Early treatment in der Immunonkologie: NSCLC

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Disclosures

- BK received honoraria for lectures or advisory board participation from the following for-profit companies: AAA, AstraZeneca, Boehringer Ingelheim, BMS, Daiichi-Sankyo, Eli Lilly, Ipsen, MSD, Novartis, Roche.

- Diese Präsentation reflektiert Wissen und Erfahrung des Vortragenden, nicht notwendigerweise Ansichten von MSD. Bitte beachten Sie beim Einsatz der genannten Produkte die jeweils gültige Fachinformation.

Lungenkrebs – weiterhin ein globales Thema

- 2 Millionen neue Fälle weltweit/Jahr
- Hauptursache für Krebstodesfälle (1.8 Mio)
- Häufigster Krebstod bei Männern, zweithäufigster bei Frauen
- Rauchen weiterhin für 90% der Lungenkrebsfälle verantwortlich
- Weltweit sind die Raten in den Ländern am höchsten, in denen der Einstieg in das Rauchen am frühesten begann, wie in Nordamerika und Europa

- Erhebliche wirtschaftliche Belastung

Created with Biorender
Torre LA et al,, Adv Exp Med Biol 2016:893:1-19
Sung Het al, CA Cancer J Clin 2021

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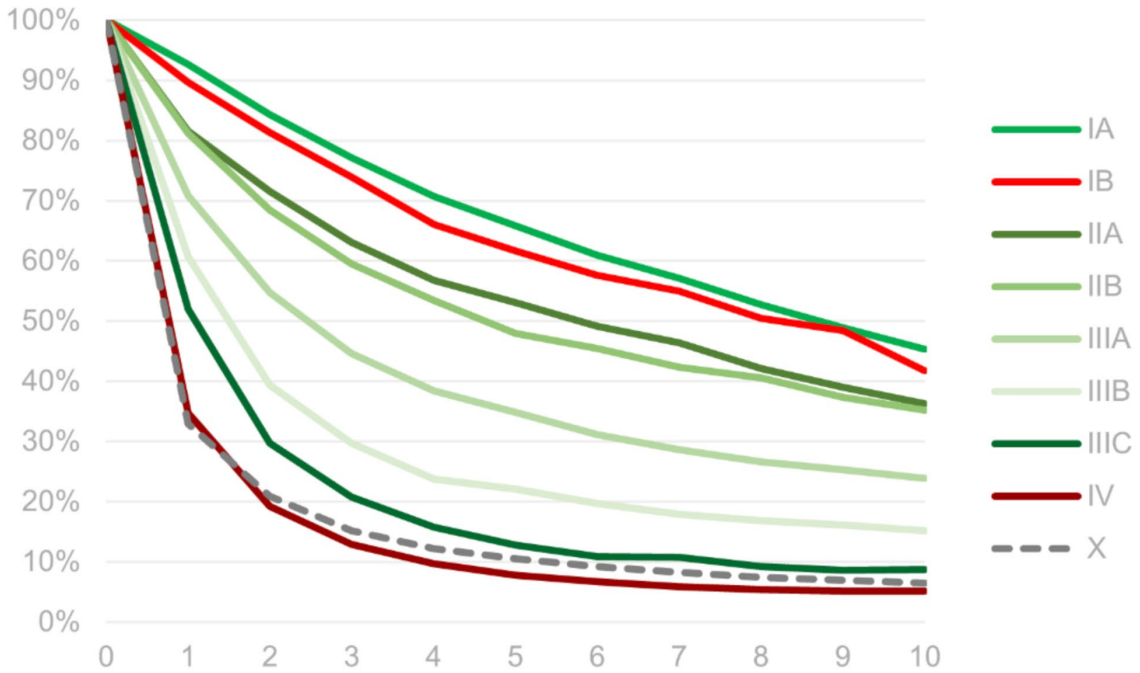

Gesamtüberleben hängt vom Stadium ab

Onkopedia Leitlinie NSCLC
Torre LA et al,, Adv Exp Med Biol 2016:893:1-19
Sung Het al, CA Cancer J Clin 2021

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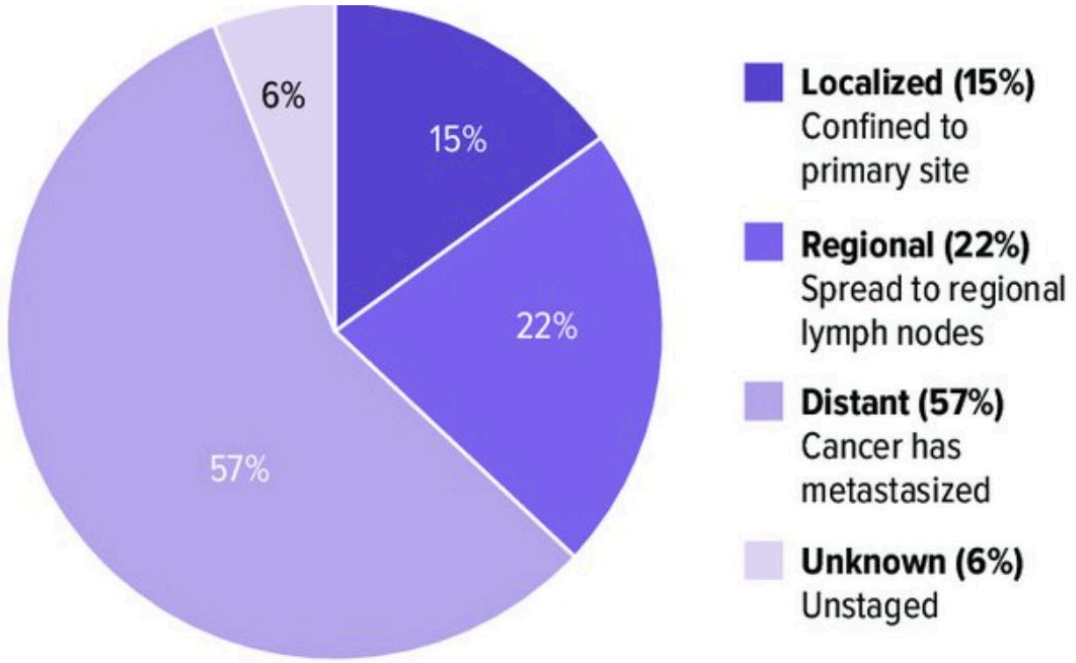
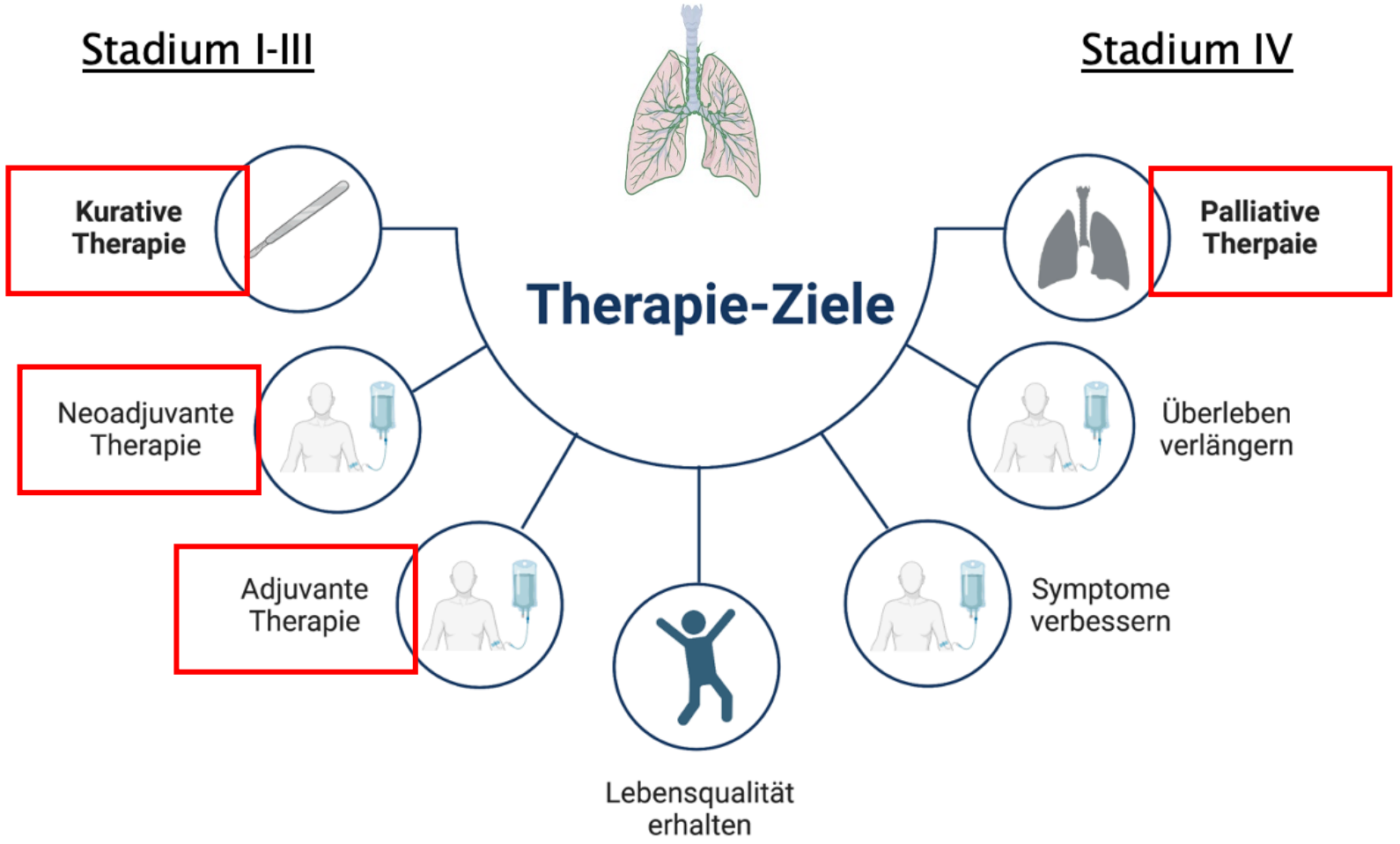


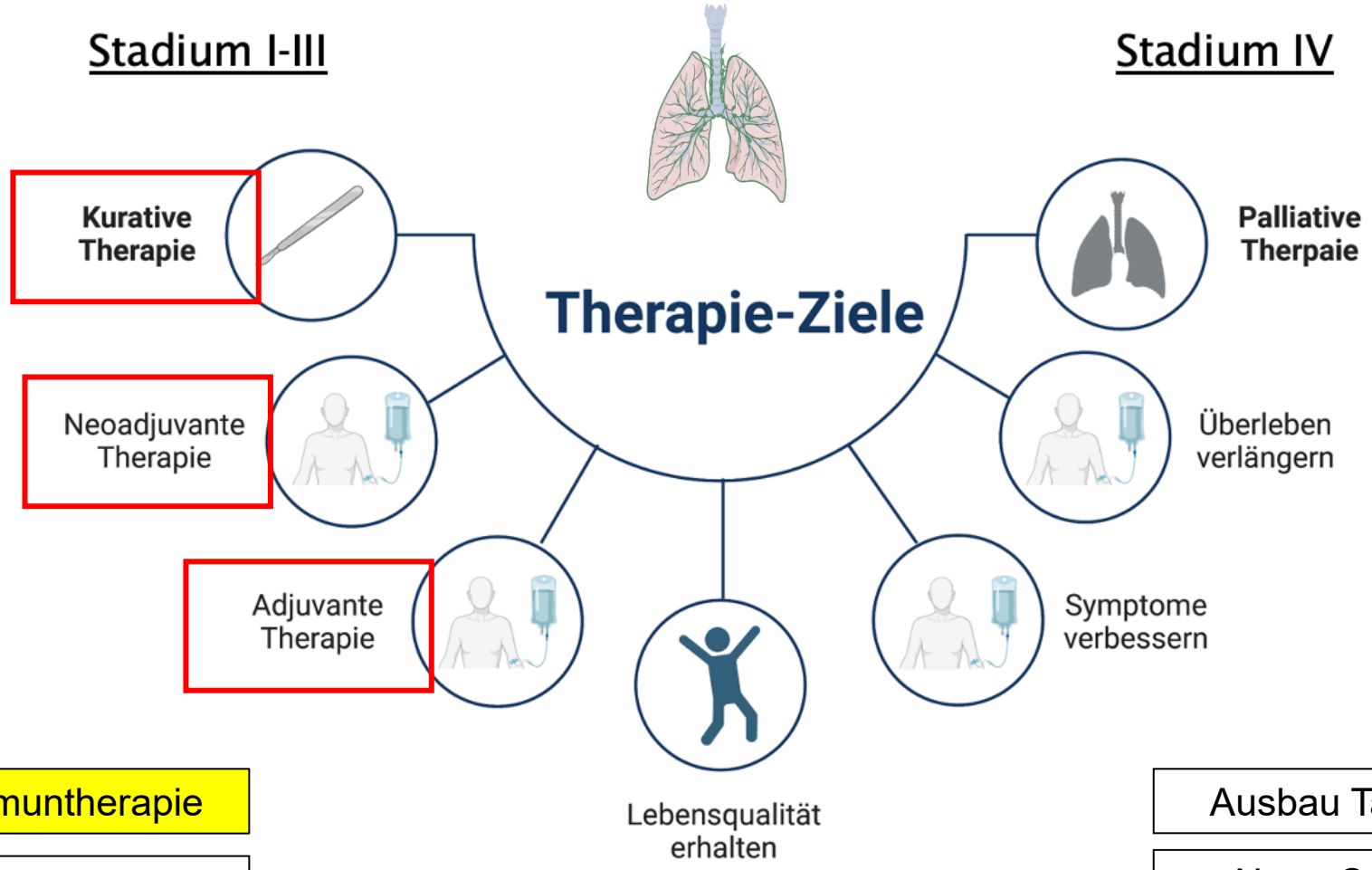
>50% Stadium werden im Stadium IV diagnostiziert

Worlex S P&T 2014;39:10

Therapiekonzepte beim NSCLC – zunehmende Bedeutung der Immuntherapie



The oncologist‘s point of view – (Personal) Hot Topics 2024



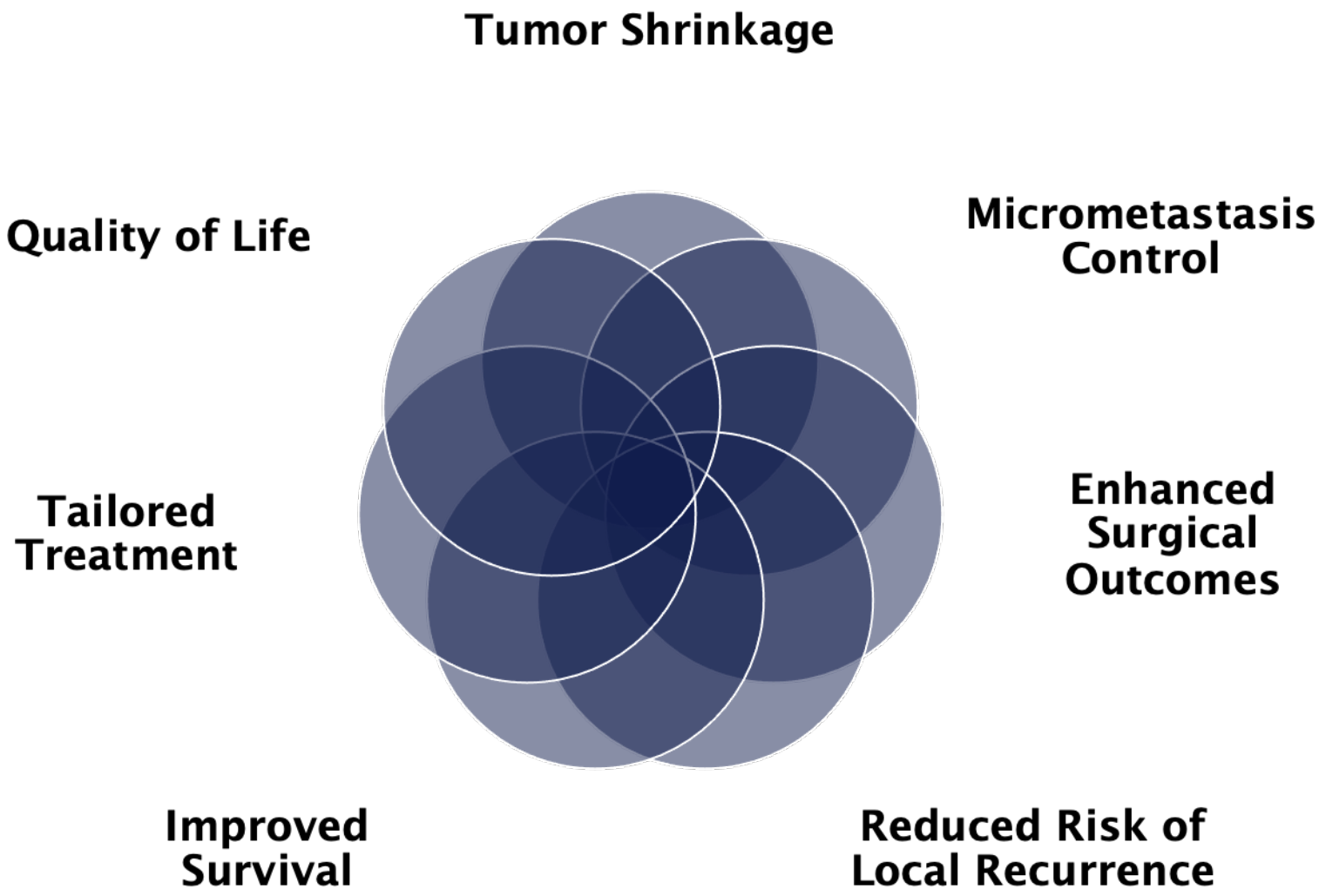
Perioperative Immuntherapie

Ausbau Targeted Therapies

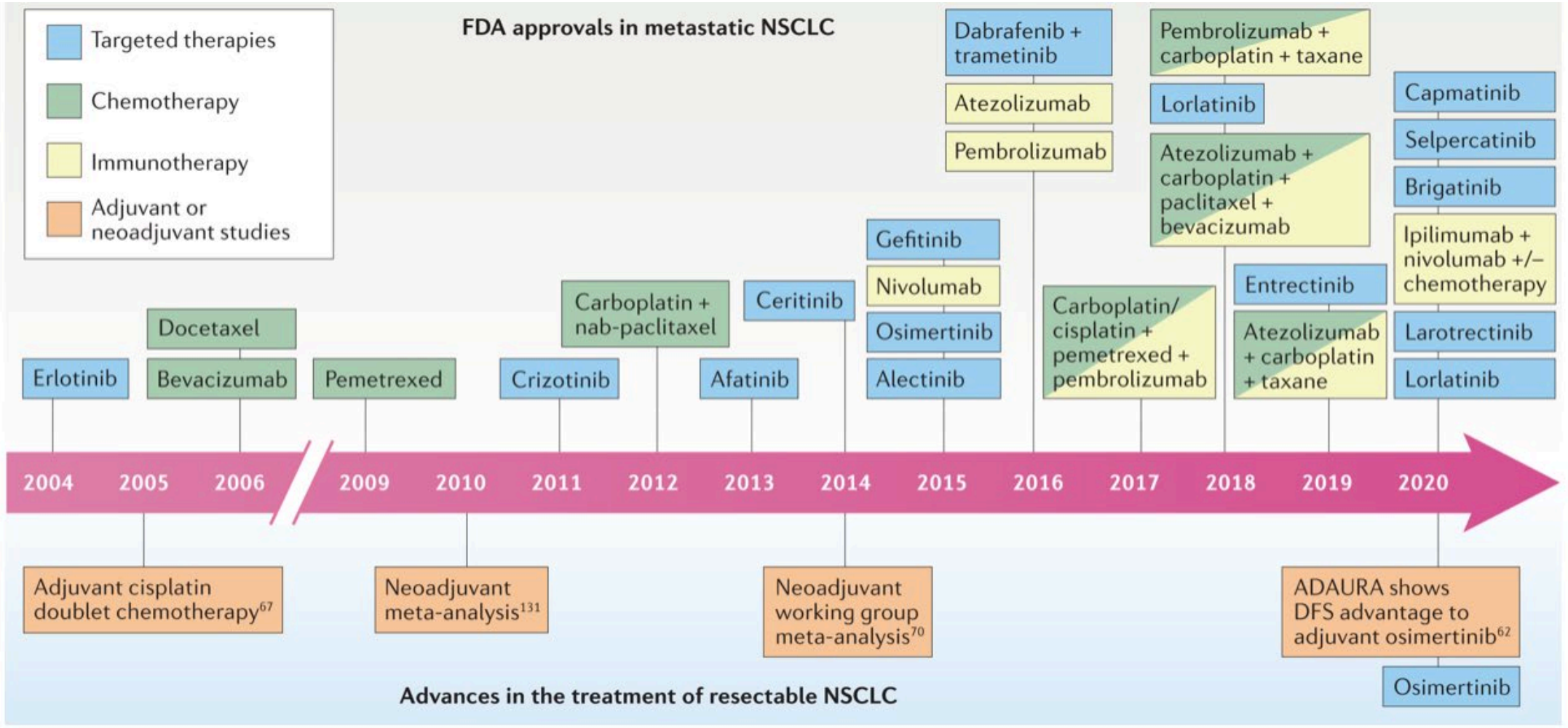
Ausbau Targeted Therapies

Neue Compunds - ADCs

Ask ChatGPT: What is the aim of perioperative systemic therapy?



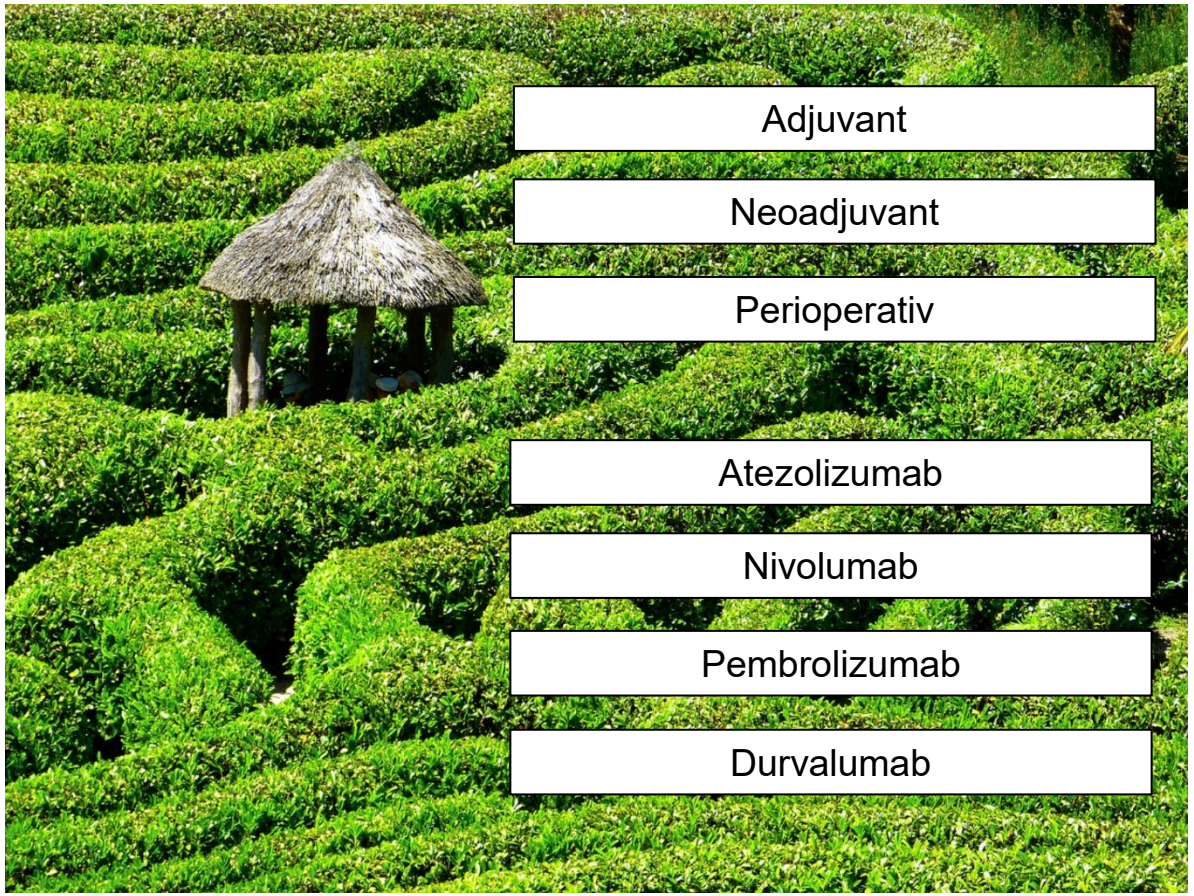
Studienlandschaft Early Stage NSCLC & Immuntherapie



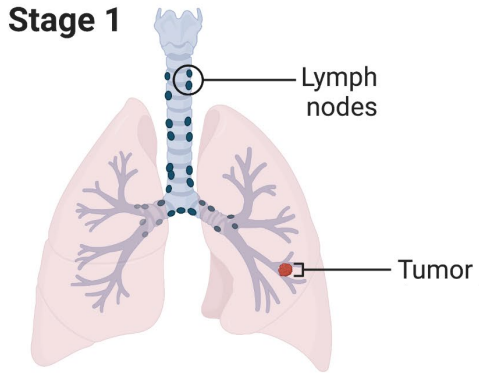
Chaft JE et al, Nature Reviews Clin Oncol 2021;18:547-57

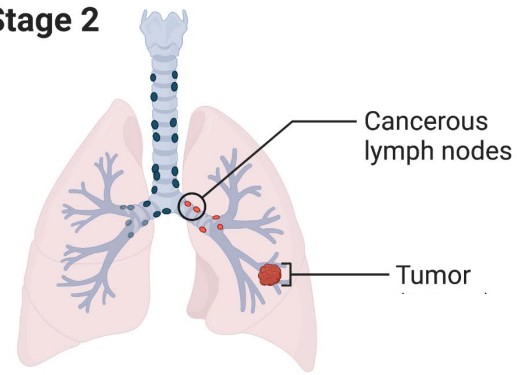
Studienlandschaft Early Stage NSCLC & Immuntherapie

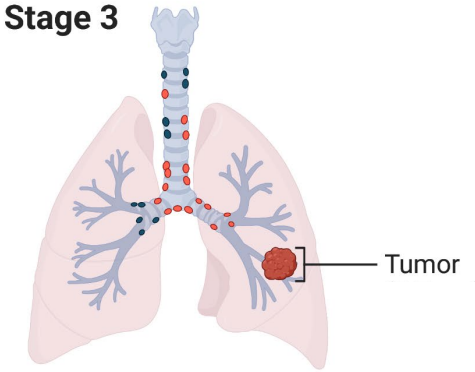
- IMPOWER 010
- KEYNOTE-091
- Checkmate 816
- Checkmate 77T
- KEYNOTE-671
- AEGEAN Trial

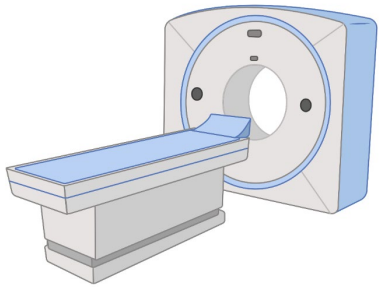


Immuntherapie in der adjuvanten Therapie beim NSCLC



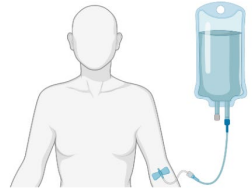




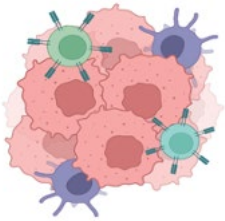


Operabel

Chirurgie



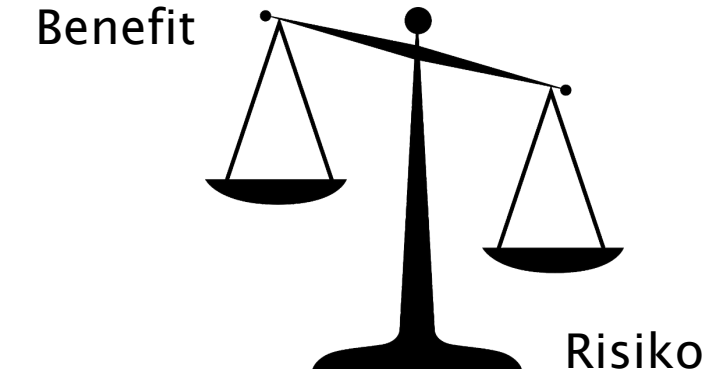
Chemotherapie



Immuntherapie

Adjuvant chemotherapy standard of care until 2021

- Adjuvant platinum-based chemotherapy changed the standard of care for completely resected early-stage NSCLC (stage IB-IIIA) over 15 years ago[1-4]
  - DFS HR, 0.84 (95% CI: 0.78, 0.91)
  - OS HR, 0.89 (95% CI: 0.82, 0.96)
  - Leads to 4%-5% OS improvement at 5 years vs observation
- Osimertinib provides substantial DFS benefit in patients whose tumors harbor *EGFR* activating mutations,[5] but there remains a high unmet need for improved adjuvant treatment in other patients with NSCLC
- IMpower010 evaluated the efficacy and safety of adjuvant atezolizumab vs best supportive care (BSC) after adjuvant chemotherapy in patients with completely resected NSCLC



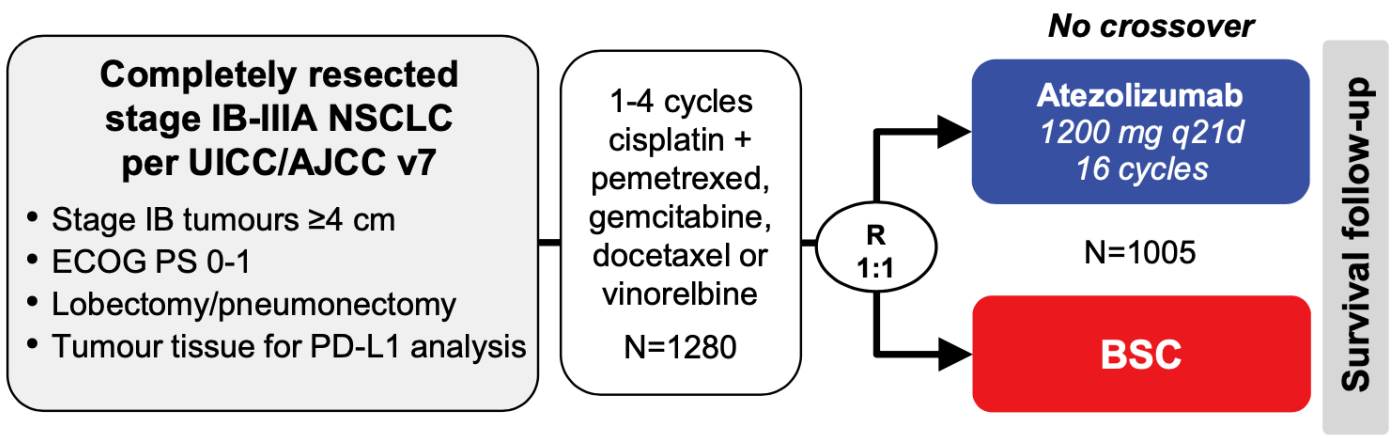
Adjuvantes Setting

Relapse rates remain high at 35-50%

2021 ASCO ANNUAL MEETING

ASCO 2021, Wakelee HA et al, Abstr 8500

IMpower010: Studiendesign

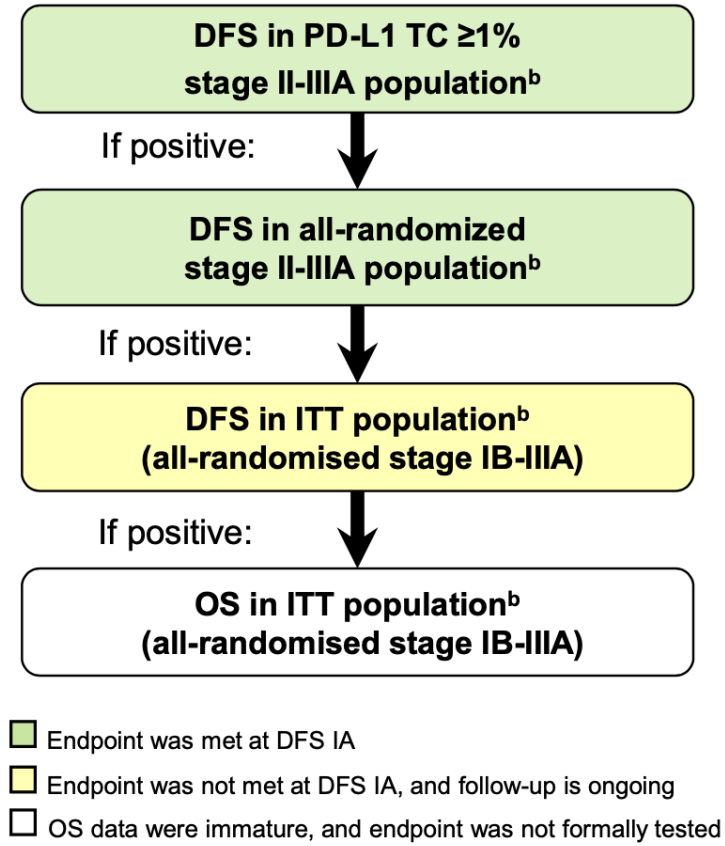


Stratification factors
- Sex
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumour expression status (TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1)[a]

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  1. PD-L1 TC ≥1% (SP263) stage II-IIIA population
  2. All-randomised stage II-IIIA population
  3. ITT (all-randomised stage IB-IIIA) population

Key secondary endpoints
- OS in ITT (all-randomised stage IB-IIIA) population
- DFS in PD-L1 TC ≥50% (SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Hierarchical statistical testing



3 analysis cohorts

2021 ASCO ANNUAL MEETING

PEARLS/KEYNOTE-091 Study Design

Randomized, Triple-Blind, Phase 3 Trial

Eligibility for Registration
- Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing
done centrally using PD-L1 IHC 22C3 pharmDx

Eligibility for Randomization
- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm) disease
  - Strongly recommended for stage II and IIIA disease
  - Limited to ≤4 cycles

R
1:1

Pembrolizumab 200 mg Q3W for ≤18 administrations (~1 yr)

Placebo Q3W for ≤18 administrations (~1 yr)

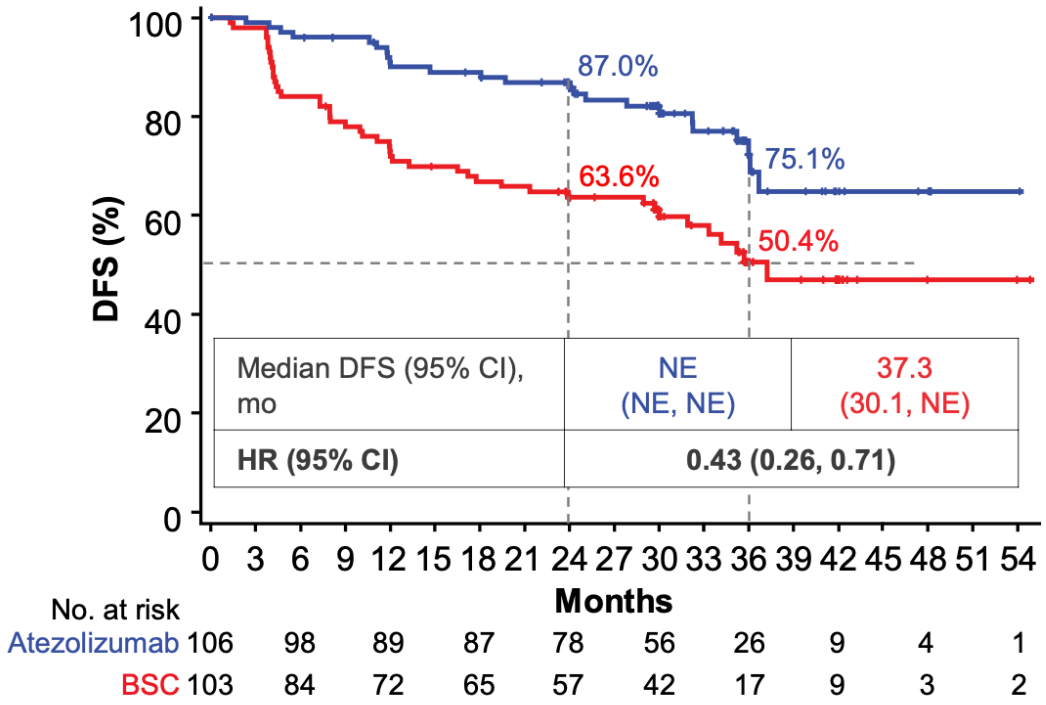
Stratification Factors
- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

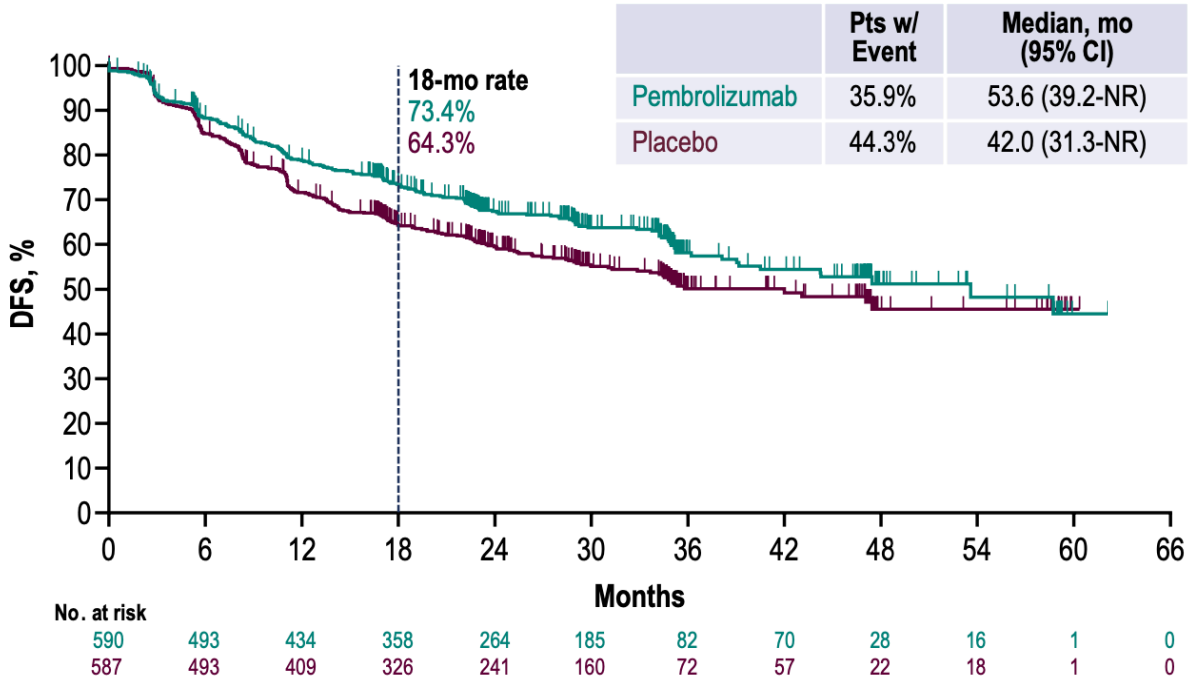
Secondary End Points
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

Adjuvant Checkpoint Inhibitors in NSCLC Status Quo

IMPOWER 010 Atezolizumab



KEYNOTE-091 Pembrolizumab



EMA Atezolizumab: high risk of recurrence, chemotherapy and PD-L1 50%+

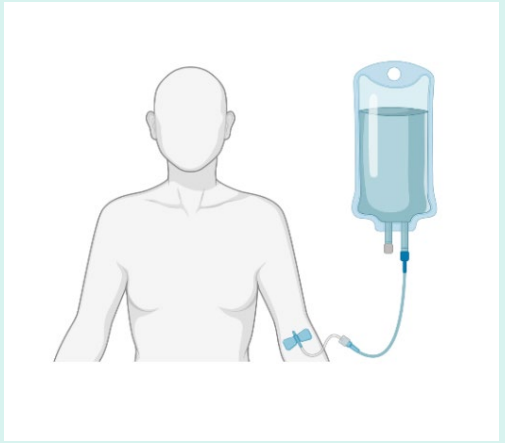
EMA Pembrolizumab: high risk of recurrence, chemotherapy, irrespective PD-L1

ELCC 2022, Felip E et al, Abs 80O
ESMO Virtual Plenary KN 091, Paz-Ares L et al

Adjuvante Checkpointinhibitor Therapie als etabliertes Therapiekonzept

Adjuvante Checkpointinhibitor Therapie als etabliertes Therapiekonzept

Safety first



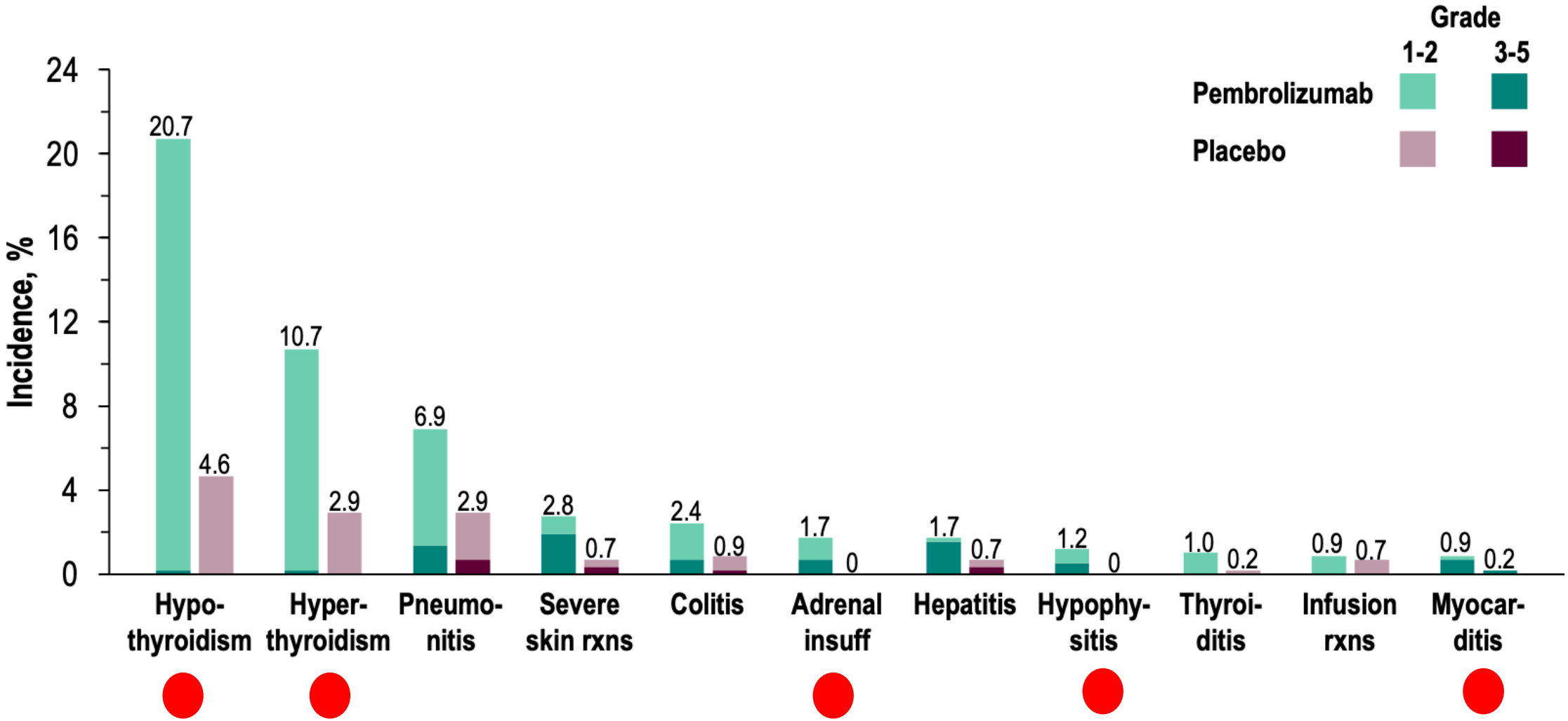
The chemo story

PEARLS/KEYNOTE-091 Summary of AEs

	Pembrolizumab (N = 580)	Placebo (N = 581)
Any	556 (95.9%)	529 (91.0%)
Grade 3-5	198 (34.1%)	150 (25.8%)
Led to death	11 (1.9%)	6 (1.0%)
Treatment-related	4 (0.7%)[a]	0 (0.0%)
Serious	142 (24.5%)	90 (15.5%)
Led to treatment discontinuation	115 (19.8%)	34 (5.9%)
Led to treatment interruption	221 (38.1%)	145 (25.0%)

[a] 1 participant each with myocarditis + cardiogenic shock, myocarditis + septic shock, pneumonia, and sudden death.

Immune-Mediates AE and Infusion Reactions



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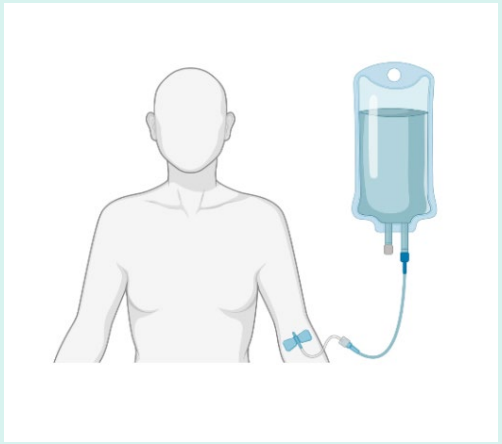


The chemo story

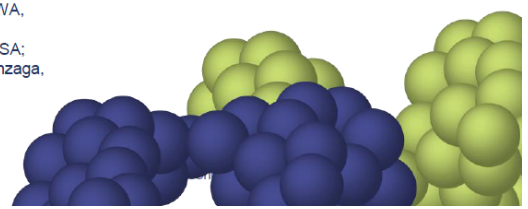
Do will still need chemotherapy in the adjuvant setting?

IMpower010: ctDNA Status in Patients With Resected NSCLC Who Received Adjuvant Chemotherapy Followed by Atezolizumab or Best Supportive Care

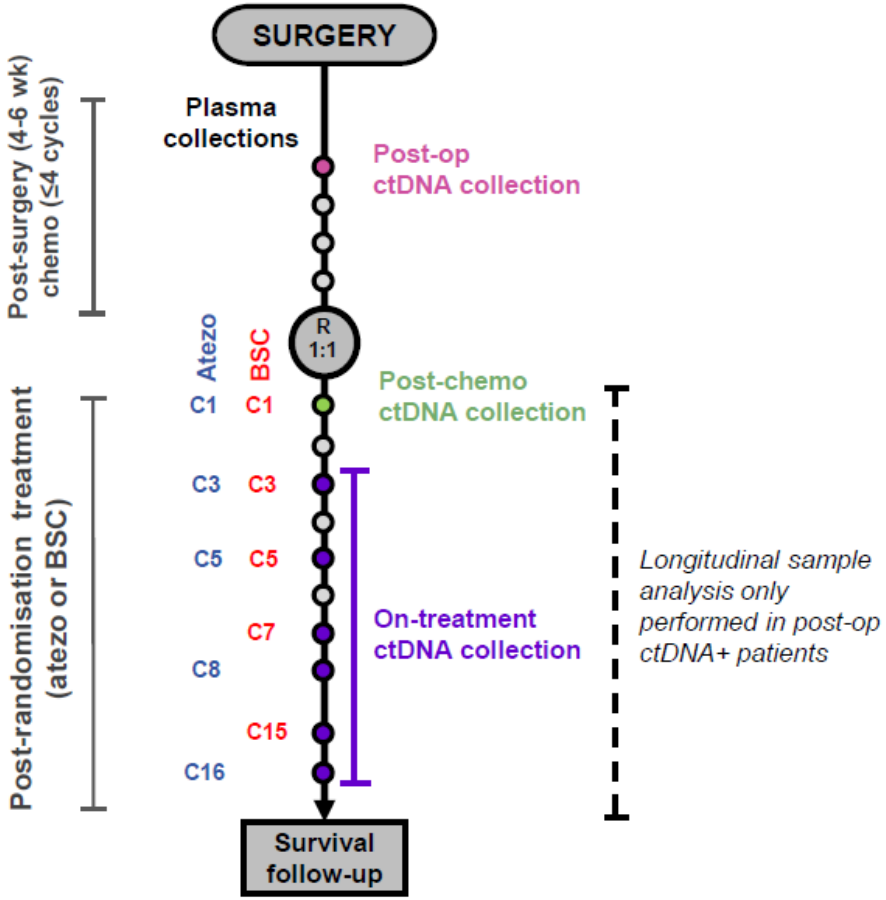
Enriqueta Felip[1], Minu K. Srivastava[2], Martin Reck[3], Heather Wakelee[4], Nasser Altorki[5], Eric Vallieres[6], Rüdiger Liersch[7], Hiroshi Tanaka[8], John T. Hamm[9], Steven McCune[10], Elizabeth Bennett[2], Barbara J. Gitlitz[2], Virginia McNally[11], Silvia Novello[12], Marcus Ballinger[13], Wei Zou[2], Barzin Y. Nabet[2], Meghna Das Thakur[2], Caicun Zhou[14]

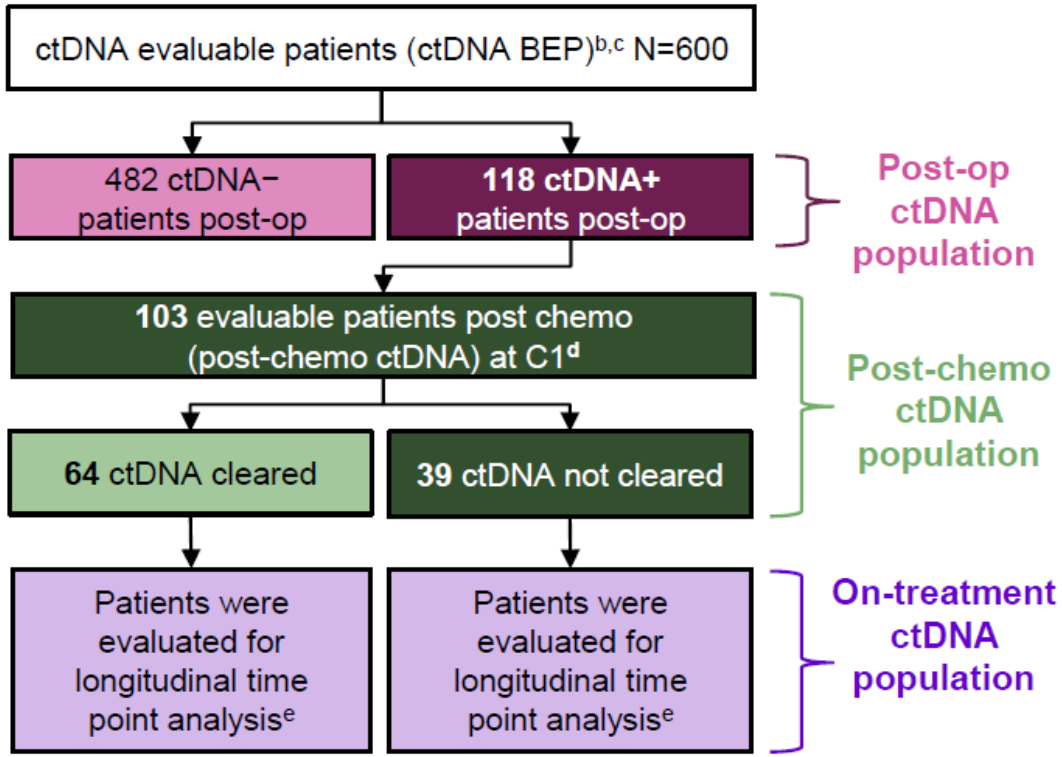
[1]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]Oncology Biomarker Development, Genentech Inc., South San Francisco, California, USA; [3]Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; [4]Stanford University School of Medicine, Stanford Cancer Institute, Stanford, CA, USA; [5]NewYork-Presbyterian Hospital, Weill Cornell Medicine, New York, NY, USA; [6]Swedish Thoracic Surgery - First Hill, Seattle, WA, USA; [7]Clemenshospital Münster, Münster, Germany; [8]Niigata Cancer Center Hospital, Niigata, Japan; [9]Norton Cancer Institute, Louisville, KY, USA; [10]Northwest Georgia Oncology Centers, Marietta, GA, USA; [11]Roche Products Ltd, Welwyn Garden City, United Kingdom; [12]University of Turin, AOU San Luigi Gonzaga, Orbassano, Turin, Italy; [13]Clinical Science, Genentech, Inc., South San Francisco, CA, USA; [14]Department of Medical Oncology, Shanghai Pulmonary Hospital, Shanghai, China

ESMO IMMUNO-ONCOLOGY Dr Enriqueta Felip



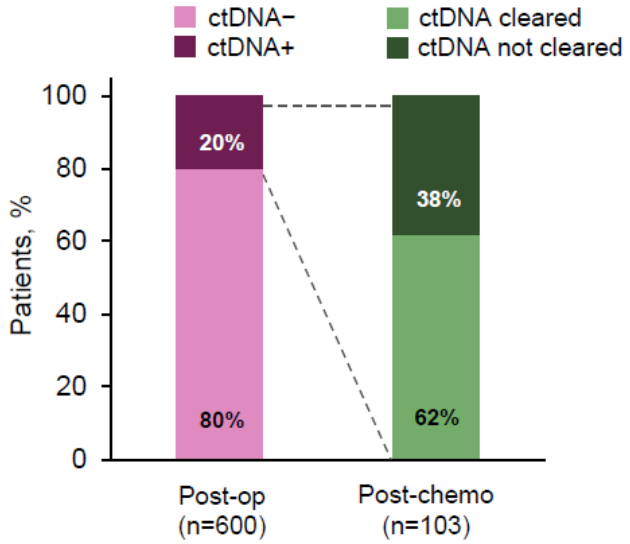
Baseline and longitudinal plasma collection for ctDNA testing



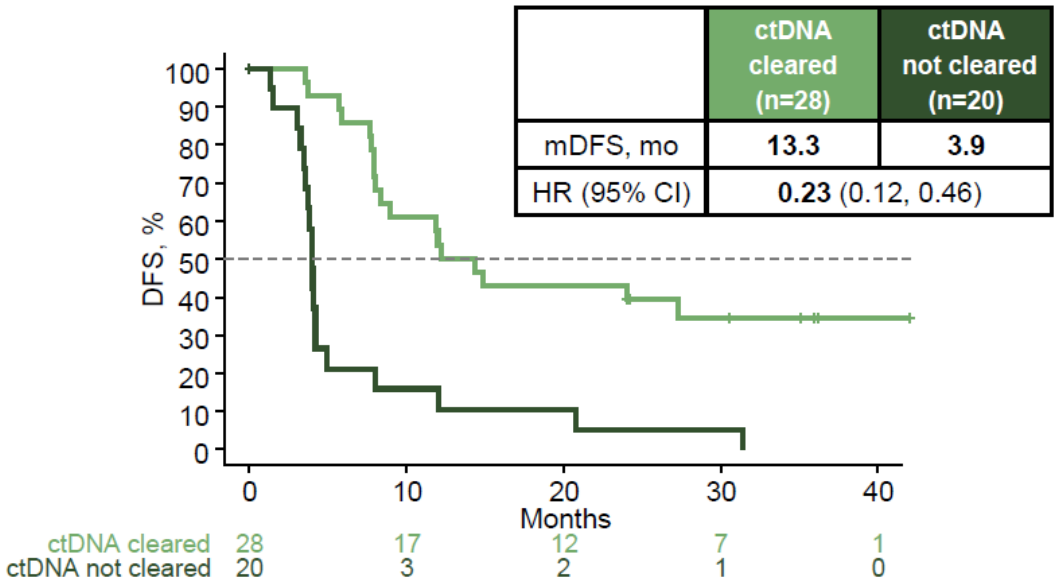


ctDNA clearance with adjuvant chemo in post-op ctDNA+ patients

Impact of chemo on ctDNA clearance status



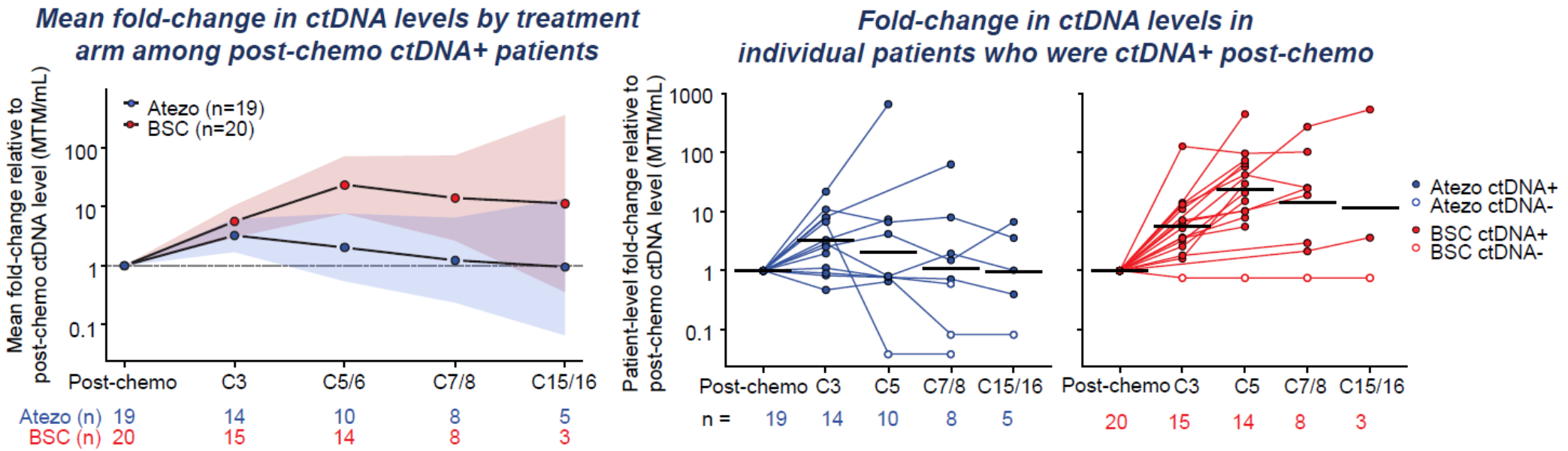
DFS by ctDNA clearance status in the BSC arm



	ctDNA cleared (n=28)	ctDNA not cleared (n=20)
mDFS, mo	**13.3**	**3.9**
HR (95% CI)	**0.23** (0.12, 0.46)	

- Adjuvant chemo was effective in clearing ctDNA in ≈62% of post-op ctDNA+ patients
- Post-chemo ctDNA positivity was linked to poor DFS outcome

ctDNA levels in post-chemo ctDNA+ patients by treatment arm



- A trend toward increased ctDNA levels was seen in the BSC arm compared with the atezolizumab arm at C5 and beyond
- Atezolizumab appeared to maintain ctDNA level in post-chemo ctDNA+ patients

PEARLS/KEYNOTE-091

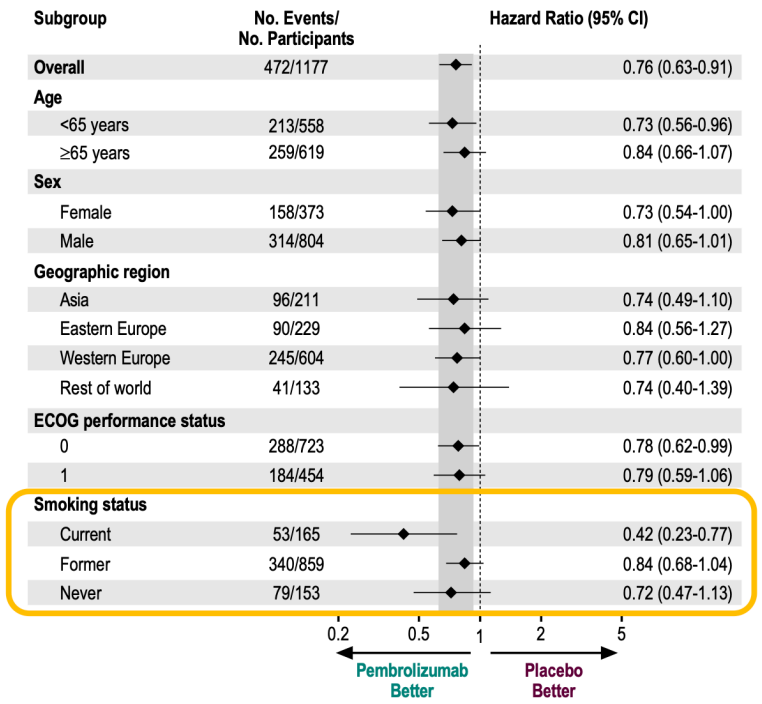
	Pembrolizumab (N = 590)	Placebo (N = 587)
Age, median (range)	65 y (31-87)	65 y (37-85)
Male	401 (68.0%)	403 (68.7%)
Geographic region		
Asia	106 (18.0%)	105 (17.9%)
Eastern Europe	116 (19.7%)	
Western Europe	303 (51.4%)	
Rest of world	65 (11.0%)	
ECOG PS 1	210 (35.6%)	
Current/former smoker	503 (85.3%)	
***EGFR* mutation**[a]	39 (6.6%)	
***ALK* translocation**[b]	7 (1.2%)	

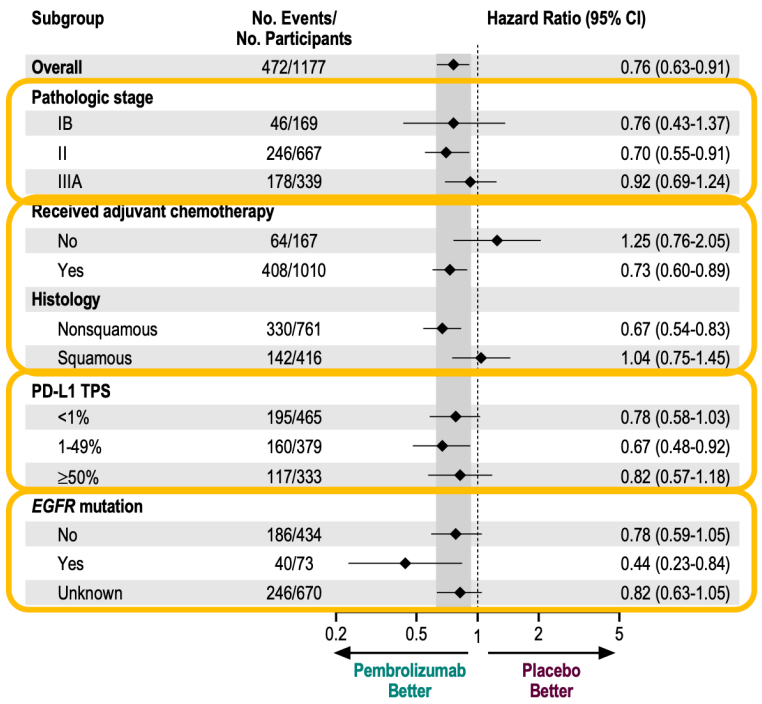
	Pembrolizumab (N = 590)	Placebo (N = 587)
Nonsquamous histology	398 (67.5%)	363 (61.8%)
Pathologic stage[c]		
IB	84 (14.2%)	85 (14.5%)
II	329 (55.8%)	338 (57.6%)

[a] *EGFR* status unknown for 333 (56.4%) in pembro arm and 337 (57.4%
[b] *ALK* status unknown for 357 (60.5%) in pembro arm and 390 (66.4%)

ESMO VIRTUAL PLENARY

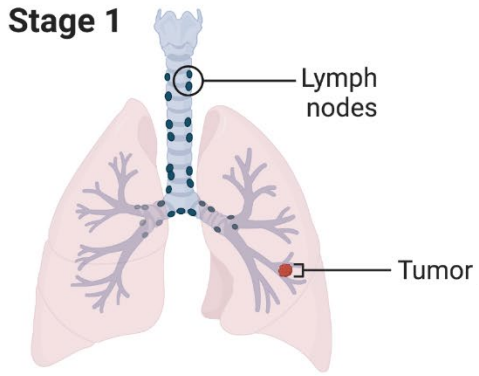
Data cutoff date: S

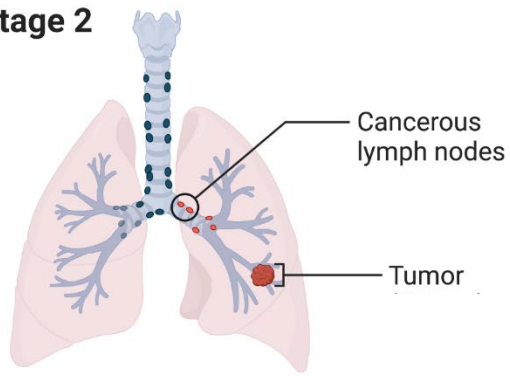


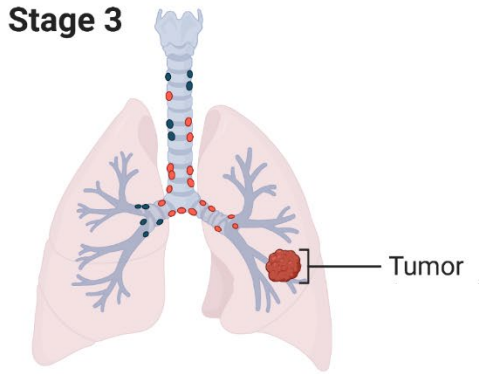


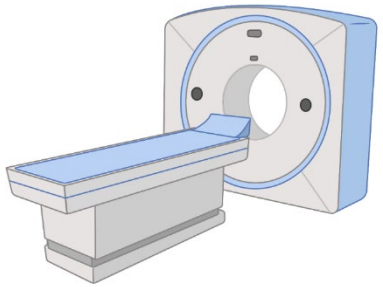
Immuntherapie in der neoadjuvanten Therapie

Immuntherapie in der neoadjuvanten Therapie





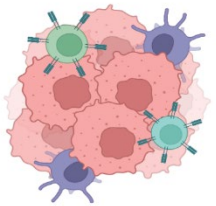


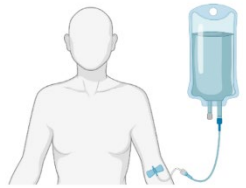


Potentiell operabel
(Staging essentiell)

Immuntherapie	Chemotherapie

?





Chirurgie

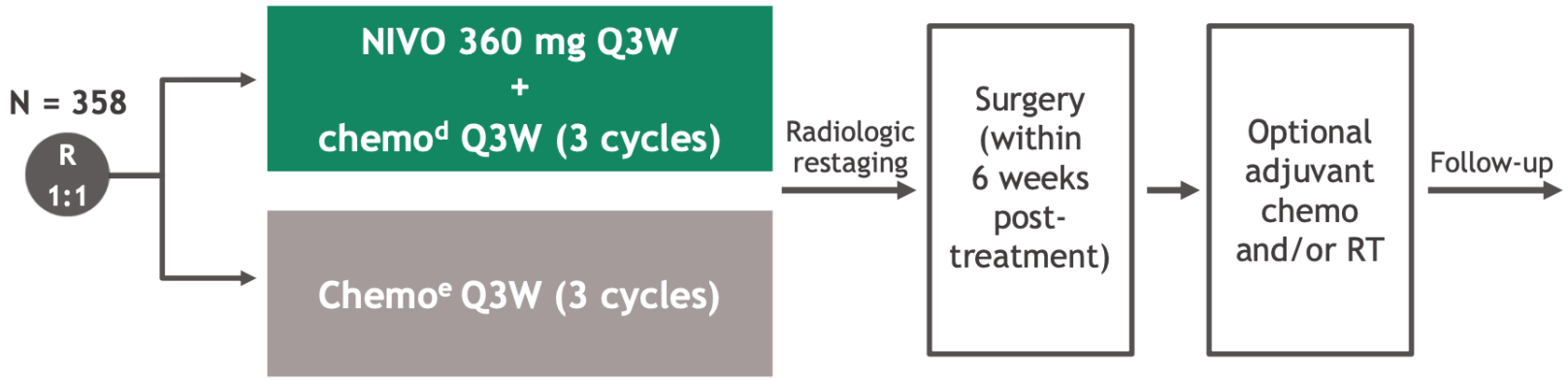
CheckMate 816 Study Design

Proof of Concept

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)–IIIA NSCLC (per AJCC TNM 7th edition)
- ECOG PS 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



Primary endpoints
- pCR by BIPR
- EFS by BICR

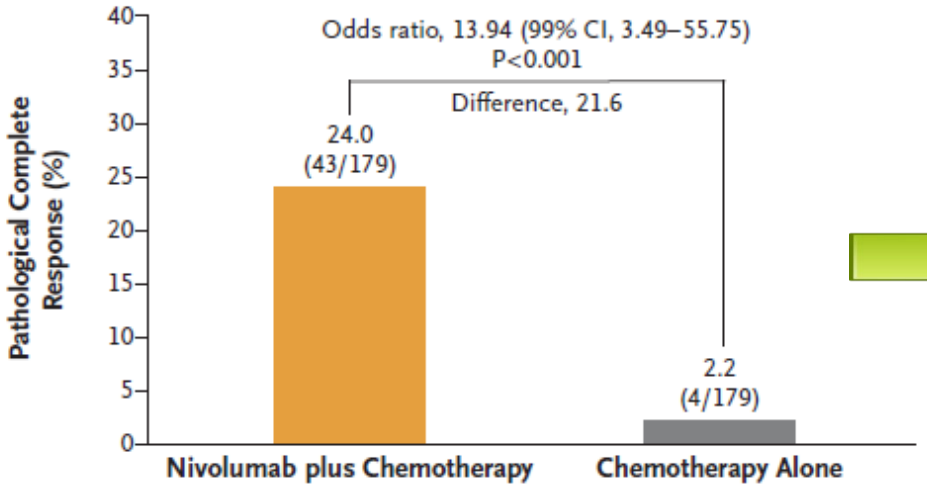
Secondary endpoints
- MPR by BIPR
- OS
- TTDM

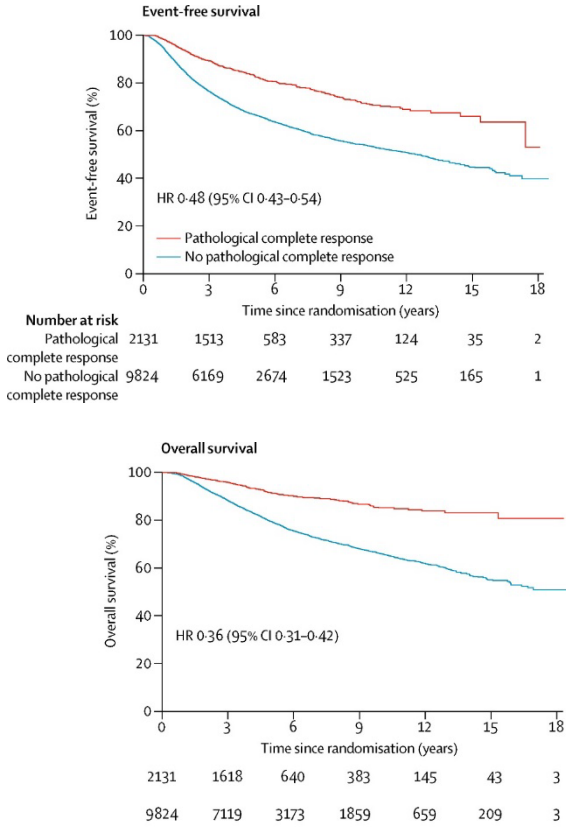
Exploratory analyses
- EFS by surgical outcomes
- pCR and EFS by 4-gene inflammatory signature score

Database lock date: October 14, 2022. Minimum/median follow-up: 32.9/41.4 months.

From *The New England Journal of Medicine*, Forde PM, et al, Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer, 2022;386:1973–1985. Copyright © 2022 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society.[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]Nonsquamous: pemetrexed + cisplatin or paclitaxel + carboplatin; squamous: gemcitabine + cisplatin or paclitaxel + carboplatin. [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pemetrexed + cisplatin (nonsquamous only), or paclitaxel + carboplatin.

CheckMate 816 Pathological Complete Remissions



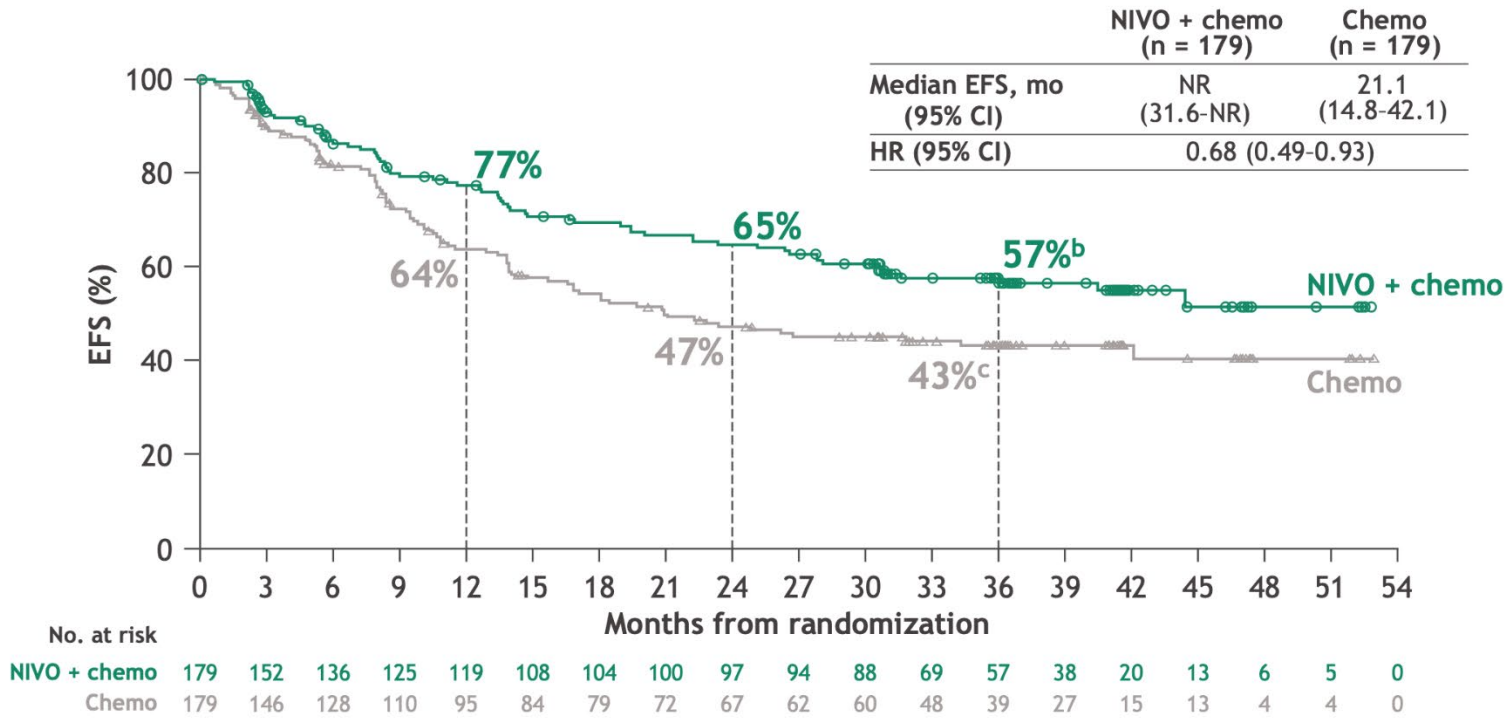


Erhöhung der Rate an CRs um >20%

pCR and long-term outcome in breast cancer

Reck M et al, NEJM 2016;375:1823-33
Cortazar P et al, Lancet 2014;384:164-72

EFS with neoadjuvant NIVO + chemo vs chemo: 3 year update ELCC 2023



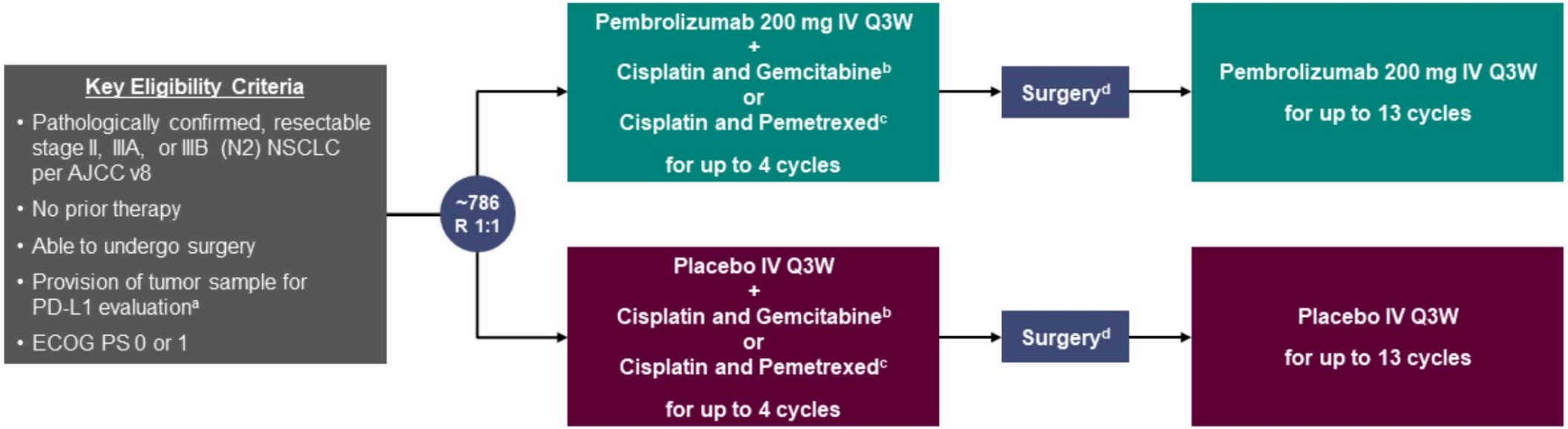
EMA: neoadjuvant, high risk, PD-L1+

Median FUP 41.4m
Minimal invasive versus srugery
Lobectomy Pneumectomy
4 Base-line gene inflammatory signature
Benefit of pCR long-term
OS trend

Proof of Concept

Verkürztes Therapiekonzept

KEYNOTE-671 Perioperative Pembrolizumab



Stratification Factors
- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

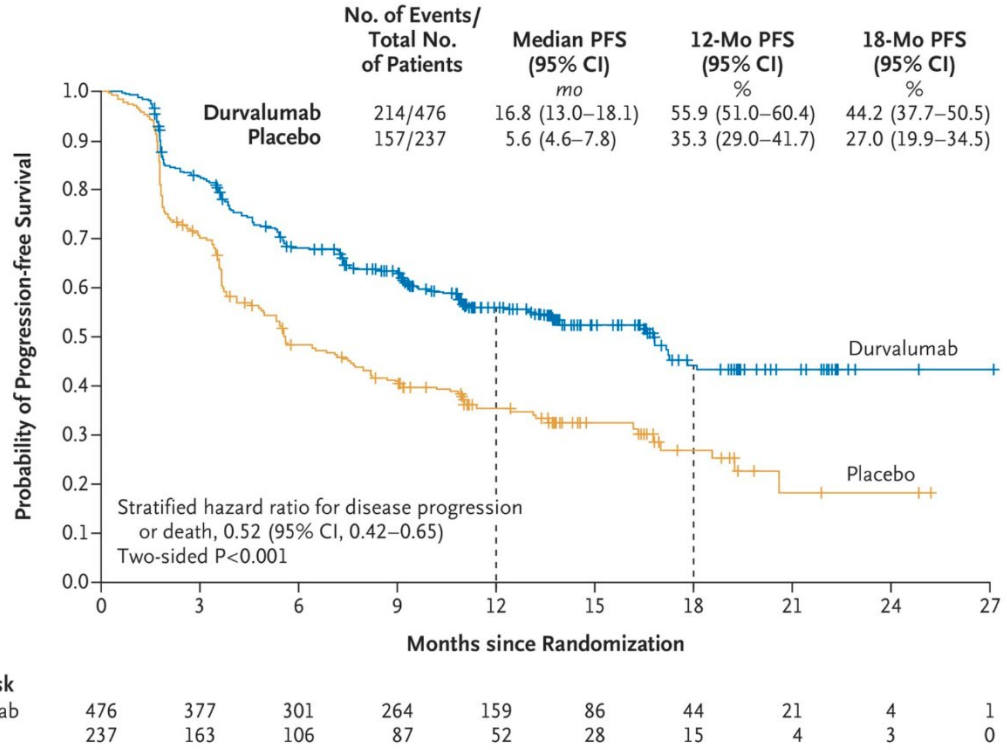
[a] Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. [b] Cisplatin 75 mg/m^2 IV Q3W + gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W was permitted for squamous histology only. [c] Cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W was permitted for nonsquamous histology only. [d] Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease. ClinicalTrials.gov identifier: NCT03425643.

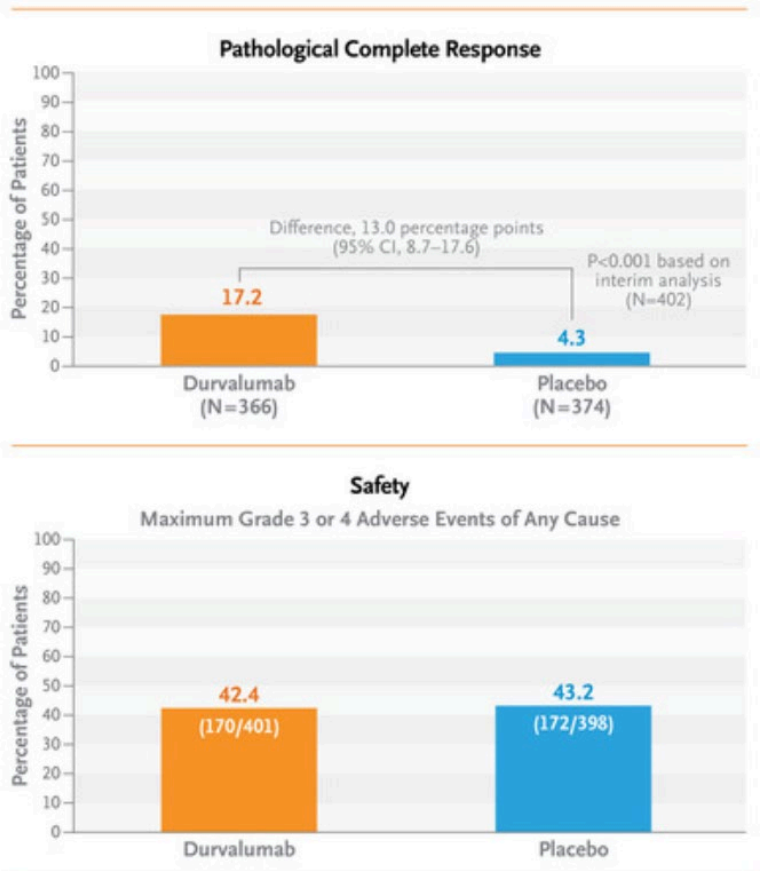
ORIGINAL ARTICLE

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

Scott J. Antonia, M.D., Ph.D., Augusto Villegas, M.D., Davey Daniel, M.D., David Vicente, M.D., Shuji Murakami, M.D., Rina Hui, Ph.D., Takashi Yokoi, M.D., Ph.D., Alberto Chiappori, M.D., Ki H. Lee, M.D., Ph.D., Maike de Wit, M.D., Ph.D., Byoung C. Cho, M.D., Ph.D., Maryam Bourhaba, M.D., et al., for the PACIFIC Investigators*

The NEW ENGLAND JOURNAL of MEDICINE



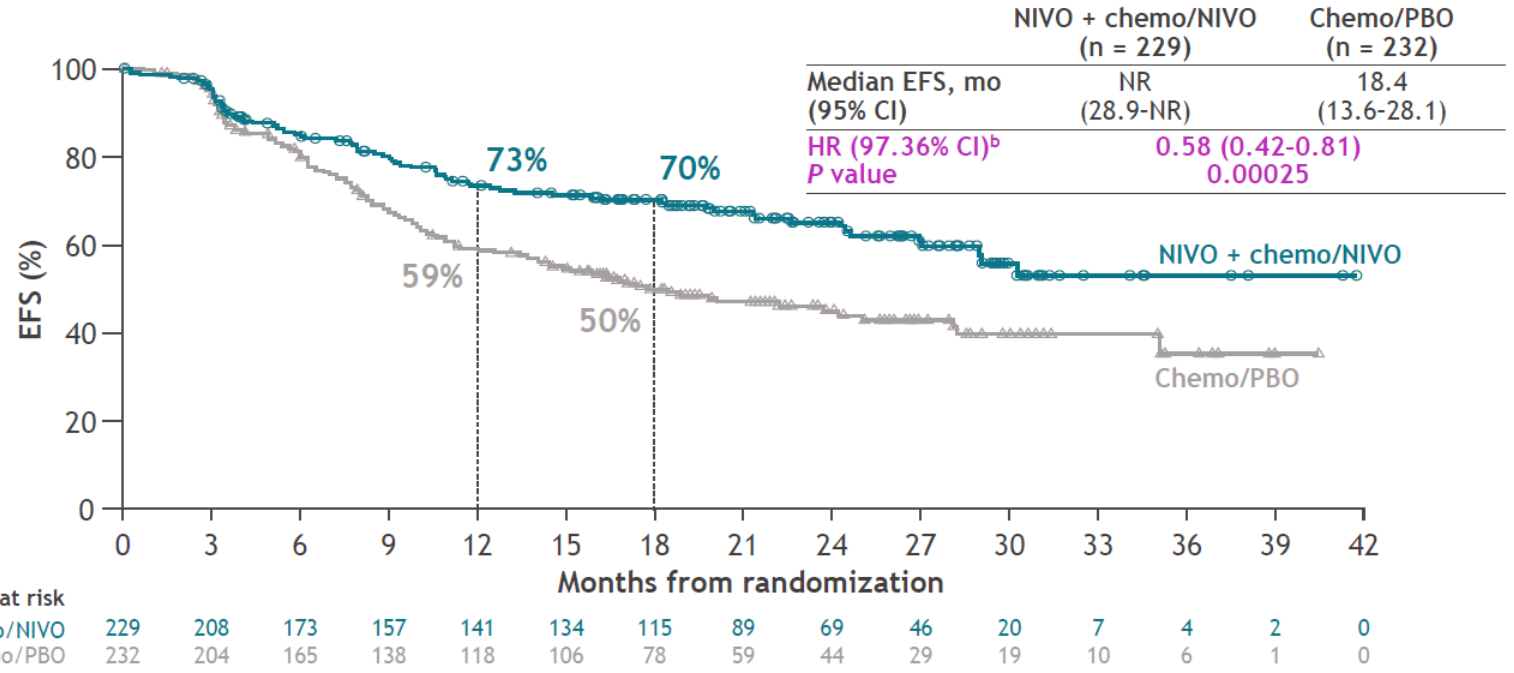


Durvalumab

Checkmate 77T – EFS - is perioperative better than neoadjuvant?

CheckMate 77T: perioperative NIVO in resectable NSCLC

Primary endpoint:
EFS[a] per BICR with neoadjuvant NIVO + chemo/adjuvant NIVO vs chemo/PBO



	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)
Median EFS, mo (95% CI)	NR (28.9-NR)	18.4 (13.6-28.1)
HR (97.36% CI)[b]	0.58 (0.42-0.81)	
P value	0.00025	

- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41-0.76

CheckMate 816

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo (95% CI)	NR (31.6-NR)	21.1 (14.8-42.1)
HR (95% CI)	0.68 (0.49-0.93)	

Challenge – Optimierung der perioperativen Konzepte.

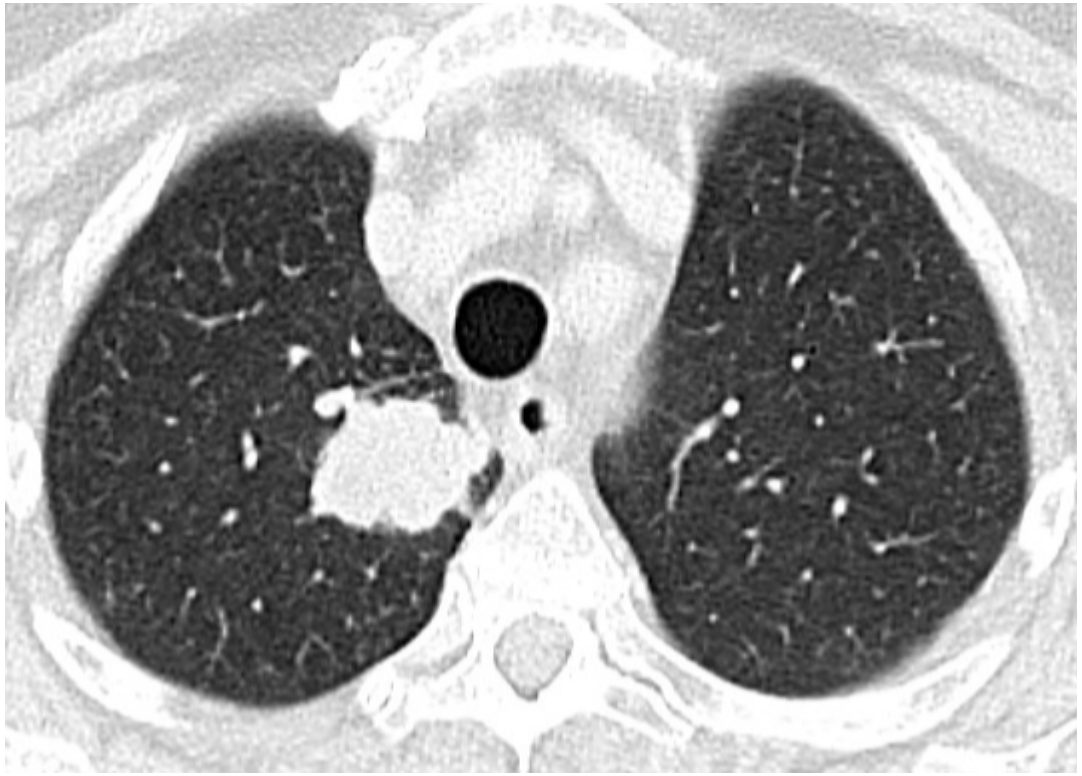
- Patientenselektion
- Tumorboard
- Risiko-Nutzen

Integration der Immuntherapie ins perioperative Setting als onkologische Herausforderung?

Realitycheck – NSCLC IO perioperativ in der Praxis: der klinische Fall

Realitycheck – NSCLC IO perioperativ in der Praxis: der klinische Fall

- 70a, w
- Rauchanamnese: 30 PY
- Ca. 3 cm große Läsion im re. Oberlappen – ED, 01/2023
- Progrediente Dyspnoe, ansonsten keine Symptome
- Komorbiditäten:
  - Allergisches Asthma
  - St.p. TIA, Clopidogrel Therapie
  - St.p. Schilddrüsenkarzinom – St.p THE, St.p. RJT
  - CAVK I
  - St.p. NN-OP (Adenom)
- ECOG 0-1, Karnofsky 90



Non-Small Cell Lung Cancer (NSCLC) – Faktencheck Patientenweg

4800 Fälle in Österreich 2020

Zufallsbefund vs. Symptome

Bronchoskopie / Biopsie

Histologie

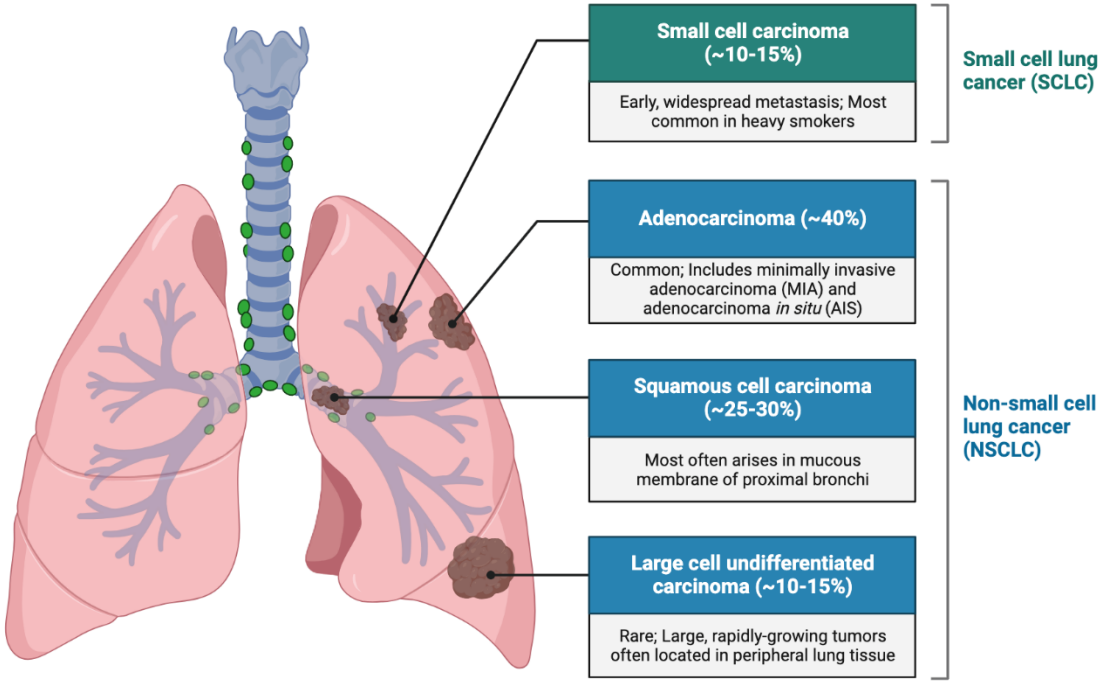
Adeno Ca

Platte

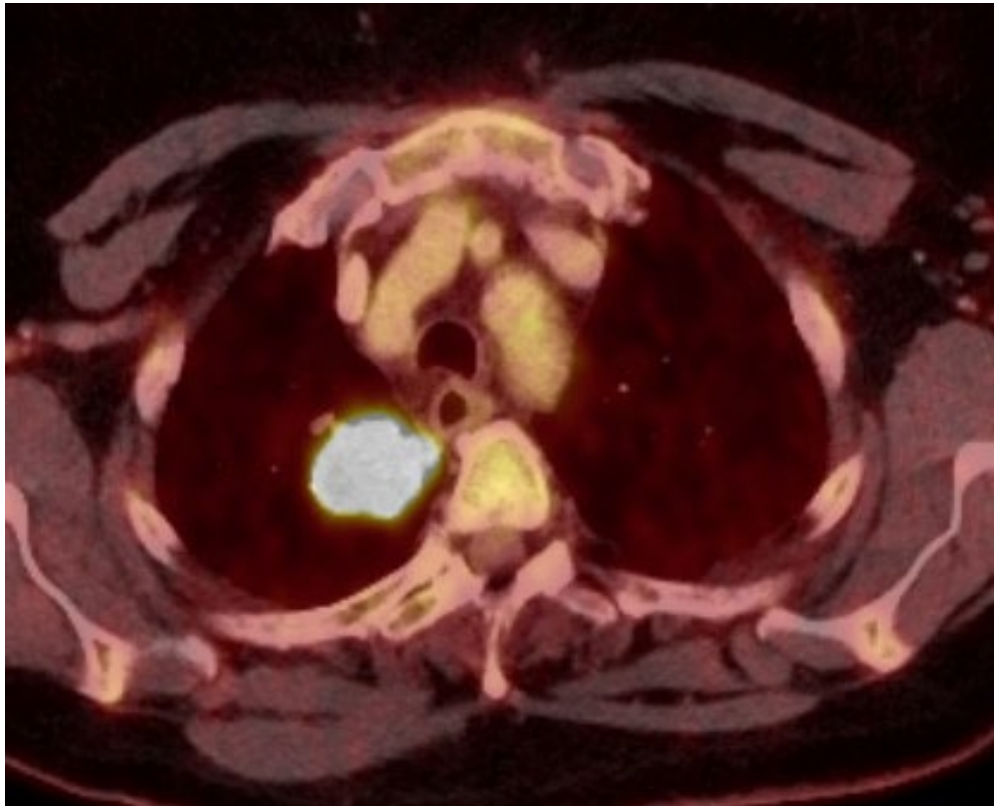
PD-L1, Molekulargenetik

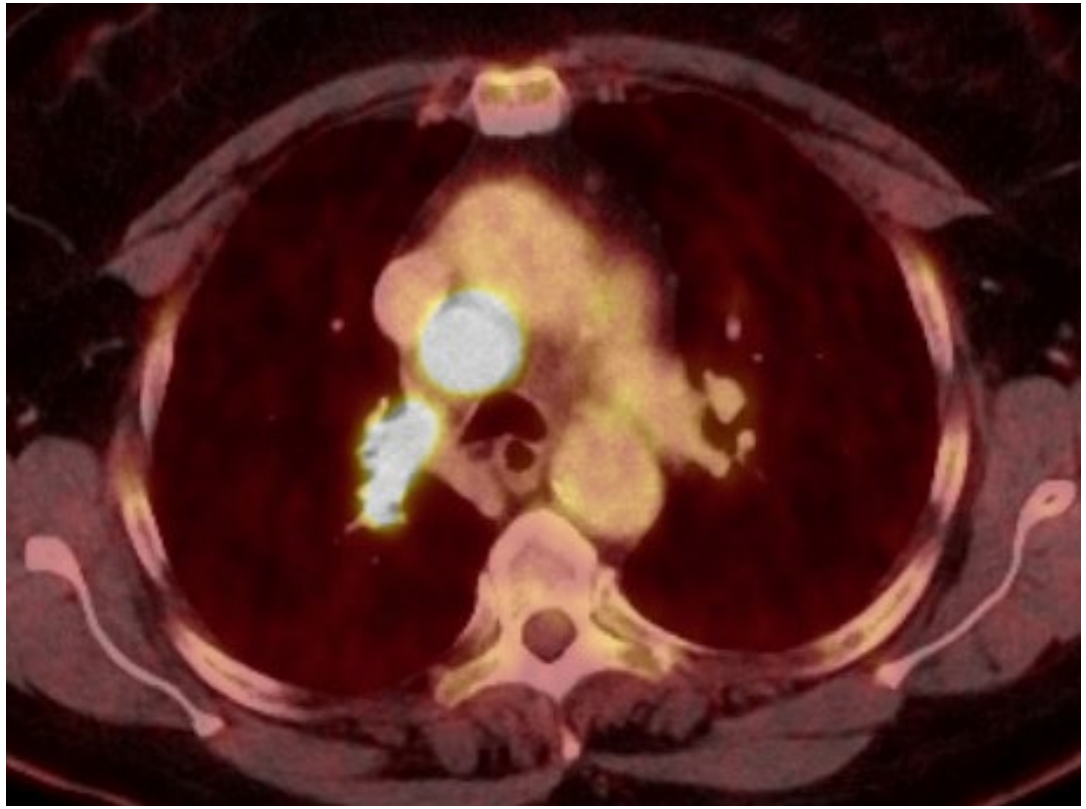
Bildgebung

Funktionelle Abklärung

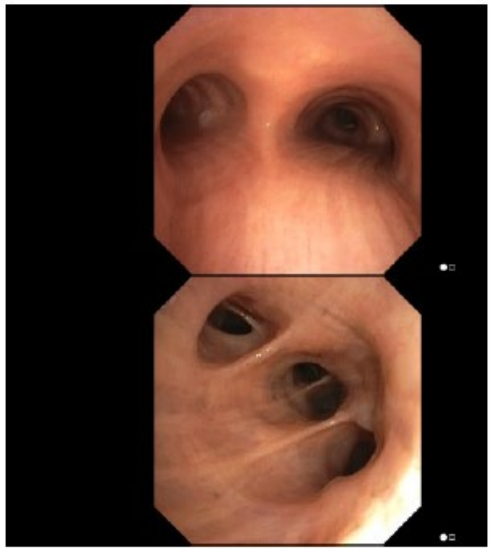


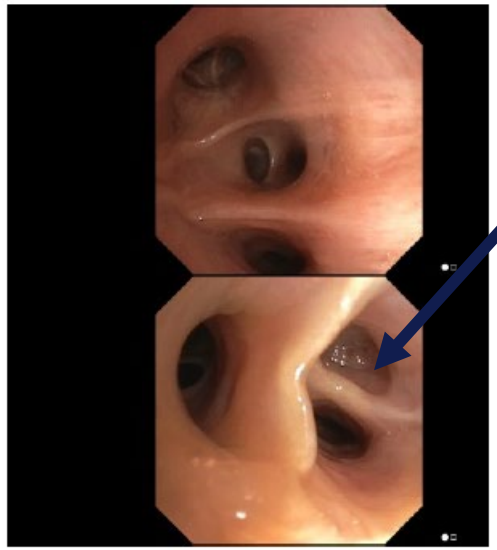
Realitycheck – der NSCLC Patient in der Praxis: FDG-PET/CT



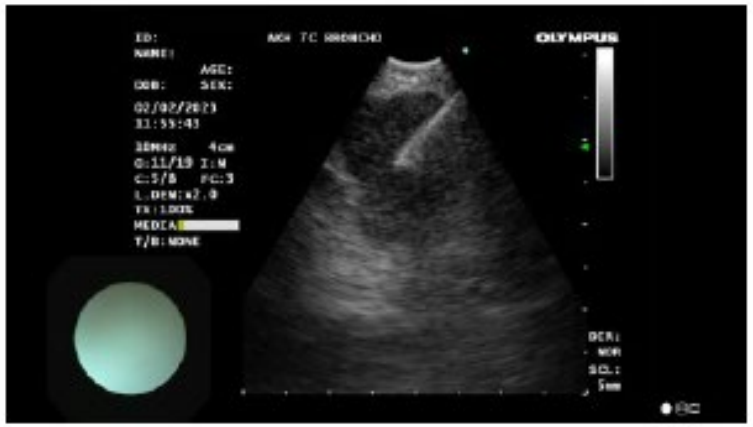


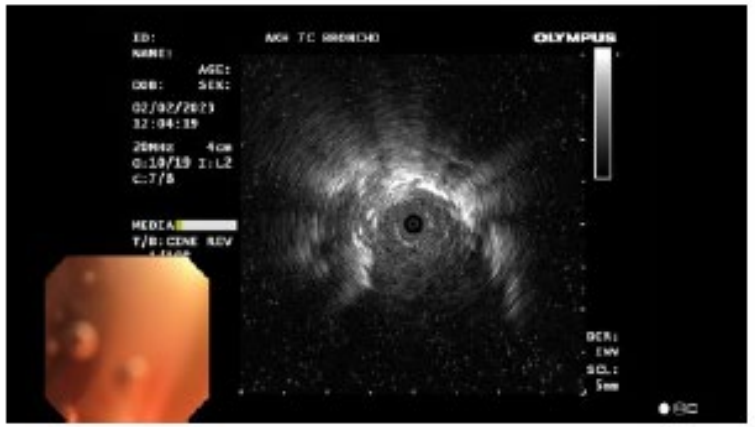
Realitycheck – der NSCLC Patient in der Praxis: Komplettierung Staging





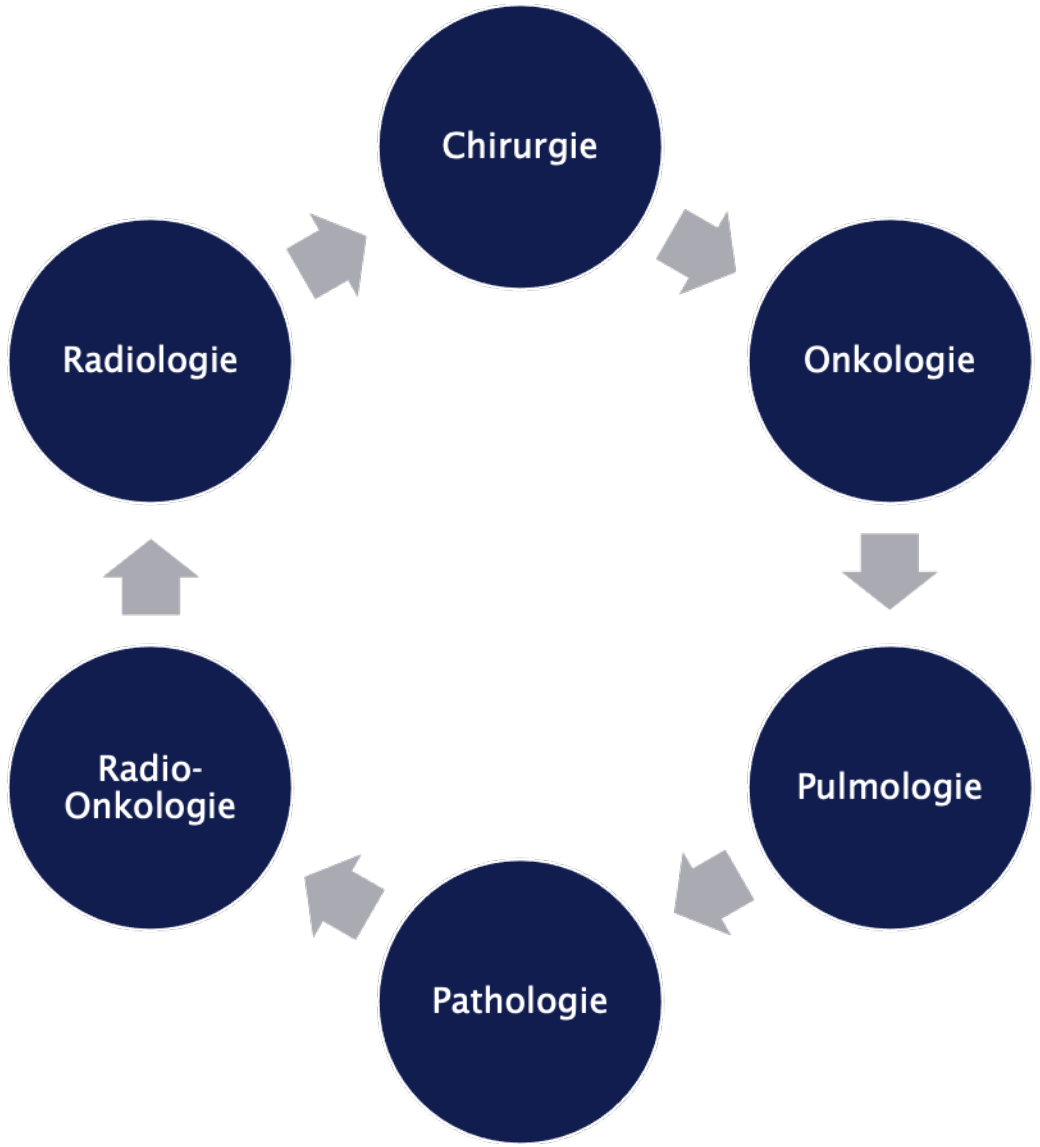
- Endo-PE aus Segment 1 , re. OL
- EBUS-TBNA aus LK 4R
- Keine weiteren LK-Bx, da diese sich nicht vergrößert zeigten und PET-negativ waren





- Histologie aus LK 4R: positiv für LK Metastase
- Histologie Tumorbiopsie: Plattenepithelkarzinom der Lunge, G3
- PDL1 (BSR 90): TPS 80 %
- NGS: keine Mutationen

Tumorboard Thoraxmalignome

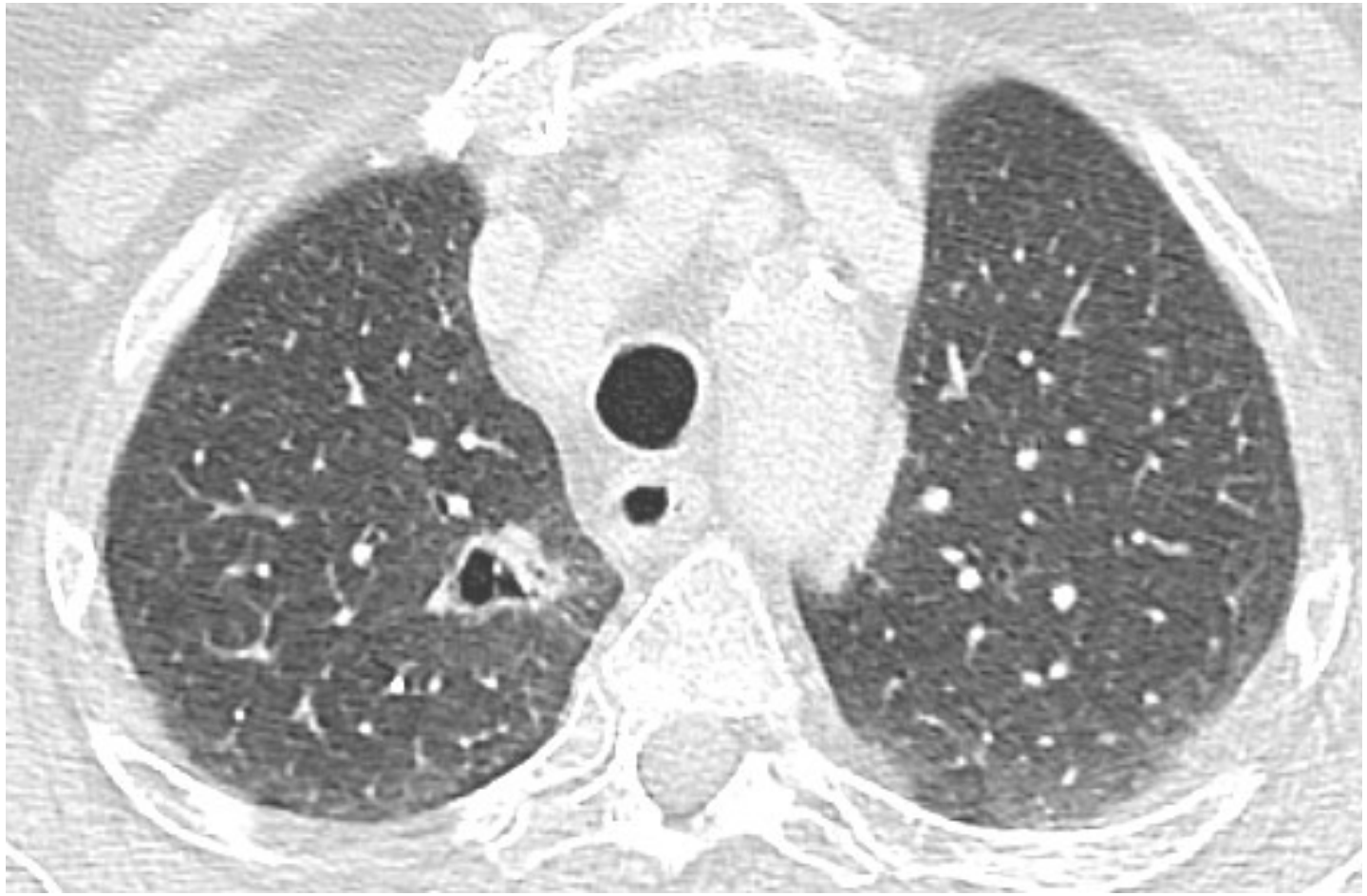


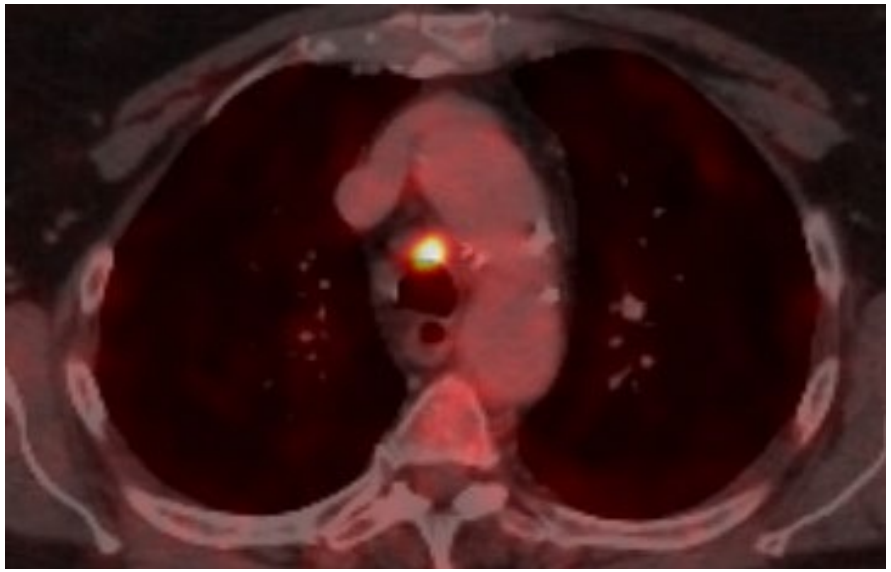
Realitycheck – der NSCLC Patient in der Praxis: Tumorboard

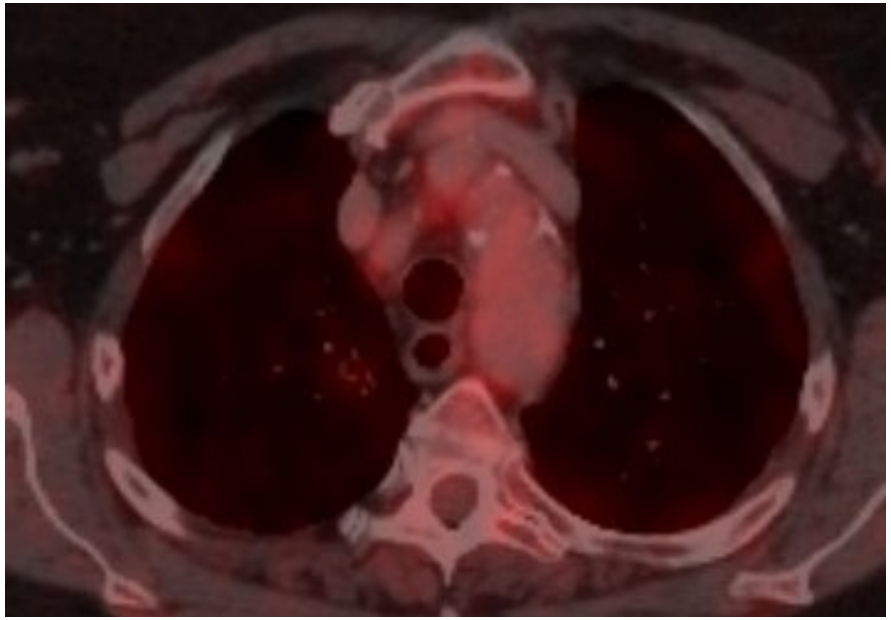
- **Staging: cT2N2 (single level) M0 Stadium IIIA**
- **Empfehlung:**
- neoadjuvante Chemo/IO, Re-Staging mittels PET-CT und Planung einer Resektion
- Tumor durch VATS lokal resektabel, Lymphknotenbefall nur in einer Station und entfernbar
- Gesamtkonstellation: fitte Patientin für multimodales Therapiekonzept in kurativer Intention

- 3 Zyklen neoadjuvante CHT/IO (Carboplatin/Paclitaxel + Nivolumab)
- Nebenwirkungen:
  - Nausea Grad II, Diarrhoe Grad I, reduzierte Belastbarkeit, Fatigue

Restaging nach 3 Zyklen Induktionstherapie

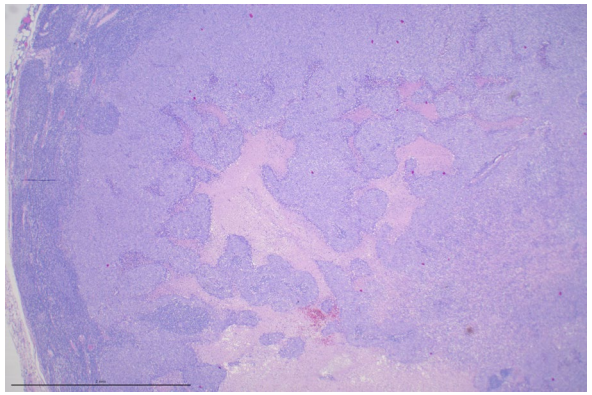
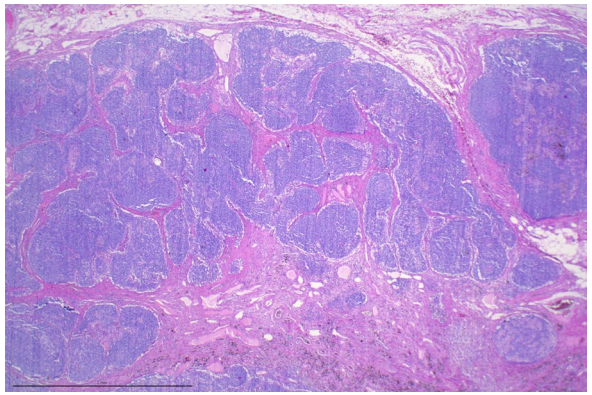
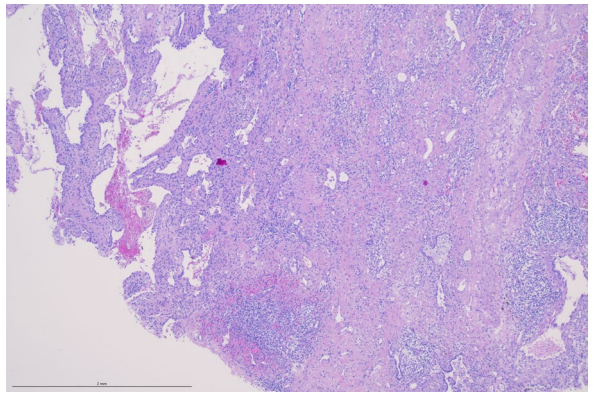






Endgültige Histologie

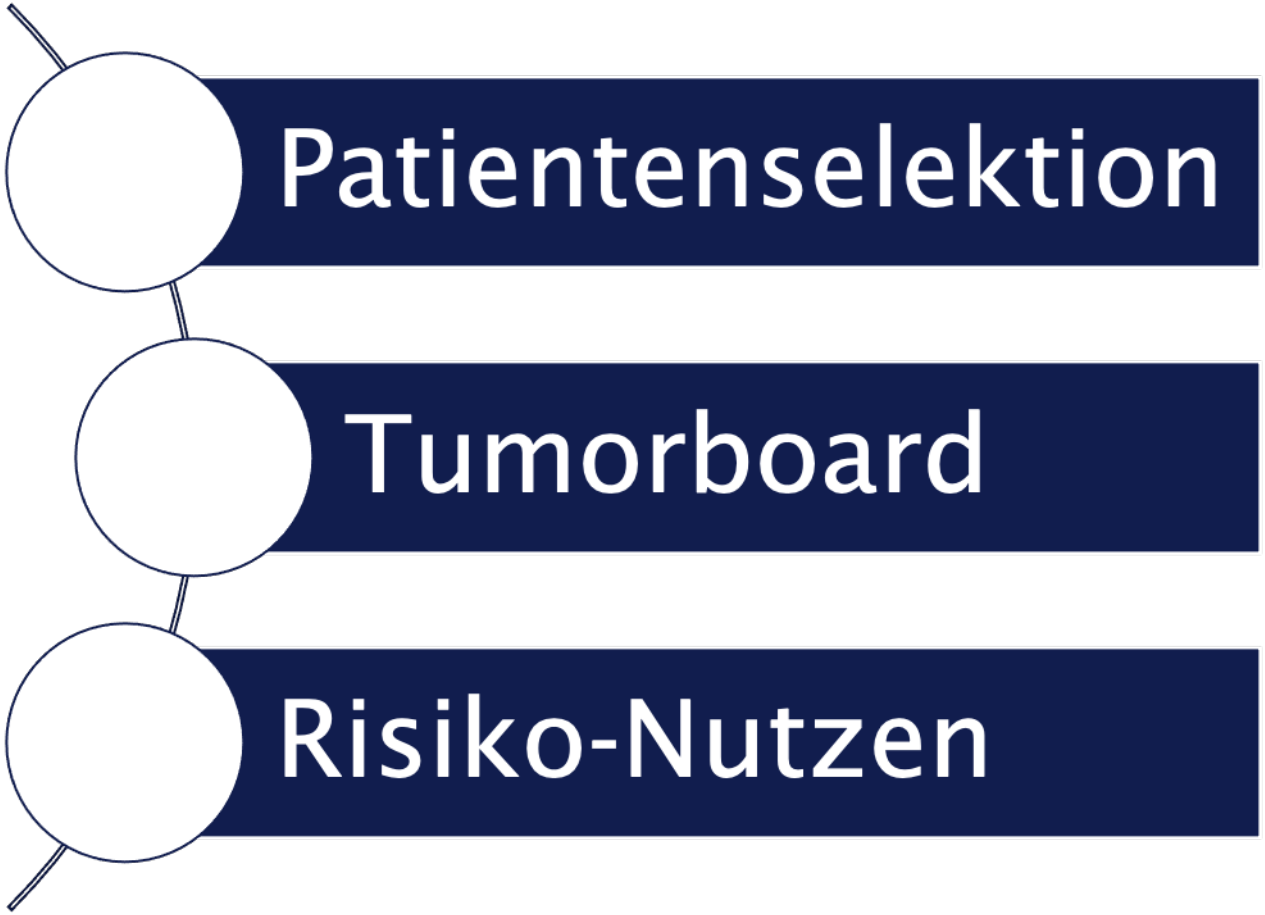
- Lobektomie re OL und radikale LND
- **pCR im Primärtumor** (keine vitalen Tumorzellen nachweisbar)
- Pathologisches Stadieneinteilung: ypT0, ypN2 (2/19), L0, V0, pn0 – R0

- Ad Nachsorge (CheckMate816 Protokoll)

01/2024 – ohne Rezidiv

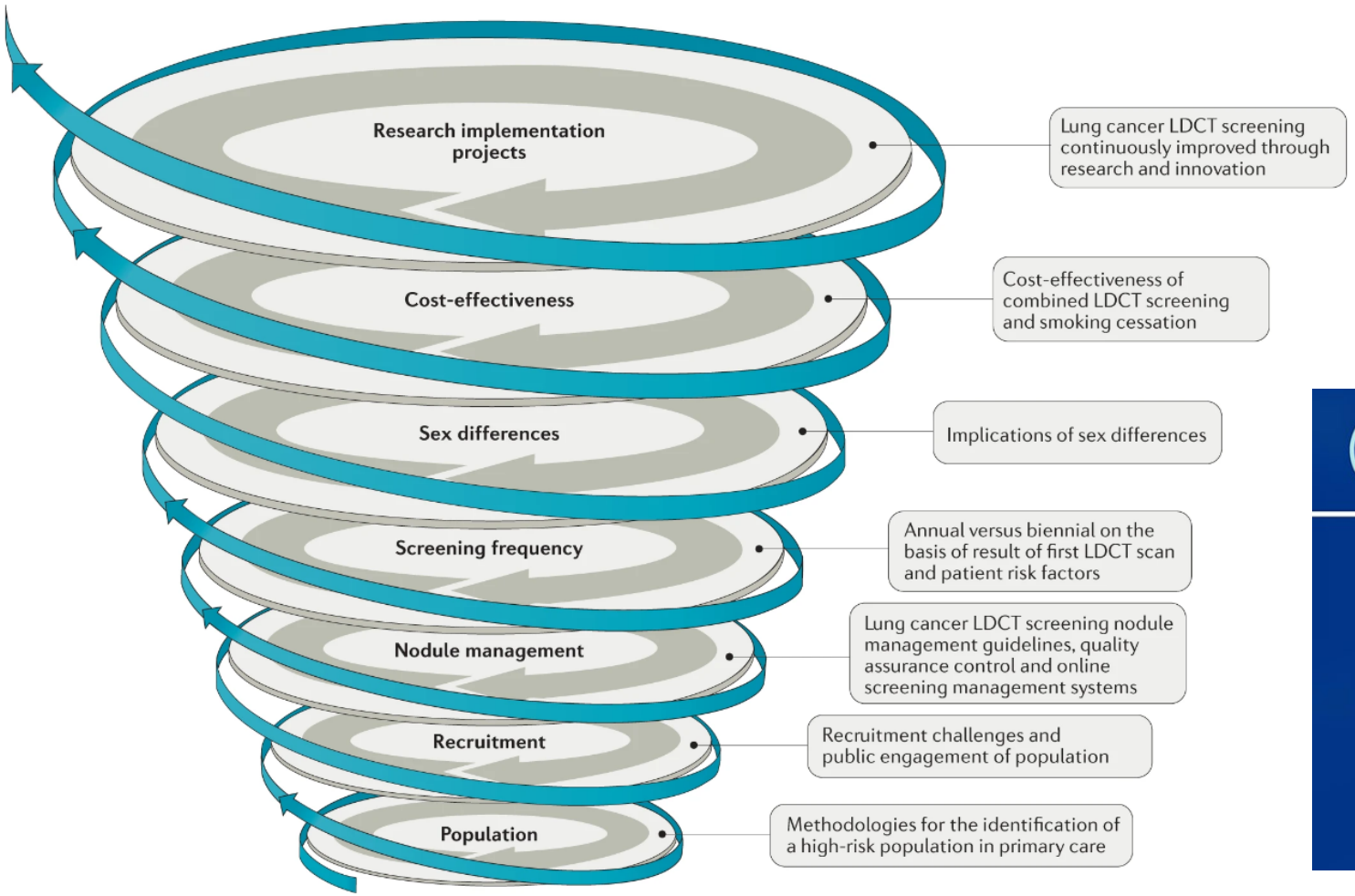
Immuntherapie – Optimierung der perioperativen Konzepte 2024



- Proof of concept definitiv erbracht
- Adjuvant Atezolizumab (50%+ PD-L1) und Pembrolizumab
- Neoadjuvant derzeit Nivolumab
- Zunehmende Evidenz für Add-on Nutzen der perioperativen Therapie (OS-Daten KEYNOTE-671, EFS Checkmate 77T, AEGEAN) – noch keine Zulassung
- Chemo-Backbone? Therapiedauer? PD-L1?

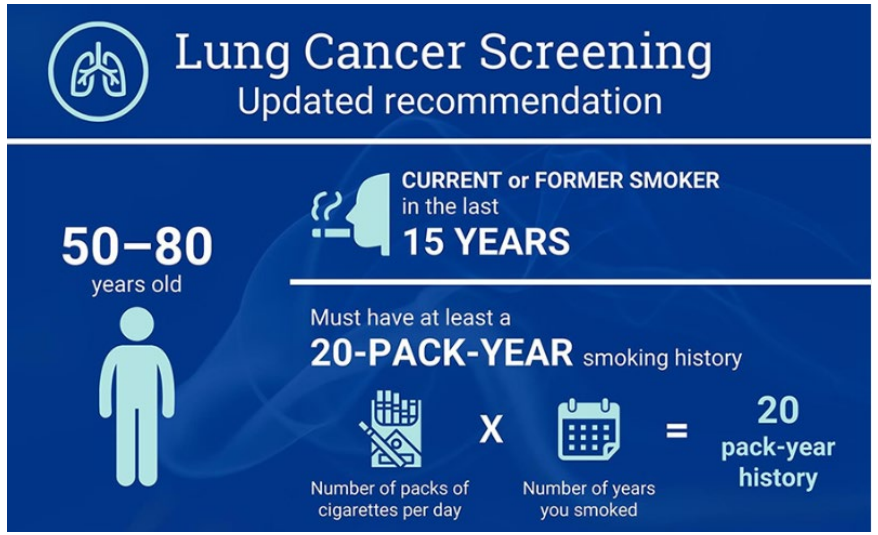
Integration der Immuntherapie Therapie ins perioperative Setting als neuer Standard

Zunehmende Bedeutung möglicher Screening Strategien – am Prüfstand



Trauen Sie sich den Rauchstopp zu!

Sie können nur gewinnen.



Oudkerk et al, Nat Rev Clin Oncol 2021;18:135-51
https://www.brighamandwomens.org/radiology