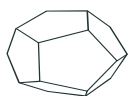


Neue Optionen zur Behandlung des Lungenkarzinoms



Romana Wass, MD, PhD

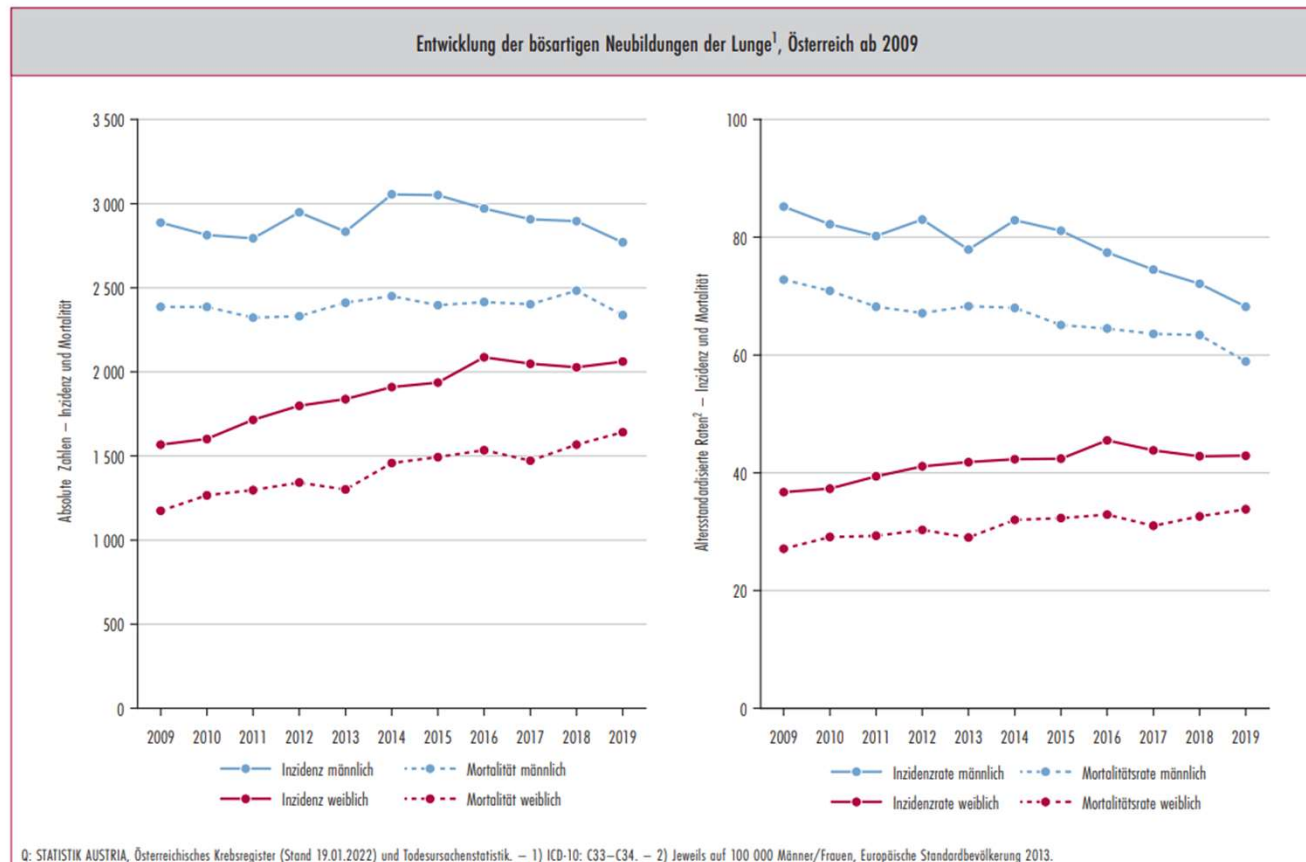


Lungenkrebs ist häufig

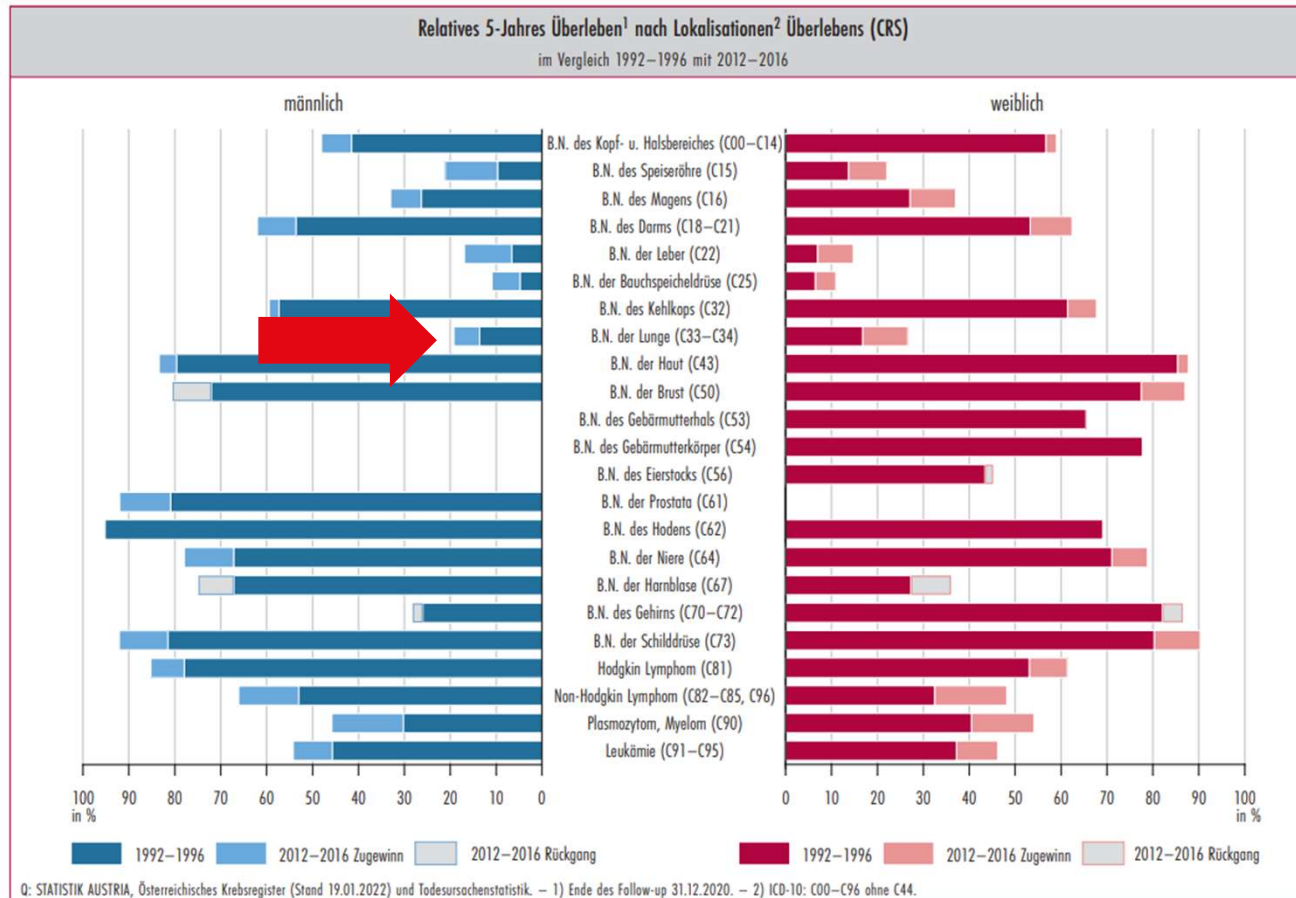


Geschlechtsverteilung gleicht sich an

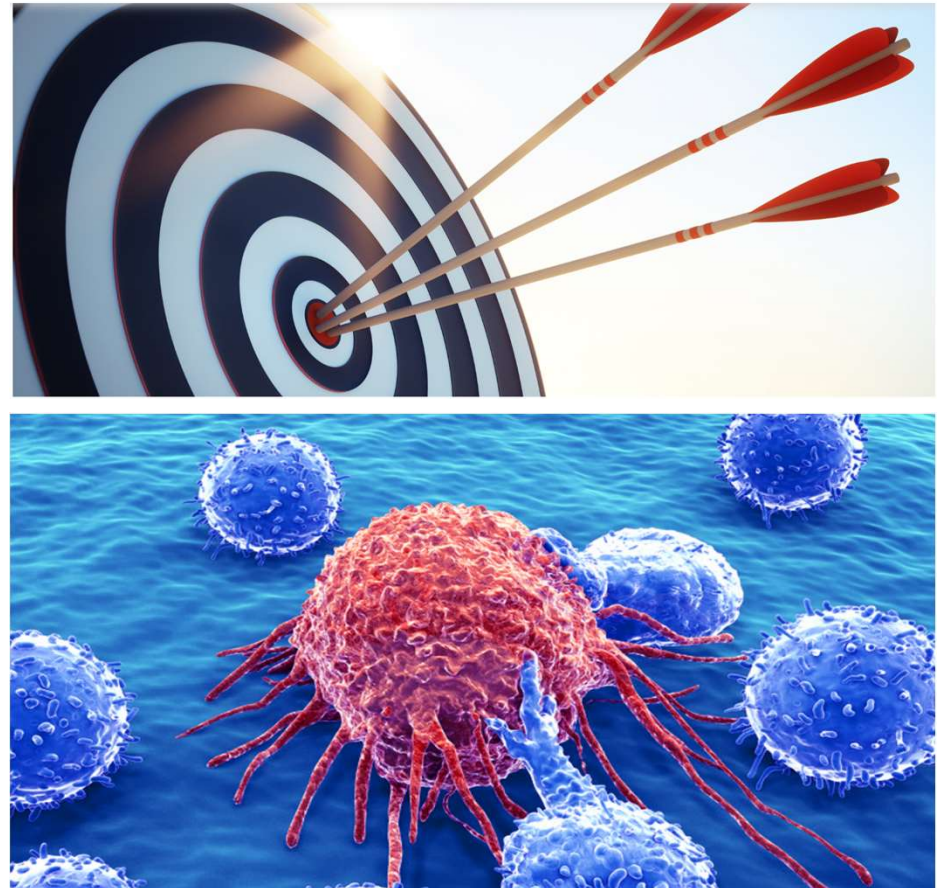
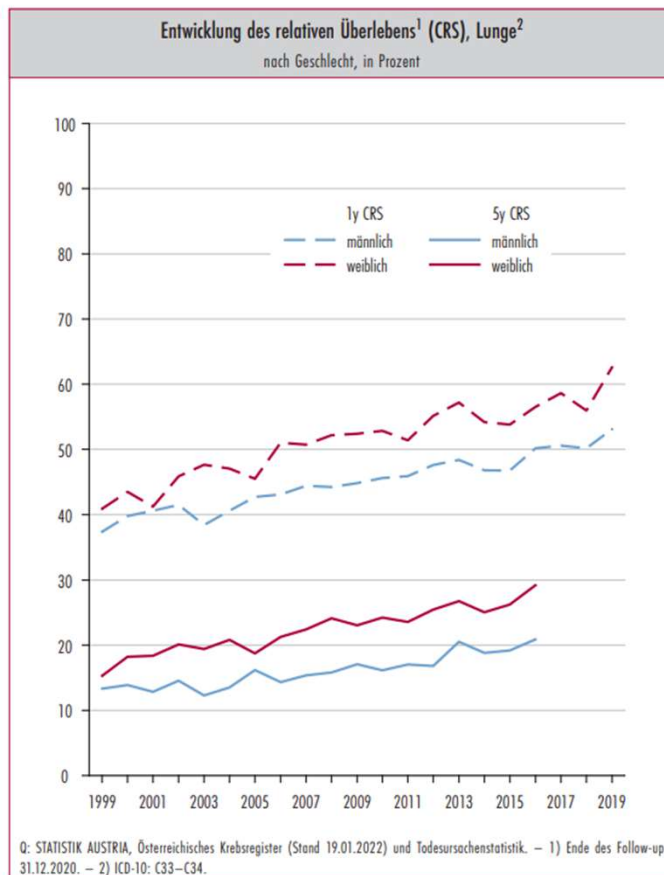
Q: STATISTIK AUSTRIA, Österreichische



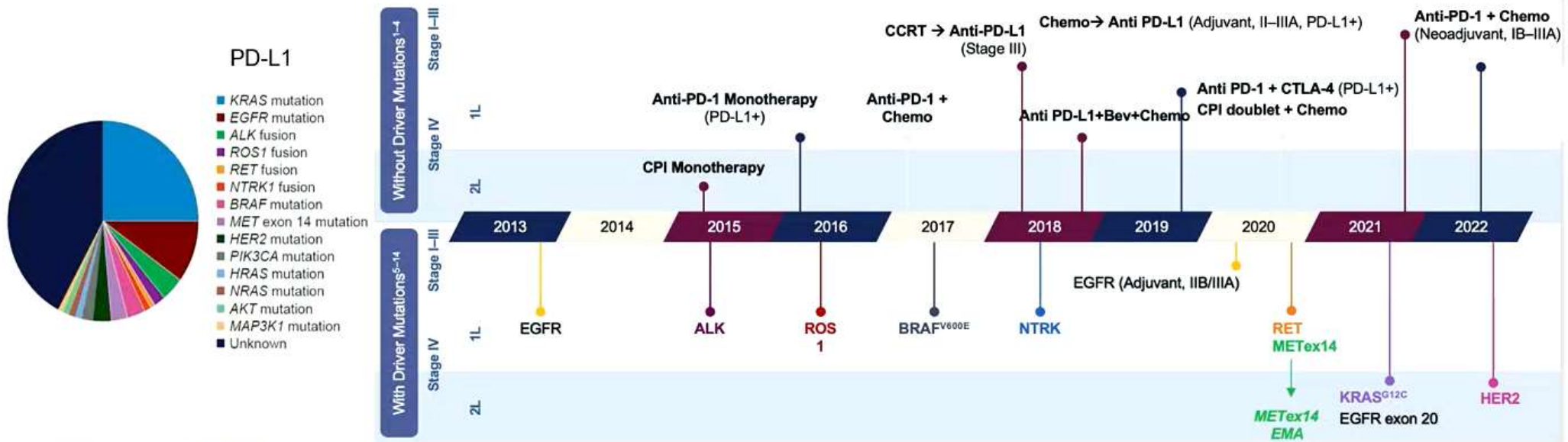
Killer Nr. 1



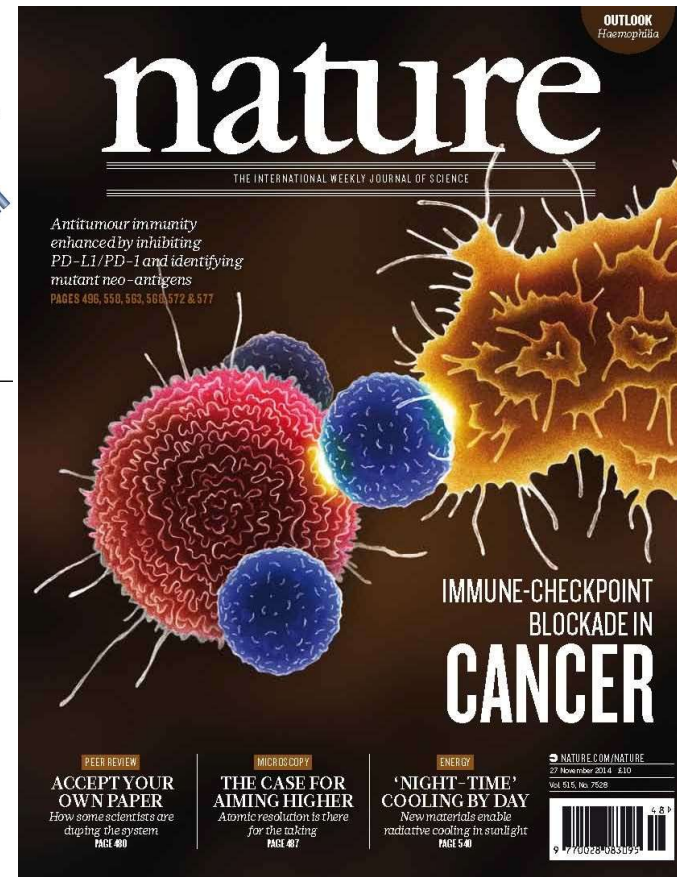
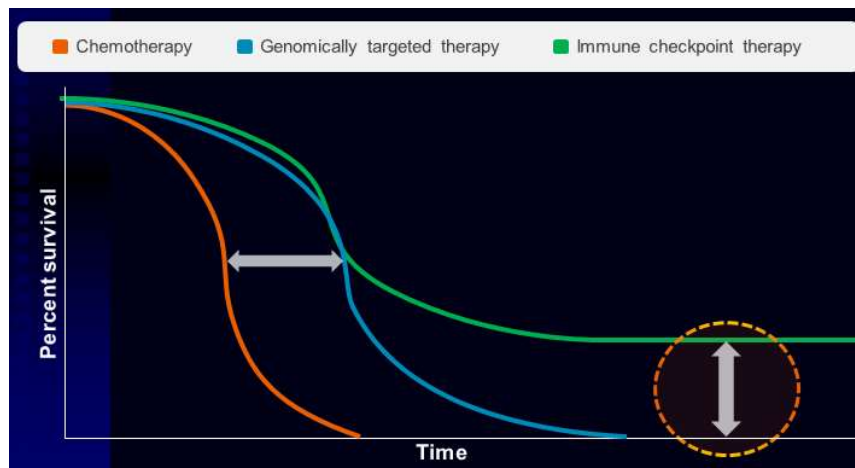
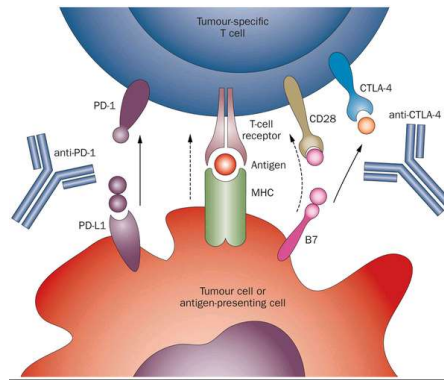
Weiterhin schlechte Prognose



Entwicklung der Therapielandschaft



Checkpointinhibitoren in der Krebstherapie



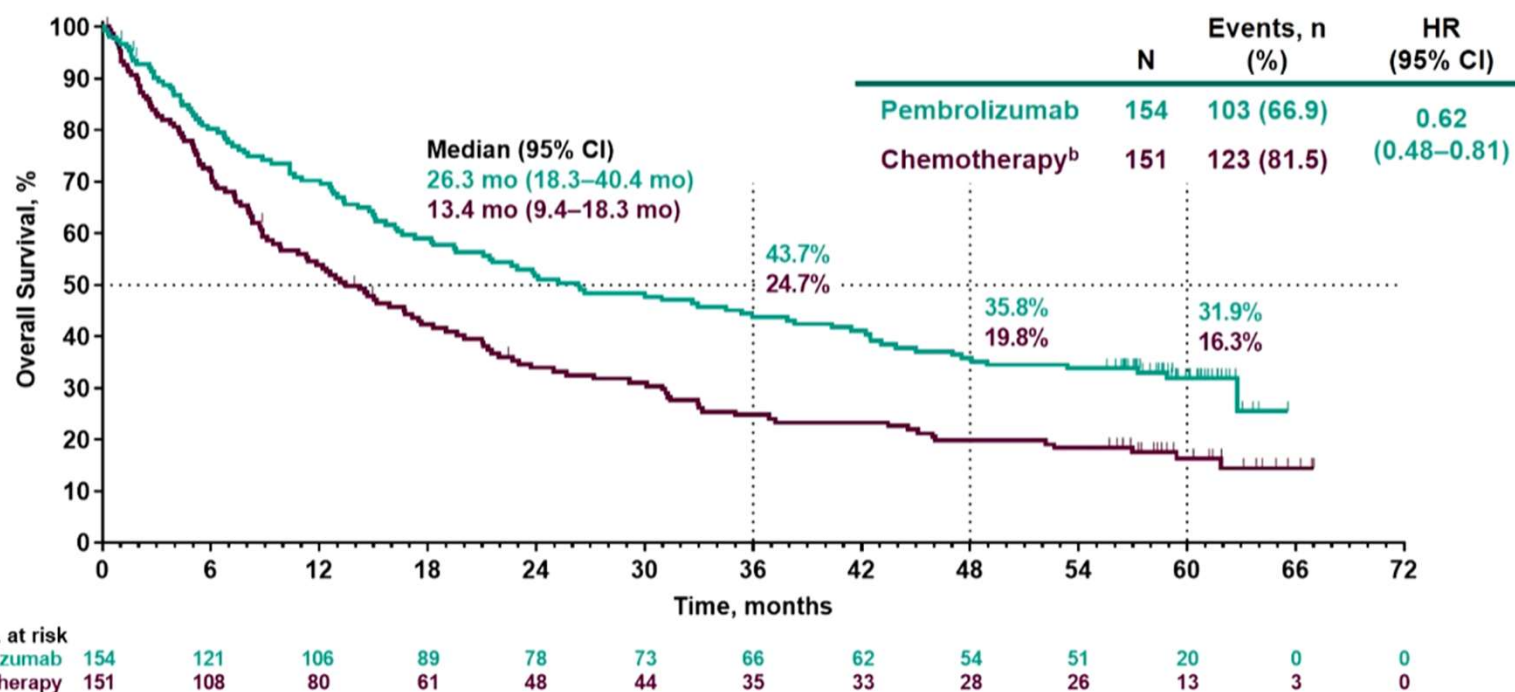
Chemotherapie vs. Immuntherapie



COPENHAGEN 2016 **ESMO** congress
7-11 OCTOBER 2016
COPENHAGEN, DENMARK



5 Jahres OS update – Keynote 024



^aITT population.

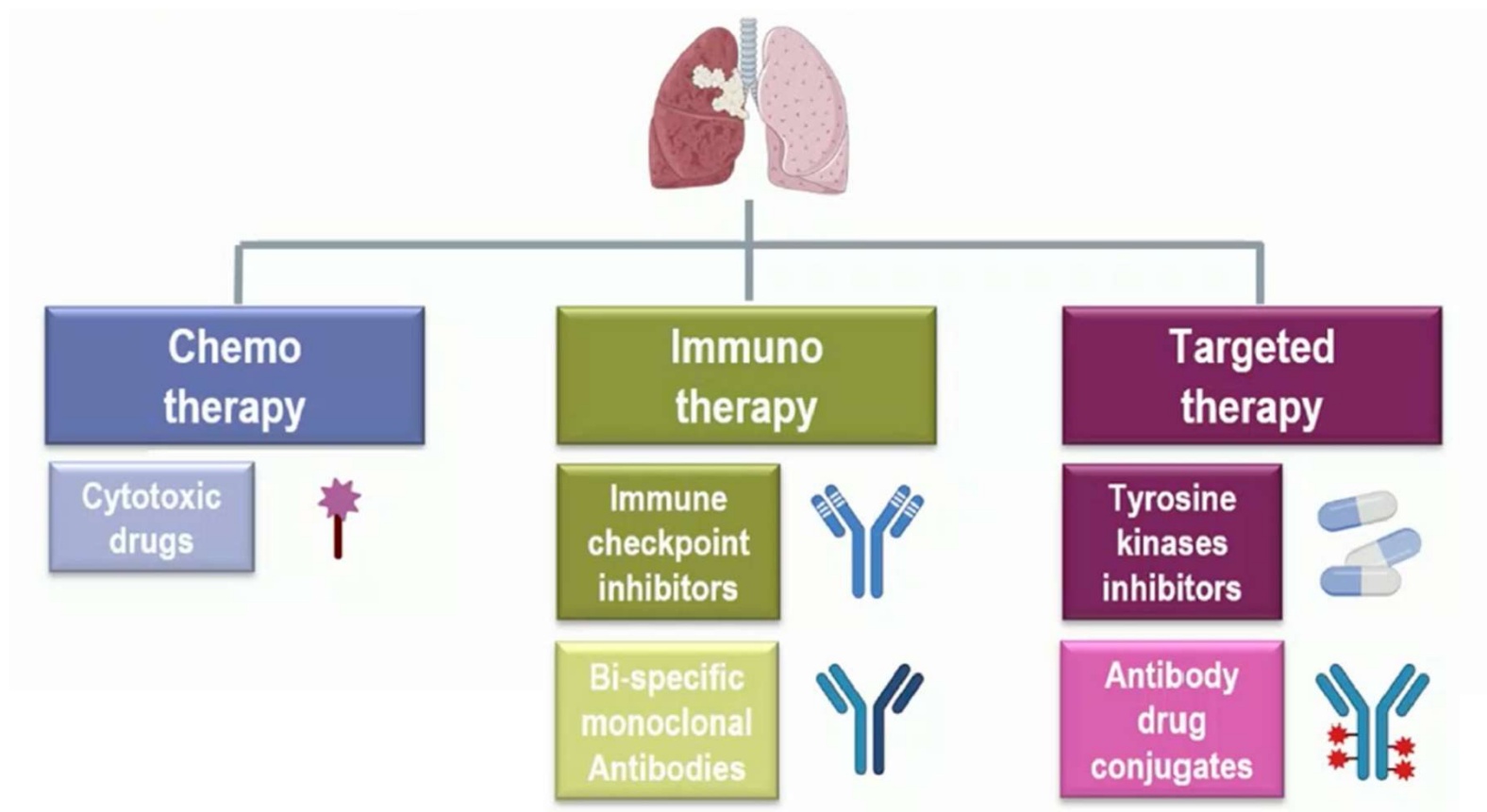
^bEffective crossover rate from chemotherapy to anti-PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti-PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti-PD-[L]1 therapy outside of crossover; patients may have received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

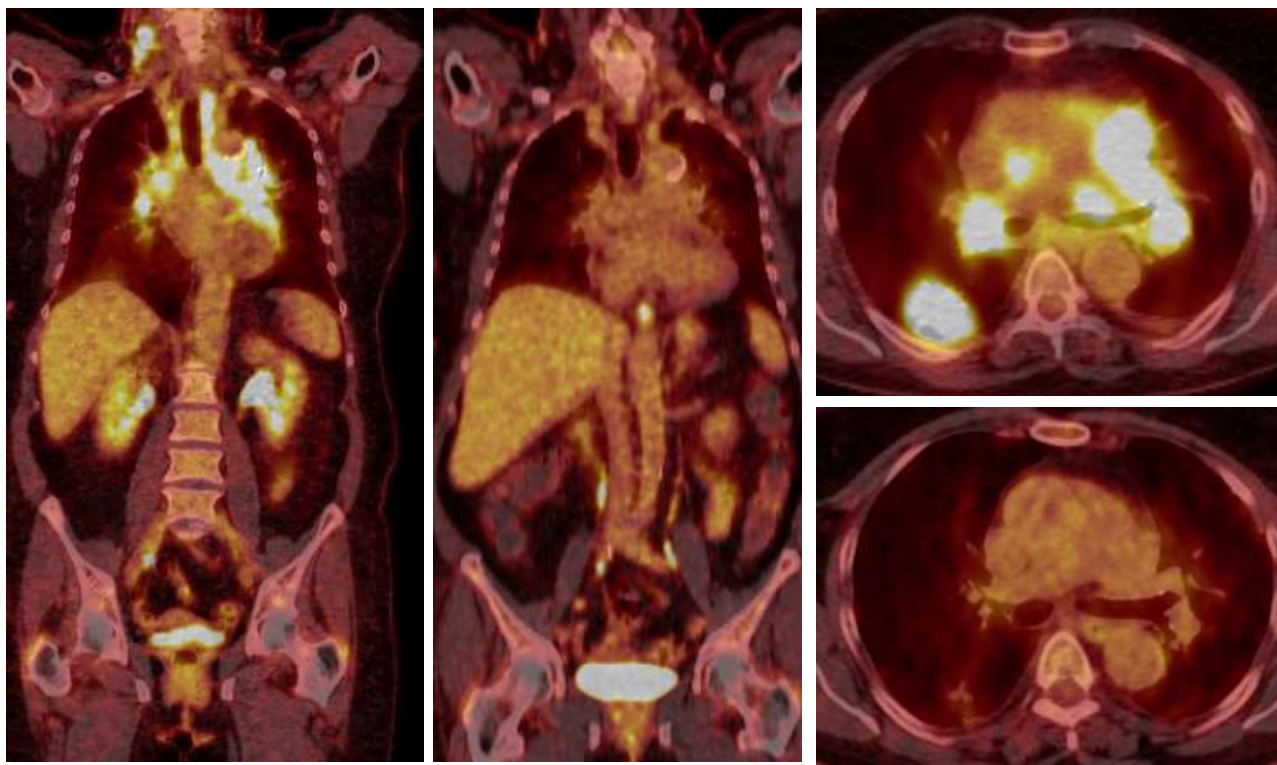
PD-L1 the key to success?



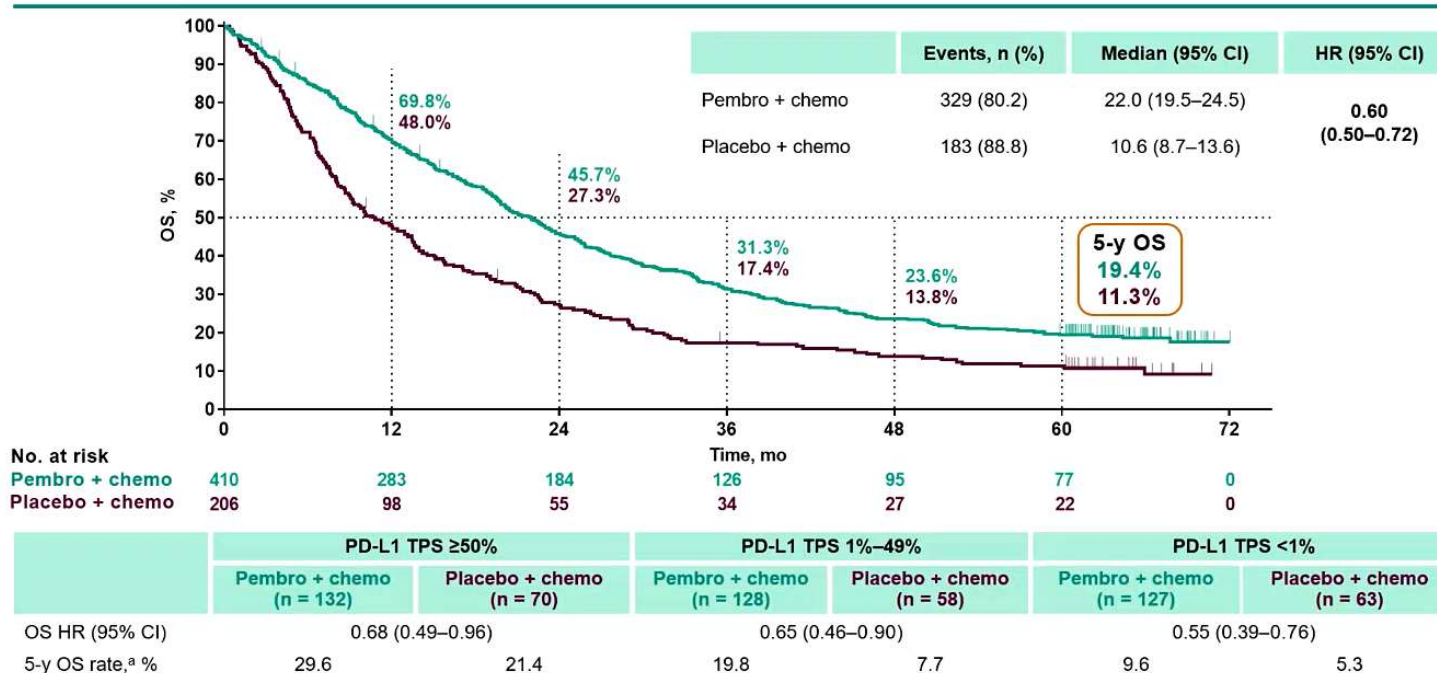


„Pillars“ of lung cancer treatment

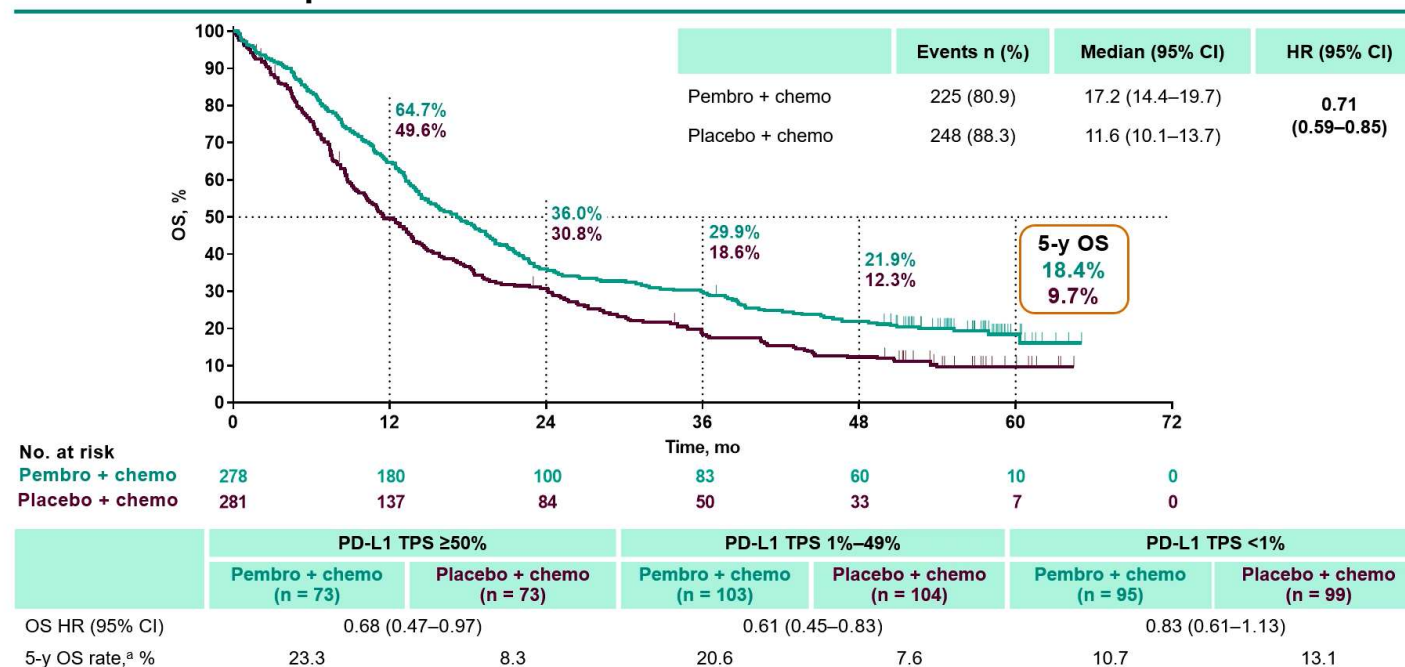




OS: ITT Population

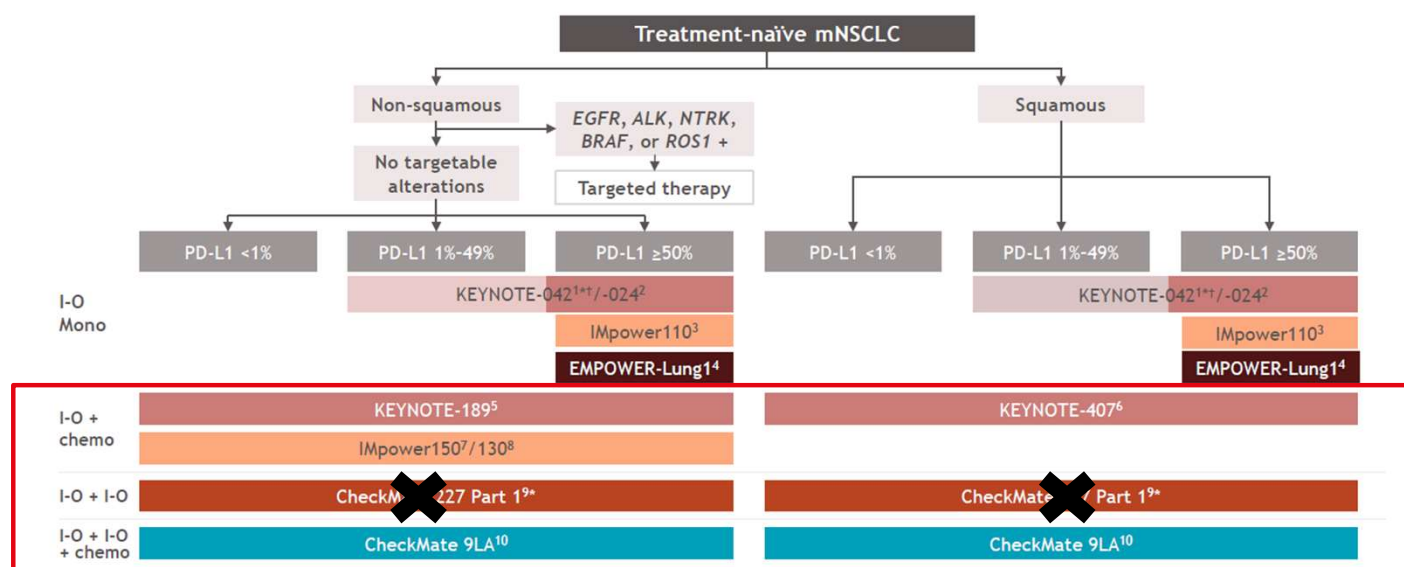


OS: ITT Population



^aKaplan-Meier estimate. Data cutoff date: February 23, 2022.

Zahlreiche Optionen in der Erstlinie

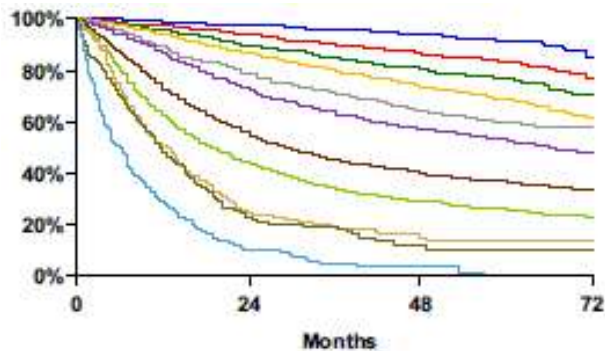


This diagram is intended for educational purposes only. It reflects the views of the presenter and not the current treatment landscape in mNSCLC.

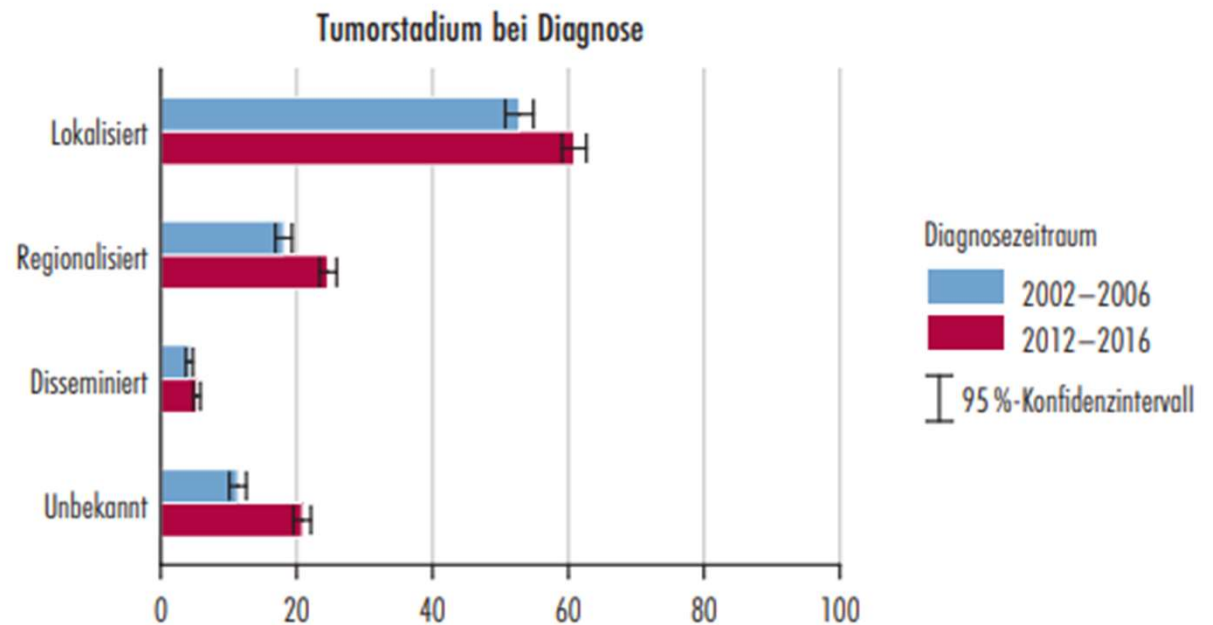
*Regulatory status varies globally. [†]ESMO guidelines indicate that benefit driven mostly by high-expressors.

1. Cho BC et al. Poster presentation at WCLC 2020. Abstract FP13.04. 2. Reck M et al. *J Clin Oncol*. 2021;39(21):2339-2349. 3. Herbst RS et al. Poster presentation at WCLC 2020. Abstract FP13.03. 4. Sezer A et al. *Lancet* 2021;397:592-604. 5. Gray JE et al. Poster presentation at WCLC 2020. Abstract FP13.02. 6. Robinson AG et al. Oral presentation at ELCC 2021. Abstract 970. 7. Socinski MA et al. Oral presentation at AACR 2020. Abstract CT216. 8. West H et al. *Lancet Oncol* 2019; 20(7):924-937. 9. Hellmann MD et al. *N Engl J Med*. 2018;378(22):2093-2104. 10. Paz-Ares L et al. *Lancet Oncol* 2021; 22(2):198-211.

Gesamtüberleben ist stark vom Stadium abhängig!

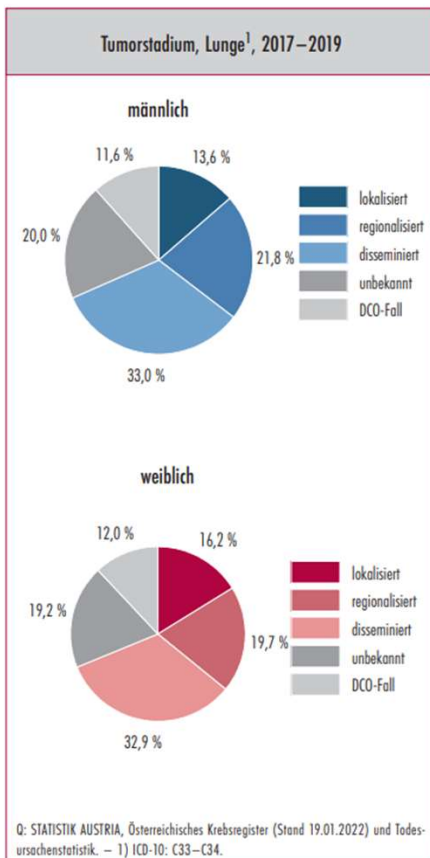


Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5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



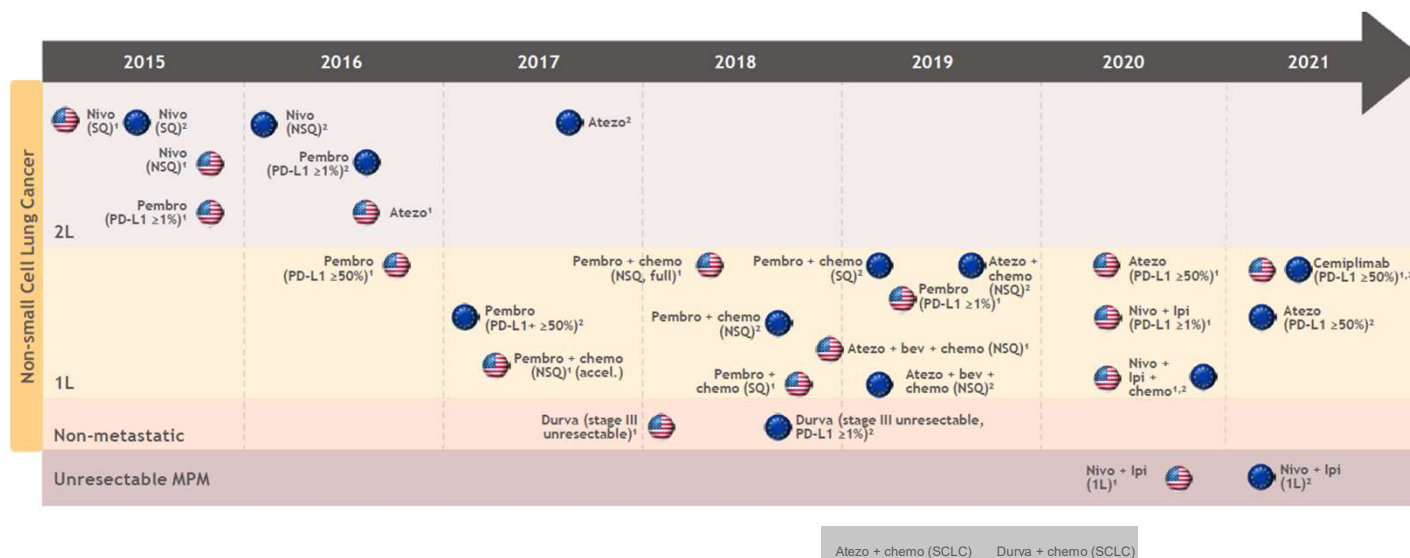
Q: STATISTIK AUSTRIA, Österreichisches Krebsregister (Stand 19.01.2022) und Todesursachenstatistik. – 1) Ende des Follow-up 31.12.2020. – 2) ICD-10: C33–C34.

Häufig (zu) späte Diagnose



1. Rang bei direkten und indirekten krebsbedingten Gesundheitskosten in Europa

... ohne Immuntherapie geht es nicht !?

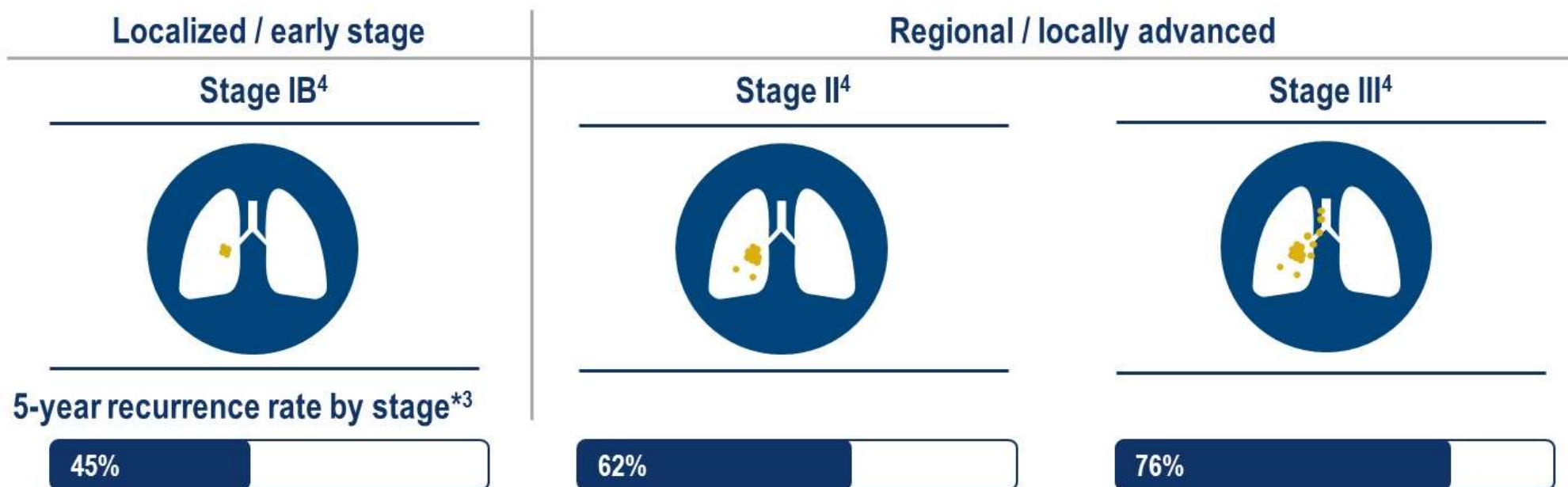


Slide reflects approvals in the US and EU as of June 2, 2021. Refer to each country's local guidance for specific therapeutic strategies.
1. US Food and Drug Administration. 2. European Medicines Agency.

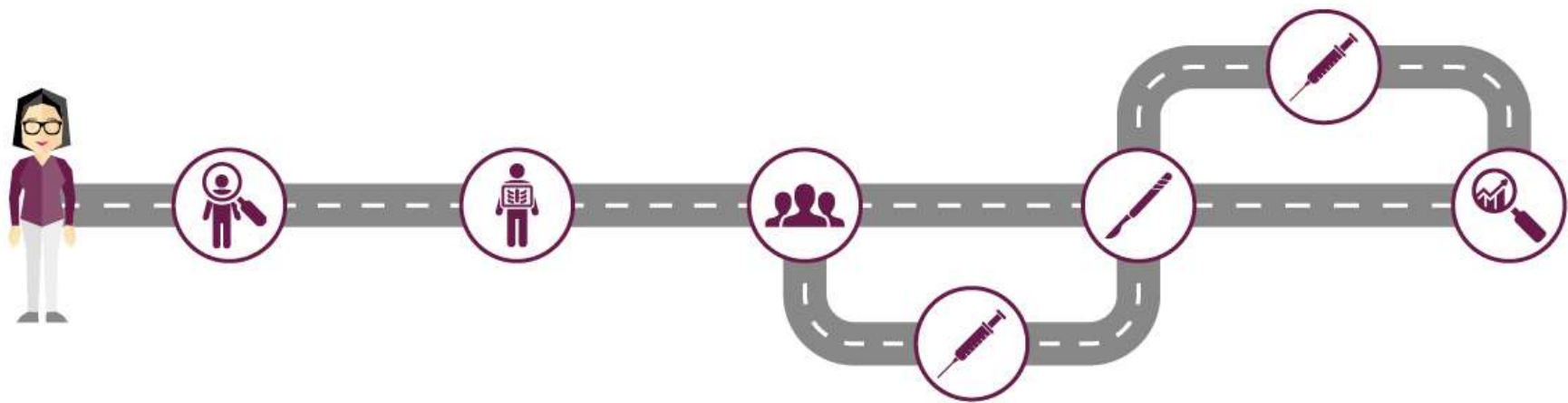
2022

Early stage NSCLC

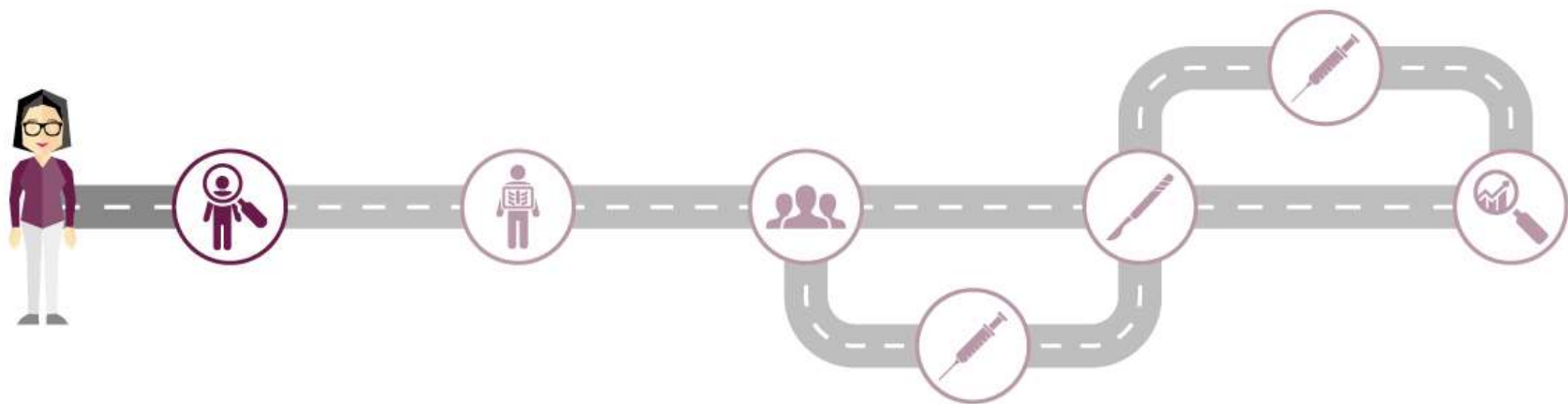
Schlechtes Outcome!!



eNSCLC Patient Journey- von der Diagnose zur Behandlung



Entdeckung einer suspekten Läsion/initiale Konsultation



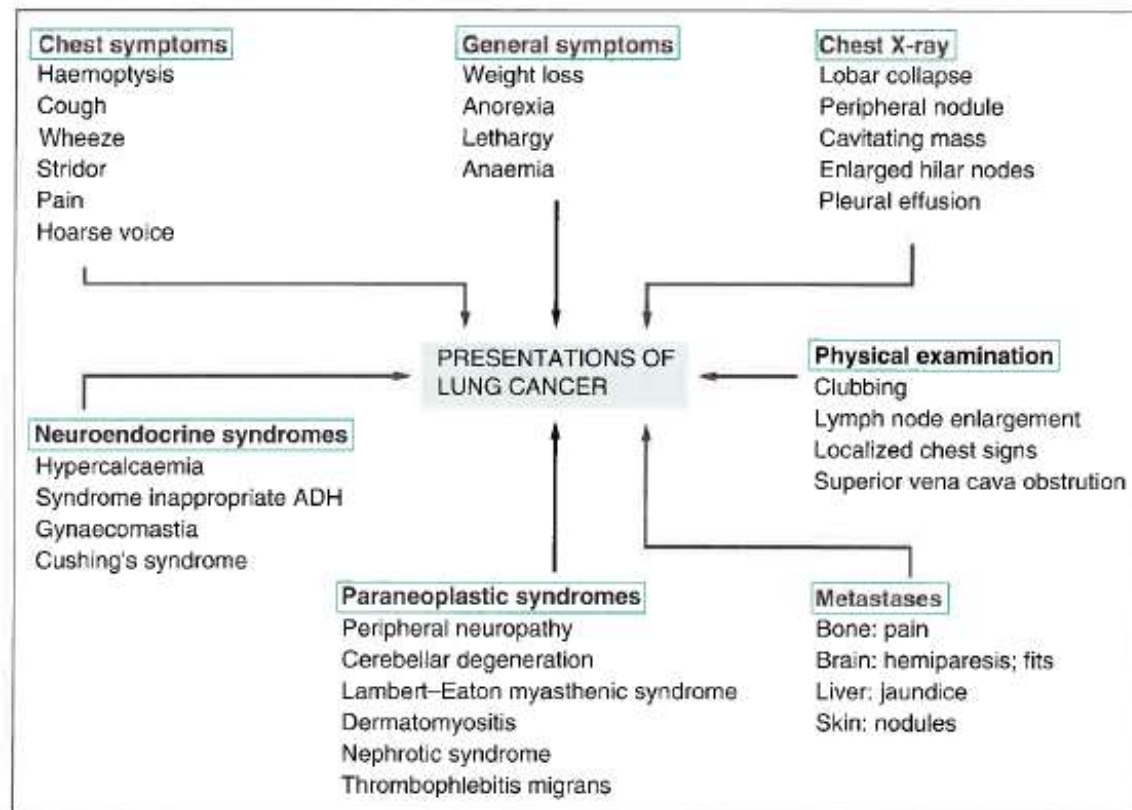
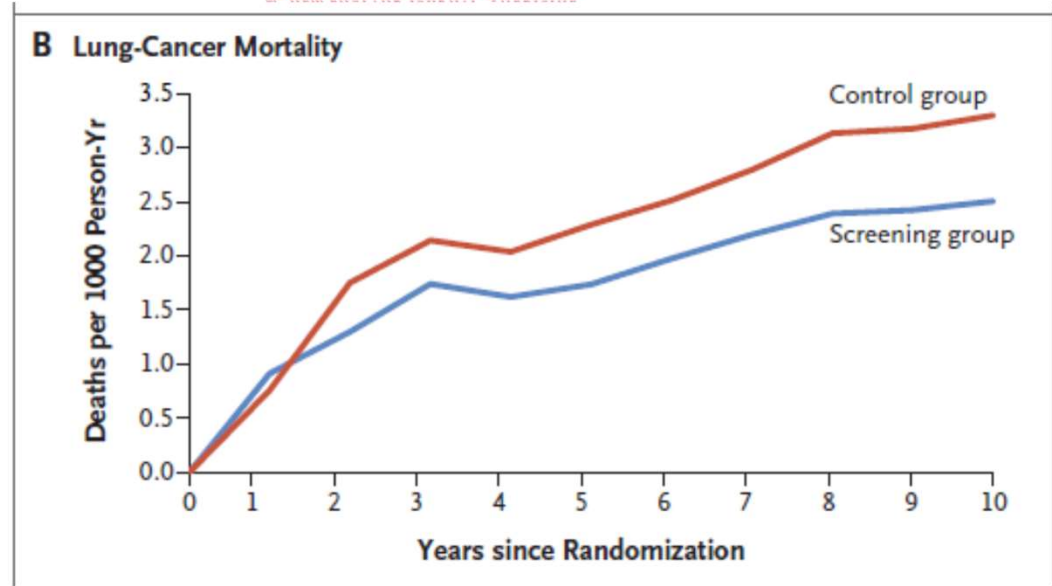
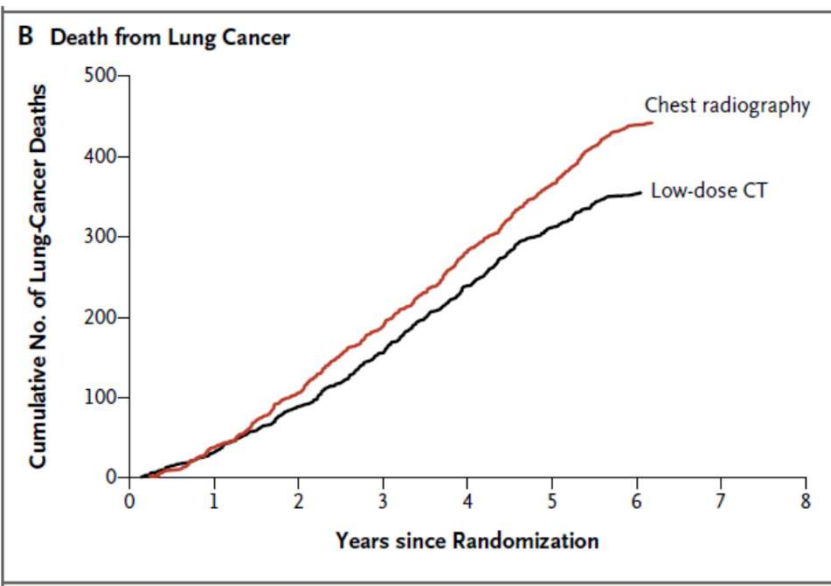


Figure 12.2 Presentations of lung cancer. ADH, antidiuretic hormone.

Korrekte Bildgebung zur Früherkennung

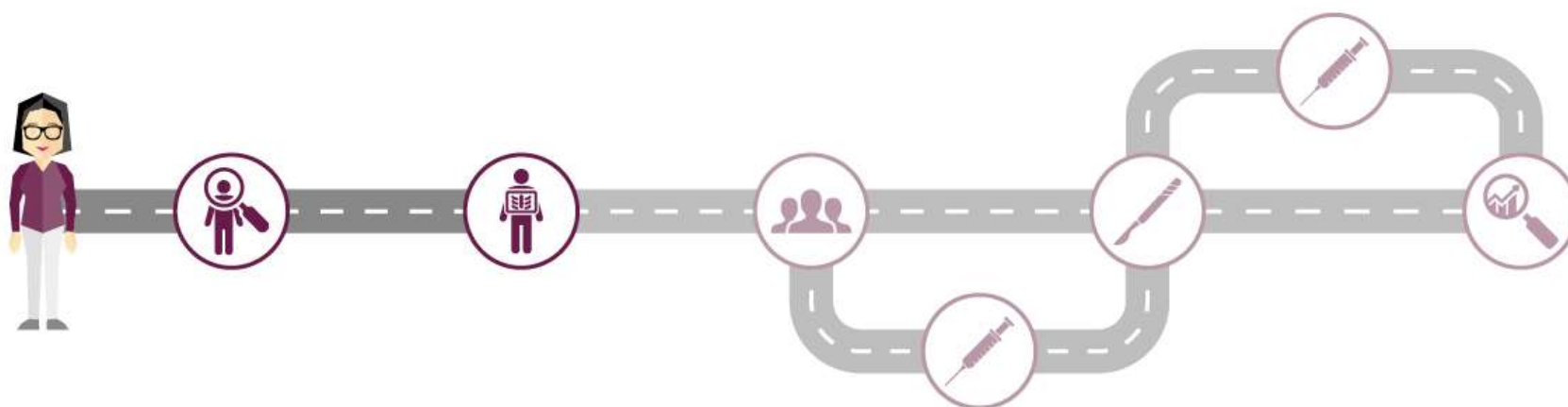


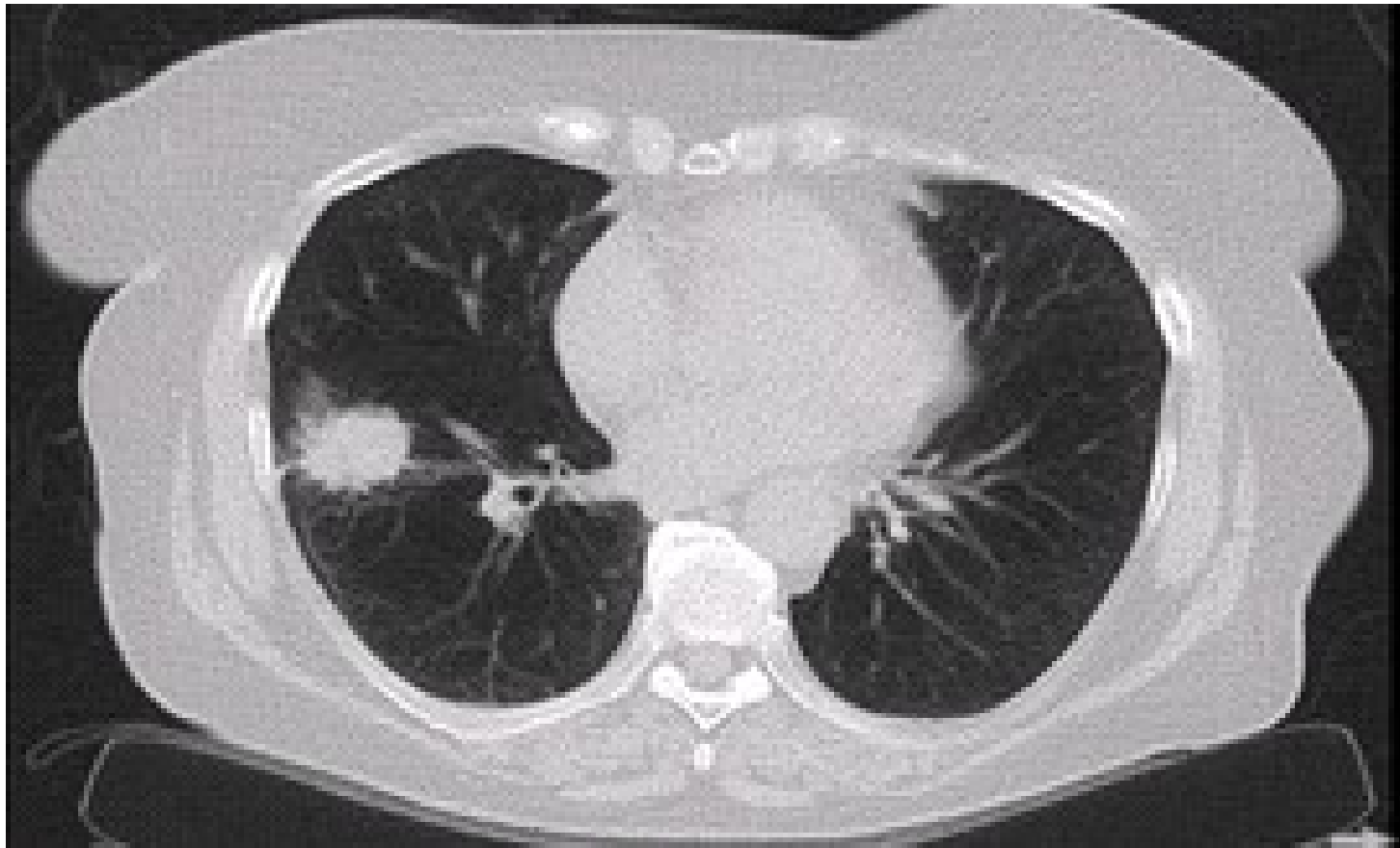
Evidenzlage zum Lungenkrebscreening

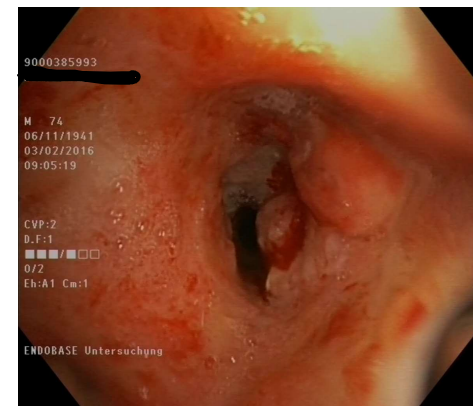
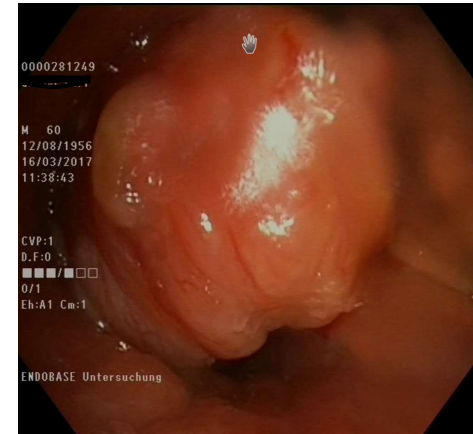
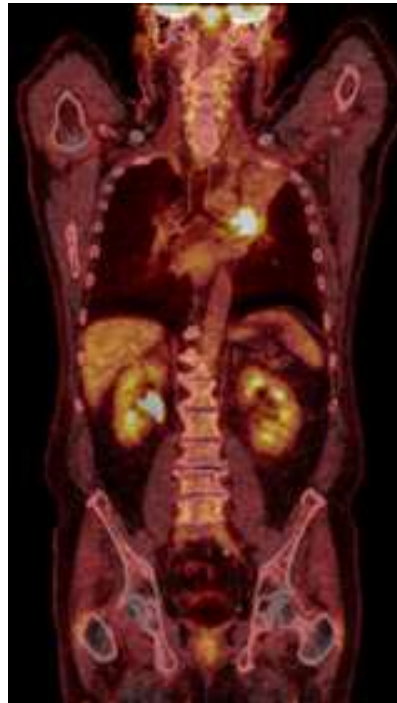
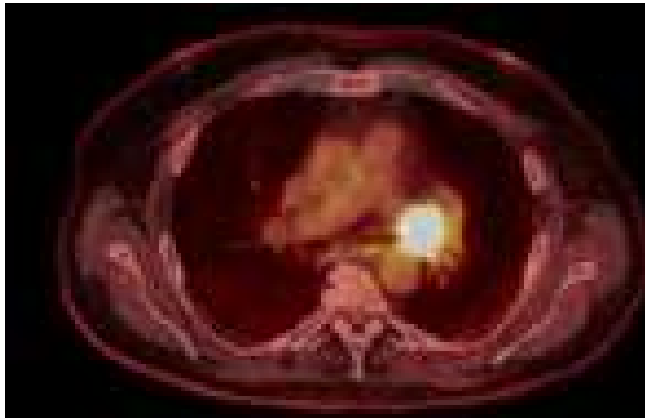


- Relative Risikoreduktion 20%
- Signifikante Senkung der Gesamtmortalität 6,7%
- Relative Risikoreduktion 25%
- Keine signifikante Senkung der Gesamtmortalität

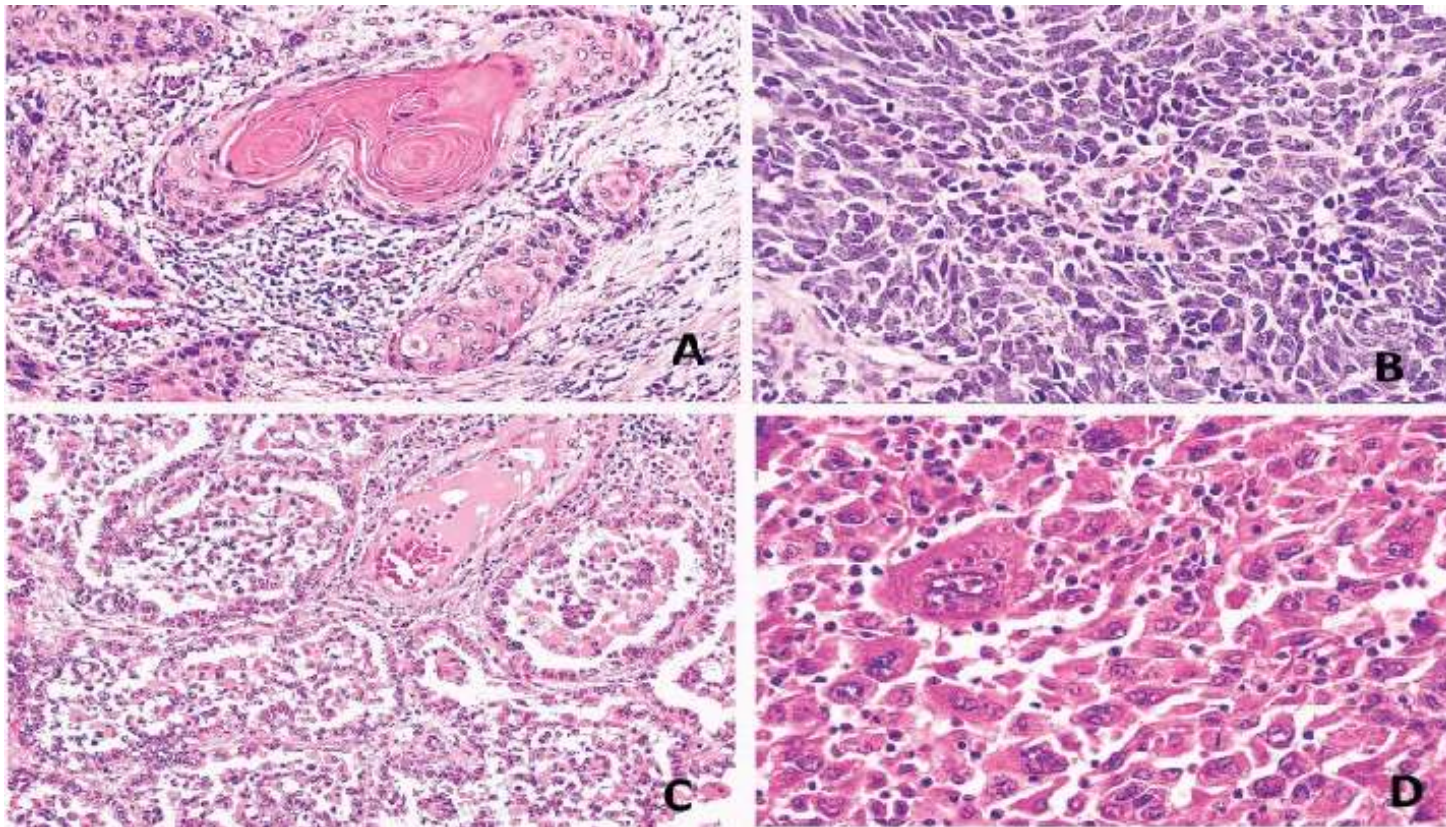
NSCLC Diagnose- Bildgebung, histologische Abklärung, Staging und Tests



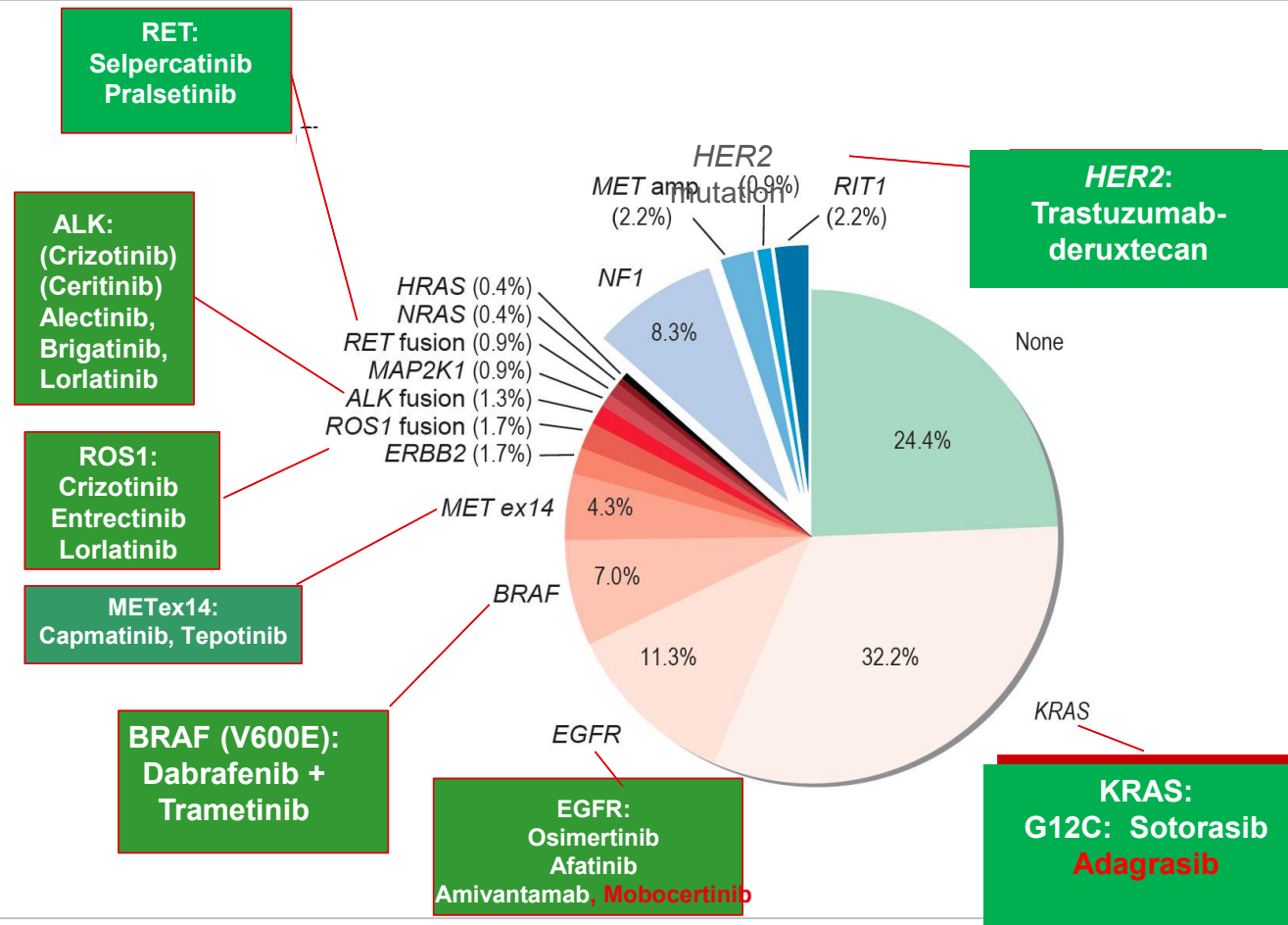




Histologie alleine genügt NICHT



Breite molekularpathologische Testung!



■ Probenentnahme zur Histologie

Bronchoskopie
Transthorakale PE
Mediastinoskopie
Thorakoskopie

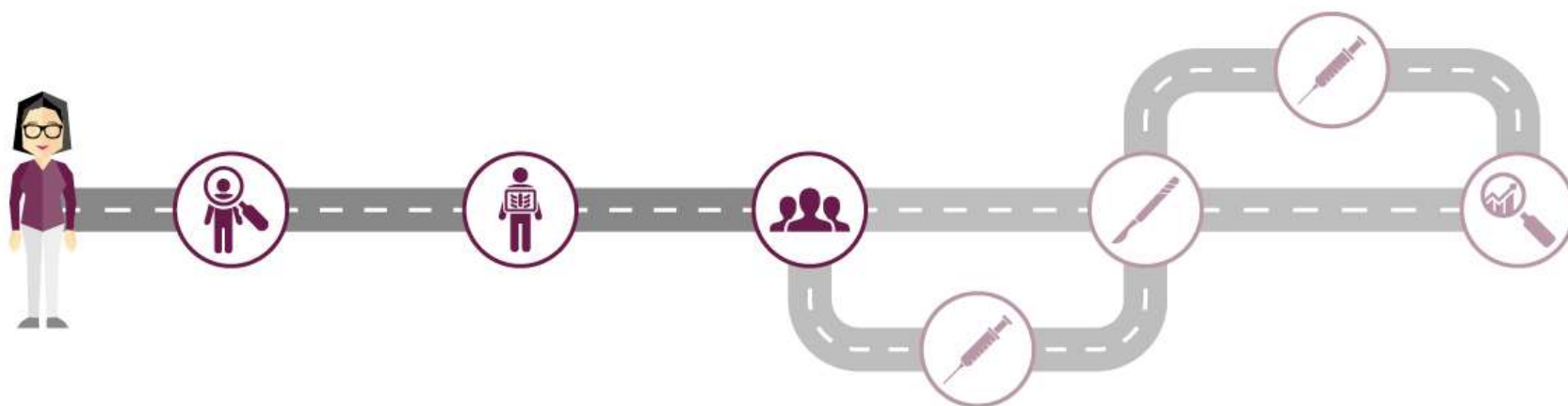
■ Staging

CT (Thorax +OB)
MR cerebrum
Skelettszintigraphie
FGD-PET

■ Erlaubt der Allgemeinzustand
eine Therapie?

z.B. ECOG, PS,
LUFU, Komorbiditäten

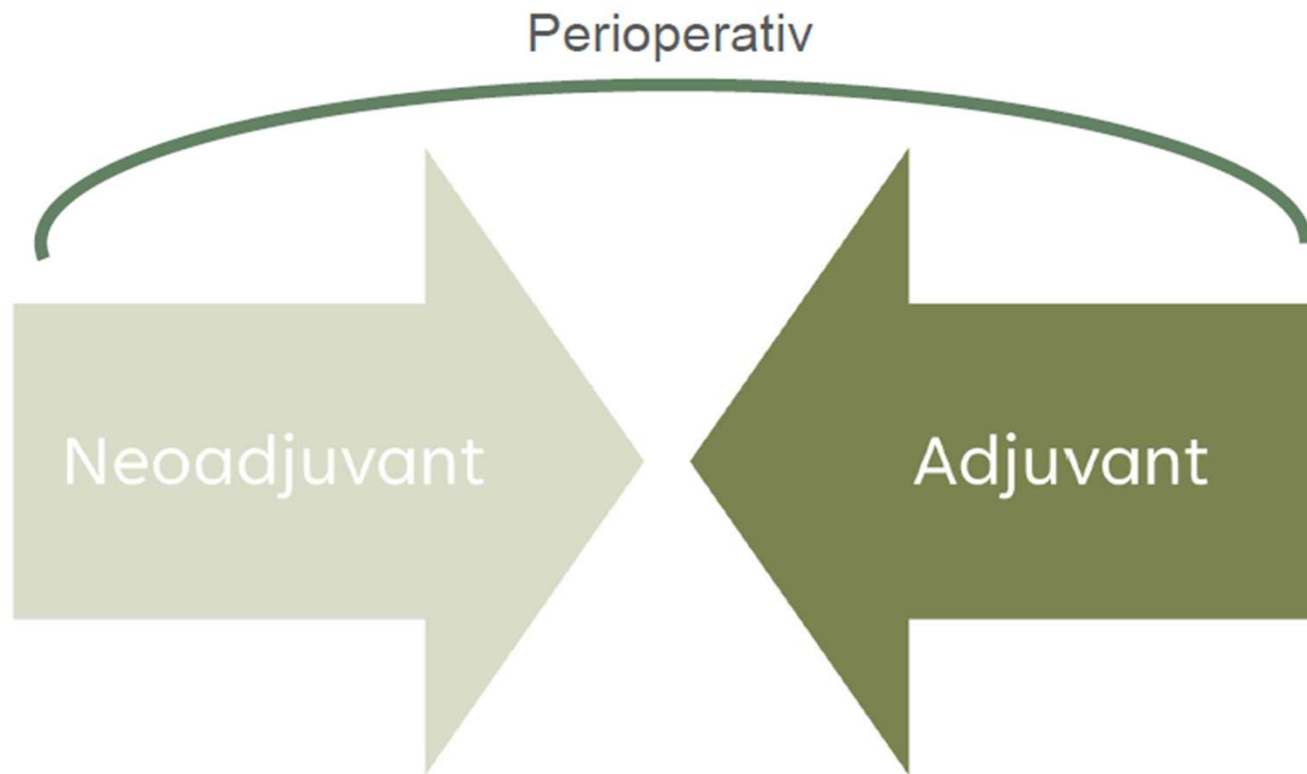
Therapieentscheidung: MDT (Multidisziplinäres Tumorboard)



Interdisziplinäre Diskussion ist zentral!



Optimales Behandlungskonzept finden



Übersicht globale Phase III Studien

Perioperativ

Studien-Name	Substanz	Primärer Endpunkt
CheckMate 816	Nivolumab + CTx	pCR, EFS
CheckMate 77T	Nivolumab + CTx → Nivolumab adjuvant	EFS
KEYNOTE-671	Pembrolizumab + CTx → Pembrolizumab adjuvant	EFS, OS
IMpower030	Atezolizumab + CTx → Atezolizumab adjuvant	MPR, EFS
AEGEAN	Durvalumab + CTx → Durvalumab adjuvant	MPR

Neoadjuvant

Neoadjuvante
Chemotherapie
± ICI

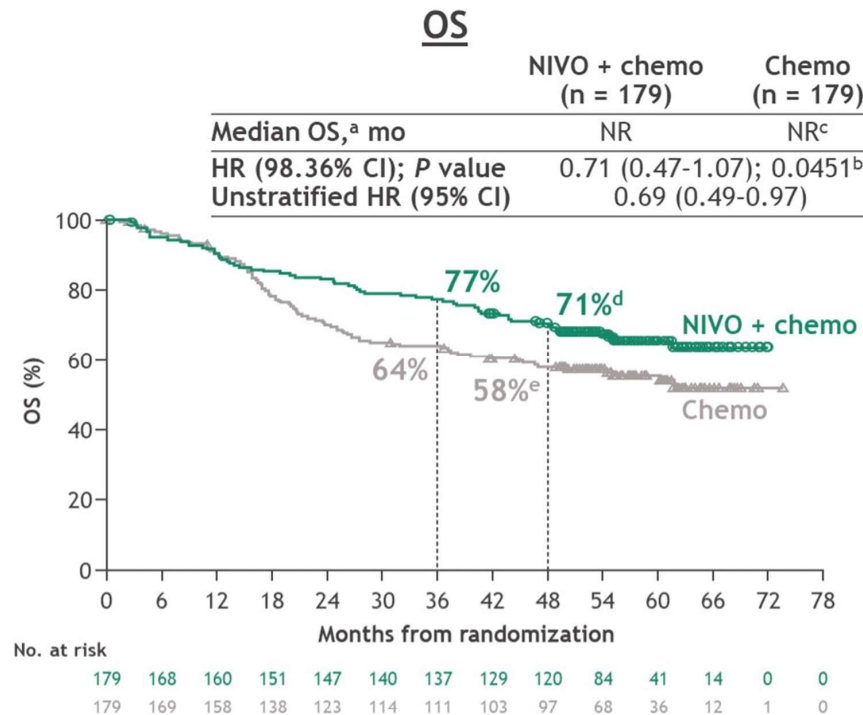
Operation

Operativer
Eingriff

Adjuvant

Adjuvante
ICI

4 Jahres update – CM816



- Patients in the NIVO + chemo arm who had pCR continued to have improved OS vs those who did not (HR [95% CI], 0.08 [0.02-0.34]; 4-year OS rates, 95% vs 63%)

Minimum/median follow-up, 49.1/57.6 months.

^aReasons for OS events (deaths) in all treated patients in the NIVO + chemo vs chemo arms (N = 176 in each arm) were disease (23% vs 33%), study drug toxicity (0% vs 2%), unknown (3% vs 3%), and other (7% vs 5%).

^bSignificance boundary for OS (0.0164) was not met at this interim analysis. ^c95% CI: ^c50.4-NR; ^d63-77; ^e50-65.

Übersicht Phase III Studien – adjuvantes Setting

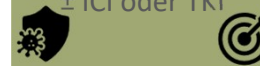
Operation

Adjuvant

Operativer
Eingriff



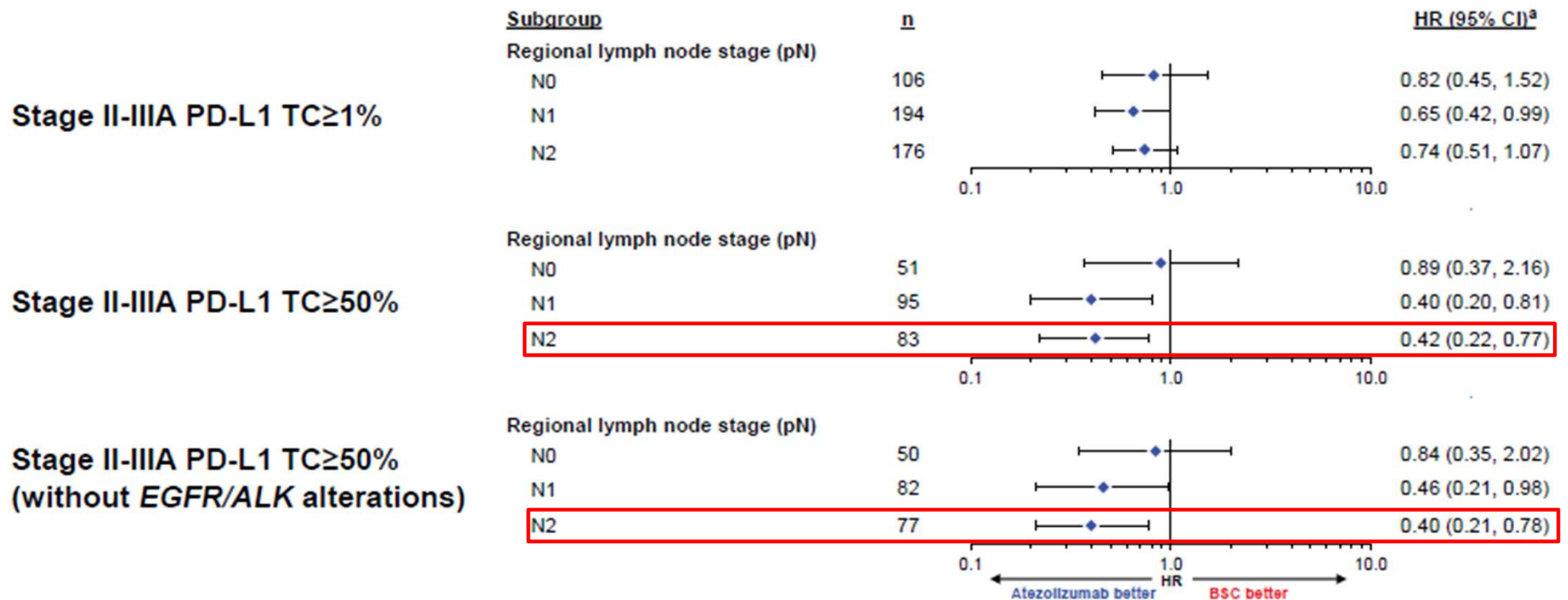
Adjuvante
Chemotherapie
± ICI oder TKI



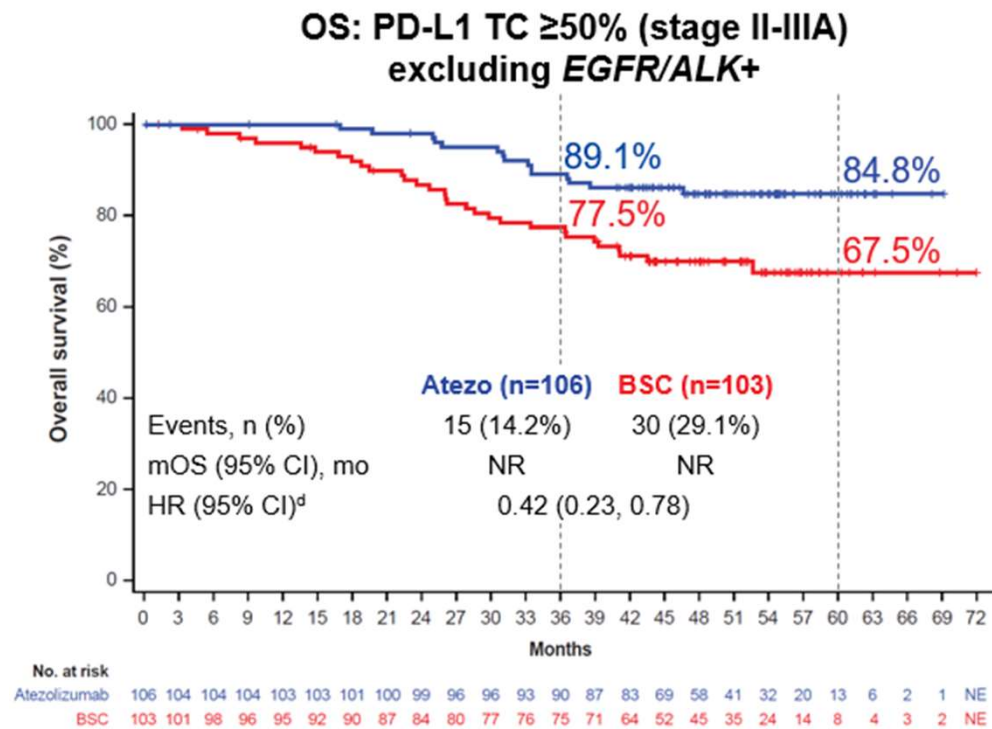
Studien-Name	Substanz	Primärer Endpunkt
Immuntherapie		
IMpower 010	Atezolizumab 1 Jahr	DFS
PEARLS/KEYNOTE-091	Pembrolizumab 1Jahr	DFS
Zielgerichtete Therapie		
ADAURA	Osimertinib 3 Jahre	DFS
ALINA	Alectinib 2 Jahre	DFS

Verbesserung im DFS nach PD-L1 Expression

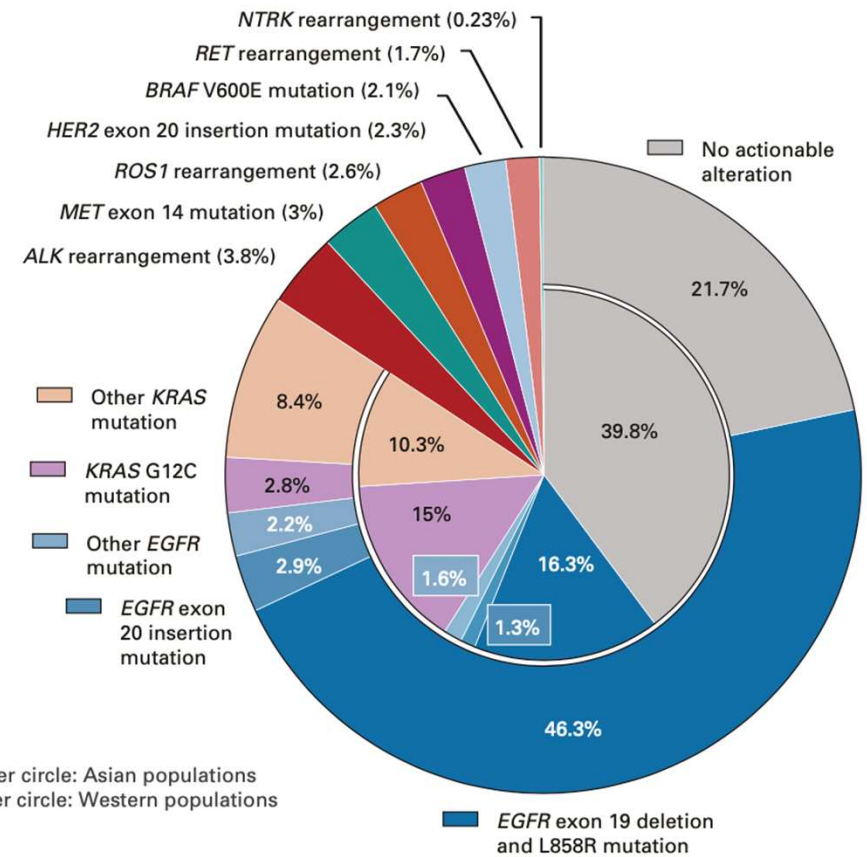
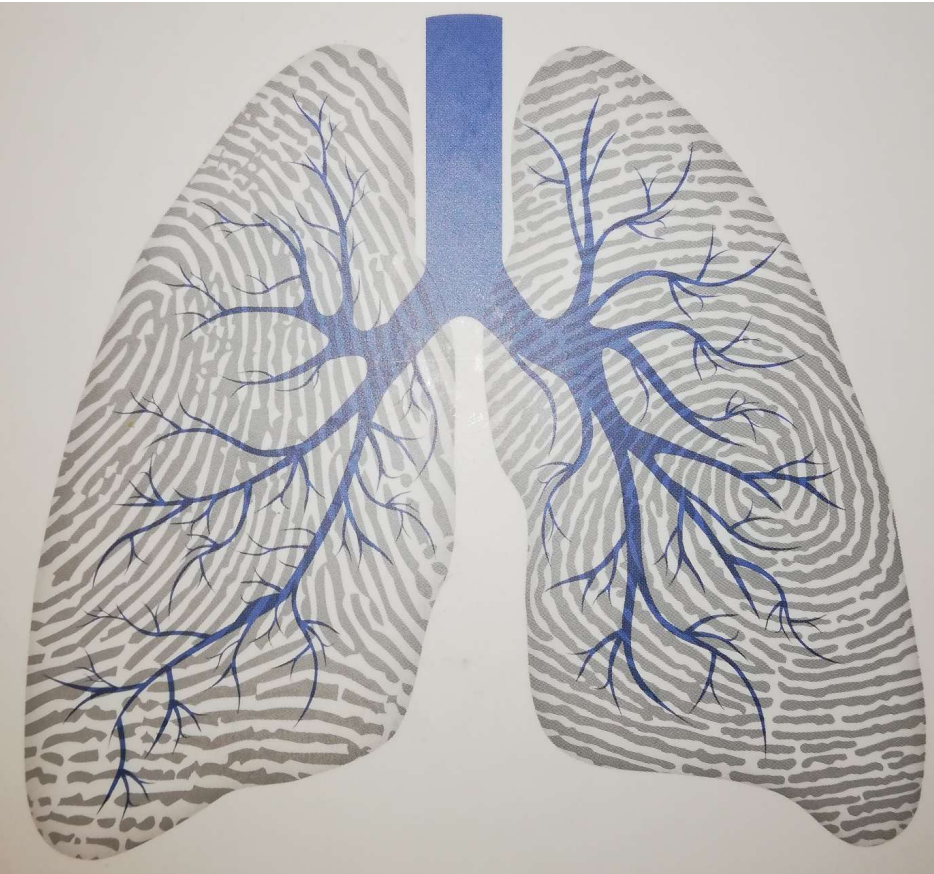
DFS by regional lymph node stage and PD-L1 status



OS Benefit noch unklar

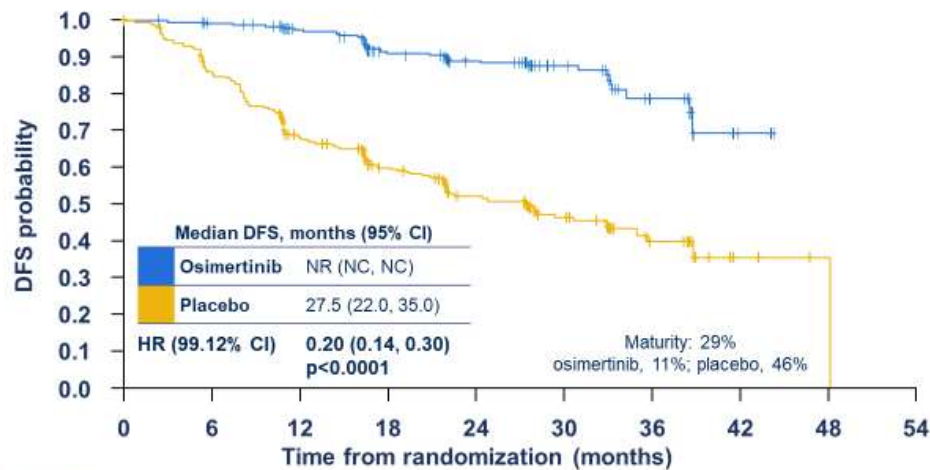


Lung cancer ≠ lung cancer



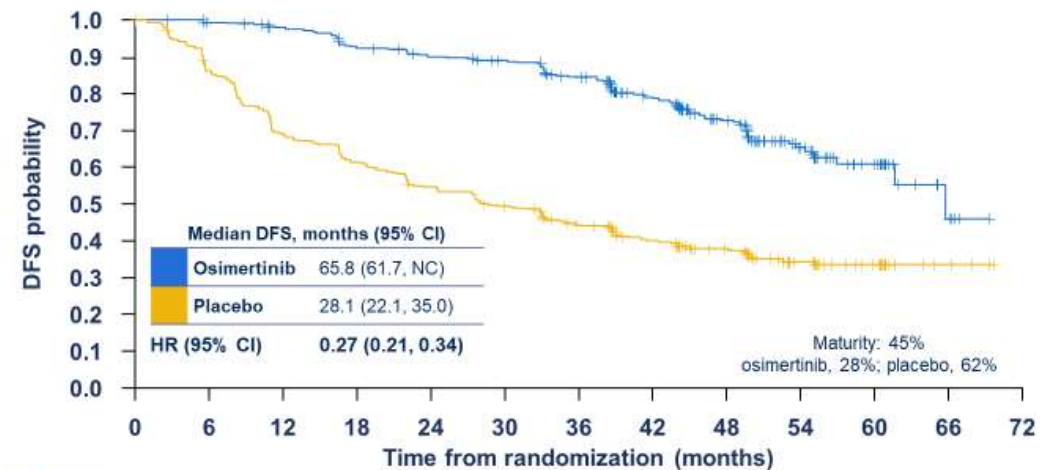
DFS Benefit im Vergleich zu Placebo

ADAURA primary DFS analysis^{1,2} (stage IB–IIIA)*
NEJM October 2020



No. at risk										
Osimertinib	339	313	272	208	138	74	27	5	0	-
Placebo	343	287	207	148	88	53	20	3	1	0

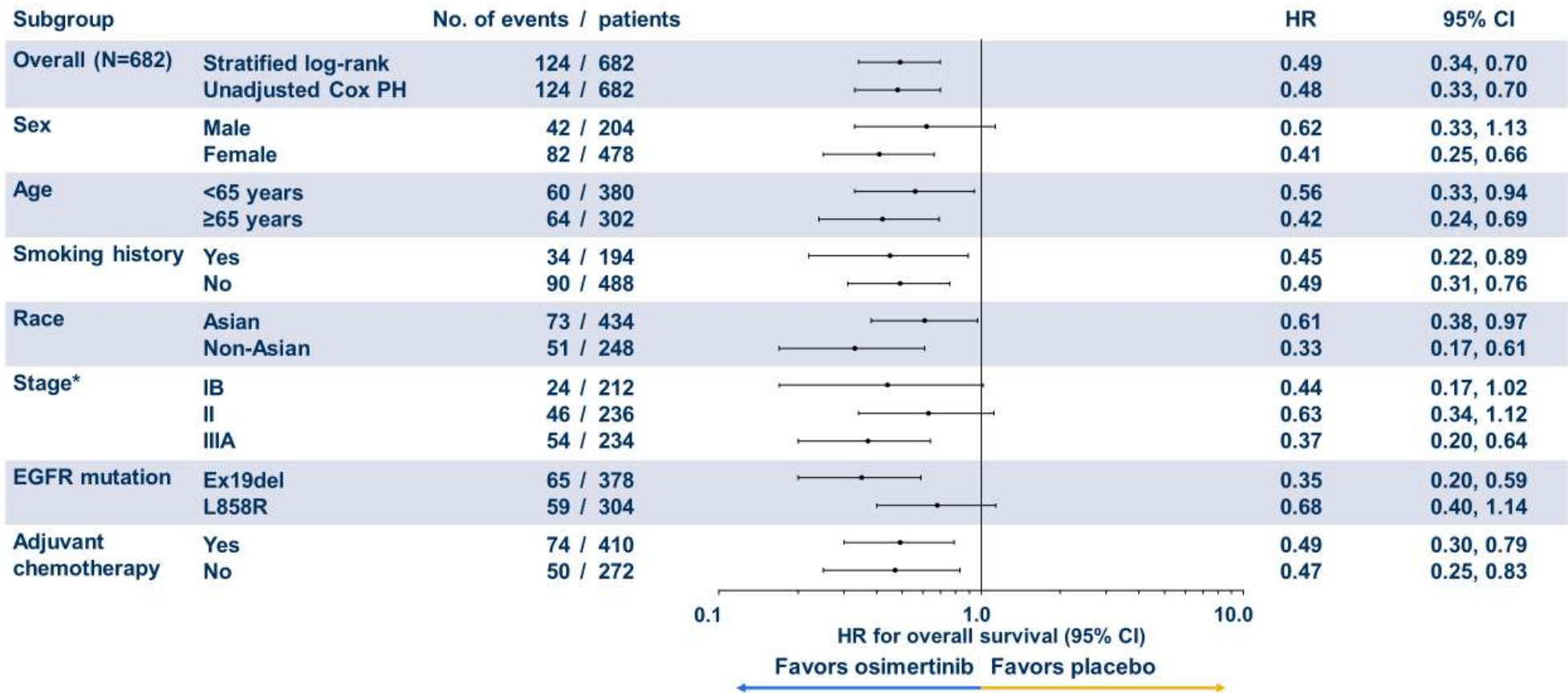
ADAURA updated DFS analysis^{3,4} (stage IB–IIIA)†
JCO January 2023



No. at risk														
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0	0

*Data cut-off: January 17, 2020. †Data cut-off: April 11, 2022.
1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38(Suppl 18): abstract / oral LBA5; 3. Herbst et al. J Clin Oncol 2023;41:1830–1840; 4. Tsuboi et al. Ann Oncol 2022;33(Suppl 7): abstract / oral LBA47

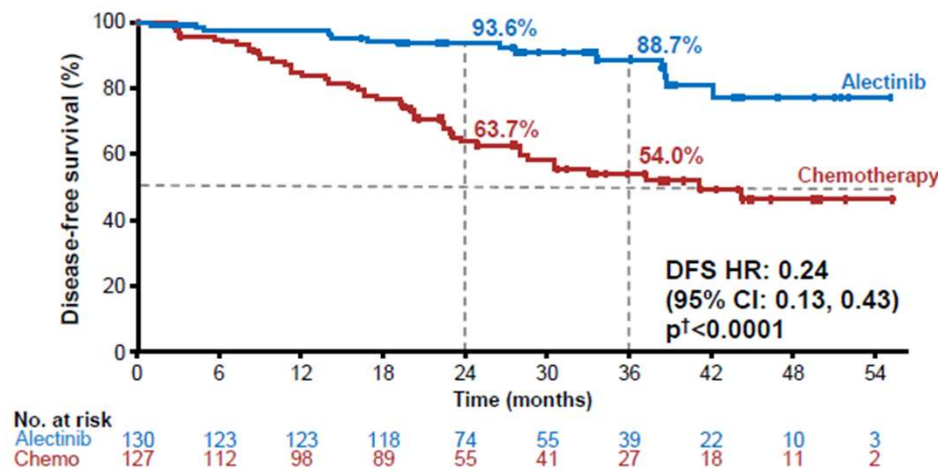
DFS Vorteil übersetzt sich in OS Vorteil!



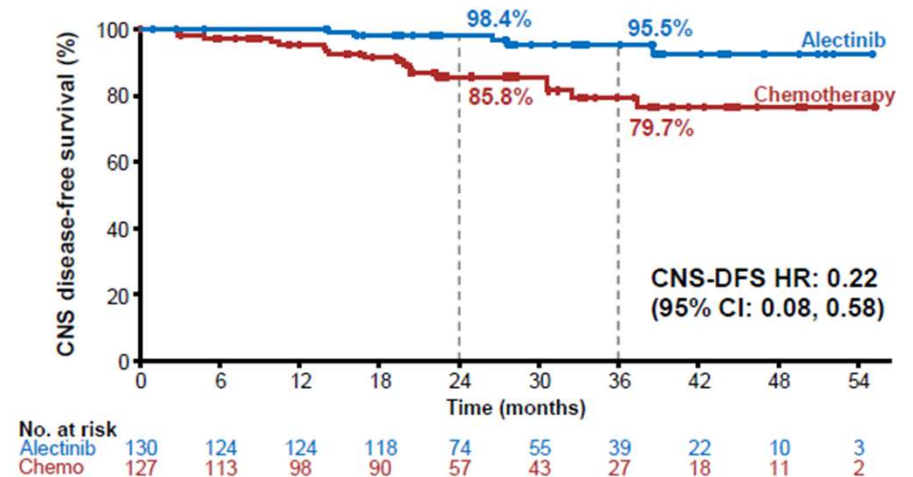
ALINA primary analysis

Treatment with adjuvant alectinib resulted in a **significant DFS benefit** and **clinically meaningful CNS-DFS benefit** compared with chemotherapy in patients with resected stage IB–IIIA ALK+ NSCLC*^{1,2}

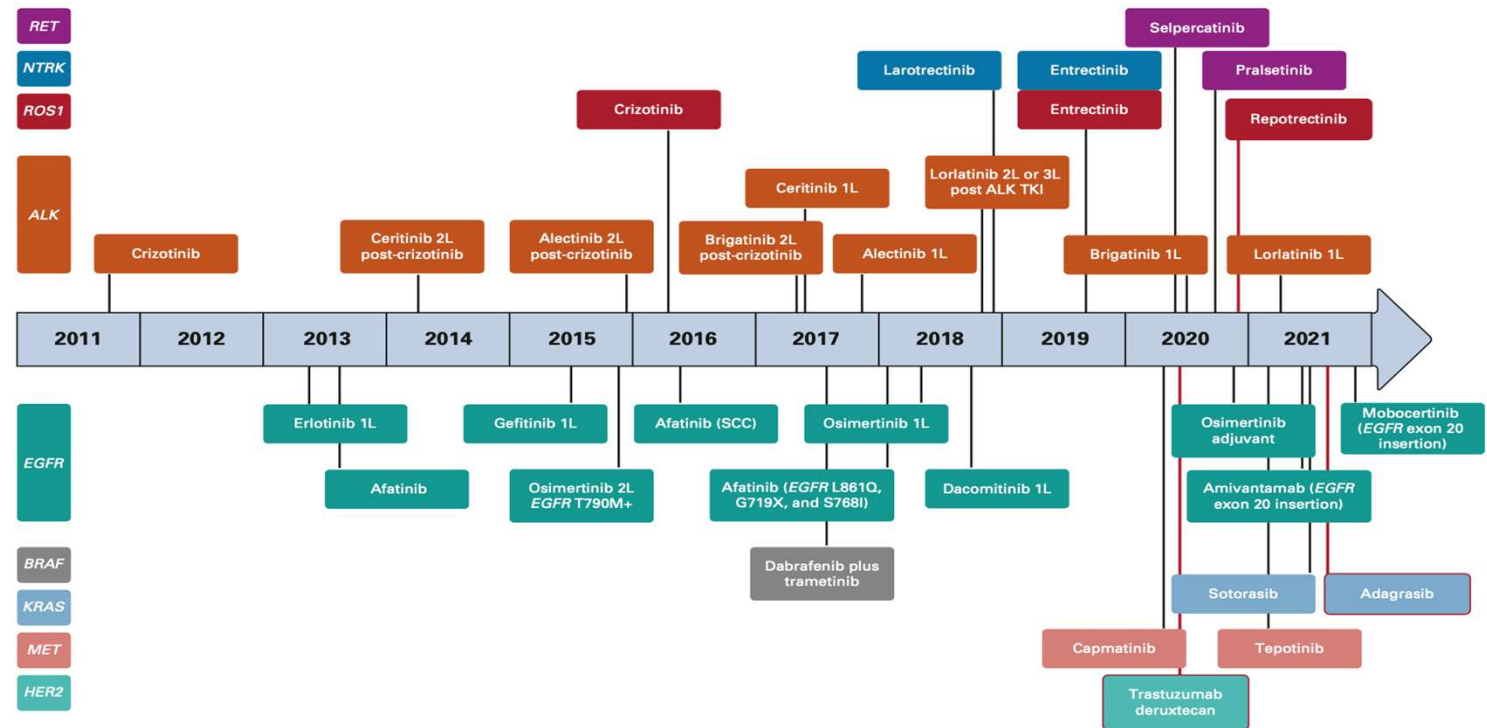
DFS in stage IB–IIIA (ITT)
Primary endpoint



CNS-DFS in stage IB–IIIA (ITT)
Exploratory endpoint



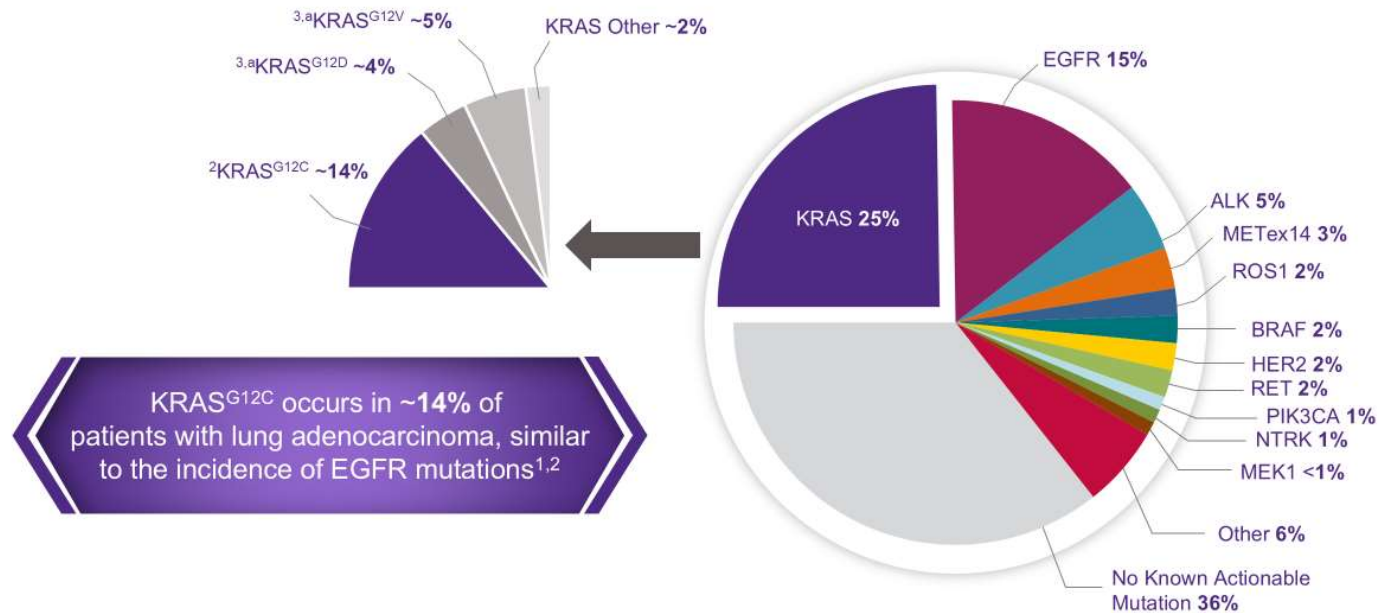
Early use of targeted therapies!



KRAS ist am häufigsten!

KRAS is the Most Prevalent Oncogenic Driver in NSCLC

KRAS mutations account for 25% of mutations in lung adenocarcinoma and are generally mutually exclusive with other oncogenic driver mutations¹

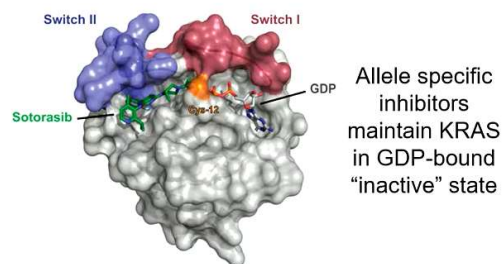


¹Value for all NSCLC histologies.

ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; MEK1, mitogen-activated protein kinase kinase 1; MET, mesenchymal-epithelial transition proto-oncogene; NSCLC, non-small cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RET, ret proto-oncogene; ROS1, ROS proto-oncogene 1.

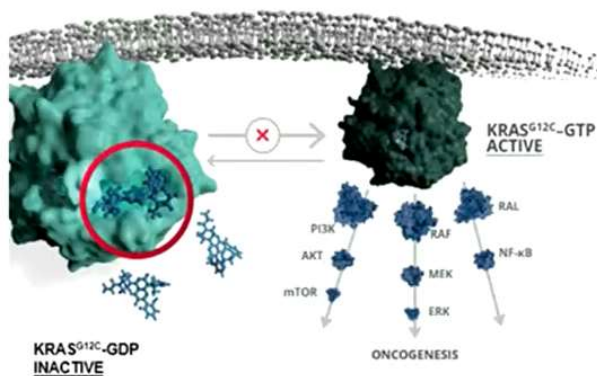
²Robinson et al. J Clin Oncol. 2006;24:3686-3690. doi:10.1200/JCO.2005.9.6631. Epub 2006 May 22.

„Undruggable“ target - KRAS

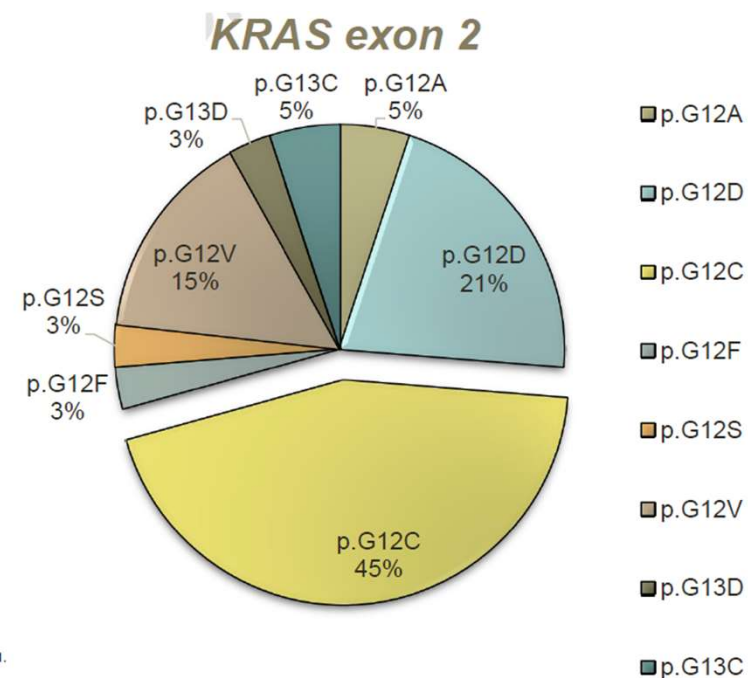


2013

Discovery of switch II "pocket"
With cysteine binding (G12C)



AOU San Luigi 2019 – Slide Novello 2021.



KRAS - bad prognosis!

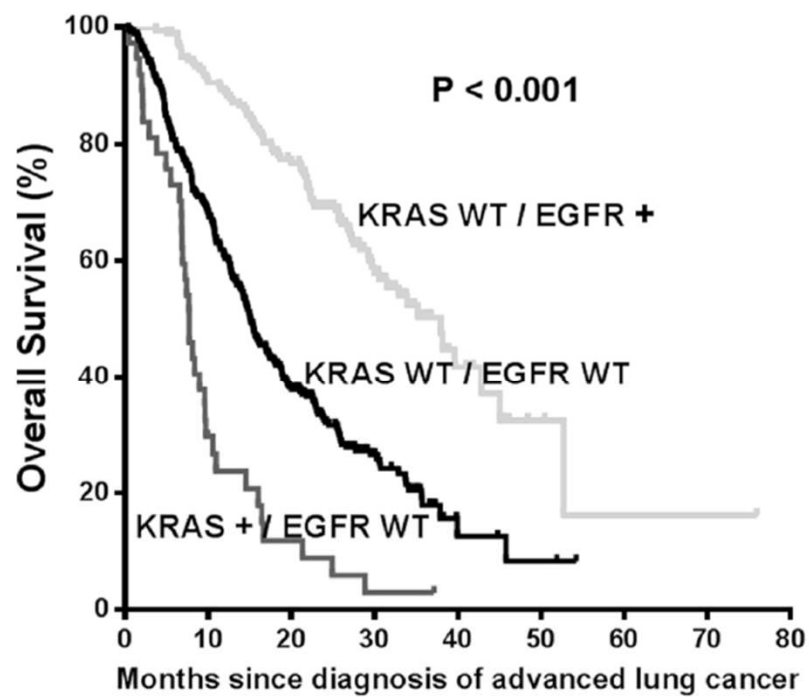


Figure 2. Overall survival by KRAS and EGFR mutation status.

Sun, PLOS ONE 2013

KRAS patient characteristics

	KRAS G12C mutant NSCLC			All NSCLC
	Flatiron* (n = 743)	AACR Genie† (n = 416)	CRISP‡ (n = 160)	Flatiron* (N = 7,069)
Median age at diagnosis, years	68	68*	66	68
Female gender, %	61%	64%	44%	50%
Current/former smoker, %	97%	97%	93%	82%
Non-squamous NSCLC, %	91%	88%	99%	76%
Distant metastases at diagnosis, %	86%	NR	94%	84%
STK11 Co-mutation, %	22%	24%	NR	12%
KEAP1 Co-mutation, %	7%	10%	NR	6%

Patients with advanced KRAS G12C-mutated NSCLC tend to be a current or former smoker with non-squamous histology; STK11 co-mutation occurs in almost one-quarter of cases

AACR, American Association for Cancer Research; **CRISP**, Clinical Research platform into molecular testing, treatment and outcome of non-small cell lung carcinoma Patients; **ECH**, erythroid cell-derived protein with cap and collar homology; **GENIE**, Genomics Evidence Neoplasia Information Exchange; **KEAP1**, Kelch-like ECH associated protein 1; **KRAS**, Kirsten rat sarcoma; **NR**, not reported; **NSCLC**, non-small cell lung cancer; **STK11**, serine/threonine kinase 11.

*Data from an analysis of the Flatiron Health-Foundation Medicine Clinico-Genomic Database (FH-FMI CGDB). FH-FMI CGDB includes over 400,00 patient samples from approximately 280 oncology practices in the US and integrates comprehensive genomic profiling results with clinical data from electronic health records (EHRs). The analysis identified N = 7,069 patients diagnosed with NSCLC between January 1, 2011 and March 31, 2019, with at least 6 months of follow-up, of which n = 743 had the KRAS G12C mutation. †Data from an analysis of the AACR Project GENIE Database that included 416 patients with the KRAS G12C mutated NSCLC, of which 270 (65%) were diagnosed in 2015 or later. ‡Data from an analysis of the German prospective, observational, nationwide CRISP Registry that includes 4,032 patients with advanced NSCLC between December, 2015 and June, 2019. *Median age at advanced diagnosis.

1. Spira AI, et al. *Lung Cancer*. 2021; in press. DOI: <https://doi.org/10.1016/j.lungcan.2021.05.026>.

2. Ricciuti B, et al. Oral presentation at the AACR Annual Meeting 2021. Virtual Meeting April 10-15, 2021. Abstract #102. 3. Sebastian M, et al. *Lung Cancer*. 2021;154:51-61.

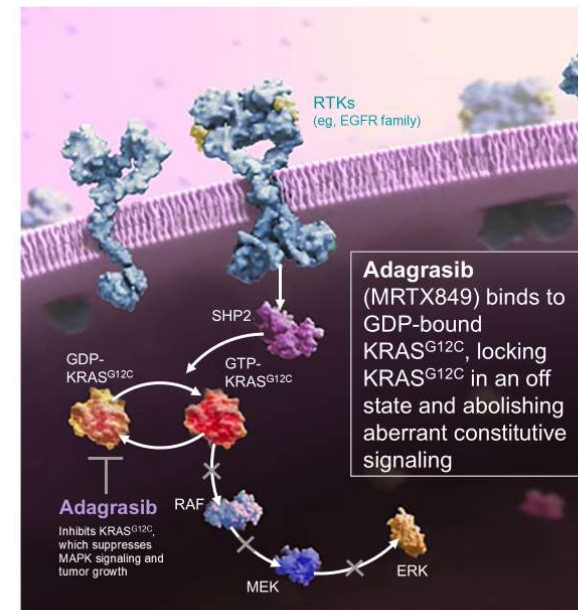
Adagrasib: a KRAS^{G12C} Inhibitor Selected for Specific Properties

Desired Properties for Adagrasib^{1,2}

- Potent covalent inhibitor of KRAS^{G12C} (cellular IC₅₀: ~5 nM)¹
- High selectivity (>1000X) for the mutant KRAS^{G12C} protein versus WT KRAS
- Favorable PK properties, including:
 - Long half-life of 23 hours, dose-dependent PK, and CNS penetration

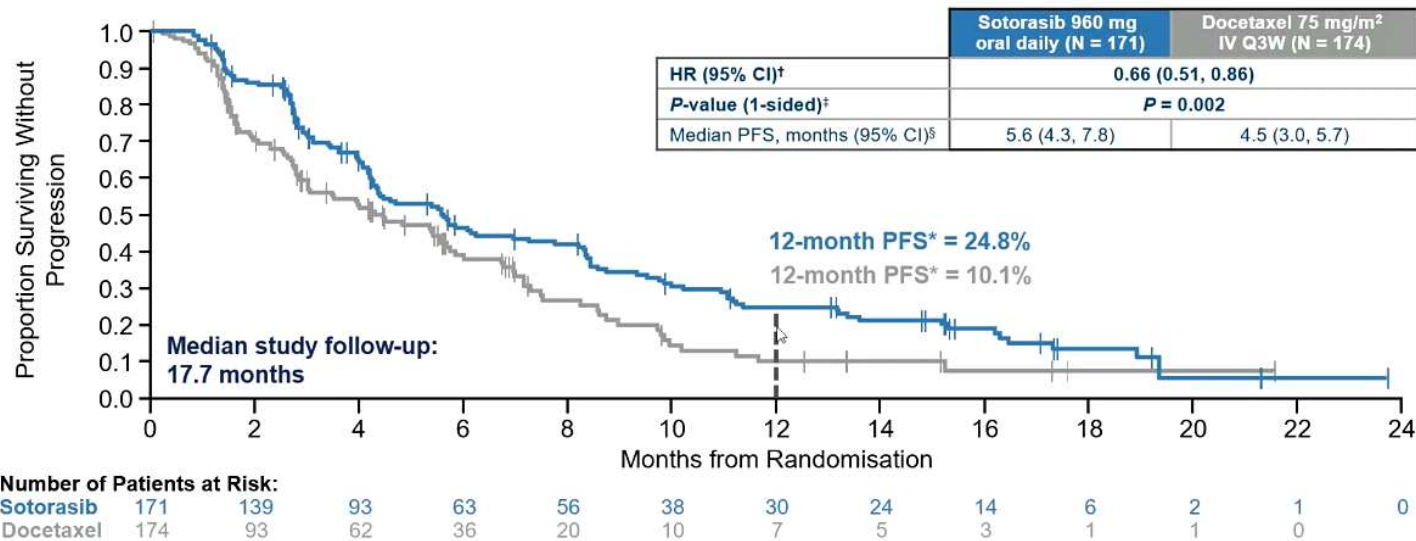
Continuous Exposure Enables Inhibition of KRAS^{G12C} Throughout the Dosing Interval

- The KRAS protein cycles between GTP-on and GDP-off states³
- The KRAS protein frequently regenerates at a rapid rate of protein resynthesis and turnover, with an approximate half-life of 24 hours^{2,4}



CNS, central nervous system; GDP, guanosine diphosphate; GTP, guanosine triphosphate; IC₅₀, half maximal inhibitory concentration; PK, pharmacokinetic; RTK, receptor tyrosine kinase; WT, wild type
1. Janne PA, et al. Presented at EORTC-NCI-AACR 2020. 2. Hallin J, et al. Cancer Discov 2019. 3. Bos JL, et al. Cell 2007. 4. Shukla S, et al. Neoplasia 2014

Hervorragendes Ansprechen!



CodeBreak 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, $P = 0.002$); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

*PFS rates estimated using Kaplan-Meier method; ITT population.

[†]HR and 95% CIs estimated using a stratified Cox proportional hazards model.

[‡]P-value calculated using a stratified log-rank test.

[§]Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

PARIS 2022 **ESMO** congress
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Patientin, 69 Jahre - Anamnese

Gewichtsverlust, B-Symptomatik, Kollaps → Notaufnahme

Röntgen - Raumforderung links mediastinal → Übernahme zur weiteren Abklärung

- CT von Thorax und Oberbauch
- PET CT
- cMRI

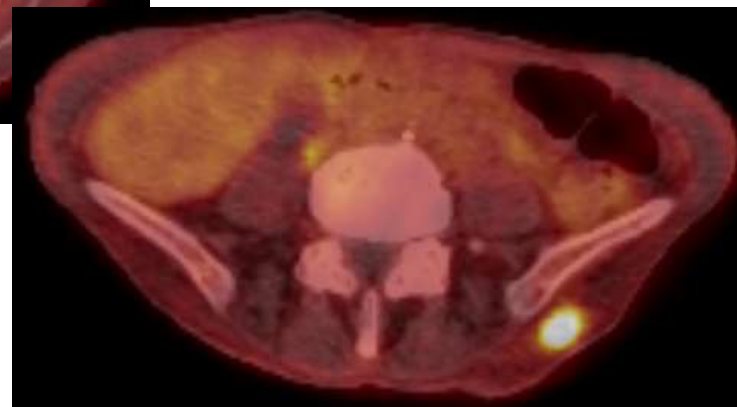
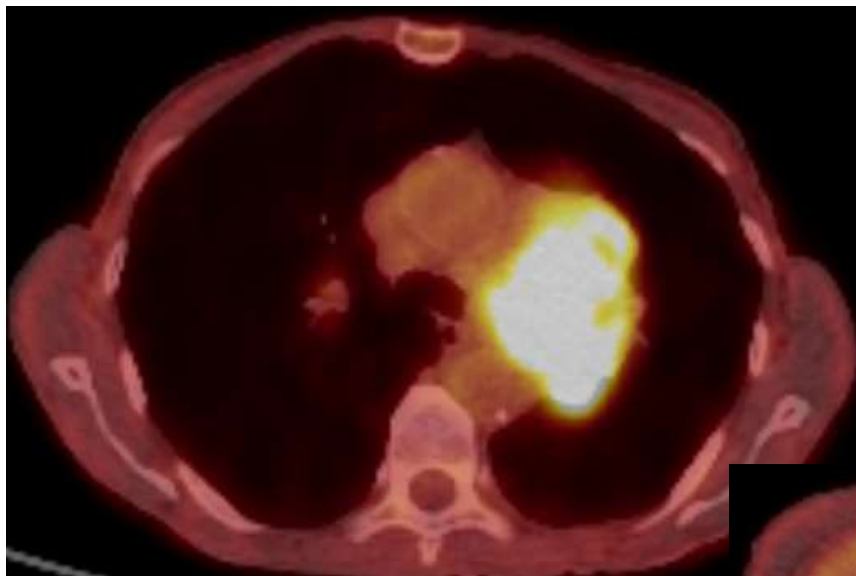
Anämie Hb 8,8 g/dl

- Gastroskopie/Coloskopie
-

CT Untersuchung Mai 2021



PET CT Untersuchung Mai 2021



Bronchoskopie mit EBUS-gezielter Punktion der einschallbaren Raumforderung, schnellzytologisch keine Tumorzellen



Exzision der PET-positiven fraglichen Metastase links gluteal

Histologie: Weichteilmetastase eines schlecht differenzierten, nicht kleinzelligen Karzinoms, in erster Linie partiell großzelliges Adenokarzinom

IHC: PD-L1 leicht positiv: TPS 5%

Molekularpathologische Untersuchungen:

EGFR, BRAF, ERBB2 (Her2): Wildtyp

Mutation im KRAS-Gen: c.34G>T(G12C), Exon2 (Allelfrequenz 39%)

RNA Fusionsanalysen:

Keine ALK-, RET-, ROS1-, NTRK- oder MET-Fusion

cT4 N2 M1c (NNR links und Haut/gluteal) - Stadium IVB

Chemo (80%)/Immuntherapie Carboplatin/Pemetrexed/Pembrolizumab
besprochen - vorausgesetzt BB stabil, Tumorboard 10.6.2021

1. Zyklus Carboplatin/Pemetrexed(80%)/Pembrolizumab am 18.6.21
2. Zyklus aufgeschoben bei prolongierter normochromer, normozytärer Anämie

2. Zyklus Carbo/Pem/Pem am 22.07.2021

Reduzierter AZ – schlechte Therapieverträglichkeit!

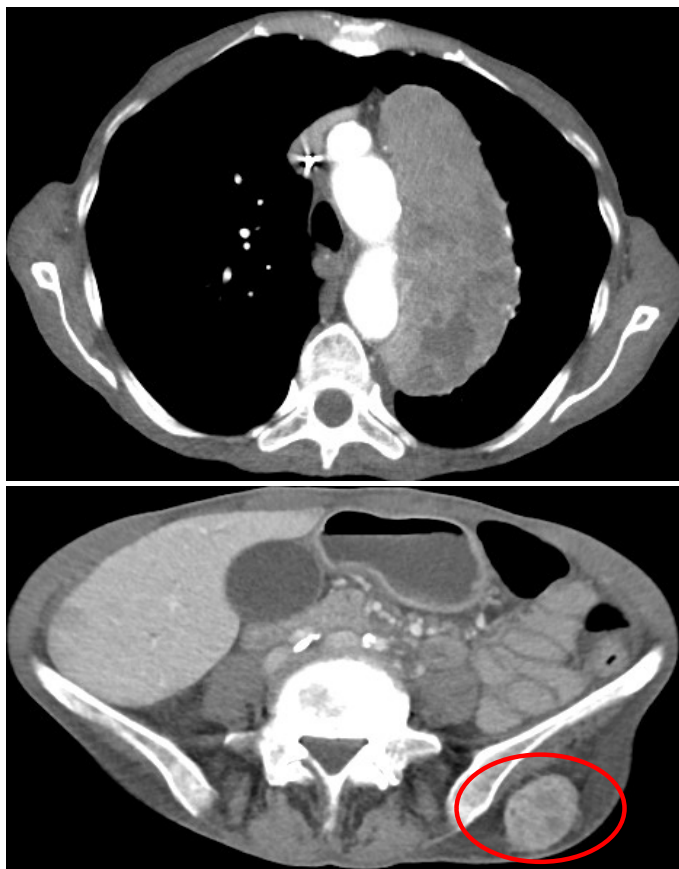
Anfang August ungeplante Aufnahme über NFA:

Hb 5,9 g/dl, Leukozyten 3,09 g/l, Neutrophile 1,83 g/l, Thrombozyten normal

vorgezogenes Restaging: thorakal sowie abdominell deutlich progredient

→ Therapieabbruch!

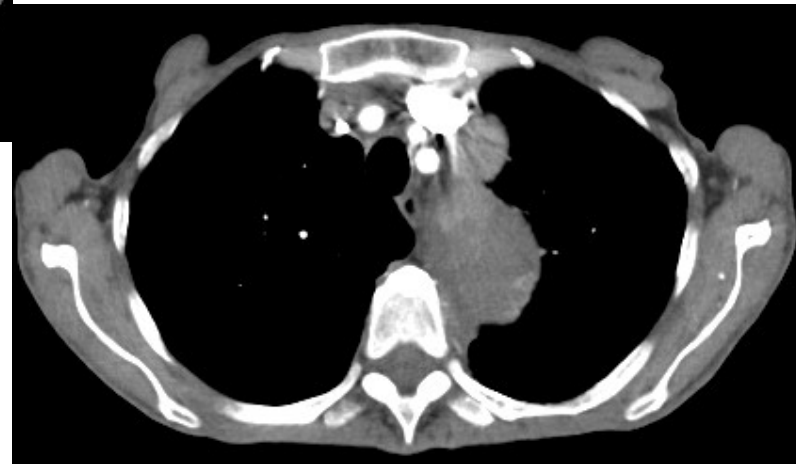
Tumorprogredienz

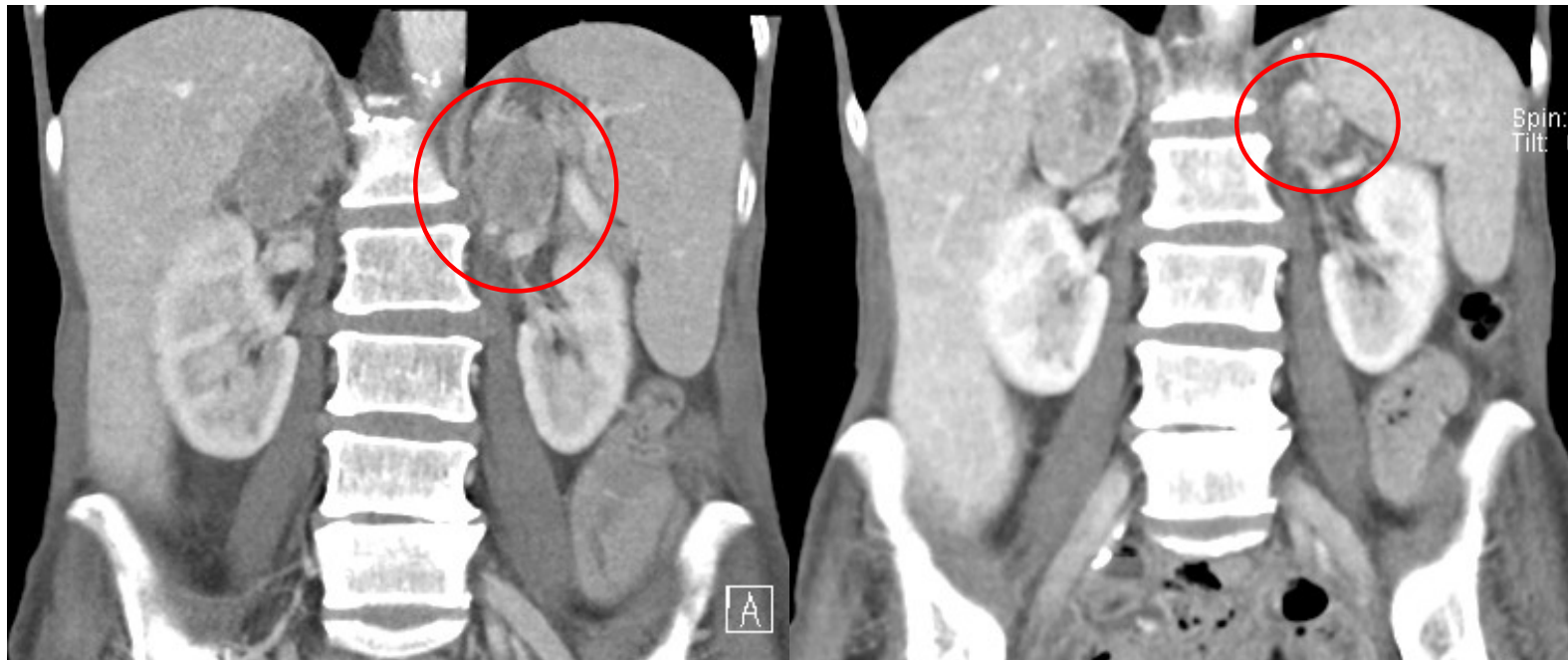


Therapieeinleitung KRAS Inhibitor



Gutes Therapieansprechen





Rasches Ansprechen!

