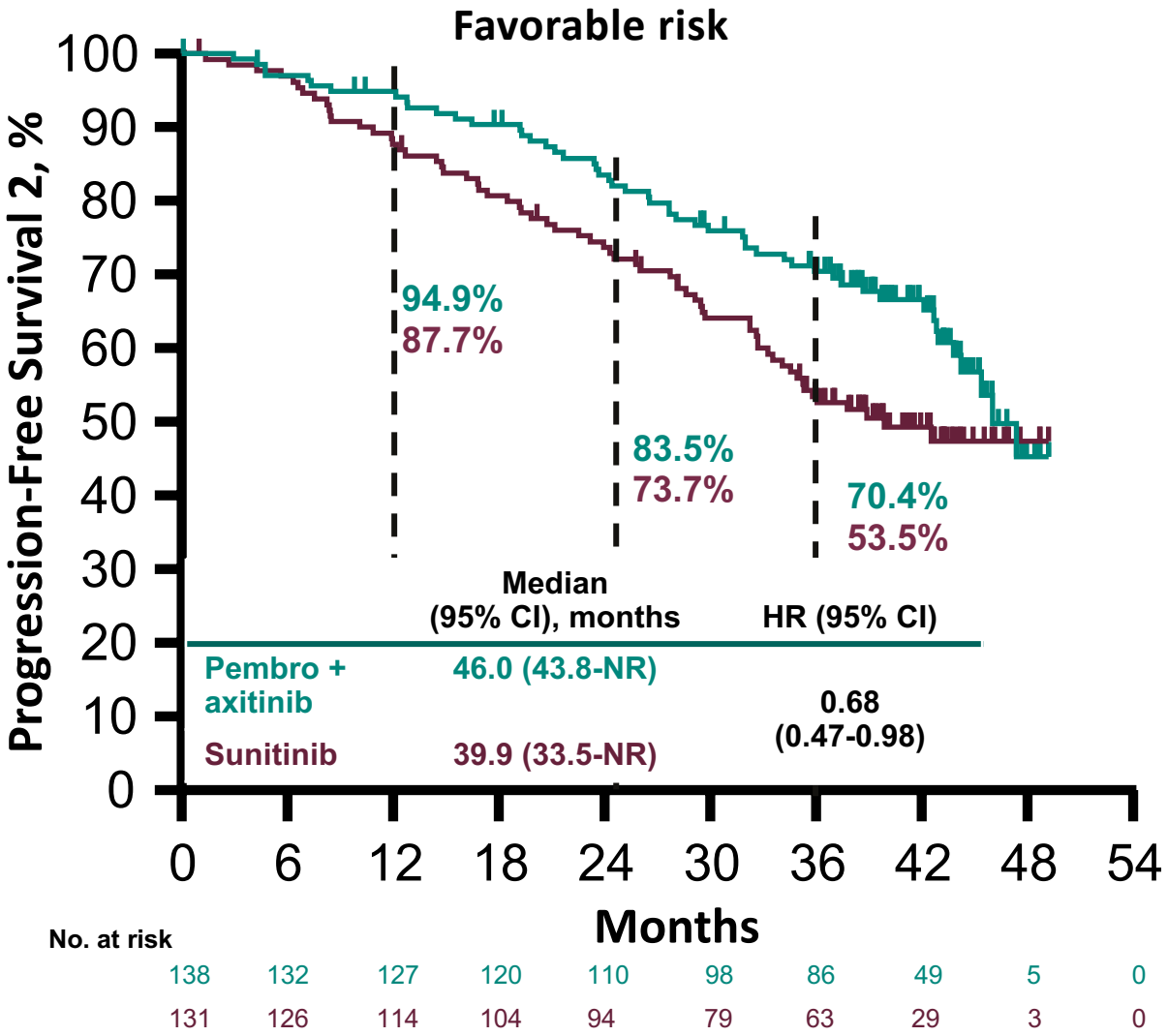
Database cutoff date: January 11, 2021.

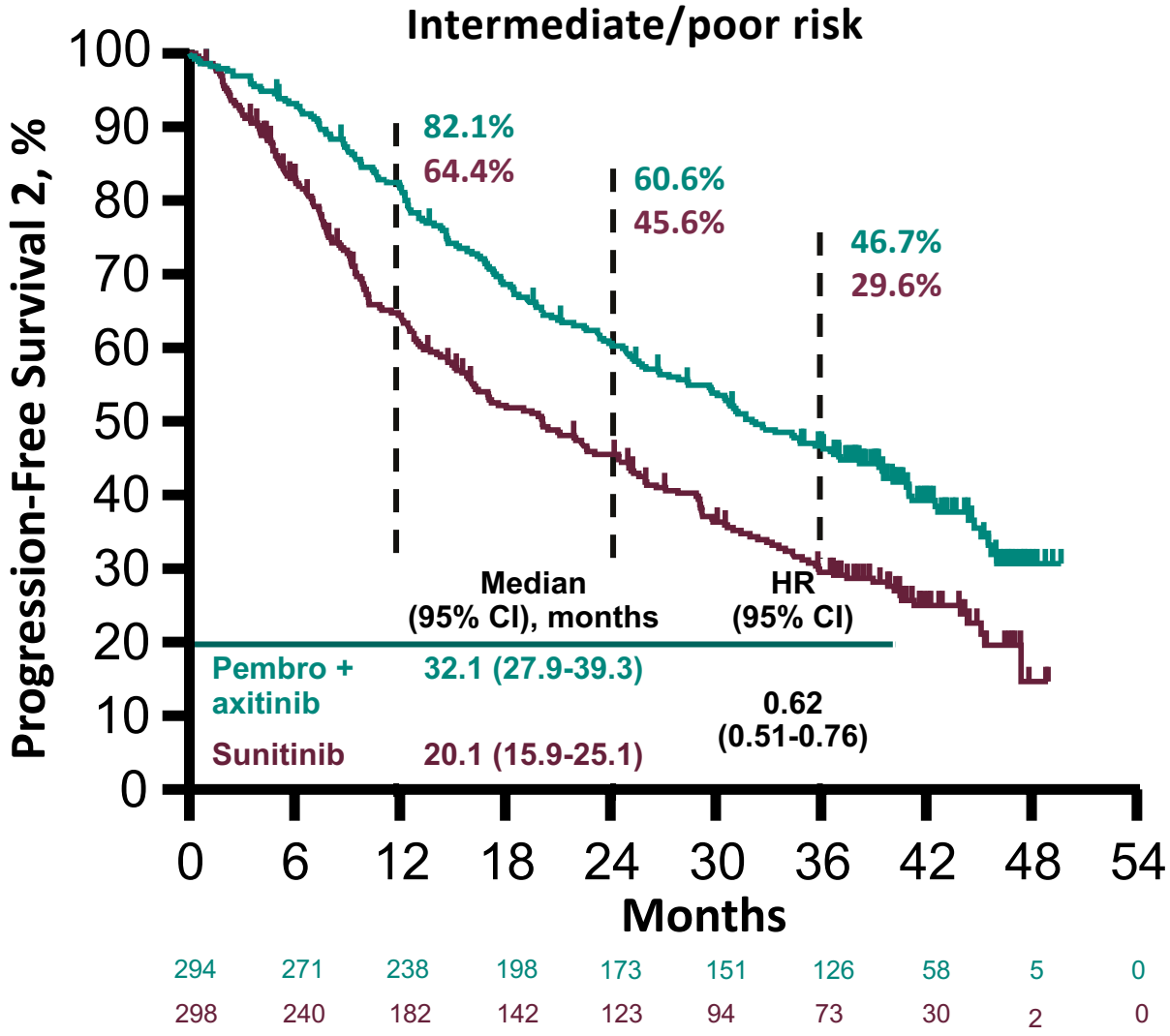
First Subsequent Systemic Therapy



Database cutoff date: January 11, 2021.

Progression-Free Survival 2: IMDC Risk Groups, longer in pembrolizumab + axitinib regardless of IMDC risk group





Database cutoff date: January 11, 2021.

Conclusions

- Long-term results of KEYNOTE-426 continue to support pembrolizumab + axitinib as standard of care for patients with previously untreated advanced ccRCC
- PFS2 was longer for patients in the pembrolizumab + axitinib group than in those in the sunitinib group, regardless of IMDC risk
- Results from this exploratory analysis of PFS2 support the long-term benefit of pembrolizumab + axitinib for first-line treatment of patients with advanced ccRCC

Updated NCCN Guidelines for subsequent therapy advanced RCC

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Cabozantinib (category 1) • Lenvatinib + everolimus • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] (category 1) • Axitinib + avelumab[b] (category 3)	• Everolimus • Bevacizumab[f] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Sorafenib (category 3) • Temsirolimus[e] (category 2B) • Belzutifan (category 2B)

2022 ASCO® ANNUAL MEETING

The relationship between health-related quality of life and clinical outcomes in patients with advanced renal cell carcinoma in CheckMate 214

David Cella,[1] Melissa Hamilton,[2] Steven Blum,[2] Cristina Ivanescu,[3] Abi Williams,[4] Flavia Ejzykowicz,[2] Robert J. Motzer[5]

[1]Robert H. Lurie Comprehensive Cancer Care Center, Northwestern University, Chicago, IL; [2]Bristol Myers Squibb, Princeton, NJ; [3]IQVIA, Amsterdam, the Netherlands; [4]IQVIA, London, UK; [5]Memorial Sloan Kettering Cancer Center, New York, NY

Abstract number 4502

Introduction

- CheckMate 214 demonstrated overall survival (OS) and progression-free survival (PFS) benefit with long-term follow-up for nivolumab plus ipilimumab compared with sunitinib[1,2]
- Nivolumab plus ipilimumab showed health-related quality of life (HRQoL) benefits versus sunitinib with long-term follow-up in CheckMate 214[3,4]
- Prior studies showed an association between HRQoL and efficacy outcomes in renal cell carcinoma (RCC), and other malignancies[5,6]
- We explore the prognostic ability of HRQoL data to help inform on risk of progression or death in patients with advanced RCC (aRCC)

1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290. 2. Motzer RJ, et al. *Cancer* 2022;128:2085-2097. 3. Cella D, et al. *Lancet Oncol* 2019;20:297-310. 4. Cella D, et al. *J Clin Oncol* 2022;40(suppl 6):307. 5. Cella D, et al. *J Oncol Pract* 2009;5:66-70. 6. Bukowski R, et al. *Am J Clin Oncol* 2007;30:220-227.

Objectives

- This analysis uses 5-year follow-up data of intermediate/poor-risk aRCC patients from CheckMate 214 to assess the following associations:

Baseline HRQoL and **PFS**	**Baseline HRQoL** and **OS**
Longitudinal HRQoL and **PFS**	**Longitudinal HRQoL** and **OS**

- **Baseline HRQoL** refers to data collected pre-treatment at randomization
- **Longitudinal HRQoL** refers to HRQoL data collected after randomization while on study
- HRQoL was assessed using the Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-19) total score and disease-related symptoms-physical (DRS-P) subscale

CheckMate 214 study design

Patients

- Treatment-naïve clear cell aRCC
- Measurable disease
- KPS ≥ 70%

Randomize 1:1

Stratified by
- IMDC prognostic score
- Region

Treatment[a]

NIVO+IPI arm

NIVO 3 mg/kg + IPI 1 mg/kg every 3 weeks for 4 doses, then NIVO 3 mg/kg every 2 weeks

Patients receiving NIVO monotherapy could switch to NIVO 240 mg dosing[a]

SUN arm

SUN 50 mg once daily for 4 weeks on, 2 weeks off (6-week cycles)

Crossover from SUN to NIVO was permitted[a]

- **HRQoL is an exploratory endpoint and included the FKSI-19 instrument**

[a]Treatment was given until progression or unacceptable toxicity. Patients could discontinue after 2 years of study treatment as of a November 2017 protocol amendment.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance status; NIVO+IPI, nivolumab plus ipilimumab; SUN, sunitinib.

FKSI-19 instrument

Disease-related symptoms (physical)

- Lack of energy
- Pain
- Weight loss
- Fatigue
- Shortness of breath
- Fever
- Bone pain
- Coughing
- Blood in urine
- Weakness
- Appetite
- Sleep

Treatment side effects[a]

- Nausea
- Diarrhea
- Side effect bother

Function/well-being

- Work
- Leisure
- Overall quality of life

Emotional

- Worry about disease worsening

	Cycles 1 and 2 (each cycle = 6 weeks)		Cycle 3 and beyond (each cycle = 6 weeks)		Follow-up
	Day 1, week 1	Day 1, week 4	Day 1, week 1	Day 1, week 5[b]	Visit 1 and visit 2[c]
FKSI-19 administration	X	X	X	X	**X**

[a]Each item treated individually. [b]Only for the first 6 months. [C]Follow-up visit 1 = 30 days from the last dose ± 7 days or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 37 days after last dose; follow-up visit 2 = 84 days (± 7 days) from follow-up visit 1.
Source: https://www.facit.org/measures/NFKSI-19.

Baseline/longitudinal HRQoL scores and Progression-Free Survival

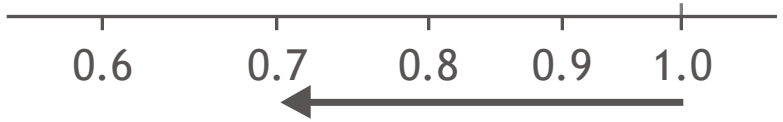
Baseline

Score	Patients	HR (95% CI); *P* value
FKSI-19 total score	770	0.91 (0.86-0.95); 0.0001
FKSI-19 DRS-P score	772	0.89 (0.84-0.94); < 0.0001

Lower HR indicates stronger association between higher HRQoL baseline score and lower risk of progression or death

Longitudinal

Score	Patients	HR (95% CI); *P* value
FKSI-19 total score	770	0.88 (0.84-0.93); < 0.0001
FKSI-19 DRS-P score	772	0.84 (0.79-0.89); < 0.0001



Lower HR indicates stronger association between greater improvement from baseline in HRQoL and lower risk of progression or death

HR is calculated as **risk of progression per X-point improvement in HRQoL score;** X is defined as 5 points for FKSI-19 total score and 4 points for FKSI-19 DRS-P.
CI, confidence interval.

Baseline/longitudinal HRQoL scores and Overall Survival

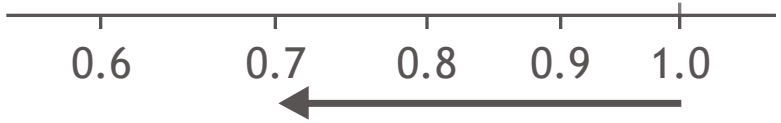
Baseline

Score	Patients	HR (95% CI); *P* value
FKSI-19 total score	813	0.83 (0.80-0.87); < 0.0001
FKSI-19 DRS-P score	815	0.80 (0.76-0.84); < 0.0001

Lower HR indicates stronger association between higher HRQoL baseline sore and lower risk of death

Longitudinal

Score	Patients	HR (95% CI); *P* value
FKSI-19 total score	813	0.69 (0.64-0.74); < 0.0001
FKSI-19 DRS-P score	815	0.65 (0.60-0.71); < 0.0001



Lower HR indicates stronger association between greater improvement from baseline in HRQoL and lower risk of death

HR is calculated as **risk of death per X-point improvement in HRQoL score;** X is defined as 5 points for FKSI-19 total score and 4 points for FKSI-19 DRS-P.

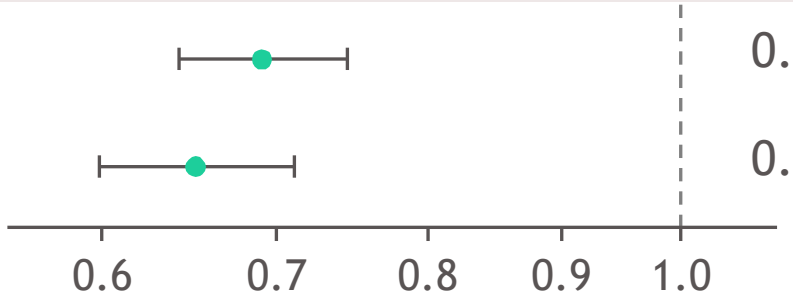
Longitudinal HRQoL scores and Overall Survival

Longitudinal model

- Improved HRQoL during the course of treatment was associated with a lower risk of death

Longitudinal

Score	Patients	HR (95% CI); *P* value
FKSI-19 total score	813	0.69 (0.64-0.74); < 0.0001
FKSI-19 DRS-P score	815	0.65 (0.60-0.71); < 0.0001



  - FKSI-19 total: 31% reduction in risk of death per 5-point improvement in total score[a]
  - FKSI-19 DRS-P: 35% reduction in risk of death per 4-point improvement in DRS-P score[a]

- These results suggest a stronger association between longitudinal HRQoL scores and OS compared with baseline HRQoL only and OS

[a]Within the timeframe of the current CheckMate 214 analyses (5-year follow-up).

Conclusions

- Better HRQoL scores were associated with a longer PFS and OS in intermediate/poor-risk RCC patients treated in the CheckMate 214 trial
- A stronger association was suggested for longitudinal HRQoL and OS, compared with the baseline HRQoL model
- These results highlight the value of PROs in measuring patients' HRQoL and for prognostic modeling

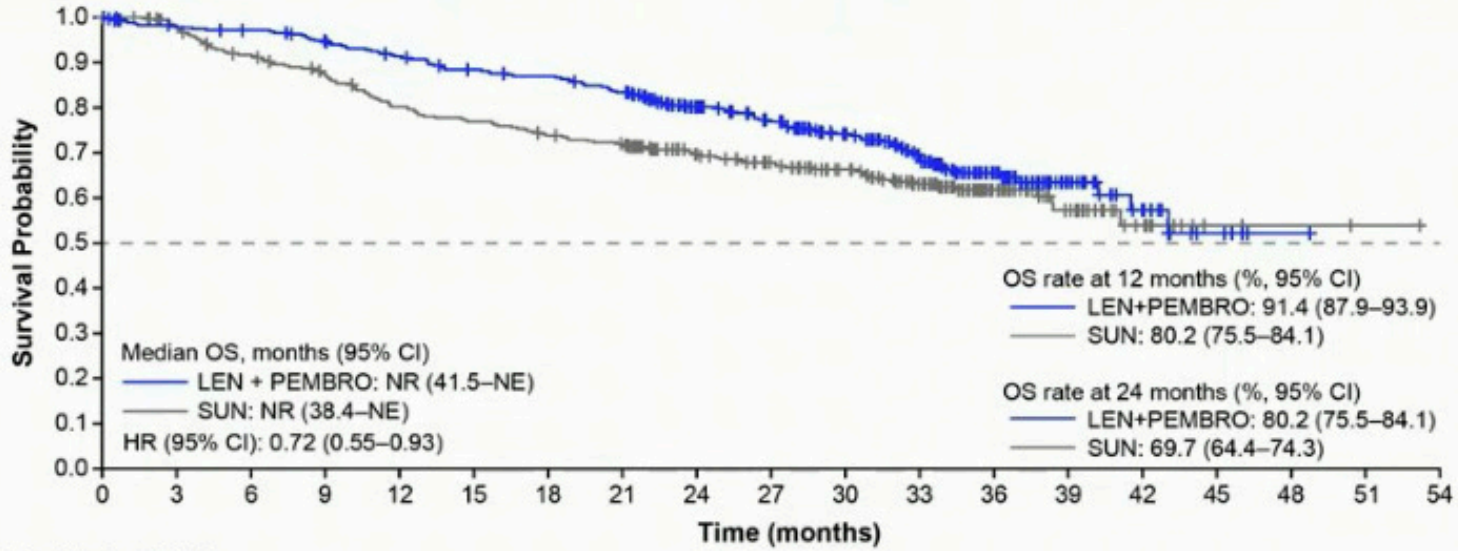
Updated efficacy of lenvatinib plus pembrolizumab versus sunitinib in patients with advanced renal cell carcinoma in the CLEAR study

Camillo G. Porta[1], Masatoshi Eto[2], Robert J. Motzer[3], Ugo De Giorgi[4], Tomas Buchler[5], Naveen S. Basappa[6], Maria Jose Mendez Vidal[7], Sergei Tjulandin[8], Se Hoon Park[9], Bohuslav Melichar[10], Thomas Hutson[11], Carlos Alemany[12], Bradley McGregor[13], Cixin Steven He[14], Rodolfo Perini[15], Kalgi Mody[16], Jodi McKenzie[16], Toni K. Choueiri[13]

[1]Interdisciplinary Department of Medicine, University of Bari 'A. Moro', Bari, Italy; [2]Department of Urology, Kyushu University, Fukuoka, Japan; [3]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; [5]Department of Oncology, Thomayer University Hospital, Prague, Czech Republic; [6]Department of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [7]Department of Medical Oncology, Hospital Universitario Reina Sofía, Maimonides Institute for Biomedical Research of Córdoba, Córdoba, Spain; [8]Department of Clinical Pharmacology and Chemotherapy, N.N. Blokhin National Medical Research Center for Oncology, Ministry of Health of the Russian Federation, Moscow, Russian Federation; [9]Division of Hematology/Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of South Korea; [10]Department of Oncology, Palacký University Medical School and Teaching Hospital, Olomouc, Czech Republic; [11]Department of Medical Oncology, Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [12]Department of Hematology and Oncology, AdventHealth Cancer Institute, Orlando, FL, USA; [13]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [14]Biostatistics, Eisai Inc., Nutley, NJ, USA; [15]Clinical Research, Merck & Co., Inc., Rahway, NJ, USA; [15]Clinical Research, Eisai Inc., Nutley, NJ, USA

PARIS 2022 ESMO congress

Continued improvement in OS with LEN + PEMBRO vs SUN



Number of patients at risk:

LEN + PEMBRO	355	342	338	327	313	300	294	280	232	207	174	133	75	31	15	5	1	0
SUN	357	332	307	289	264	253	242	234	195	177	153	116	66	34	14	3	2	1	0

Beyond the median duration of follow-up, there was a high rate of censoring

	MSKCC			IMDC		
	Poor risk	Intermediate risk	Favorable risk*	Poor risk	Intermediate risk	Favorable risk*
LEN +PEMBRO vs SUN HR (95% CI)	0.50 (0.25–1.02)	0.71 (0.52–0.97)	1.00 (0.51–1.96)	0.39 (0.20–0.77)	0.72 (0.52–1.00)	1.22 (0.66–2.26)*

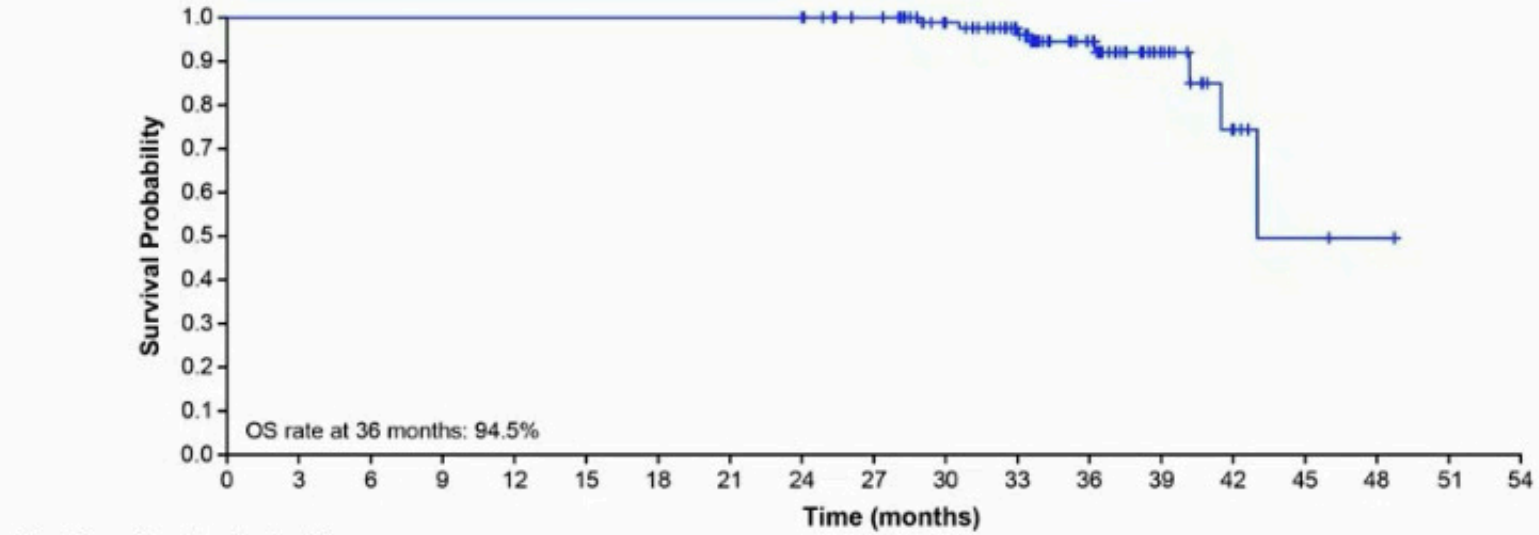
*Median OS was not reached for either arm, and few events were observed for patients in these risk groups.

Tumor response by IIR per RECIST v1.1

	Lenvatinib + Pembrolizumab (N = 355)	Sunitinib (N = 357)
Objective response rate, n (%)	252 (71.0)	129 (36.1)
95% CI[a]	(66.3, 75.7)	(31.2, 41.1)
Difference (%) (95% CI)[a]	34.9 (28.0, 41.7)	
Relative risk[b]	1.97 (1.69, 2.29)	
Best overall response, n (%)		
Complete response	61 (17.2)	15 (4.2)
Partial response	191 (53.8)	114 (31.9)
Stable disease[c]	68 (19.2)	136 (38.1)
Progressive disease	19 (5.4)	50 (14.0)
Unknown/Not evaluable	16 (4.5)	42 (11.8)
Median duration of objective response, mo (95% CI)	26.0 (22.2, 41.4)	14.7 (9.4, 16.8)

[a]95% CI is constructed using the method of normal approximation; [b]relative risk is calculated using the Cochran-Mantel-Haenszel method, stratified by IxRS stratification factors; [c]must be ≥ 7 weeks after randomization

Overall survival in patients who completed 2 years of PEMBRO and continued on LEN monotherapy



Of pts who completed 2 yrs of PEMBRO (n = 101 of 355 pts), most (n = 65) had IMDC intermediate/ poor risk disease and fewer (n = 36) had favorable risk disease, consistent with the ITT population

Enfortumab Vedotin for Previously Treated Advanced Urothelial Carcinoma

- The 5-year relative survival rate for metastatic bladder cancer is ≈8%[1]
- Enfortumab vedotin (EV), an antibody–drug conjugate directed against Nectin-4, demonstrated overall survival (OS) and progression-free survival (PFS) benefit in patients with locally advanced or metastatic (la/m) urothelial carcinoma (UC) in the open-label, confirmatory phase 3 EV-301 trial (NCT03474107) at the prespecified interim analysis[2]

Efficacy and safety are presented for EV vs chemotherapy over a median follow-up period of ≈2 years

Key eligibility criteria:
- Histologically/Cytologically confirmed UC
- Radiographic progression/ relapse during or after PD-1/L1 treatment for advanced UC
- Prior platinum-containing regimen for advanced UC
- ECOG PS 0–1

1:1 randomization with stratification

Enfortumab vedotin (N=301)
1.25 mg/kg
on days 1, 8, and 15 of each 28-d cycle

Preselected chemotherapy (N=307)
Docetaxel 75 mg/m^2 or paclitaxel 175 mg/m^2 or vinflunine 320 mg/m^2
on day 1 of each 21-d cycle

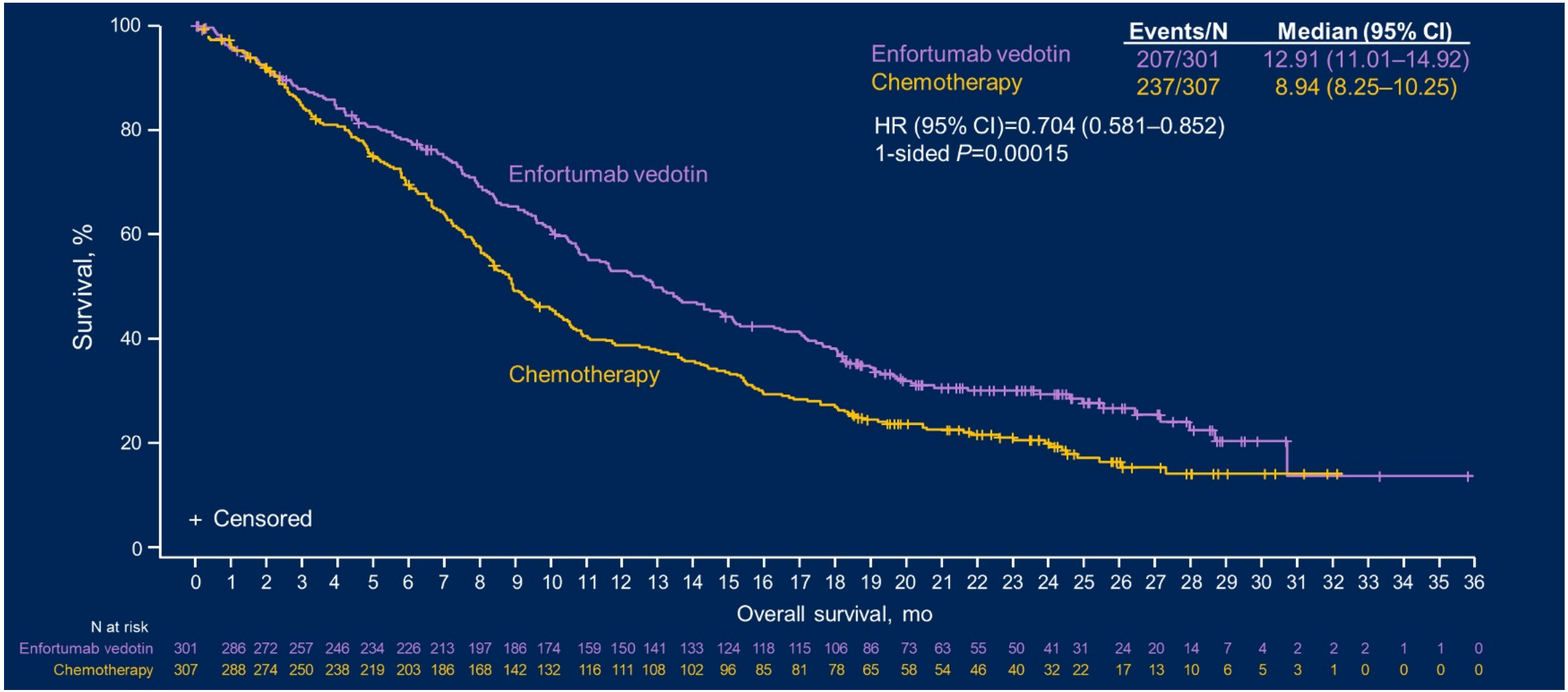
Primary end point: Overall survival

Secondary end points:
- Progression-free survival
- Disease control rate
- Overall response rate

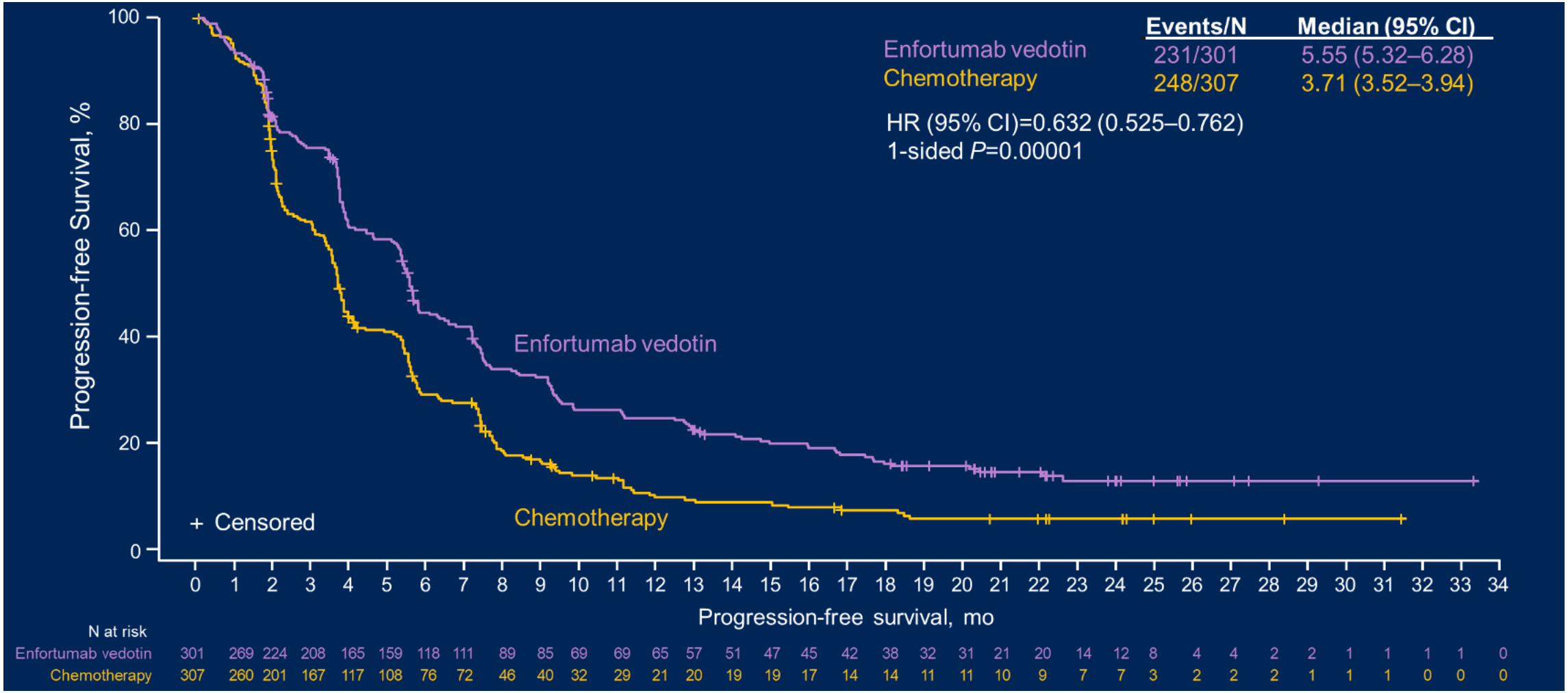
Investigator-assessed per RECIST v1.1
- Safety

Findings from the prespecified, event-driven OS analysis when 439 deaths occurred are presented

Overall Survival



Progression free Survival



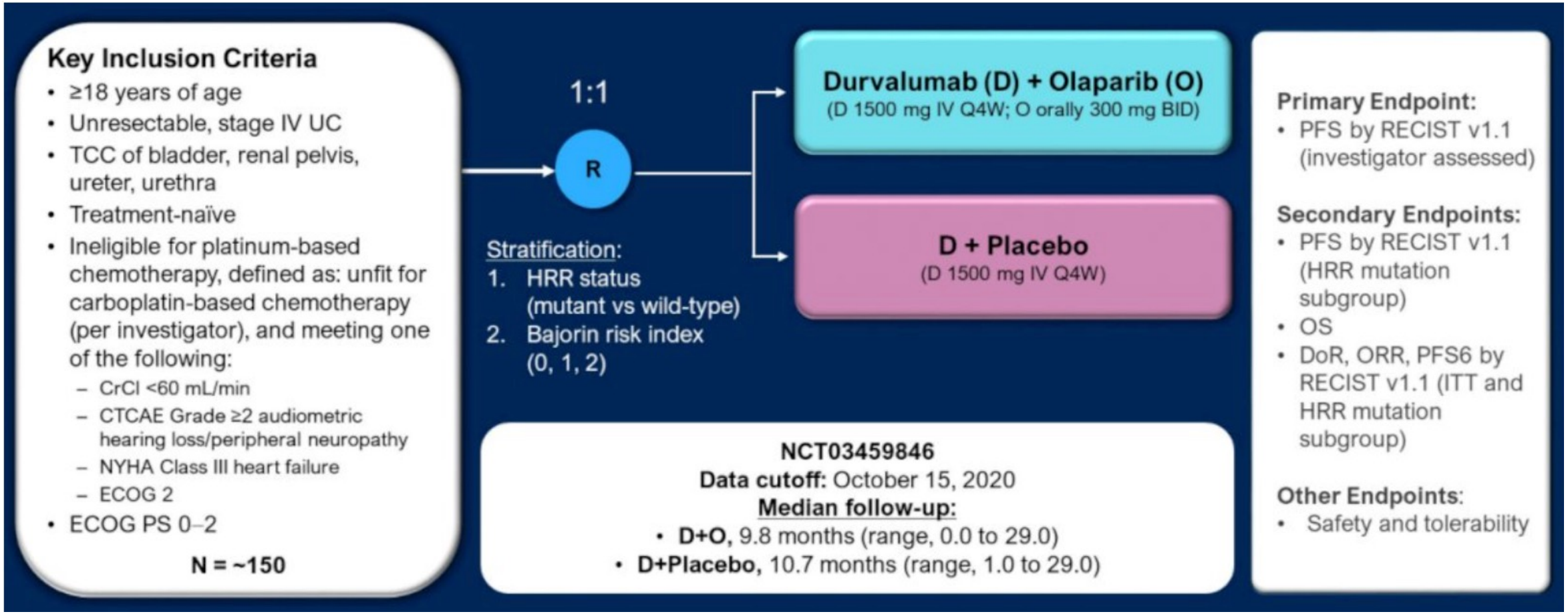
Safety/Tolerability

Treatment-related adverse event, n (%)	Enfortumab vedotin (N=296)		Chemotherapy (N=291)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Alopecia	135 (45.6)	NR	108 (37.1)	NR
Peripheral sensory neuropathy	103 (34.8)	15 (5.1)	63 (21.6)	6 (2.1)
Pruritus	96 (32.4)	4 (1.4)	14 (4.8)	1 (0.3)
Fatigue	93 (31.4)	20 (6.8)	66 (22.7)	13 (4.5)
Decreased appetite	92 (31.1)	9 (3.0)	69 (23.7)	5 (1.7)
Diarrhea	74 (25.0)	10 (3.4)	49 (16.8)	5 (1.7)
Dysgeusia	73 (24.7)	NR	22 (7.6)	NR
Nausea	71 (24.0)	3 (1.0)	64 (22.0)	4 (1.4)
Maculopapular rash	50 (16.9)	22 (7.4)	5 (1.7)	NR
Anemia	34 (11.5)	8 (2.7)	63 (21.6)	23 (7.9)
Decreased neutrophil count	31 (10.5)	18 (6.1)	51 (17.5)	41 (14.1)
Neutropenia	20 (6.8)	14 (4.7)	25 (8.6)	18 (6.2)
Decreased white blood cell count	15 (5.1)	4 (1.4)	32 (11.0)	21 (7.2)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

Conclusions

- After 2 years of follow up, EV had clinically significant OS compared to chemotherapy
- PFS and ORR were consistent with what was noted in the interim and final analysis
- Safety and tolerability were consistent with findings from interim and final analysis

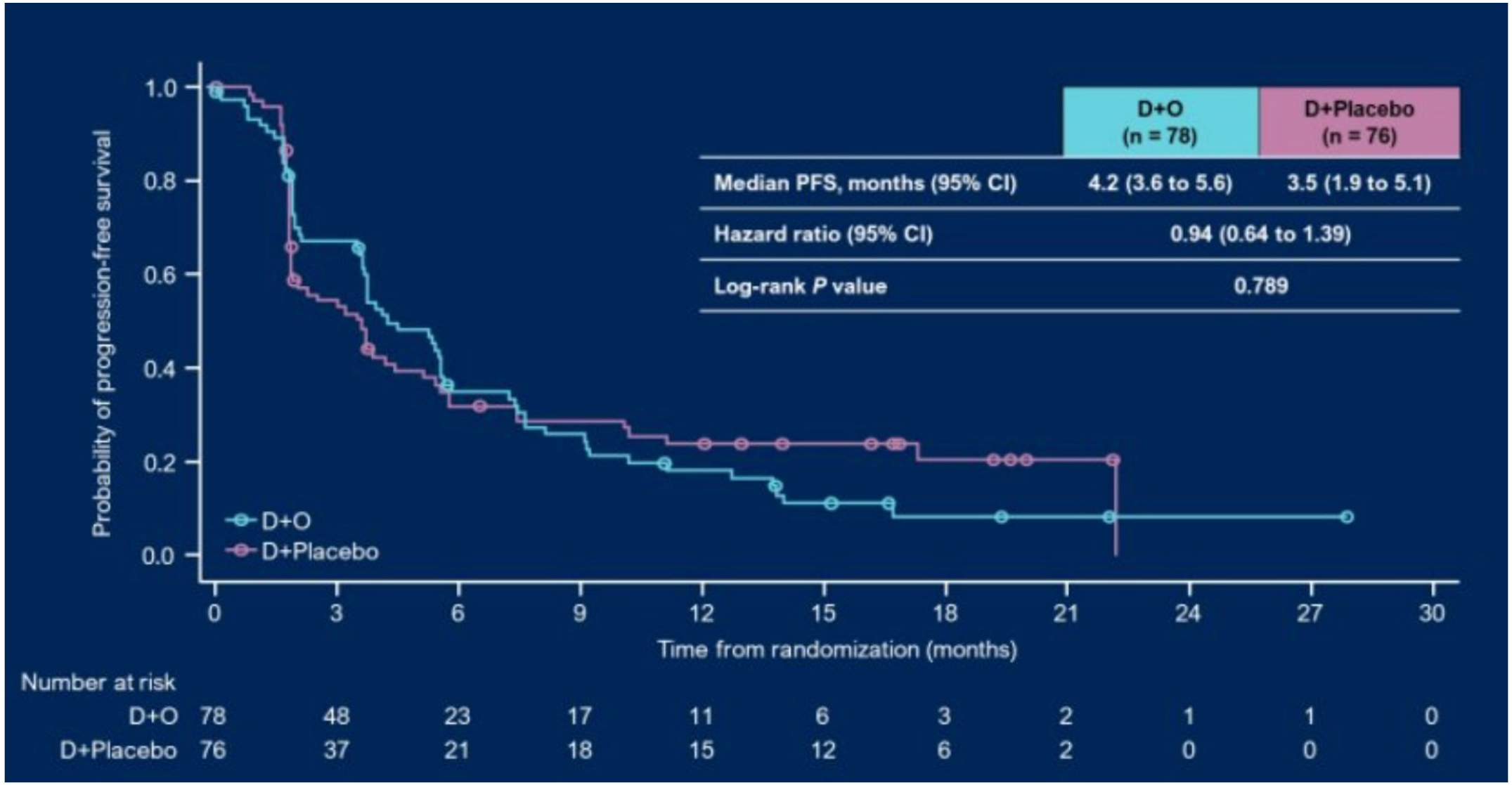
BAYOU: Phase II durvalumab in combination with Olaparib for first line mUC



Which mutations were evaluated?

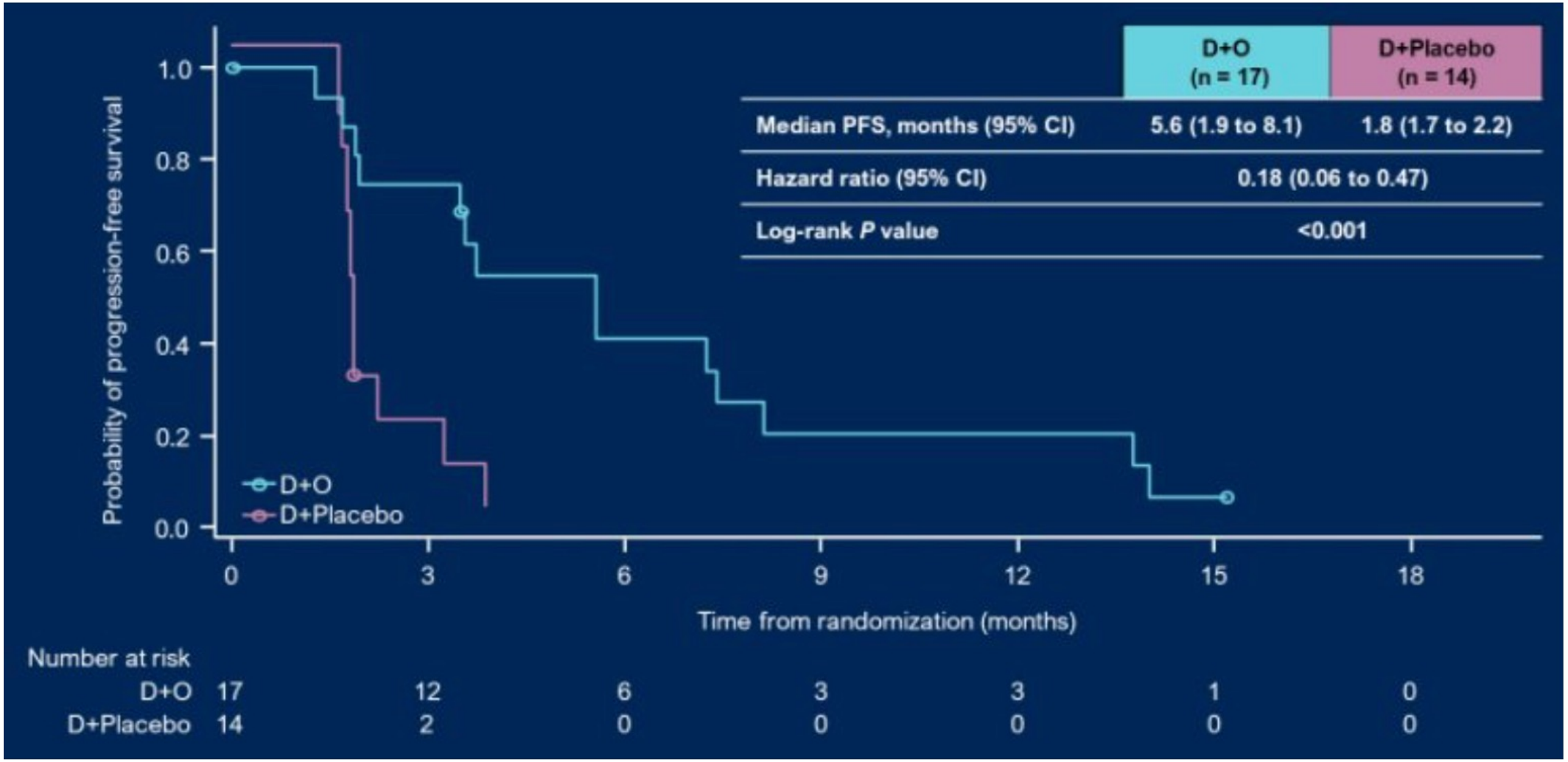
	D+O (n = 17)	D+Placebo (n = 14)
HRR mutation, n (%)		
ATM	7 (41.2)	6 (42.9)
BRCA2	3 (17.6)	4 (28.6)
BARD1	2 (11.8)	0
BRIP1	2 (11.8)	0
CDK12	2 (11.8)	2 (14.3)
BRCA1	1 (5.9)	2 (14.3)
FANCL	1 (5.9)	0
RAD51B	1 (5.9)	0
RAD51C	1 (5.9)	0
CHEK2	0	1 (7.1)

PFS Total ITT Population



	D+O (n = 78)	D+Placebo (n = 76)
Median PFS, months (95% CI)	4.2 (3.6 to 5.6)	3.5 (1.9 to 5.1)
Hazard ratio (95% CI)	0.94 (0.64 to 1.39)	
Log-rank *P* value	0.789	

PFS in HRR Mutations



	D+O (n = 17)	D+Placebo (n = 14)
Median PFS, months (95% CI)	5.6 (1.9 to 8.1)	1.8 (1.7 to 2.2)
Hazard ratio (95% CI)	0.18 (0.06 to 0.47)	
Log-rank *P* value	<0.001	

Overall Survival