

foro debate oncología

Zaragoza 26-29 septiembre 2023



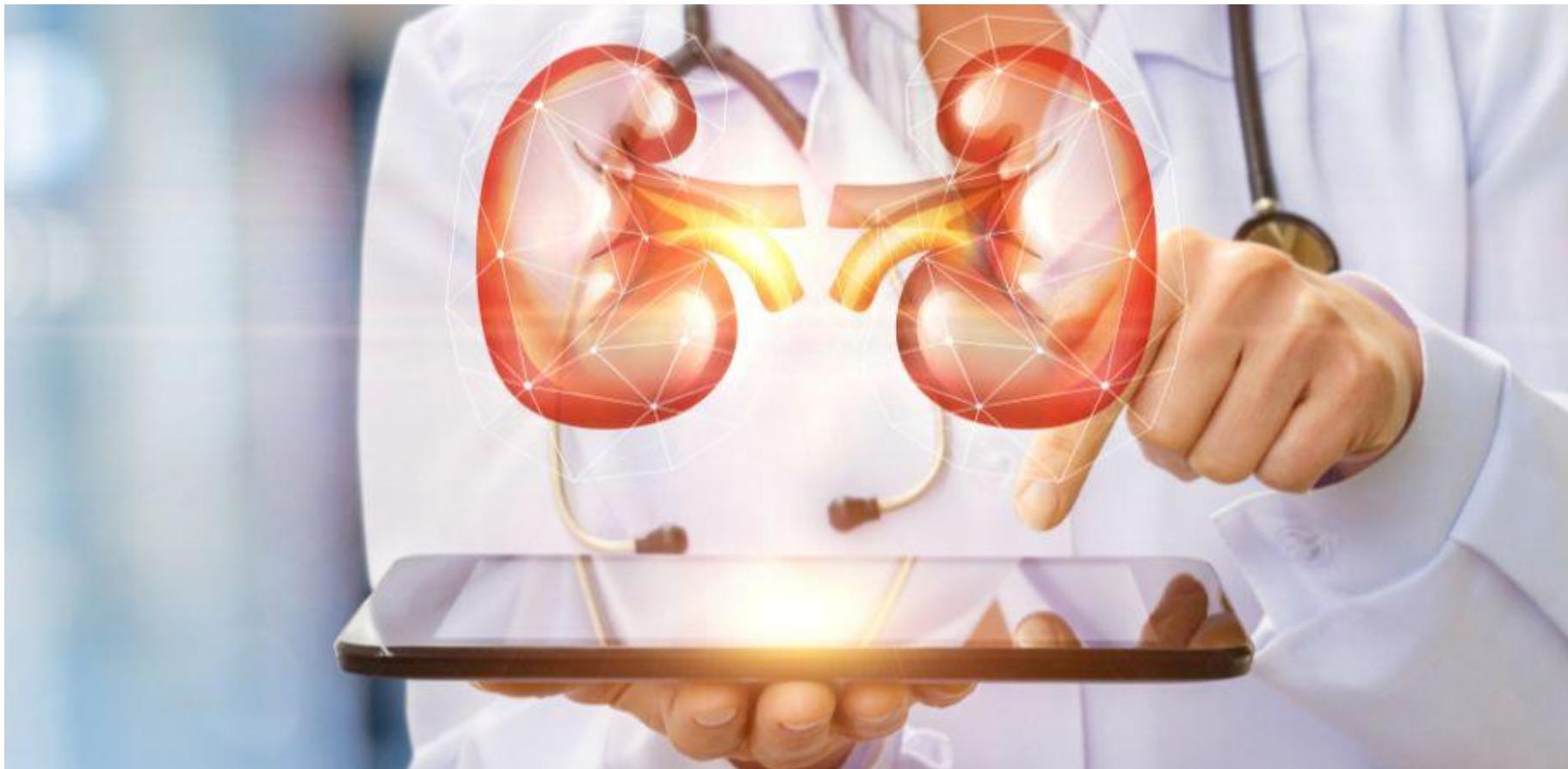
CÁNCER RENAL TRATAMIENTO DE ENFERMEDAD LOCALIZADA

Julio Lambea Sorrosal

Servicio de Oncología Médica del Hospital Clínico Lozano Blesa de Zaragoza



ADJUVANCIA





Adjuvant Cytokine Therapy Did NOT Improve Survival

Trial	Population	Arms	N	Primary	Outcome
Porzsolt et al (1992)	pT3-4N0 or pTxN1-3	IFN- α vs. Observation	270	TTF/Survival	No Difference
Trump et al (1996)	pT3-4aN0 or pTxN1-3	L-IFN vs. Observation	294	Recurrence	No Difference
Pizzocaro et al (2001)	pT3-4aN0 or pTxN1-3	IFN- α vs. Observation	247	5-year DFS	No Difference
Messing et al (2003)	pT3-4aN0 or pTxN1-3	IFN- α vs. Observation	283	5-year OS	No Difference
Clark et al (2003)	pT3b-4Nx or pTxN1-3	IL-2 vs. Observation	138	2-year DFS	No Difference
Atzpodien et al (2005)	pT3b-4Nx or pTxN1-3	IL-2/IFN- α /5-FU vs. Observation	203	2-year DFS	No Difference
Aitchison et al (2014)	pT3b-4Nx or pTxNa-2 or +margin/vascular invasion	IL-2/IFN- α /5-FU vs. Observation	309	3-year DFS	No Difference

IFN- α =Interferon alpha; L-IFN=Lymphoblastoid interferon; IL-2=Interleukin 2; 5-FU=5-Fluorouracil; TTF= Time to treatment failure; DFS=Disease-free survival; OS=Overall survival.
 Porzsolt et al, Proceedings of ASCO, 1992; Trump et al, Proceedings of ASCO, 1996; Pizzocaro et al, JCO, 2001; Messing et al, NEJM, 2003; Clark et al, JCO, 2003; Atzpodien et al Br J Cancer, 2005; Aitchison et al, EJC, 2014

Adjuvant Targeted Therapy with Mixed Results

Trial	Arms	Years	N	Primary Endpoint	Clear Cell Only	Eligibility	Hazard Ratio Confidence Interval
ASSURE (Haas, Lancet, 2016)	Sunitinib vs. Sorafenib vs. Placebo*	1	1943	DFS	No	pT1bG3-4N0, pT2-4GxN0, TxGxN+	Sunitinib – 1.02 (97.5% CI 0.85-1.23) Sorafenib – 0.97 (97.5% CI 0.80-1.17)
STRAC (Ravaud, NEJM, 2016)	Sunitinib vs. Placebo	1	615	DFS	Yes	pT3-4GxN0-x, TxGxN1-2	0.76 (95% CI 0.59-0.98)
PROTECT (Motzer, JCO, 2017)	Pazopanib vs. Placebo*	1	1538	DFS	Yes	pT2G3-4N0, pT3-4N0, pTxN1	0.86 (95% CI 0.70-1.06)
ATLAS (Gross-Goupli, Ann Oncol, 2018)	Axitinib vs. Placebo	1-3	724	DFS	Yes	pT2-4GxN0, pTxN1	0.870 (95% CI 0.66-1.147)
SORCE (Eisen, JCO, 2020)	Sorafenib vs. Placebo)*	1-3	1711	DFS	No	Leibovich score 3-11	1.01 (95% CI 0.83-1.23)
EVEREST	Everolimus vs. Placebo	1	1545	RFS	No	pT1bG3-4N0, pT2-4N1	HR 0.85 (95% CI, 0.72, 1.00) ASCO 2022. INTERIM ANALYSIS

*Starting dose change during study; DFS=Disease-free survival; RFS=Recurrence-free survival; CI=Confidence interval.

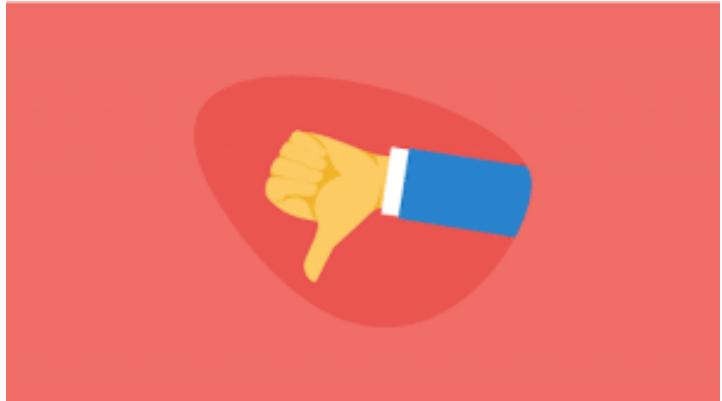
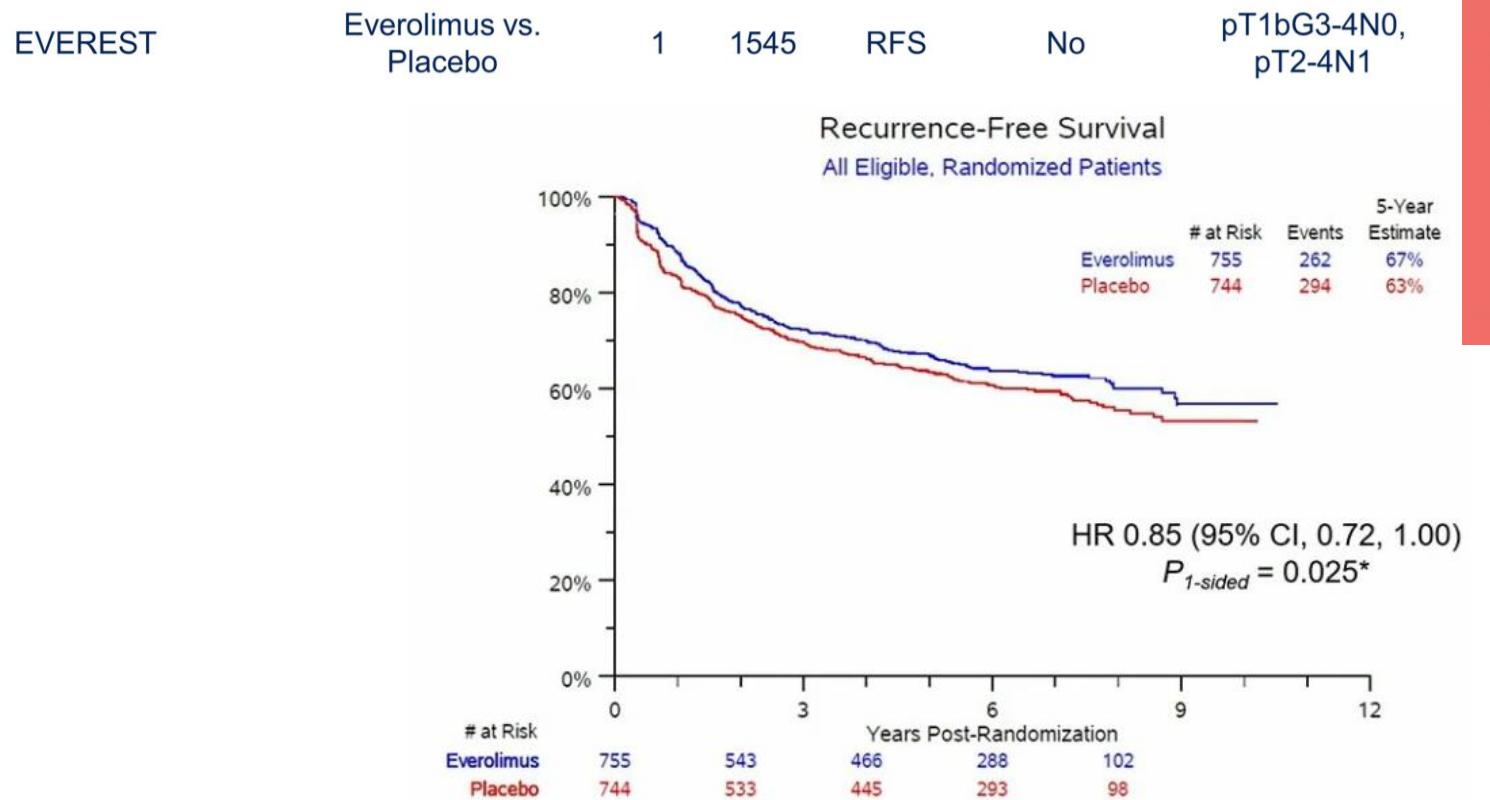
Presented By: **Rana R. McKay @DrRanaMcKay**

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2021 ASCO
ANNUAL MEETING

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ASCO 2022. INTERIM ANALYSIS





ORIGINAL ARTICLE

Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy

A. Ravaud, R.J. Motzer, H.S. Pandha, D.J. George, A.J. Pantuck, A. Patel, Y.-H. Chang, B. Escudier, F. Donskov, A. Magheli, G. Carteni, B. Laguerre, P. Tomczak, J. Breza, P. Gerletti, M. Lechuga, X. Lin, J.-F. Martini, K. Ramaswamy, M. Casey, M. Staehler, and J.-J. Patard, for the S-TRAC Investigators*

ABSTRACT

Overall Survival

Data for overall survival, a secondary end point, were not mature at the time of the data cutoff, with deaths reported in 64 patients (20.7%) in the sunitinib group and 64 (20.9%) in the placebo group. The median overall survival was not reached in either group, and the hazard ratio for the comparison between sunitinib and placebo was 1.01 (95% CI, 0.72 to 1.44; $P=0.94$) (Fig. S1 in the Supplementary Appendix).

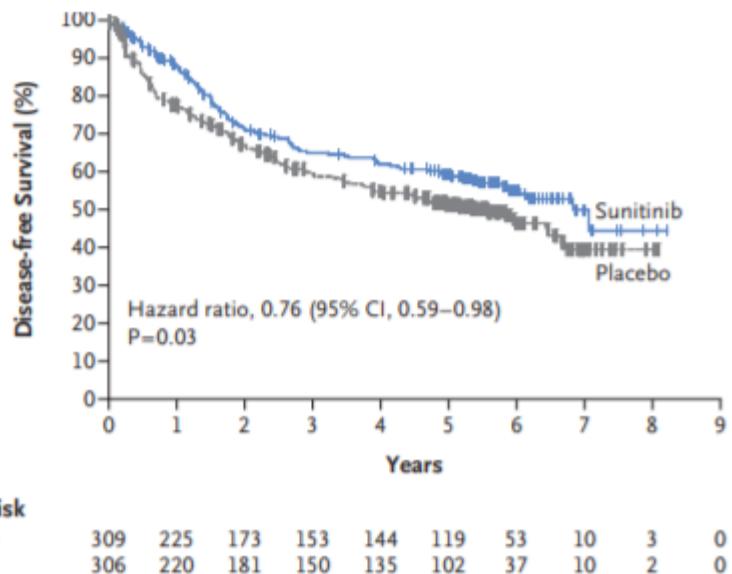


Figure 2. Disease-free Survival.

This article was published on October 10, 2016, at NEJM.org.

N Engl J Med 2016;375:2246-54.

DOI: 10.1056/NEJMoa1611406

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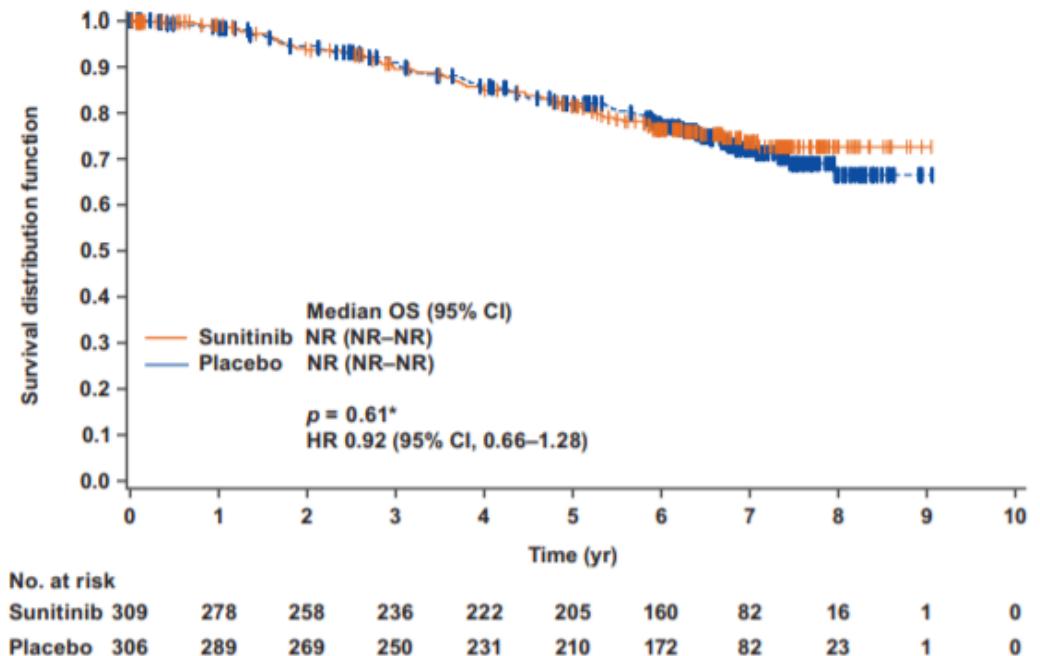
Platinum Priority – Kidney Cancer

Editorial by Jozefina Casuscelli and James J. Hsieh on pp. 69–70 of this issue

Adjuvant Sunitinib for High-risk Renal Cell Carcinoma After Nephrectomy: Subgroup Analyses and Updated Overall Survival Results

Robert J. Motzer ^a , Alain Ravaud ^b, Jean-Jacques Patard ^c, Hardev S. Pandha ^d, Daniel J. George ^e, Anup Patel ^f, Yen-Hwa Chang ^g, Bernard Escudier ^h, Frede Donskov ⁱ, Ahmed Magheli ^j, Giacomo Carteni ^k, Brigitte Laguerre ^l, Piotr Tomczak ^m, Jan Breza ⁿ, Paola Gerletti ^o, Mariajose Lechuga ^o, Xun Lin ^p, Michelle Casey ^q ... Michael Staehler ^{t, †}

At the cutoff date for the updated OS analysis (January 31, 2017), 67 patients in the sunitinib arm and 74 patients in the placebo arm had died. The median follow-up time was 6.6 yr in the sunitinib arm and 6.7 yr in the placebo arm. The median OS was not reached in either arm. The HR for sunitinib versus placebo was 0.92 (95% CI 0.66–1.28; $p = 0.6$; Fig. 3).



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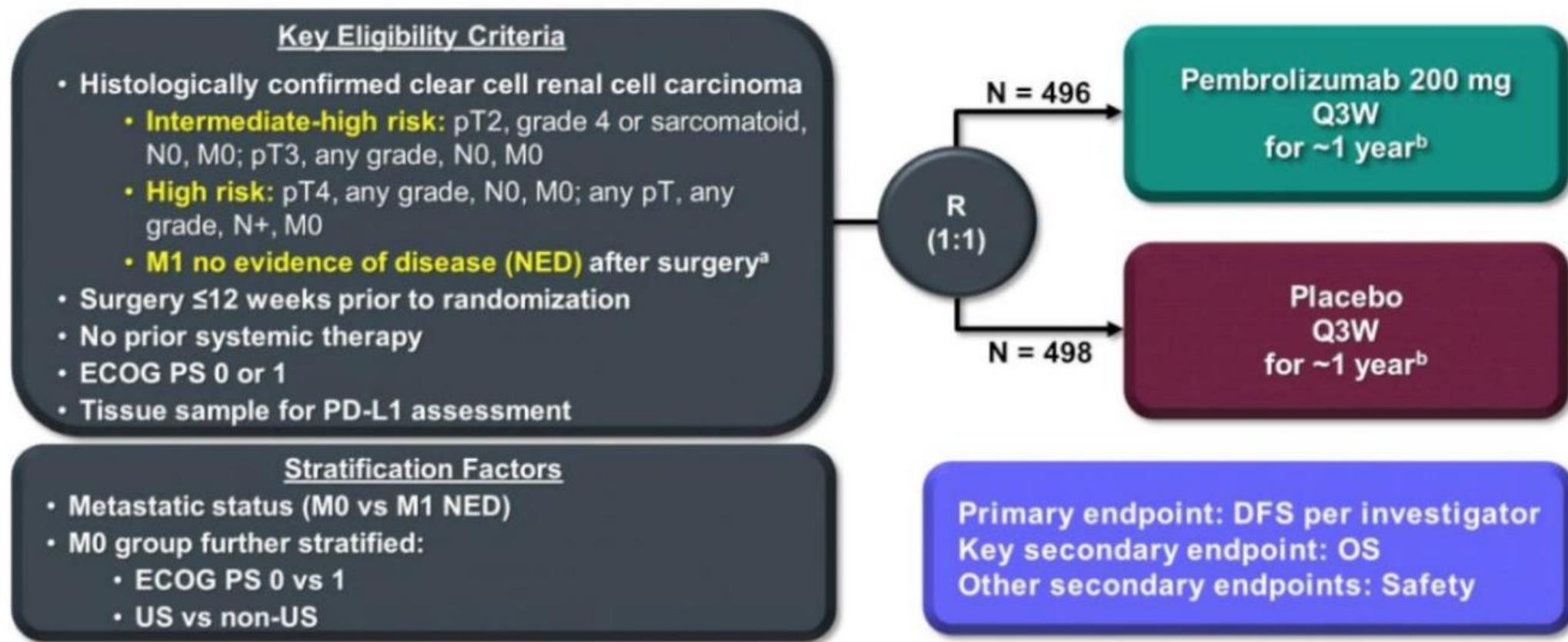
Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma

T.K. Choueiri, P. Tomczak, S.H. Park, B. Venugopal, T. Ferguson, Y.-H. Chang, J. Hajek, S.N. Symeonides, J.L. Lee, N. Sarwar, A. Thiery-Vuillemin, M. Gross-Goupil, M. Mahave, N.B. Haas, P. Sawrycki, H. Gurney, C. Chevreau, B. Melichar, E. Kopyltsov, A. Alva, J.M. Burke, G. Doshi, D. Topart, S. Oudard, H. Hammers, H. Kitamura, J. Bedke, R.F. Perini, P. Zhang, K. Imai, J. Willemann-Rogerio, D.I. Quinn, and T. Powles, for the KEYNOTE-564 Investigators*



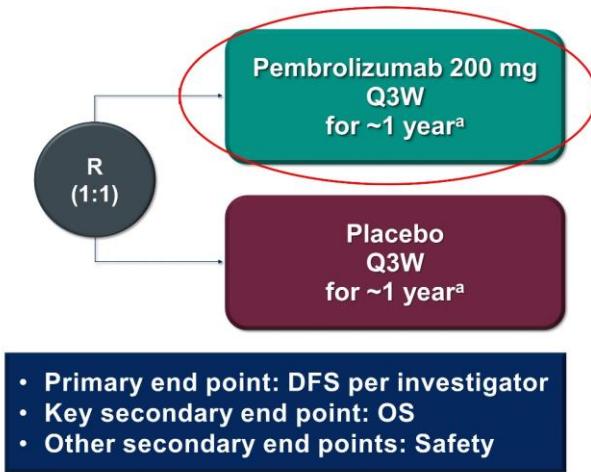


Keynote 564: pembrolizumab adyuvante



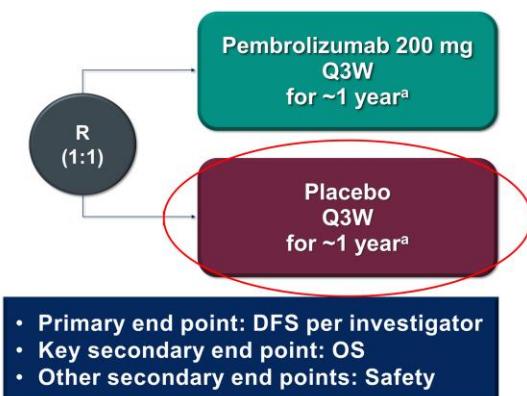


KEYNOTE-564 – Treatment Arm



- Single agent pembrolizumab for 1 year**
 - Single agent PD-1 inhibition is approved for advanced/metastatic RCC (nivolumab)
 - While pembrolizumab not approved as a single agent for advanced/metastatic RCC, single agent activity demonstrated in Keynote 427 study
 - Duration of therapy somewhat arbitrary and inferred from other adjuvant studies

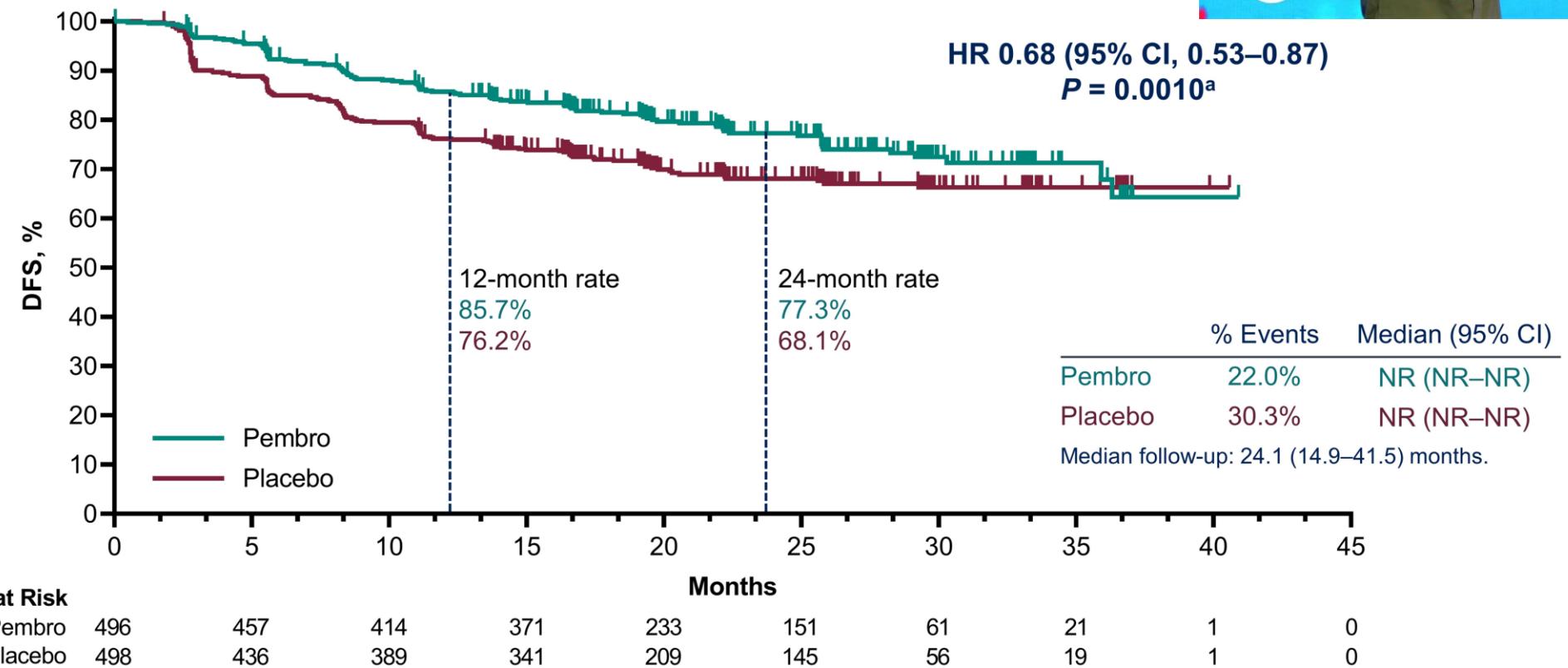
KEYNOTE-564 – Control Arm



- Non-active placebo control**
 - Appropriate control arm given mixed data of benefit of sunitinib on DFS and limited utilization in clinical practice



DFS by Investigator, ITT Population

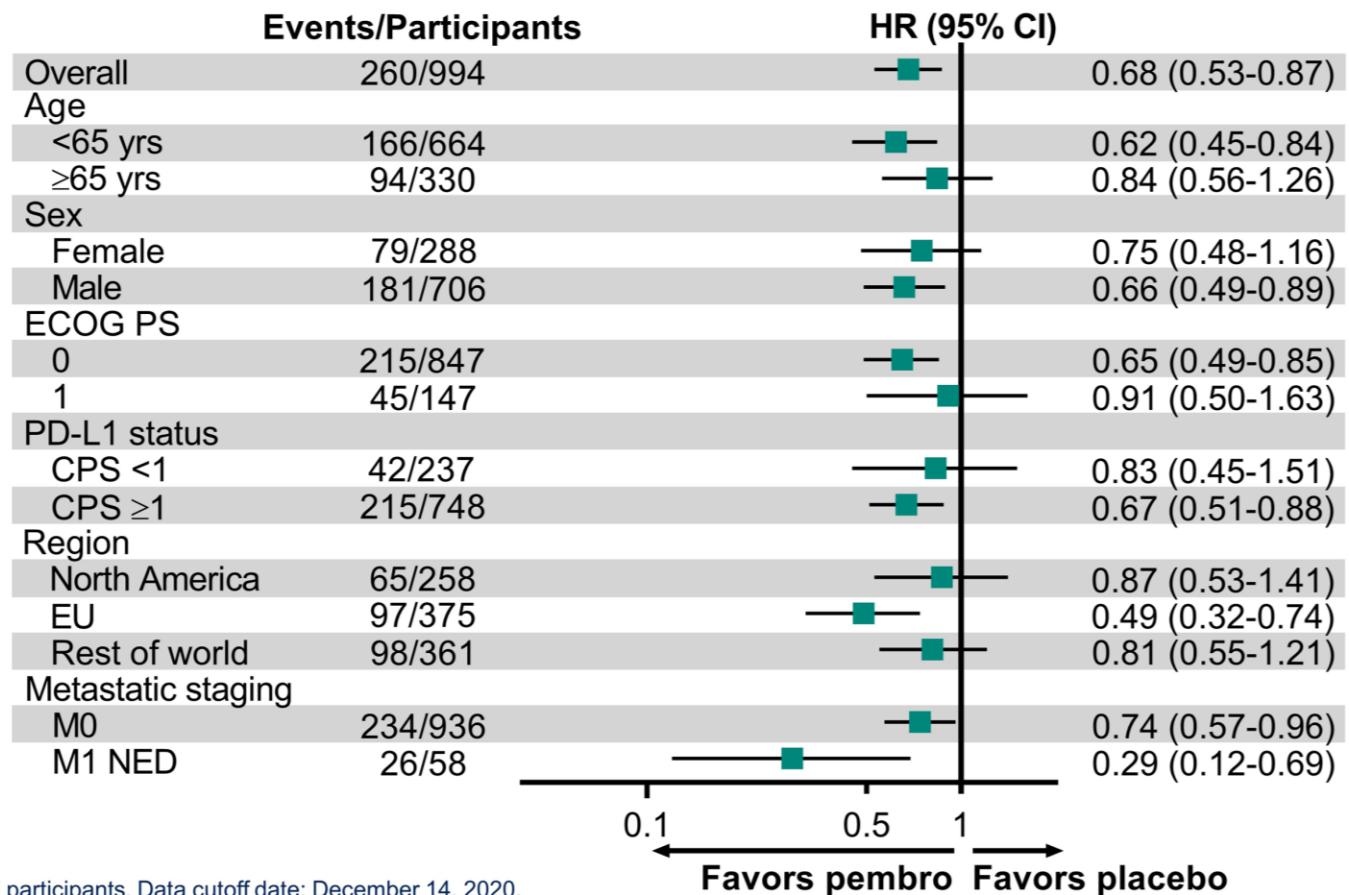


^aCrossed prespecified p-value boundary for statistical significance of 0.0114.

ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.



DFS by Investigator in Subgroups, ITT Population



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



Interim OS Results, ITT Population



^aDid 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.

INVESTIGAR - APRENDER - DIVULGAR - CURAR

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



^aSerious 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.

FDA approves pembrolizumab for adjuvant treatment of renal cell carcinoma

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On November 17, 2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) for the adjuvant treatment of patients with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

European Commission Approves Merck's KEYTRUDA® (pembrolizumab) as Adjuvant Therapy for Certain Patients With Renal Cell Carcinoma (RCC) Following Surgery

[Save](#)

January 27, 2022 6:45 am ET

KEYTRUDA Is Now Approved as Monotherapy for Adults With RCC at Increased Risk of Recurrence Following Nephrectomy, or Following Nephrectomy and Resection of Metastatic Lesions

KEYTRUDA Is the First Immunotherapy Approved in Europe in the Adjuvant Setting for These Patients With RCC

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions (for selection criteria, please see section 5.1).



ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma

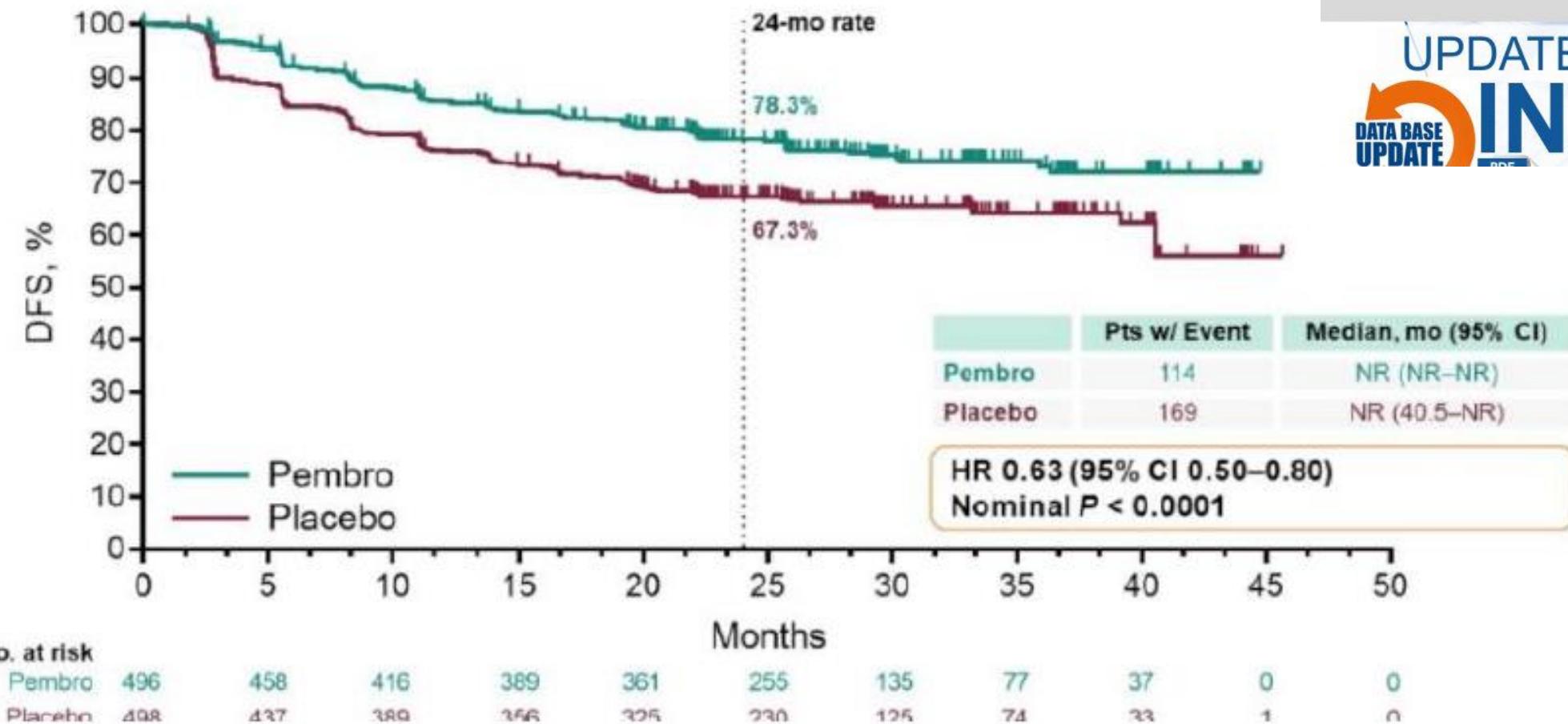
<https://doi.org/10.1016/j.annonc.2021.09.014>

T. Powles¹, L. Albiges², A. Bex^{3,4}, V. Grünwald⁵, C. Porta^{6,7}, G. Procopio⁸, M. Schmidinger⁹, C. Suárez¹⁰ & G. de Velasco¹¹,
on behalf of the ESMO Guidelines Committee*



Recommendations

- Adjuvant pembrolizumab should be considered optional for patients with intermediate- or high-risk operable ccRCC (as defined by the study) after careful patient counselling regarding immature OS and potential long-term adverse events [I, C]. Further data are required in the future including positive OS data. Treatment should start within 12 weeks of surgery and continue for up to 1 year.
- Regarding the M1 NED population, systemic therapy with programmed cell death protein 1 (PD-1)-based combination therapy is the standard of care for patients who relapse within 1 year of nephrectomy [I, A].
- Metastasectomy as an alternative to this systemic therapy in patients with synchronous or early oligometastatic disease is not usually recommended [I, D] and requires a multidisciplinary team decision.
- Adjuvant pembrolizumab can be offered to these patients after complete resection of their oligometastatic disease [II, B].
- Incomplete resection should not be offered to patients with oligometastatic disease [III, D].



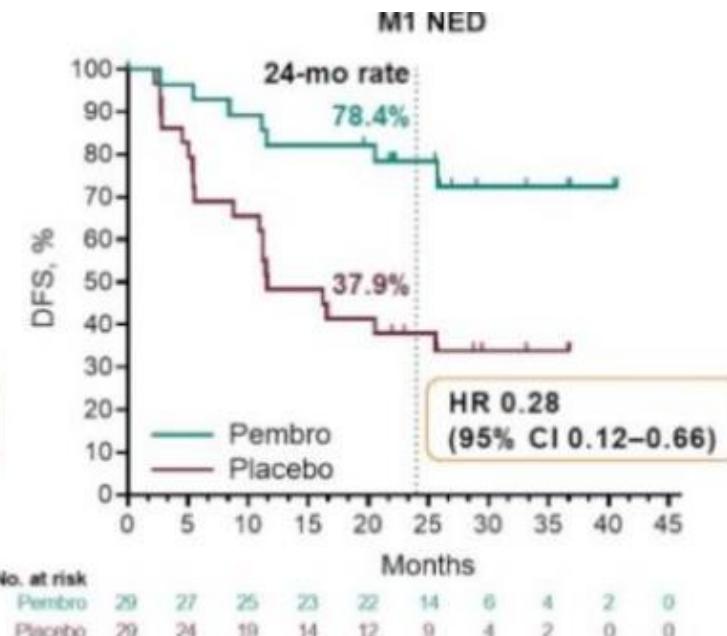
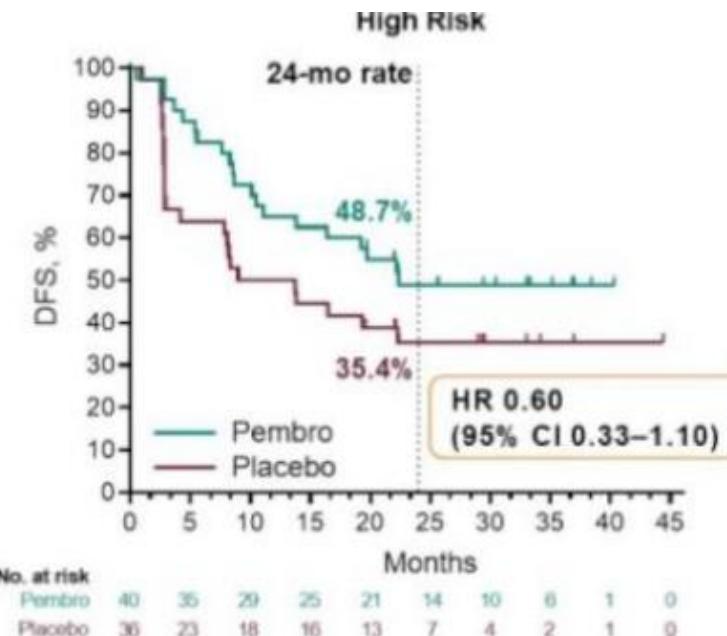
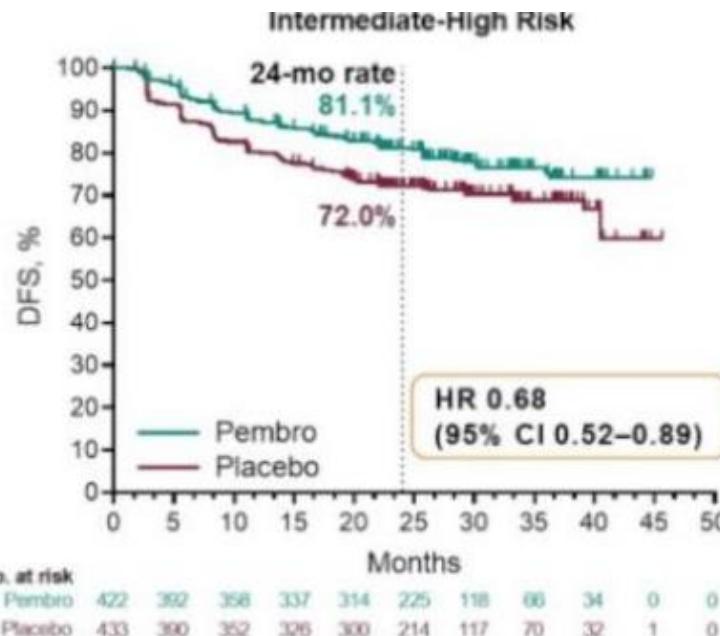
UPDATE 2022
INFO
DATA BASE UPDATE

Choueiri ASCO GU 2022. Results from 30-month follow-up of KEYNOTE-564

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A MAYOR RIESGO MAYOR BENEFICIO



Choueiri ASCO GU 2022. Results from 30-month follow-up of KEYNOTE-564

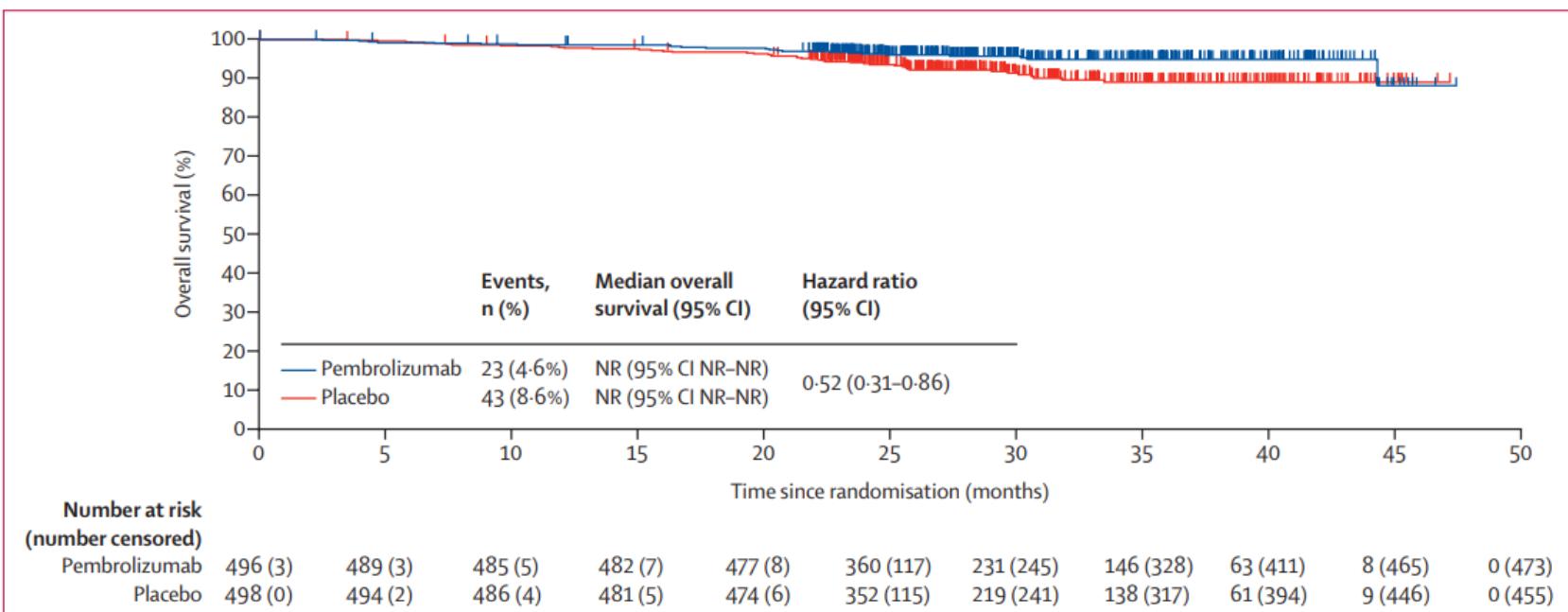
ARTICLES | VOLUME 23, ISSUE 9, P1133-1144, SEPTEMBER 01, 2022

Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Thomas Powles, MD • Piotr Tomczak, MD PhD • Se Hoon Park, MD PhD • Balaji Venugopal, MD •

Thomas Ferguson, MBBS • Stefan N Symeonides, MD PhD • et al. Show all authors • Show footnotes

Open Access • Published: September, 2022 • DOI: [https://doi.org/10.1016/S1470-2045\(22\)00487-9](https://doi.org/10.1016/S1470-2045(22)00487-9)





Appendix: SECOND LINES

THE LANCET
Oncology

ARTICLES | VOLUME 23, ISSUE 9, P1133-1144, SEPTEMBER 01, 2022

Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

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Open Access • Published: September, 2022 • DOI: [https://doi.org/10.1016/S1470-2045\(22\)00487-9](https://doi.org/10.1016/S1470-2045(22)00487-9)

Table S3: Summary of subsequent anticancer therapy for renal cell carcinoma

Category*	Pembrolizumab N=496	Placebo N=498
Any subsequent anticancer therapy	84 (17)	124 (25)
Subsequent drug therapy†	67 (14)	99 (20)
Anti-PD-1/PD-L1 therapy	16 (3)	59 (12)
Anti-PD-1/PD-L1 monotherapy	4 (1)	21 (4)
Anti-PD-1/PD-L1 therapy + VEGF/VEGFR targeted therapy (\pm other)	4 (1)	17 (3)
Anti-PD-1/PD-L1 therapy + anti-CTLA-4 therapy‡	7 (1)	18 (4)
Anti-PD-1/PD-L1 therapy + other	1 (<1)	4 (1)
VEGF/VEGFR targeted therapy	60 (12)	85 (17)
VEGF/VEGFR targeted monotherapy	57 (11)	68 (14)
VEGF/VEGFR targeted therapy + anti-PD-1/PD-L1 therapy (\pm other)	4 (1)	17 (3)
VEGF/VEGFR targeted therapy + VEGF/VEGFR targeted therapy or other	3 (1)	4 (1)
Other monotherapy	6 (1)	5 (1)
Subsequent radiation	17 (3)	19 (4)
Subsequent surgery	23 (5)	36 (7)
Metastasectomy	22 (4)	32 (6)
Nephrectomy	1 (<1)	3 (1)
Metastasectomy and nephrectomy	0	1 (<1)



¿OTRAS ARMAS EN ADYUVANCIA?

PARIS
2022 ESMO congress



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Proffered Paper session 1: GU tumours, non-prostate

LBA66 - IMmotion010: Efficacy and safety from the phase III study of atezolizumab (atezo) vs placebo (pbo) as adjuvant therapy in patients with renal cell carcinoma (RCC) at increased risk of recurrence after resection

Date

10 Sep 2022

Presenters

Axel Bex

PARIS
2022 ESMO congress



Proffered Paper session 1: GU tumours, non-prostate

LBA67 - Phase III randomized study comparing perioperative nivolumab (nivo) versus observation in patients (Pts) with renal cell carcinoma (RCC) undergoing nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial

Date

10 Sep 2022

Presenters

Mohamad Allaf

Presidential Symposium II

LBA4 - Adjuvant nivolumab plus ipilimumab (NIVO+IPI) vs placebo (PBO) for localized renal cell carcinoma (RCC) at high risk of relapse after nephrectomy: Results from the randomized, phase III CheckMate 914 trial

Date

11 Sep 2022

Session

Presidential Symposium II

Presenters

Robert Motzer

Citation

Annals of Oncology (2022) 33 (suppl_7): S808-S869.
10.1016/annonc/annonc1089





Adjuvant nivolumab plus ipilimumab versus placebo for localized renal cell carcinoma at high risk of relapse after nephrectomy: results from the randomized, phase 3 CheckMate 914 trial

Robert J. Motzer,¹ Paul Russo,¹ Viktor Grünwald,² Yoshihiko Tomita,³ Bogdan Zurawski,⁴ Omi Parikh,⁵ Sebastiano Buti,⁶ Philippe Barthélémy,⁷ Jeffrey C. Goh,⁸ Dingwei Ye,⁹ Alejo Lingua,¹⁰ Jean-Baptiste Lattouf,¹¹ Bernard Escudier,¹² Saby George,¹³ Brian Shuch,¹⁴ Burcin Simsek,¹⁵ Julia Spirigliozi,¹⁵ Aleksander Chudnovsky,¹⁵ Axel Bex¹⁶

¹Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²West-German Cancer Center Essen, University Hospital Essen, Essen, Germany;
³Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; ⁴Prof. Franciszek Łukaszczuk Oncology Centre, Bydgoszcz, Poland;
⁵Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust, Preston, UK; ⁶University Hospital of Parma, University of Parma, Parma, Italy;
⁷Institut de Cancérologie Strasbourg Europe, Strasbourg, France; ⁸Royal Brisbane and Women's Hospital, Herston, QLD, Australia; ⁹Fudan University Shanghai Cancer Center, Shanghai, China; ¹⁰Instituto Médico Río Cuarto, Rio Cuarto, Argentina; ¹¹CHUM - Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; ¹²Gustave Roussy, Villejuif, France; ¹³Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; ¹⁴University of California, Los Angeles, Los Angeles, CA, USA; ¹⁵Bristol Myers Squibb, Princeton, NJ, USA; ¹⁶Netherlands Cancer Institute, Amsterdam, the Netherlands

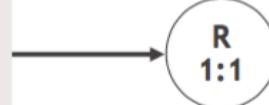
Study design (Part A)

N = 816

Key inclusion criteria¹

- 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



*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

^aStratification was based on the following TNM staging groups: pT2a, G3 or G4, N0 M0 or pT2b, G any, N0 M0 vs pT3, G any, N0 M0 vs pT4, G any, N0 M0 or pT any, G any, N1 M0.

^bTreatment could be extended up to 36 weeks to accommodate dose delays.

BICR, blinded independent central review; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; Q×W, every × weeks; TNM, tumor, node, metastasis.

1. ClinicalTrials.gov. Accessed August 2, 2022. <https://clinicaltrials.gov/ct2/show/NCT03138512>.

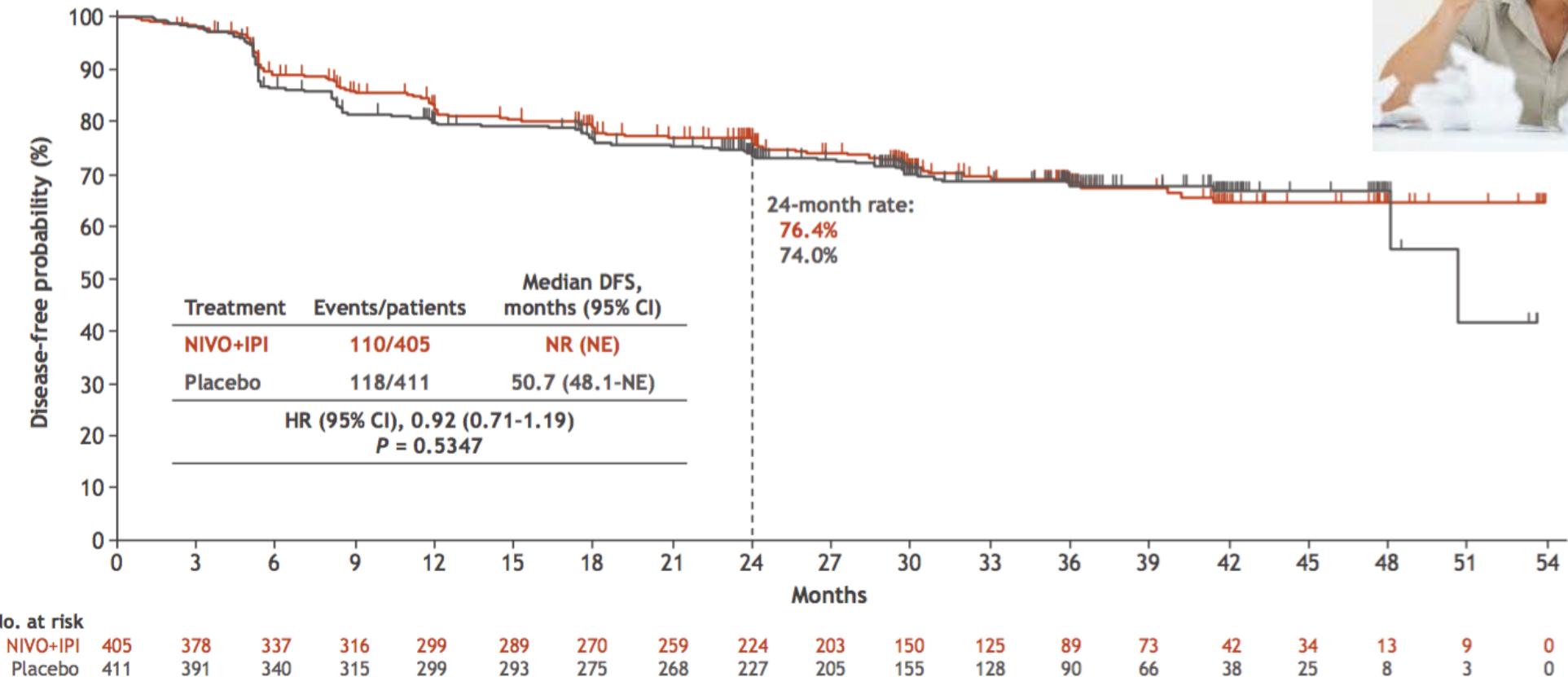


Key baseline characteristics

	NIVO + IPI (N = 405)	Placebo (N = 411)
Median age (range), years	58 (28-83)	57 (29-81)
Male / female, n (%)	286 (71) / 119 (29)	294 (72) / 117 (28)
Geographic region, n (%)		
Europe and Canada	160 (40)	167 (41)
United States	64 (16)	73 (18)
Rest of the world	181 (45)	171 (42)
Type of nephrectomy, n (%) ^a		
Radical	378 (93)	381 (93)
Partial	27 (7)	30 (7)
Pathological TNM staging, n (%) ^a		
pT2a, G3 or G4, N0 M0 or pT2b, G any, N0 M0	60 (15)	62 (15)
pT3, G any, N0 M0	315 (78)	316 (77)
pT4, G any, N0 M0 or pT any, G any, N1 M0	30 (7)	33 (8)
Sarcomatoid features, n (%)	19 (5)	21 (5)



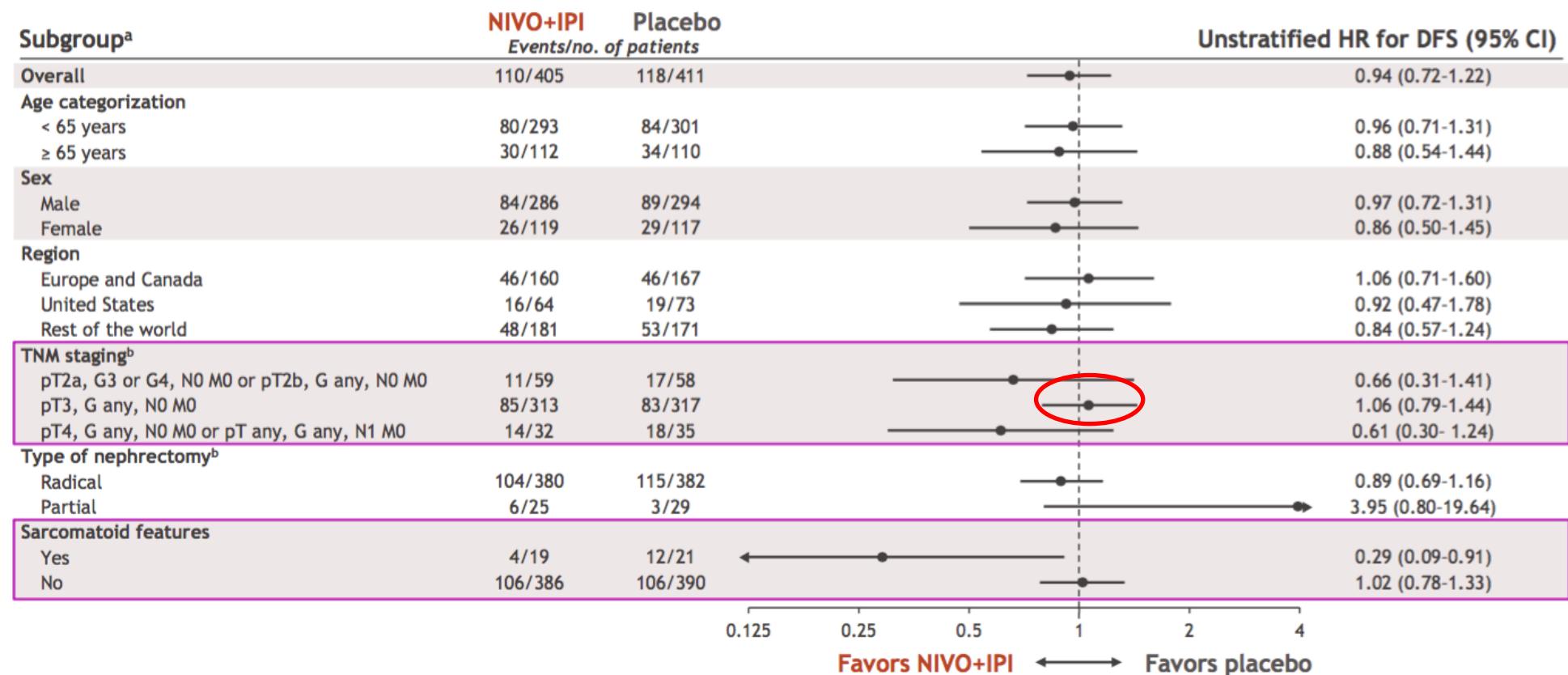
Primary endpoint: disease-free survival per BICR



Median (range) follow-up, 37.0 (15.4-58.0) months.
As the DFS endpoint was not met, no formal analysis of OS was performed (in total, there were 33 deaths in the NIVO+IPI arm and 28 deaths in the placebo arm).



Disease-free survival per BICR in subgroups



^aThe influence of demographic and baseline clinical characteristics on DFS among randomized patients was assessed via exploratory subgroup analyses for age, sex, TNM staging, type of nephrectomy, risk group, region, race, ethnicity, ECOG performance status, time from diagnosis to randomization, lactate dehydrogenase level, hemoglobin, corrected calcium, alkaline phosphatase, and sarcomatoid features. ^bThe statistical analysis plan prespecified that subgroup analyses for stratification factors (TNM staging and type of nephrectomy) would only be displayed using subgroups based on case report form data.



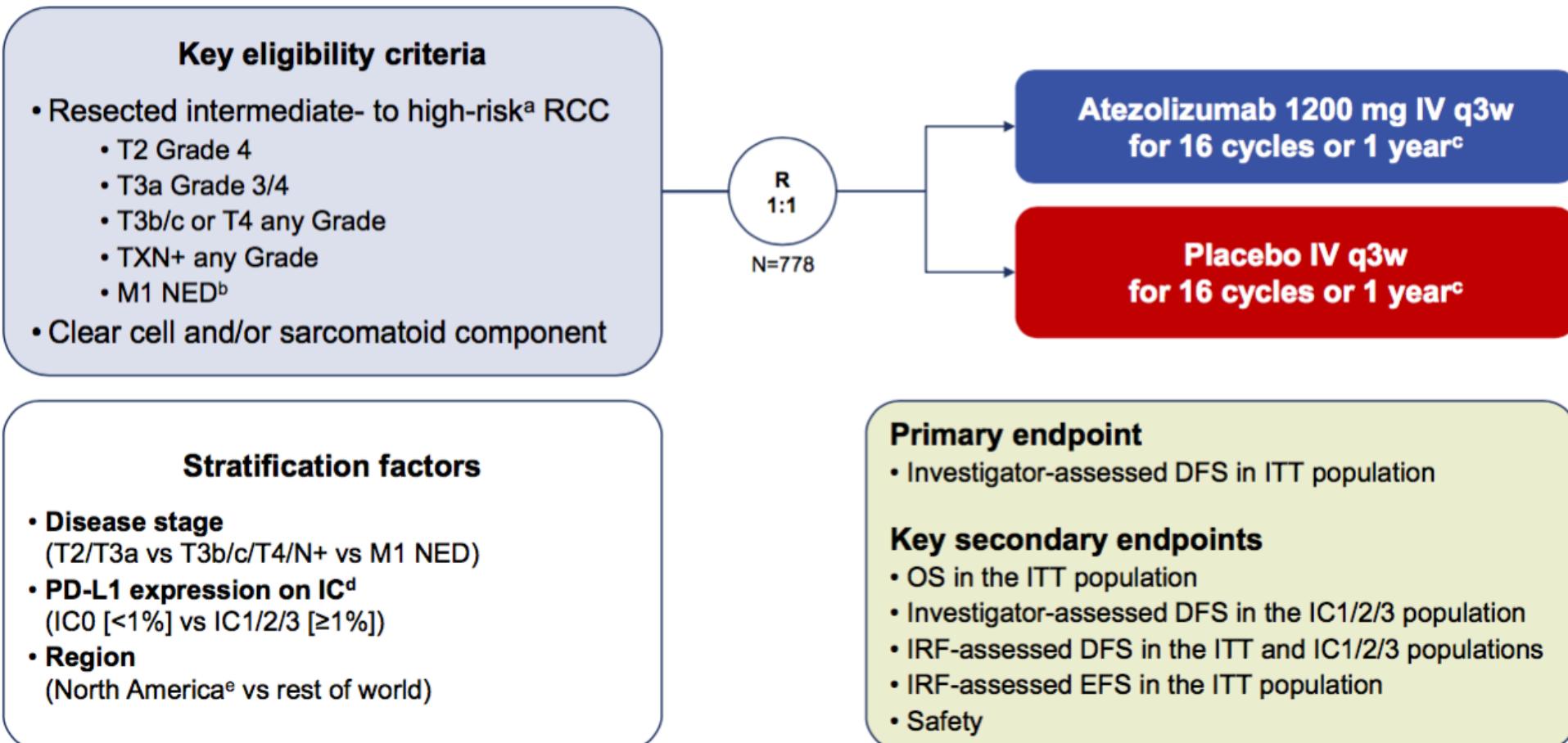
Drug exposure, patient disposition, and topline safety

	NIVO+IPI (n = 404)	Placebo (n = 407)
Median duration of therapy (range), months Q1, Q3	5.1 (< 0.1-8.3) 2.8, 5.3	5.1 (< 0.1-8.1) 5.1, 5.3
Median number of doses received (range)	NIVO, 12 (1-12) IPI, 4 (1-4)	12 (1-12) ^a 4 (1-4) ^b
Completed all 12/4 doses of NIVO/IPI, n (%)	231 (57)	361 (89)
Discontinued treatment, n (%) ^c	173 (43)	46 (11)
Discontinued due to study drug toxicity, n (%)	132 (33)	5 (1)
All-cause AEs, n (%) ^d	392 (97)	361 (89)
Grade ≥ 3	155 (38)	42 (10)
Led to treatment discontinuation	129 (32)	9 (2)
Treatment-related AEs, n (%) ^d	359 (89)	231 (57)
Grade ≥ 3	115 (28)	8 (2)
Led to treatment discontinuation ^e	117 (29)	4 (1)
Deaths due to study drug toxicity, n (%)	4 (1) ^f	0

^aDoses of NIVO placebo equivalent. ^bDoses of IPI placebo equivalent. ^cReasons were reported per investigator at the time of discontinuation and included disease recurrence, study drug toxicity, death, AE unrelated to study drug, request to discontinue treatment, withdrawal of consent, lost to follow-up, poor/non-compliance, pregnancy, or COVID-19. ^dIncludes events reported in all treated patients between first dose and 30 days after the last dose of study drug. ^eMost common any-grade treatment-related AEs leading to discontinuation were diarrhea (3.7%), ALT increased (2.5%), and hypophysitis (2.5%). ^fFour deaths were considered due to study drug toxicity in the NIVO+IPI arm (cardiac arrest, immunotherapy induced diarrhea/colitis, aortic dissection/ischemic cerebral infarction/pulmonary embolism, and drug-induced myocarditis). ALT, alanine aminotransferase.



IMmotion010 (NCT03024996) study design



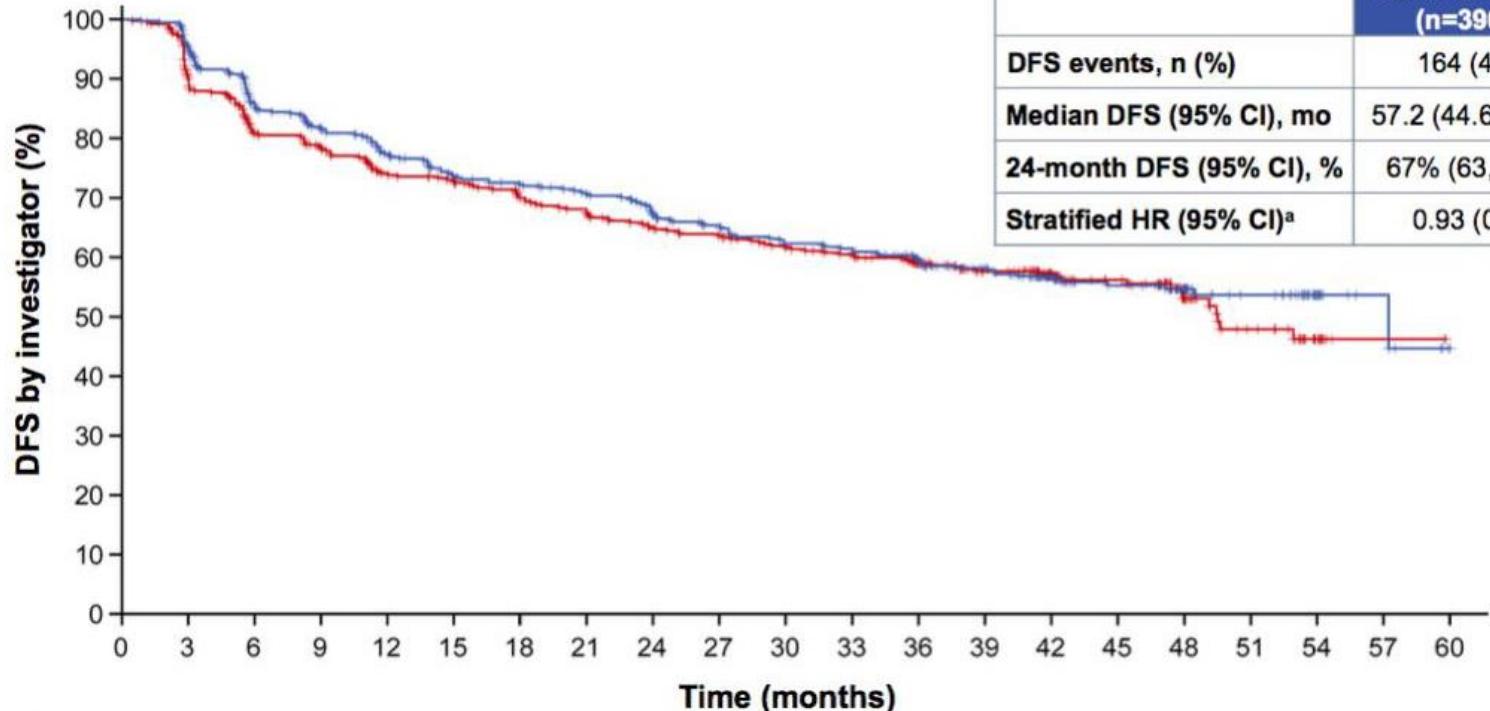
EFS, event-free survival; IC, tumour-infiltrating immune cells; IRF, independent review facility; ITT, intention to treat; IV, intravenous; NED, no evidence of disease; OS, overall survival; q3w, every 3 weeks; R, randomised; TNM, tumour, node, metastasis.

^a Per TNM/grading system or status post metastasectomy. ^b Including patients with synchronous metastasectomy and patients with metachronous metastasectomy ≥12 months after primary surgery. ^c Whichever occurred first. ^d Per VENTANA SP142 immunohistochemistry assay. ^e Not including Mexico.

Bex A et al. IMmotion010 [abstract 4634]



Investigator-assessed DFS in the ITT population



Data cutoff: 3 May 2022. Minimum follow-up, 38.6 months; Median follow-up, 44.7 months (range, 0-62.6).

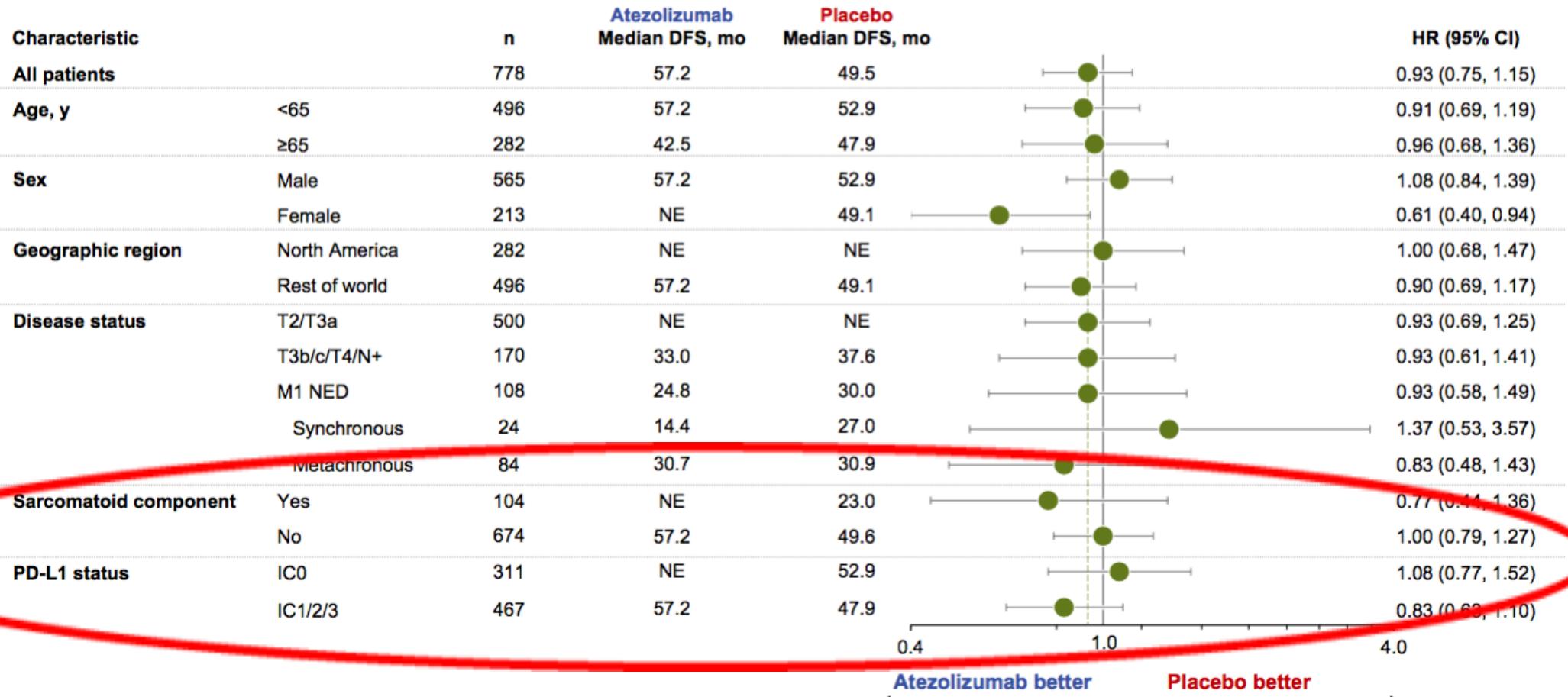
NE, not estimable.

^a Stratified for disease status and PD-L1 status. ^b Not significant at $\alpha=0.05$.

Bex A et al. IMmotion010 [abstract 4634]



Investigator-assessed DFS: subgroup analysis

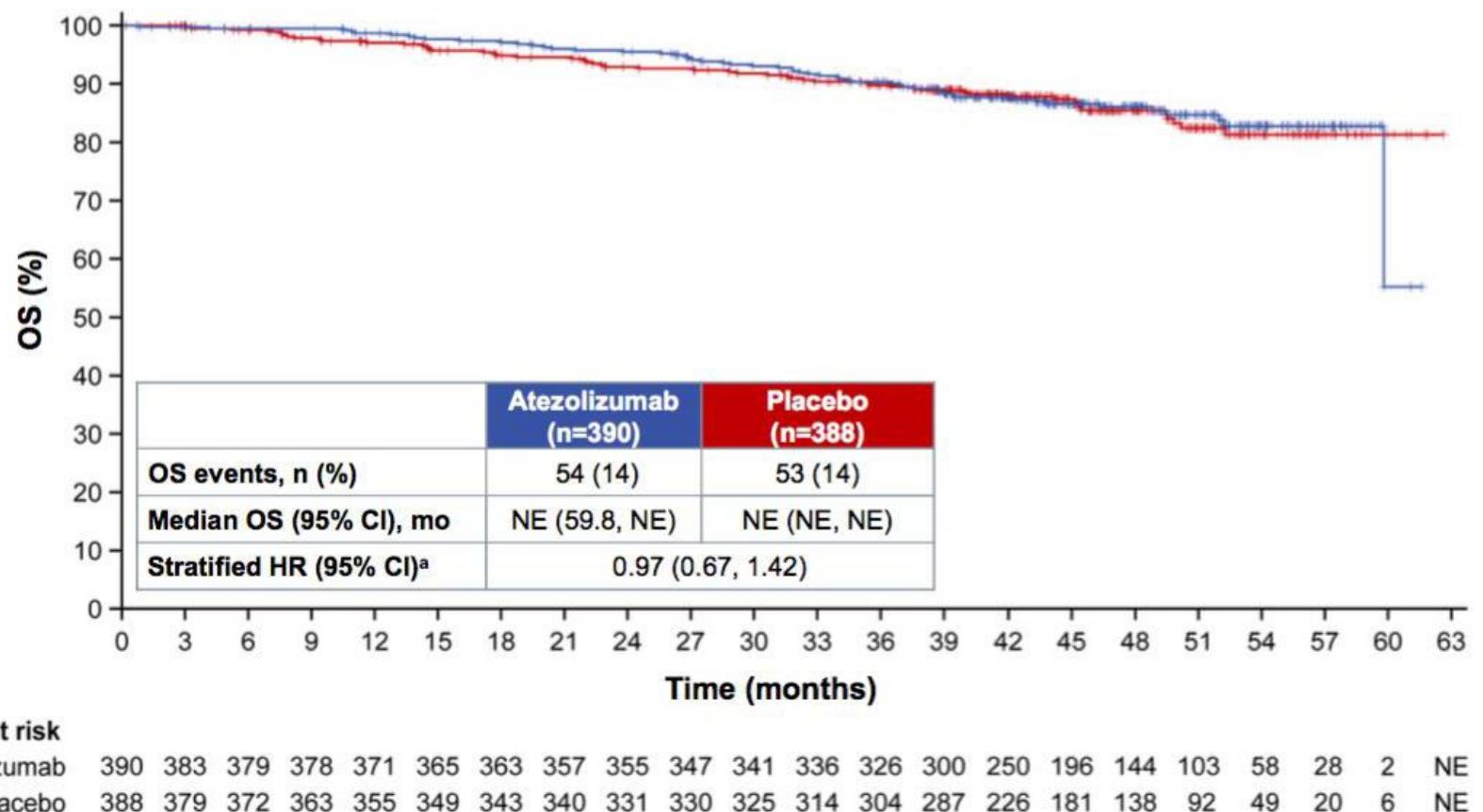


Data cutoff: 3 May 2022.

Bex A et al. IMmotion010 [abstract 4634]



OS in the ITT population



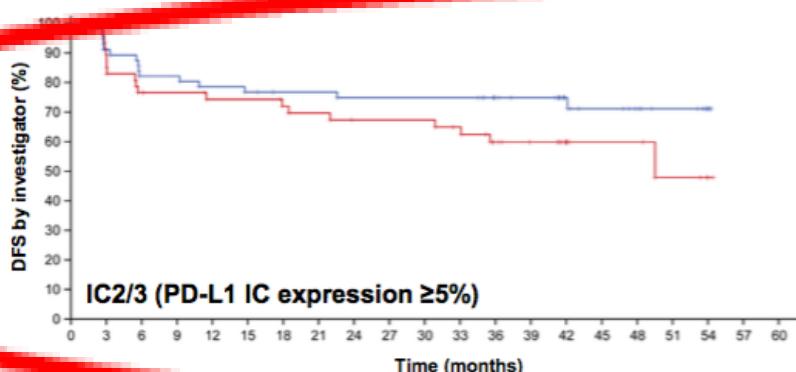
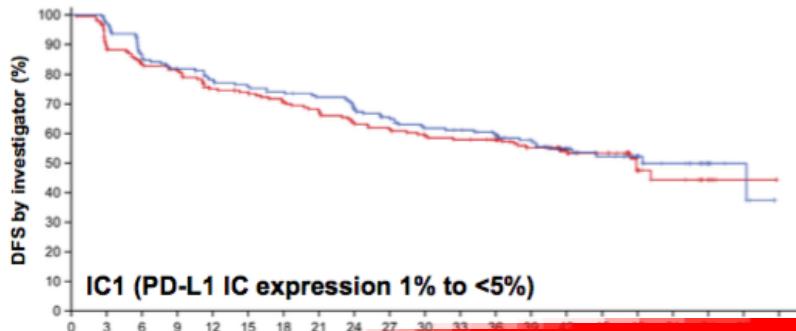
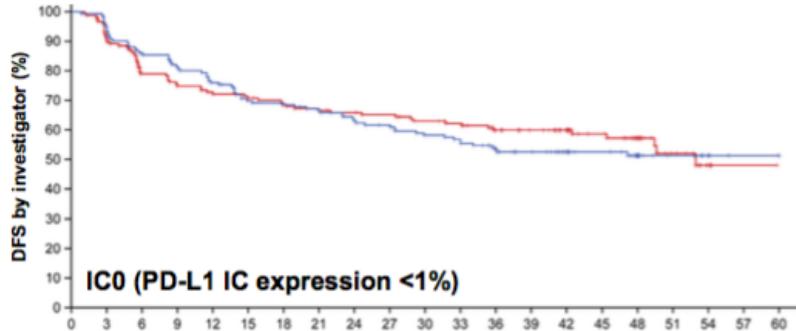
Data cutoff: 3 May 2022.

^a Stratified for PD-L1 status.

Bex A



investigator-assessed DFS by PD-L1 status



Bex A et al. IMmotion010 [abstract 4634]
<https://bit.ly/3A17...>



Safety summary

	Atezolizumab (n=390)	Placebo (n=383)
Treatment duration, median (range), mo	10.4 (0-14)	10.4 (0-12)
Any-grade AE, any cause, n (%)	373 (95.6)	341 (89.0)
Treatment related	296 (75.9)	203 (53.0)
Grade 3/4 AE, any cause, n (%)	106 (27.2)	81 (21.1)
Treatment related	55 (14.1)	18 (4.7)
Grade 5 AE, any cause, n (%)	1 (0.3) ^a	3 (0.8) ^b
Treatment related	0	0
Any-grade serious AE, n (%)	69 (17.7)	46 (12.0)
Treatment related	34 (8.7)	3 (0.8)
AE leading to discontinuation of atezolizumab or placebo, n (%)	45 (11.5)	10 (2.6)

Data cutoff: 3 May 2022.

AE, adverse event.

^a Patient died due to AE of acute myeloid leukemia.

^b Patients died of respiratory failure (n=1), sepsis (n=1) and unknown cause (n=1).

Bex A et al. IMmotion010 [abstract 4634]



Cross-trial comparison in adjuvant renal cell carcinoma

Drug (company)	Trial	Disease-free survival			Status
		Medians	Stats		
Keytruda (Merck & Co)	Keynote-564	NR vs NR	HR=0.68 (0.53, 0.87), p=0.001		US approved Nov 2021
Opdivo + Yervoy (Bristol Myers Squibb)	Checkmate-914	NR vs 50.7mth	HR=0.92 (0.71, 1.19), p=0.535		Study fail
Tecentriq (Roche)	Immation-010	57.2 vs 49.5mth	HR=0.93 (0.75, 1.15), p=0.495		Study fail

NR=not reached. HR=hazard ratio (95% confidence intervals in brackets). Source: product label & Esmo.



¿POR QUÉ SON NEGATIVOS?

- Podrían reflejar diferencias en las poblaciones de pacientes, proporciones de pacientes con enfermedad ganglionar muy avanzada o metastásica resecada,
- Diferente mecanismo de acción de los respectivos agentes de immunoterapia probados.
- Diferencias en los tiempos de seguimiento.
- La toxicidad obliga a discontinuar tratamiento.
- Los análisis de subgrupos que utilizan datos de los tres ensayos de fase III son importantes para determinar qué pacientes tendrán el mayor beneficio, y para investigar la presencia o ausencia de biomarcadores predictivos.
- Necesidad de biomarcadores



¿POR QUÉ SON NEGATIVOS? TOXICIDAD

	KN-564 (Pembro)	CM-914 (Ipi/Nivo)	IMmotion010 (Atezo)	PROSPER (Periop Nivo)
Gr 3+ AEs	32%	38%	27%	33%
Tx-related Gr 3+ AEs	19%	28%	14%	15%
Discontinuation due to AE	21%	33%	12%	13%
Received steroids for an irAE	8%	23%	10%	N/A

→ In CM-914, only 57% of patients completed all 4 doses of both drugs

Choueiri et al. NEJM. 2021; Powles et al. Lancet. 2022; Motzer et al. ESMO 2022; Pal et al. Lancet. 2022; Allaf et al. ESMO 2022



Table. Adjuvant Immune Checkpoint Inhibitor Trials in RCC

	KEYNOTE-564 ¹ (994 patients)	IMmotion010 (778 patients)	PROSPER RCC (766 patients)	RAMPART (1,750 patients)	CheckMate-914 (1,600 patients)
Experimental arm(s)	Pembrolizumab	Atezolizumab	Nivolumab	Durvalumab (q4w) plus tremelimumab (q4w for 2 cycles only) or durvalumab (q4w)	Ipilimumab plus nivolumab or nivolumab
Control arm	Placebo	Placebo	Observation	Observation	Placebo
Treatment length	1 year	1 year	10 months (1 month neoadjuvant; 9 months adjuvant)	1 year	6 months
Primary endpoint(s)	DFS (by investigator)	DFS (ICR)	EFS	DFS (by investigator) and OS	DFS (ICR)
Histology	Clear cell component (+/- sarcomatoid)	Clear cell component or sarcomatoid histology	Any malignant RCC (+/- sarcomatoid)	Any RCC (except for collecting duct, medullary, an-	Clear cell predominant (+/- sarcomatoid)



BETTER PERIOPERATIVE?

NEOADJUVANT

- NEOADJUVANT
- ADJUVANT + NEOADJUVANT
- PHASE III



Proffered Paper session 1: GU tumours, non-prostate

LBA67 - Phase III randomized study comparing perioperative nivolumab (nivo) versus observation in patients (Pts) with renal cell carcinoma (RCC) undergoing nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial

Date

10 Sep 2022

Presenters

Mohamad Allaf



NEOADJUVANT

Neoadjuvant TKI Experience in RCC

Trial	Patient Population	Intervention	Key Findings
NCT01158521 (Rini et al)	<u>25</u> pts with R.E.N.A.L. score 10-12	Pazopanib 800 mg daily x 8-16 weeks	-92% experienced reduction in tumor volume -Six additional pNx possible
NCT01263769 (Karam et al)	<u>24</u> pts with cT2-cT3b	Axitinib 5 mg bid x 12 weeks	-46% with a PR per RECIST -28% median tumor reduction -No PD
NCT04022343 (Bilen et al, GU ASCO 2022)	<u>17</u> pts with cT3-T4	Cabozantinib 60 mg daily x 12 weeks	-29% with a PR per RECIST -23% median tumor reduction -100% tumor shrinkage

Neoadjuvant IO Experience in RCC

Trial	Patient Population	Intervention	Key Findings
NCT02575222 (Gorin et al)	<u>17</u> pts with cT2-cT3	Nivolumab Q2 weeks x 3	-100% with SD per RECIST -59% with grade 1-2 AEs
NCT02595918 (Carolo et al)	<u>18</u> pts with >20% risk of recurrence	Nivolumab Q2 weeks x 4	-100% with SD per RECIST -100% had a nephrectomy -0% pCR
NCT02762006 (Ornstein et al)	<u>29</u> pts with T2-T4 and/or N1 80% clear cell	Durvalumab + Tremelimumab	-Dual CPI therapy led to a >40% discontinuation rate (p.s. ipi/nivo in M1 setting → ~35% PR in kidney) Meerveld-Eggink et al 2022; Albiges L et al 2020

Neoadjuvant TKIs lead to ~30% PR and are tolerable and safe for 8-16 weeks pre-surgery

Neoadjuvant single agent IO leads to primarily SD per RECIST with mild tumor reduction; effect on long term immunologic memory is unknown



Proffered Paper session 1: GU tumours, non-prostate

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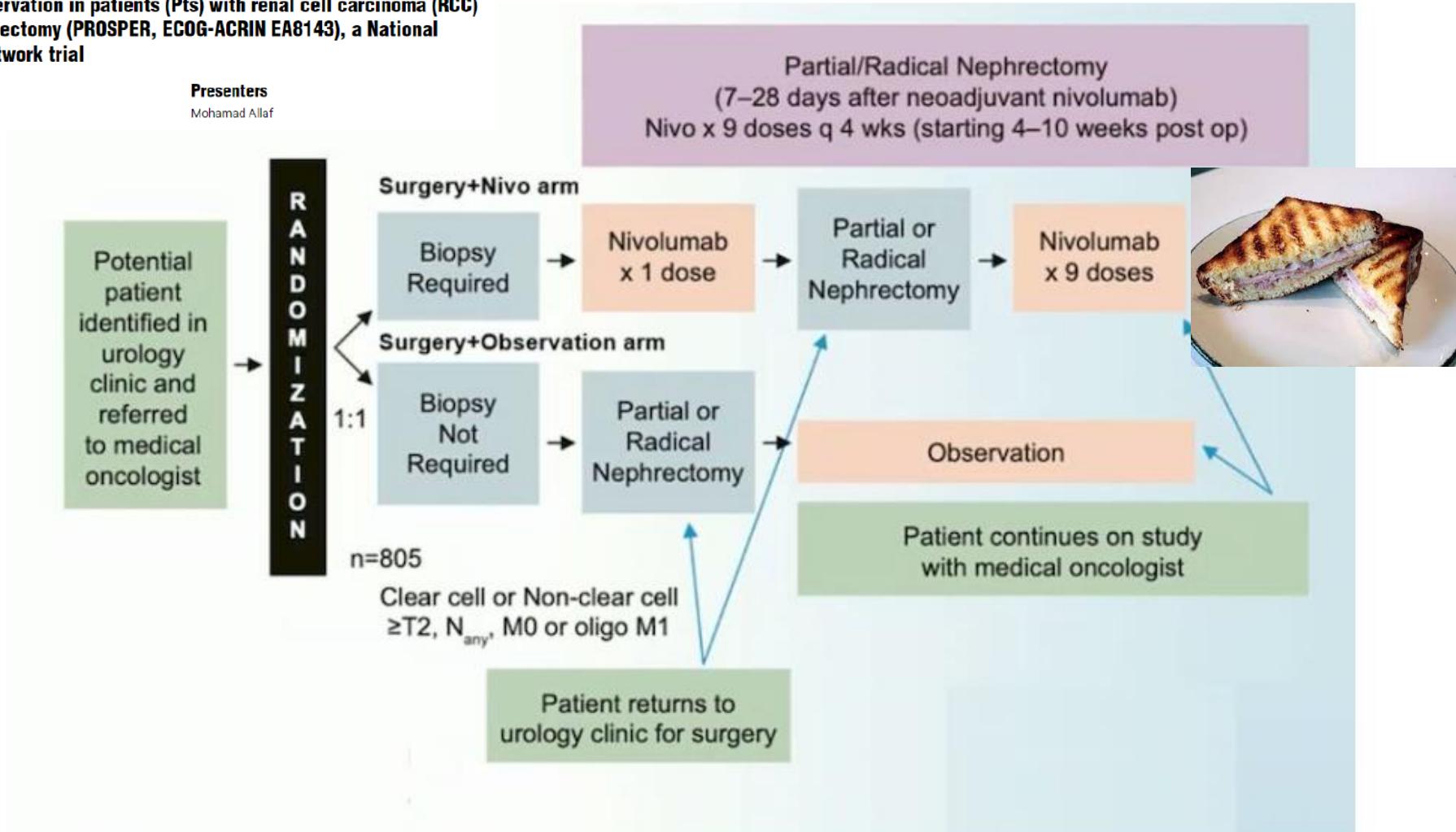


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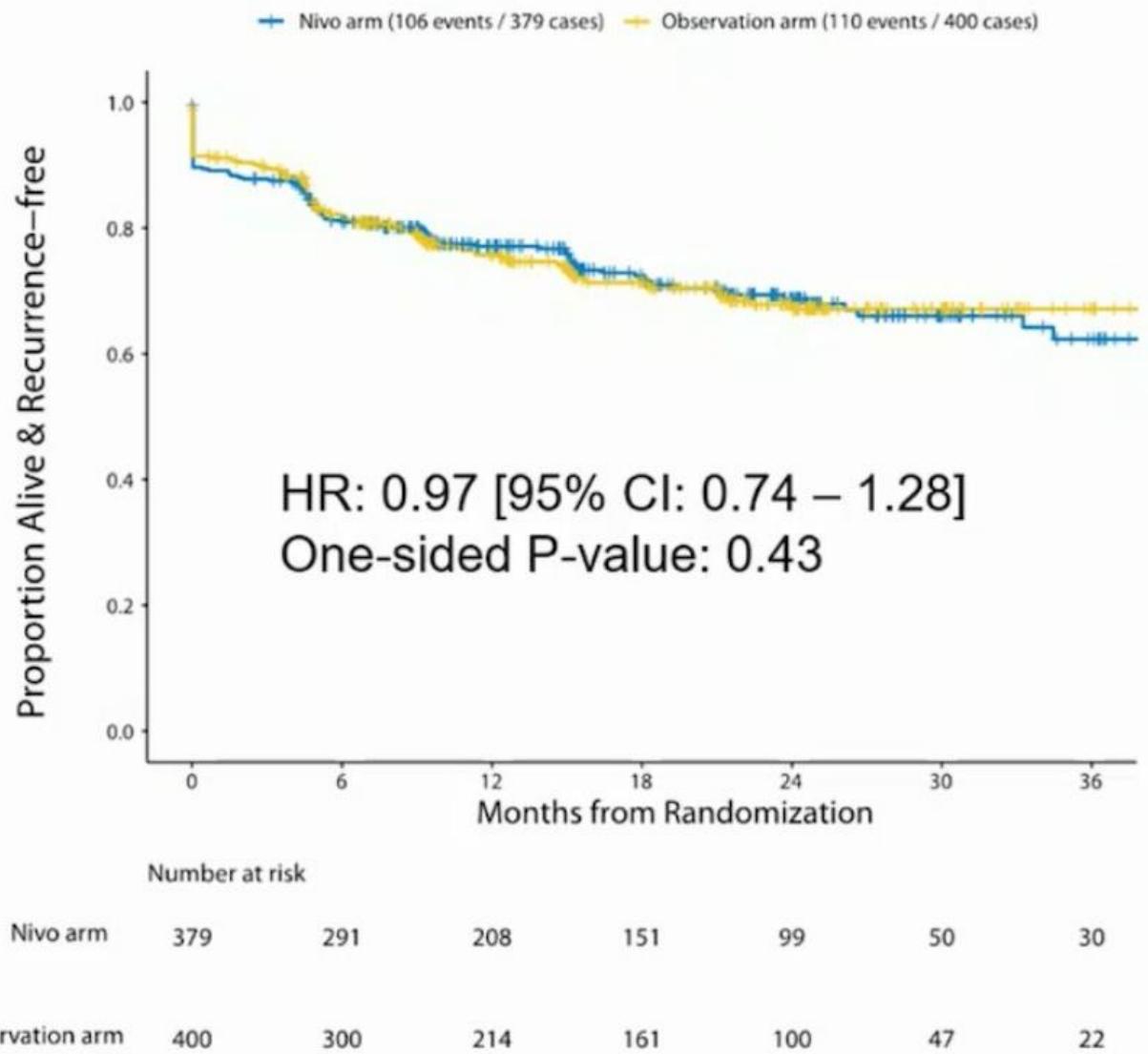


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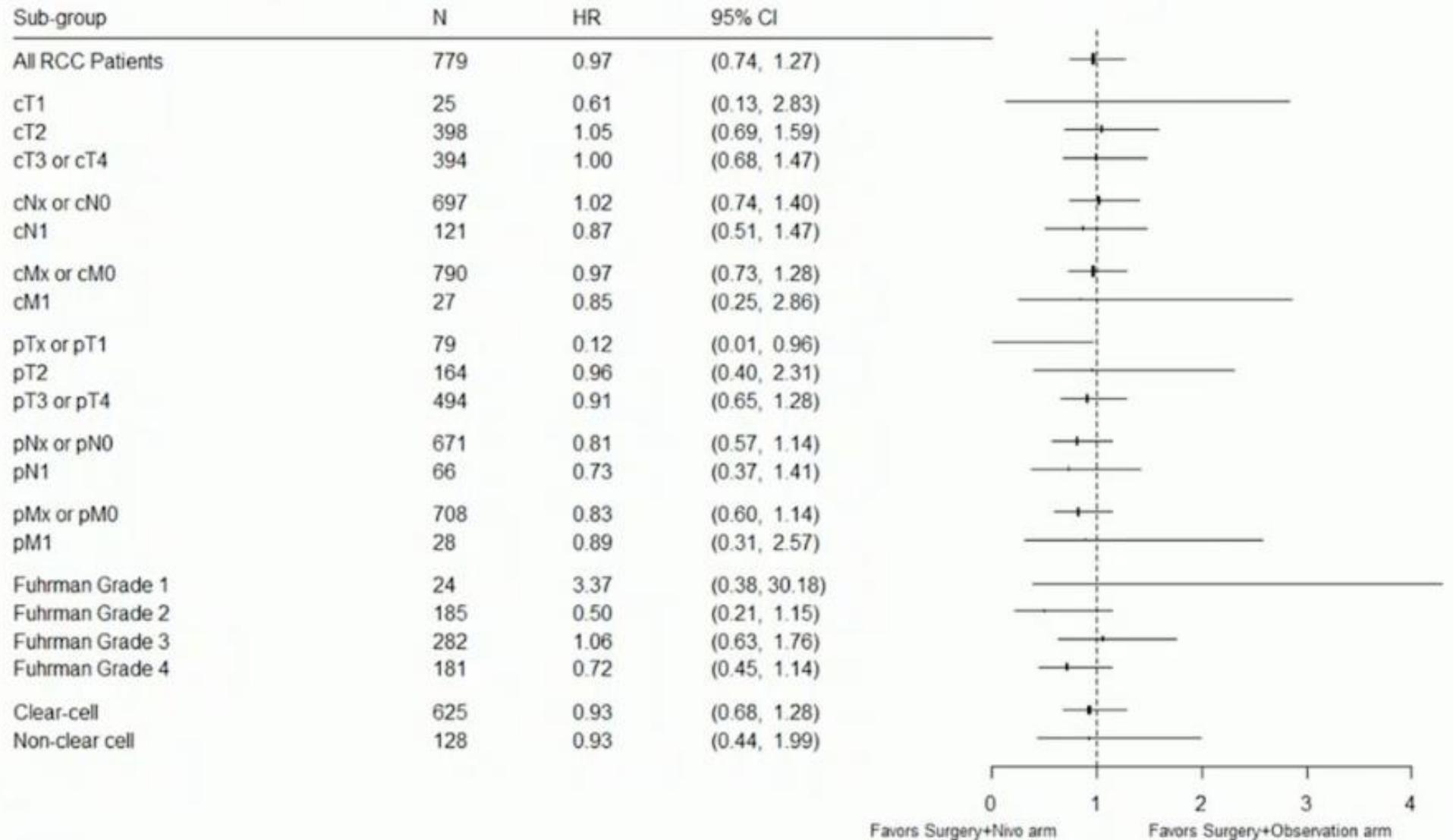


	Surgery+Nivo arm n = 404	Surgery+Observation arm n = 415	Total n = 819
	N (%)	N (%)	N (%)
Age (year)			
Median	60	61	61
Sex			
Female	120 (30)	128 (31)	248 (30)
Race			
Black or African American	31 (8)	30 (8)	61 (8)
White	332 (88)	340 (88)	672 (88)
Clinical T stage			
T1	12 (3)	13 (3)	25 (3)
T2	204 (50)	194 (47)	398 (49)
T3 or T4	186 (46)	208 (50)	394 (48)
Clinical N stage			
Nx/N0	342 (85)	355 (86)	697 (85)
N1	62 (15)	59 (14)	121 (15)
Clinical M stage			
Mx/M0	391 (97)	399 (96)	790 (97)
M1	12 (3)	15 (4)	27 (3)

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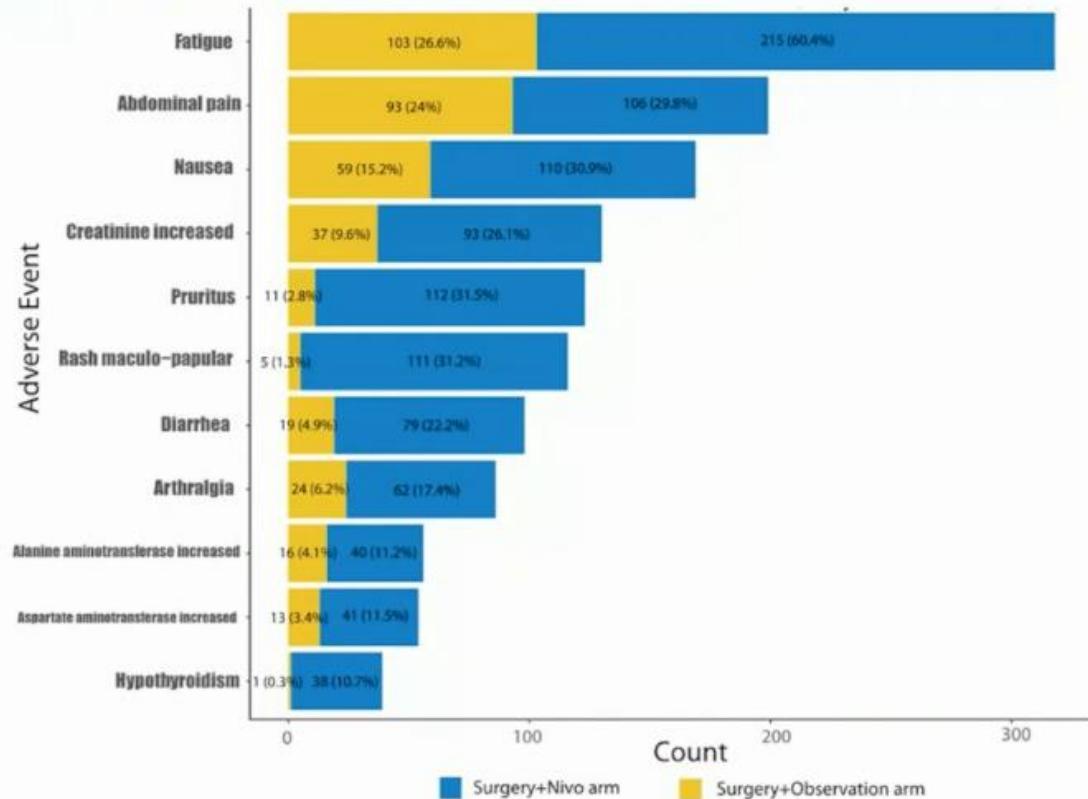


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TOXICITY



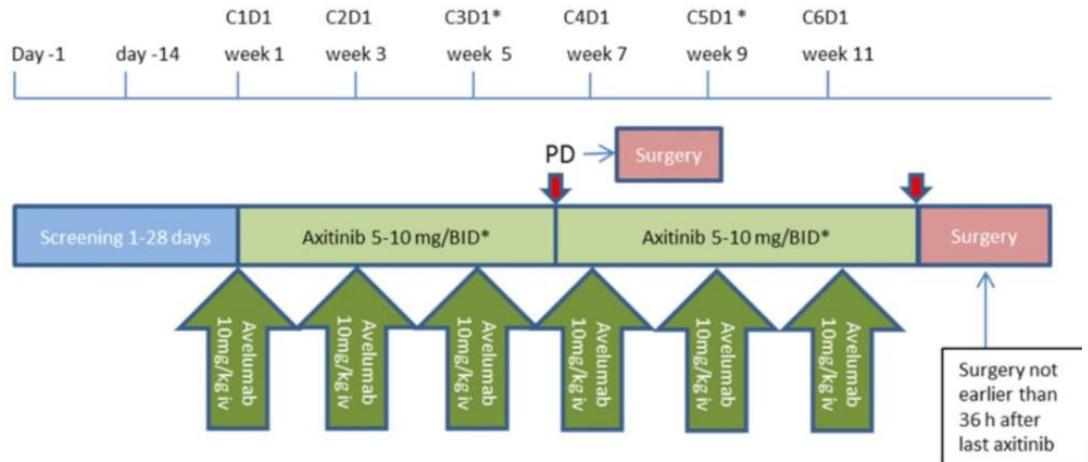
PARIS
2022 ESMO congress

There were 15 (4%) deaths from RCC in the nivolumab arm and 18 (4%) deaths from RCC in the surgery-alone arm.

- This is the first phase III neoadjuvant IO trial in RCC
- Perioperative nivolumab did not improve RFS in RCC patients at high risk for recurrence
- OS data remains immature but is not statistically different between arms
- Adverse events in the surgery + nivolumab arm were consistent with the toxicity profile of other nivolumab trials
- Ongoing radiomic, pathomic, and other biomarker analyses within this trial may inform the design of future neoadjuvant RCC trials
- Further analyses of patient subsets within this unique trial design should help inform future research

NEOAVAX. PHASE II

IO+TKI



*after week 4: if tolerated well, switch to 7 mg Axitinib BID
after week 8: if tolerated well, switch to 10 mg Axitinib BID



40 PATIENTS. 30% RR.

83% of the 12 patients with a primary response were disease-free at the time of analysis



The horizon in neoadjuvant trials

- Neoadjuvant trials with immunotherapy are ongoing.
- Endpoints of neoadjuvant trials should assess tumor shrinkage, surgical feasibility, long-term disease-free and overall survival benefit, and exploratory biomarkers to understand predictors of response.
- Although no head-to-head neoadjuvant versus adjuvant clinical trials are ongoing, there is a strong biological rationale to treat with immunotherapy with the tumor in place.



CONCLUSIONES

- Pembrolizumab es el único fármaco aprobado en Europa como adyuvancia en cáncer renal.
- El dilema de la SG y la toxicidad que sufre un paciente potencialmente sano es una limitación.
- Es muy difícil sacar conclusiones de estudios distintos aunque similares.
- La neoadyuvancia es un escenario anticipado de test de efectividad de los esquemas utilizados en enfermedad avanzada

GRACIAS

