COMPREHENSIVE CANCER CENTER VIENNA

KH Pharmazie 2022

MEDICAL UNIVERSITY OF VIENNA

Hot Topics in der Immunonkologie

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Univ.Klinik für Innere Medizin I &CCC, MUW

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Disclosure

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Ich habe keinen potenziellen Interessenkonflikt zu berichten.

x Ich habe folgende(n) potenzielle(n) Interessenskonflikt(e) zu berichten:

Art der Zugehörigkeit/Finanzielles Interesse:

Erhalt von Zuschüssen/Forschungsförderung: MERCK; MSD

Empfang von Honoraren oder Beratungsgebühren: MERCK,MSD,BMS;
ROCHE, Böhringer Ingelheim, Astra Zeneca, Accord, Sanofi, Novartis, Pfizer;
Amgen

Teilnahme an von einer Firma gesponsertem Sprecherbüro:

Aktionär:

Ehepartner/Partner:

Andere Unterstützung(en):

COMPREHENSIVE CANCER CENTER VIENNA

Hot Topics

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- Background
- Langzeitüberleben mit Immuntherapie im Stadium IV
- Langzeitüberleben mit Immuntherapie in Frühstadien
- Immuntherapie und Nebenwirkungen
- Immuntherapie bei Hämodialyse
- Organtransplantation und Immuntherapie

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Immunsystem

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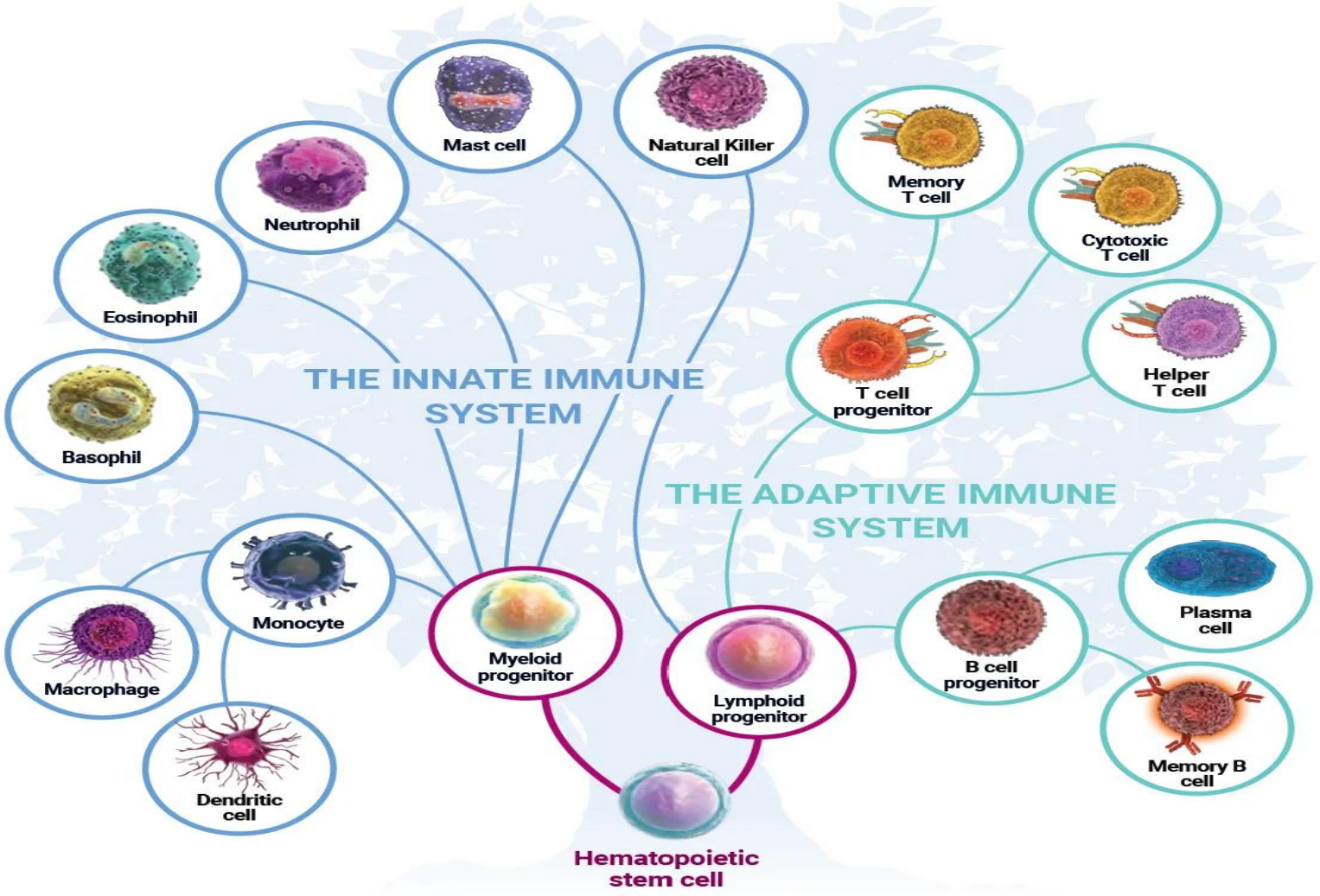

https://lab-a-porter.com/2019/12/cells-of-the-immune-system/

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Immunantwort

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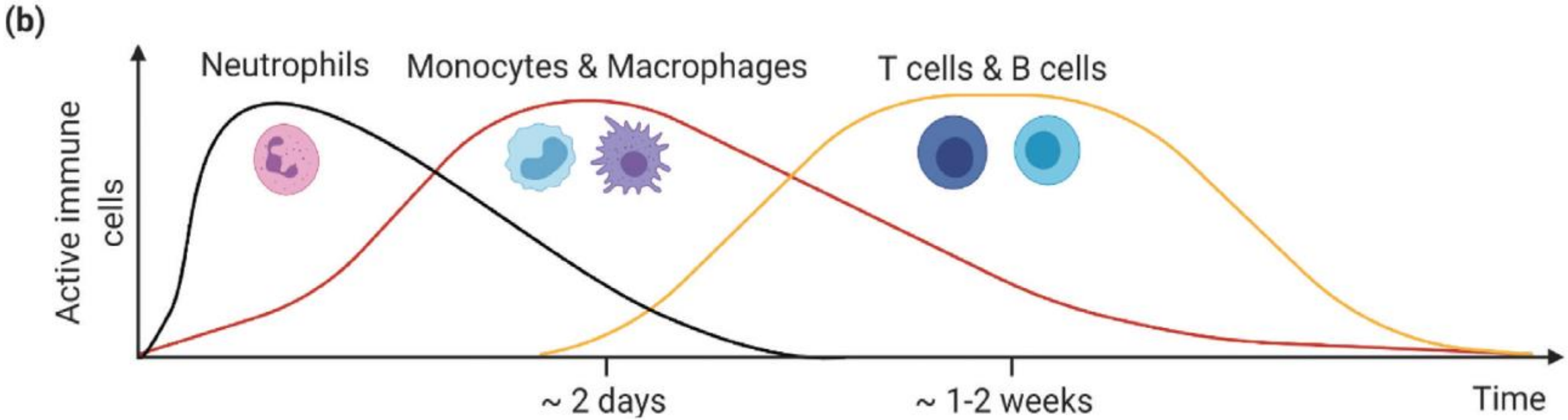

Zhang et al; Advanced Science 2021

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Dysfunktionale Immunantwort

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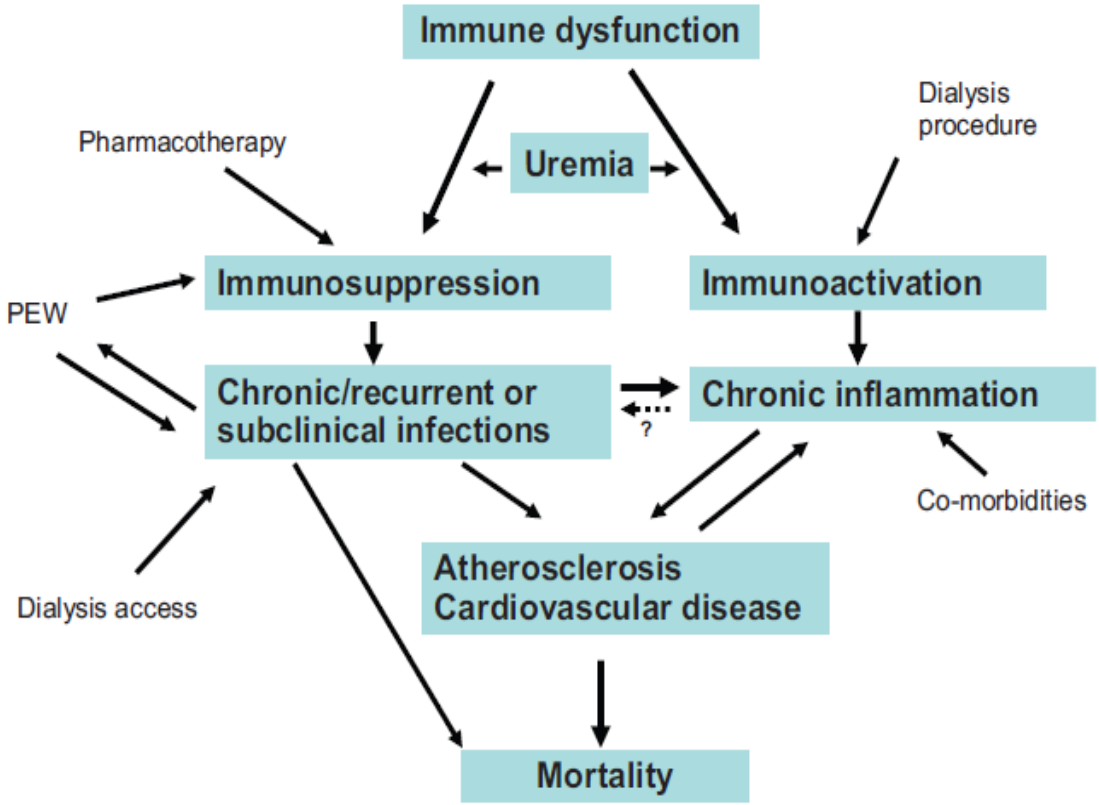

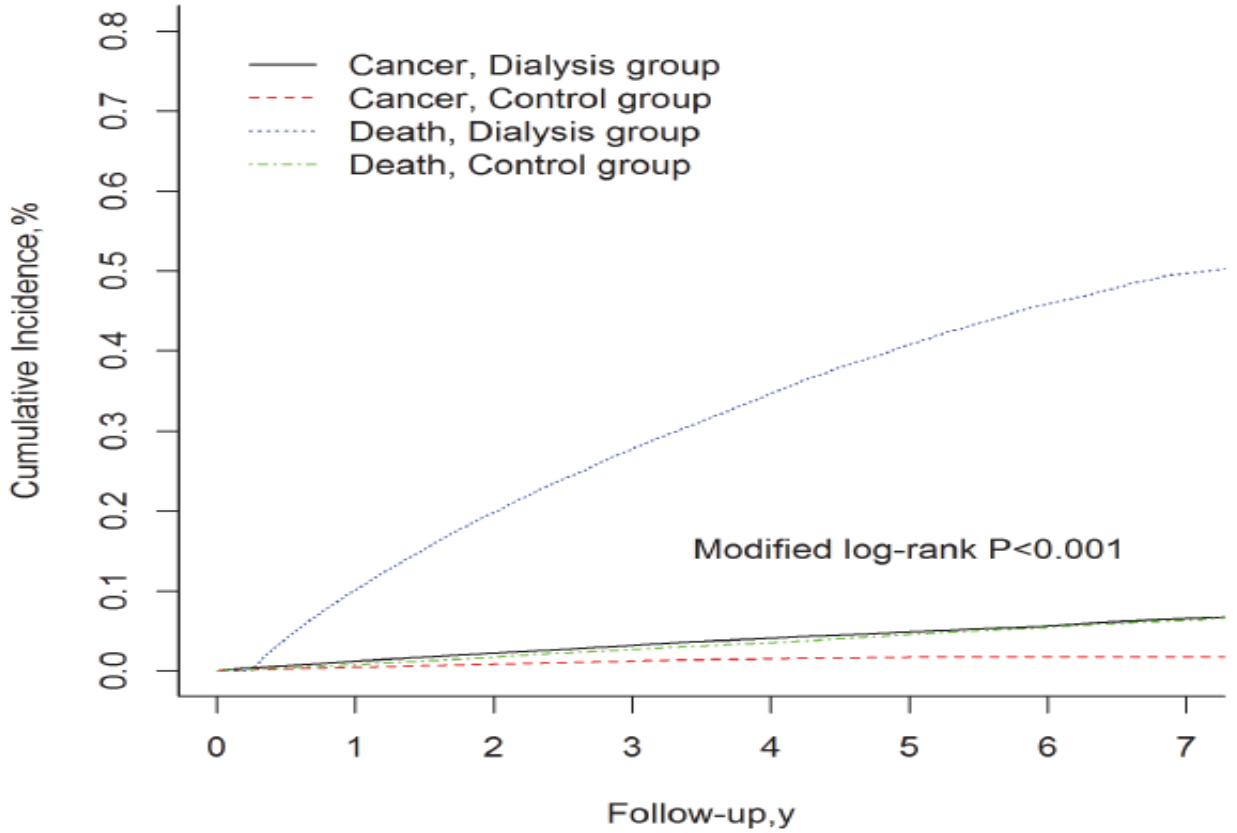

Kato et al; Clin J Am Soc 2008; Lin et al.; Plos One 2015

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Immunüberwachung

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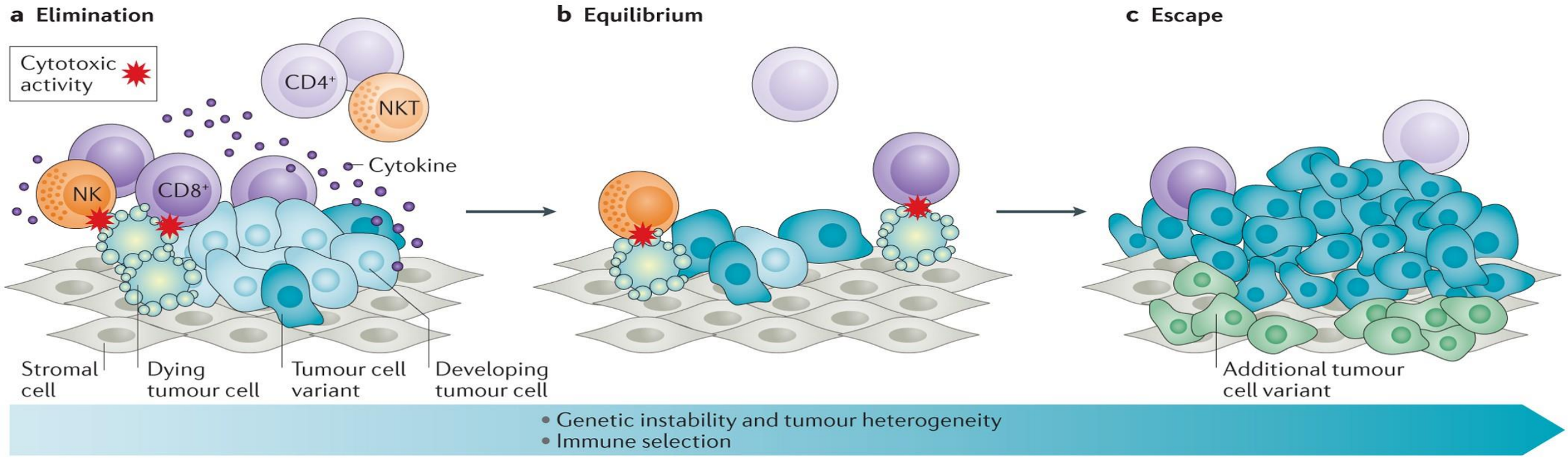

Sjoerd et al., Nature Reviews Cancer 2016

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Dysfunktionale Immunantwort und Cachexie

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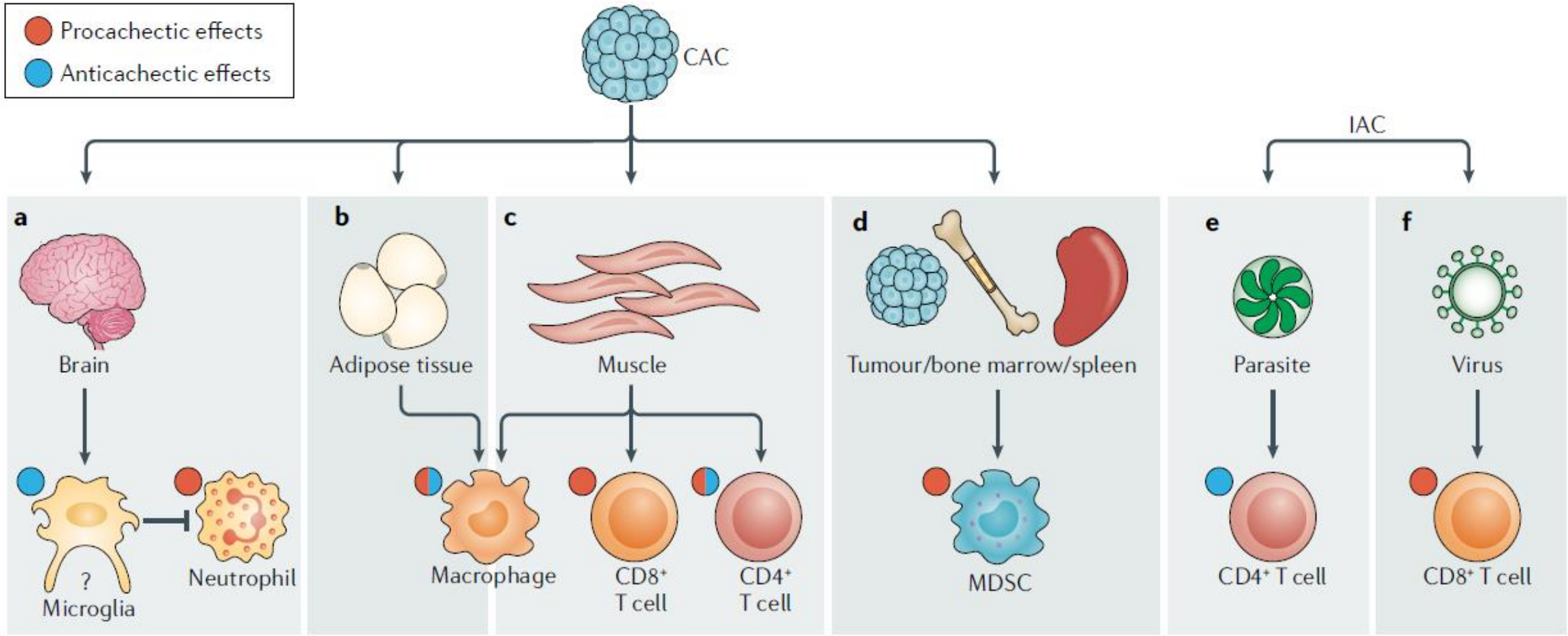

Baazim et al., Nature Reviews Immunology 2021

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Tumor Immune Microenvironment

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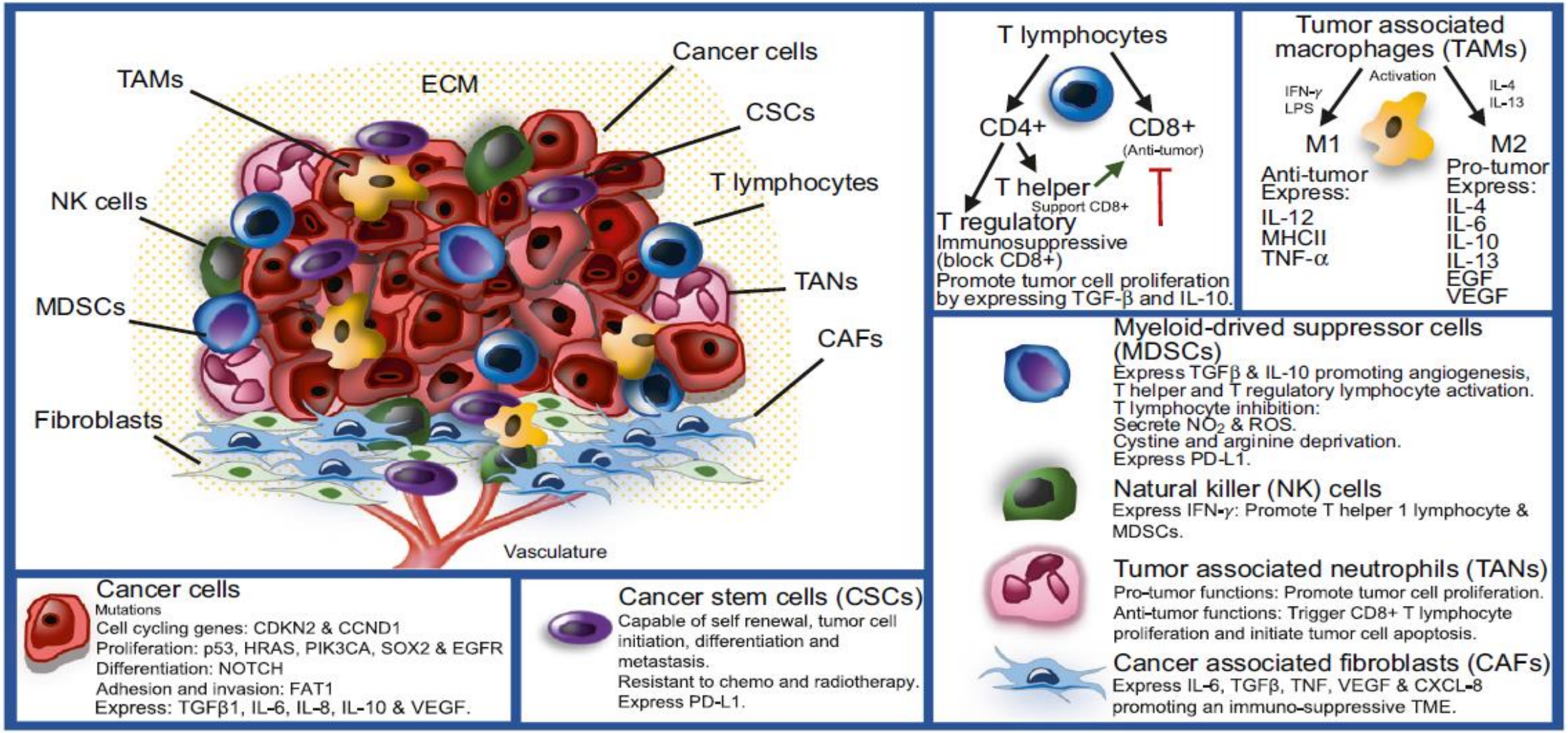

Elmusrati et al.; International Journal of Oral Science 2021

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„Single cell“ Analyse

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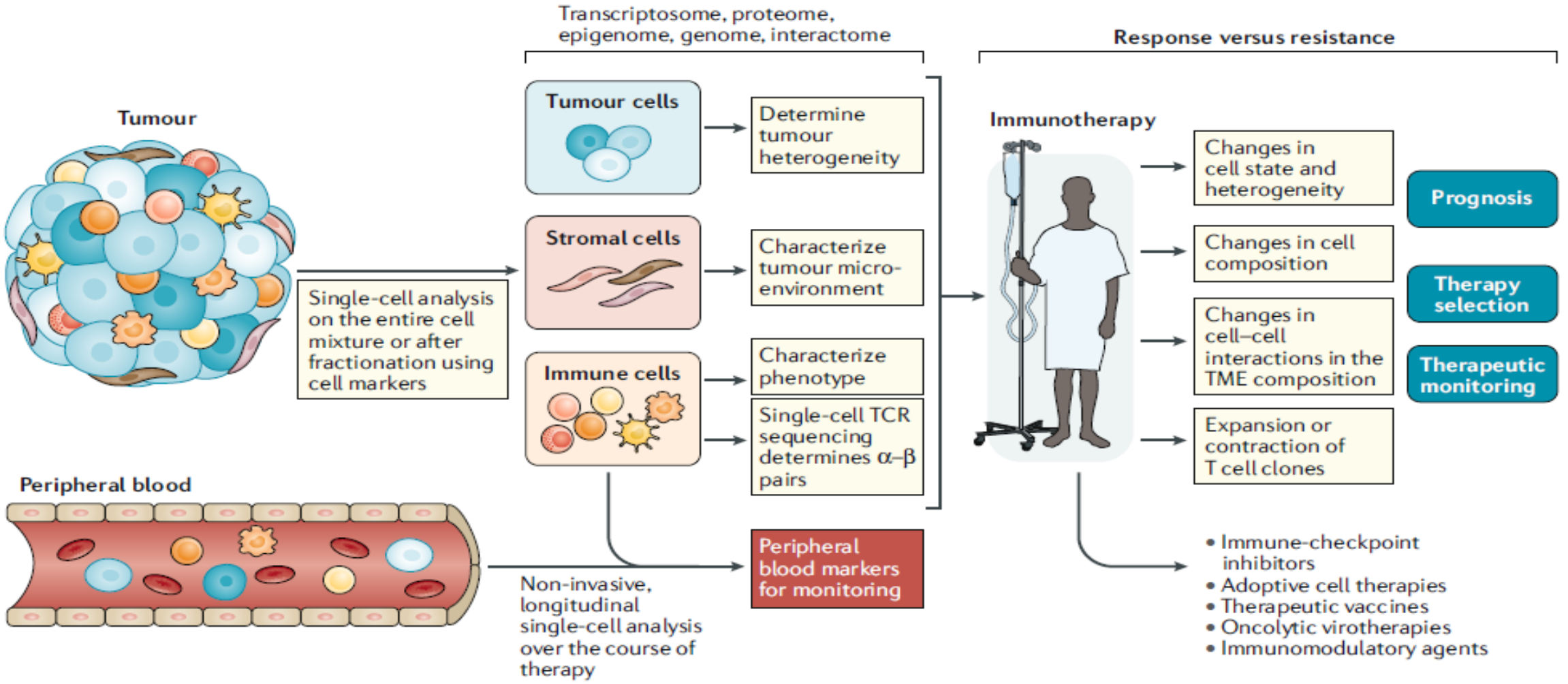

Gohil et al.; Nature Reviews Clinical Oncology 2021

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Single cell Analyse

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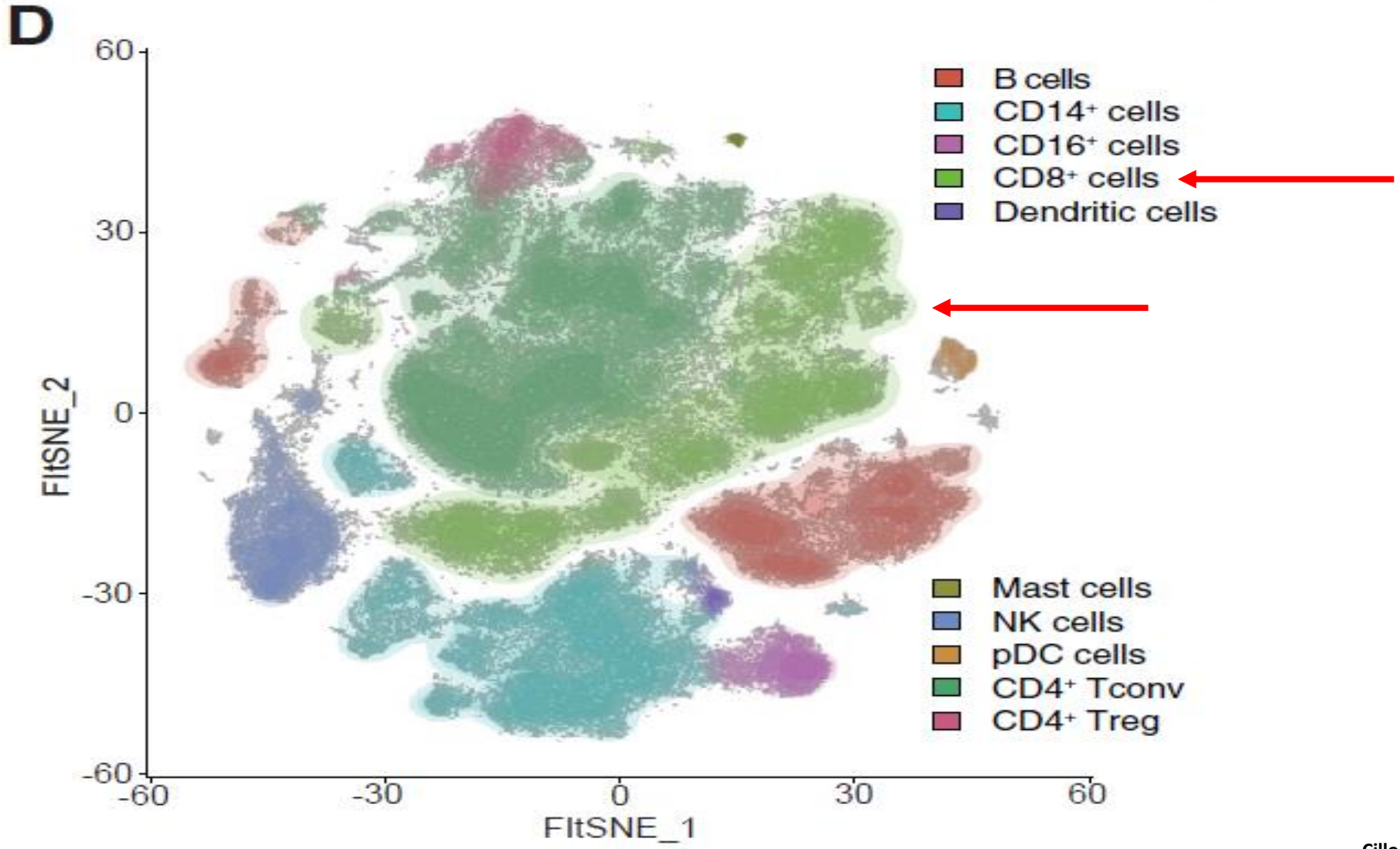

Cillo et al; Immunity 2020

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Immuntherapien

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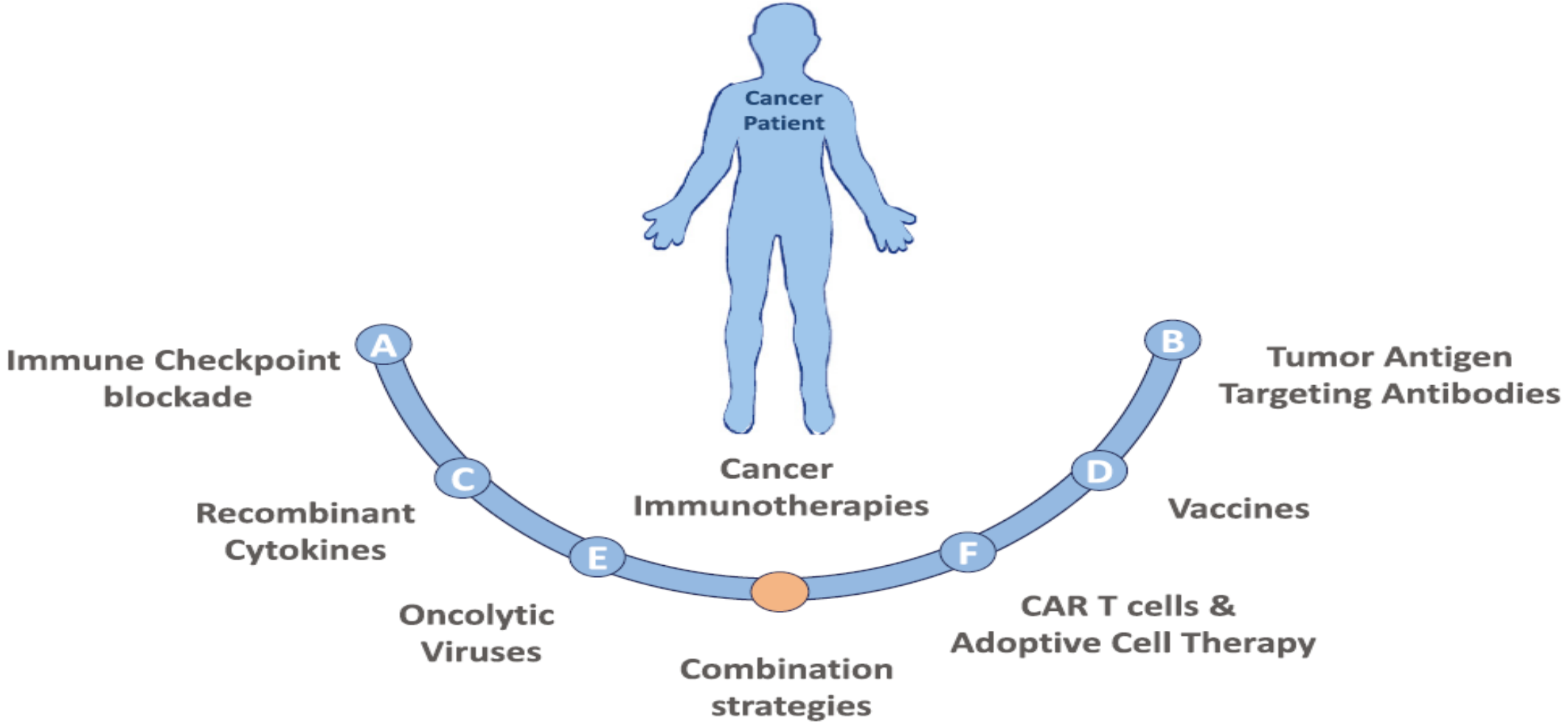

Shi et al.; Frontiers in Pharmacology 2021

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Immuntherapien

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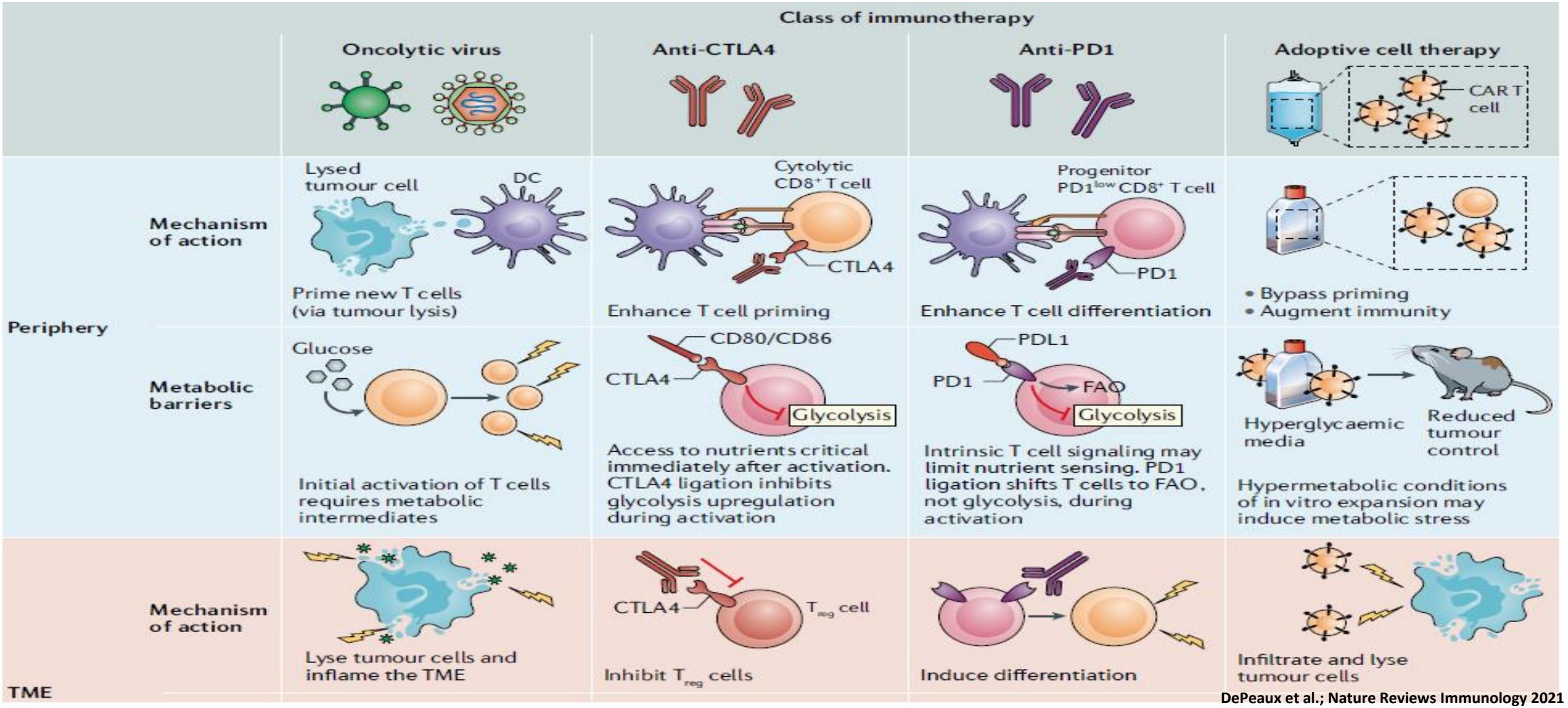

DePeaux et al.; Nature Reviews Immunology 2021

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Checkpointblockade

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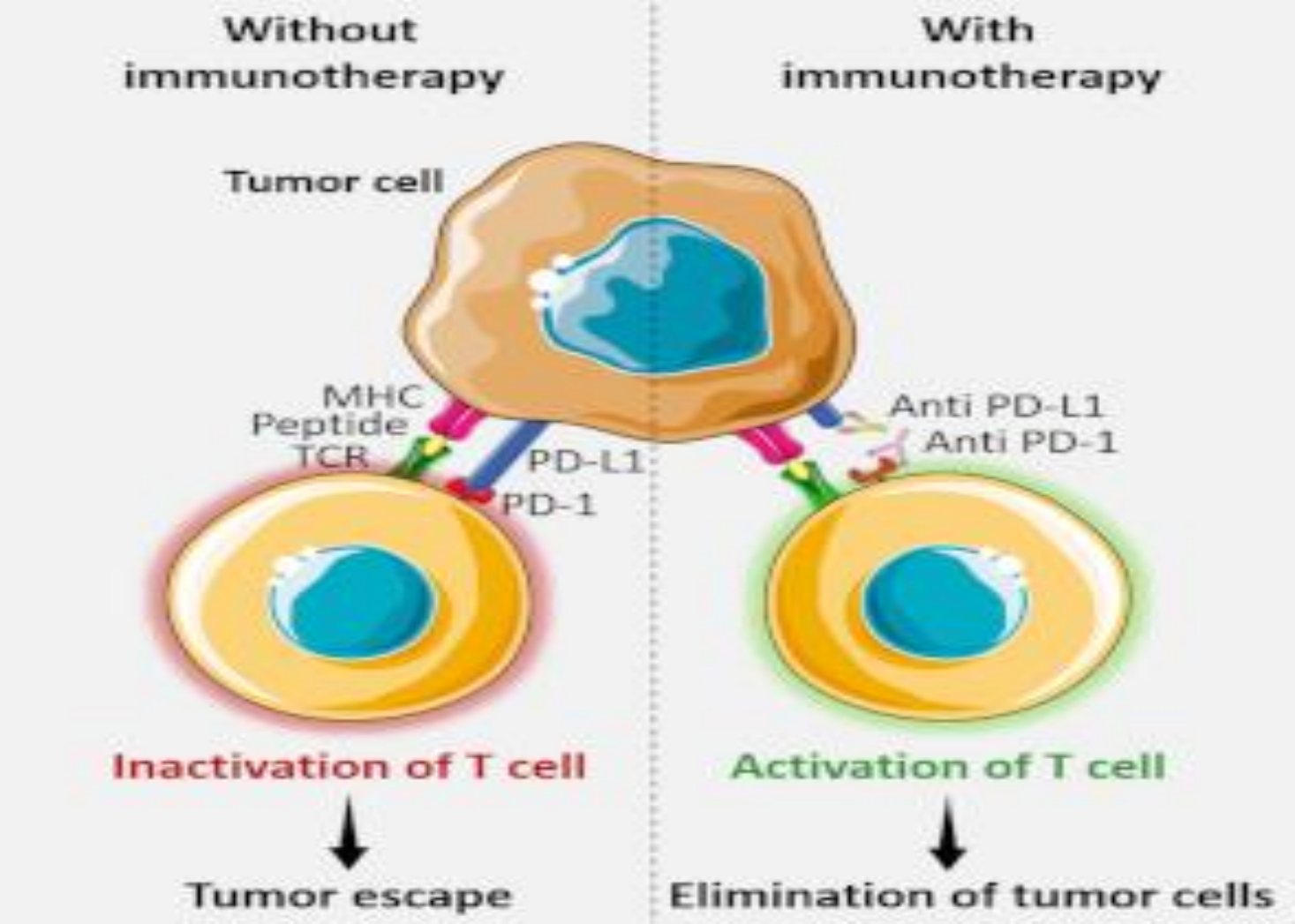

Zugelassen in Ö:

- Pembrolizumab
- Nivolumab
- Cemiplimab
- Atezolizumab
- Durvalumab
- Avelumab
- Dostarlimab

https://www.genoway.com/commentaries/comment-icp.htm

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Langzeitüberleben im palliativen Setting

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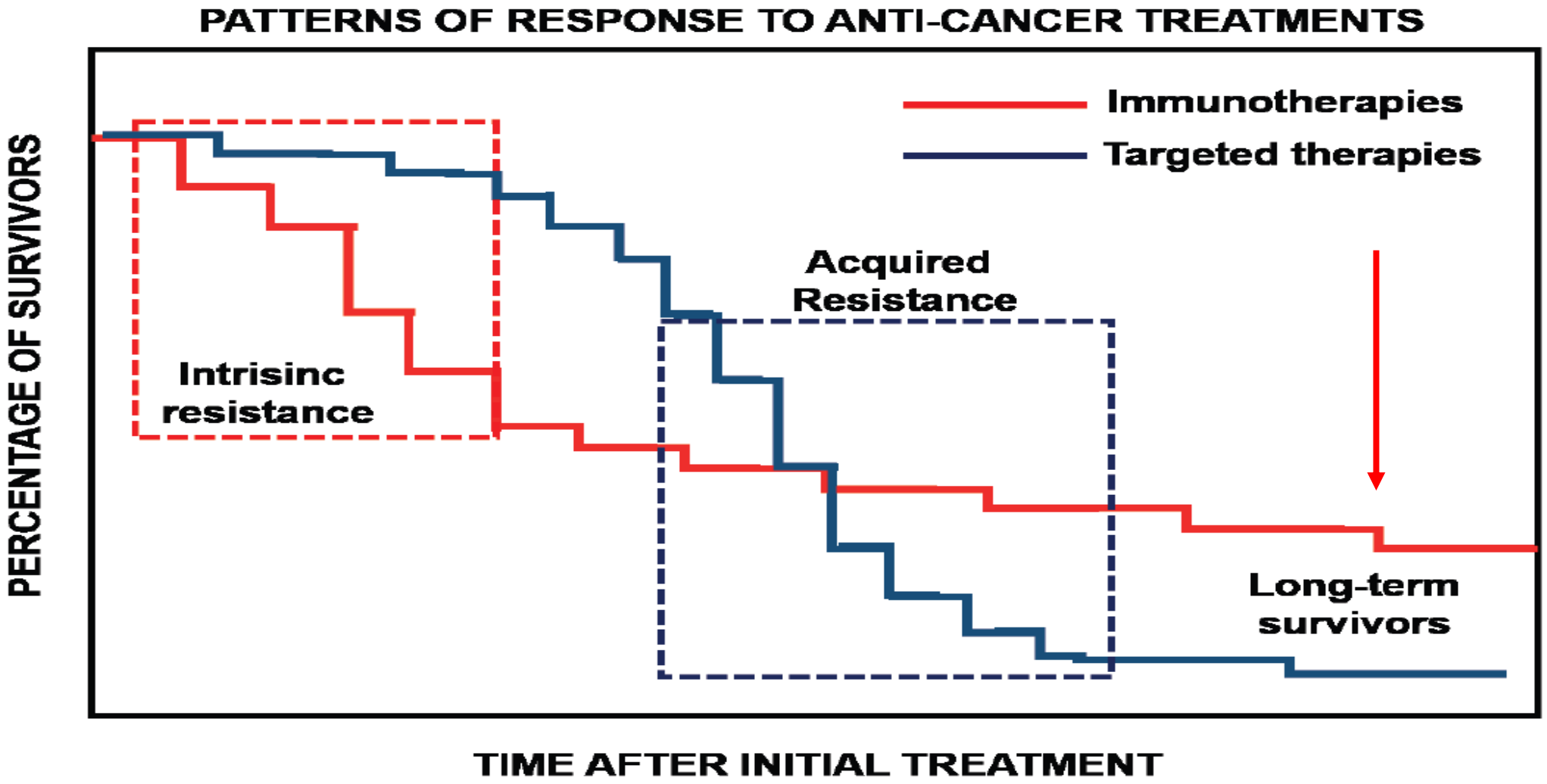

Arasanz et al.; Oncotarget 2017

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NSCLC met.: Entwicklung OS prä. IO

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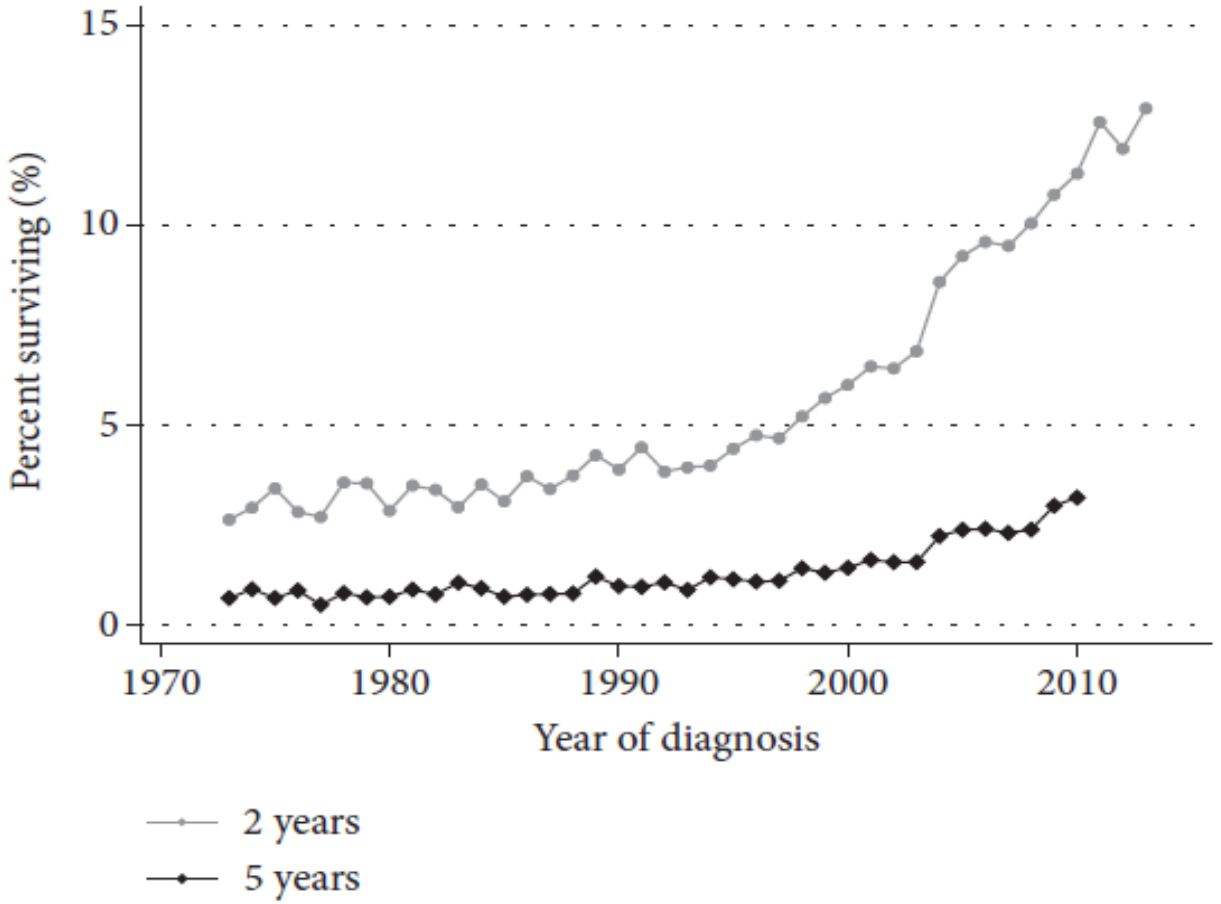
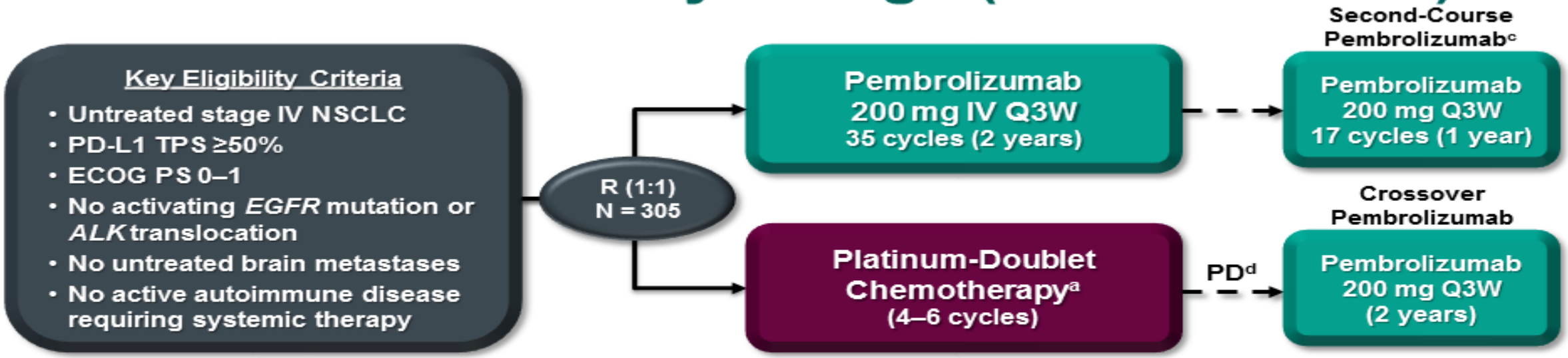


Bar et al.; Journal of Oncology 2021

Pembrolizumab 5 Jahres Update NSCLC

J Brahmer. ESMO 2020

KEYNOTE-024 Study Design (NCT02142738)



End Points

Primary:	PFS (RECIST v1.1 per blinded, independent, central review)
Key secondary:	OS
Secondary:	ORR, safety, PFS (RECIST v1.1 per investigator review)
Exploratory:	DOR

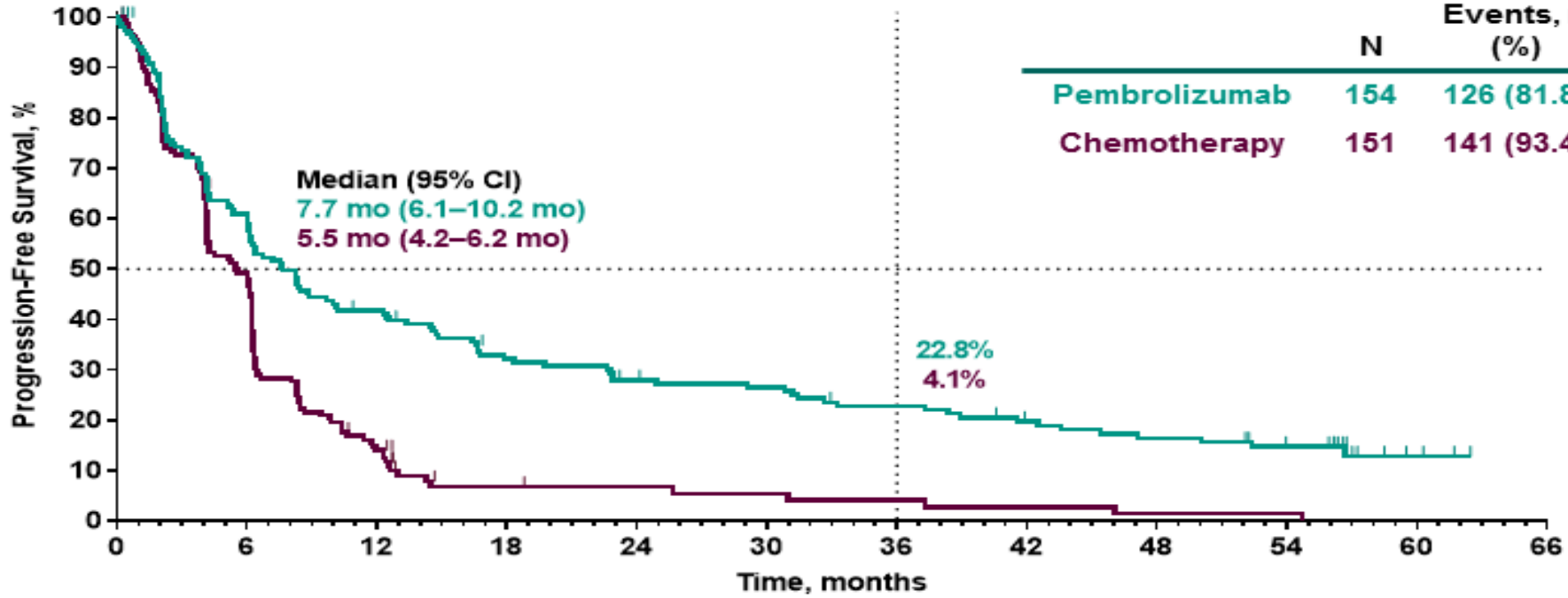
[a]Optional pemetrexed maintenance therapy for nonsquamous disease. [b]Permitted for nonsquamous disease only. [c]Patients randomized to pembrolizumab who completed 2 years of therapy or who stopped pembrolizumab after achieving CR and then had PD were eligible for a second course of pembrolizumab monotherapy. [d]Before the DMC recommendation and amendment 8, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis 2 data), patients were eligible for crossover when PD was confirmed by blinded, independent, central radiology review.

Brahmer; ESMO 2020

Pembrolizumab 5 Jahres PFS Update NSCLC

J Brahmer. ESMO 2020

Progression-Free Survival[a]
By RECIST v1.1 per Investigator Review[b]



	N	Events, n (%)	HR (95% CI)
Pembrolizumab	154	126 (81.8)	0.50 (0.39–0.65)
Chemotherapy	151	141 (93.4)	

No. at risk

Pembrolizumab	154	92	62	46	38	36	30	24	20	15	3	0
Chemotherapy	151	73	20	6	5	4	3	2	1	1	0	0

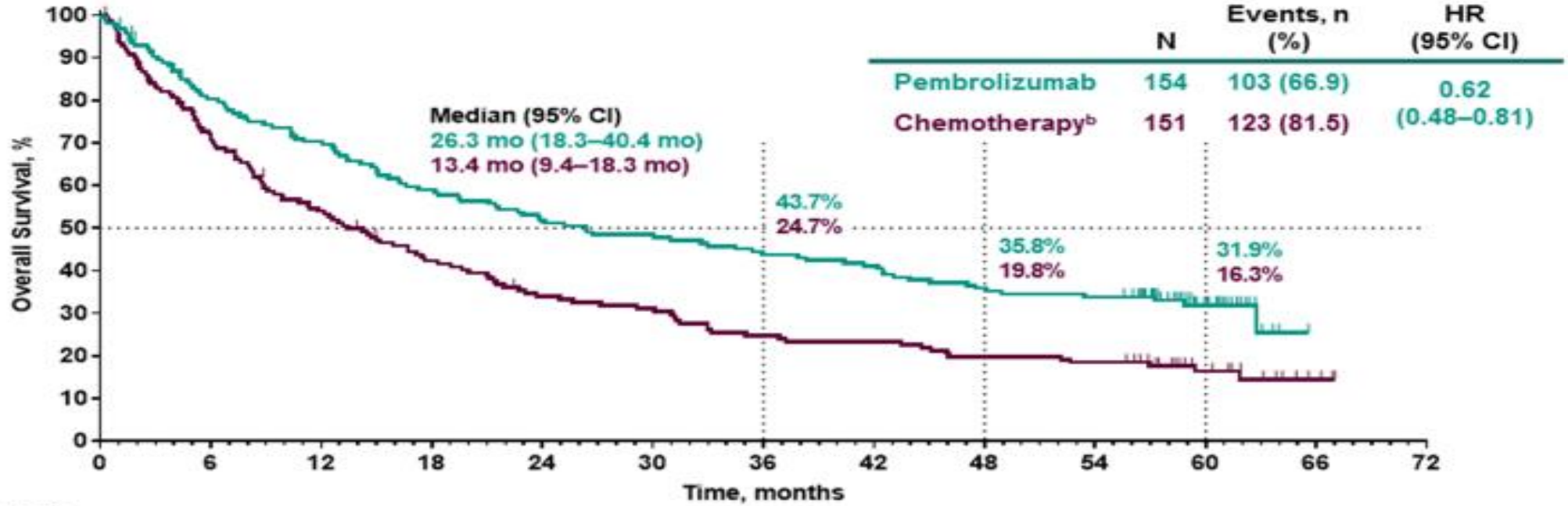
NR, not reached.
[a]ITT population. [b]Secondary endpoint; primary endpoint was PFS assessed per blinded, independent, central radiology review.
Data cutoff: June 1, 2020.

Brahmer; ESMO 2020

Pembrolizumab 5 Jahres PFS Update NSCLC

J Brahmer. ESMO 2020

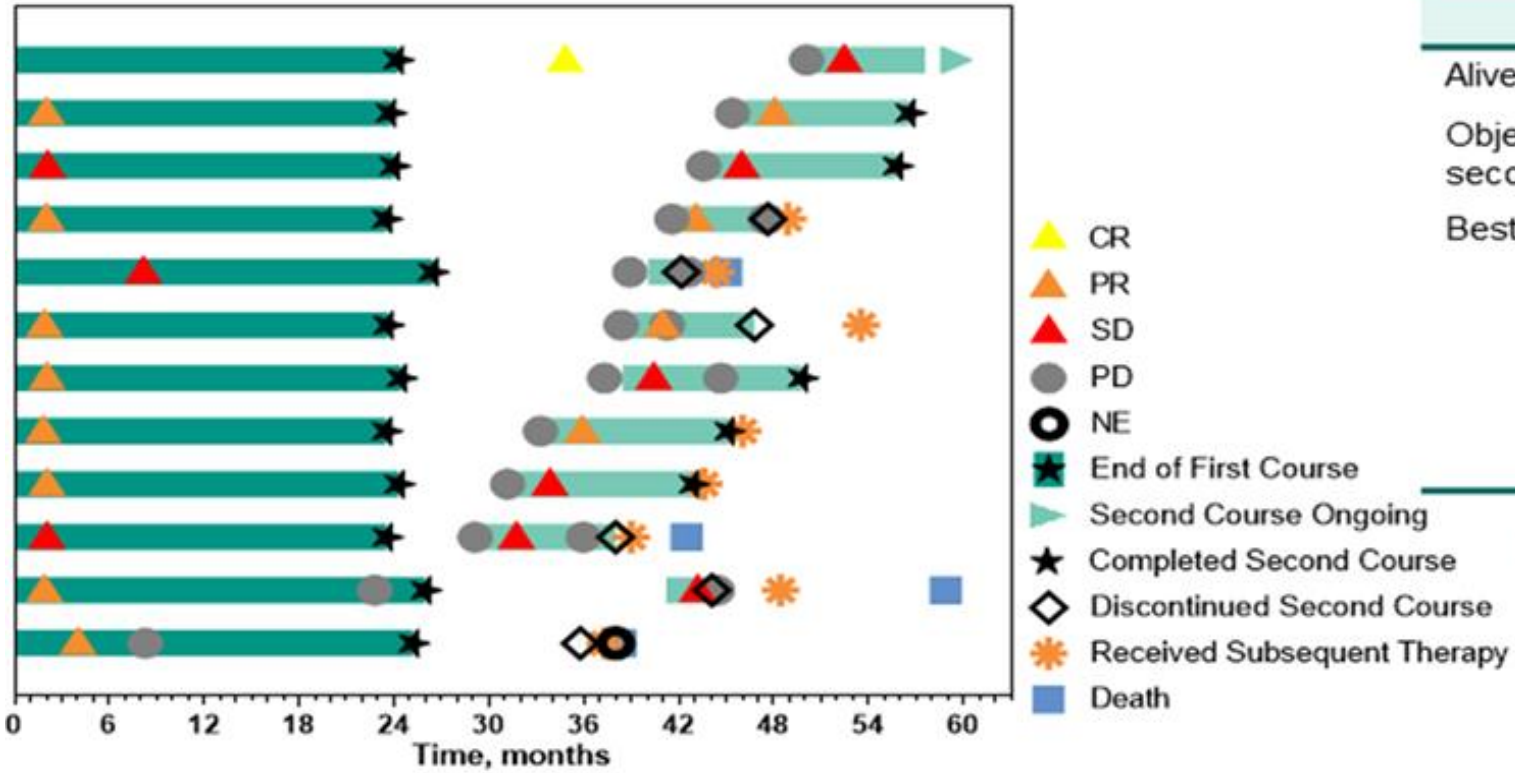
Overall Survival[a]



[a]ITT population.
[b]Effective crossover rate from chemotherapy to anti–PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-[L]1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-[L]1 therapy). Data cutoff: June 1, 2020.

Brahmer; ESMO 2020

Pembrolizumab 5 Jahres Update NSCLC



	N = 12[c]
Alive at data cutoff, n (%)	8 (67)
Objective response during second course, n (%)	4 (33)
Best objective response, n (%)	
Complete response	0
Partial response	4 (33)
Stable disease	6 (50)
Progressive disease	1 (8)

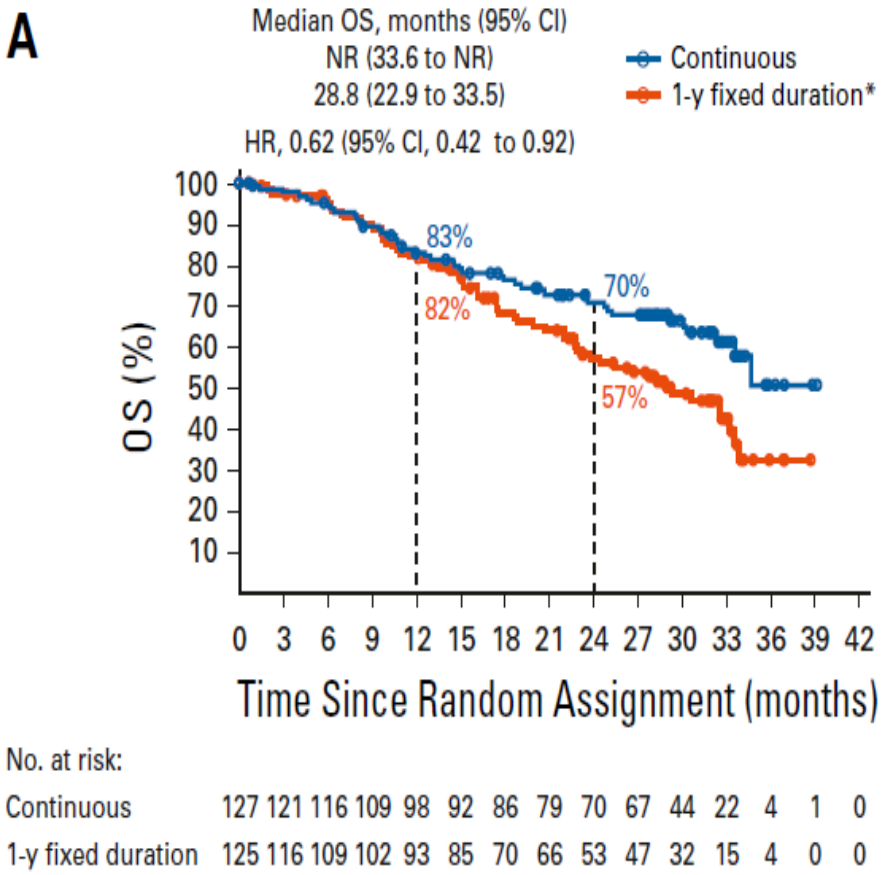
- **At data cutoff, 5/12 patients (42%) were alive without PD per investigator assessment**
  - **3 (25%) did not receive subsequent therapy**

NE, not evaluable. [a]Dark green bars indicate first course treatment duration and light green bars indicate second course treatment duration. Follow-up was defined as the time to progression or last non-progression assessment by investigator. Response was assessed by RECIST version 1.1 per investigator review. [b]For a maximum of 17 cycles. [c]5 patients (42%) experienced treatment-related AEs during second-course treatment, all grade 1–2; 1 was an immune-mediated AE (grade 1 hypothyroidism).
Data cutoff: June 1, 2020.

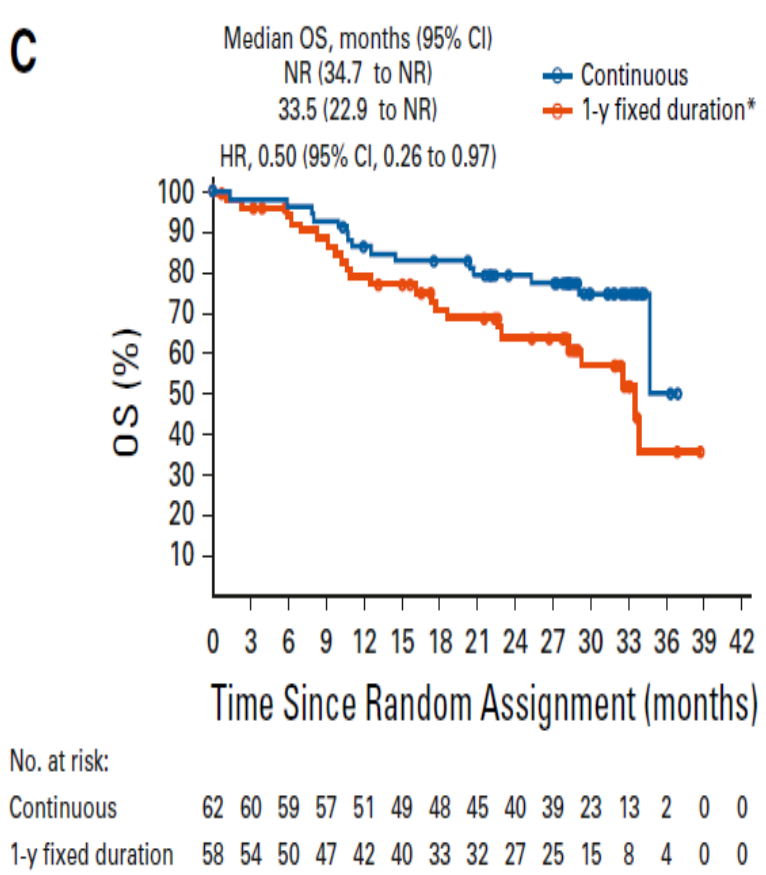
Brahmer; ESMO 2020

Immuntherapie- wie lange?

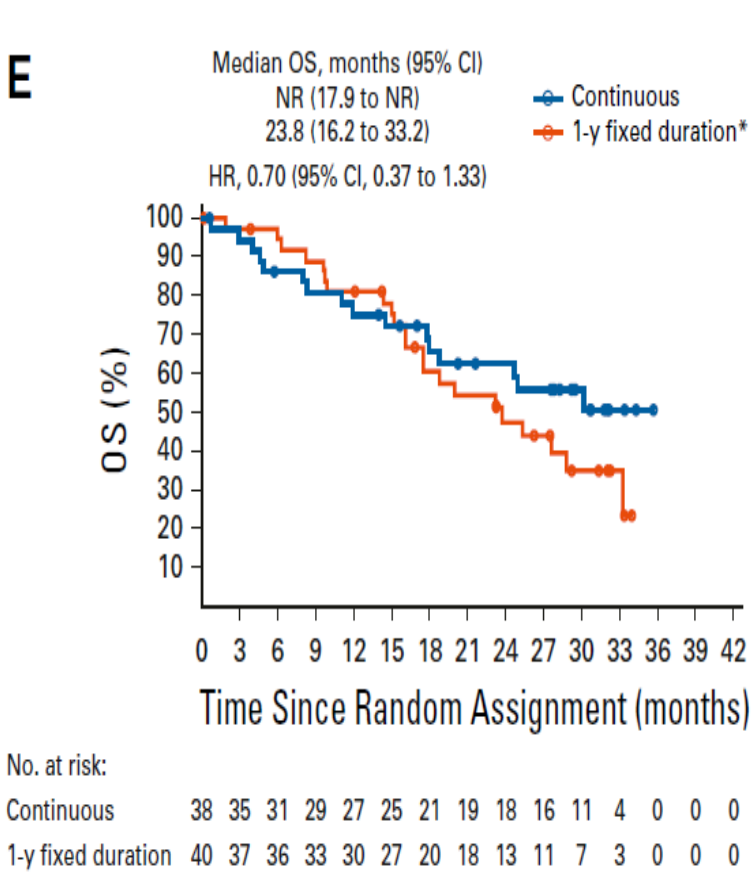
Gesamtpopulation



CR/PR



PD



Waterhouse; JCO 2020

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Sensitivierung auf Nachfolgetherapien?

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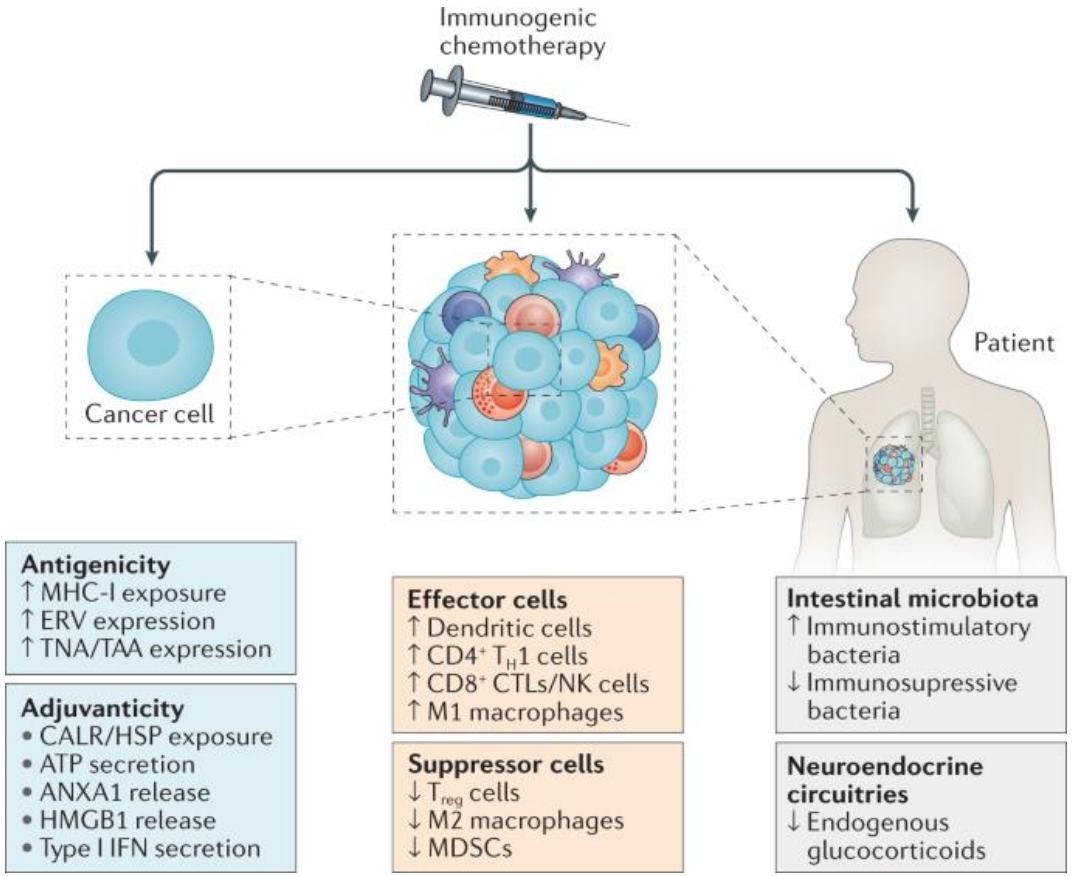

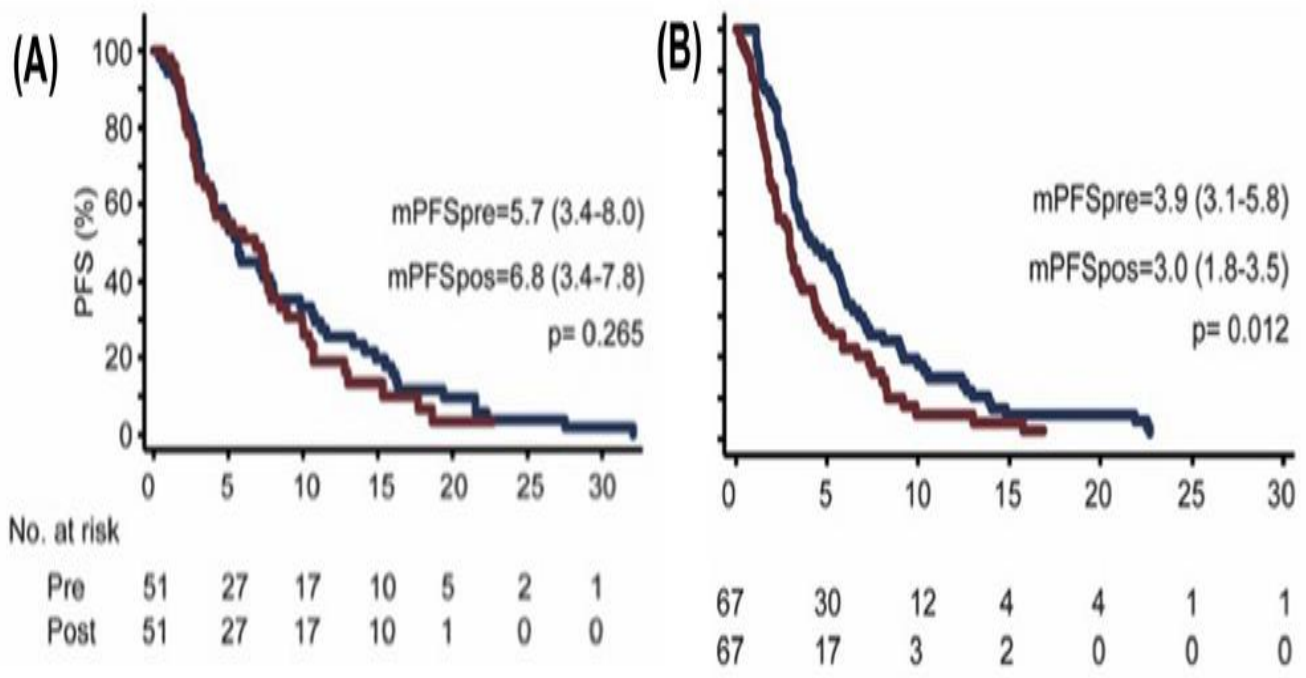

Aspeslagah et al; EJC 2017; Galluzzi et al.; Nature Reviews Clinical Oncology 2020

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Immuntherapie beim Melanom met.

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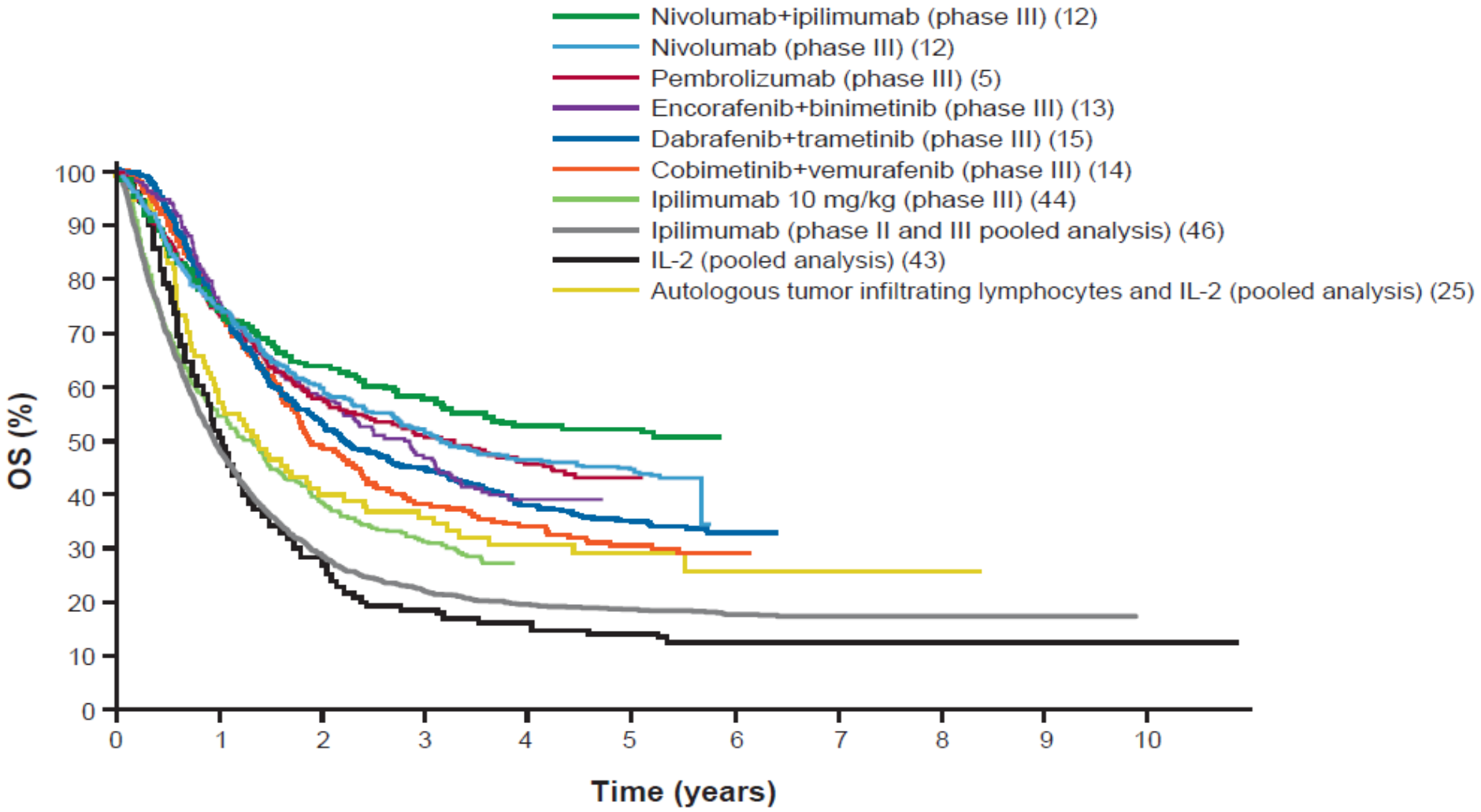

Michelin et al; JITC 2020

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6.5 Jahres Update Melanom Ipi/Nivo

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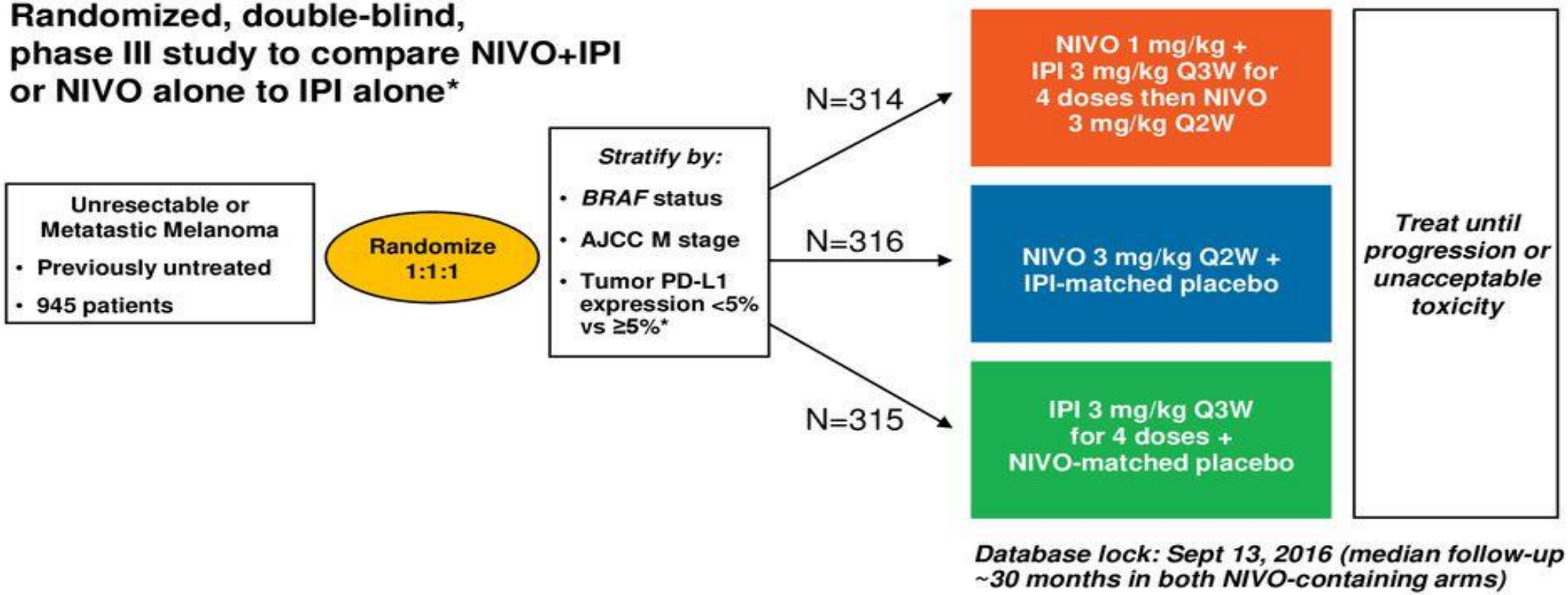
CheckMate 067: Study Design



*The study was not powered for a comparison between NIVO and NIVO+IPI

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6.5 Jahres Update Melanom Ipi/Nivo

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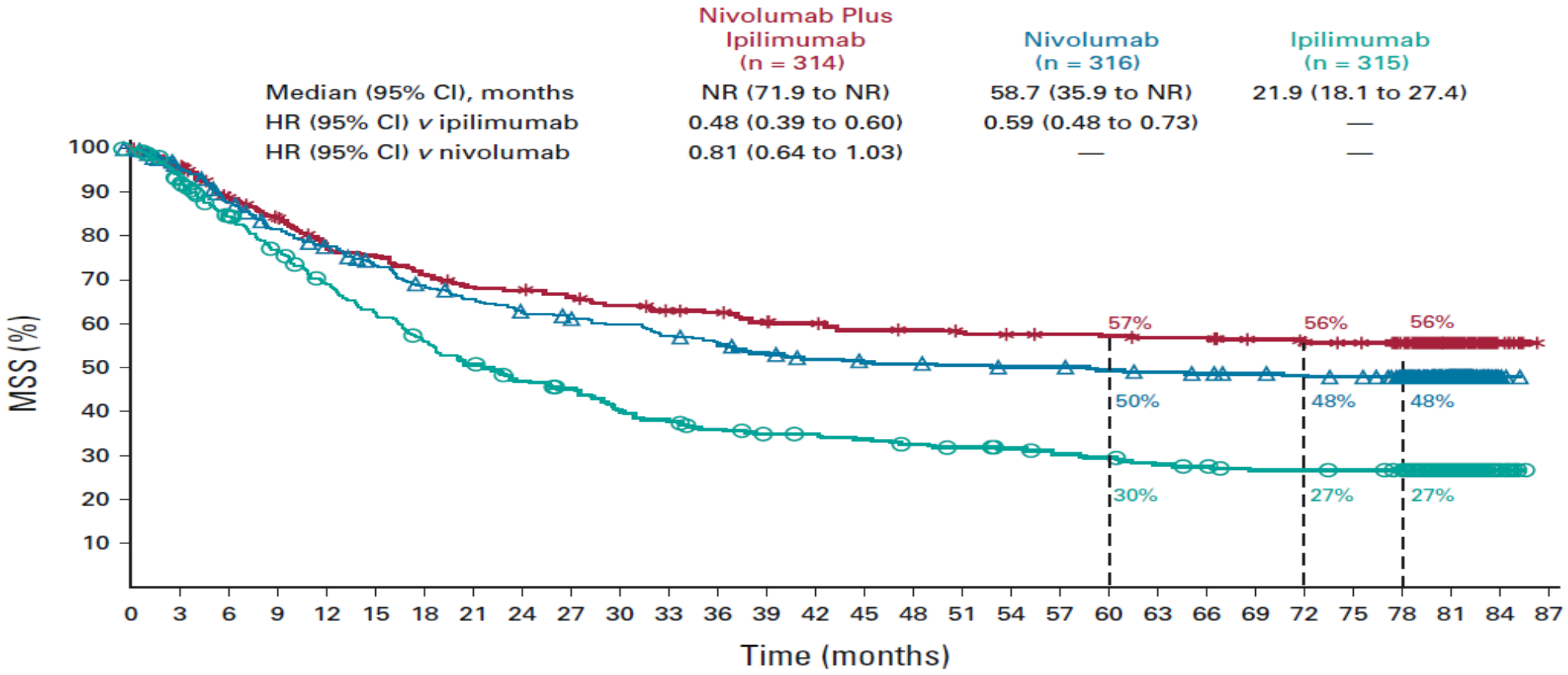

No. at risk:

Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	138	66	10	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	117	59	3	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	61	32	7	0

Wolcok et al; JCO 2021

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6.5 Jahres Update Melanom Ipi/Nivo

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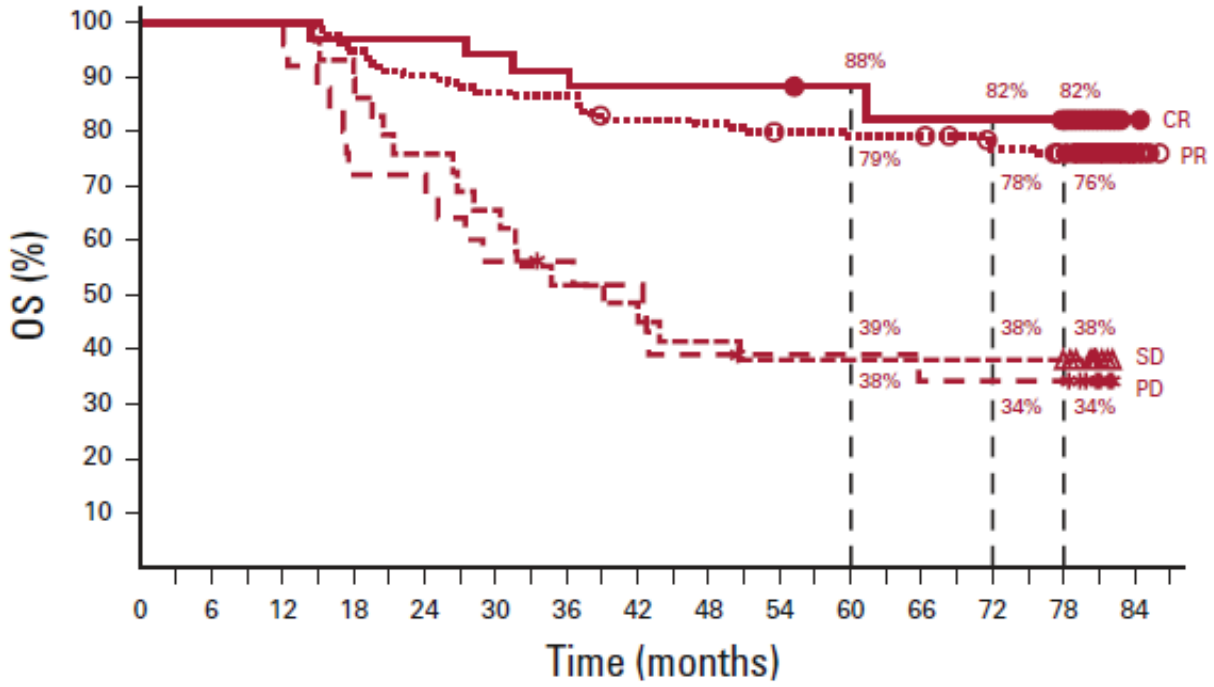

No. at risk:

CR	34	34	34	33	33	32	31	30	30	30	29	27	27	26	1
PR	134	134	134	127	121	117	116	109	108	105	104	104	99	92	9
SD	29	29	29	27	22	19	15	14	12	11	11	11	11	11	0
PD	25	25	25	18	18	14	13	12	9	8	8	7	7	7	0

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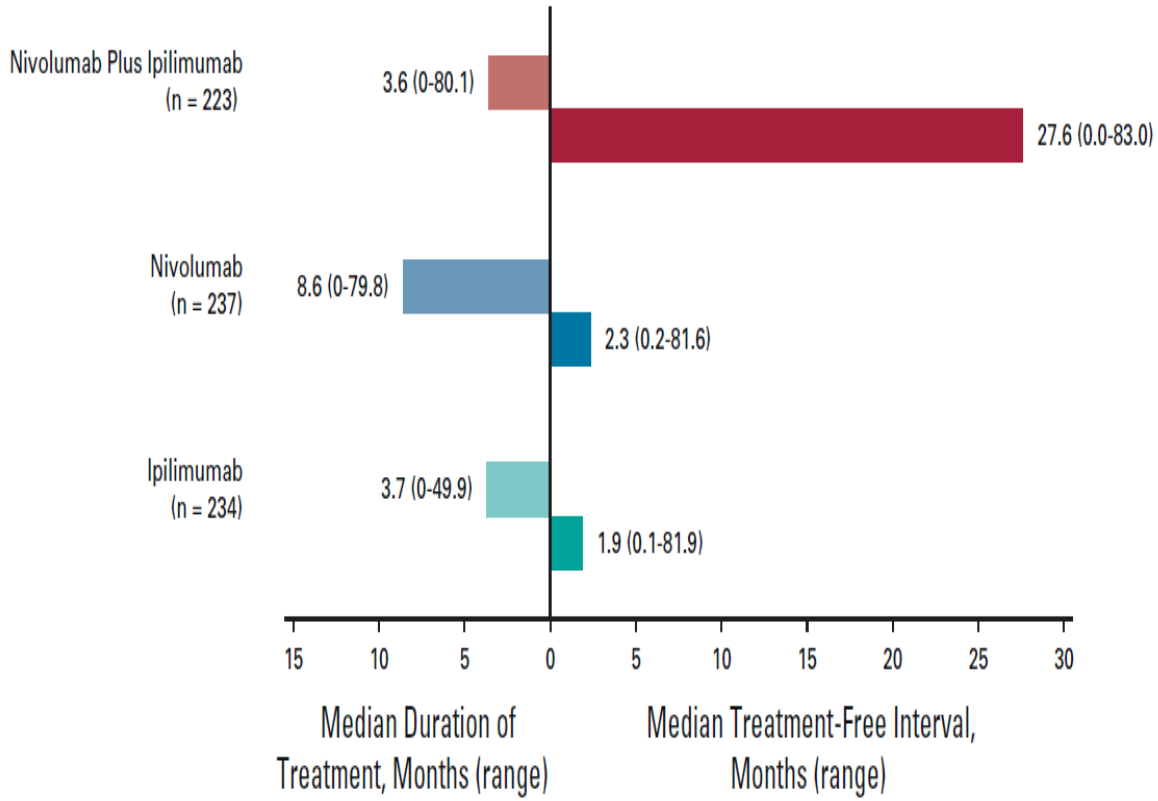

Wolcok et al; JCO 2021

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Response und OS

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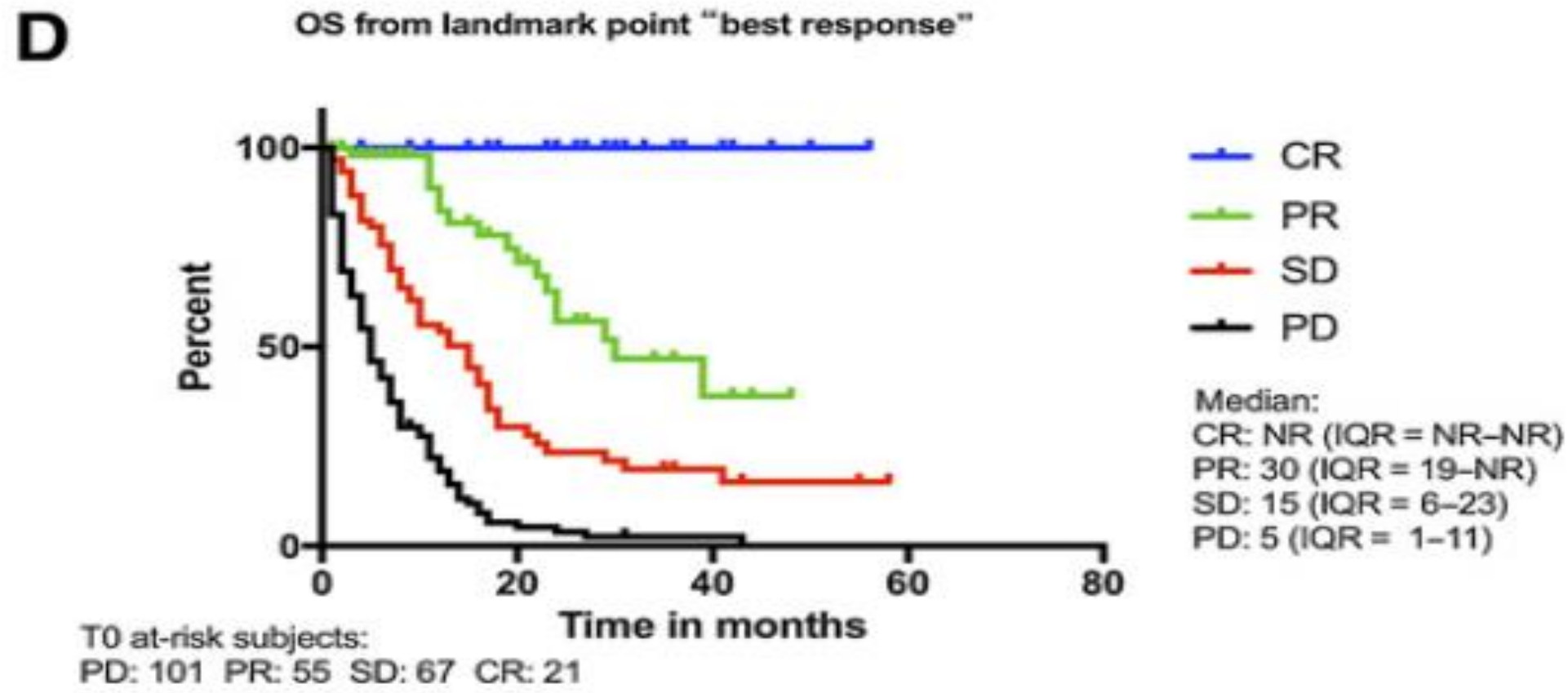
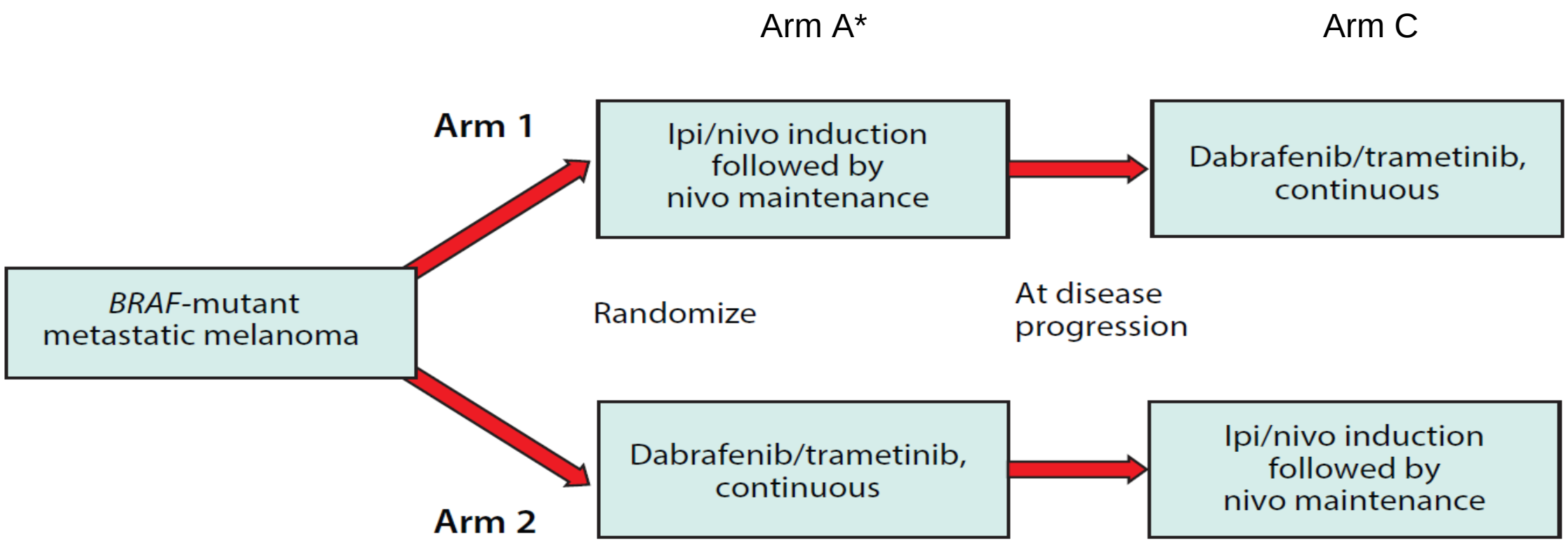


Gauci et al; CCR 2018

Sequenzfragen: Dream Seq



Atkins et al; Asco plenary 2021

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Sequenzfragen: Dream Seq

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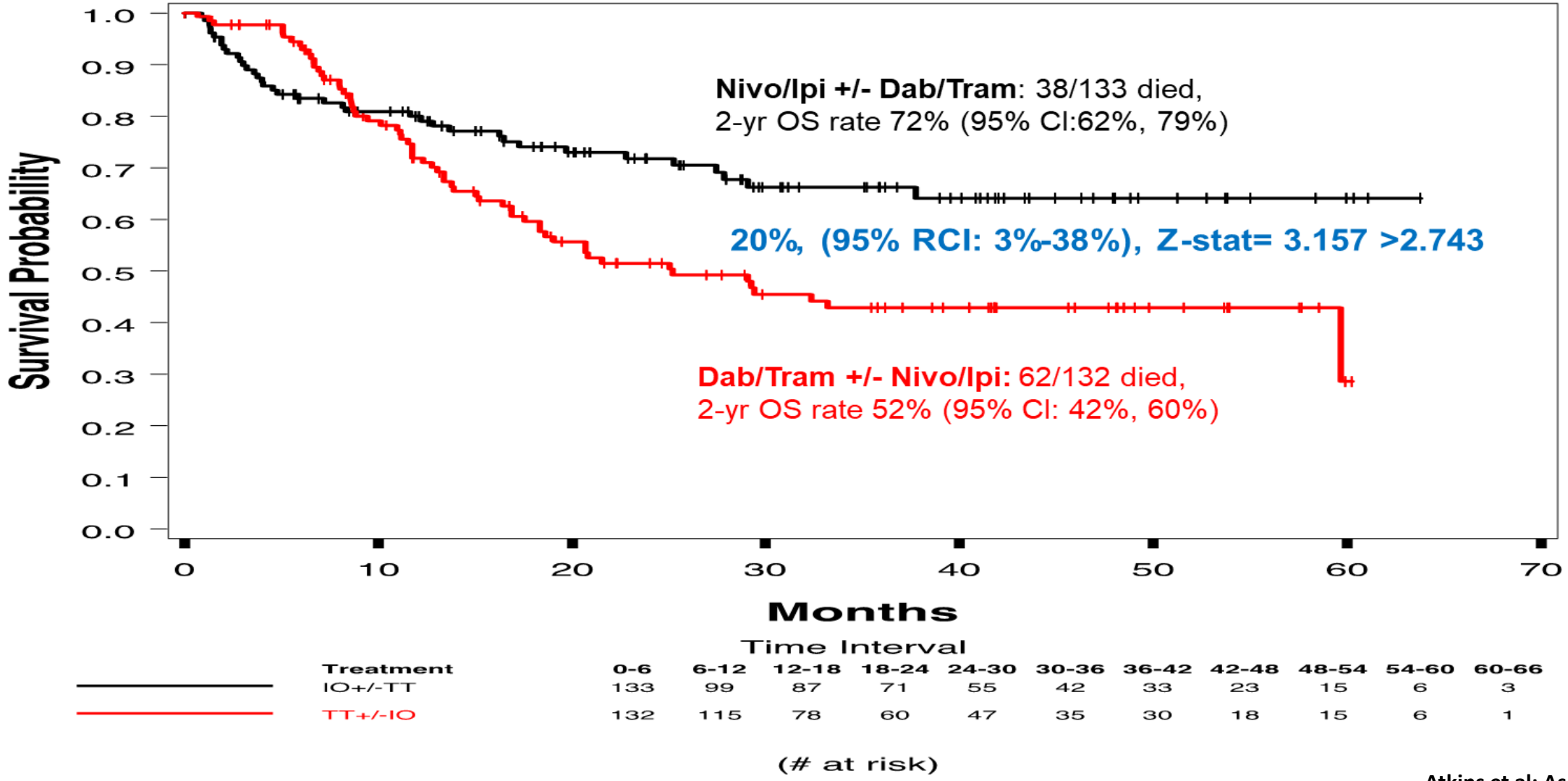

Atkins et al; Asco plenary 2021

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Take home message I

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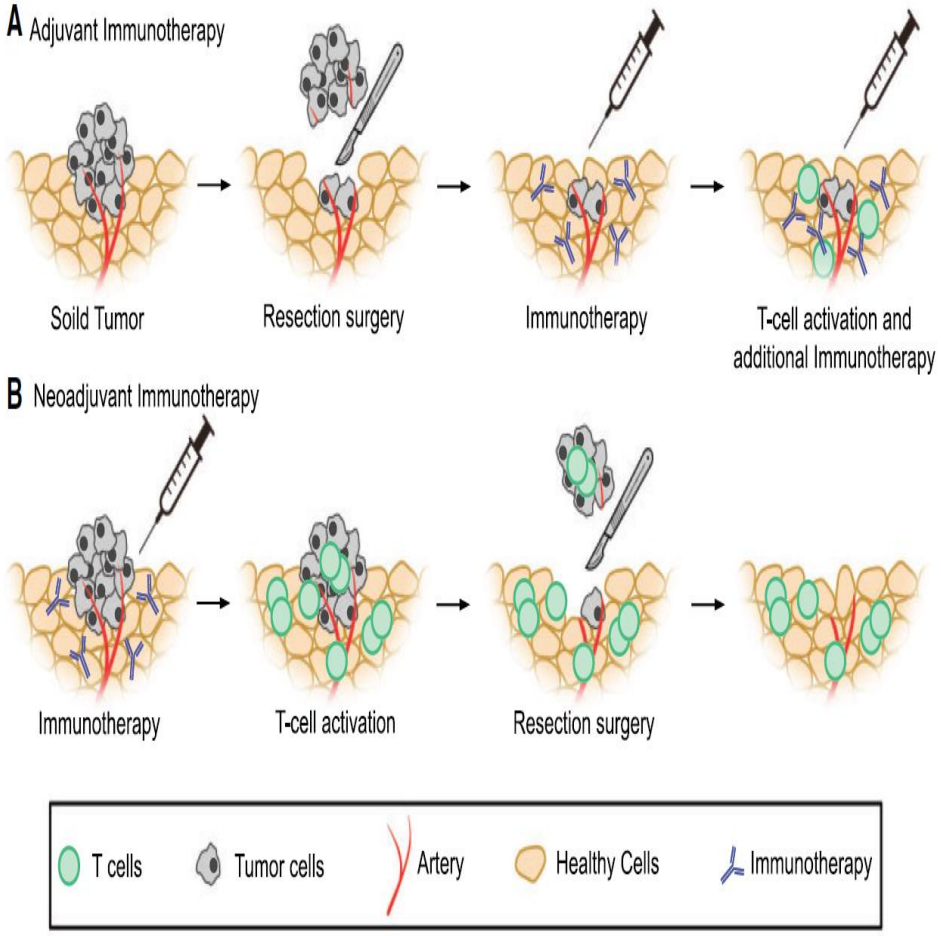
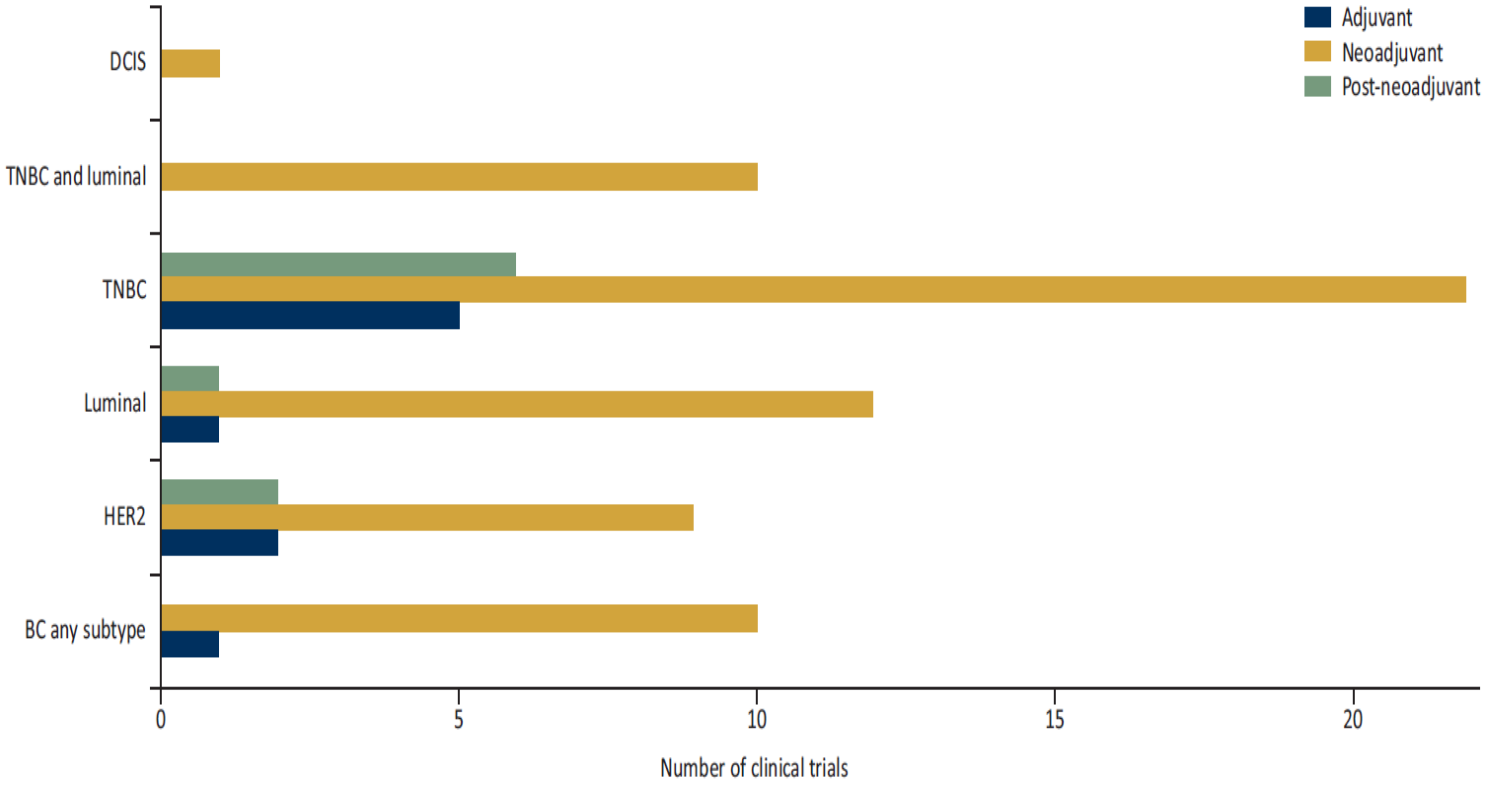
- Langzeitüberleben im Stadium IV durch Immuntherapie
- Outcome ist langfristig mit Response assoziiert
- Teil der Patienten ggf. „geheilt“ (?)

Immuntherapie in Frühstadien





Krishnamoorthy et al; JNCI 2021; Franzoni et al., Annals of Oncology 2020

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Neoadjuvante Immuntherapie

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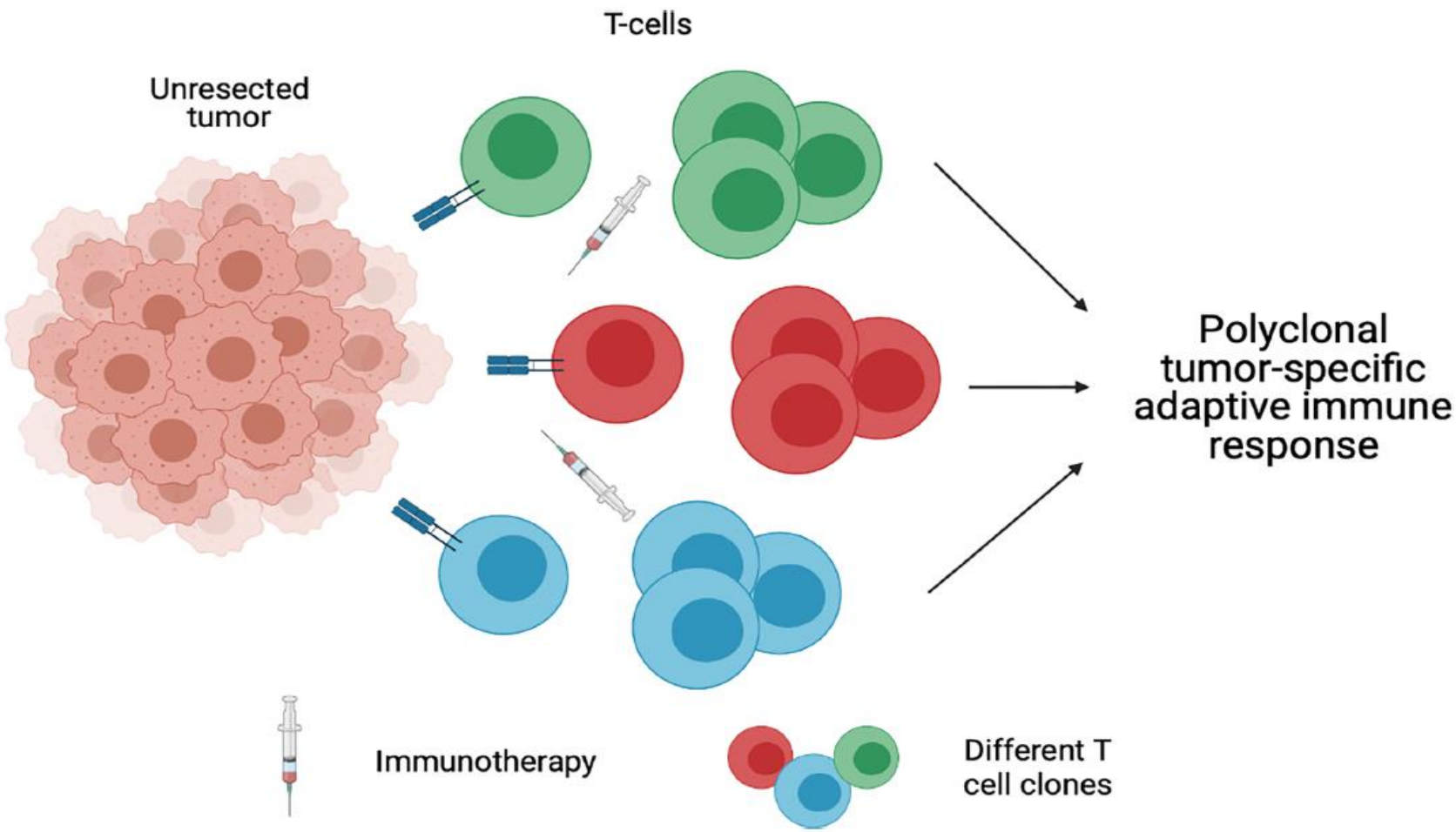
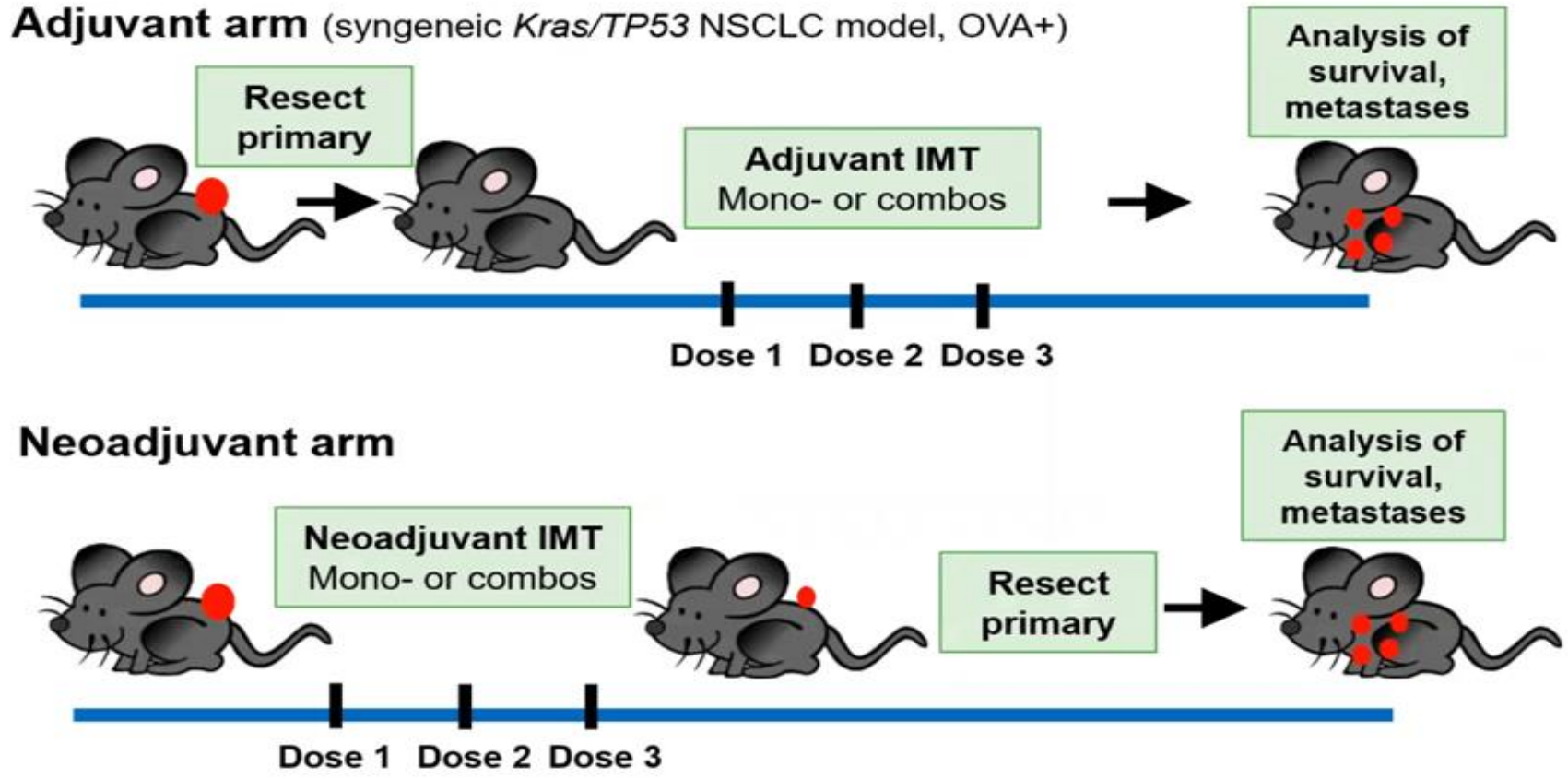


Philips et al; Frontiers in Oncology 2021

Neoadjuvante vs. adjuvante Immuntherapie

Adjuvant vs. neoadjuvant ICIs in a murine model of NSCLC

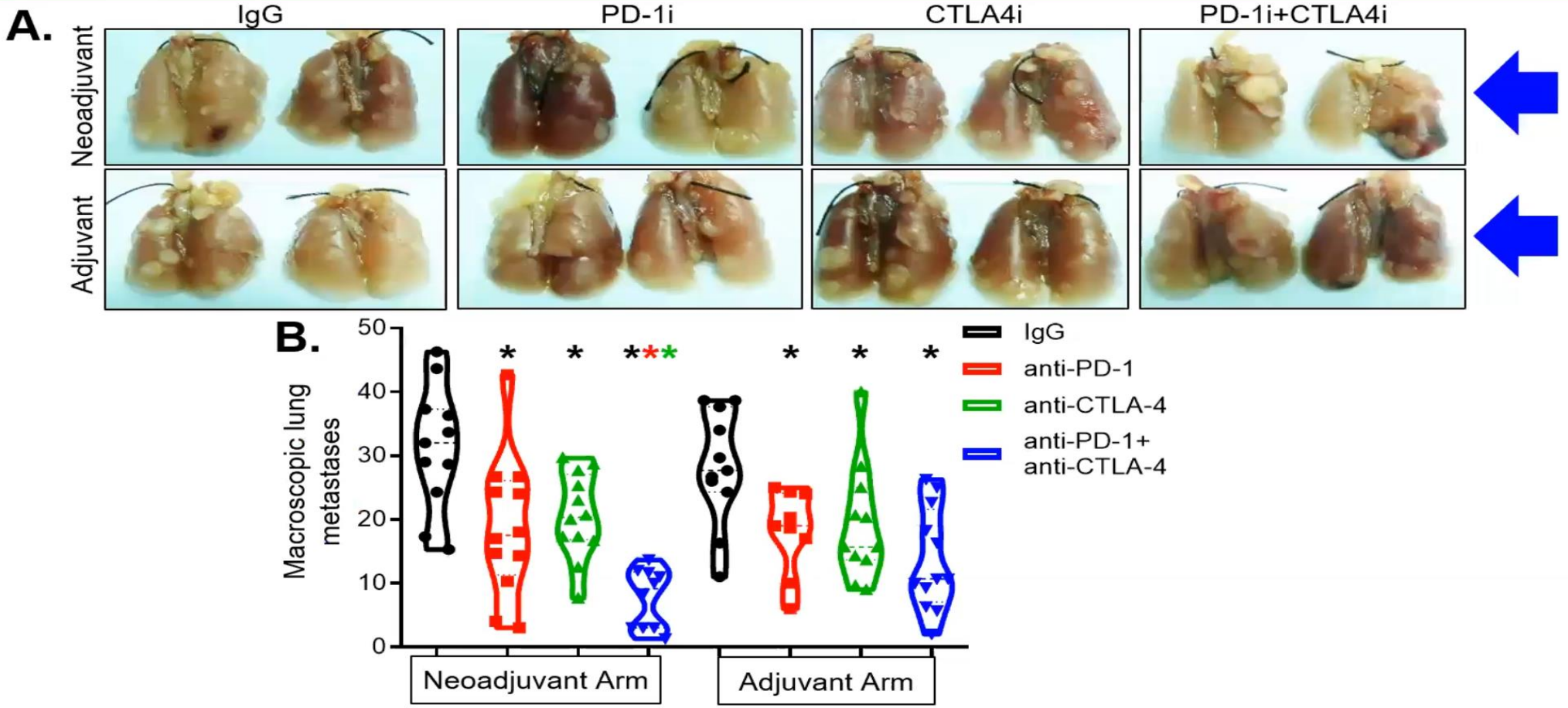


Cascone; AACR 2021

Neoadjuvant vs. adjuvante Immuntherapie

Neoadjuvant combined ICIs are superior to adjuvant therapy at reducing lung metastases

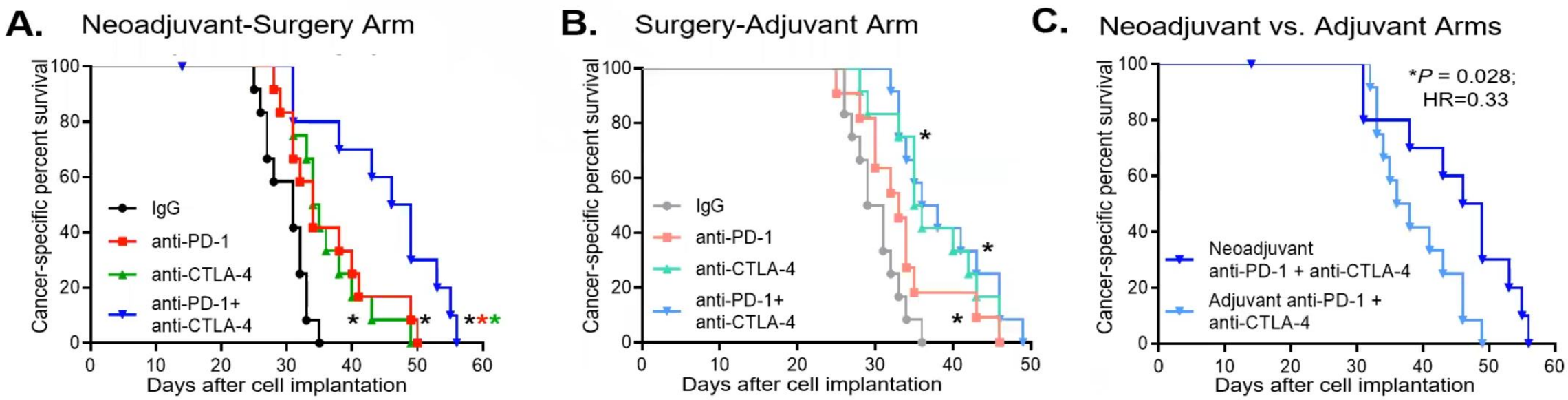
American Association for Cancer Research
FINDING CURES TOGETHER



Cascone; AACR 2021

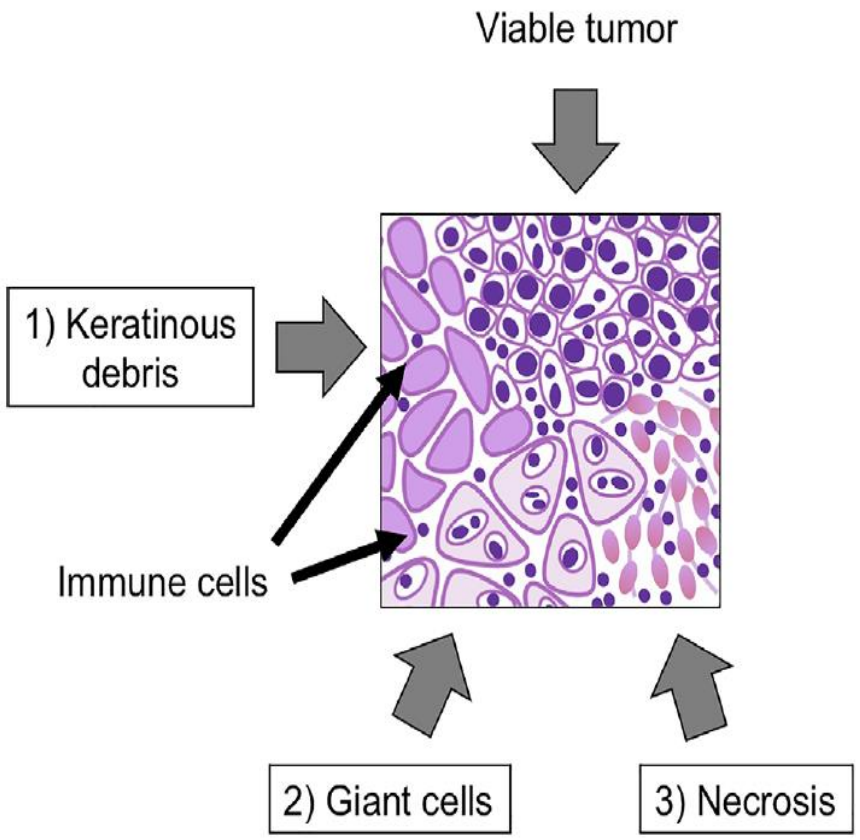
Neoadjuvante vs. adjuvante Immuntherapie

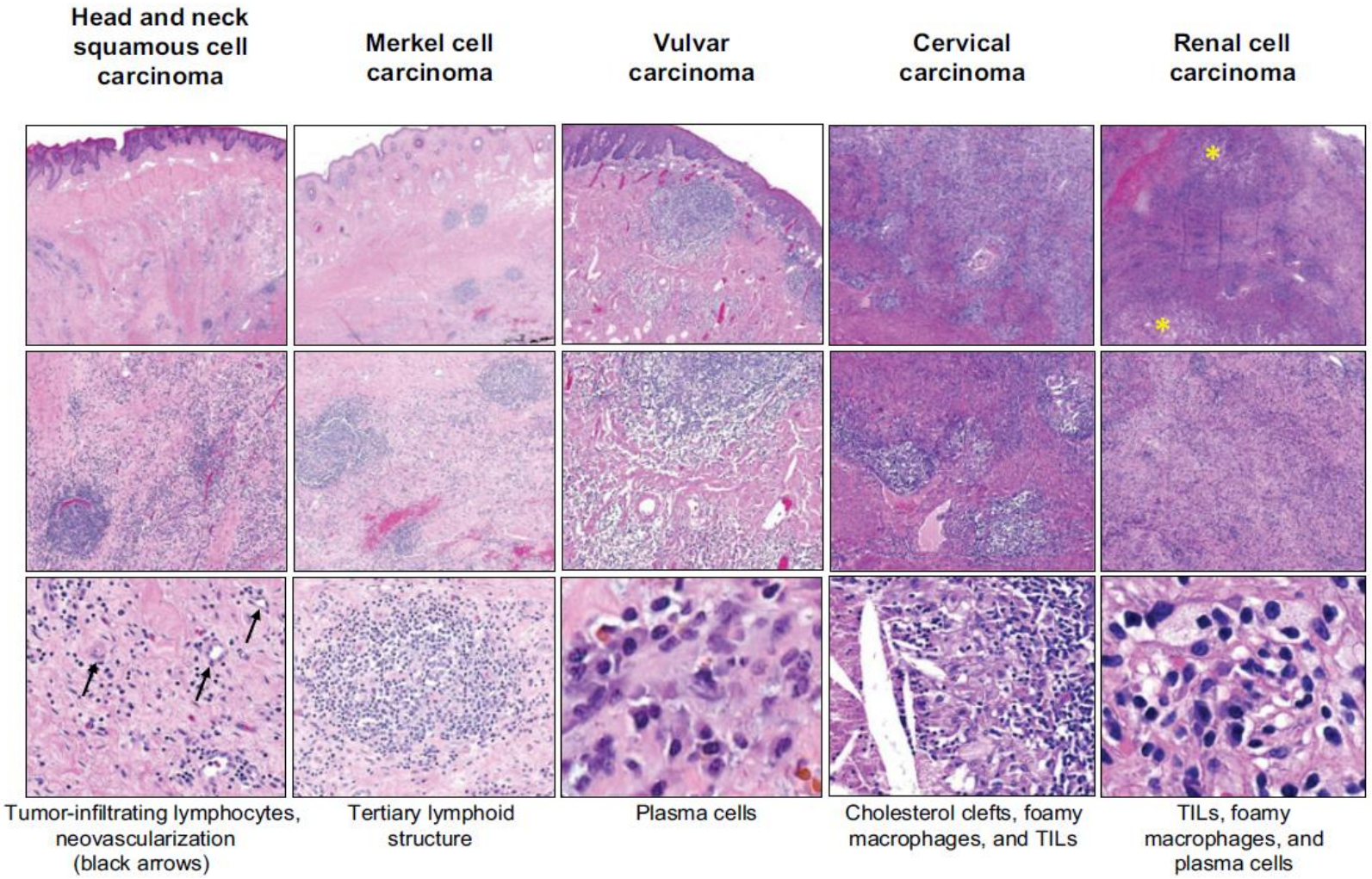
Neoadjuvant combined ICIs are superior to adjuvant therapy at prolonging survival in a NSCLC model



Cascone; AACR 2021

Neoadjuvante Immuntherapie: MPR





Shibataa et al; Frontiers in Oncology 2021; Stein et al. CCR 2019

COMPREHENSIVE CANCER CENTER VIENNA

Disconcordance: Imaging und MPR?

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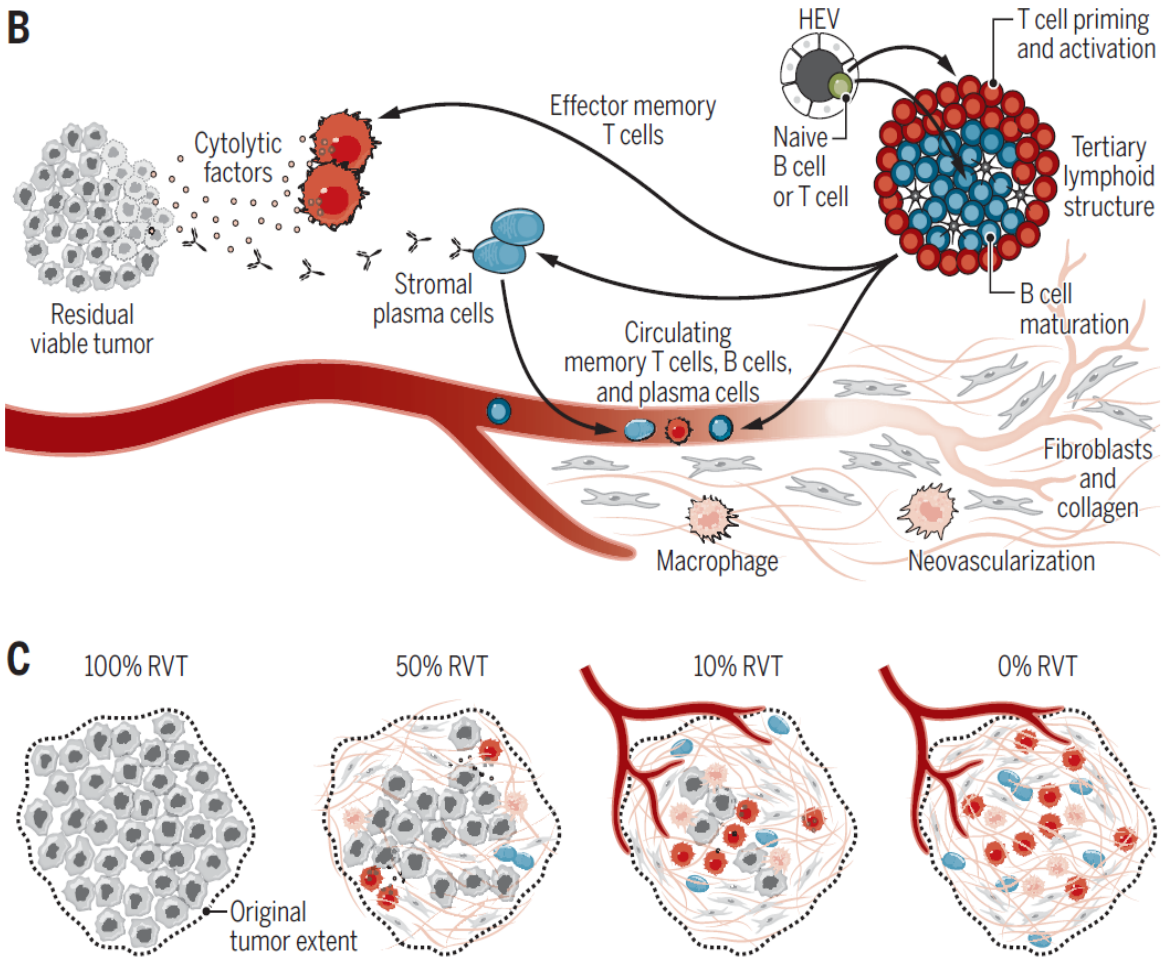

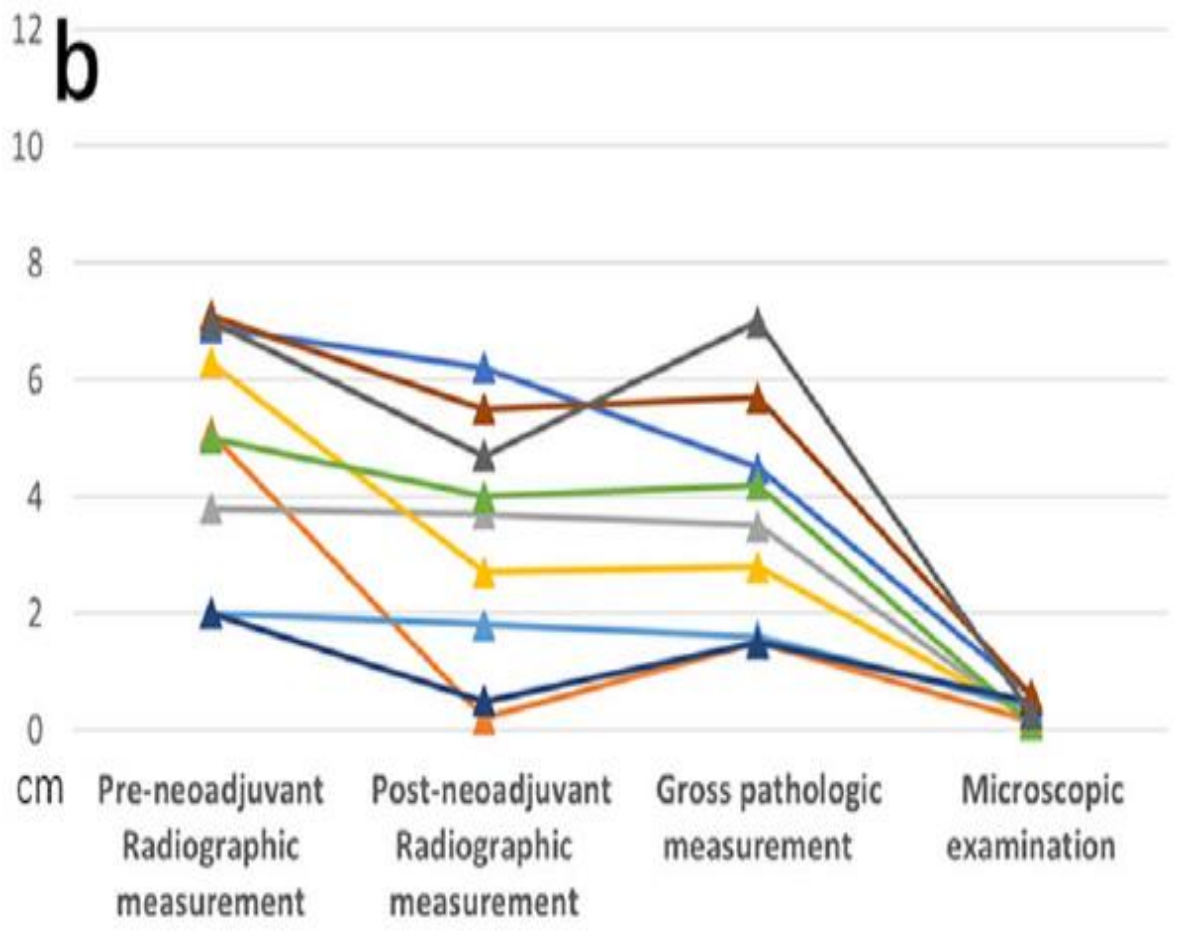

Topalian et al.; Science 2020; Ling et al.; Precision Oncology 2020

COMPREHENSIVE CANCER CENTER VIENNA

Neoadj.Immuntherapie Hyperprogression

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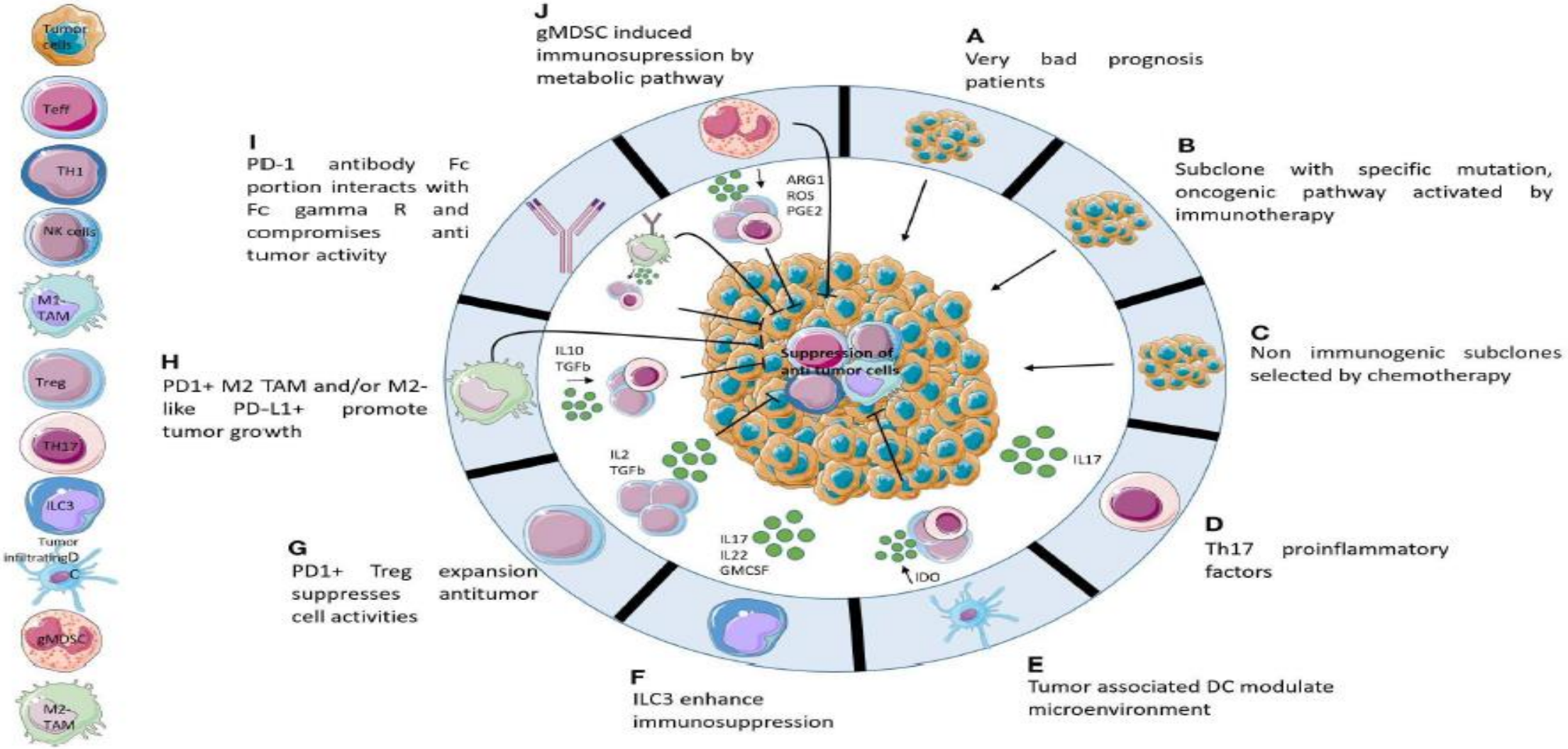

Dennis et al.; Frontiers in Immunology 2020

COMPREHENSIVE CANCER CENTER VIENNA

Case

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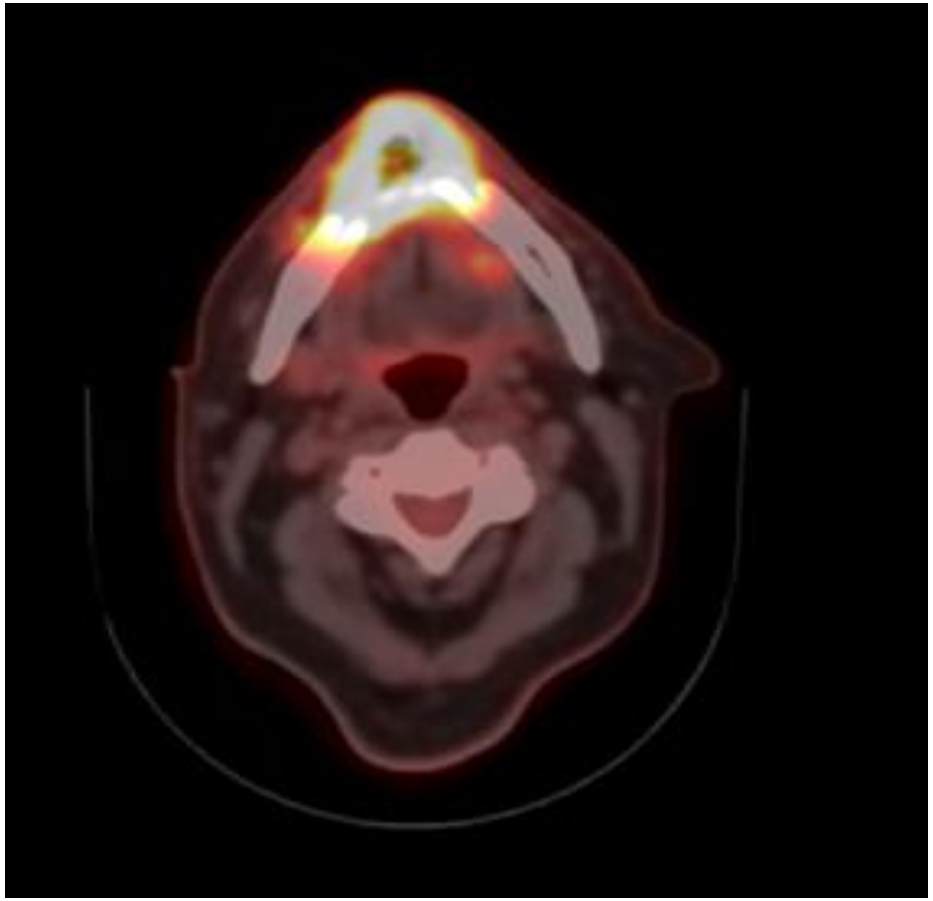
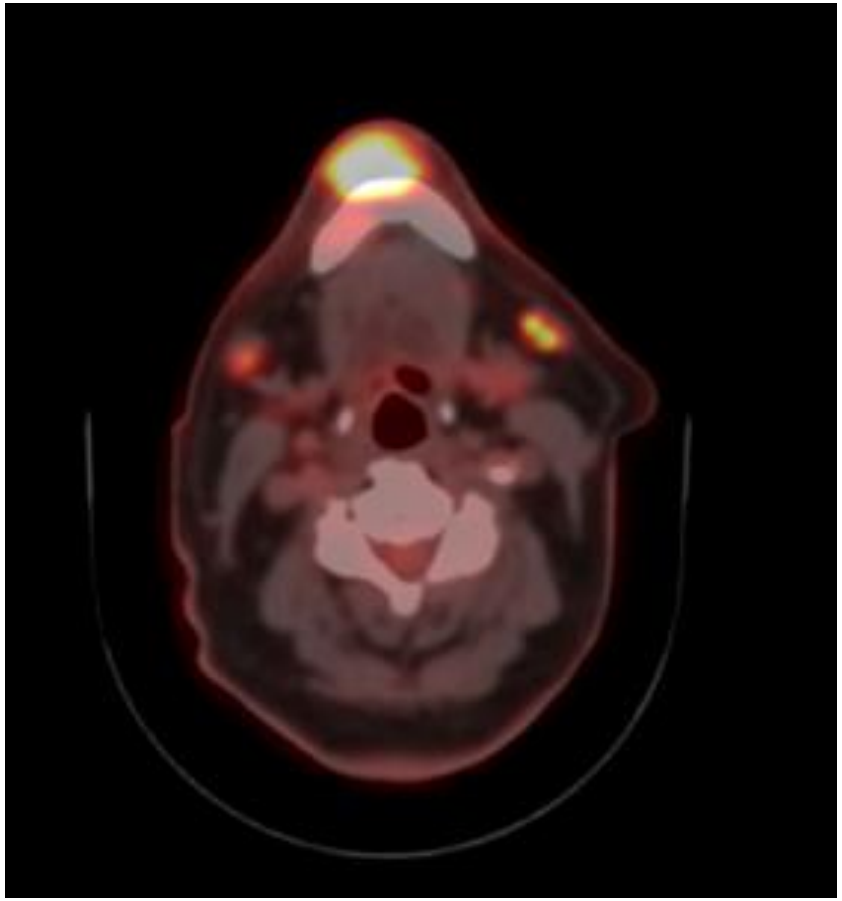
- 71 jähriger männlicher Patient
- ECOG: 0
- Nikotin 20 pack years
- Diabetes
- Hypertonie

Imaging

Oral cavity carcinoma, cT4,cN0,M0

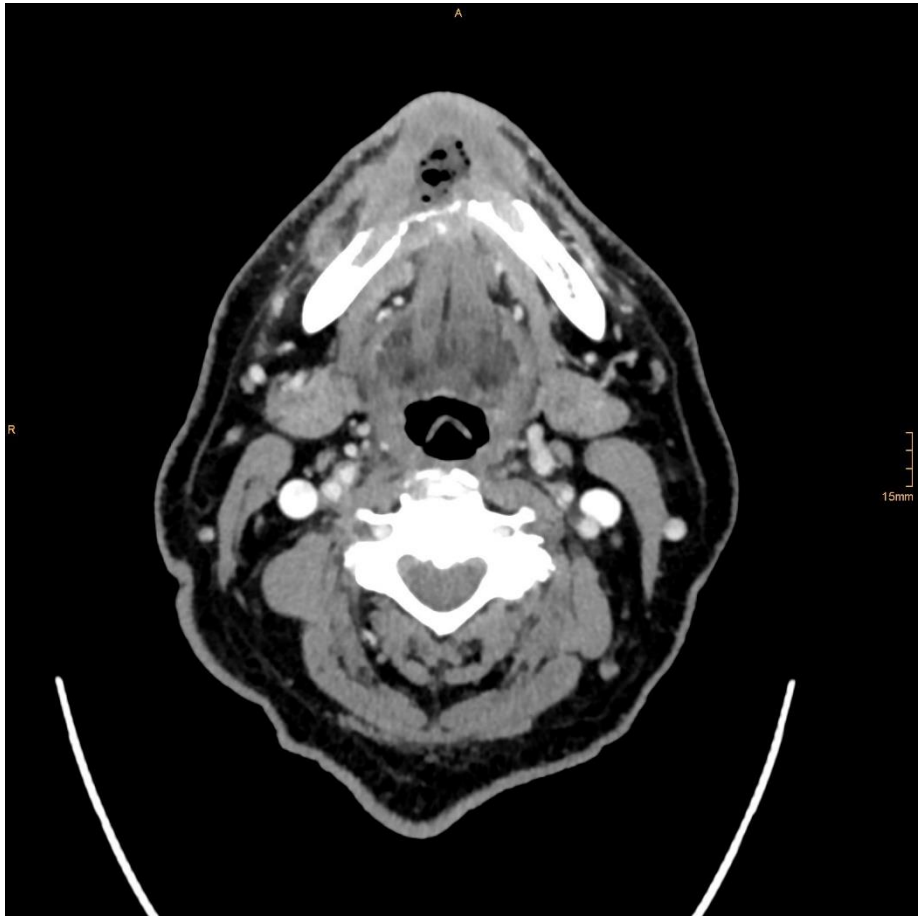




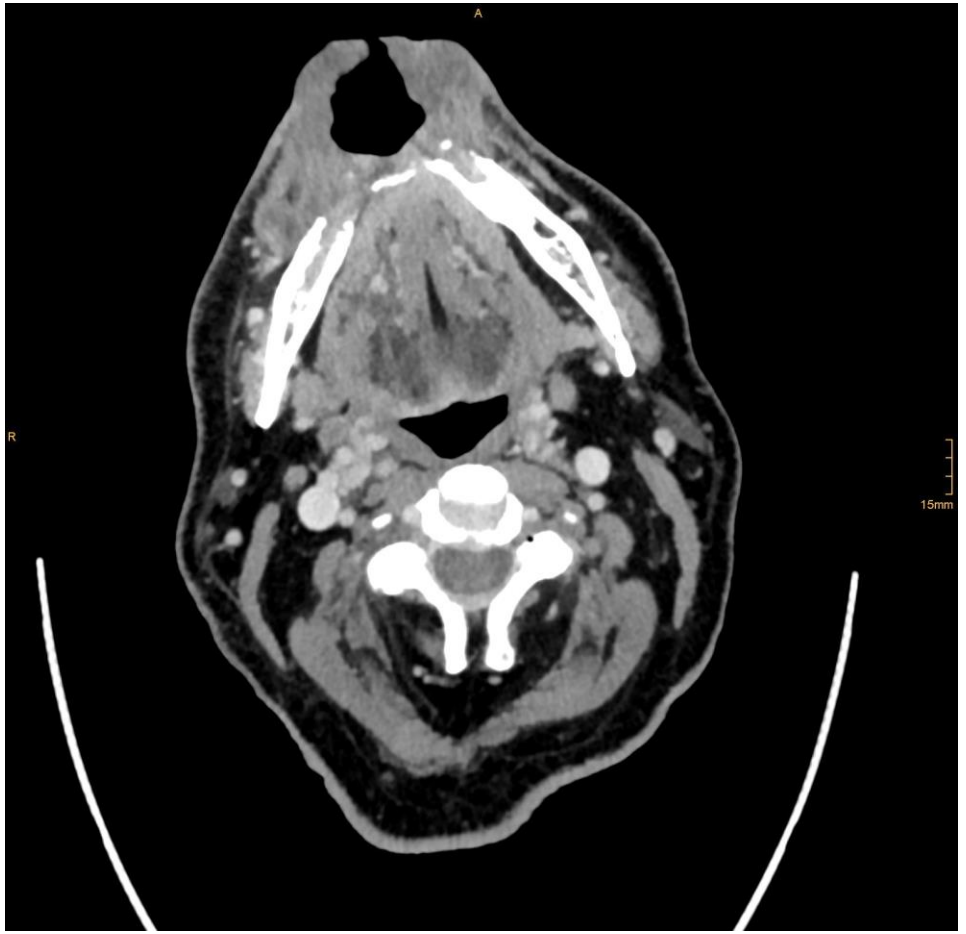
09/2020

Imaging

Neoadjuvant Immuntherapie: Rapid PD



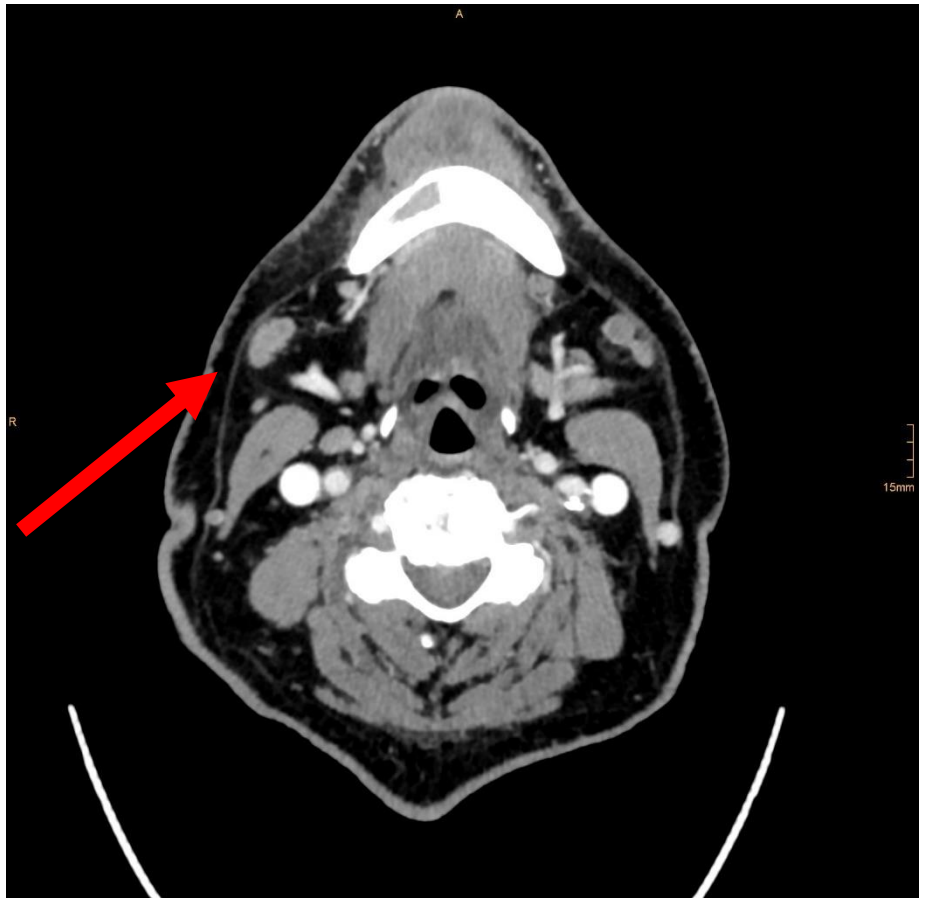
09/2020



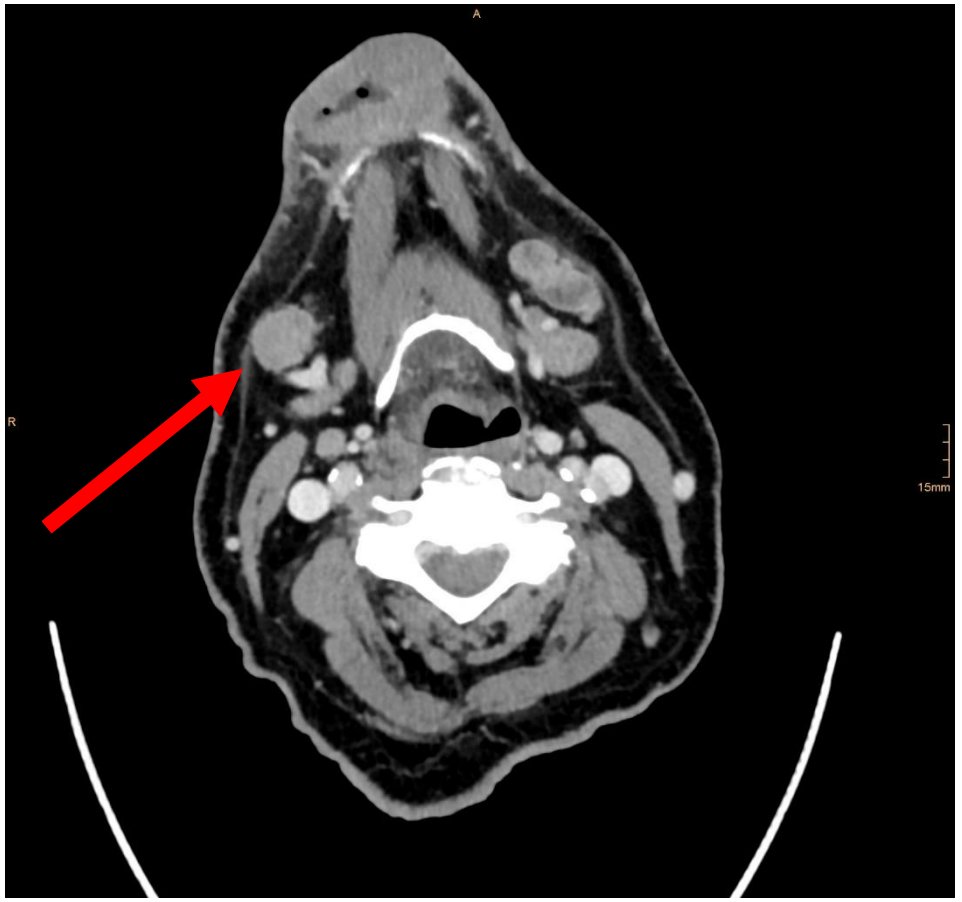
10/2020

Imaging

Neoadjuvant Immuntherapie : Rapid PD



09/2020



10/2020

COMPREHENSIVE CANCER CENTER VIENNA

PD-L1 Expression

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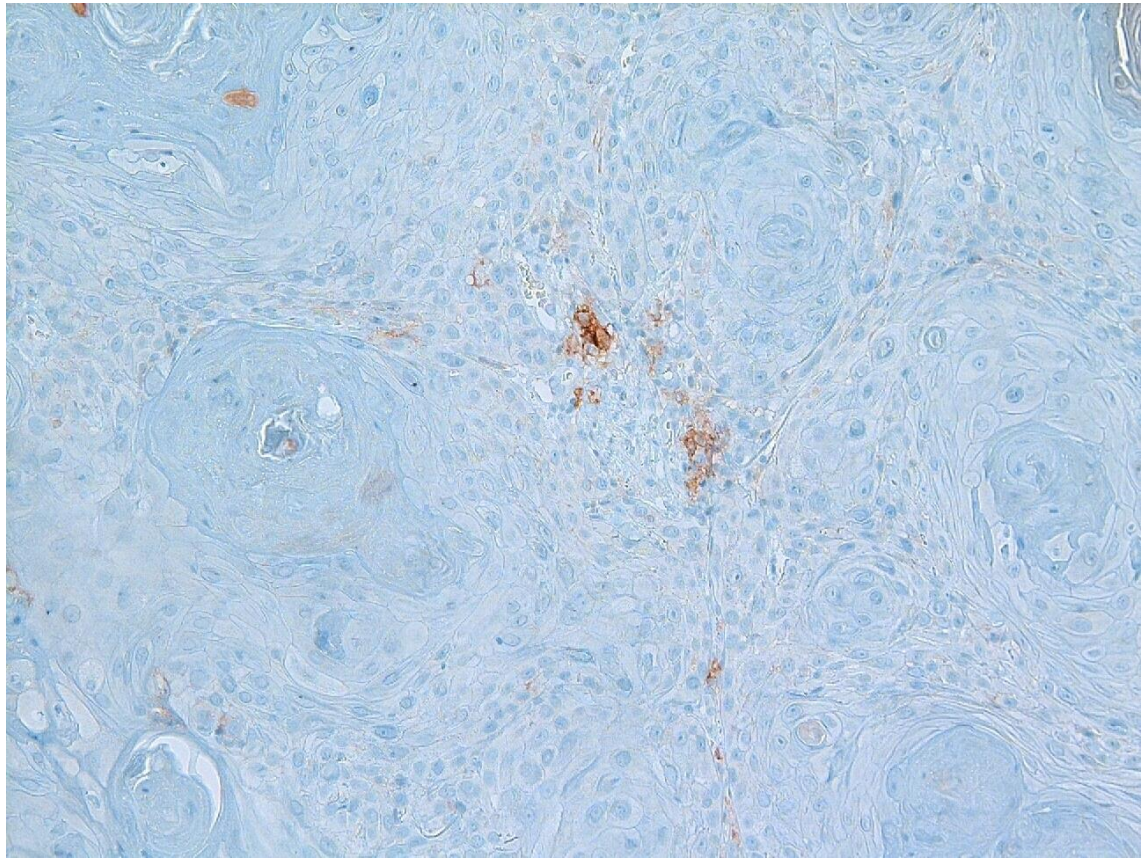
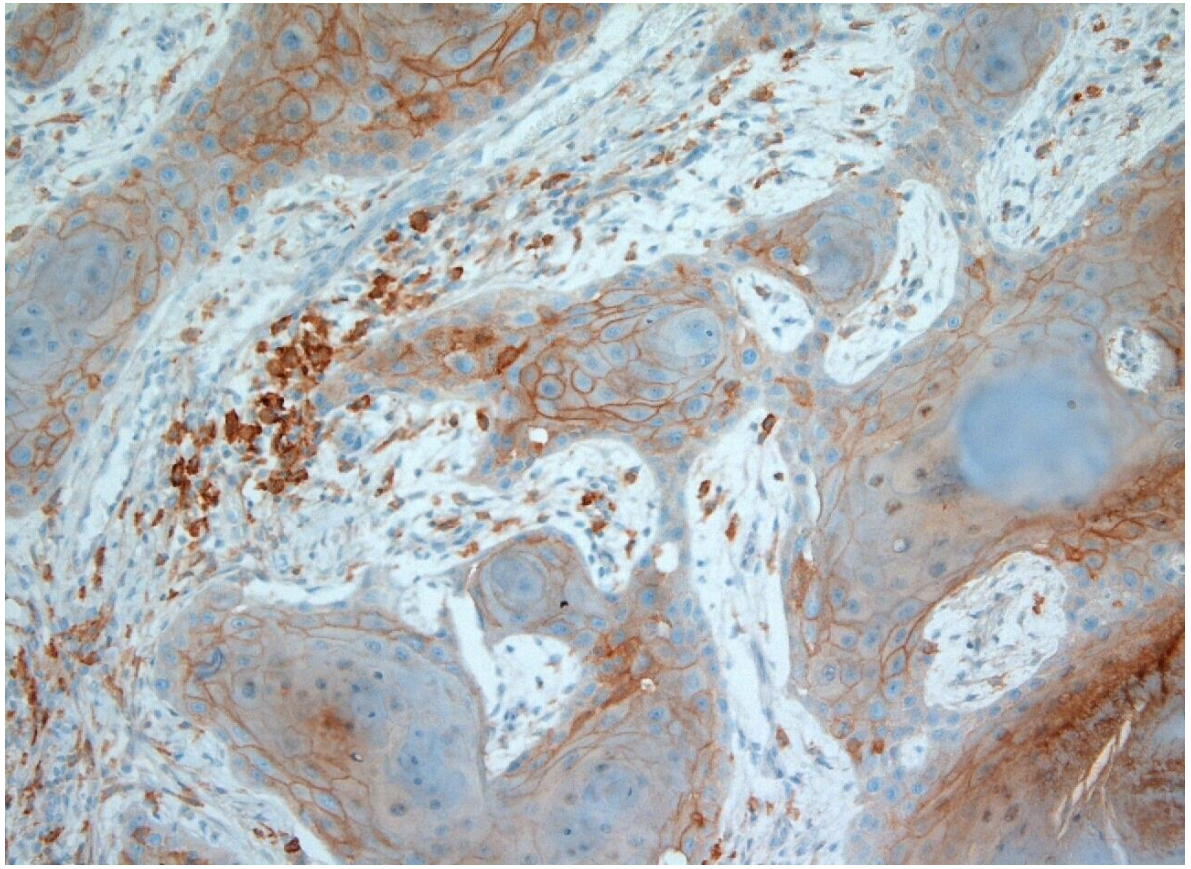
Prä-OP



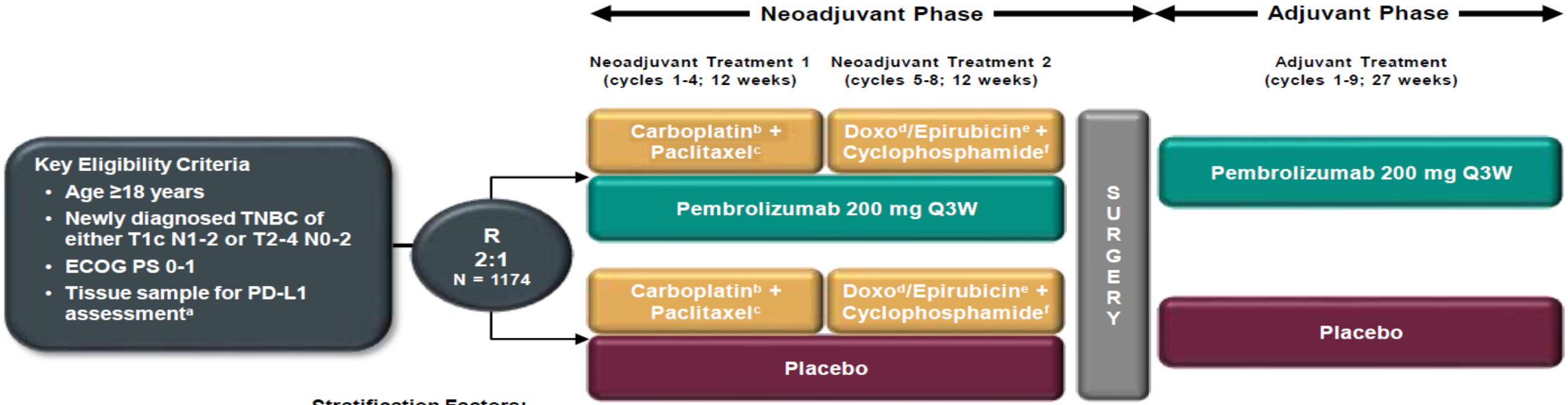
Post-OP



Images: Prof.Pammer, Pathology Department; MUV

Pembrolizumab+ Chemo neoadjuvant Mamma CA

KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m^2 QW.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Schmid et al.; Esmo virtual plenary 2021

COMPREHENSIVE CANCER CENTER VIENNA

Immunoradiotherapy: Rationale

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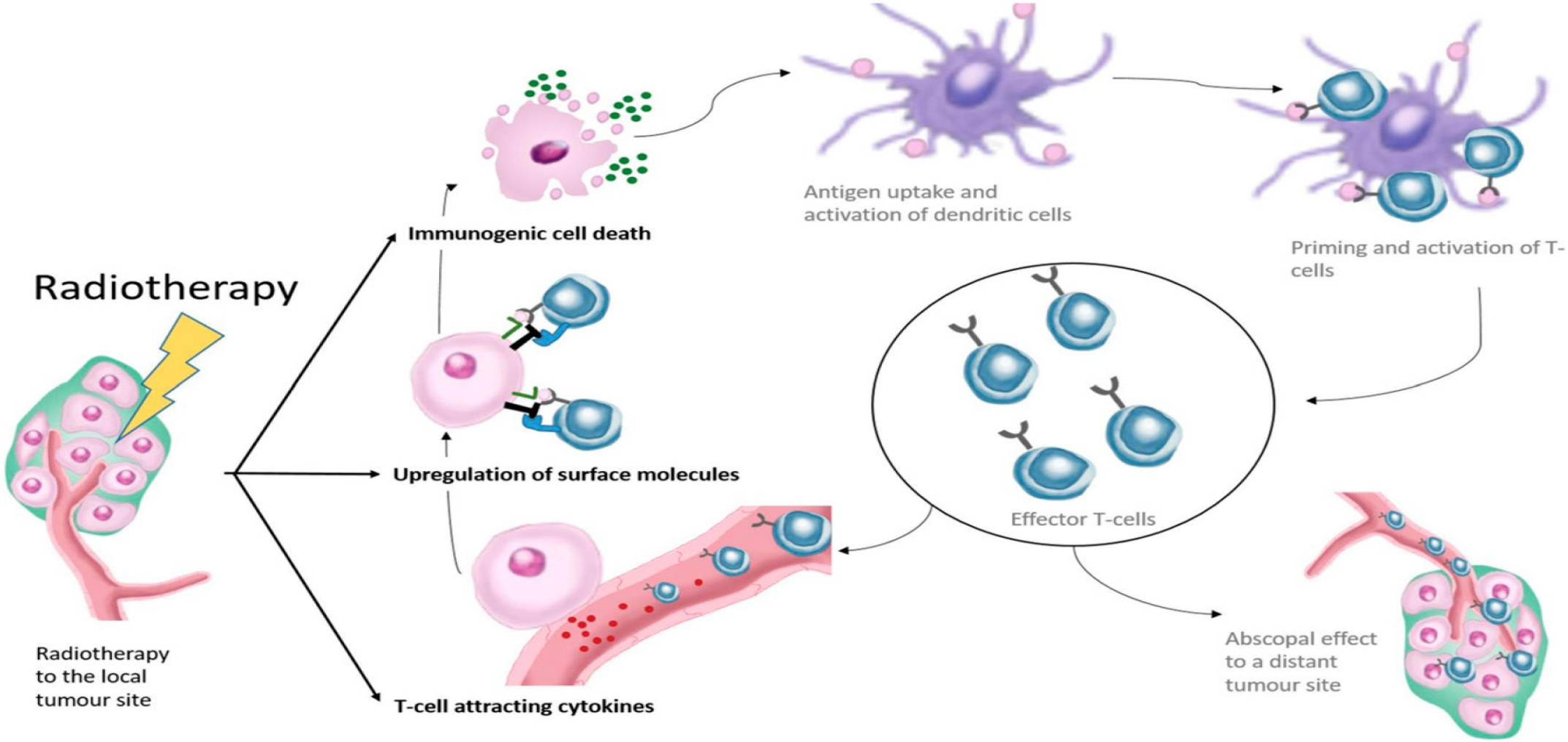

Limbergen et al.; British Journal of Radiology 2017

COMPREHENSIVE CANCER CENTER VIENNA

5 Jahres
Update NSCLC Durvalumab

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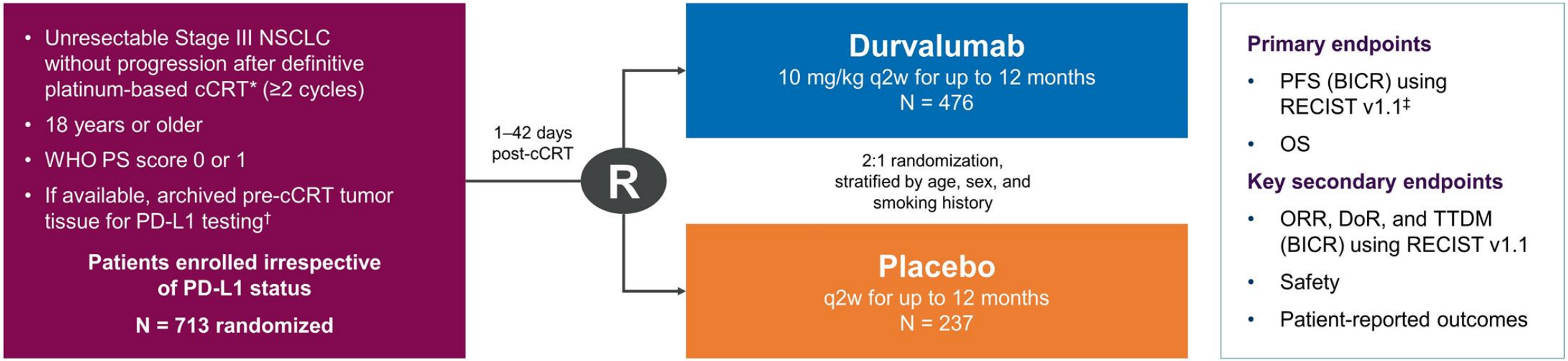


- **Updated analyses of OS and PFS, assessed ~5 years after the last patient was randomized (data cutoff: 11 January 2021; exploratory, post-hoc analysis)**
  - **Treatment effects were estimated using stratified log-rank tests in the ITT population**
  - **Medians and yearly landmark rates were estimated using the Kaplan–Meier method**

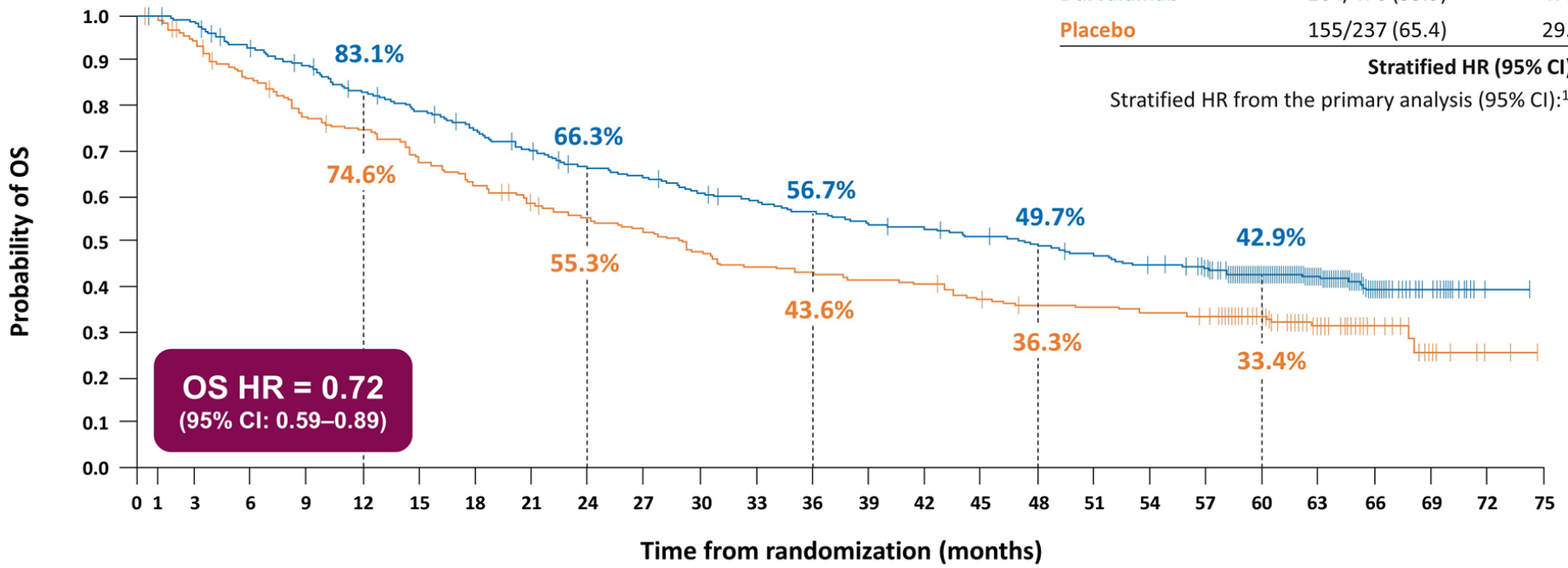
Spigel et al.; Asco 2021

5 Jahres
Update NSCLC Durvalumab

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	264/476 (55.5)	47.5 (38.1–52.9)
Placebo	155/237 (65.4)	29.1 (22.1–35.1)

Stratified HR (95% CI): 0.72 (0.59–0.89)

Stratified HR from the primary analysis (95% CI):[1,2] 0.68 (0.53–0.87)



No. at risk

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).

1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

Spigel et al.; Asco 2021

COMPREHENSIVE CANCER CENTER VIENNA

5 Jahres Update NSCLC Durvalumab

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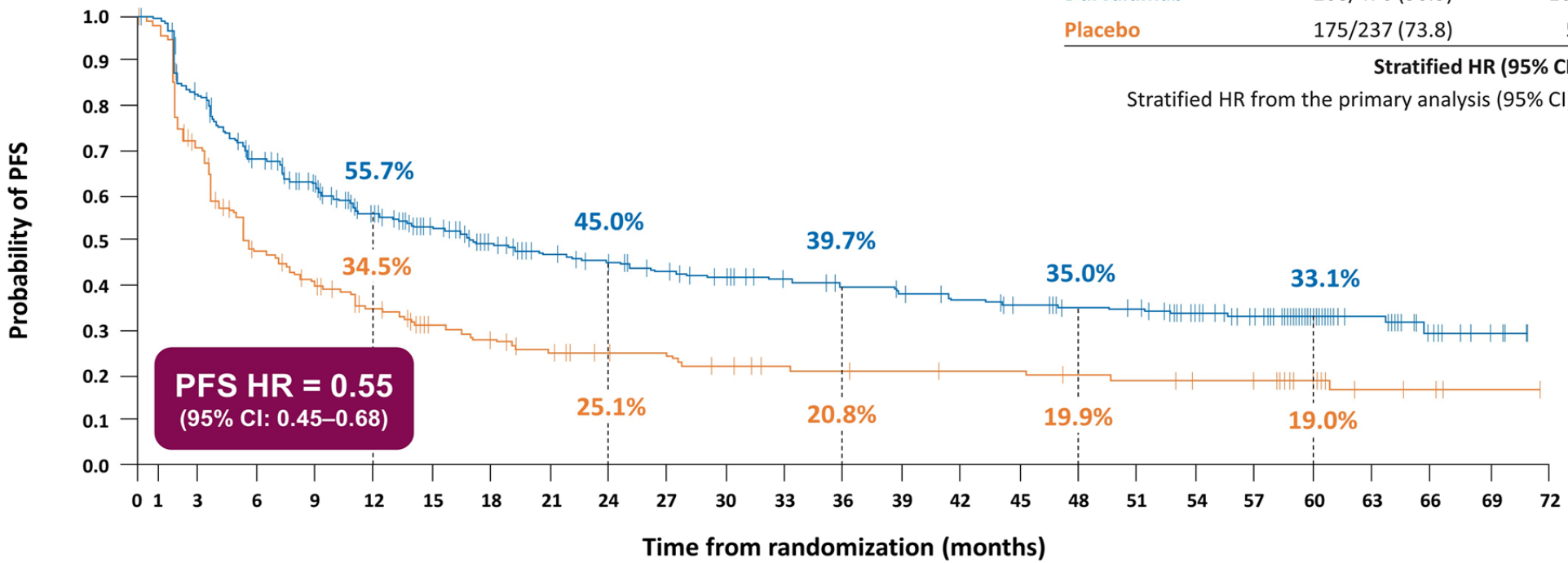
	No. of events/ total no. of patients (%)	Median PFS (95% CI), months
Durvalumab	268/476 (56.3)	16.9 (13.0–23.9)
Placebo	175/237 (73.8)	5.6 (4.8–7.7)

Stratified HR (95% CI): 0.55 (0.45–0.68)

Stratified HR from the primary analysis (95% CI):[1] 0.52 (0.42–0.65)



No. at risk

Durvalumab	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

Spigel et al.; Asco 2021

5 Jahres
Update NSCLC Durvalumab

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
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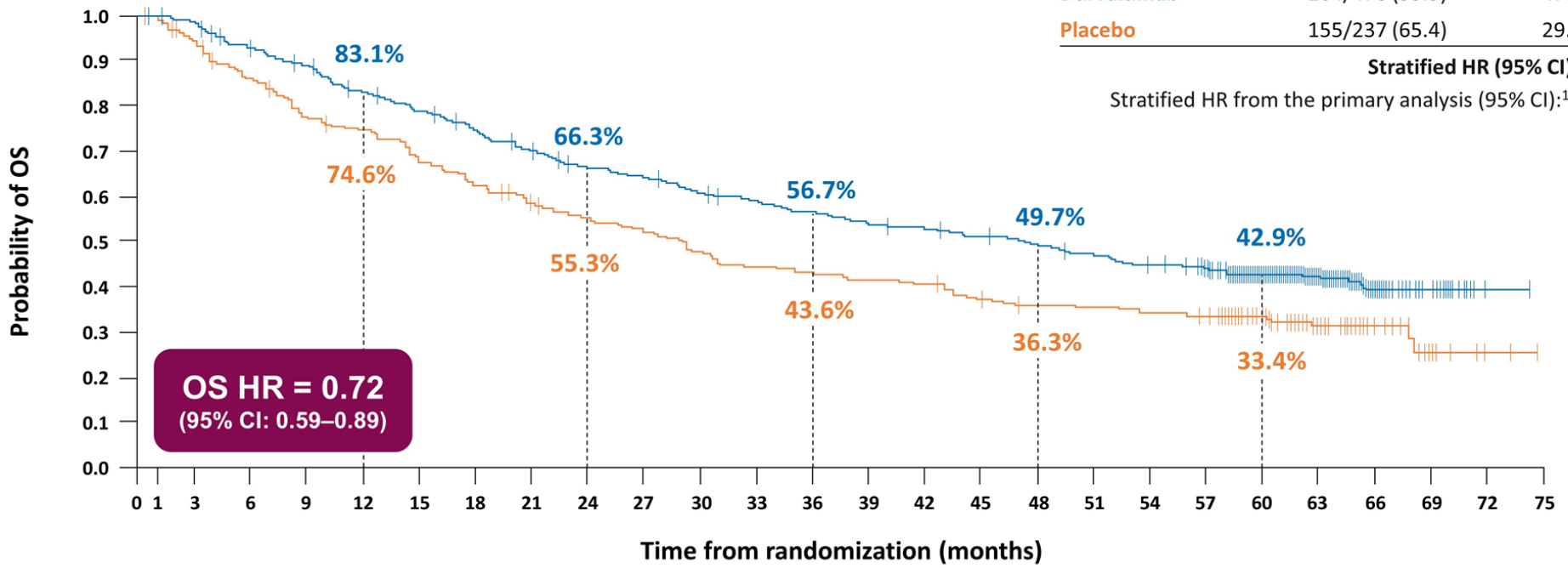

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Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

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1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

Spigel et al.; Asco 2021

COMPREHENSIVE CANCER CENTER VIENNA

Take home message II

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- Neoadjuvante Immuntherapie vielversprechend
- Höhere pathologische Complete response
- Teil der Patienten langfristig „geheilt“ (?)

COMPREHENSIVE CANCER CENTER VIENNA

Wo kommen Nebenwirkungen vor?

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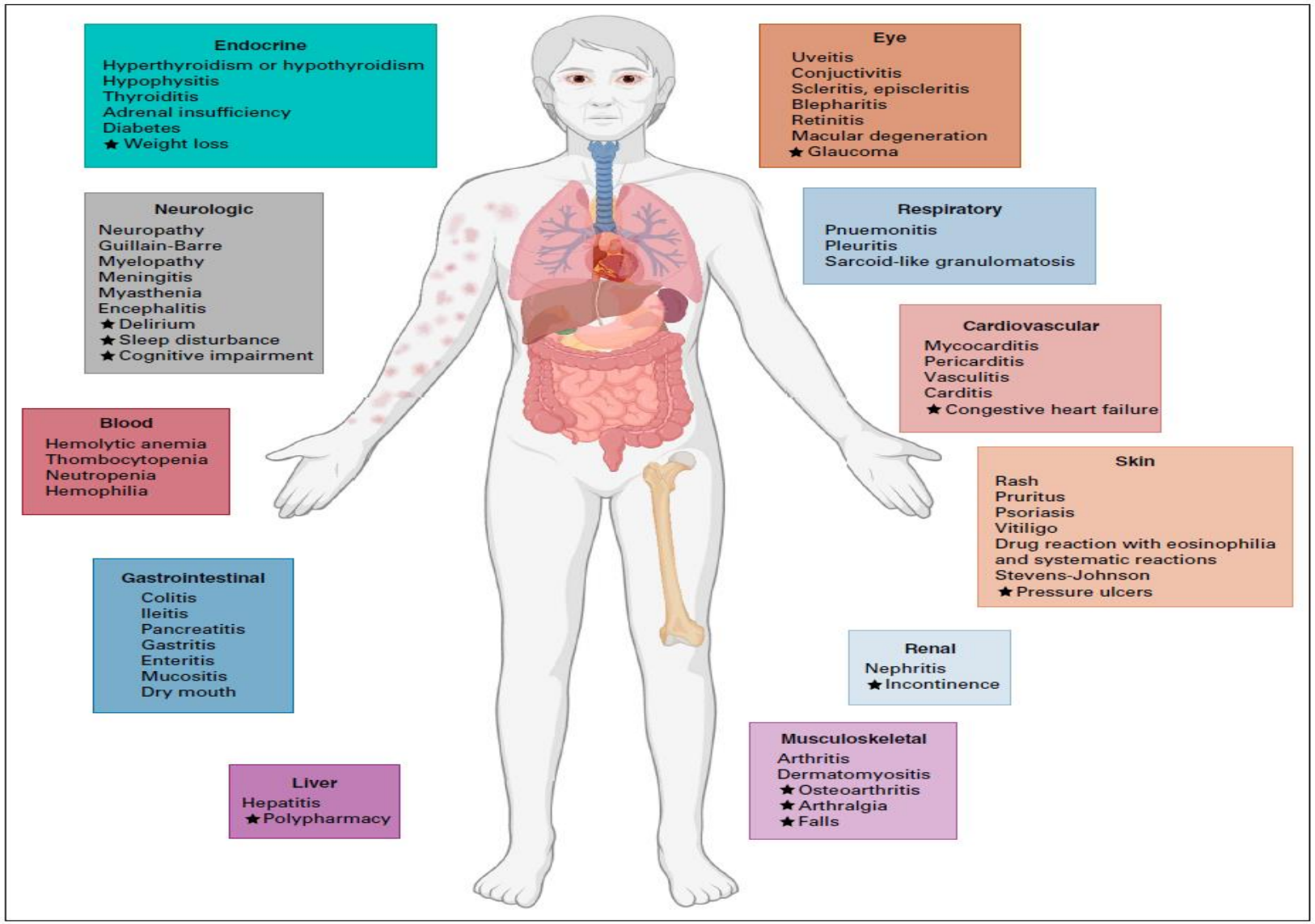

Presley et al.; JCO 2021

COMPREHENSIVE CANCER CENTER VIENNA

Nebenwirkung und Outcome

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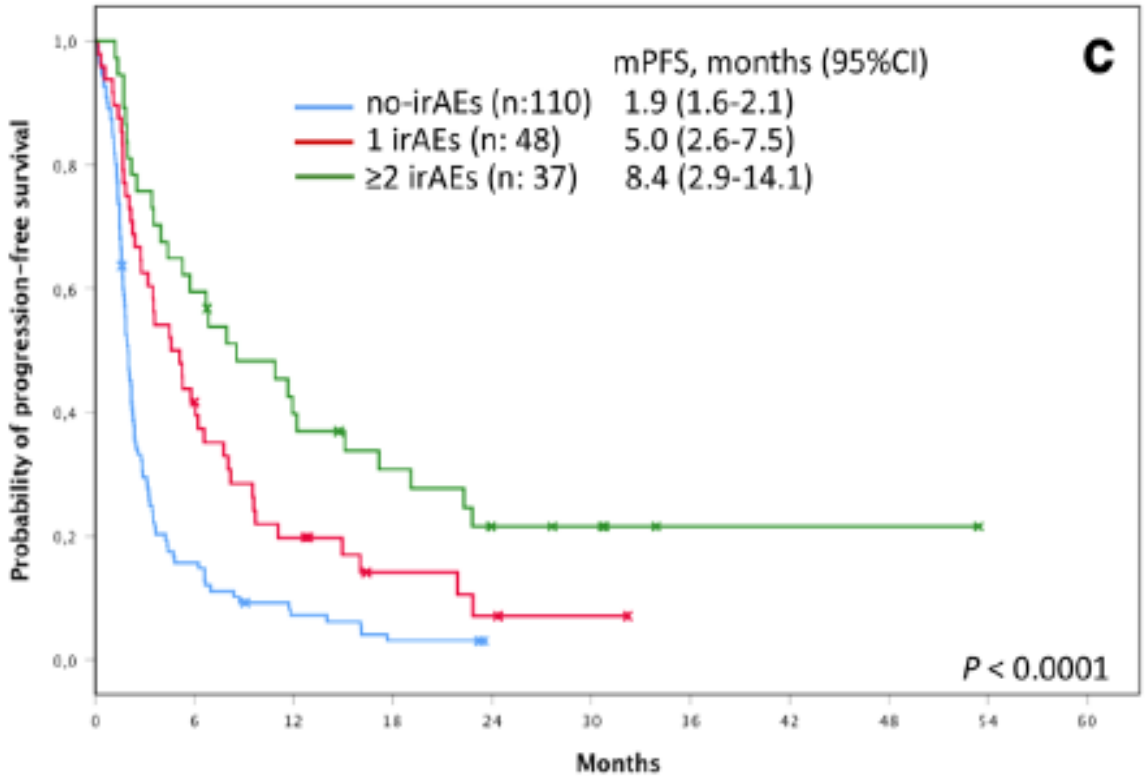

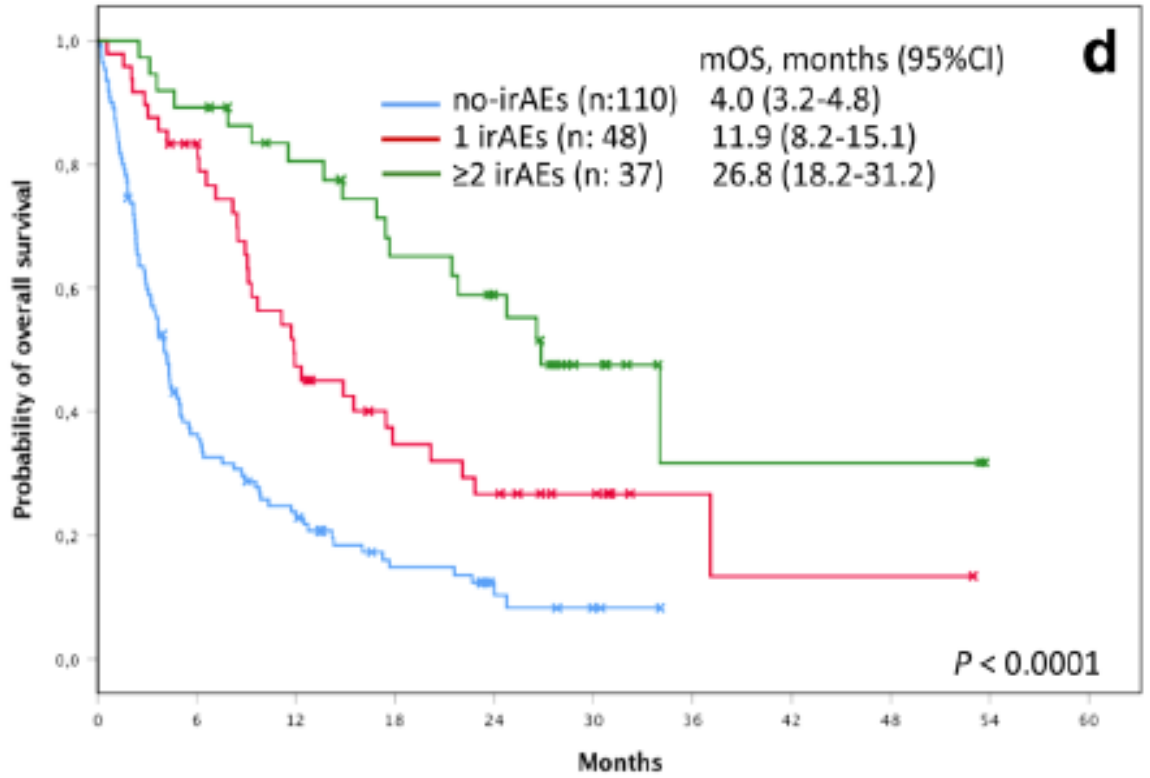

Ricciuti et al.; Journal of Cancer Research and Clinical Oncology 2019

COMPREHENSIVE CANCER CENTER VIENNA

Case

MEDICAL UNIVERSITY OF VIENNA

- 76 jährige weibliche Patientin
- ECOG: 0
- Nikotin 20 pack years
- Mundboden Ca 3/2021; St.p. Radiatio
- Rezidiv 10/2021+Lungenmetastasen
- Histo: Plattenepithel Ca.; PD-L1 CPS 30

COMPREHENSIVE CANCER CENTER VIENNA

Bildgebung

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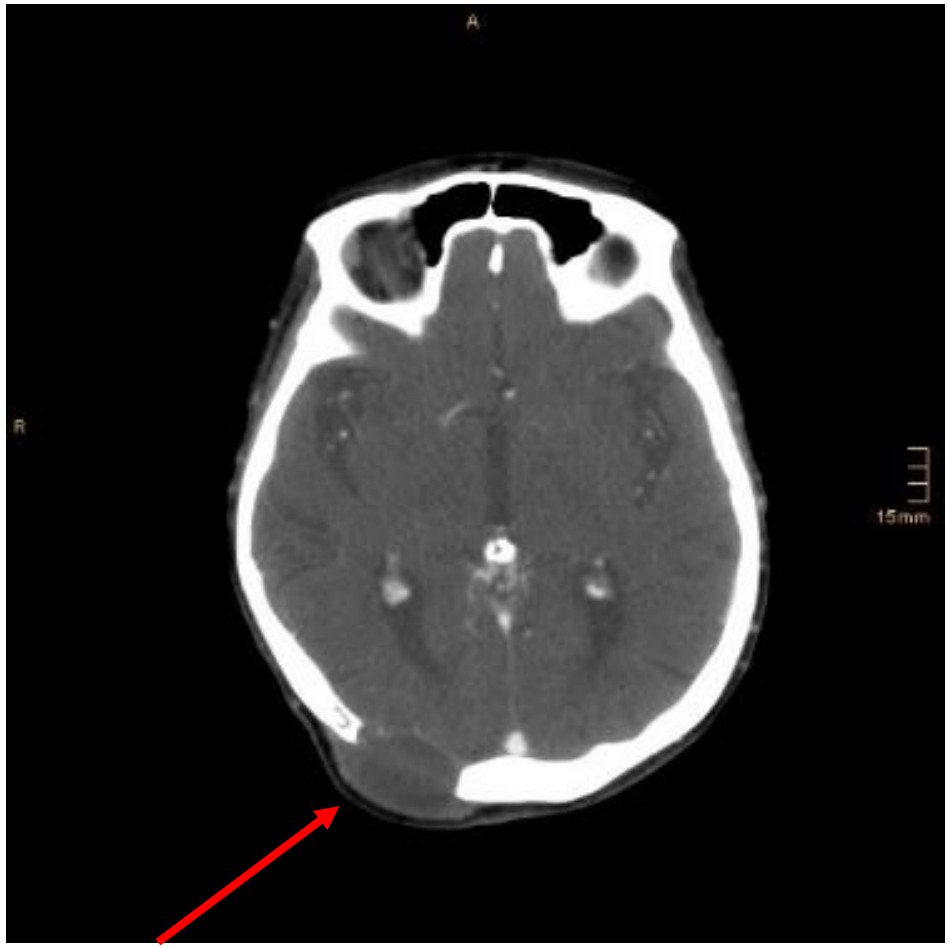
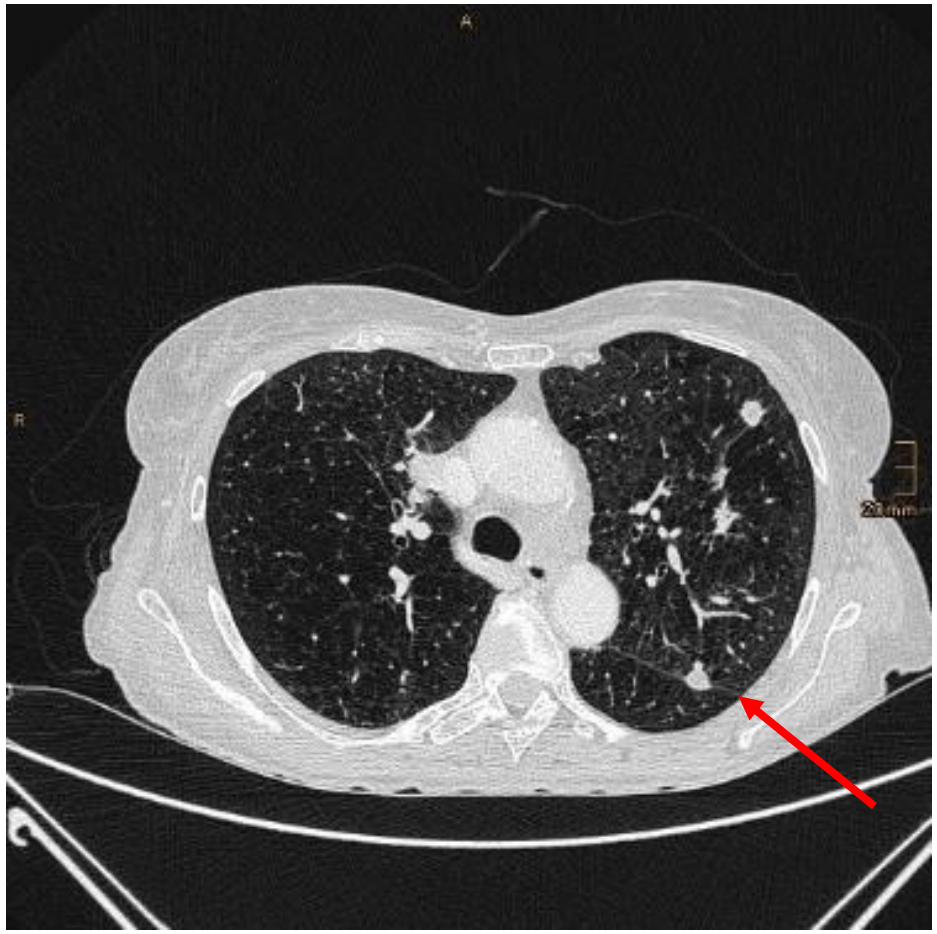
Ad Pembrolizumab Monotherapie 200mg (einmalig verabreicht)



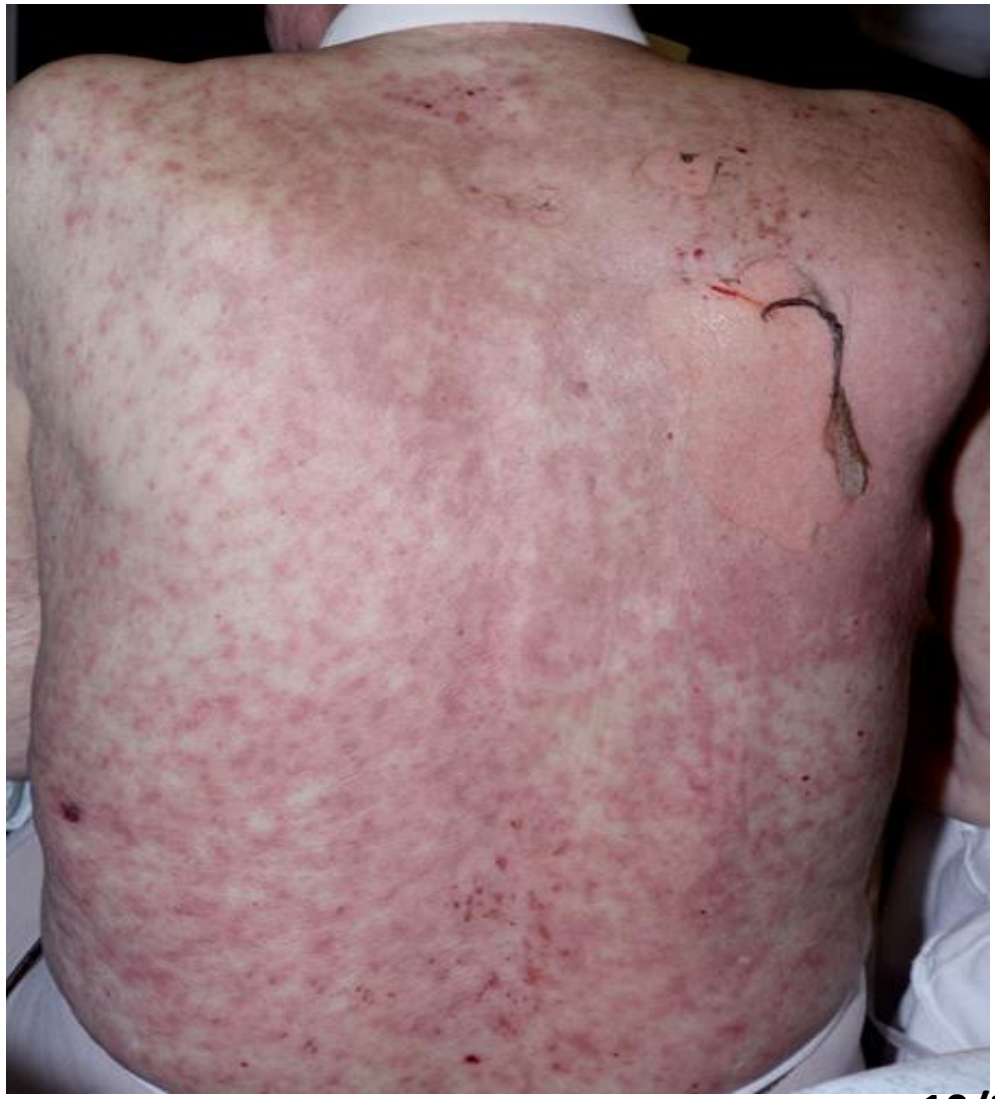


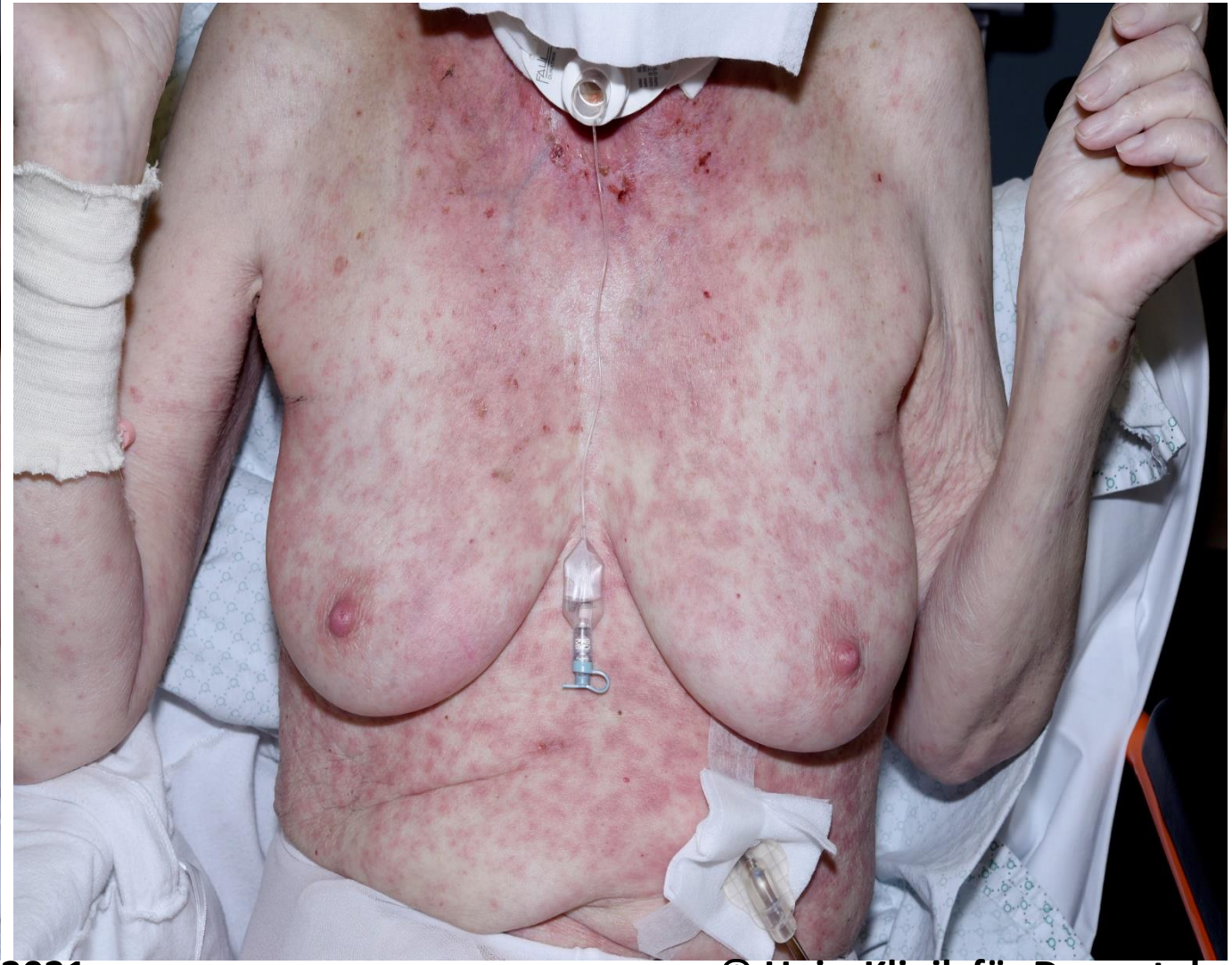
10/2021

COMPREHENSIVE CANCER CENTER VIENNA

Stevens Johnson Syndrom

MEDICAL UNIVERSITY OF VIENNA





COMPREHENSIVE CANCER CENTER VIENNA

Stevens Johnson Syndrom

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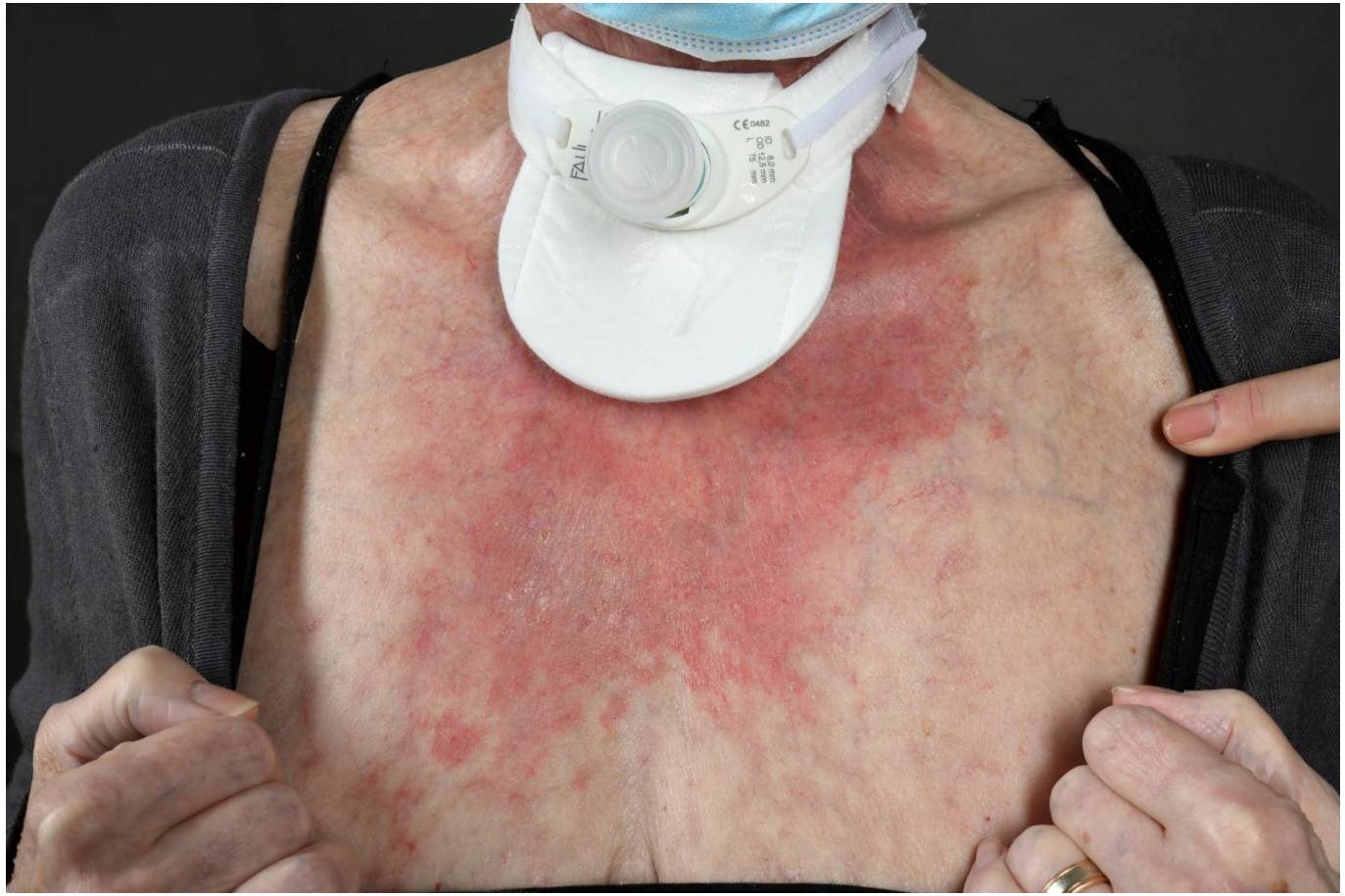
Lokaltherapie, Corticosteroide und Immunglobuline



12/2021

COMPREHENSIVE CANCER CENTER VIENNA

Bildgebung

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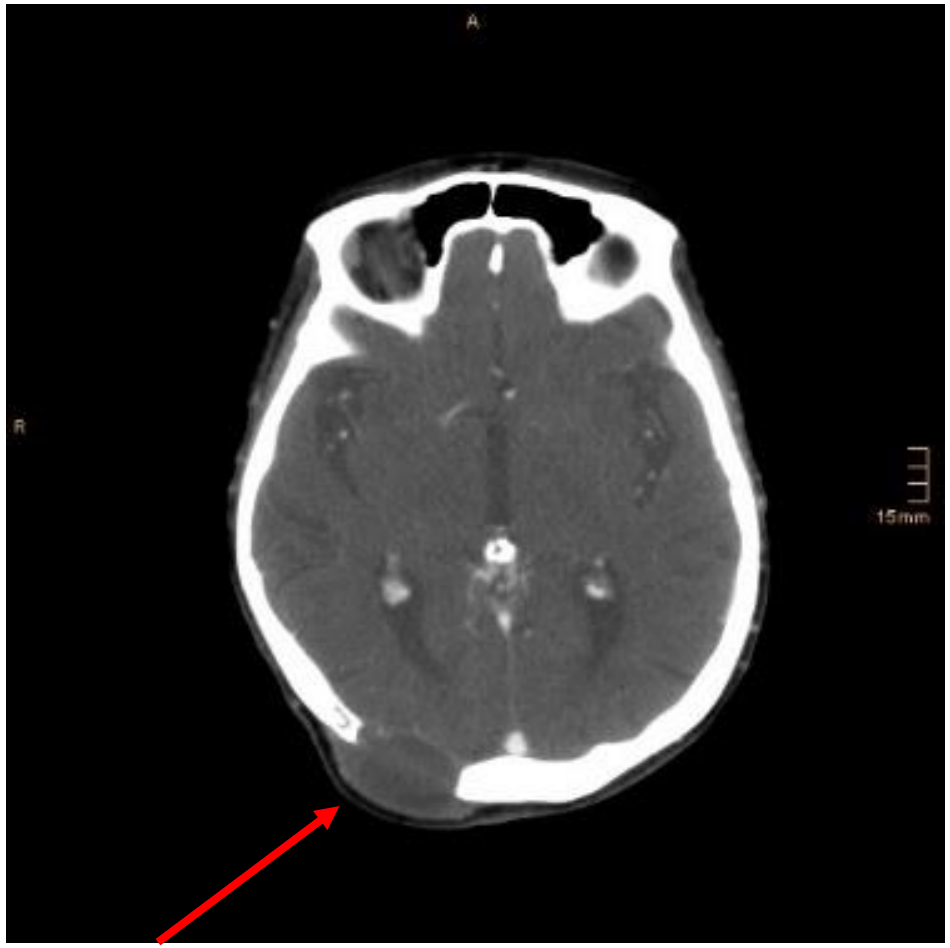
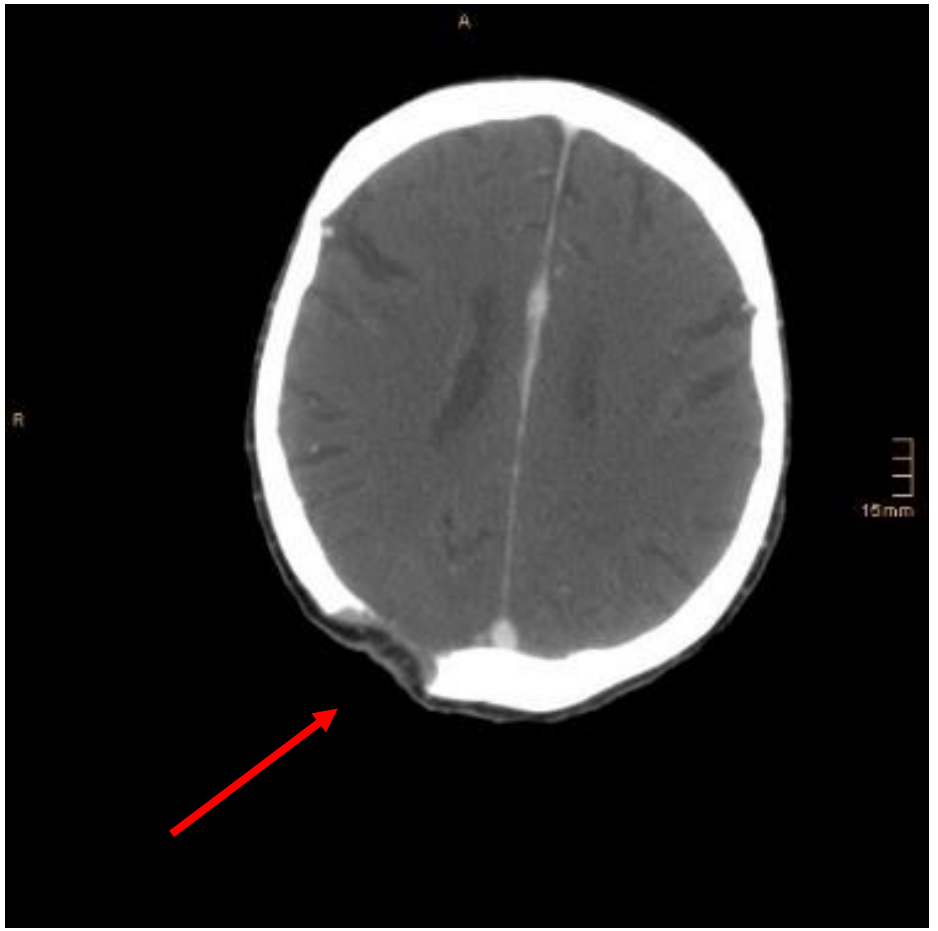
Pembrolizumab Monotherapie 200mg (einmalig verabreicht)



10/2021



12/2021

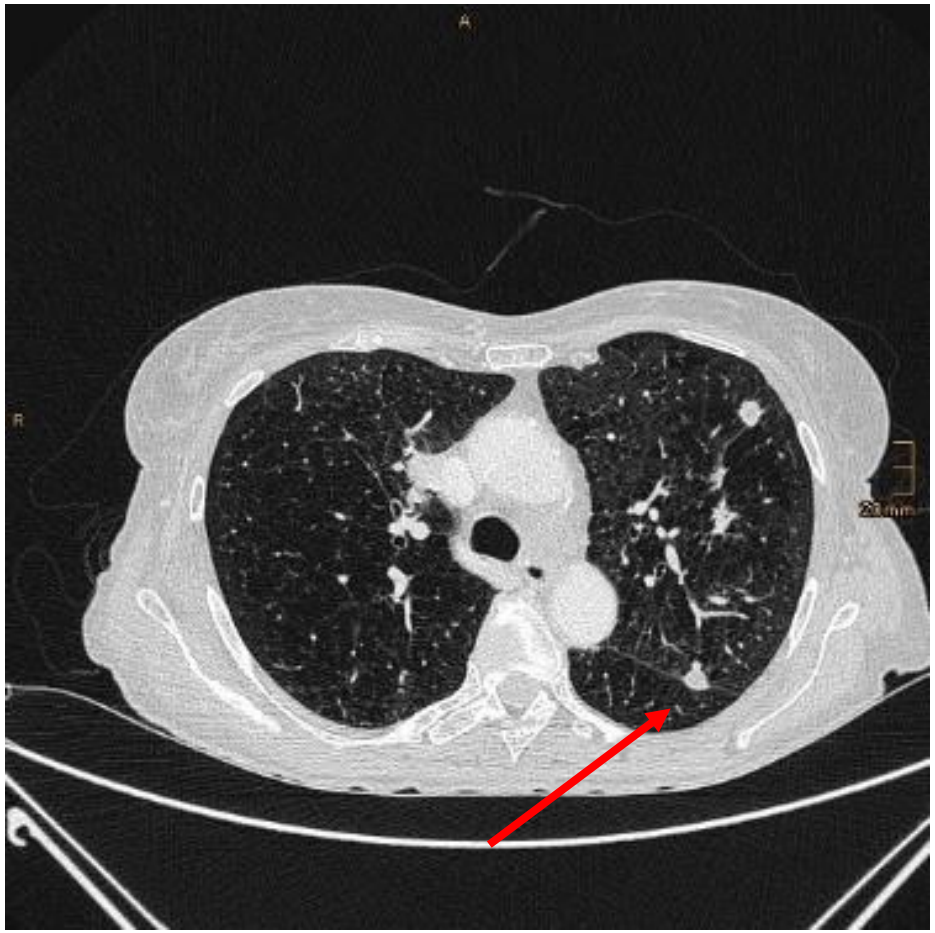
Images: Prof.Nemec; Univ.Klinik für Radiologie

COMPREHENSIVE CANCER CENTER VIENNA

Bildgebung

MEDICAL UNIVERSITY OF VIENNA

Pembrolizumab Monotherapie 200mg (einmalig verabreicht)



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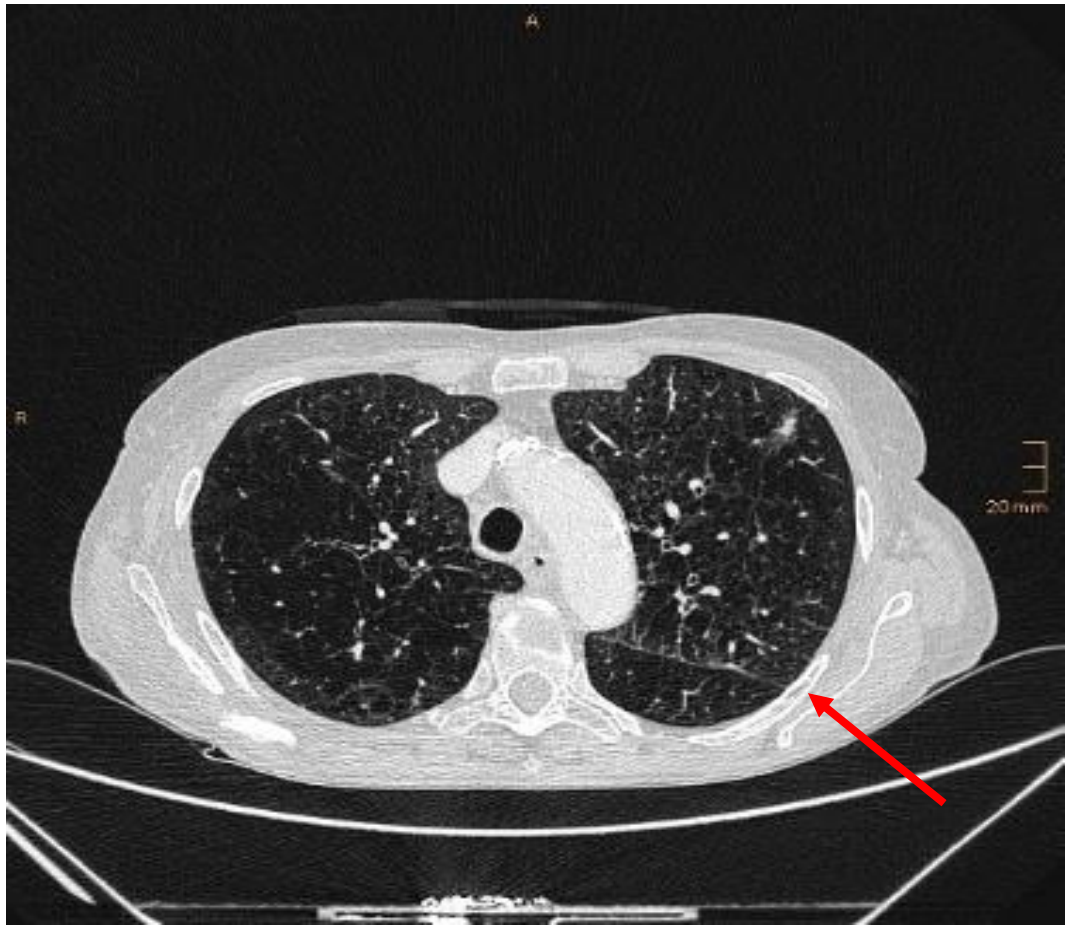

12/2021

Images: Prof.Nemec; Univ.Klinik für Radiologie

COMPREHENSIVE CANCER CENTER VIENNA

Schwere irAEs und Outcome

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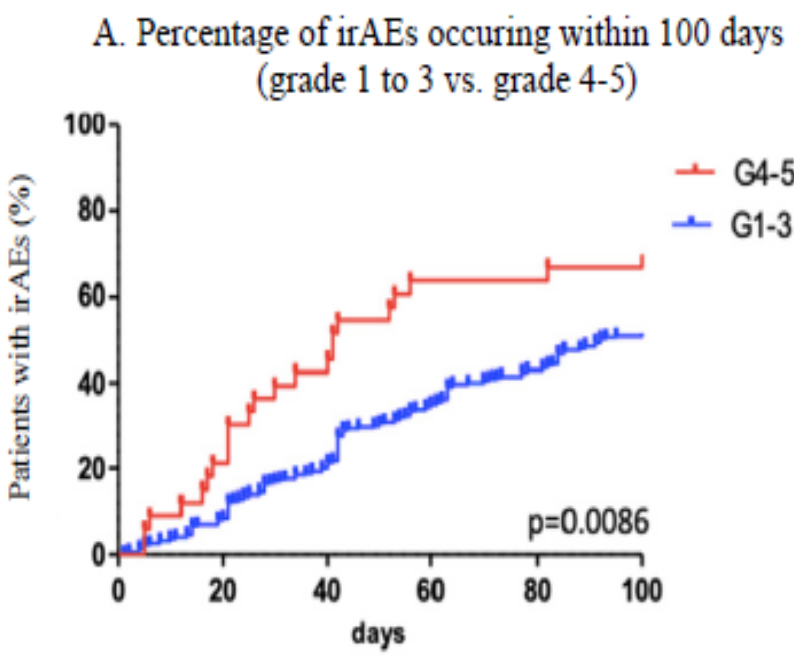

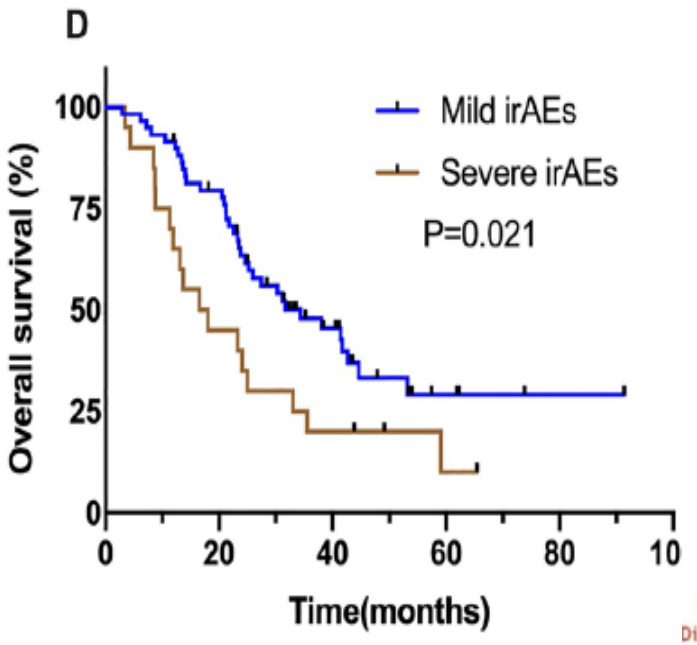

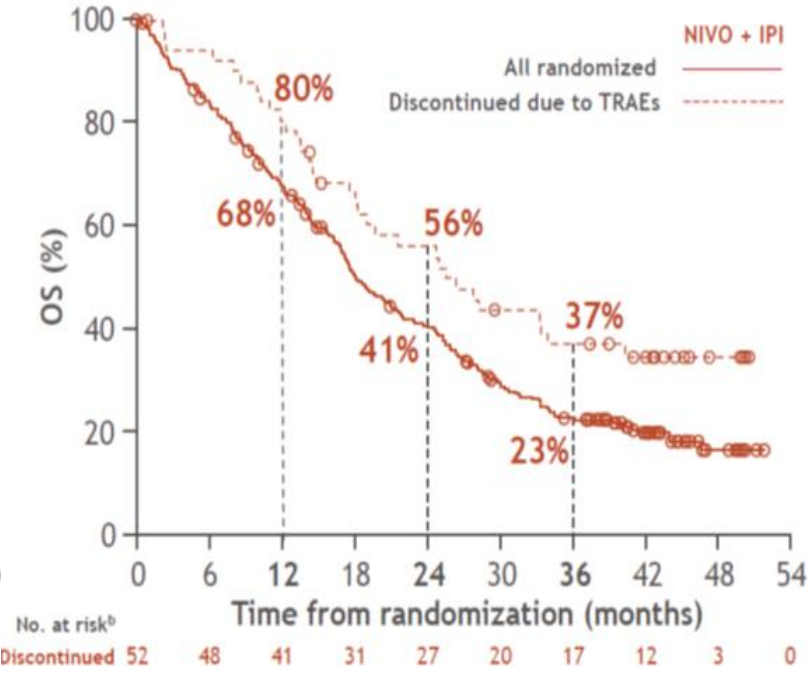

Ruste et al.; EJC 2021; Wang et al.; Cancer Immuology 2021; Peters, ESMO 2020

COMPREHENSIVE CANCER CENTER VIENNA

Take home message III

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- irAes sind mit dem Outcome assoziiert
- Schwere irAEs treten früher auf als leichte irAes
- Wirkung reicht über das Absetzen hinaus

COMPREHENSIVE CANCER CENTER VIENNA

CPI und Dialyse

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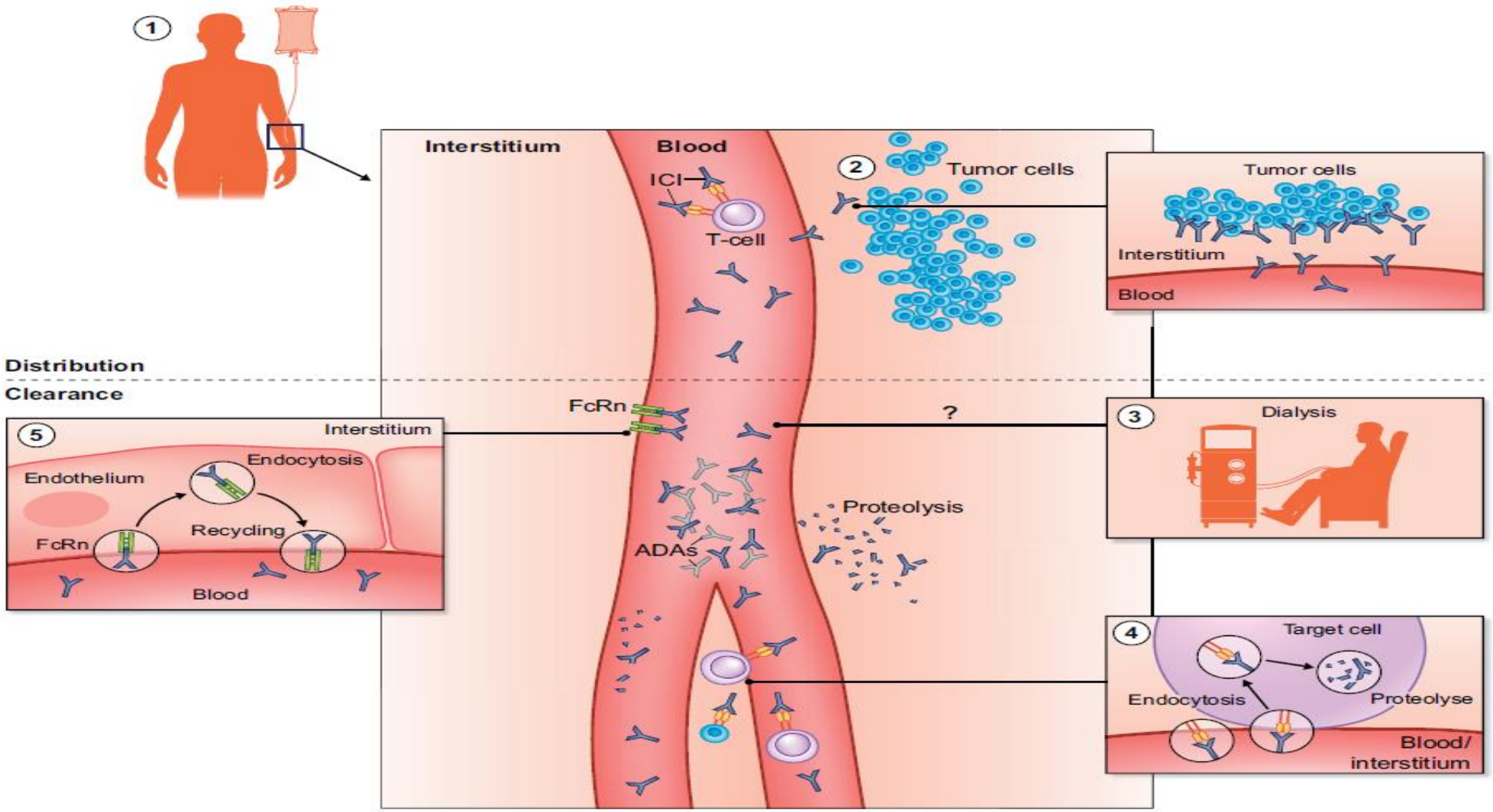
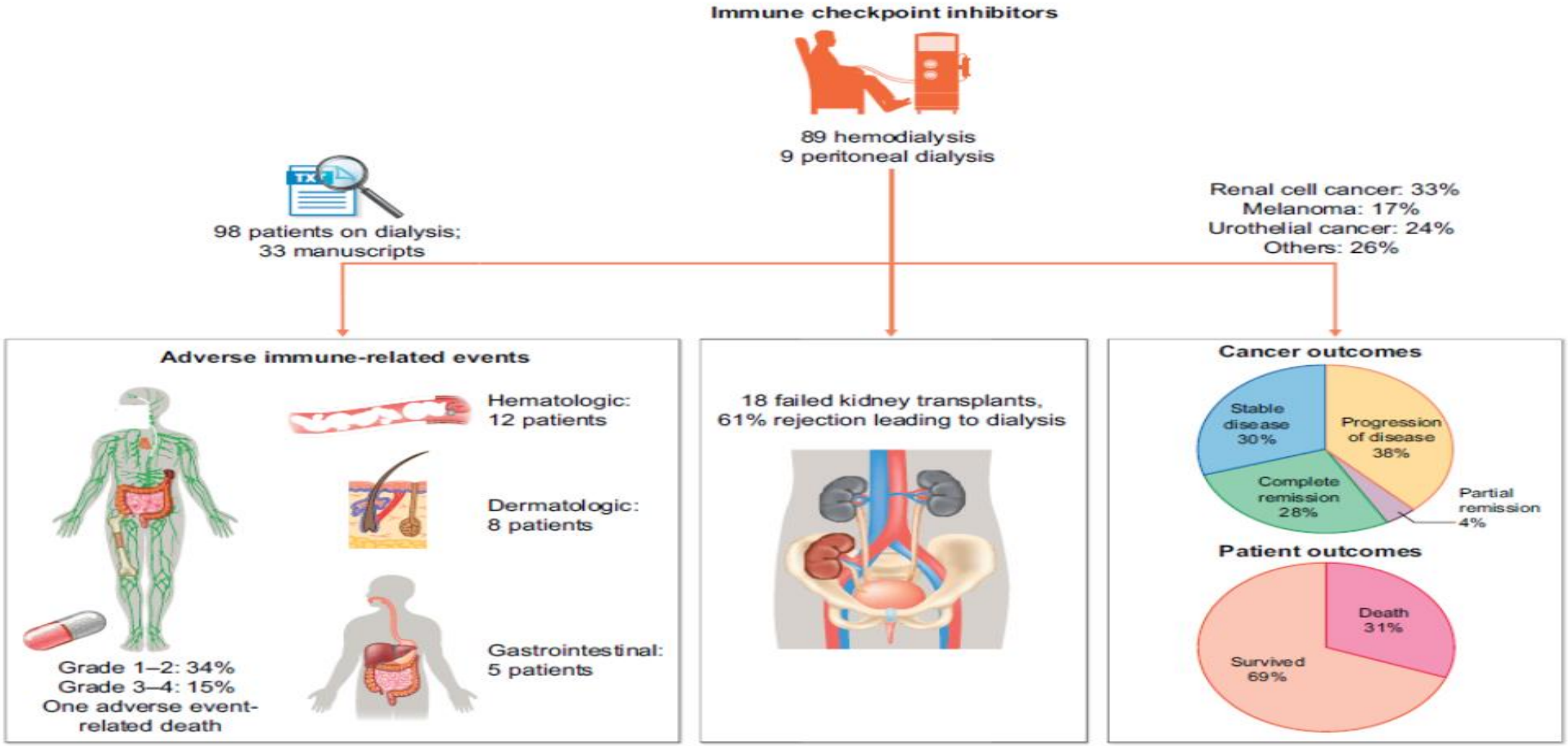


Kitchlu et al.; Clinical Kidney Journal 2021

COMPREHENSIVE CANCER CENTER VIENNA

CPI und Dialyse

MEDICAL UNIVERSITY OF VIENNA



Kitchlu et al.; Clinical Kidney Journal 2021

COMPREHENSIVE CANCER CENTER VIENNA

Organtransplantation

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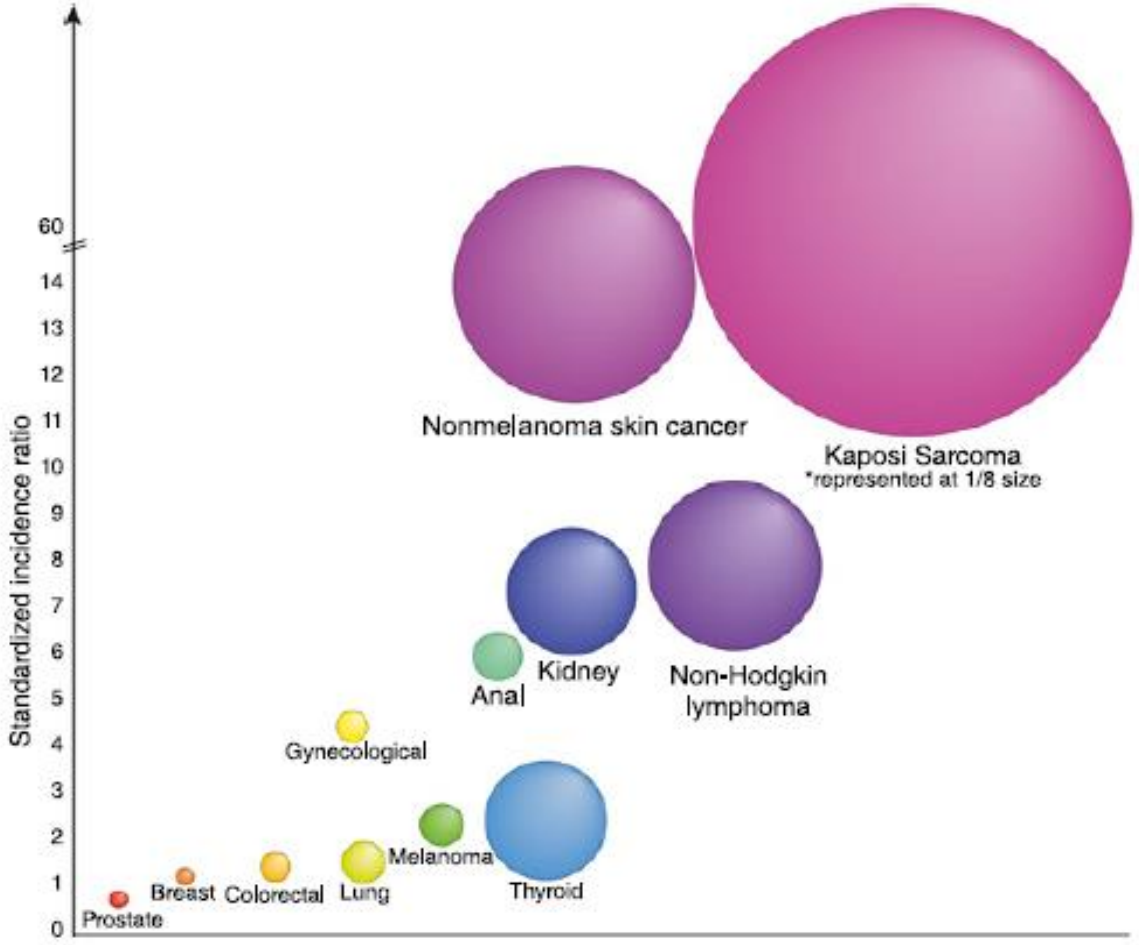
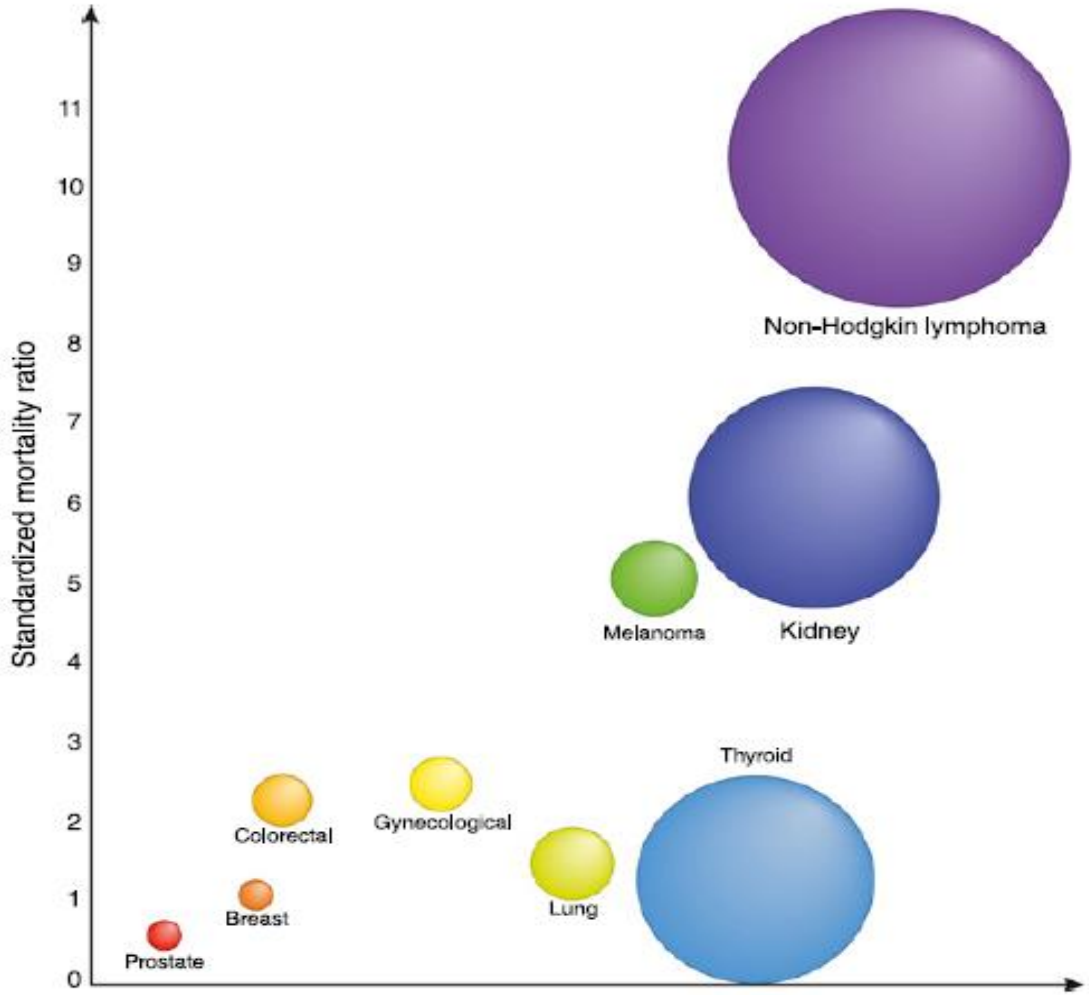


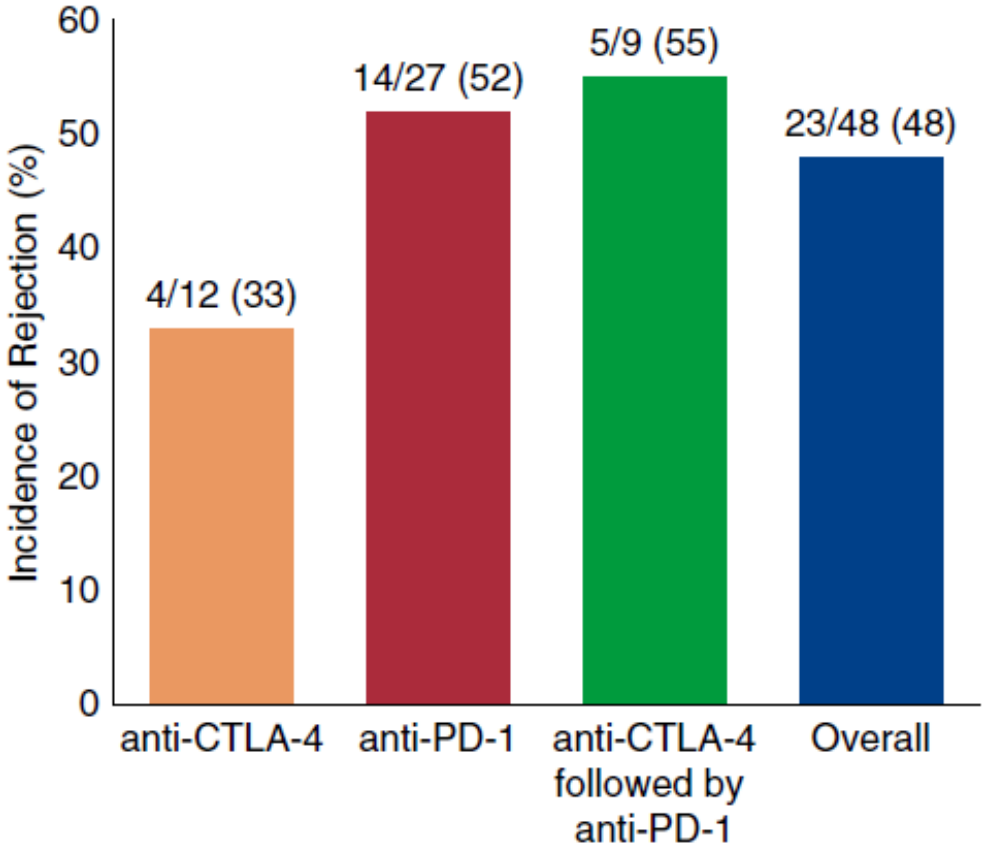


AL-Adra et al; CJASN 2021

COMPREHENSIVE CANCER CENTER VIENNA

Immuntherapie bei Organtransplatierten

MEDICAL UNIVERSITY OF VIENNA



Mittal et al.; American Journal of Transplantation 2017

COMPREHENSIVE CANCER CENTER VIENNA

Immuntherapie bei Organtransplatierten

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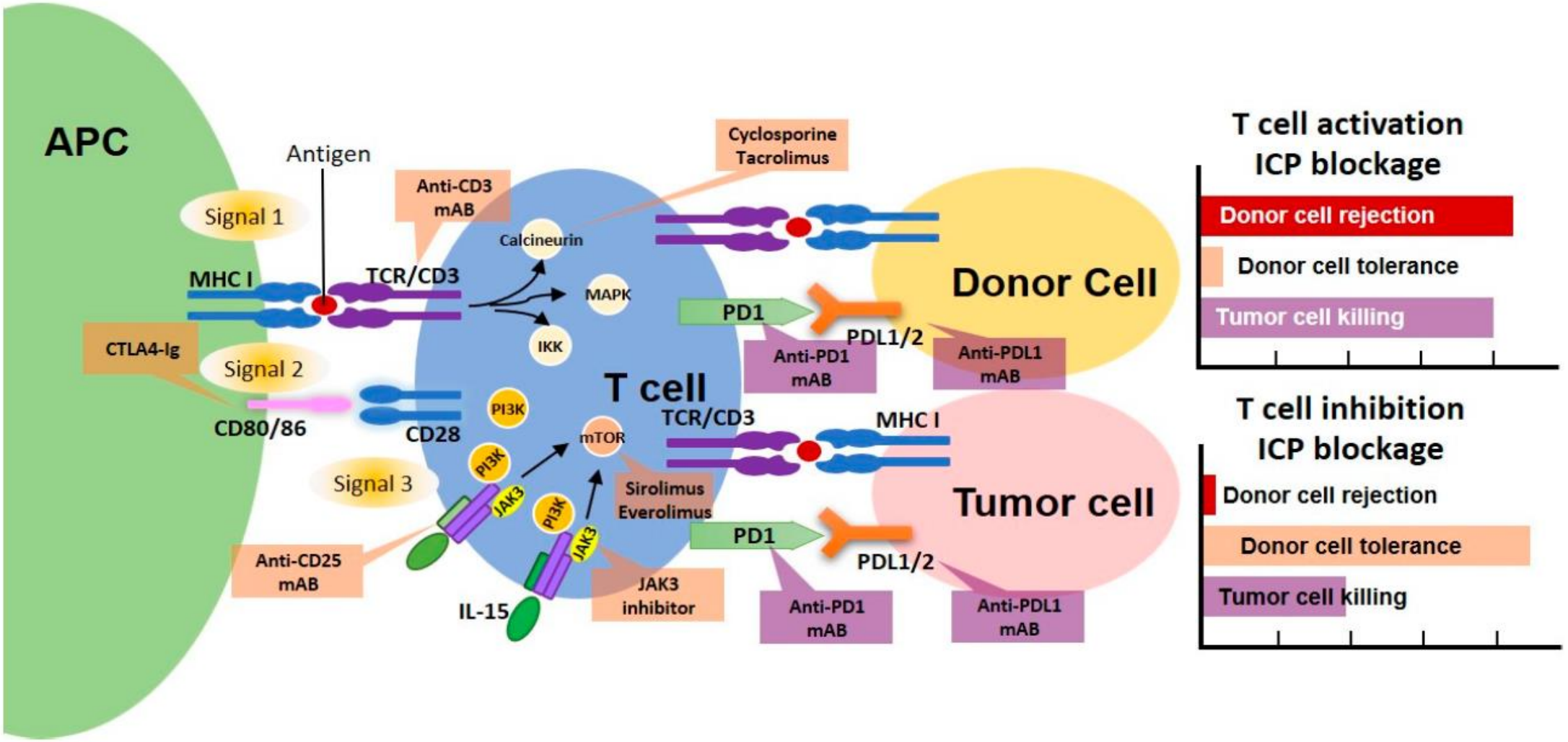

Lai et al.; International Journal of Molecular Sciences 2019

COMPREHENSIVE CANCER CENTER VIENNA

Case

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- 55 jähriger männlicher Patient
- ECOG: 2
- NTX 2008 wg. Schrumpfnieren
- cSCC mit multiplen Resektionen
- St.p. Radiatio
- Rezidiv 12/21

COMPREHENSIVE CANCER CENTER VIENNA

Bildgebung

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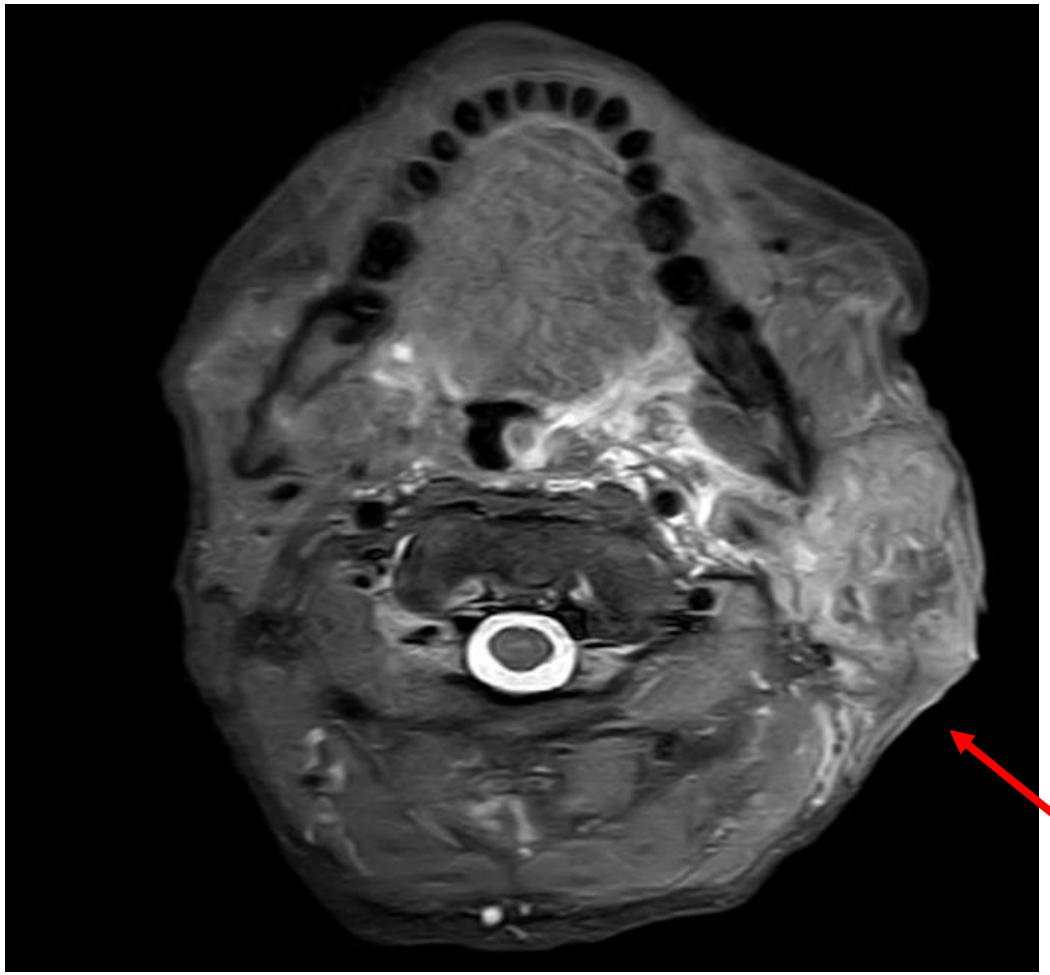

BX Transplantat

Fortgeschrittener, chronischer Schaden des Transplantates mit dem Bild einer sklerosierenden Glomerulopathie nach Art einer abgelaufenen Glomerulonephritis mit sekundären Schlingensklerosen - über die Ergebnisse der elektronenmikroskopischen Untersuchung zwecks Beurteilung der podozytären Fußfortsätze wird in einem Nachtragsbefund berichtet.
Zusätzlich hochgradige Arterio-Arteriolosklerose (hypertensive +/- Calcineurininhibitortoxizität-assoziierte Angiolopathie?).
Hochgradige interstitielle Fibrose mit Tubulusatrophie.

TB Empfehlung: Cemiplimab

11/2021

COMPREHENSIVE CANCER CENTER VIENNA

Case

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Prä-Cemiplimab

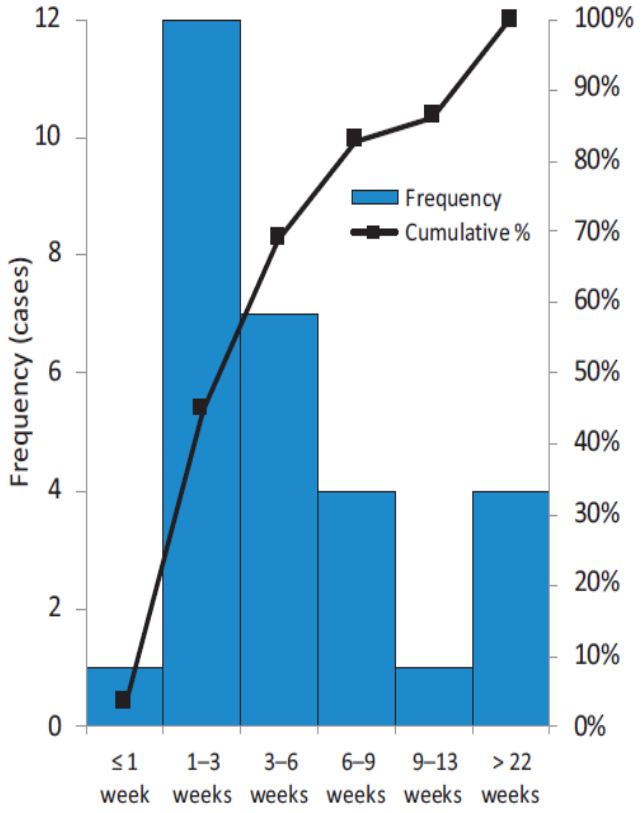
Natrium	↓	131	136 - 145	mmol/L
Kalium	↓	3,28	3,5 - 5,1	mmol/L
Chlorid	↓	90	98 - 107	mmol/L
Kalzium		2.17	2.15 - 2.50	mmol/L
Anorganisches Phosphat	↑	1.96	0.81 - 1.45	mmol/L
Magnesium		0,84	0,66 - 1,07	mmol/L
Kalzium - Phosphat - Produkt		4.25		mmol^2/L^2
Kreatinin	↑	7.84	0.70 - 1.20	mg/dL
Harnstoff - N	↑	110.2	6 - 20	mg/dL
Hämolyseindex		2		
Albumin		36.8	35 - 52	g/L
LDH	↑	341	< 250	U/L

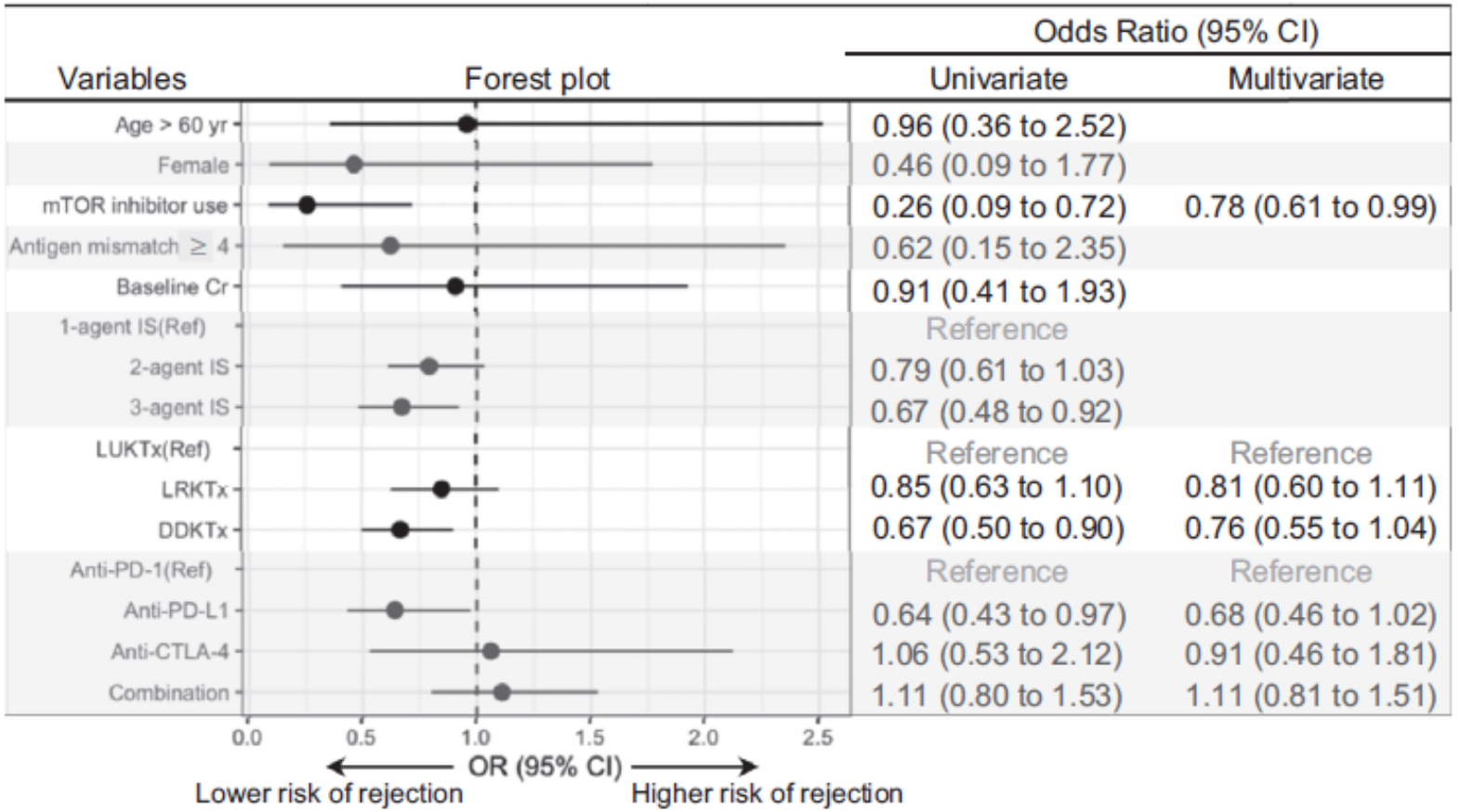
Post-Cemiplimab

>	Natrium	↓	129	136 - 145	mmol/L
>	Kalium		3.85	3.5 - 5.1	mmol/L
>	Chlorid	↓	87	98 - 107	mmol/L
>	Kalzium		2.15	2.15 - 2.50	mmol/L
>	Kalzium (Albumin korrigiert) *auf 40 g/L Albumin korrigiert*		2.32		mmol/L
>	Anorganisches Phosphat	↑	3.00	0.81 - 1.45	mmol/L
>	Magnesium		0,90	0,66 - 1,07	mmol/L
>	Eisen		90	33 - 193	µg/dL
>	Kreatinin	↑	9.33	0.70 - 1.20	mg/dL
>	Harnstoff - N	↑	148.8	6 - 20	mg/dL
>	Harnsäure	↑	16.2	3.4 - 7.0	mg/dL
>	Gesamt Bilirubin		0.46	0.0 - 1.2	mg/dL
>	Hämolyseindex		1		
>	Eiweiß, gesamt	↓	54.8	64 - 83	g/L
>	Albumin	↓	33.1	35 - 52	g/L
>	Cholinesterase	↓	3.22	5.32 - 12.92	kU/L
>	Alkalische Phosphatase		51	40 - 130	U/L
>	ASAT (GOT)		12	< 50	U/L
>	ALAT (GPT)		8	< 50	U/L
>	Gamma - GT		13	< 60	U/L
>	LDH	↑	362	< 250	U/L

Immuntherapie und NTX

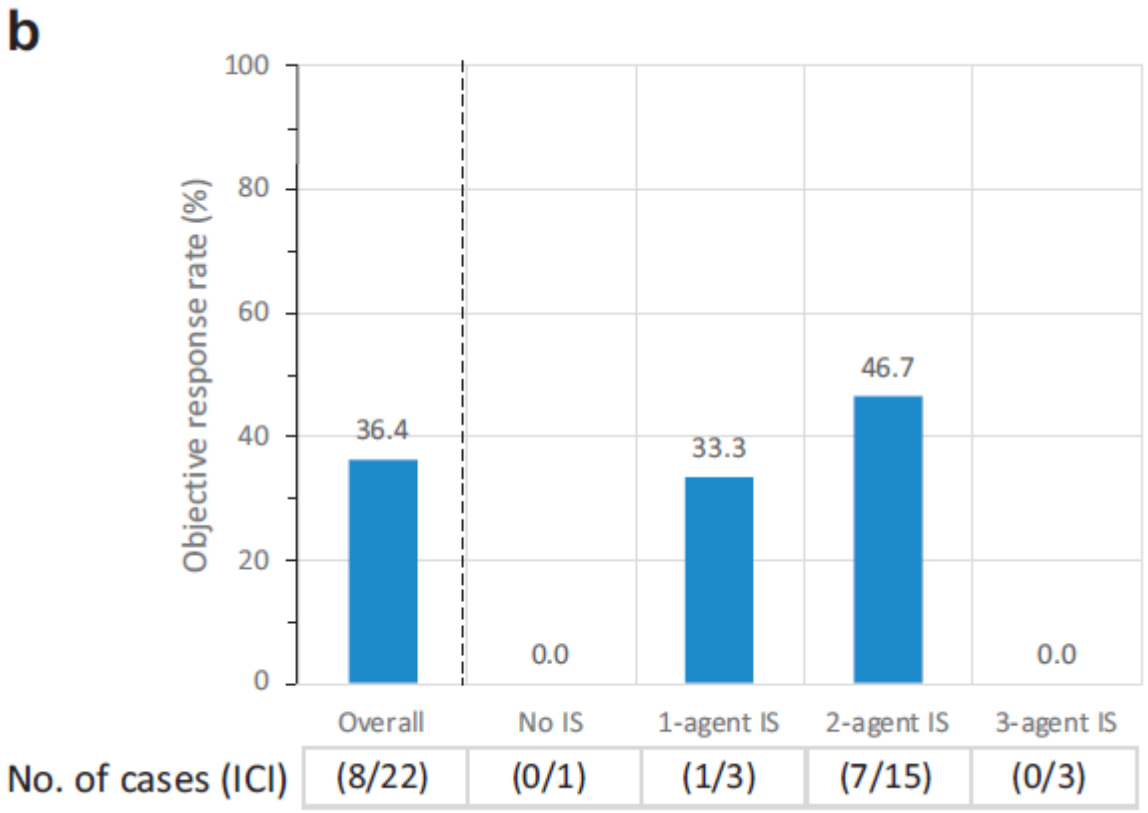
b





Murkami et al.; Kidney International 2021

Immuntherapie und NTX: ORR bei cSCC



mOS: 19.6 Monate

Murkami et al.; Kidney International 2021

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Take home message IV

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- Hohe Abstoßungsrate I bei Organtransplantierten
- Abstoßung frühes Event (mTOR Inhibitoren günstig)
- Längeres OS mit CPI aber kein Langzeitüberleben

COMPREHENSIVE CANCER CENTER VIENNA

Fragen?

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