COMPREHENSIVE CANCER CENTER VIENNA

MEDIZINISCHE UNIVERSITÄT WIEN

Allgemeines Krankenhaus der Stadt Wien

IKIM 2024

Lungenkrebs- ein Überblick

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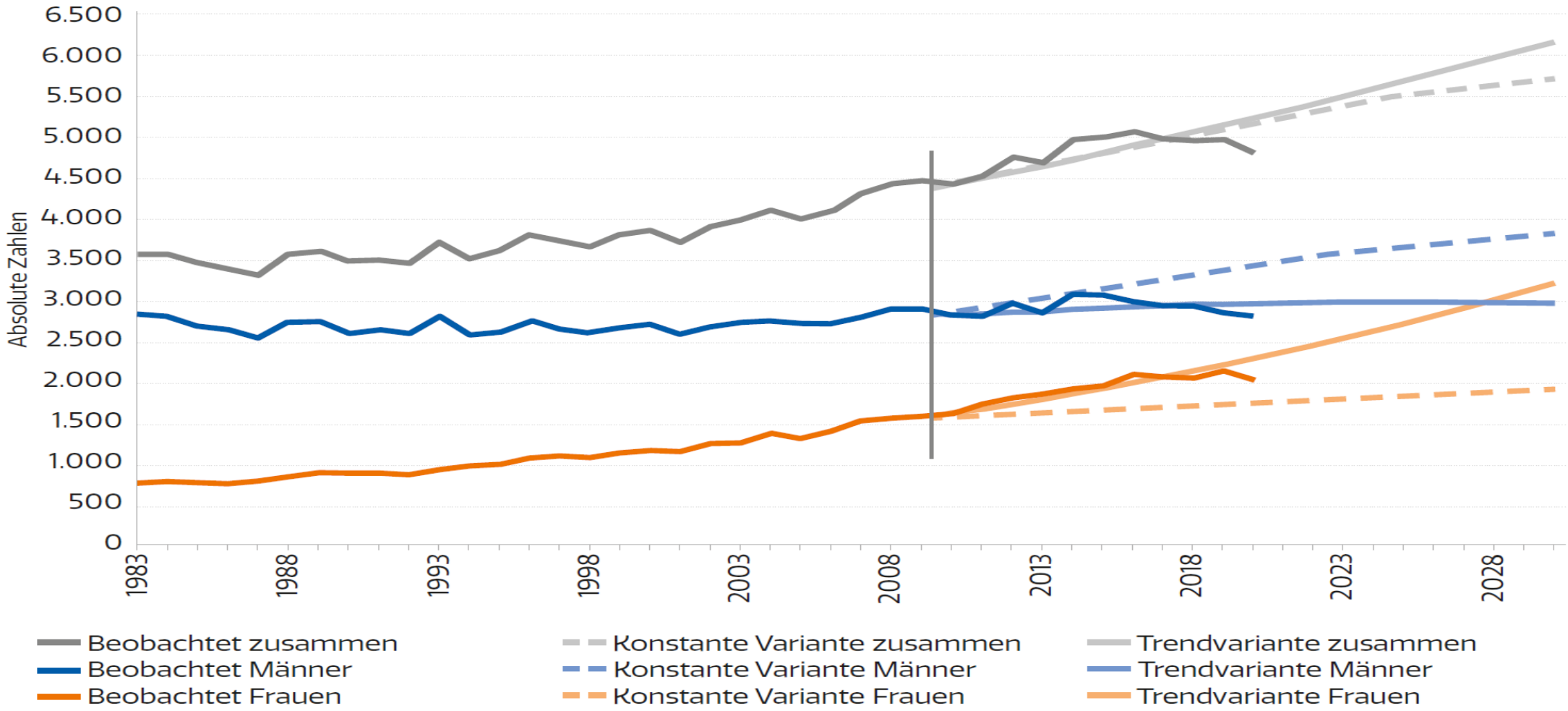
Lungenkrebs in Österreich

Entwicklung der Neuerkrankungen an Lungenkrebs in Österreich



Statistik Austria; Krebsreport 2023

Frage

Die häufigste Ursache für Lungenkrebs bei never smokern ist?

1) Radon Exposition
2) Asbest Exposition
3) Feinstaub Exposition
4) Beryllium Exposition

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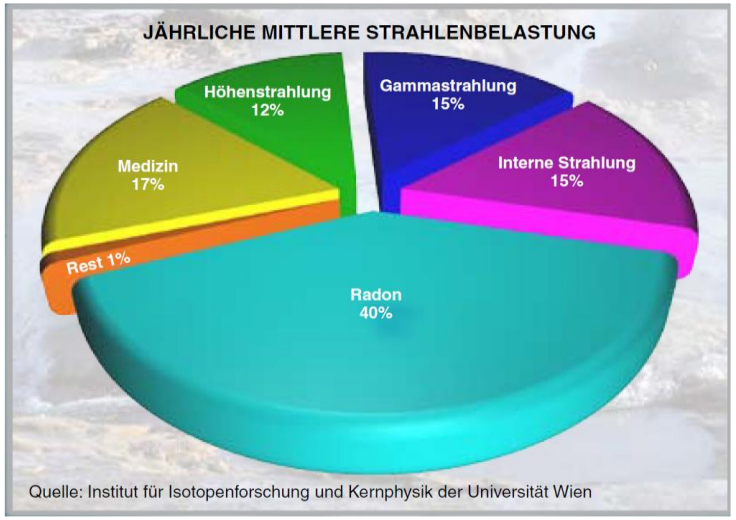
Lungenkrebs: Ursachen

80% durch Nikotinabusus



Radon häufigste Ursache bei never-smoker

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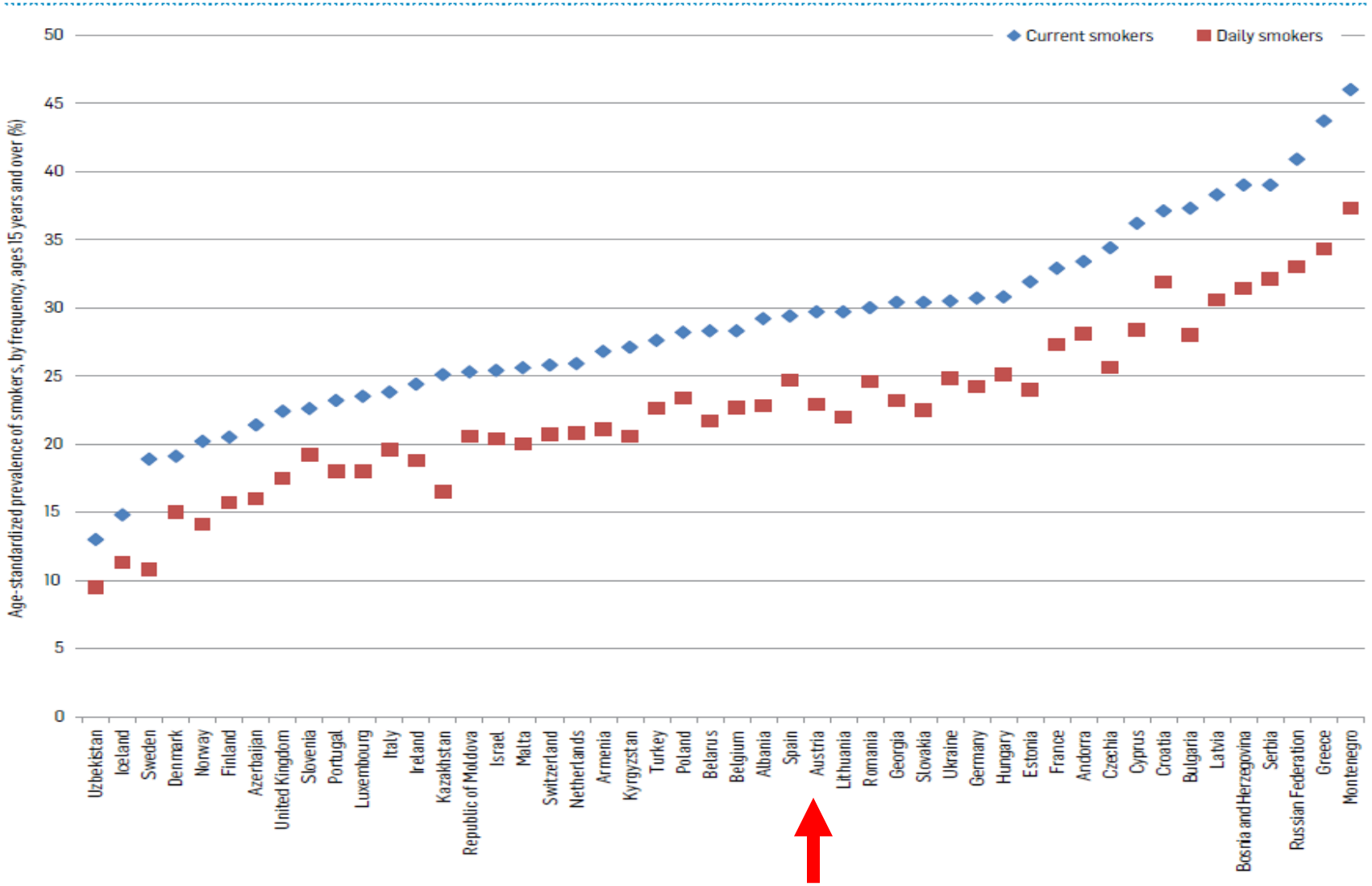
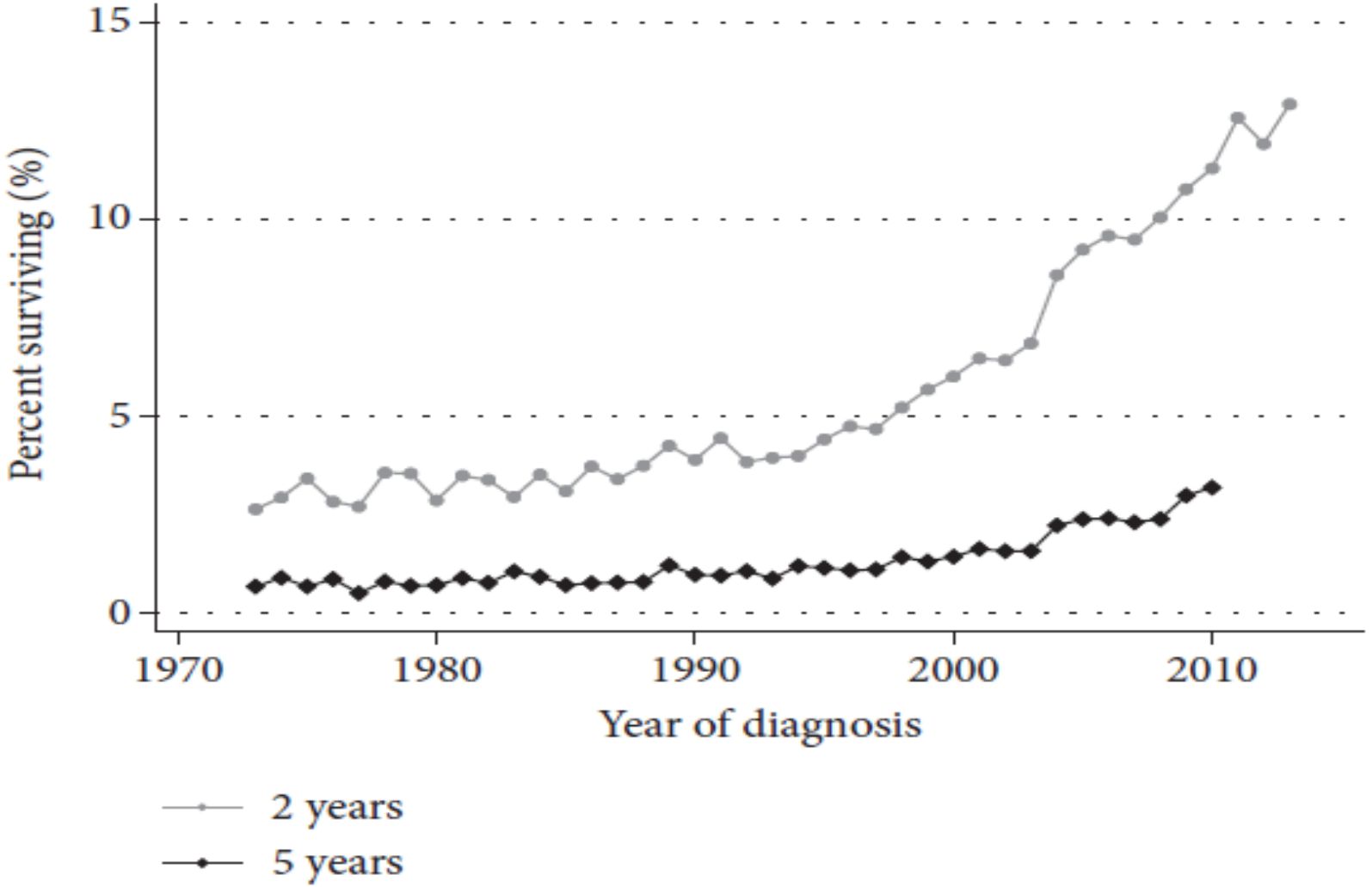
Rauchen in Österreich



European Tobacco Use; WHO 2019

NSCLC met.: Entwicklung OS

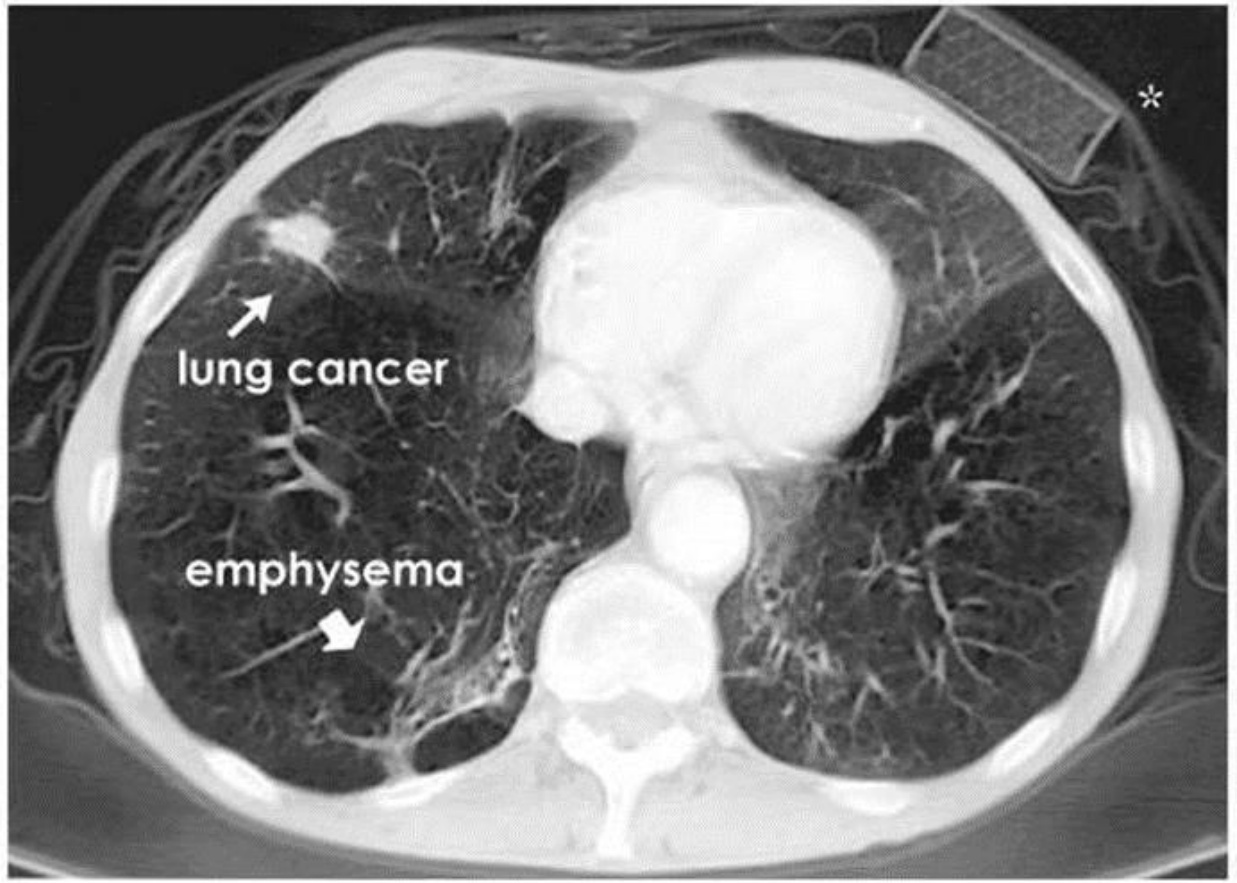


Bar et al.; Journal of Oncology 2021

Lungenkrebs: Symptome

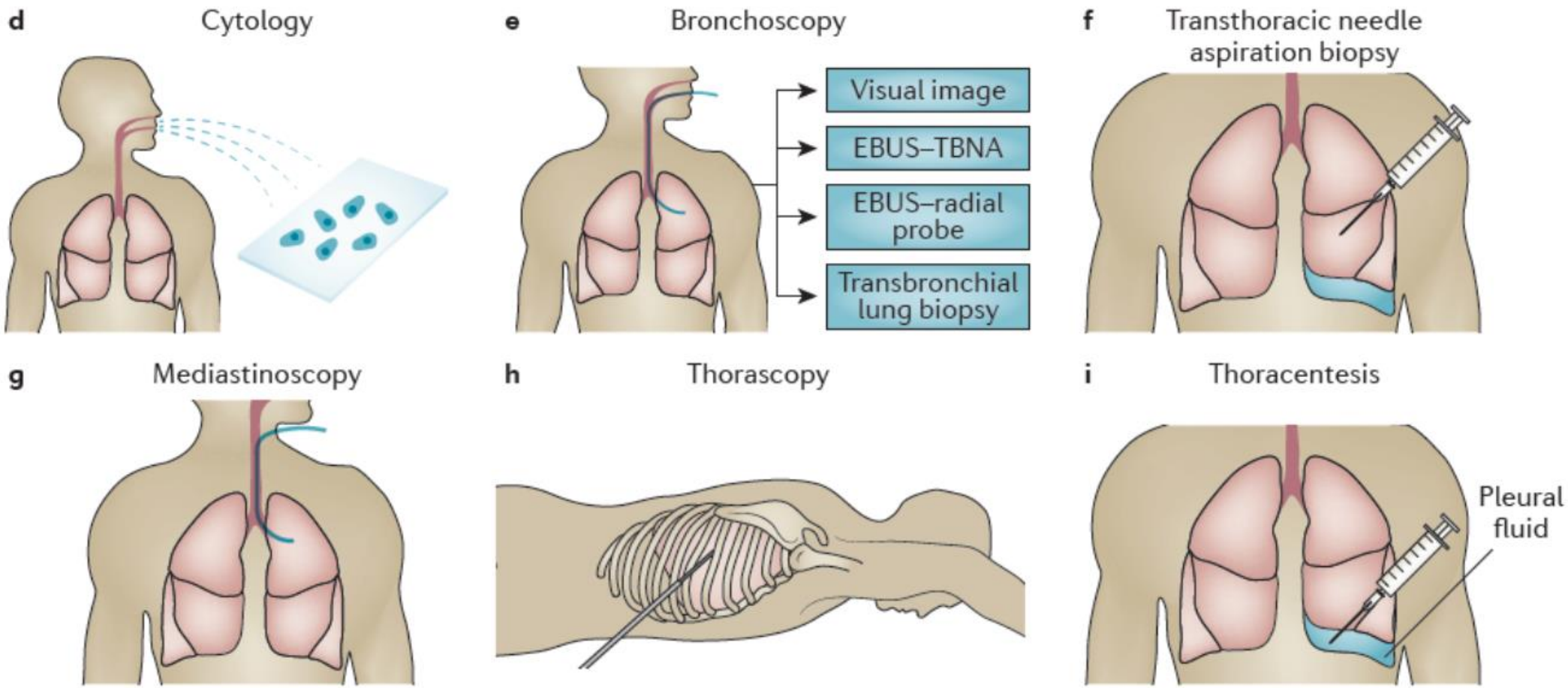
- Cough – 50 to 75 percent
- Hemoptysis – 25 to 50 percent
- Dyspnea – 25 percent
- Chest pain – 20 percent

Lungenkrebs: Diagnostik



McMullan; NEJM 2006

Lungenkrebs: Diagnostik



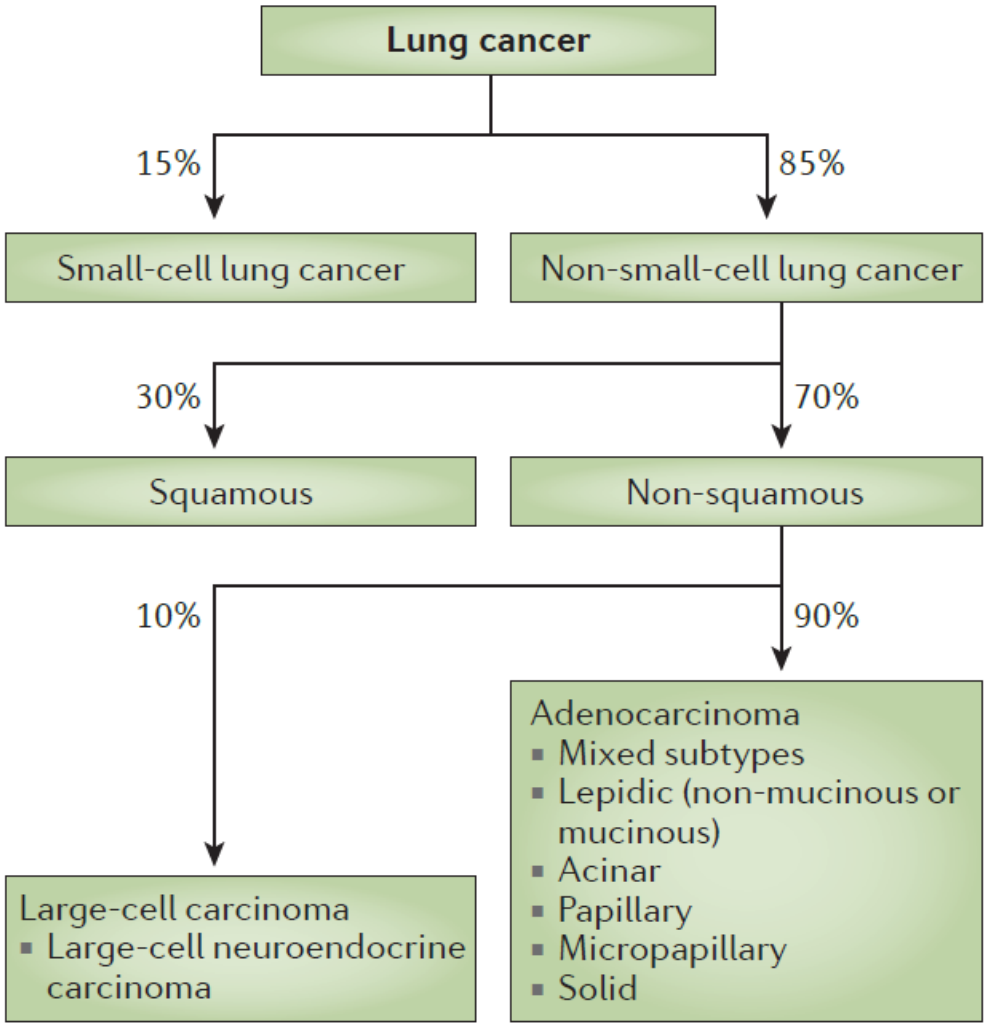
Gridelli et al. Nature reviews disease Primers 2015

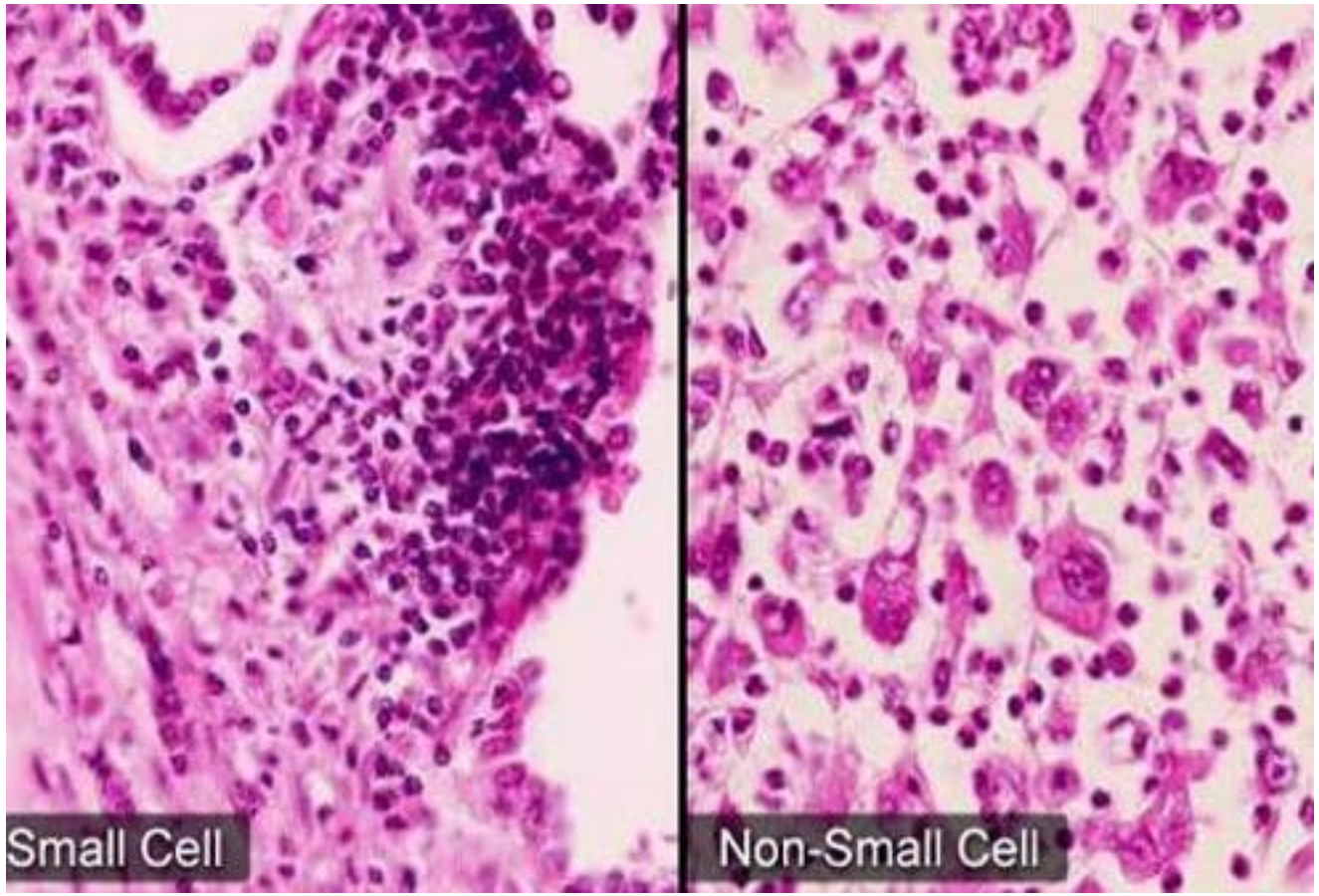
Frage

Der häufigste Subtyp ist?

1) Adenokarzinom
2) Kleinzellige Karzinom
3) Plattenepithelkarzinom

Lungenkrebs: Subtypen





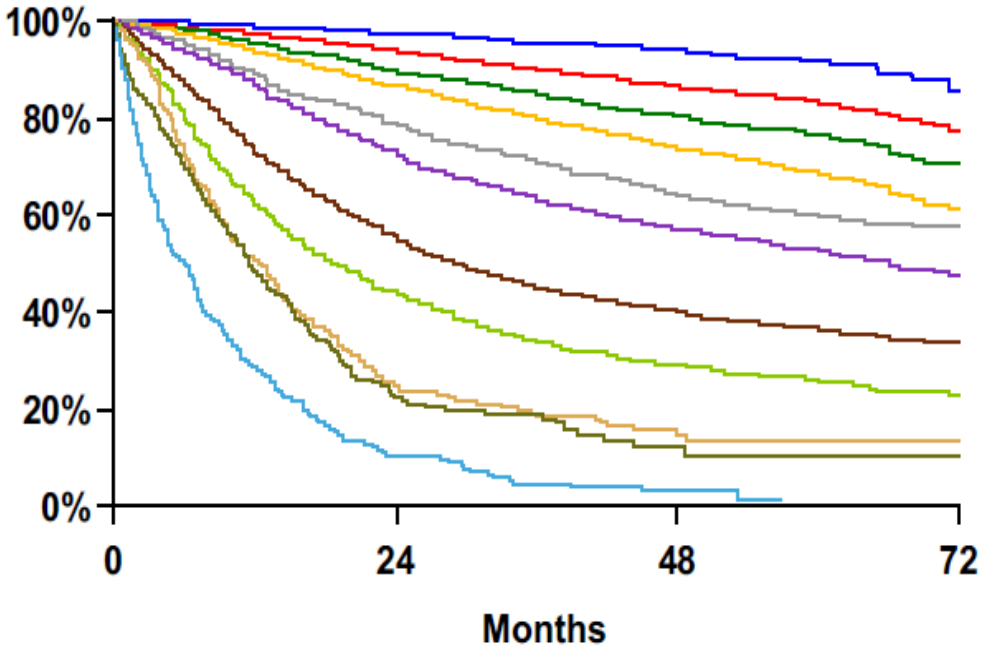
https://www.emedicinehealth.com/non-small-cell_lung_cancer/article_em.htm; Gridelli et al. Nature reviews disease Primers 2015

NSCLC: Stadium

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	**T1a(mi)**	**N0**	**M0**
	T1a	**N0**	**M0**
Stage IA2	**T1b**	**N0**	**M0**
Stage IA3	**T1c**	**N0**	**M0**
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	**T1a to c**	**N1**	**M0**
	T2a	**N1**	**M0**
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	**T1a to c**	**N2**	**M0**
	T2a to b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	**T1a to c**	**N3**	**M0**
	T2a to b	N3	M0
	T3	**N2**	**M0**
	T4	N2	M0
Stage IIIC	**T3**	**N3**	**M0**
	T4	**N3**	**M0**
Stage IVA	**Any T**	**Any N**	**M1a**
	Any T	**Any N**	**M1b**
Stage IVB	**Any T**	**Any N**	**M1c**

UptoDate Datenbank

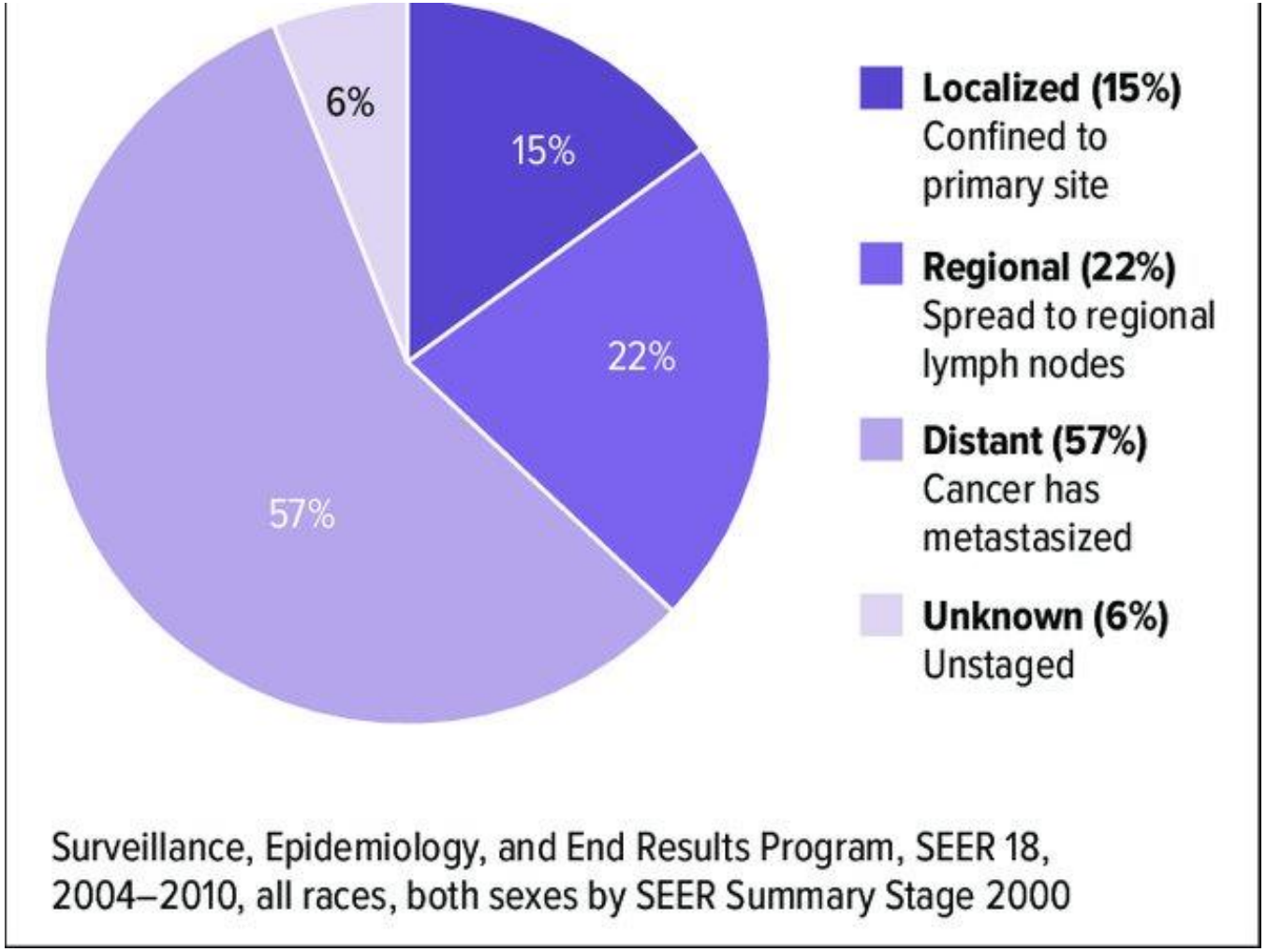
NSCLC: Stadium und Überleben



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Kalinke et al.; Molecular Oncology 2020

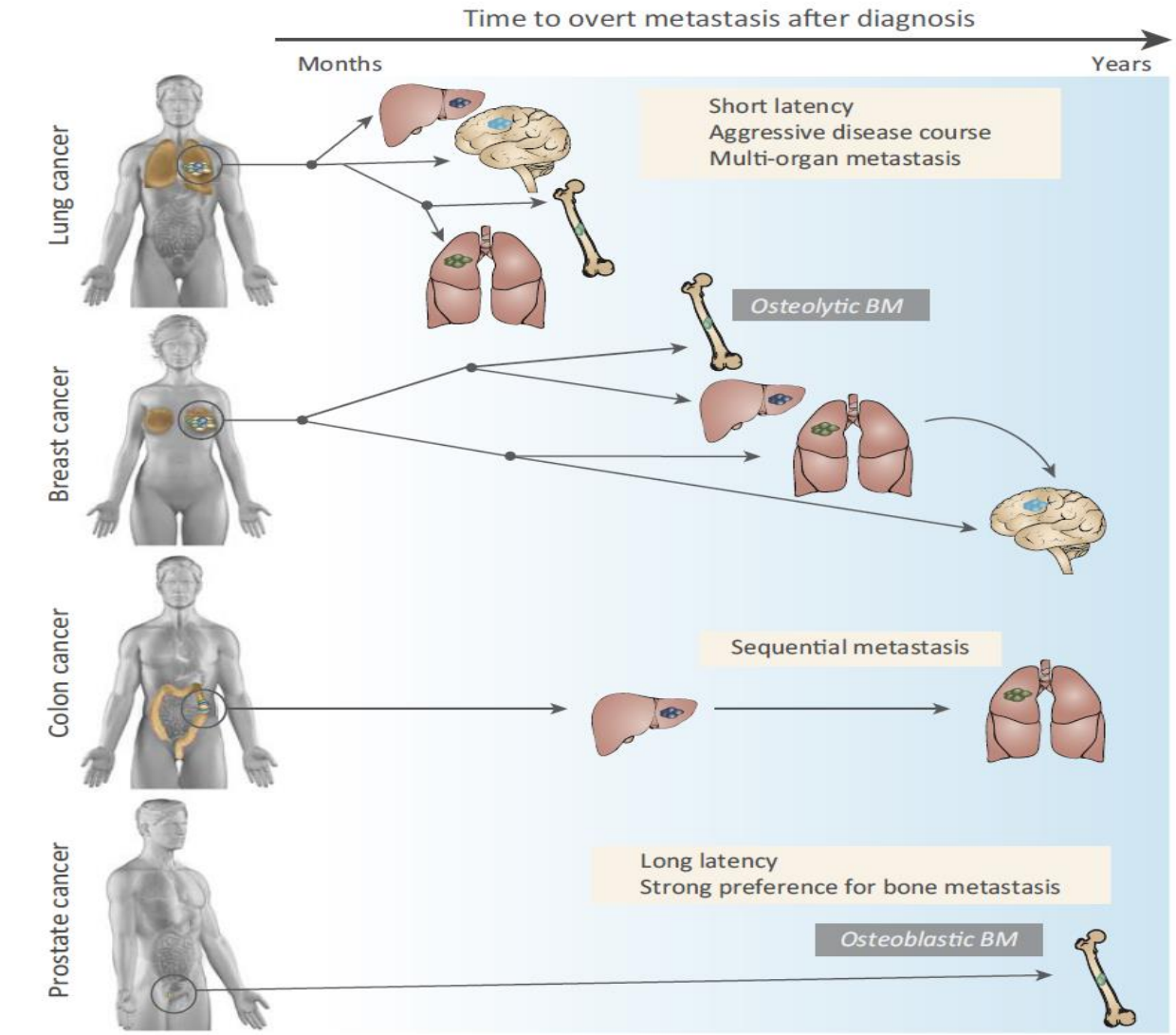
NSCLC: Stadium bei Diagnose

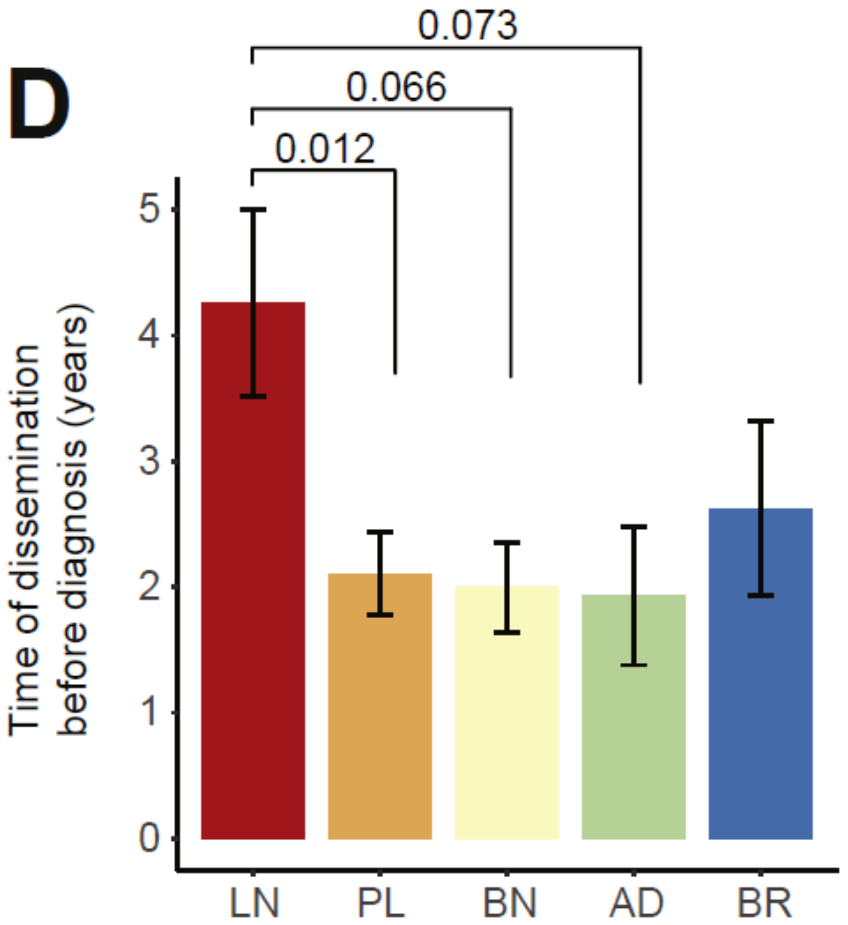


Surveillance, Epidemiology, and End Results Program, SEER 18, 2004–2010, all races, both sexes by SEER Summary Stage 2000

Worley et al; Lung Cancer review 2014

NSCLC: Metastasierungsmuster

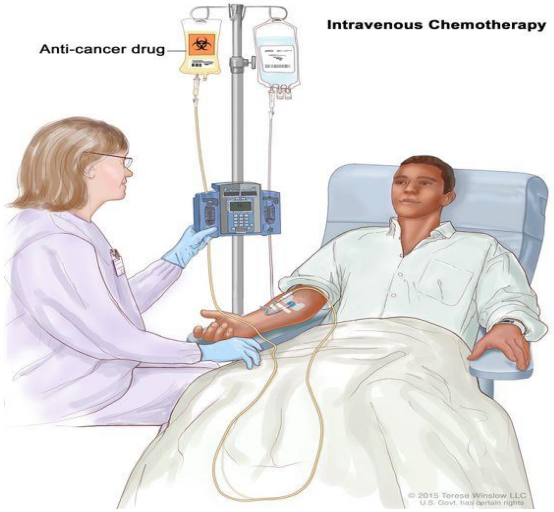


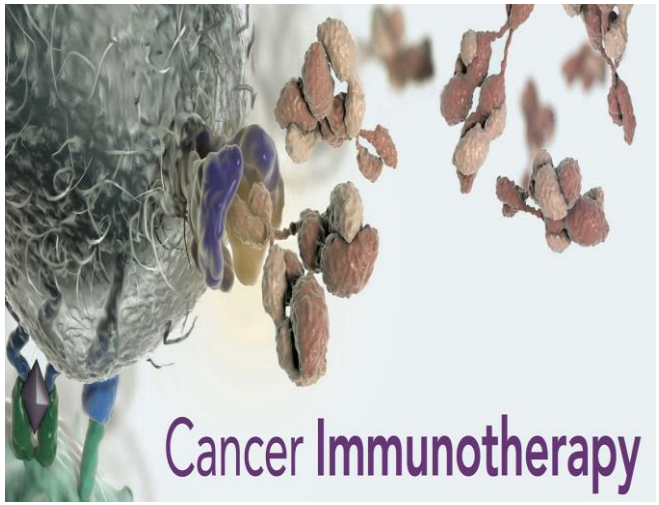


Obenauf et al.; Trends in Cancer 2015; Tang et al.; JTO 2021

Therapiemodalitäten

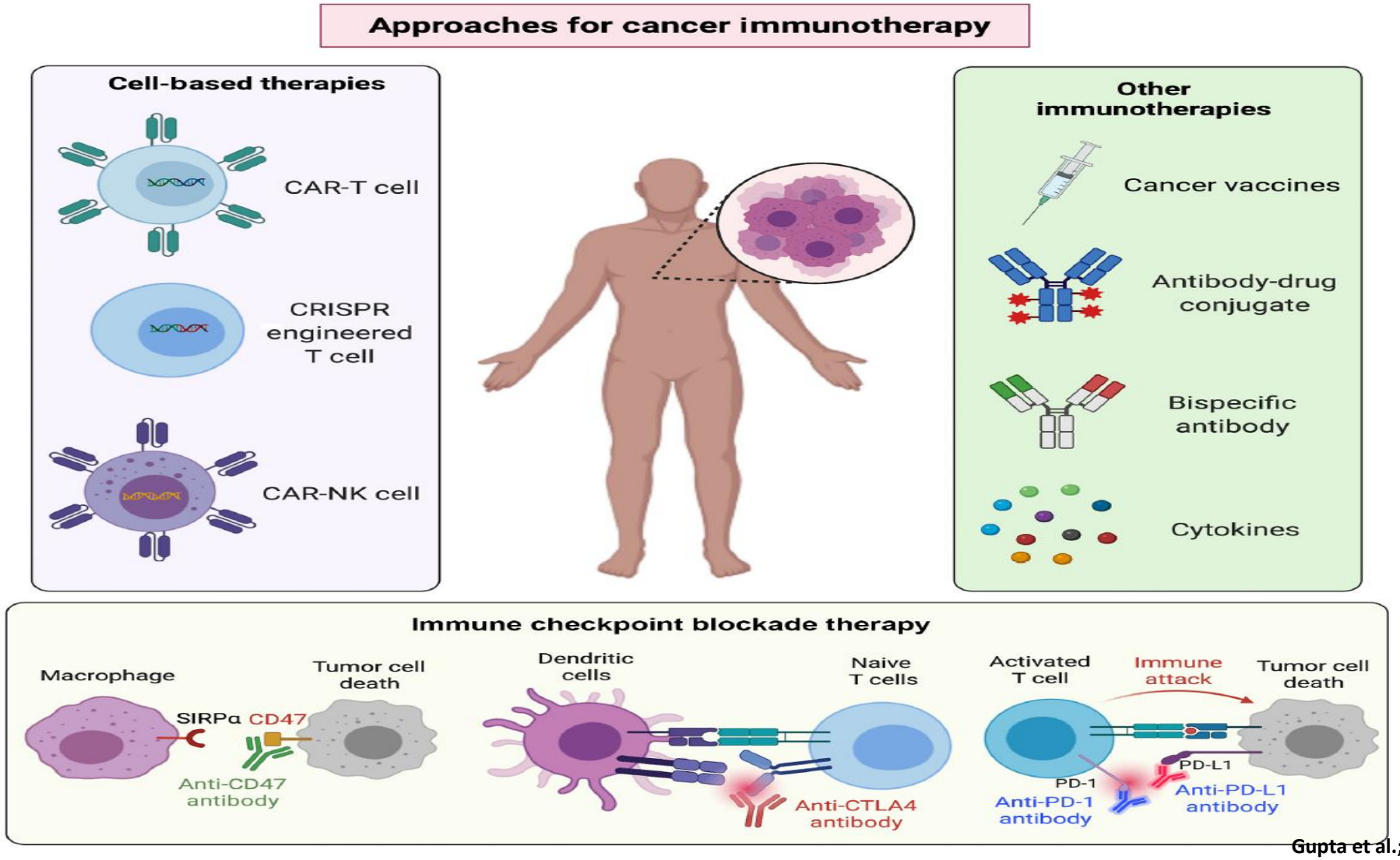
Lokaltherapie





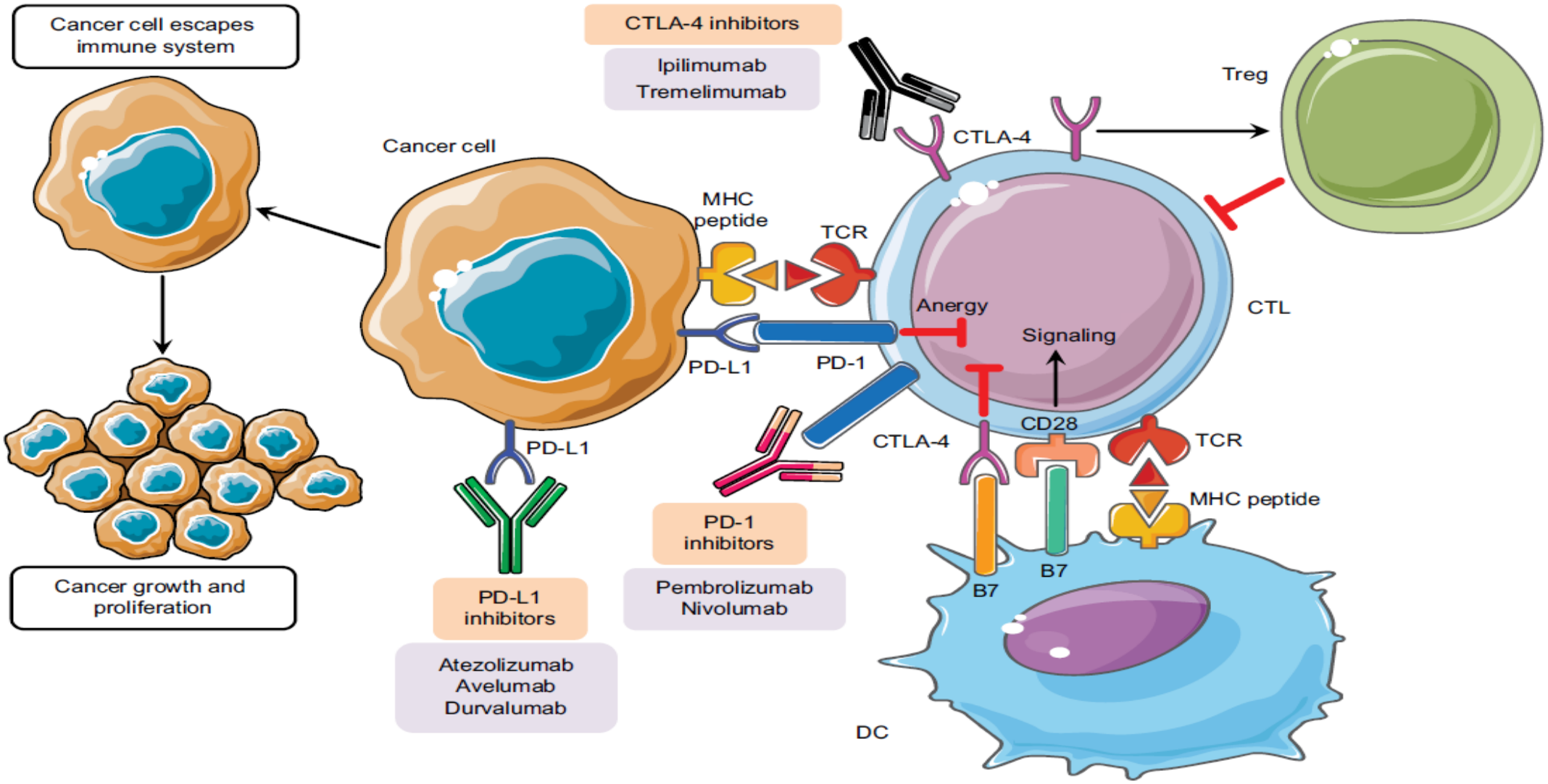
Systemische Therapie

Immuntherapie 2024



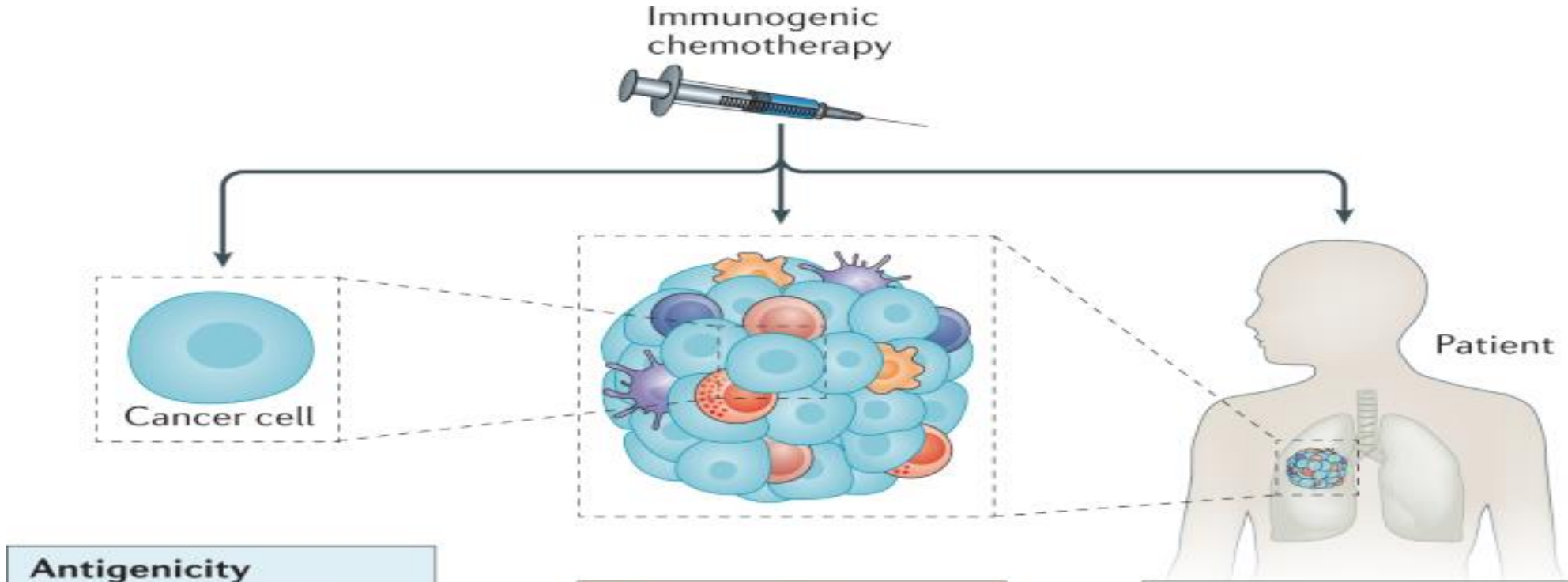
Gupta et al.; Trends in Cancer 2022

Checkpointblockade



Ayoub et al.; Breast Cancer Targets and Therapy 2019

Immunogene Chemotherapie



Antigenicity
↑ MHC-I exposure
↑ ERV expression
↑ TNA/TAA expression

Adjuvanticity
- CALR/HSP exposure
- ATP secretion
- ANXA1 release
- HMGB1 release
- Type I IFN secretion

Effector cells
↑ Dendritic cells
↑ $CD4^+$ T_H1 cells
↑ $CD8^+$ CTLs/NK cells
↑ M1 macrophages

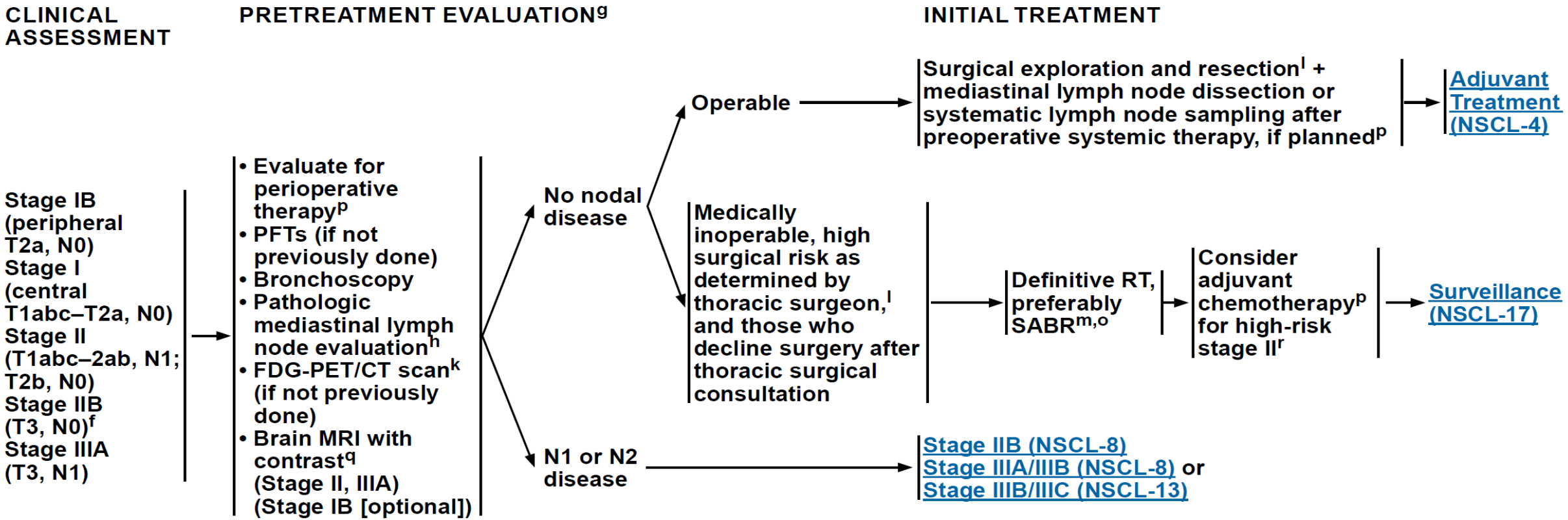
Suppressor cells
↓ T_{reg} cells
↓ M2 macrophages
↓ MDSCs

Intestinal microbiota
↑ Immunostimulatory bacteria
↓ Immunosupressive bacteria

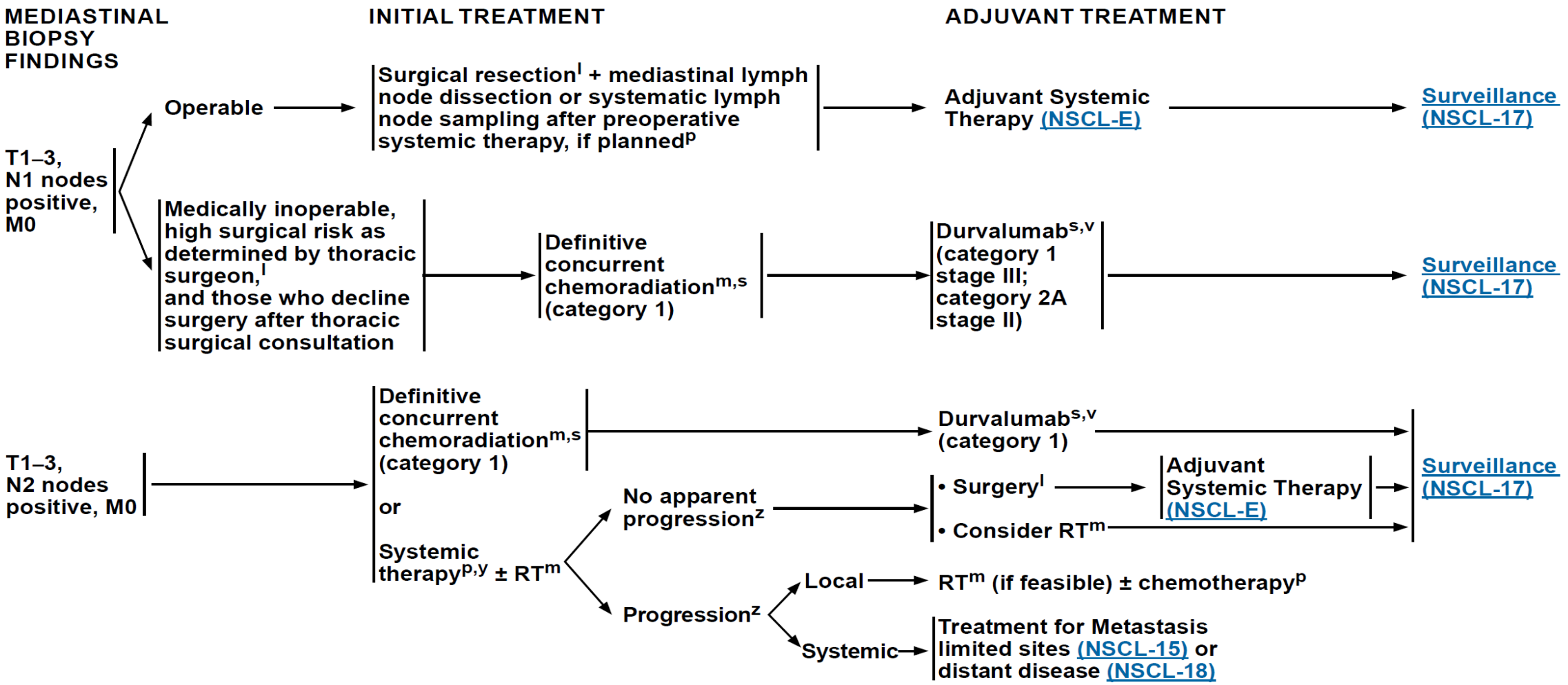
Neuroendocrine circuitries
↓ Endogenous glucocorticoids

Galluzzi et al.; Nature Reviews Clinical Oncology 2020

NCCN Leitlinien: early stage



NCCN Leitlinien: advanced stage non-metastatic NSCLC



Frage

Lokal fortgeschrittenes NSCLC ist?

1) Heilbar (=kuratives Setting)
2) Nicht heilbar (=palliatives Setting)

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Optionen resektables NSCLC

TREATMENT STRATEGIES FOR PATIENTS WITH A RESECTABLE NSCLC IN 2023

1
- NeoAdjuvant
- Surgery

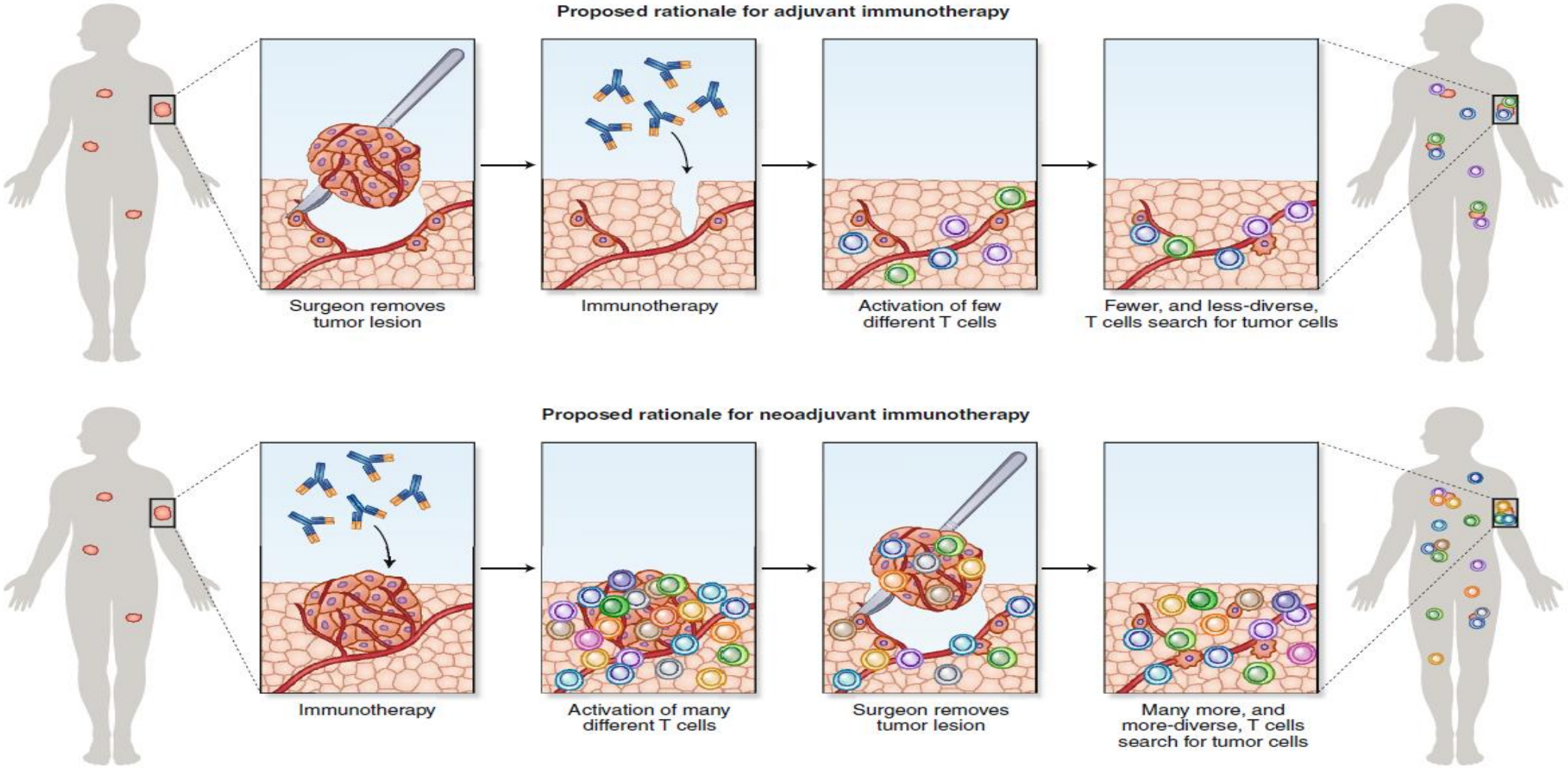
2
- Surgery
- Adjuvant

3
- NeoAdjuvant
- Surgery
- Adjuvant

MADRID 2023 ESMO congress

Garassino; ESMO 2023

Neoadjuvante vs. adjuavnte Immuntherapie



Verslius et al; Nature Medicine 2020

Checkmate 816 Studie

CheckMate 816 study design[a]

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG performance status 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by
Stage (IB-II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex

N = 358
R 1:1

Primary analysis population

- NIVO 360 mg Q3W + chemo[d] Q3W (3 cycles)
- Chemo[e] Q3W (3 cycles)

NIVO 3 mg/kg Q2W (3 cycles) + IPI 1 mg/kg (cycle 1 only)[f]

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± RT[g] → Follow-up

Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

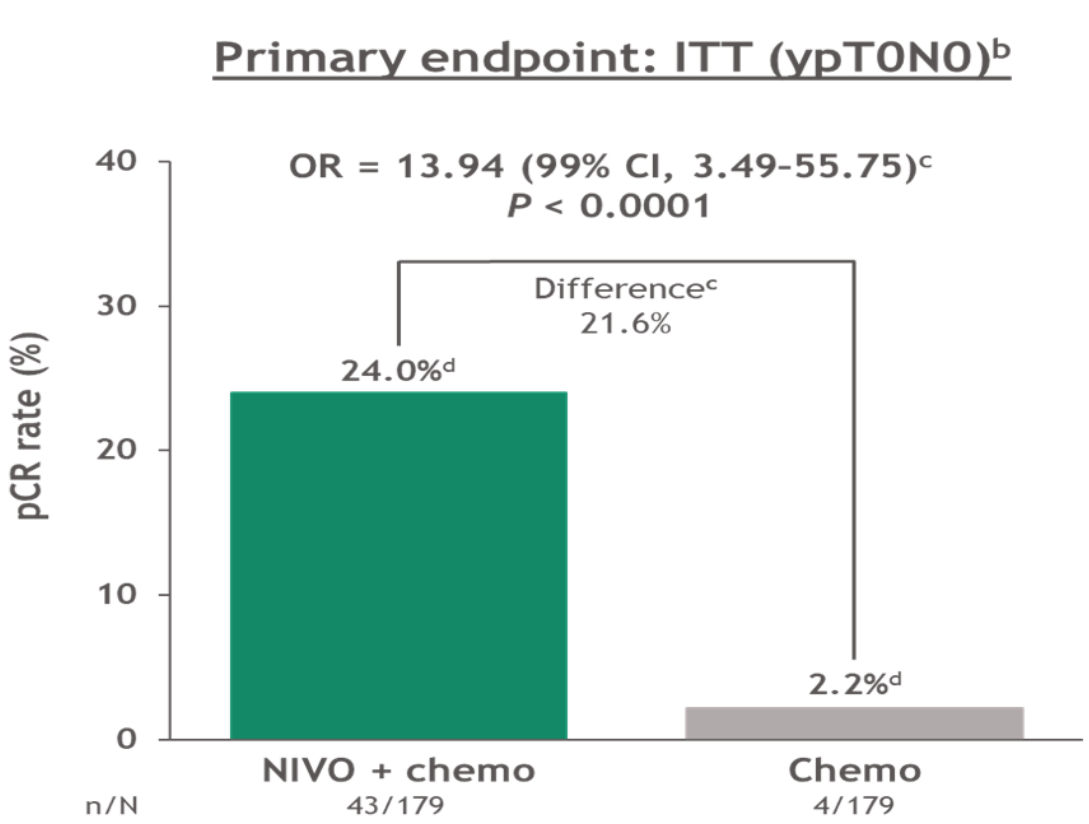
Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

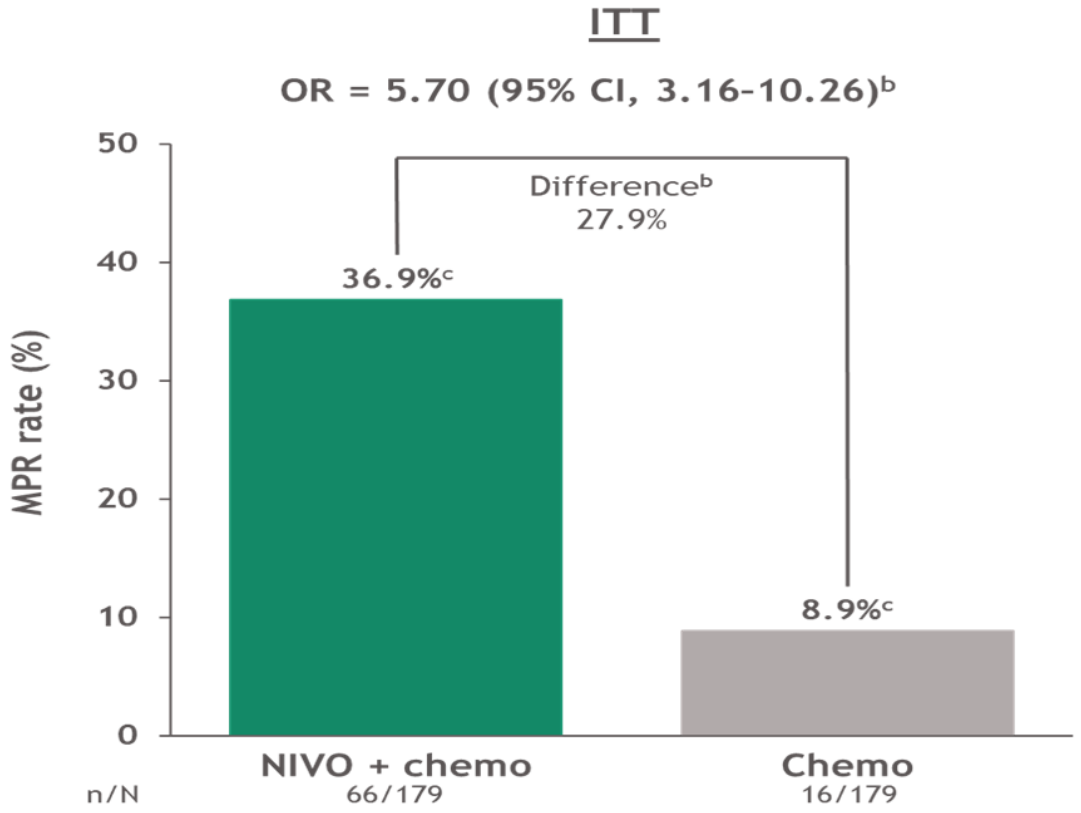
Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

[a]NCT02998528; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; [f]Randomized exploratory arm (enrollment closed early); [g]Per healthcare professional choice; [h]Performed using tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring).

Forde ; AACR 2021

Checkmate 816 Studie

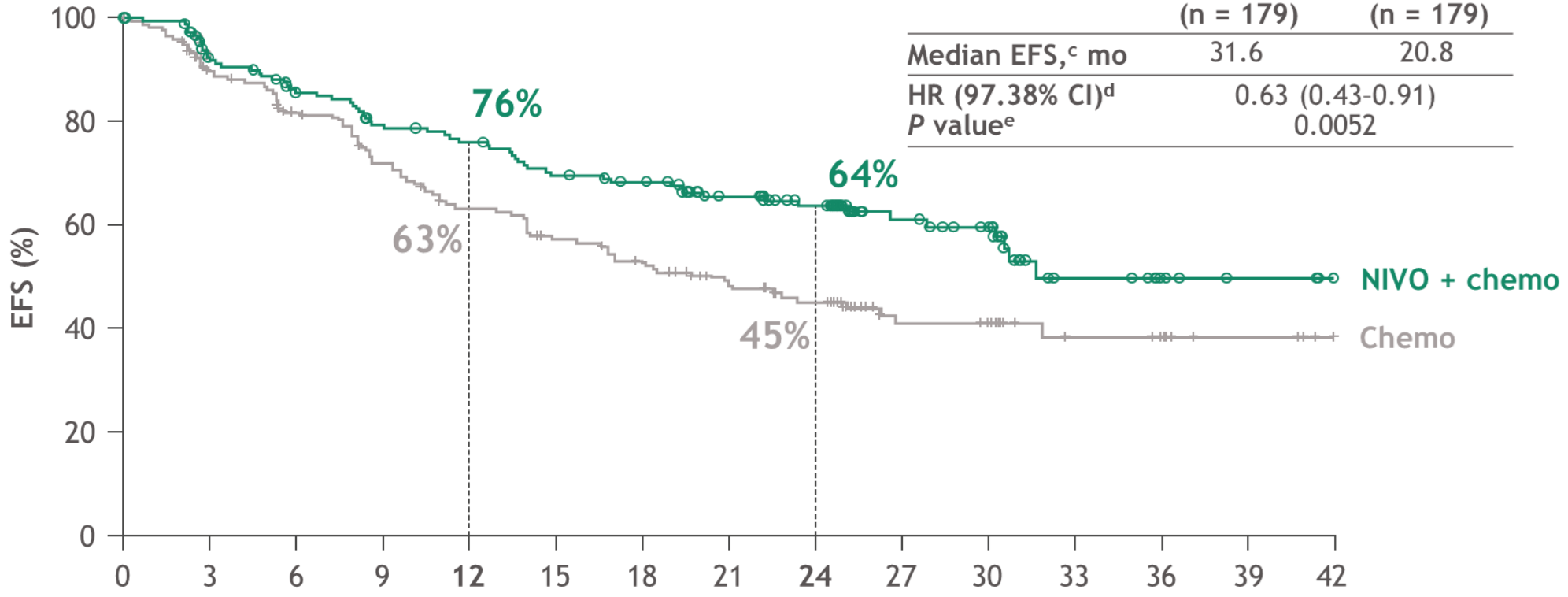




Forde ; AACR 2021

Checkmate 816 Studie- EFS

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS,[c] mo	31.6	20.8
HR (97.38% CI)[d]	0.63 (0.43-0.91)	
P value[e]	0.0052	



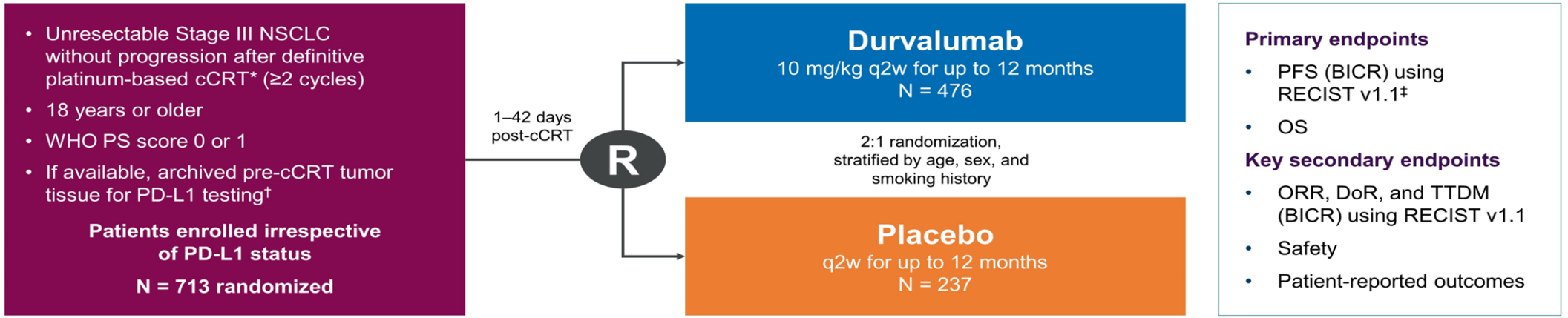
No. at risk

NIVO + chemo	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemo	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

Girard ; AACR 2022

Pacific Studie

PACIFIC: Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Trial



- **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**

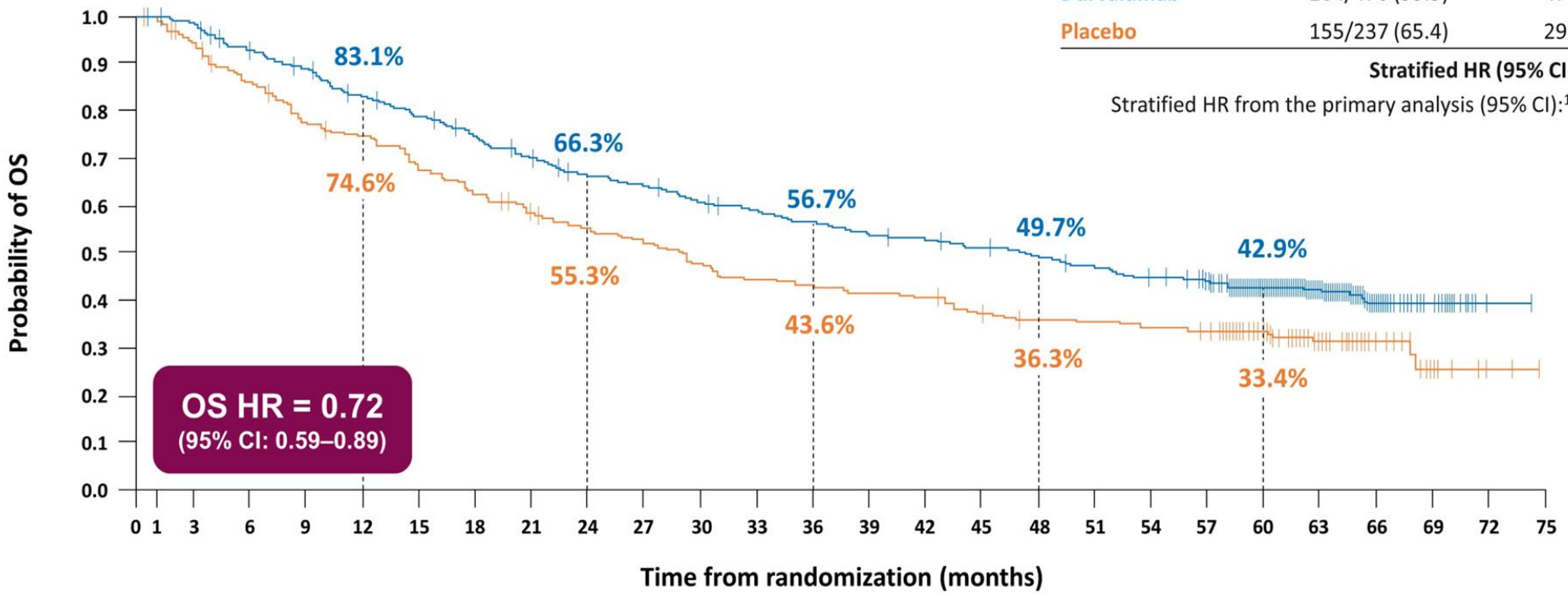
Spigel et al.; ASCO 2021

Pacific Studie-OS

	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

Spigel et al.; ASCO 2021

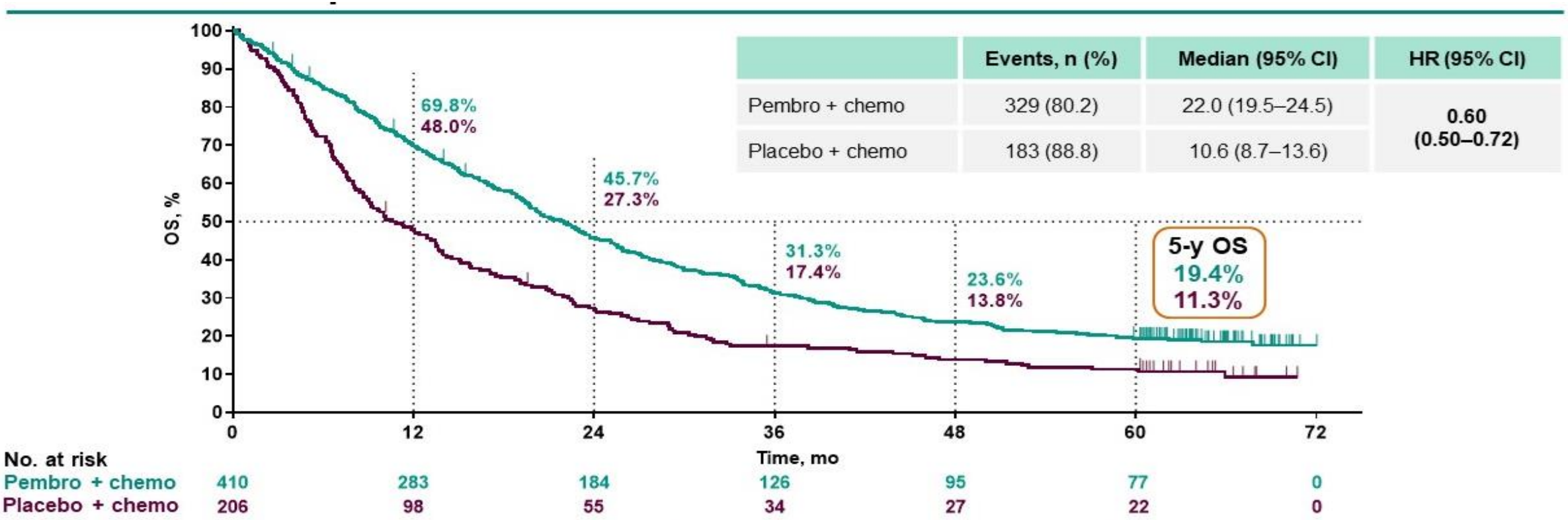
NSCLC:
Palliatives Setting

Frage

Die Prognose bei metastasierten NSCLC ist:

1) OS >12 Monate
2) OS <12 Monate

Keynote 189- 5 Year Update



	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

Garassino; ESMO 2022

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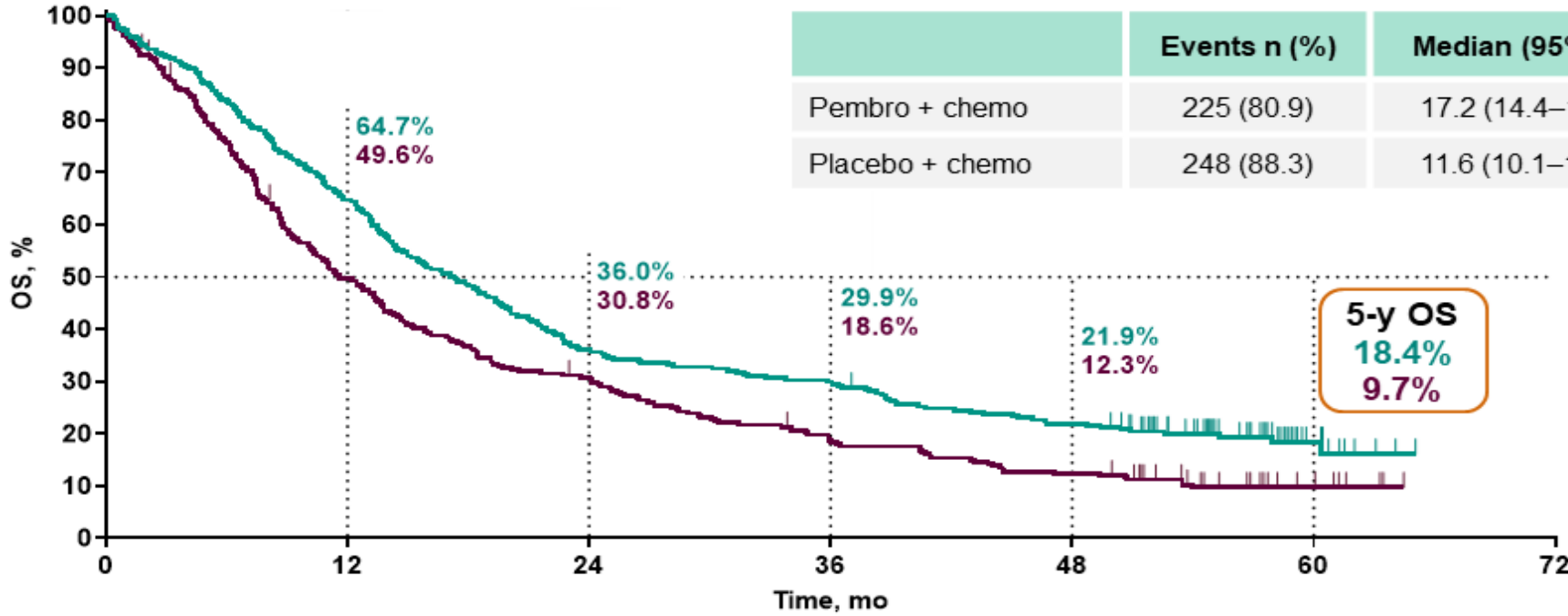
Keynote 407- 5 Year Update



	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85)
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	

No. at risk							
Pembro + chemo	278	180	100	83	60	10	0
Placebo + chemo	281	137	84	50	33	7	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

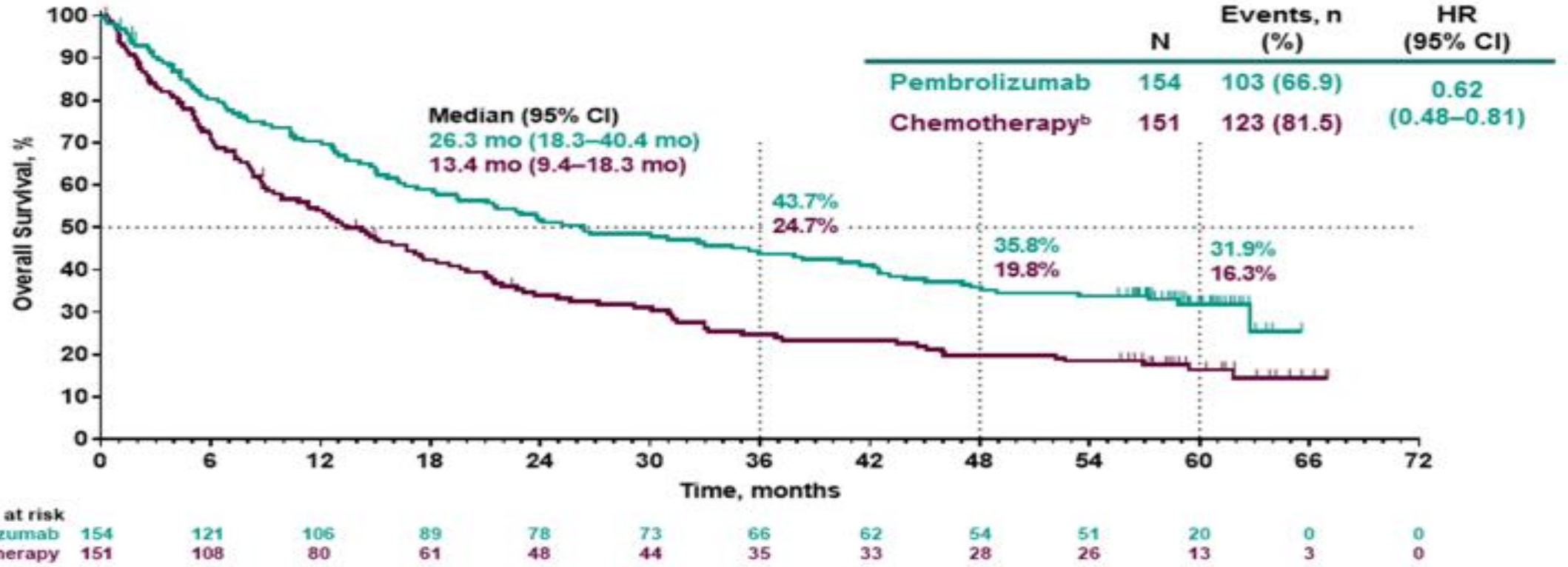
[a]Kaplan-Meier estimate. Data cutoff date: February 23, 2022.

Novello et al.; ESMO 2022

Keynote 24- Pembro Mono
5 year update: OS

J Brahmer. ESMO 2020

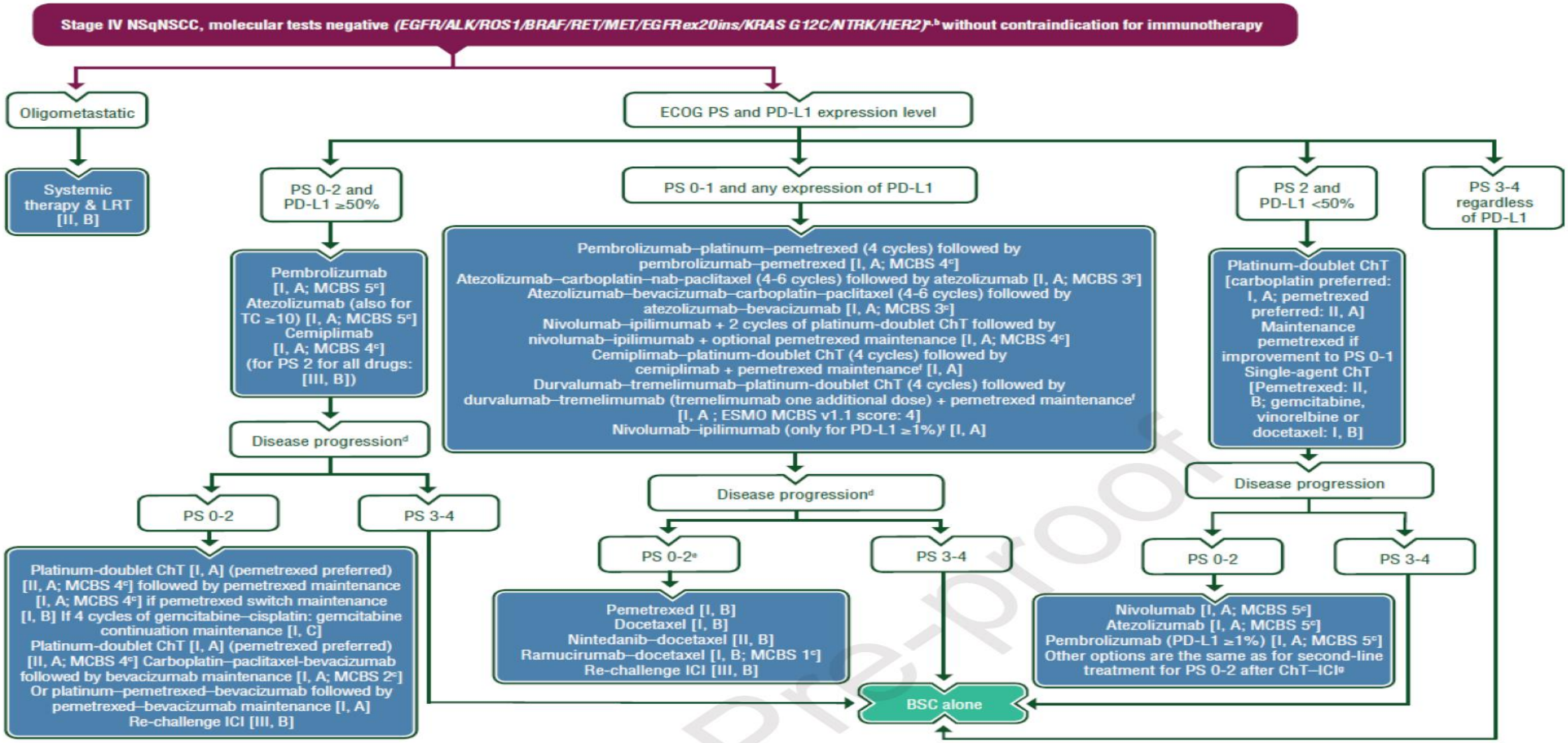
Overall Survival[a]



[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.

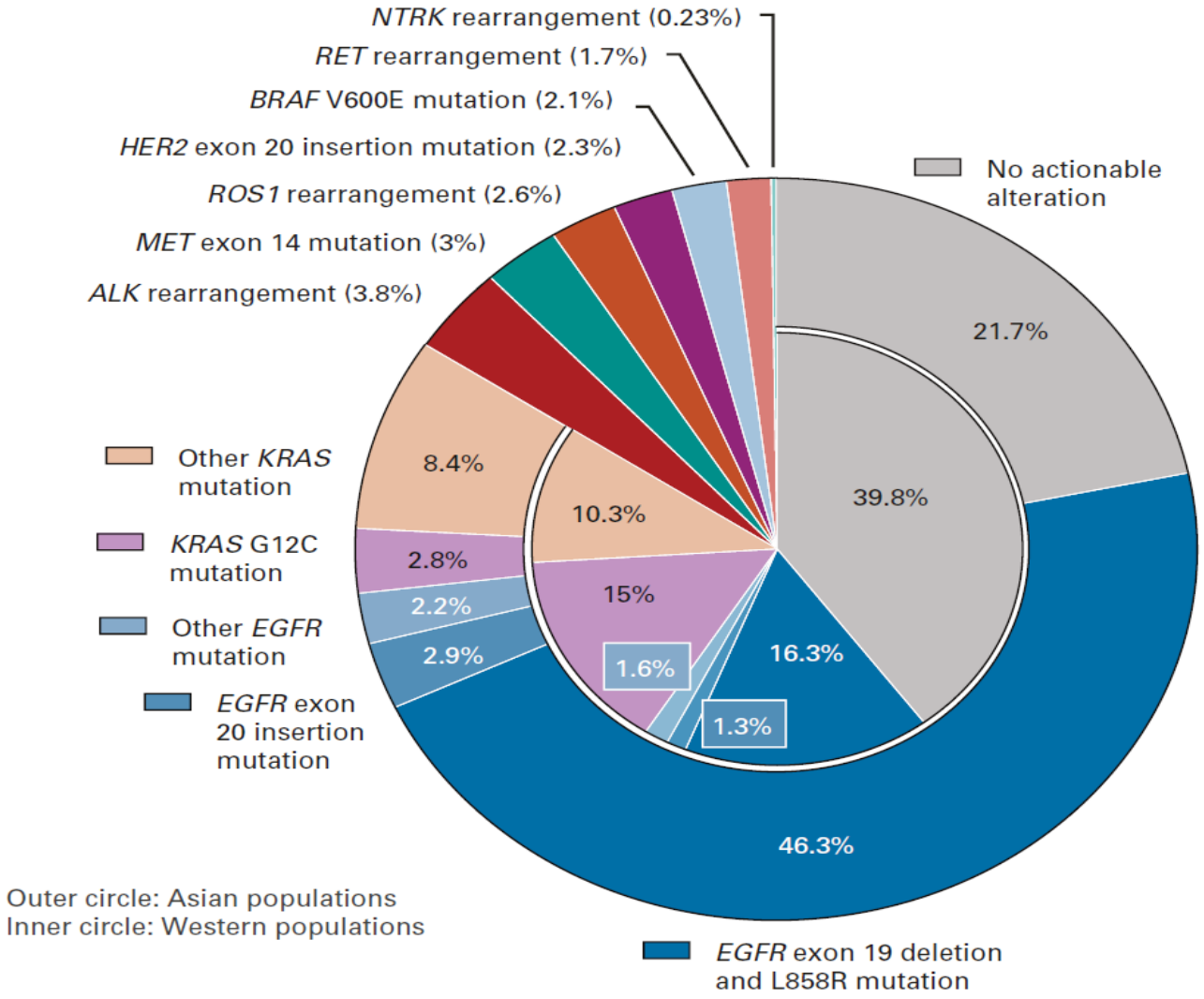
Brahmer; ESMO 2020

ESMO Leitlinien



ESMO Leitlinien 2022

Personalisierte Medizin beim NSCLC



Tan et al.; JCO 2022

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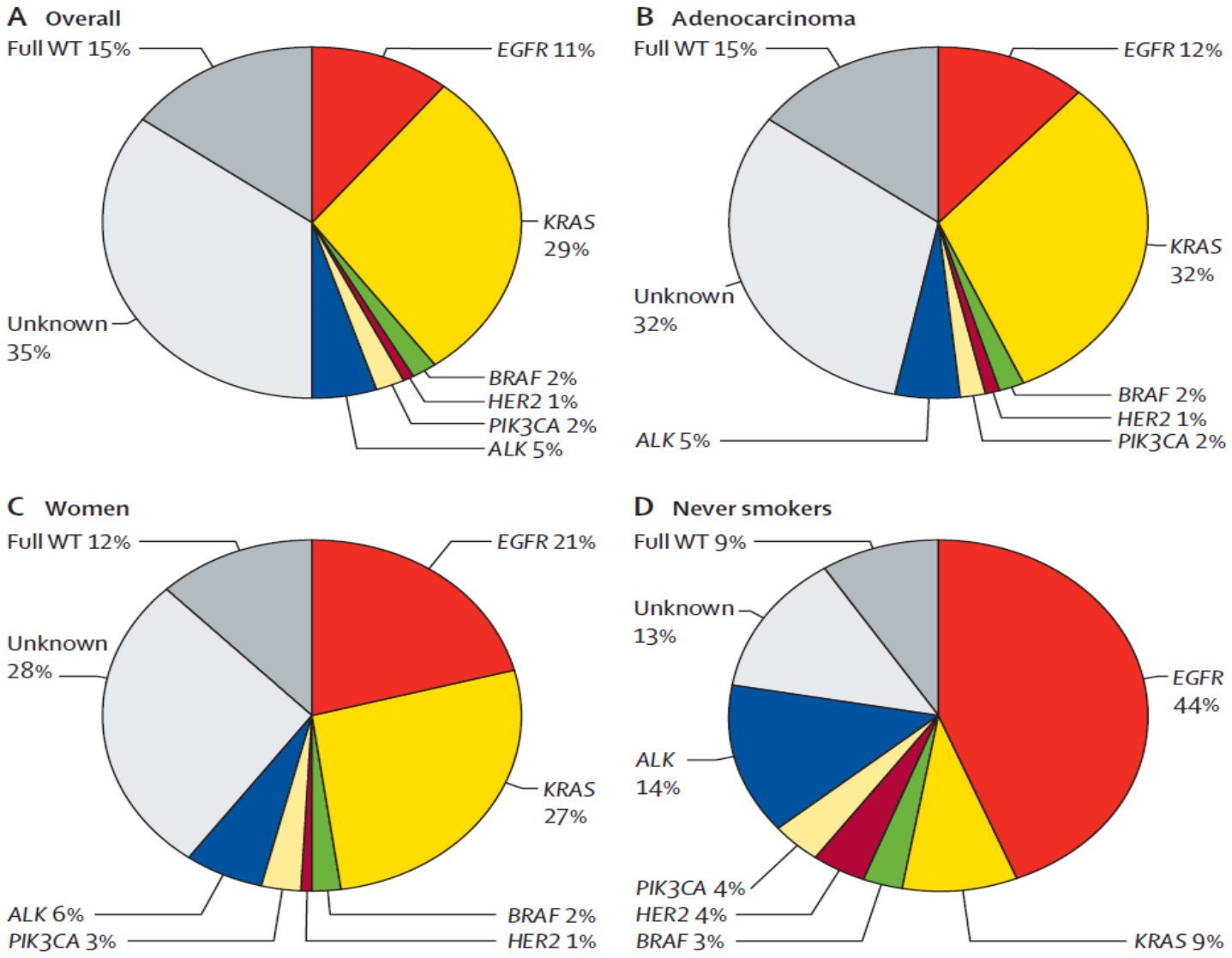
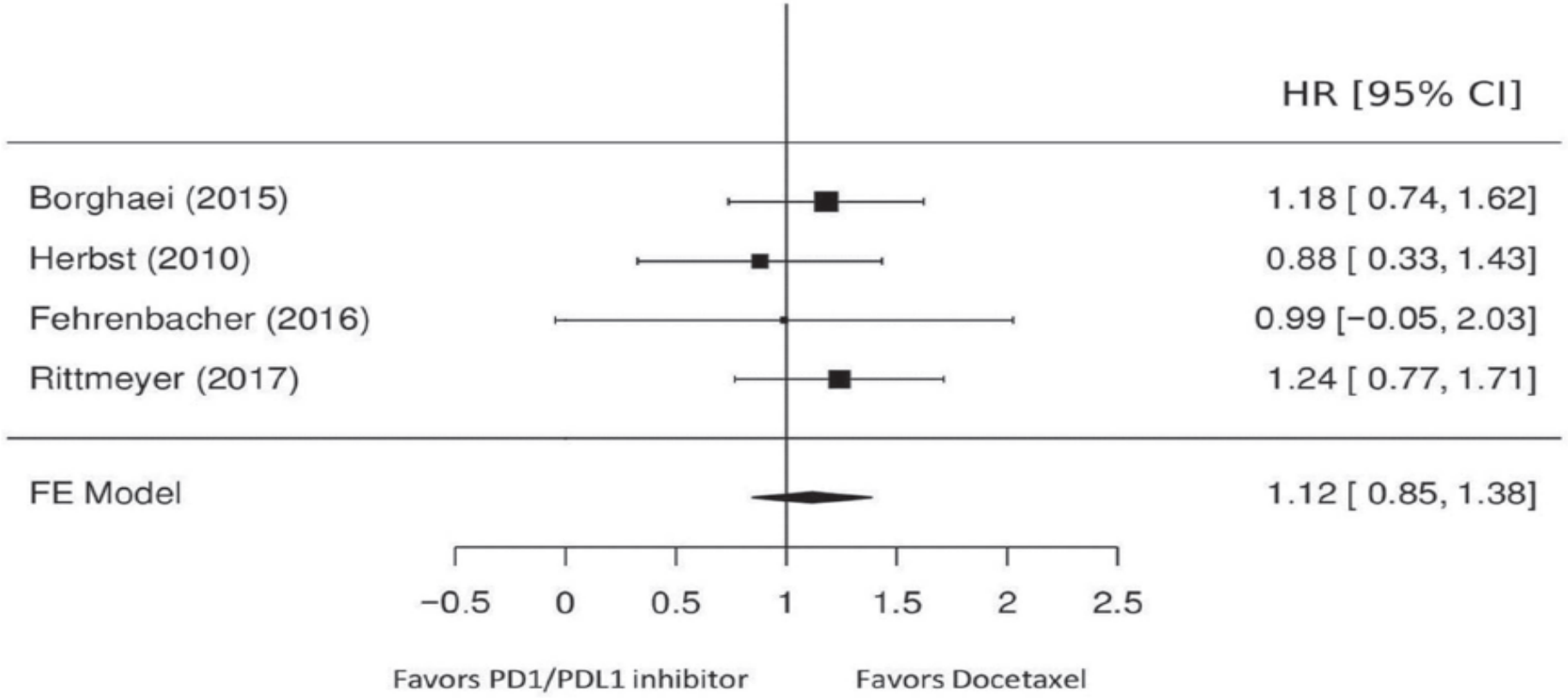
Personalisierte Medizin beim NSCLC



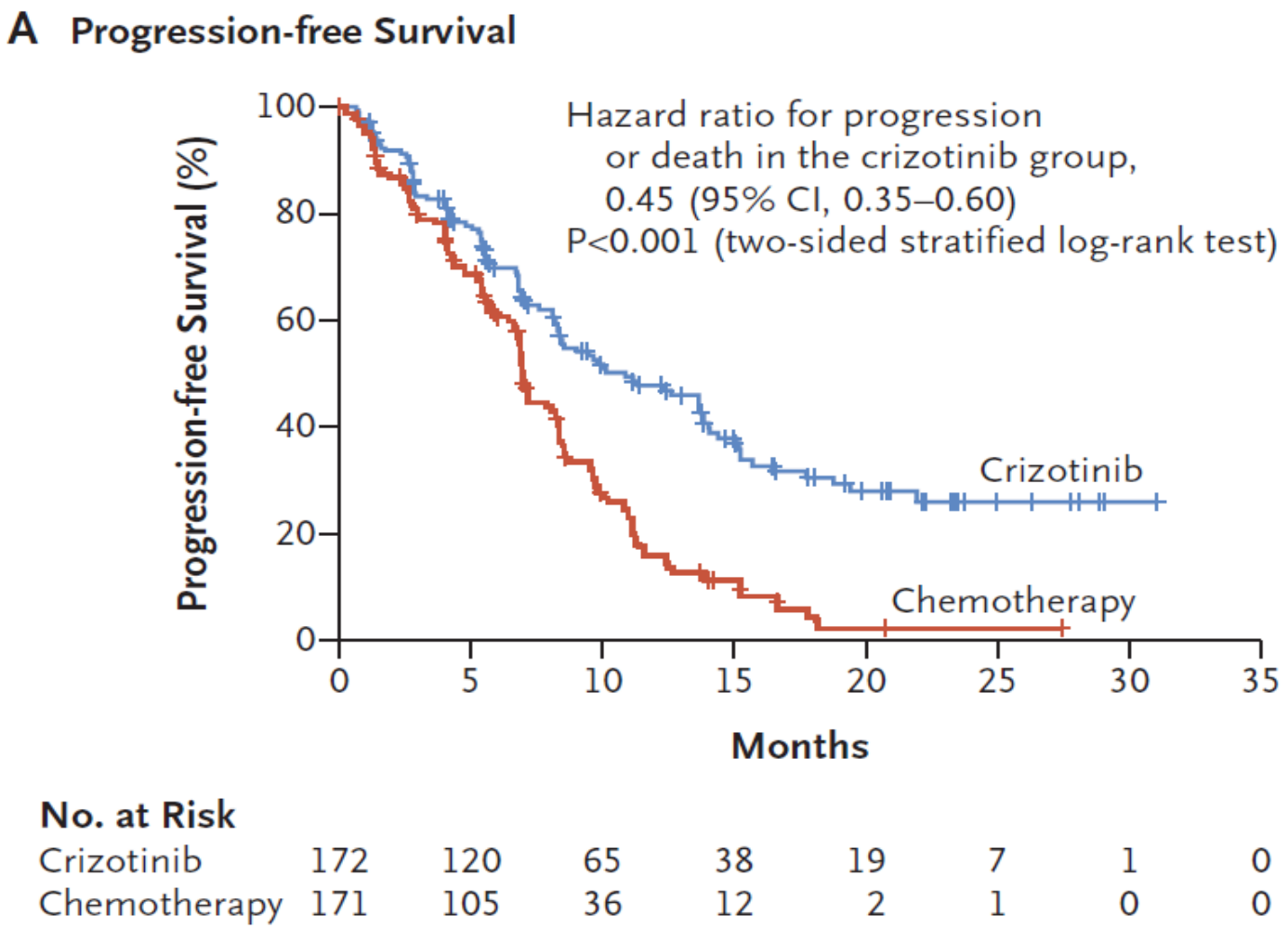
Barlesi et al.; Lancet 2016

Aktivierende Mutationen und Immuntherapie



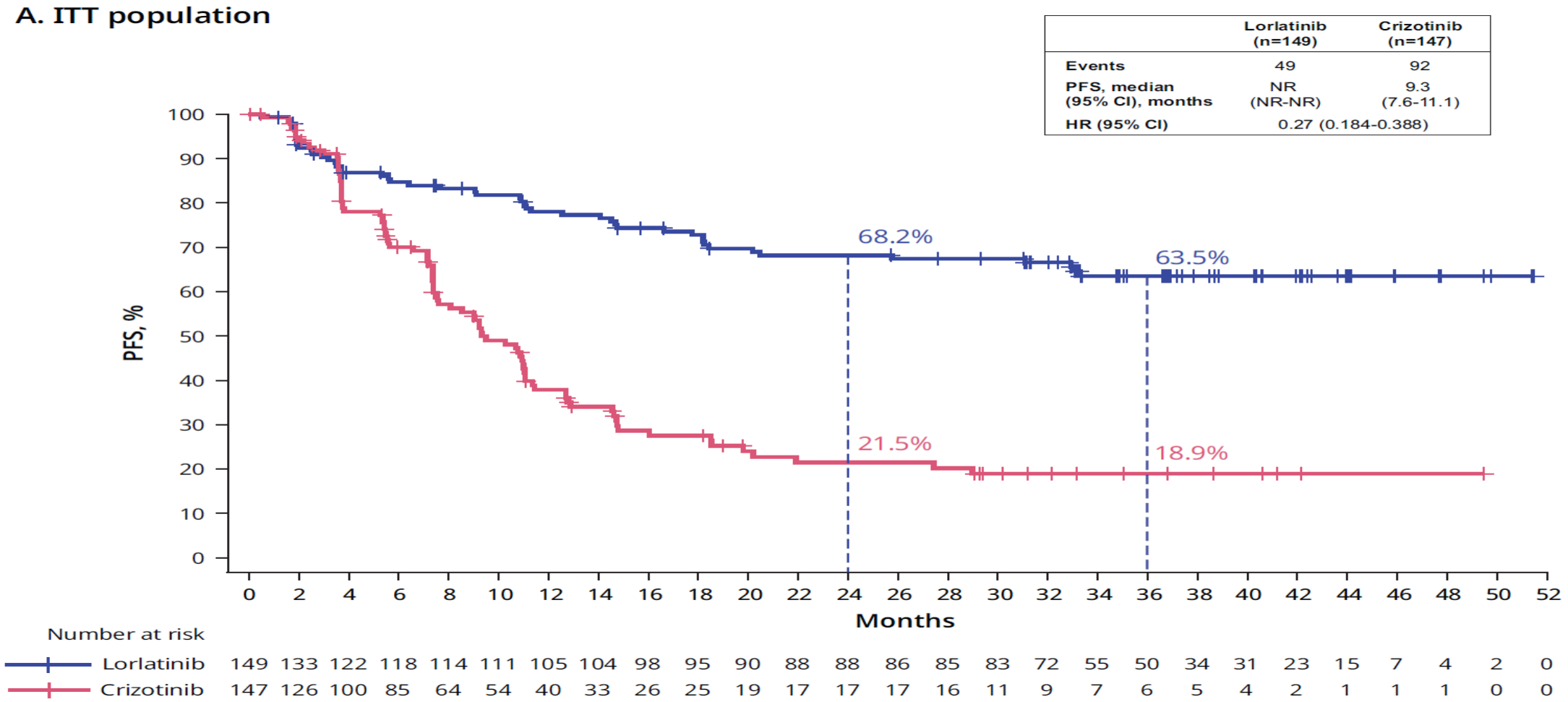
Cavanna et al., Oncotarget 2019

Targeted Therapy vs. Chemo
ALK Fusion



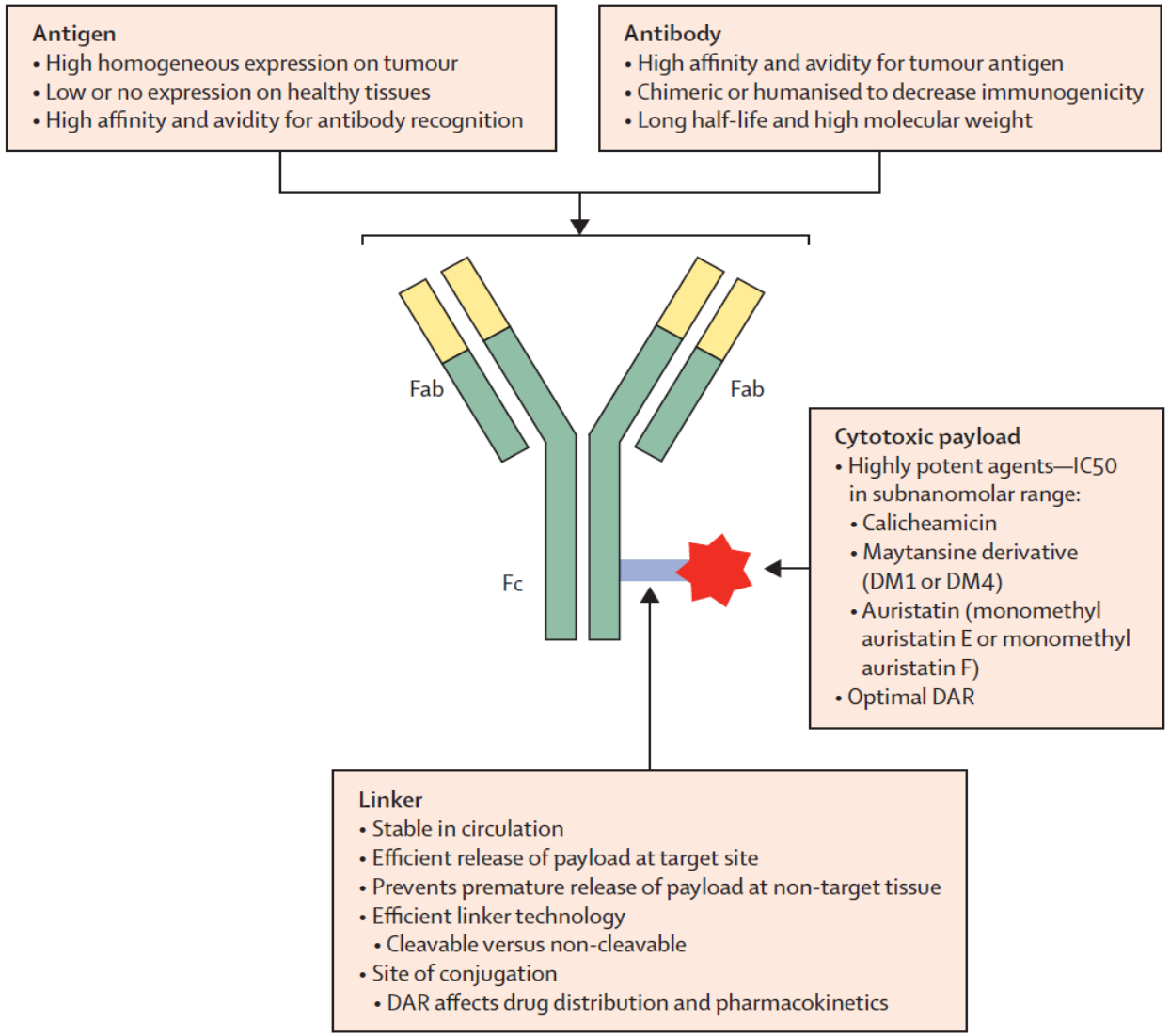
Solomon et al., NEJM 2016

Crown Studie: ALK fusion 3.Generation ALK Inhibitor



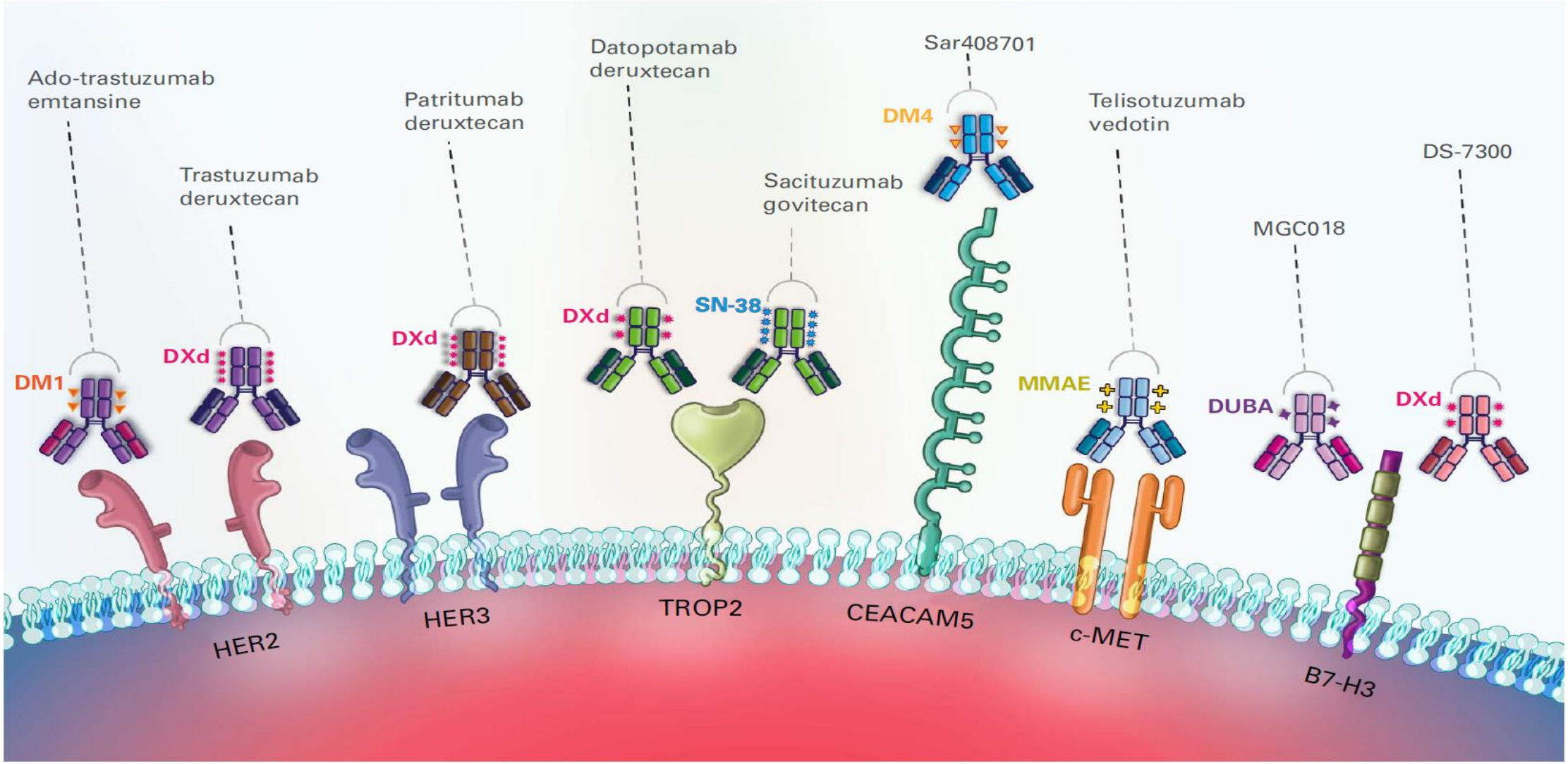
Solomon et al., ESMO 2022

Antibody Drug Conjugates



Chau et al.; Lancet 2019

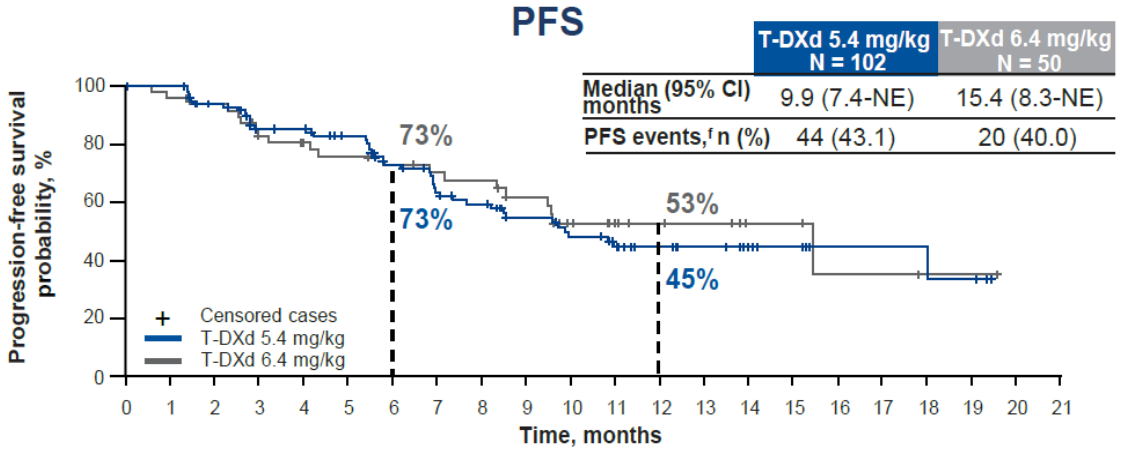
ADC in NSCLC-Zielstrukturen-Biomarker

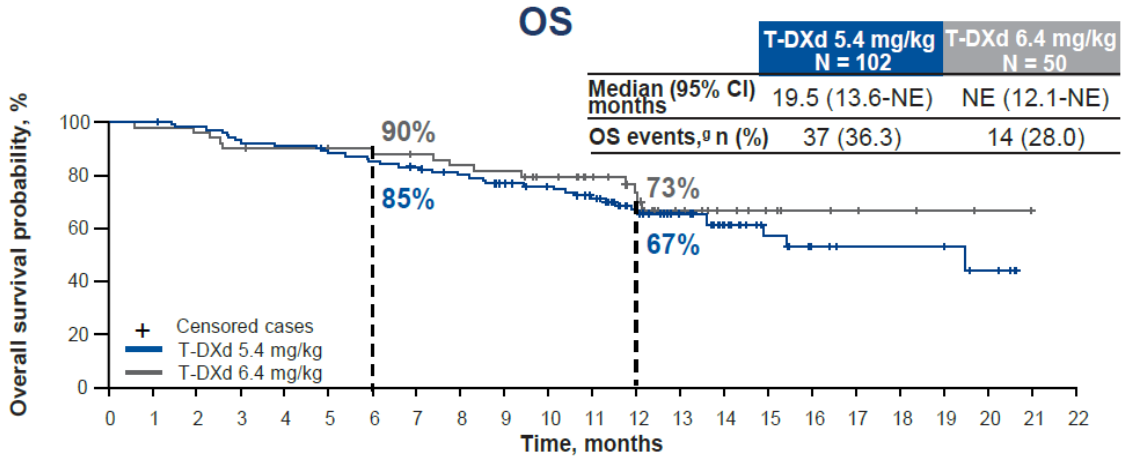


Passaro et al.; JCO 2023

Destiny Lung02 Studie

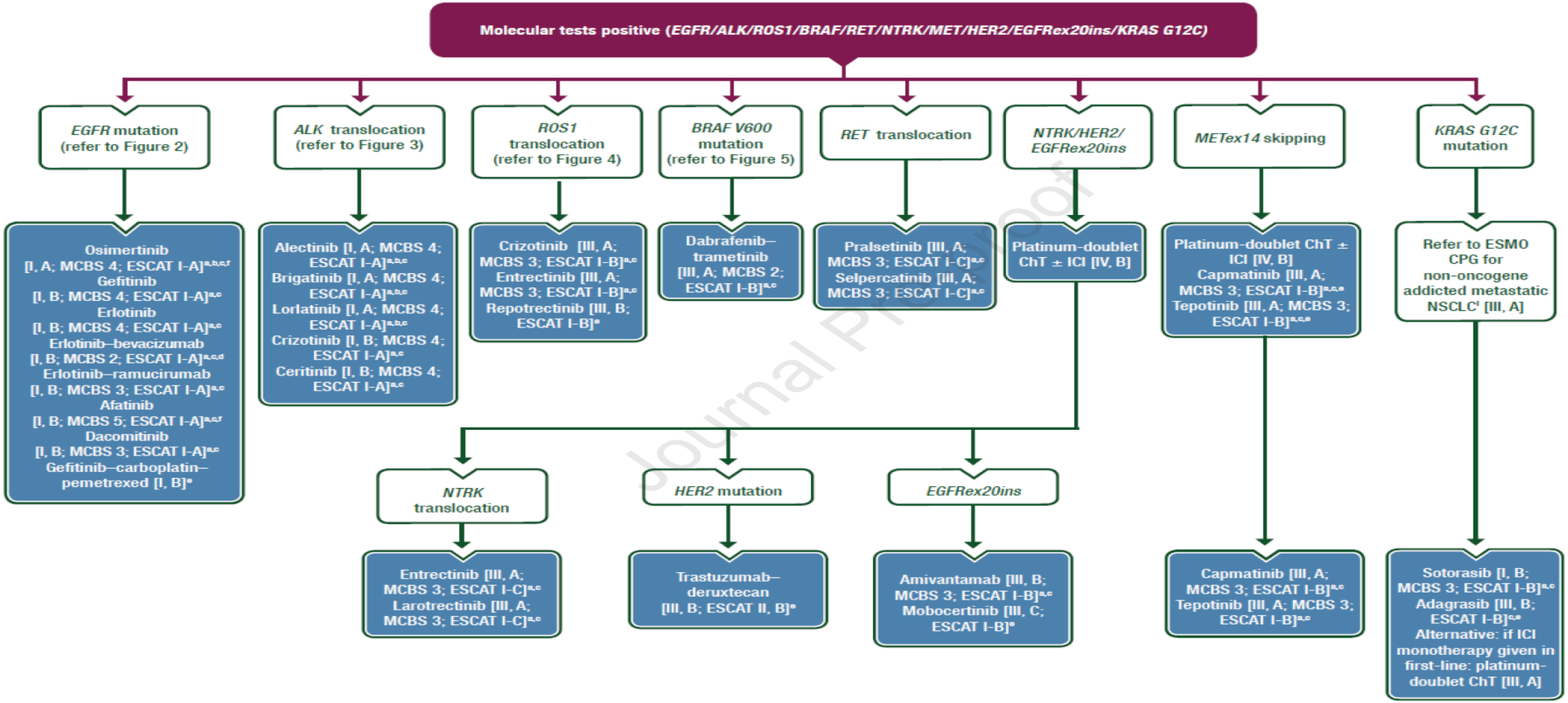
Efficacy summary	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Confirmed ORR,[a] n (%) [95% CI]	**50 (49.0)** [39.0-59.1]	**28 (56.0)** [41.3-70.0]
CR | PR	1 (1.0) | 49 (48.0)	2 (4.0) | 26 (52.0)
SD | PD	45 (44.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable[b]	3 (2.9)	2 (4.0)
DCR,[c] n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0) [80.8-97.8]
Median DoR,[d,e] months (95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median TTIR,[d] months (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median follow-up, months (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)





Jänne et al.; WCLC 2023

ESMO Leitlinien



Patientenfall

COMPREHENSIVE CANCER CENTER VIENNA

MEDIZINISCHE UNIVERSITÄT WIEN

Allgemeines Krankenhaus der Stadt Wien

Patientenfall: BRAF Mutation

- 70 jähriger männlicher Patient
- ECOG: 0
- Myasthenia gravis, Bluthochdruck
- Adenoca. der Lunge met.; PD-L1 neg.; BRAF mut

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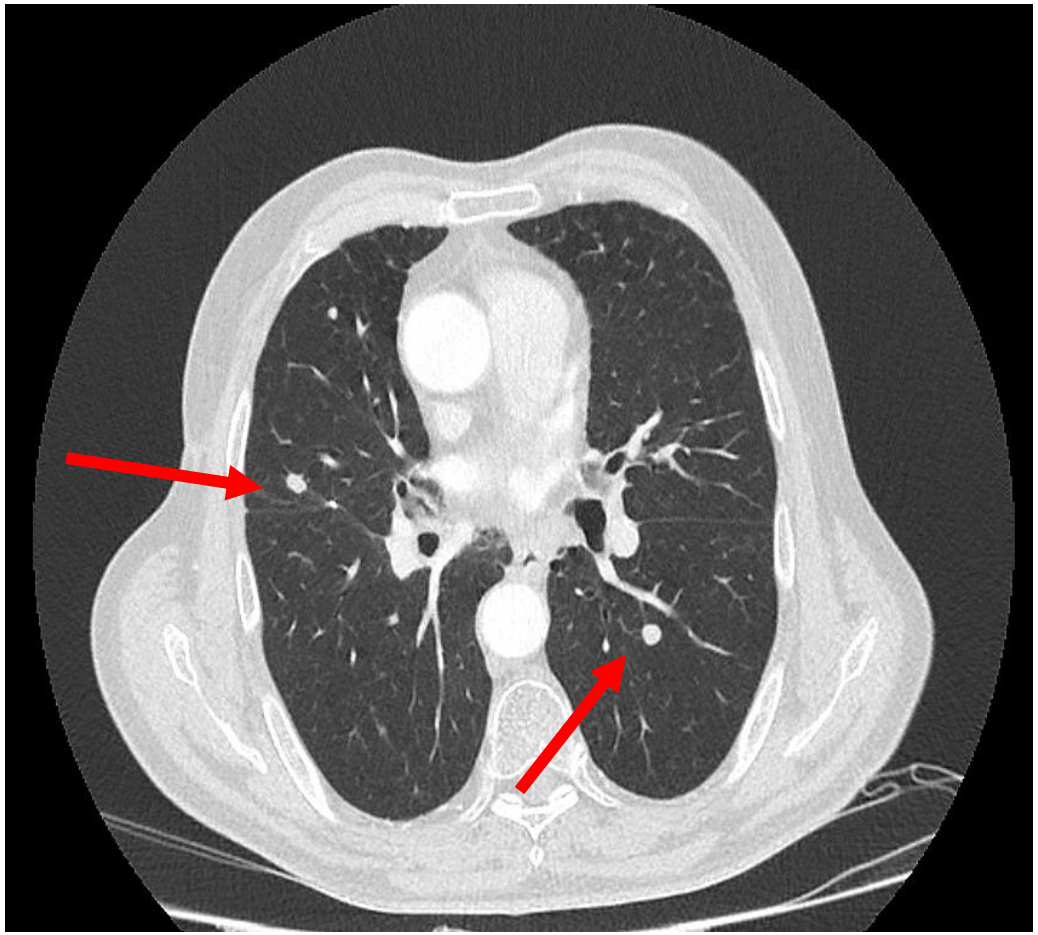
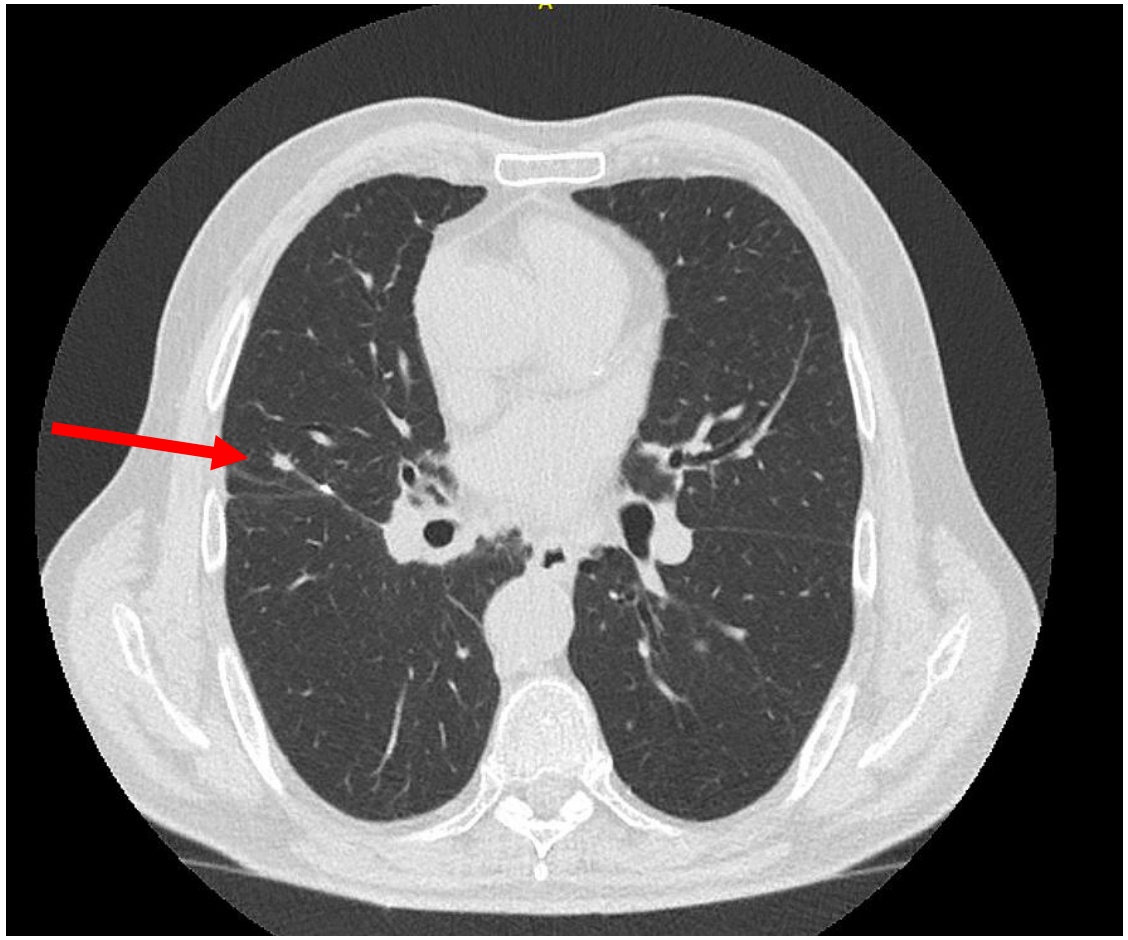
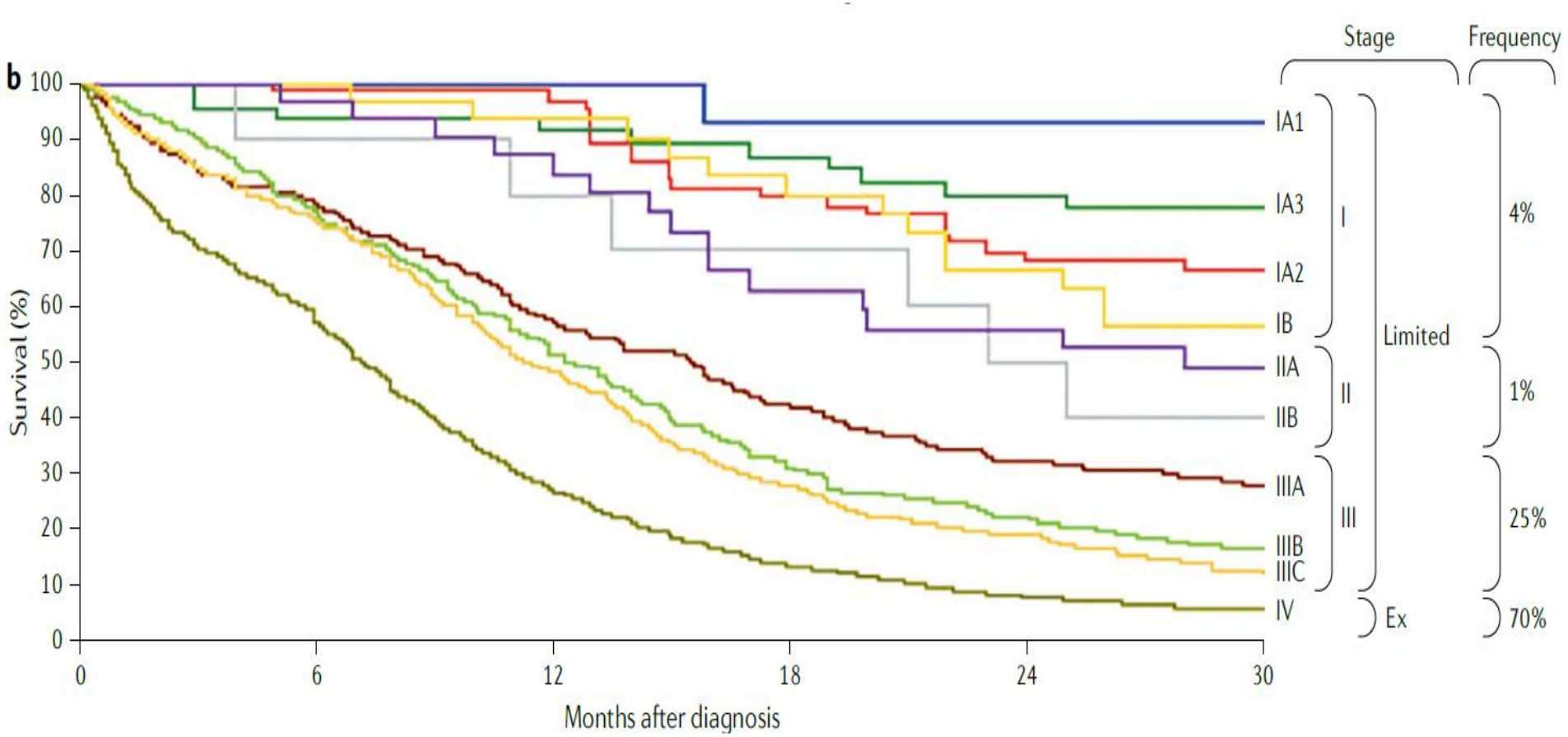
Patientenfall: BRAF Mutation



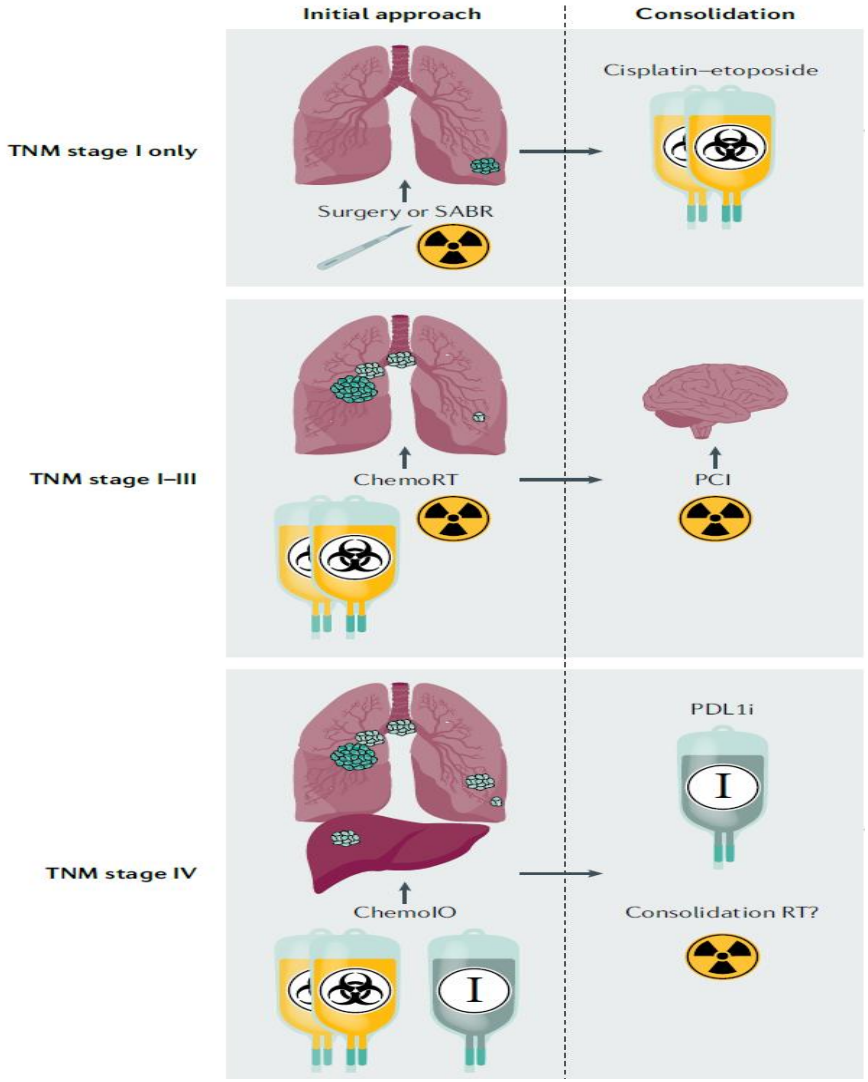


Small cell lung cancer

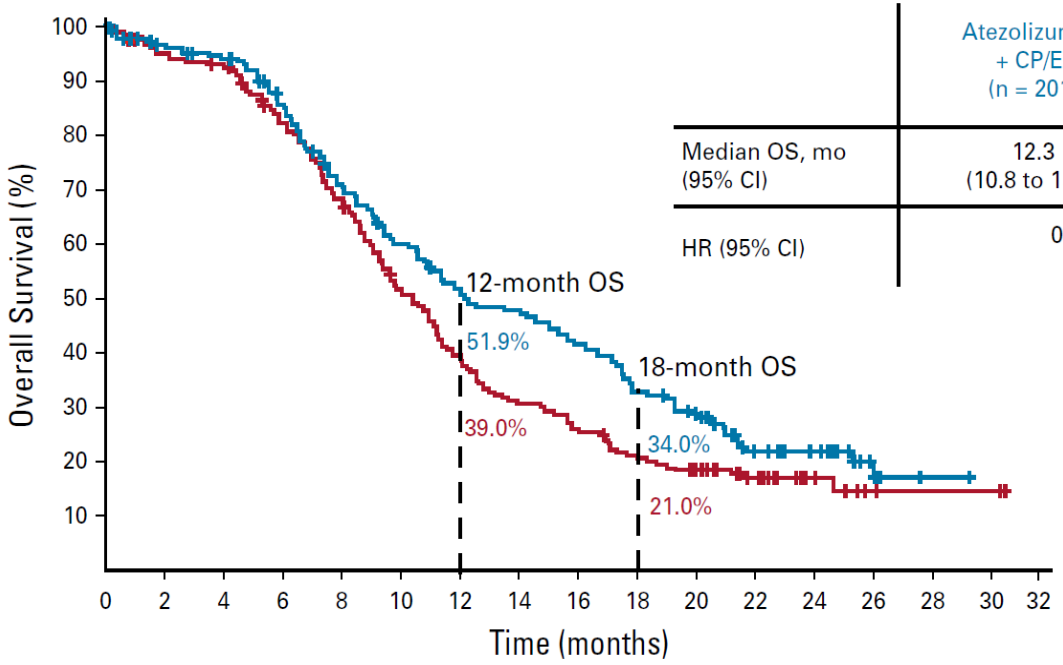


Rudin et al., Nature Reviews Disease Primer 2021

Small cell lung cancer



A



	Atezolizumab + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8 to 15.8)	10.3 (9.3 to 11.3)
HR (95% CI)	0.76 (0.60 to 0.95) *P* = .0154*	

No. of Patients at Risk

Atezolizumab + CP/ET	201	187	180	159	130	109	93	86	75	61	51	28	21	8	1
Placebo + CP/ET	202	189	183	160	131	97	74	58	49	39	33	20	8	3	2	2

Rudin et al., Nature Reviews Disease Primer 2021; Liu et al.; JCO 2021

COMPREHENSIVE CANCER CENTER VIENNA

MEDIZINISCHE UNIVERSITÄT WIEN

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Take home message

- Lungenkrebs ist weltweit die häufigste Krebs assoziierte Todesursache
- Moderne Therapien ermöglichen Langzeitüberleben
- Personalisierte Medizin und molekulare Marker sind essentiell im klinischen Alltag
- SCLC met. bleibt Herausforderung

Fragen?