Early treatment in der Immunonkologie

RCC

Fortbildungsveranstaltung der Österreichischen Gesellschaft für Krankenhauspharmazie in Kooperation mit MSD

Dora Niedersüß-Beke

1. MEDIZINISCHE ABTEILUNG
Zentrum für Onkologie und Hämatologie
mit Ambulanz und Palliativstation

Wilhelminen Cancer Research Institute
Vienna Cancer Center
Wiener Gesundheitsverbund
Klinik Ottakring
Für die Stadt Wien

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Interessenskonflikte

- Empfang von Honoraren oder Beratungsgebühren: MSD, BMS, Merck Serono, Astellas
- Grant: Astellas
- Teilnahme an von einer Firma gesponsertem Sprecherbüro: BMS, MSD, Merck Serono, Amgen, Astellas; AstraZeneca; Janssen

Chirurgische Resektion

Die einzige kurative Therapie

des Nierenzellkarzinoms

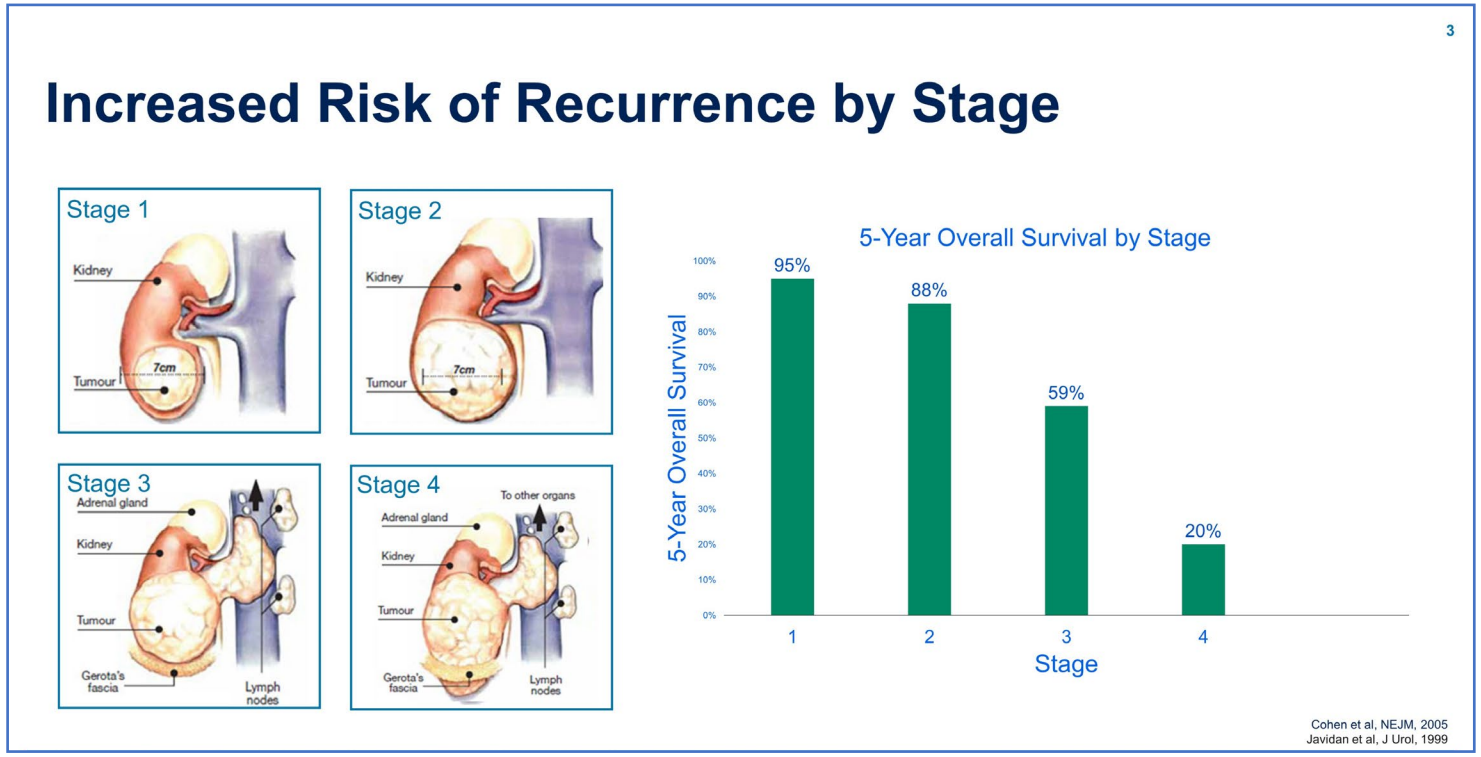
ist eine partielle bzw. komplette Nephrektomie

Aber, ~ 50% der Patienten erleiden ein Rezidiv[1-3]

[1-3]Marconi et al., Clin Genitourin Cancer 2021; Sun et al. Eur Urol. 2018; Correa et al JCO 2019

Risikofaktoren für ein Rezidiv

- Tumorgröße
- Differenzierung (Grading)
- Lymphknotenbefall
- M1, NED nach einer Metastasenresektion im oligometastatischem Bereich



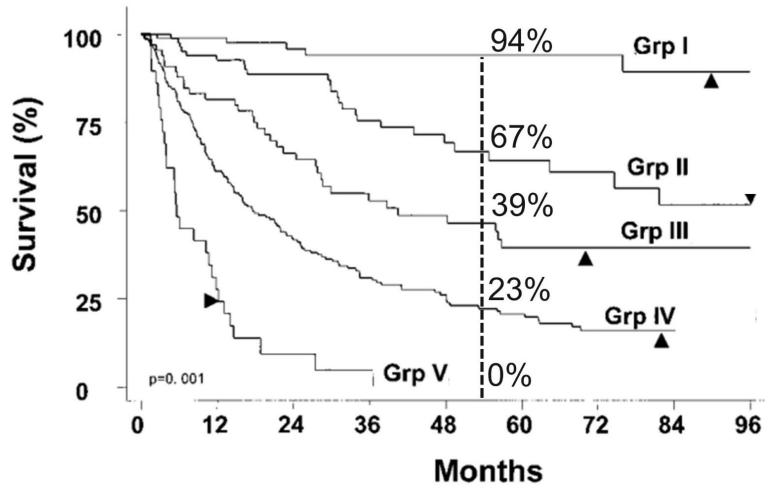
Weitere Risikofaktoren

Model	Parameters	Outcome	Type
UISS	TNM, grade, ECOG PS	OS	KM Analysis
SSIGN	TNM, pN+, pM+, tumor size, grade, tumor necrosis	CSS	Algorithm
Leibovich	TNM, pN+, tumor size, grade, tumor necrosis	MFS	Algorithm
MSKCC	TNM, tumor size, grade, tumor necrosis, symptoms	RFS	Nomogram
Kattan	TNM, tumor size, histology, symptoms	RFS	Nomogram
Yaycioglu	Tumor size, symptoms	RFS	Formula
Karakiewic	TNM, age, sex, + margin, tumor size, symptoms	CSS	Nomogram
Cindolo	Tumor size, symptoms	RFS	Formula

UISS=University of California at Los Angeles Integrated Staging System; SSIGN=Stage, Size, Grade, and Necrosis Score; MSKCC=Memorial Sloan Kettering Cancer Center; ECOG PS=Eastern Cooperative Oncology Group performance status; OS=Overall survival; CSS=Cancer-specific survival; MFS=Metastasis-free survival; RFS=Recurrence-free survival; KM=Kaplan-Meier.

UCLA Integrated Staging System

pTNM Stage, Grade, Performance status



Zisman et al, J Clin Oncol, 2002; Frank et al, J Urol, 2002; Leibovich et al, Cancer, 2003; Sorbellini et al, J Urol, 2005; Kattan et al, J Urol, 2001; Yaycioglu et al, Urology, 2001; Karakiewicz et al, JCO, 2007; Cindolo et al, BJU Int, 2003

Adapted from McKay R. ASCO 2021

Adjuvante Therapie – was bisher geschah (Cytokine)

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 a;, Proceedings of ASCO, 1996; Pizzacaro et al, JCO, 2001; Messing et al, NEJM, 2003; Clark et al, JCO, 2003; Atzpodien et al Br J Cancer, 2005; Aitchizon et al, EJC, 2014

Adjuvante Therapie – was bisher geschah (TKI)

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-Goupil, 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	0.85 (95% 0.72-1.00)

Toxizität

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2021 VOL. 385 NO. 8

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 Study Design

Key Eligibility Criteria

- Histologically confirmed clear cell renal cell carcinoma
- Nephrectomy ≤12 weeks prior to randomization
- No prior systemic therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment

Stratification Factors

- M0 vs M1 NED
- M0 group further stratified:
  - ECOG PS 0 vs 1
  - US vs non-US

R (1:1)

Pembrolizumab 200 mg Q3W for ~1 year[a]

Placebo Q3W for ~1 year[a]

- Primary end point: DFS per investigator
- Key secondary end point: OS
- Other secondary end points: Safety

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

Choueri, NEJM 2021

Keynote – 564, prespecified 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	

Choueri, NEJM 2021

Baseline Characteristics

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

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

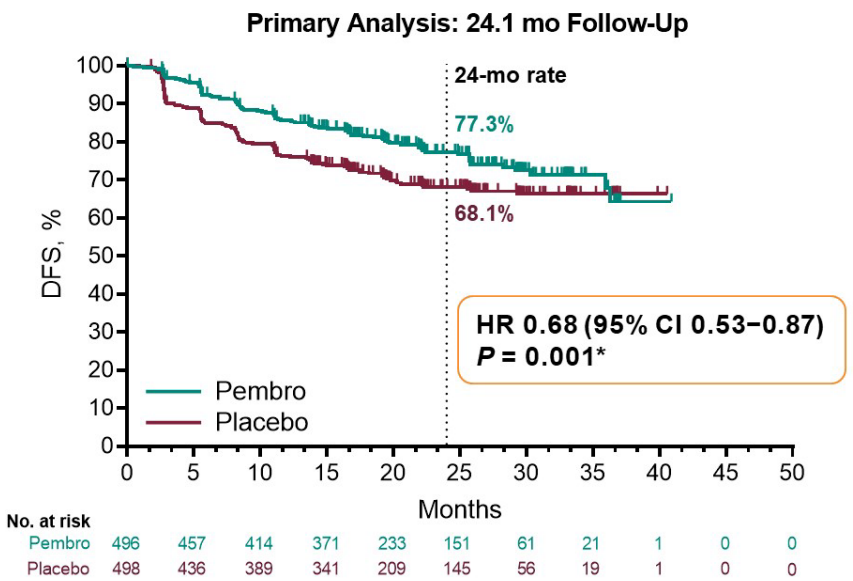
Intermediate-high risk: pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0 M0
High risk: pT4, any grade, N0 M0; or pT any stage, any grade, N+ M0
M1 NED: No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy
[a]Included 5 participants with T2, grade ≤3, N0 M0 or T1 N0 M0. [b]Assessed using the PD-L1 IHC 22C3 pharmDx assay. CPS (combined positive score) is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. Data cutoff date: December 14, 2020.

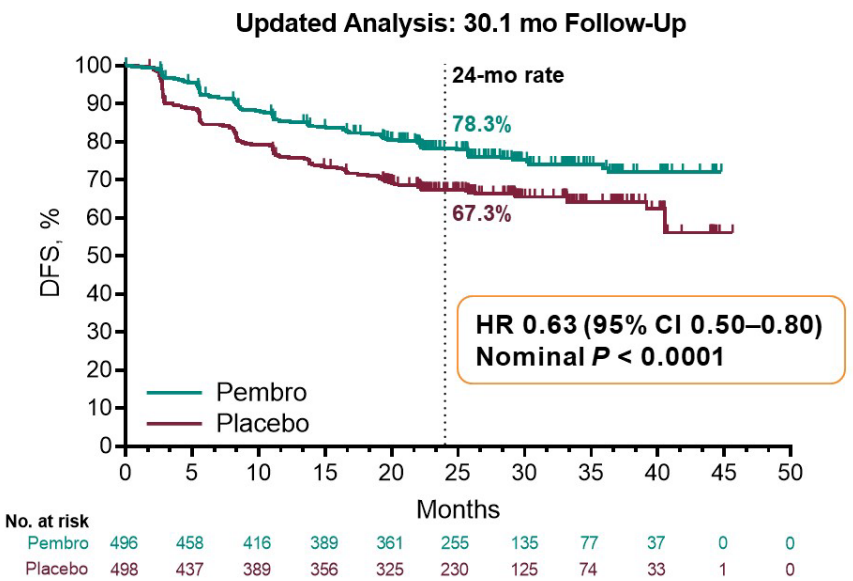
Pembrolizumab as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Results from 30-month Follow-up of KEYNOTE-564

Toni K. Choueiri[1]; Piotr Tomczak[2]; Se Hoon Park[3]; Balaji Venugopal[4]; Thomas Ferguson[5]; Stefan Symeonides[6]; Jaroslav Hajek[7]; Yen-Hwa Chang[8]; Jae Lyun Lee[9]; Naveed Sarwar[10]; Antoine Thiery-Vuillemin[11]; Marine Gross-Goupil[12]; Mauricio Mahave[13]; Naomi Haas[14]; Piotr Sawrycki[15]; Lei Xu[16]; Joseph E. Burgents[16]; Kentaro Imai[16]; Jaqueline Willemann-Rogerio[16]; David I. Quinn[17]; Thomas Powles[18], on behalf of the KEYNOTE-564 Investigators

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Poznań University o
Center, Seoul, South Korea; [4]Beatson West of Scotland Cancer Centre,
Perth, Australia; [6]Edinburgh Cancer Centre and University of Edinburgh
General Hospital, Taipei, Taiwan; [9]Asan Medical Center, University of U
Trust, London, UK; [11]University Hospital Jean Minjoz, Besançon, France
[13]Fundacion Arturo Lopez Perez FALP, Santiago, Chile; [14]Abramson Ca
Rydygiera w Toruniu, Torun, Poland; [16]Merck & Co., Inc., Kenilworth, NJ
[18]Royal Free Hospital NHS Trust, University College London, London, U

Primary Endpoint: DFS, ITT Population





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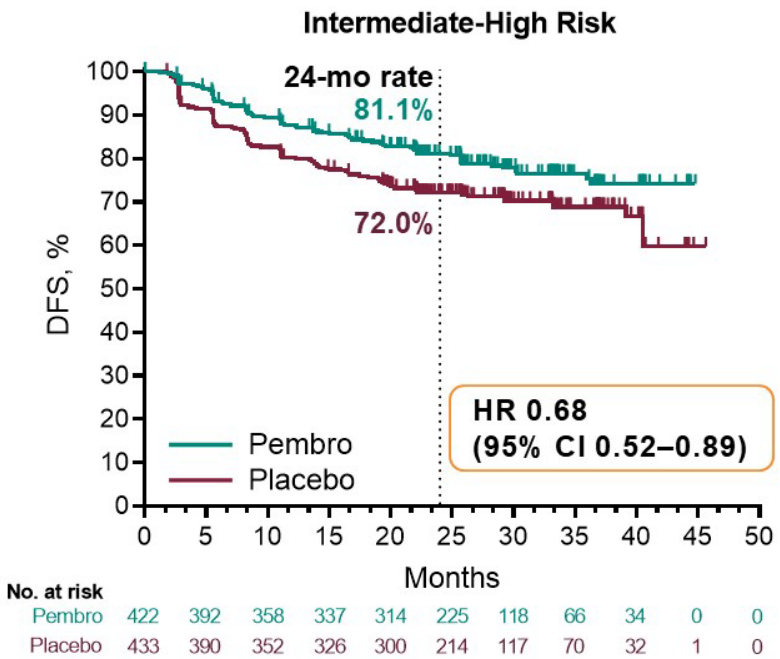
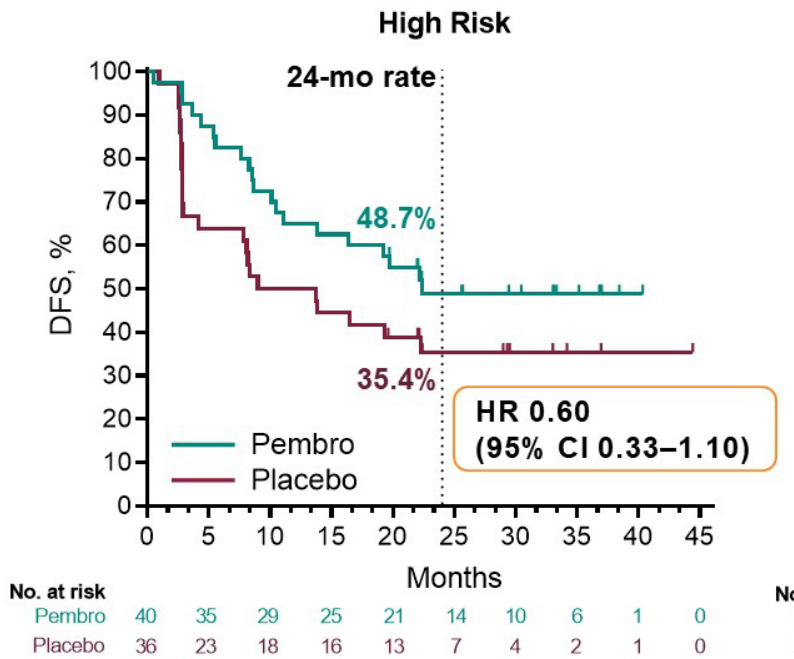
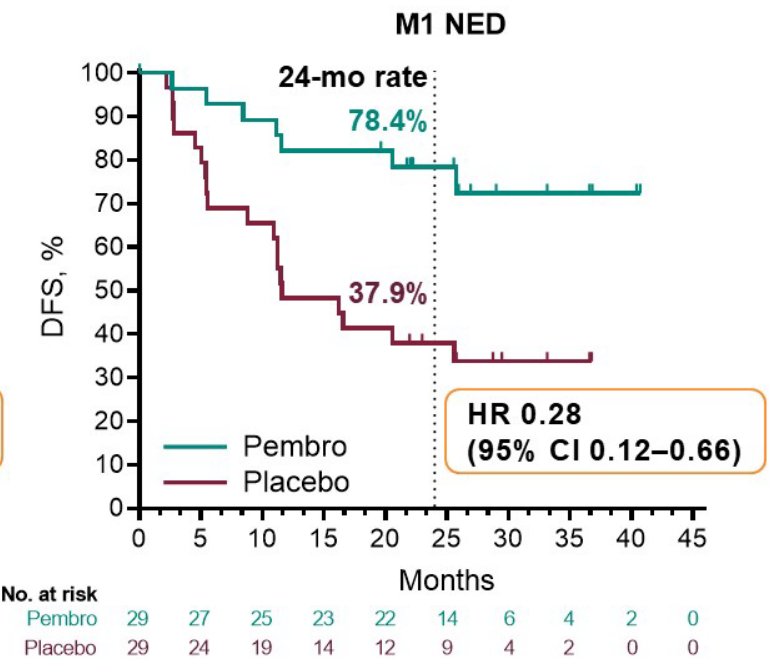
DFS by Recurrence Risk Subgroups



	Pts w/ Event	Median, mo (95% CI)
Pembro	87	NR (NR–NR)
Placebo	127	NR (40.5–NR)



	Pts w/ Event	Median, mo (95% CI)
Pembro	20	22.4 (11.1–NR)
Placebo	23	11.4 (2.9–NR)



	Pts w/ Event	Median, mo (95% CI)
Pembro	7	NR (25.7–NR)
Placebo	19	11.6 (5.6–NR)

Intermediate-high risk: pT2, grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0;
High risk: pT4, any grade, N0, M0; or pT any stage, any grade, N+, M0;
M1 NED: No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy.
DFS, disease-free survival; NR, not reached. Data cutoff date: June 14, 2021.

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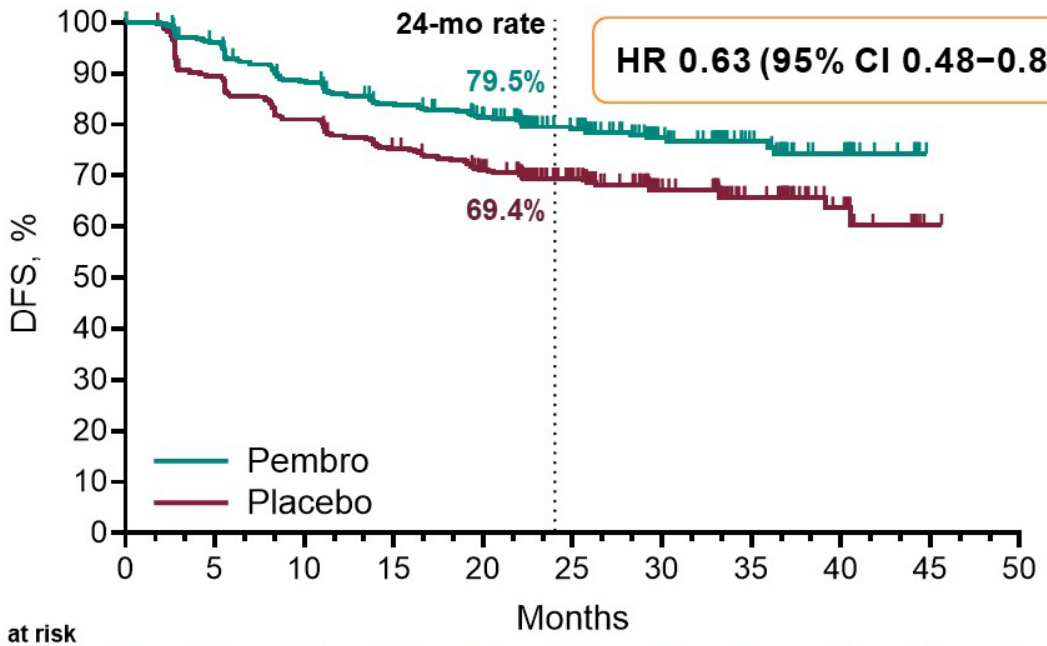
DFS by Sarcomatoid Status Subgroups

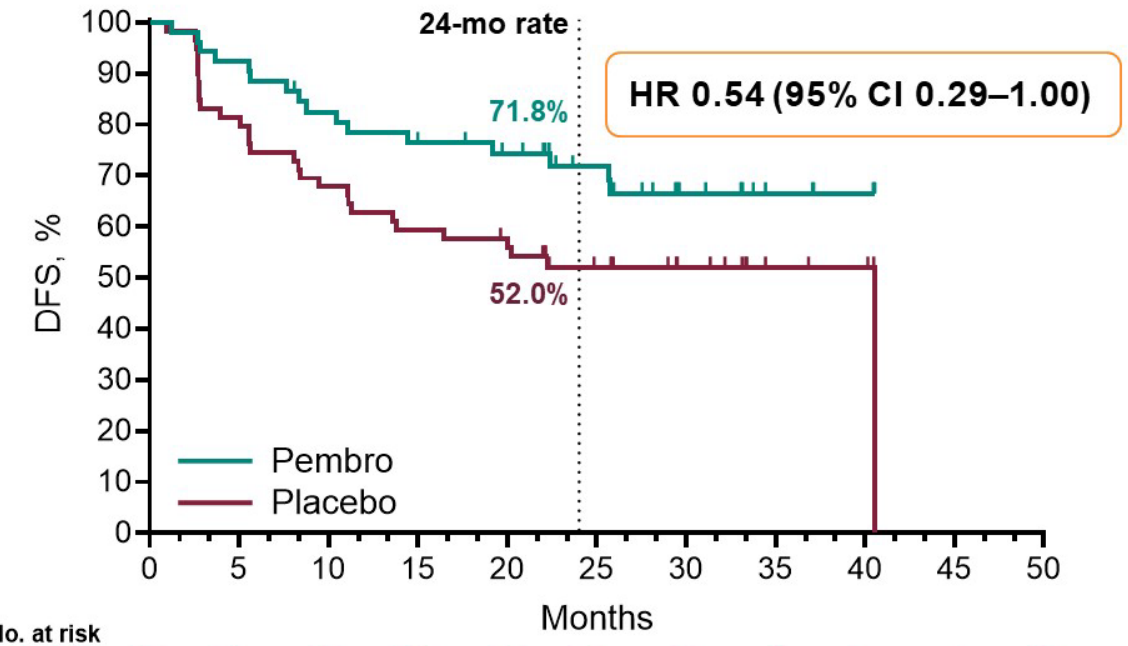
Sarcomatoid Features Absent



No. at risk											
Pembro	414	385	350	327	305	216	117	67	32	0	0
Placebo	415	367	331	304	277	201	110	68	30	1	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	88	NR (NR–NR)
Placebo	133	NR (NR–NR)

Sarcomatoid Features Present



No. at risk											
Pembro	52	48	41	37	34	27	11	5	3	0	0
Placebo	59	48	40	35	33	21	12	4	3	0	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	16	NR (NR–NR)
Placebo	29	40.5 (11.3–NR)

DFS, disease-free survival; NR, not reached. Data cutoff date: June 14, 2021.

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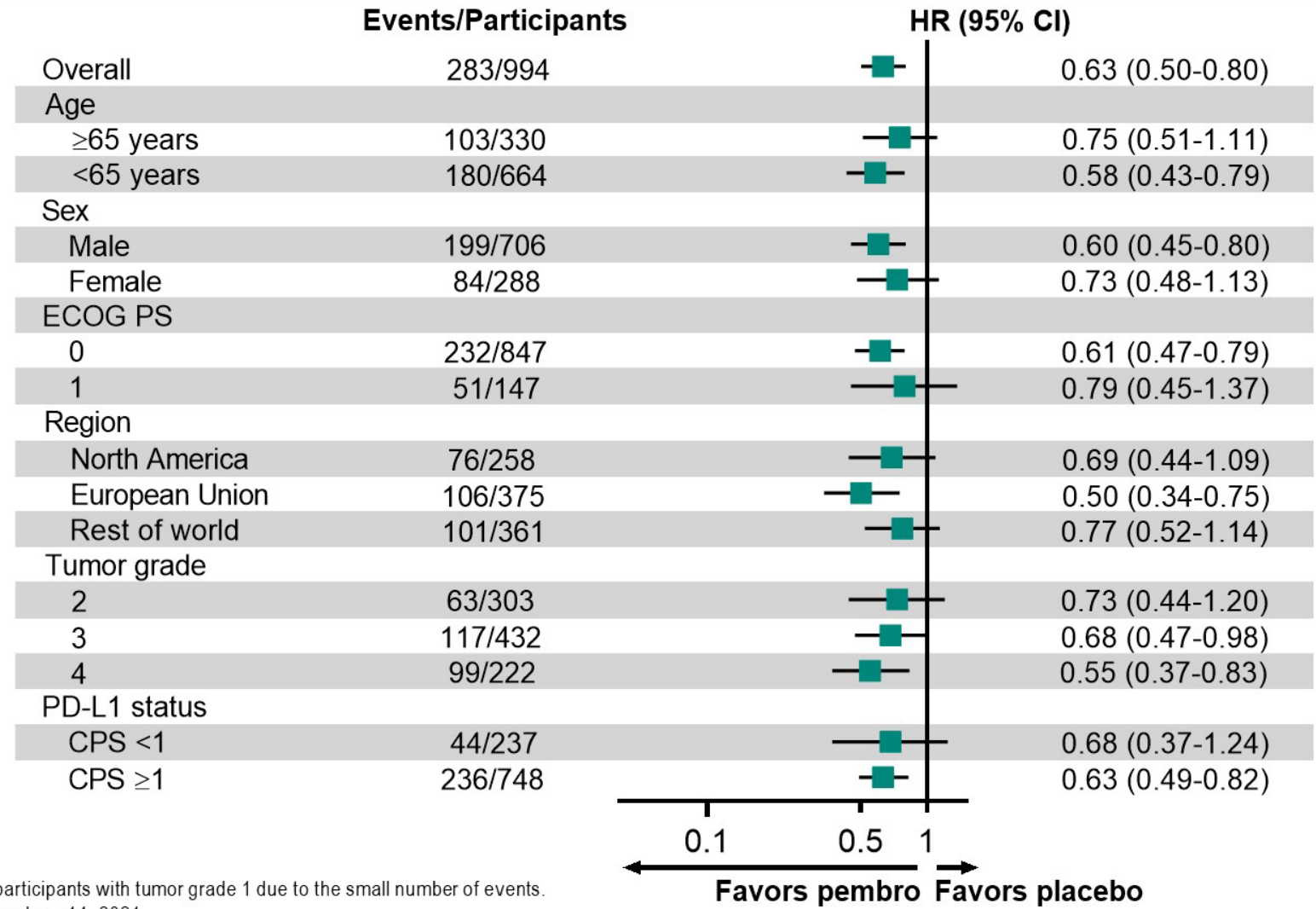
DFS in Key Subgroups



Subgroup analysis was not performed for participants with tumor grade 1 due to the small number of events.
DFS, disease-free survival. Data cutoff date: June 14, 2021.

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Key Secondary Endpoint: OS, ITT Population

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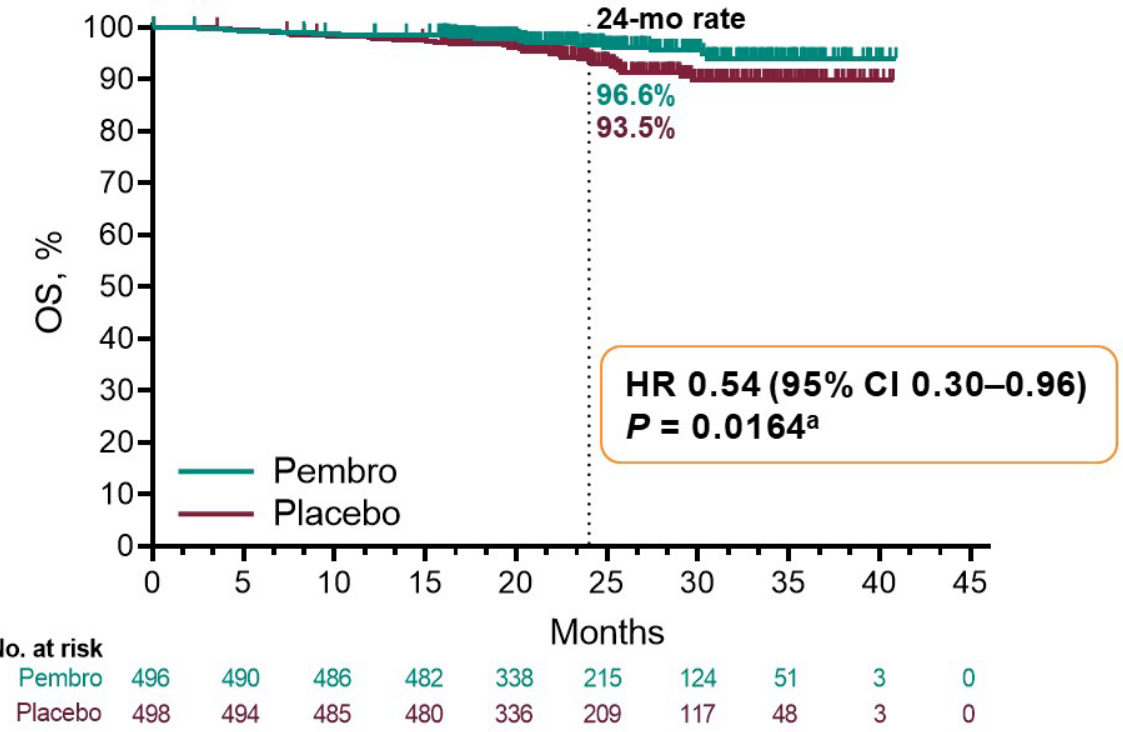
Primary Analysis: 24.1 mo Follow-Up

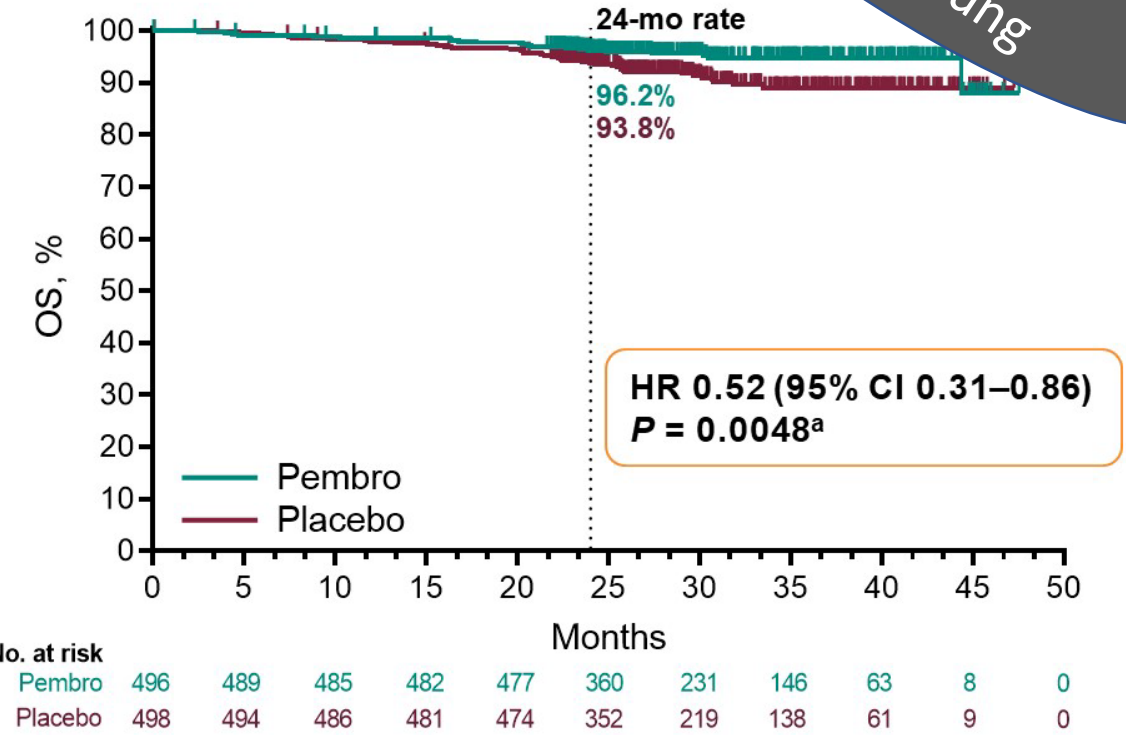


No. at risk

Pembro	496	490	486	482	338	215	124	51	3	0
Placebo	498	494	485	480	336	209	117	48	3	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	18	NR (NR–NR)
Placebo	33	NR (NR–NR)

Updated Analysis: 30.1 mo Follo



No. at risk

Pembro	496	489	485	482	477	360	231	146	63	8	0
Placebo	498	494	486	481	474	352	219	138	61	9	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	23	NR (NR–NR)
Placebo	43	NR (NR–NR)

[a]Did not cross prespecified p-value boundary for statistical significance.
ITT population included all randomized participants. NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

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Summary of Safety Results, As-Treated Population

Participants with ≥1 AE, n (%)	Primary Analysis (24.1 mo)		Updated Analysis (30.1 mo)	
	Pembro Arm (N = 488)	Placebo Arm (N = 496)	Pembro Arm (N = 488)	Placebo Arm (N = 496)
All-cause AEs	470 (96.3%)	452 (91.1%)	470 (96.3%)	453 (91.3%)
Grade 3–5	158 (32.4%)	88 (17.7%)	157 (32.2%)	88 (17.7%)
Led to treatment discontinuation	101 (20.7%)	10 (2.0%)	103 (21.1%)	11 (2.2%)
Led to death	2 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.2%)
Serious all-cause AEs[a]	100 (20.5%)	56 (11.3%)	101 (20.7%)	57 (11.5%)
Led to treatment discontinuation	49 (10.0%)	5 (1.0%)	49 (10.0%)	5 (1.0%)
Treatment-related AEs	386 (79.1%)	265 (53.4%)	386 (79.1%)	265 (53.4%)
Grade 3–4	92 (18.9%)	6 (1.2%)	91 (18.6%)	6 (1.2%)
Led to treatment discontinuation	86 (17.6%)	3 (0.6%)	89 (18.2%)	4 (0.8%)
Led to death	0	0	0	0
Immune-mediated AEs[b]	169 (34.6%)	29 (5.8%)	170 (34.8%)	29 (5.8%)
Grade 3–4	42 (8.6%)	3 (0.6%)	43 (8.8%)	3 (0.6%)
High-dose (≥40 mg/day) systemic corticosteroid treatment for AEs prespecified to be immune-mediated, n (%)	36 (7.4%)	3 (0.6%)	37 (7.6%)	3 (0.6%)

[a]Serious AEs were AEs that were life-threatening, required hospitalization, resulted in death or persistent/significant disability/incapacity, or were judged as serious per investigator. [b]Based on a prespecified list of terms included regardless of attribution to study treatment by investigator. No deaths due to immune-mediated AEs occurred.
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.
Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

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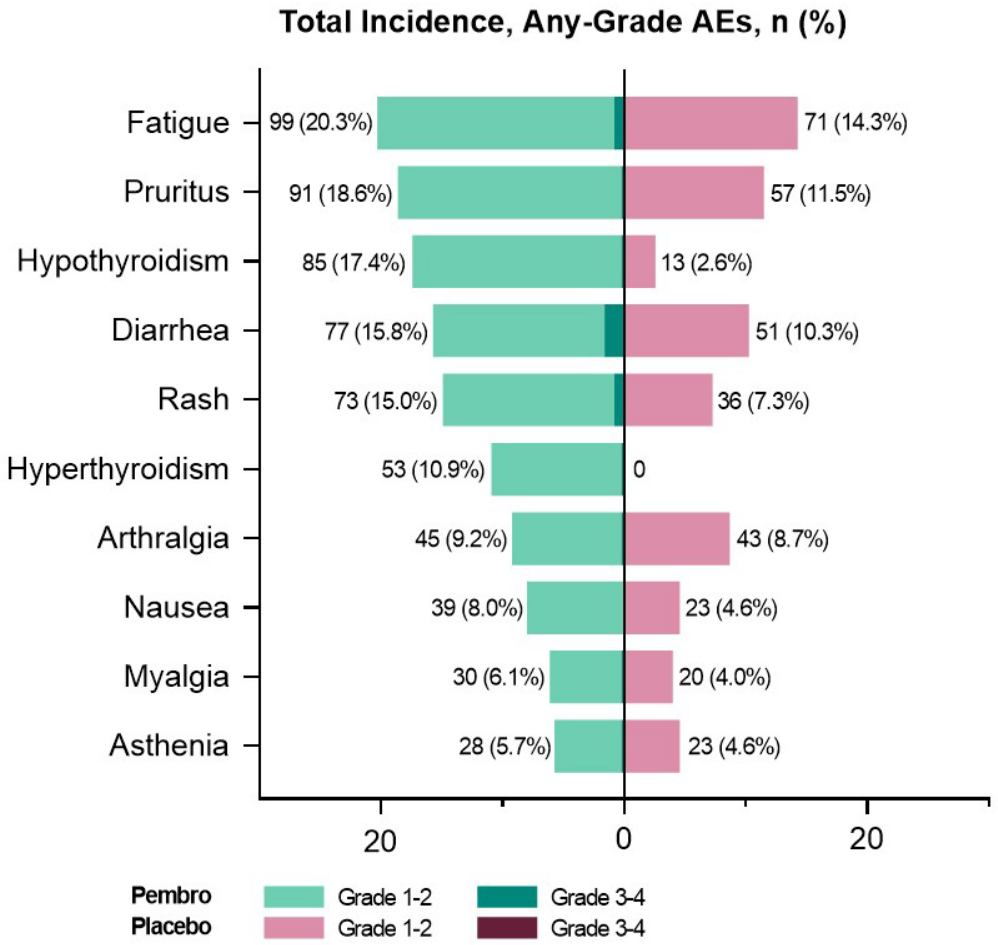
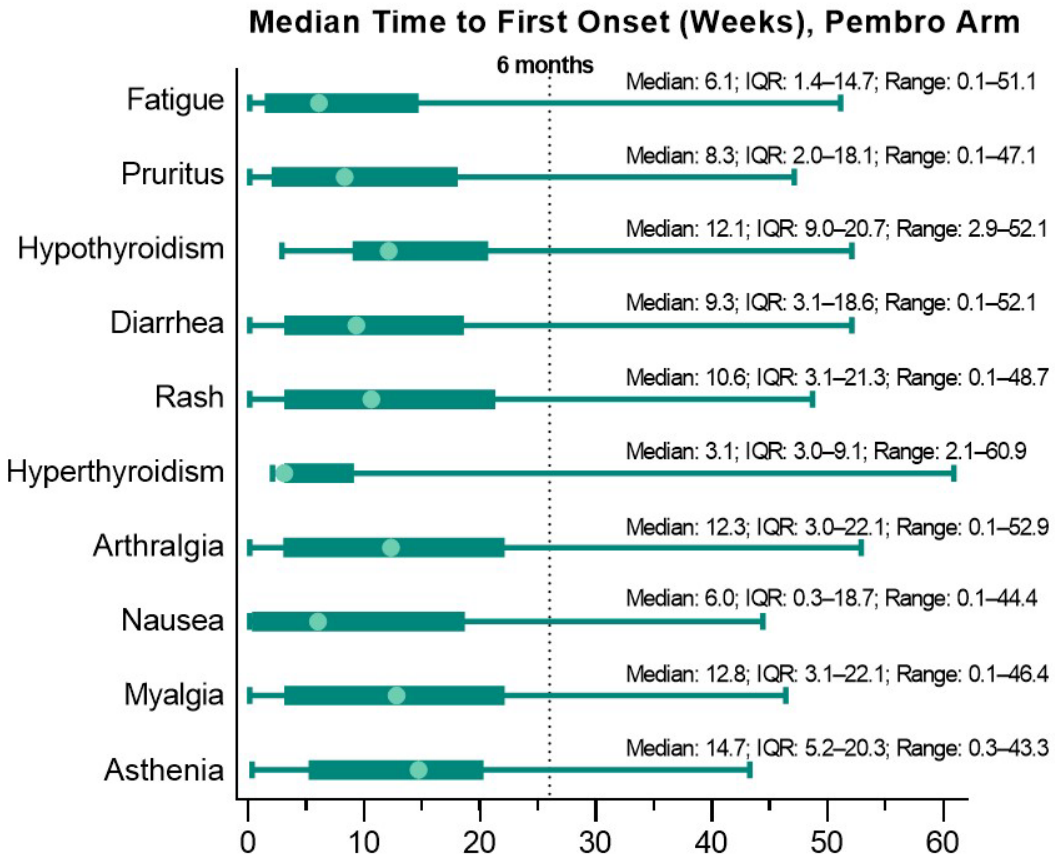
Treatment-Related AEs with Incidence ≥5%, As-Treated Population





AE, adverse event.
As-treated population included all participants who received ≥1 dose of study treatment. Data cutoff date: June 14, 2021.

01/2022
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Key Se

MERCK

November 1, 2023 6:30 am ET

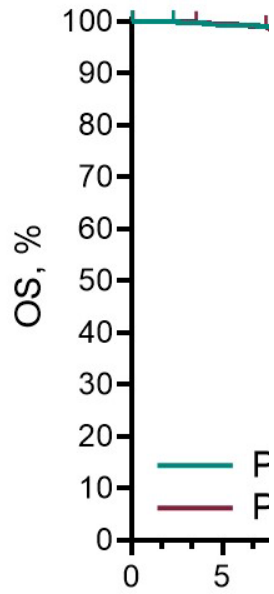
KEYTRUDA is the first therapy to show a statistically significant improvement in OS as adjuvant therapy in patients with RCC at a higher risk of recurrence following nephrectomy

New OS results build on the significant disease-free survival benefit previously reported from the KEYNOTE-564 trial

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced that the Phase 3 KEYNOTE-564 trial evaluating KEYTRUDA, Merck's anti-PD-1 therapy, met its key secondary endpoint of overall survival (OS), 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. At a pre-specified interim analysis review conducted by an independent Data Monitoring Committee, KEYTRUDA demonstrated a statistically significant and clinically meaningful improvement in OS compared to placebo. The safety profile of KEYTRUDA was consistent with that observed in previously reported studies; no new safety signals were observed. Results will be presented at an upcoming medical meeting and submitted to regulatory authorities. This is the second study of KEYTRUDA in an earlier stage of cancer to demonstrate an overall survival benefit, following the recent presentation of OS data in earlier stages (stages II, IIIA or IIIB) of non-small cell lung cancer from KEYNOTE-671 at the European Society for Medical Oncology (ESMO) Congress 2023.

"As we continue to evaluate the potential of KEYTRUDA in earlier stages of disease across multiple types of cancer, we hope to reduce disease recurrence and ultimately, improve overall survival outcomes," said Dr. Marjorie Green, senior vice president and head of late-stage oncology, global clinical development, Merck Research Laboratories. "These new results from KEYNOTE-564 are notable and mark the first time a therapy has demonstrated a statistically significant survival benefit compared to placebo in patients with RCC at a higher risk of recurrence following surgery, building on the positive disease-free survival findings from this study that led to approvals around the world for this KEYTRUDA-based regimen."

As previously reported, at an earlier pre-specified interim analysis with a median follow-up of 23.9 months, KEYNOTE-564 met its primary endpoint of disease-free survival (DFS), reducing the risk of disease recurrence or death by 32% (HR=0.68 [95% CI, 0.53-0.87]; p=0.0010) compared to placebo. These DFS results, which were first presented at the



No. at risk

Pembro	496	490
Placebo	498	494

	P
Pembro	
Placebo	

.1 mo Follo

no rate

%

%

R 0.52 (95% CI 0.31–0.86)

= 0.0048[a]

30 35 40 45 50

S

	231	146	63	8	0
	219	138	61	9	0

Median, mo (95% CI)
NR (NR–NR)
NR (NR–NR)

[a]Did not cross prespecified p-value bo

ITT population included all randomized participants. NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

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Aber…

PARIS 2022 ESMO congress

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 Spiridigliozzi,[15] Aleksander Chudnovsky,[15] Axel Bex[16]

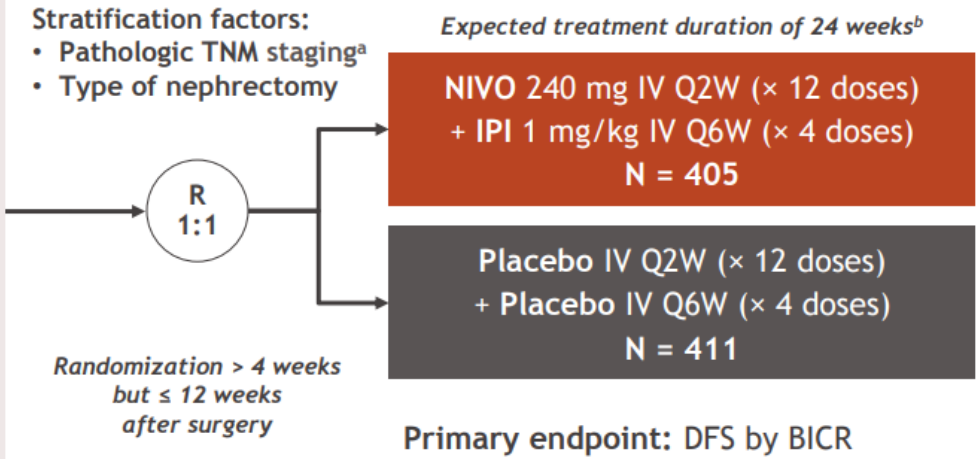
[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]West-German Cancer Center Essen, University Hospital Essen, Essen, Germany; [3]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [4]Prof. Franciszek Łukaszczyk Oncology Centre, Bydgoszcz, Poland; …spital of Parma, University of Parma, Parma, Italy; …ospital, Herston, QLD, Australia; [9]Fudan University [11]CHUM - Centre Hospitalier de l'Université de Montréal, …r Center, Buffalo, NY, USA; [14]University of California, …ncer Institute, Amsterdam, the Netherlands

Study design (Part A)

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



Primary endpoint: DFS by BICR

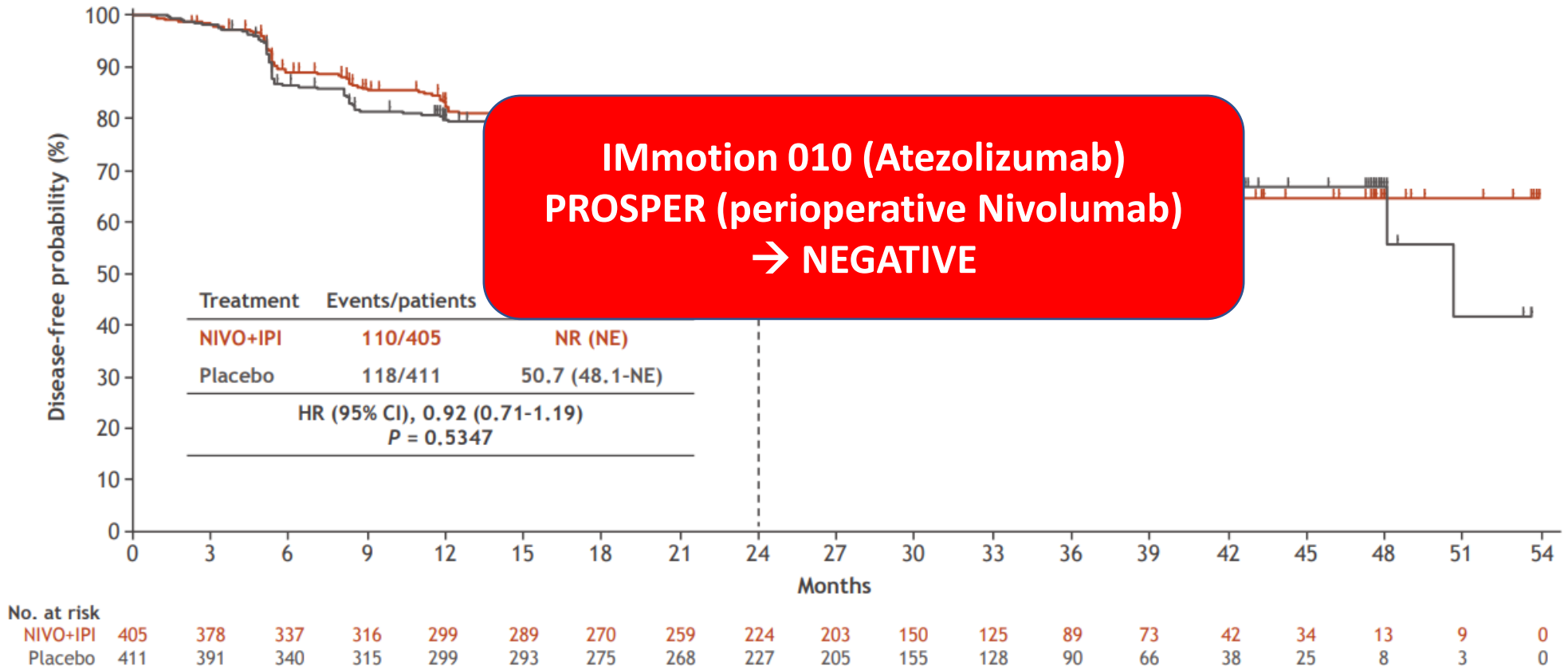
Secondary endpoints: OS and safety

Motzer ESMO 2022

DFS

CheckMate 91

Primary endpoint: disease-free survival per BICR



IMmotion 010 (Atezolizumab)
PROSPER (perioperative Nivolumab)
→ NEGATIVE

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).

Motzer ESMO 2022 et al., Allaf et al. ESMO 2022, Bex et al. ESMO 2022

Adjuvante Therapie, wo stehen wir aktuell?

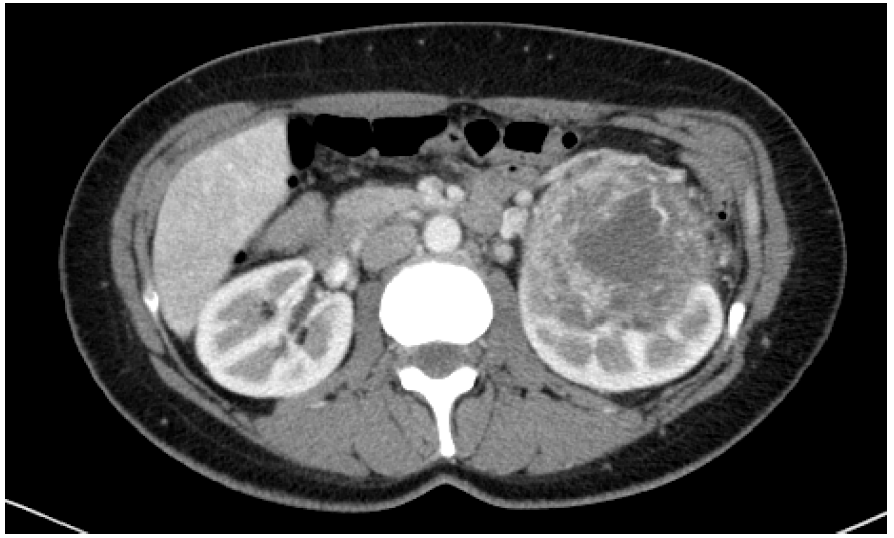
- Eine positive (KN 564) und drei negative adjuvante Studien
- OS signifikant verlängert - positive Pressemitteilung 11/2023

Mögliche Ursachen für die negativen Studien:

- Substanzen (PD1 vs PD-L1), Studienpopulation (M1/M0)
- Unterschiedliche Studien-Design (PROSPER, perioperative setting)
- Mono Therapiearm (Arm B, Nivo mono) der CM 914 – negative Pressemitteilung
- Weiterhin fehlende Biomarker
- TOXIZITÄT!

Patientenfälle

Weiblich, 47a



St.p. **schmerzlose Makrohämaturie**, 11/2017
Sono Niere: 8,2-9,3cm RF mittleres/caudales Nierendrittel li
Keine Komorbiditäten, keine Dauermedikation

CT Staging
Thorax: Im rechten apicalen Oberlappen dorsal, subpleural gelegen findet sich eine **8 mm** große Verdichtung. Eine weitere ist im linken Unterlappen dorsal, subpleural gelegen mit **9 mm**.
Daneben finden sich **mehrere bis etwa 4 mm** im Querdurchmesser große Verdichtungen in beiden Lungen.

Abdomen:
9 cm großes Hypernephrom links mit pathologisch vergrößerten Lymphknoten im Nierenhilus und fraglicher Infiltration in den angrenzenden Dünndarmschlingen.
Unter Annahme eines RCC: rTNM: T4, N1, M1?

Weiblich, 47a

• **Transperitoneale Tumornephrektomie**, Mesenterialresektion und Lymphadenektomie am 05.12.2017 (Urologie, WSP); Histo: 9cm, klarzellig bis klarzellig-eosinophiles Nierenzellkarzinom, Durchbruch durch [illegible]la fibrosa, Tumoreinbruch in einen größeren Venenast

Stadium pT3a, L0, V2, pN0 (0/8), G3 nach ISUP

Adjuvant IO?

→ Leibovich Score: intermediate risk (5 Pkte)

Keynote – 564, prespecified 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 et al NEJM 2021

Keynote - 564, DFS subgroups

The forest plot below demonstrates subgroup analysis of DFS:

A

	Events/N (%)	HR (95% CI)	24-mo rate, %	
			Pembrolizumab	Placebo
ITT[2]	283/994 (28.5)	0.63 (0.50-0.80)	78.3	67.3
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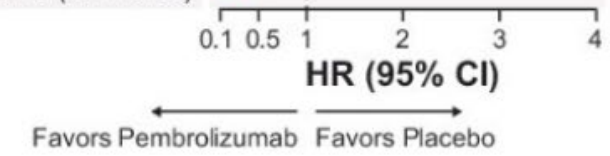
AJCC stage 2[a]	19/41 (46.3)	0.74 (0.30-1.83)	57.3	47.4
AJCC stage 3	227/870 (26.1)	0.67 (0.52-0.88)	79.9	70.7
AJCC stage 4	37/82 (45.1)	0.37 (0.19-0.74)	72.4	41.5
T2, G4, N0, M0 or T3, G1-2, N0, M0	69/328 (21.0)	0.79 (0.49-1.27)	83.5	78.3
T3, G3-4, N0, M0	145/523 (27.7)	0.63 (0.45-0.88)	79.3	68.0
T4, N0, M0	9/22 (40.9)	0.63 (0.17-2.36)	63.6	54.5
N1, M0	34/54 (63.0)	0.57 (0.29-1.12)	42.8	27.4
M1 NED	26/58 (44.8)	0.28 (0.12-0.66)	78.4	37.9



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Adjuvante Therapie

- **Nivolumab/Ipilimumab adjuvant 01-09/2018** (CA209-914 Studie); vorzeitiger Abbruch nach 9/12 Zyklen bei Nachweis einer Lebermetastase
- CT-Thorax/Abdomen am 24.07.2018: neu aufgetretene 5,9 x 4,8 cm haltende Herdläsion im linken Leberlappen/Segment 3, dringend SBL-verdächtig; zu 4/2018 größenkonstante pulmonale RH

→**laparoskopisch assistierte atypische Leberresektion** der Segmente II+III **am 10.09.2018**; Histologie: Metastase des bekannten Nierenzellkarzinom

CT-Thorax/Abdomen am 29.01.2019: pulmonale Herde konstant, Leber frei

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Presentation number: LBA4

Study design (Part A)

N = 816

Key inclusion criteria[1]

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  - 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

R 1:1

Expected treatment duration of 24 weeks[b]

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

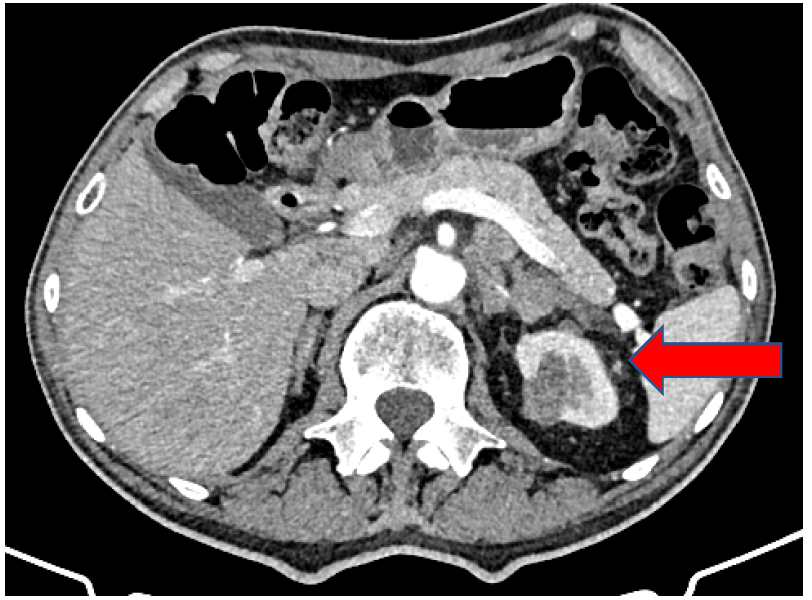
Placebo IV Q2W (× 12 doses) + **Placebo** IV Q6W (× 4 doses) **N = 411**

Primary endpoint: DFS by BICR

Secondary endpoints: OS and safety

Motzer ESMO 2022

Männlich, 80a



- Linksseitige Raumforderung
  Tumornephrektomie mit LA 2/2022

- Histologie: ccRCC mit Infiltration ins p[illegible] Fettgewebe,
  Nebennierenmetastase und ein Lymphkn[illegible]nerat
  TNM: **pT3a, L1, V0, pN1 (1/1), pM1; G3 (Fu[illegible]**

- Leibovich Score (7): high risk

- **Komorbiditäten:**
  St.p. TIA 07/21, ACI-stenosis dext.
  Hyperlipidämie, KHK
  Presbyakusis, St.p. Cholesteatoma bds., **ECOG 0**

Adjuvant IO?

Keynote – 564, prespecified risk categories

Intermediate-High Risk		High Risk		M1 NED
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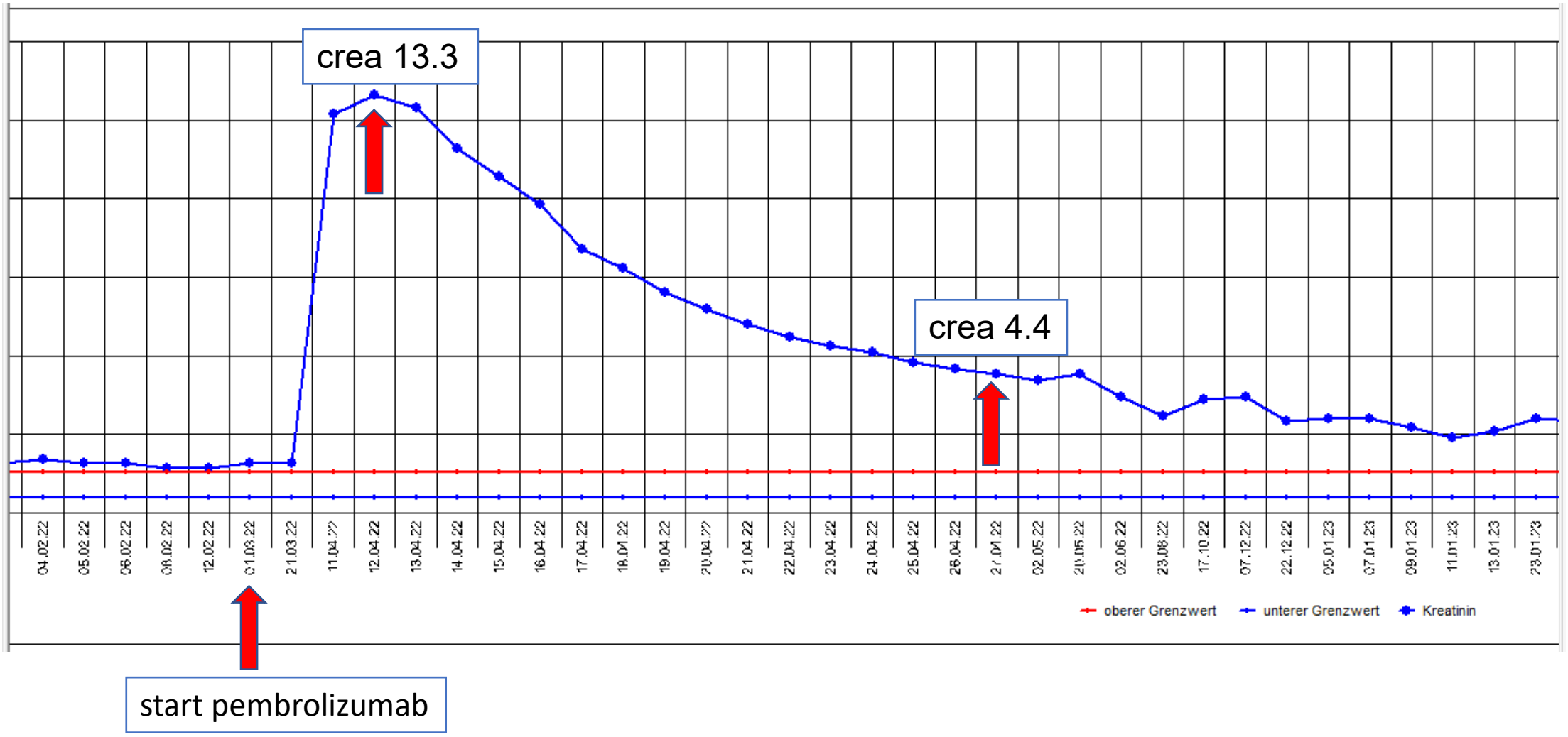
N0	N0	N0	N+	
M0	M0	M0	M0	

Choueiri et al NEJM 2021

ANV nach 2 Zyklen



IO assoziierte Nephritis, Grad IV

- **12.4.: acute renal failure: crea 13.3,** BUN 123,
  vBGA: pH 7.279, potassium 4.6, BE-5
- Urology consultation: no postrenal cause
- No nephritic sediment, autoimmune serology neg, reduced C3c (complement factor)
- Therapy: prednisolon 1mg/kg, Crea declined to 4.4, BUN 96

GUIDELINES

Rare immune-related toxicities

ICPi-related toxicity: Management of nephritis: **grade 3-4**

Renal injury occurs in around 1–4% of patients treated with ICPis, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate

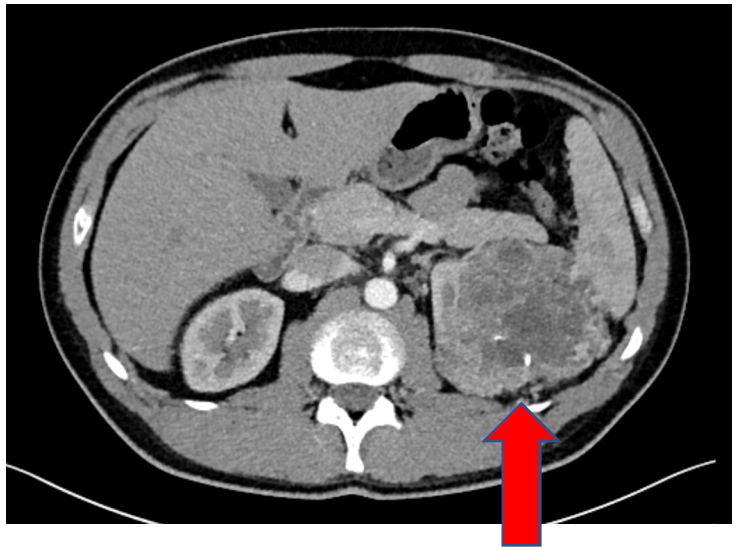
Attention needs to be paid to the patient's baseline creatinine, not just abnormal results per biochemistry ULN

Confounding diagnoses include dehydration, recent IV contrast, urinary tract infection, medications, hypotension or hypertension

Symptom Grade	Management escalation pathway	Assessment and Investigations
Grade 3: Creatinine > 3 x baseline or > 3–6 x ULN	Withhold ICPi; admit patient for monitoring and fluid balance; repeat creatinine every 24 hours; early discussion with nephrologist and need for biopsy; if worsening, initiate IV (methyl)prednisolone 1–2 mg/kg	As above for grade 3
Grade 4: Creatinine > 6 x ULN	As per grade 3; patient should be managed inhospital where renal replacement therapy is available	As above for grade 4

Haanen, Annals of Oncol 2022

Männlich, 42a



- Tumor linke Niere, kranial (7,5 x 8 x 7,5 cm)
- CT: keine weiteren Läsionen
- 3/2023: Nephrektomie und LA
- Histologie: ccRCC mit Infiltration ins perirenal[illegible]G1 (Fuhrman).
- TNM: **pT3a, pN0 (0/6), L0, V0, Pn0**.
- Leibovich Score: 4 , intermediate risk
- Komorbiditäten: keine, ECOG 0

Adjuvant IO?

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Choueiri et al NEJM 2021

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NO adjuvant IO

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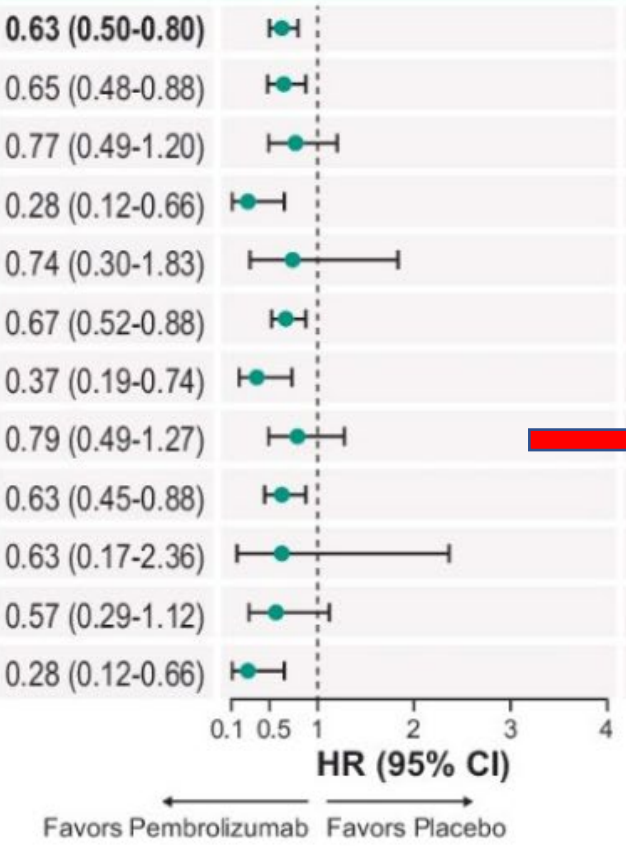

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Zusammenfassung

- Positive Phase III Studie mit Pembrolizumab mit signifikantem Benefit im DFS und OS
- Sorgfältige Patientenselektion vor adjuvanter IO-Therapie!
- Toxizität, akut aber auch verzögert, nicht unterschätzen

dora.niedersuess-beke@gesundheitsverbund.at

1. MEDIZINISCHE ABTEILUNG
Zentrum für Onkologie und Hämatologie
mit Ambulanz und Palliativstation

WCRI Wilhelminen Cancer Research Institute

VCC Vienna Cancer Center

Wiener Gesundheitsverbund
Klinik Ottakring

Für die Stadt Wien