LungCancerGroup Cologne

nNGM National Network Genomic Medicine Lung Cancer

CIO Centrum für Integrierte Onkologie Aachen Bonn Köln Düsseldorf

Aktuelle Therapieansätze beim Lungenkarzinom

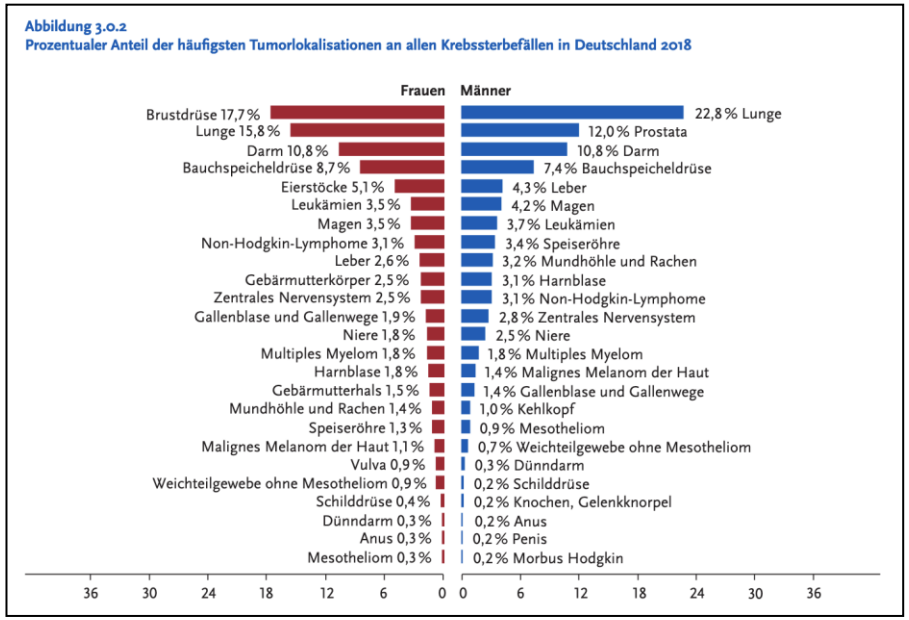
Jürgen Wolf
Klinik I für Innere Medizin, Centrum für Integrierte Onkologie
Uniklinik Köln

Potentielle Interessenskonflikte

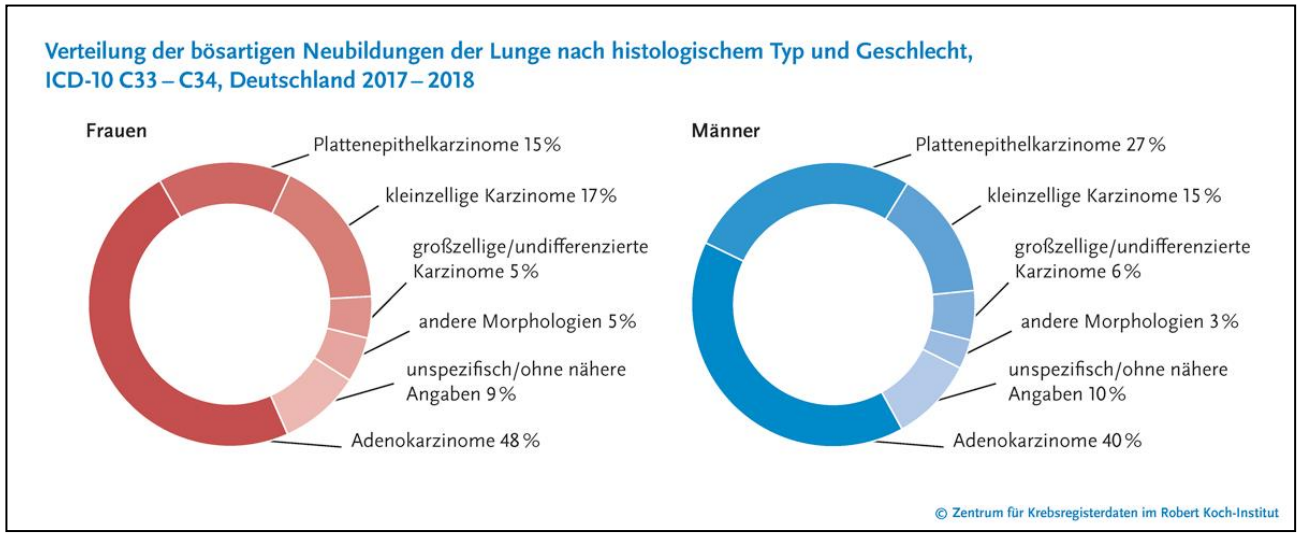
- **Advisory boards und Vortragshonorare:**
  Amgen, AstraZeneca, Bayer, Blueprint, BMS, Boehringer-Ingelheim, Chugai, Daiichi Sankyo, Ignyta, Janssen, Lilly, Loxo, MSD, Novartis, Pfizer, Roche, Seattle Genetics, Takeda

- **Forschungsförderung (an UKK):**
  Amgen, BMS, Janssen Pharmaceutica, Novartis, Pfizer

Lung Cancer in Germany: Fact Sheet I



Most frequent cause of cancer death

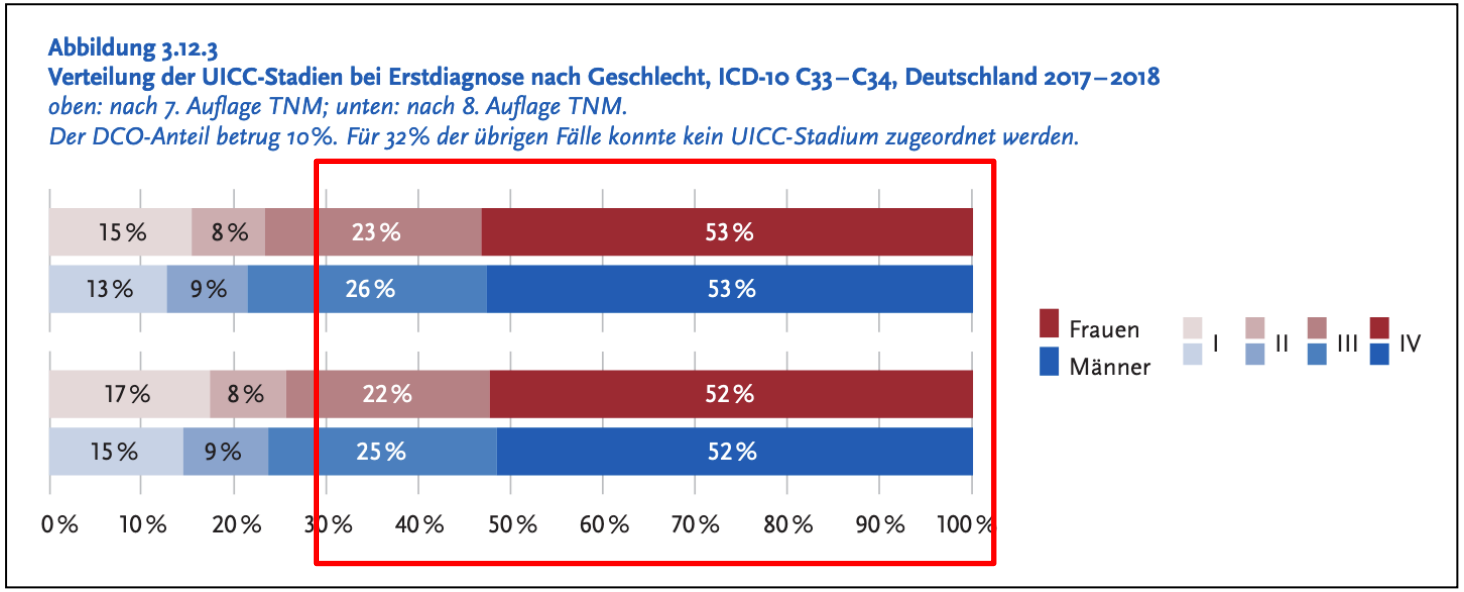


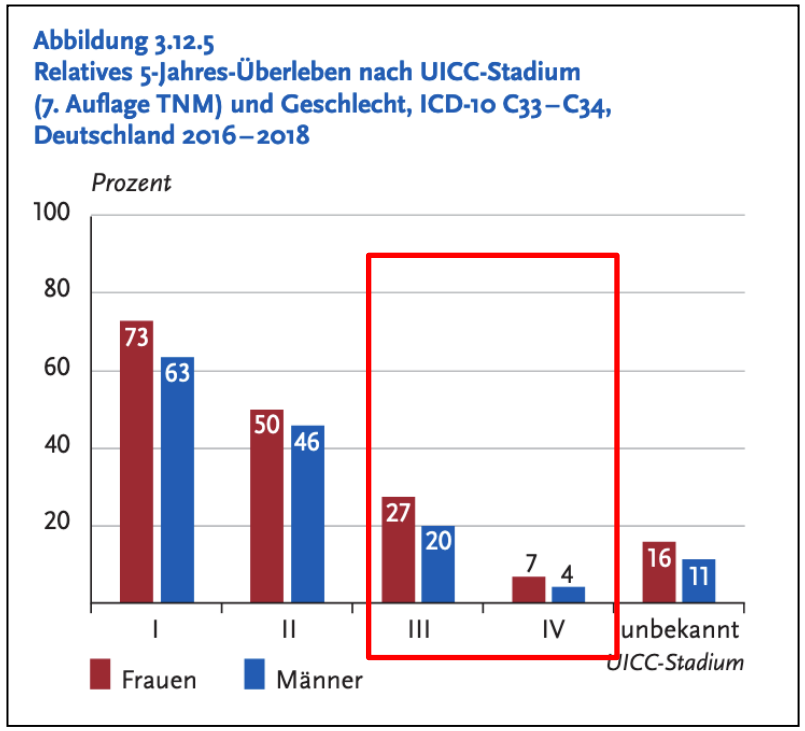
85% NSCLC, 15% SCLC
most frequent subtype: adenocarcinoma

> Lung cancer since decades *major cancer killer*

https://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Lungenkrebs/lungenkrebs_node.html

Lung Cancer in Germany: Fact Sheet II





around 75% of patients locally advanced or stage IV

> no curative (surgical) treatment

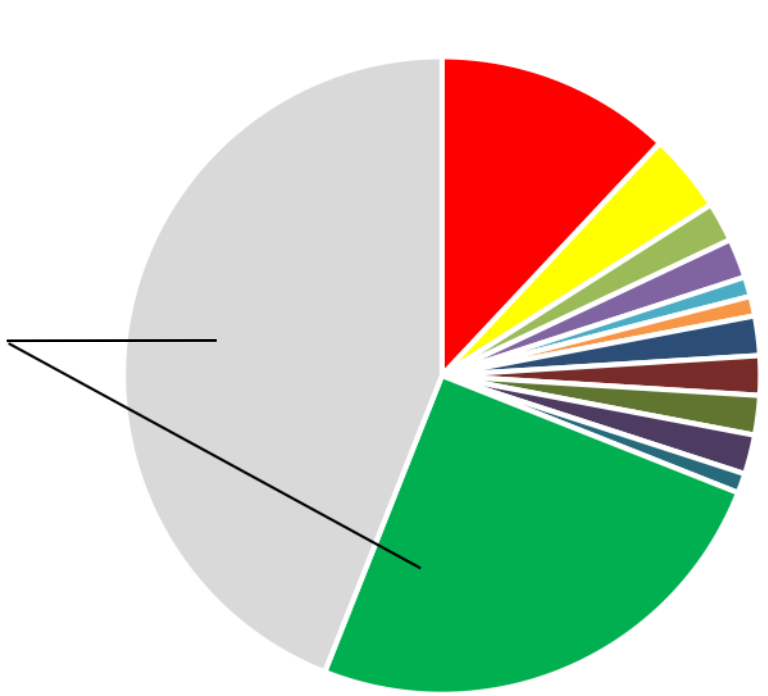
https://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Lungenkrebs/lungenkrebs_node.html

A selection of current developments

PD-L1 ≥ 50% TCS:
> PD(L)1 inhibitor mono
> chemo / IO - combinations

PD-L1 < 50% TCS:
> chemo / IO - combinations

PD-L1 independent
> nivolumab + ipilimumab + 2 cycles platin-bas.CT

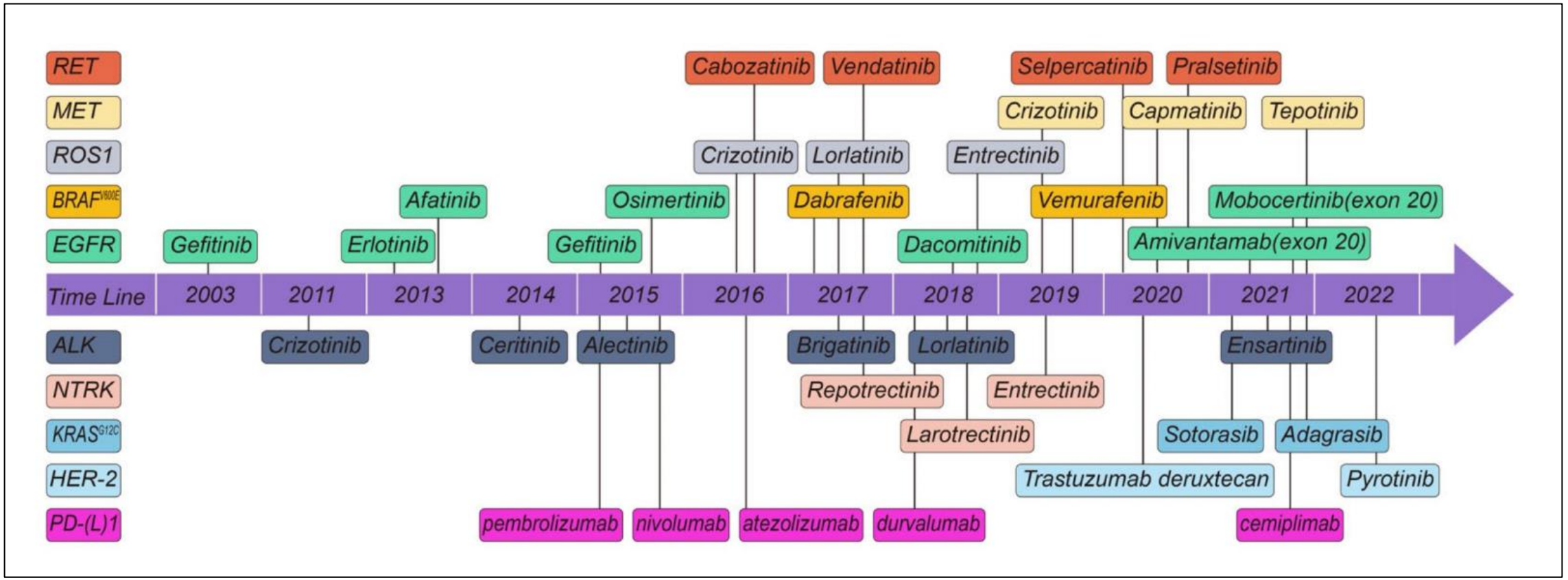


- EGFRmut
- ALKfus
- ROS1fus
- BRAFmut
- NTRK1-3fus
- RETfus
- METex14
- METhl-amp
- EGFRex20
- HER2ex20
- NRG1
- KRAS

EMA approved 1st line therapy

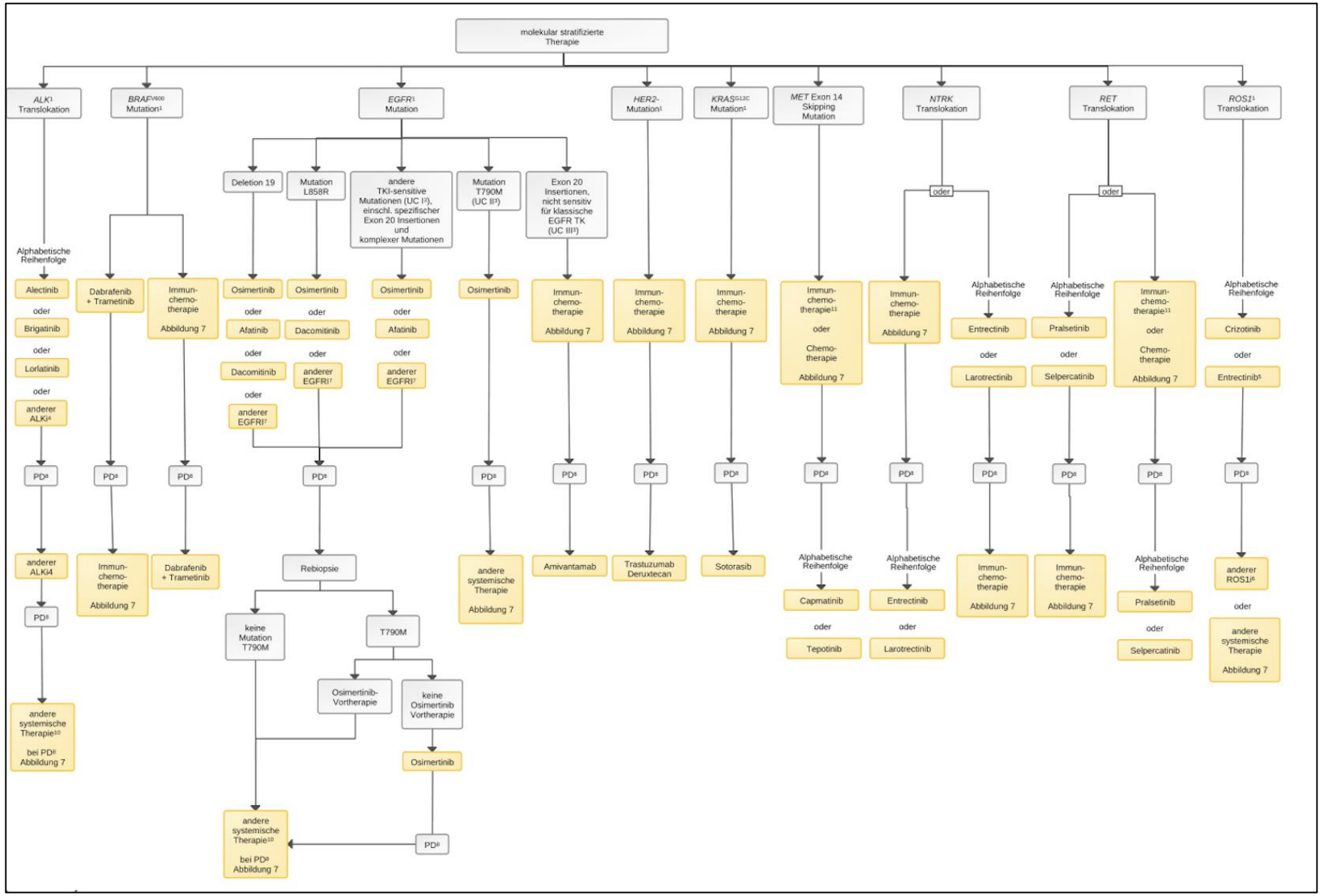
EMA approved after failure of 1st line therapy (KRAS: only G12C)

Impressive drug approval dynamics in oncogene-addicted lung cancer



Guo et al, Cells 2022

Onkopedia guidelines advanced NSCLC (Nov. 2022)



A selection of current developments

IO + IO/chemo
in early and
Intermediate stages

PD-L1 < 50% TCS:
> chemo / IO -
combinations

PD-L1 independent
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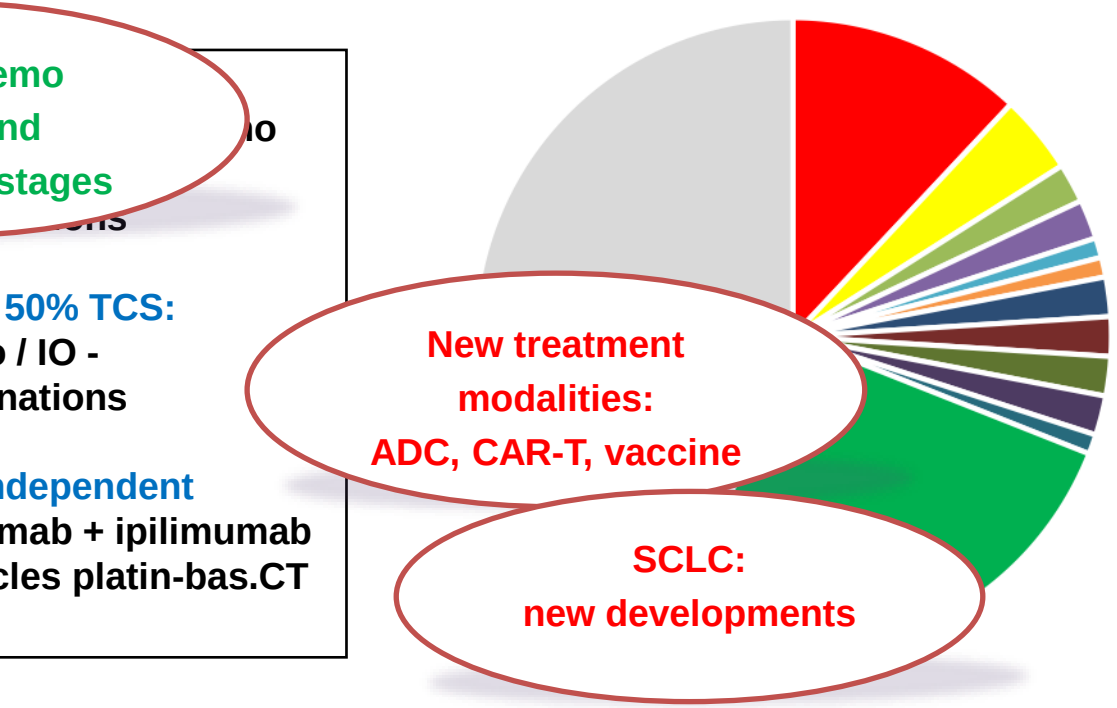
+ 2 cycles platin-bas.CT

New treatment
modalities:
ADC, CAR-T, vaccine

SCLC:
new developments



EGFR: new
combinations

ALK:
adjvuvant therapy

ROS1:
new inhibitors

EGFRex 20, HER2:
current highlights

after failure of
1st line therapy
(KRAS: only G12C)

KRAS:
new inhibitors

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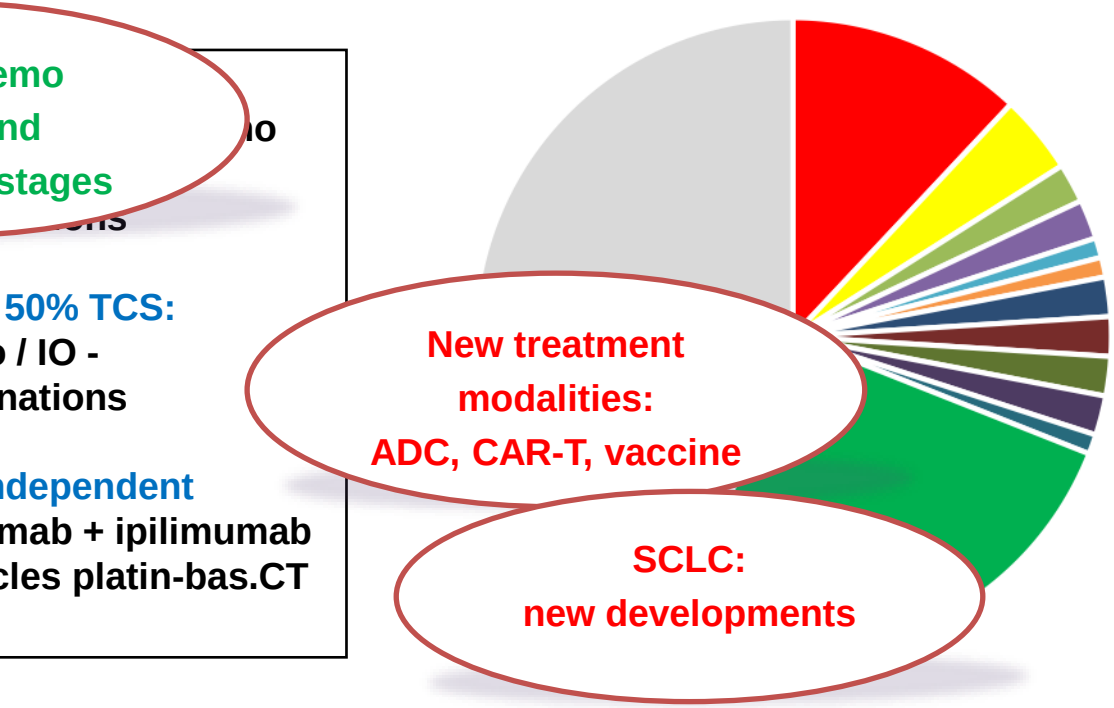

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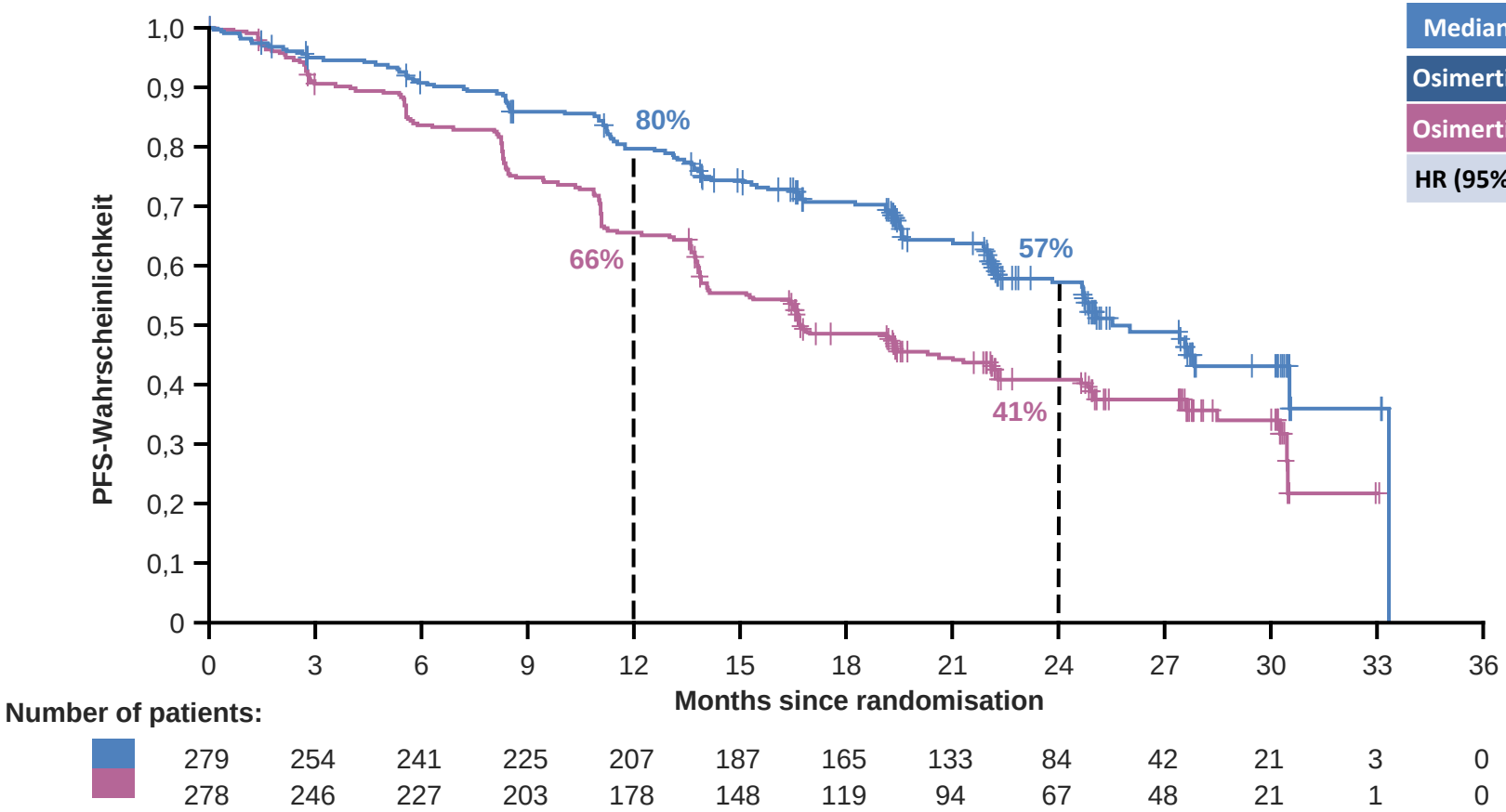
FLAURA 2: Phase III 1L: Osimertinib + 4 cycles Carbo/Pem vs. Osimertinib + Placebo

Progression free survival (PFS) according to investigator



Median PFS, months (95% KI)	
Osimertinib + Platin-Pemetrexed	25,5 (24,7; NC)
Osimertinib-Monotherapy	16,7 (14,1; 21,3)
HR (95% KI)	**0,62 (0,49; 0,79); P<0,0001**

Data maturitiy: 51%

Median Follow-Up für PFS*, Months (range):

Osimertinib + Platin-Pemetrexed, 19,5 (0; 33,3)

Osimertinib-Monotherapy, 16,5 (0; 33,1)

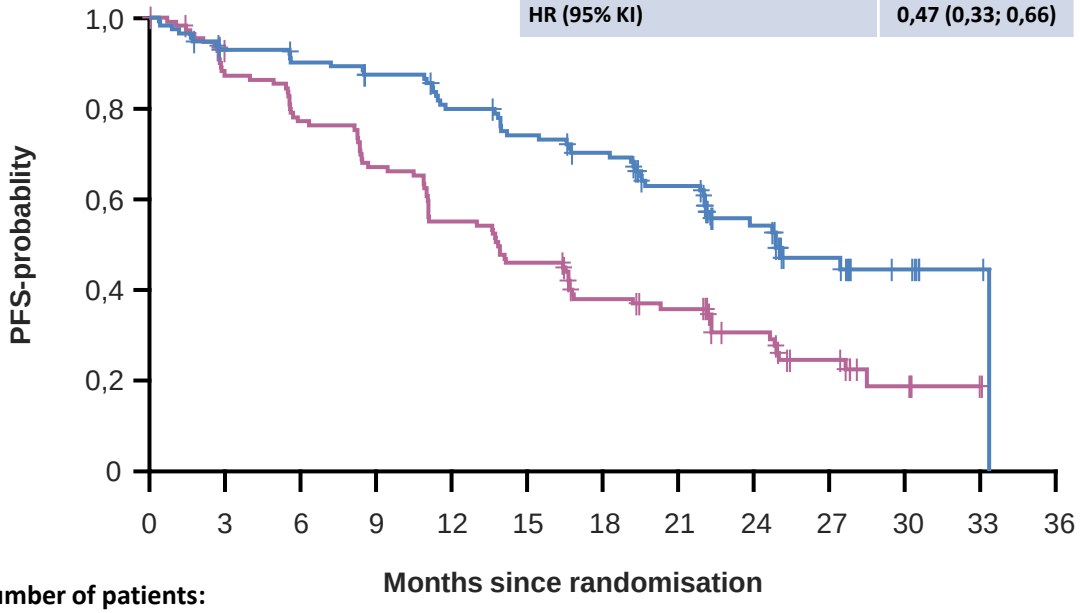
> Significant improvement of PFS, not of OS, increased toxicity

Jänne PA et al., WCLC 2023, Singapur & virtuell, PL03.13

FLAURA 2: Evaluation dependent on CNS - metastases

With CNS-metastases

Median PFS, months (95% KI)	
Osimertinib + Platin-Pemetrexed	24,9 (22,0; NC)
Osimertinib-Monotherapy	13,8 (11,0; 16,7)
HR (95% KI)	**0,47 (0,33; 0,66)**

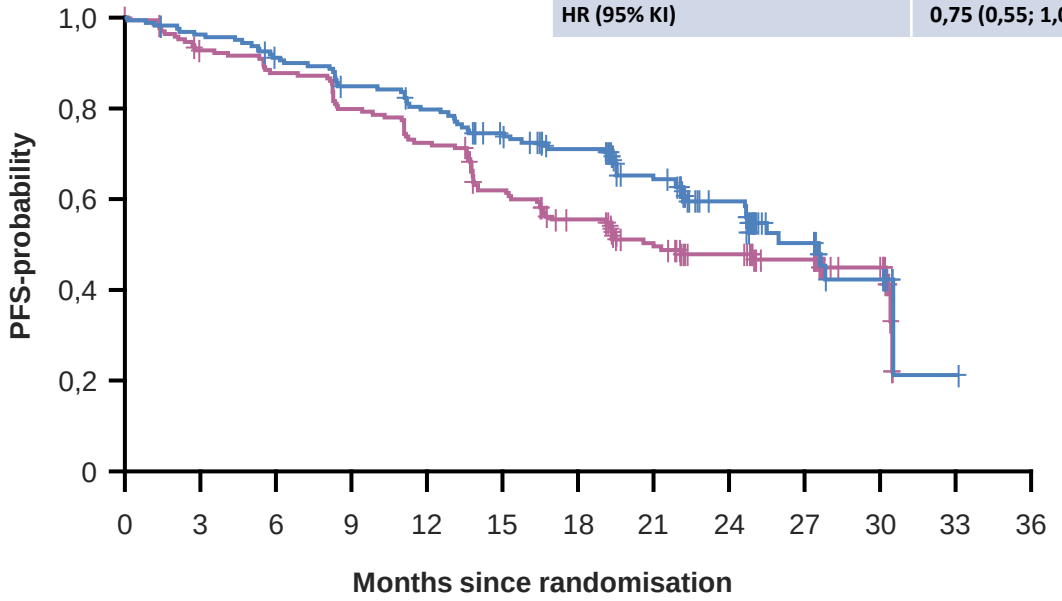


Number of patients:

	116	101	98	93	84	77	70	58	34	19	8	2	0
	110	95	84	73	60	50	37	32	21	13	5	1	0

Without CNS-metastases

Median PFS, months (95% KI)	
Osimertinib + Platin-Pemetrexed	27,6 (24,7; NC)
Osimertinib-Monotherapy	21,0 (16,7; 30,5)
HR (95% KI)	**0,75 (0,55; 1,03)**



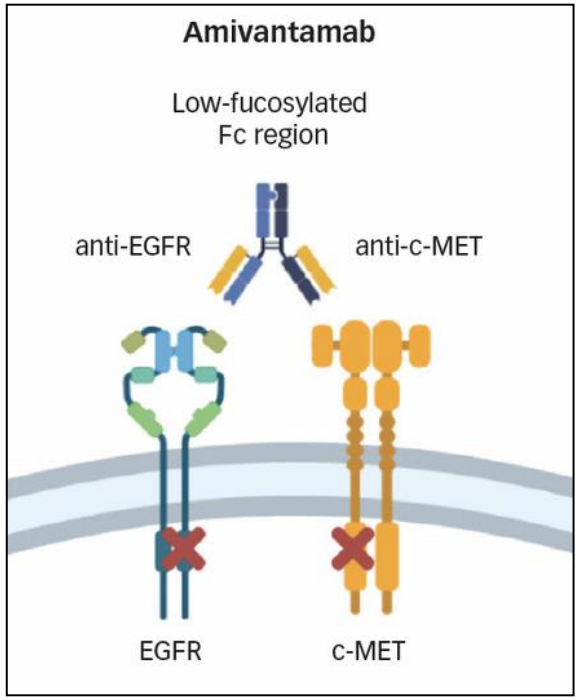
	163	153	143	132	123	110	95	75	50	23	13	1	0
	168	151	143	130	118	98	82	62	46	35	16	0	0

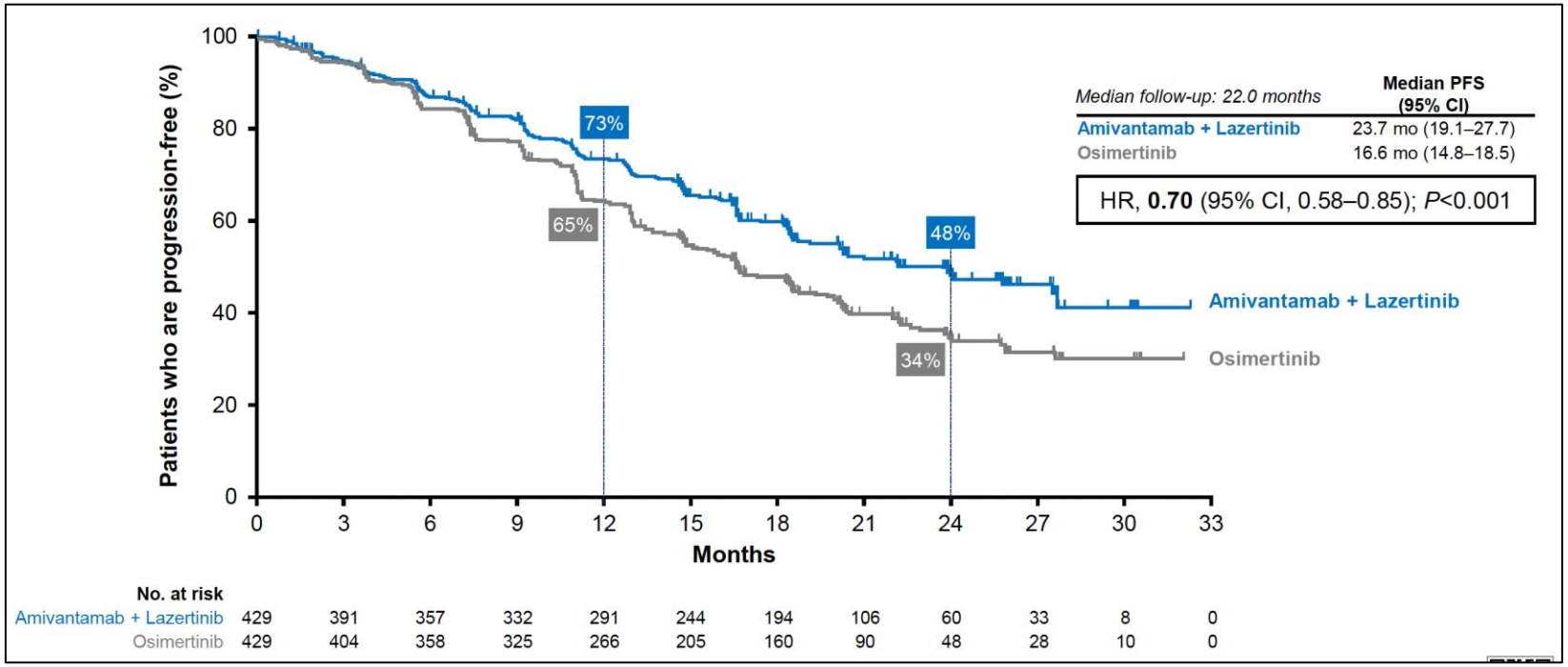
> Superiority predominantly in patients with CNS-metastases

Jänne PA et al., WCLC 2023, Singapur & virtuell, PL03.13

MARIPOSA: Phase III 1L Osimertinib vs. Lazertinib + Amivantamab (vs. Lazertinib)

Primary endpoint: BIRC assessed PFS





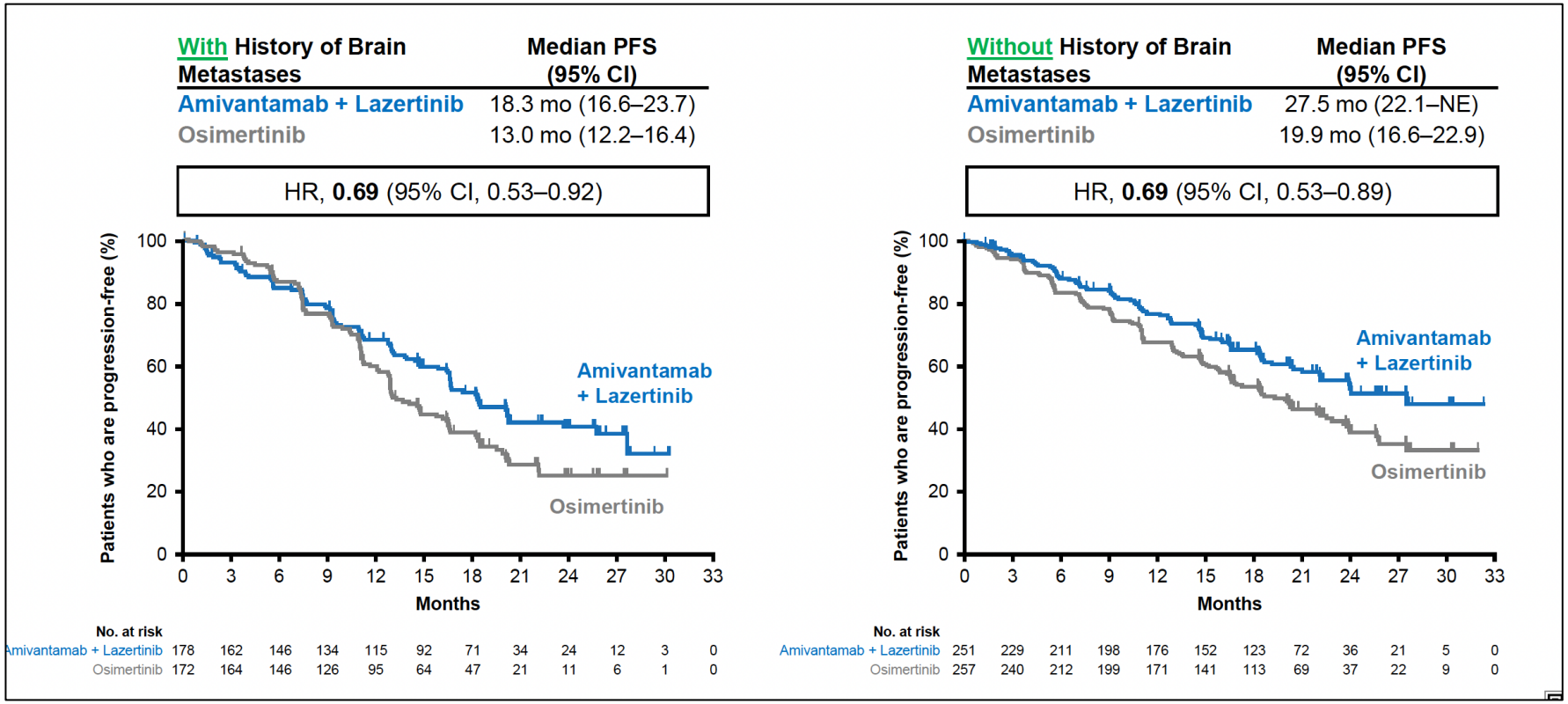
> Risk reduction for progression or death by 30%

> Overall survival interim analysis: no significant benefit (HR 0.8, p 0.1, trend)

Cho et al., ESMO 2023

MARIPOSA: Phase III 1L Osimertinib vs. Lazertinib + Amivantamab

PFS dependent on CNS-metastases



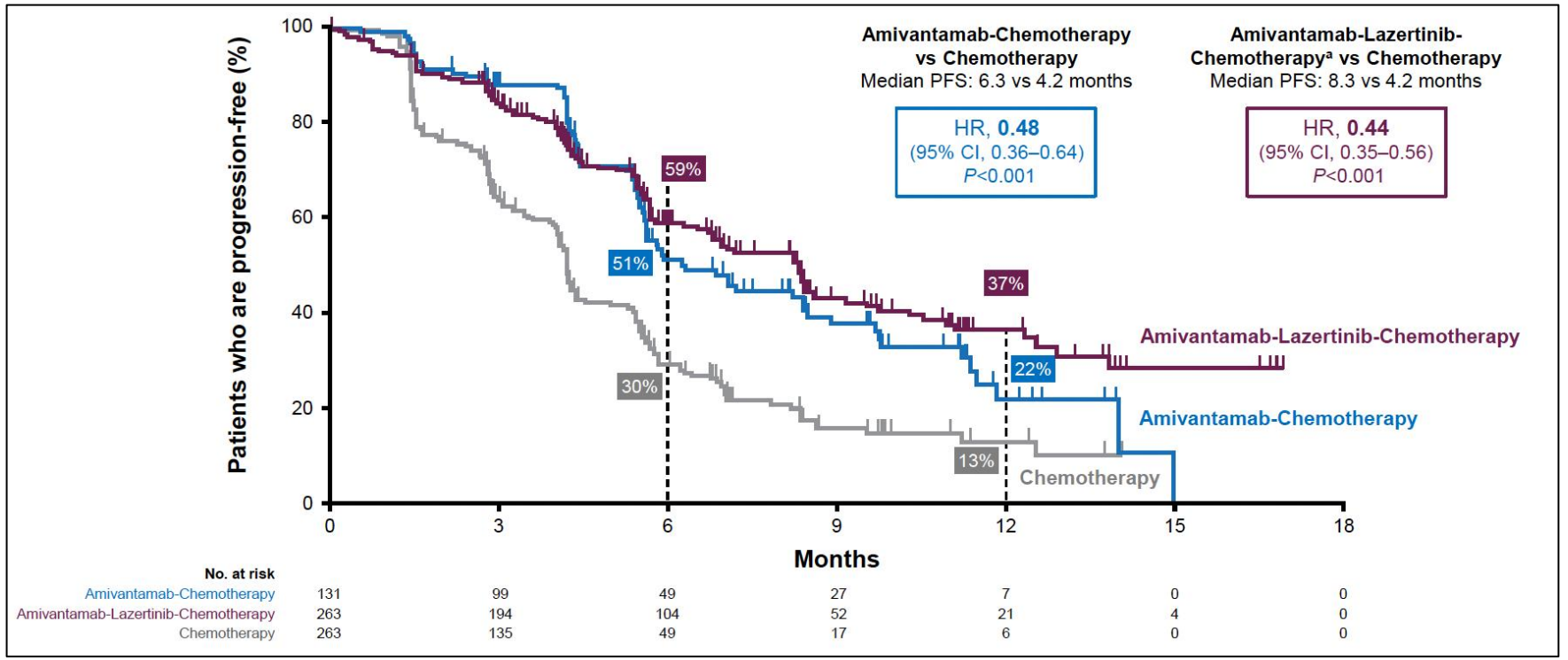
> Efficacy comparable with or without CNS-metastases

> Up to 37% venous thromboembolism events in combination arm: prophylactic anticoagulation for the first 4 months of treatment

Cho et al., ESMO 2023

MARIPOSA-2: Phase III osimertinib failure: chemotherapy (CT) vs. CT + amivantamab vs. CT + amivantamab + lazertinib

Primary endpoint PFS by BIRC

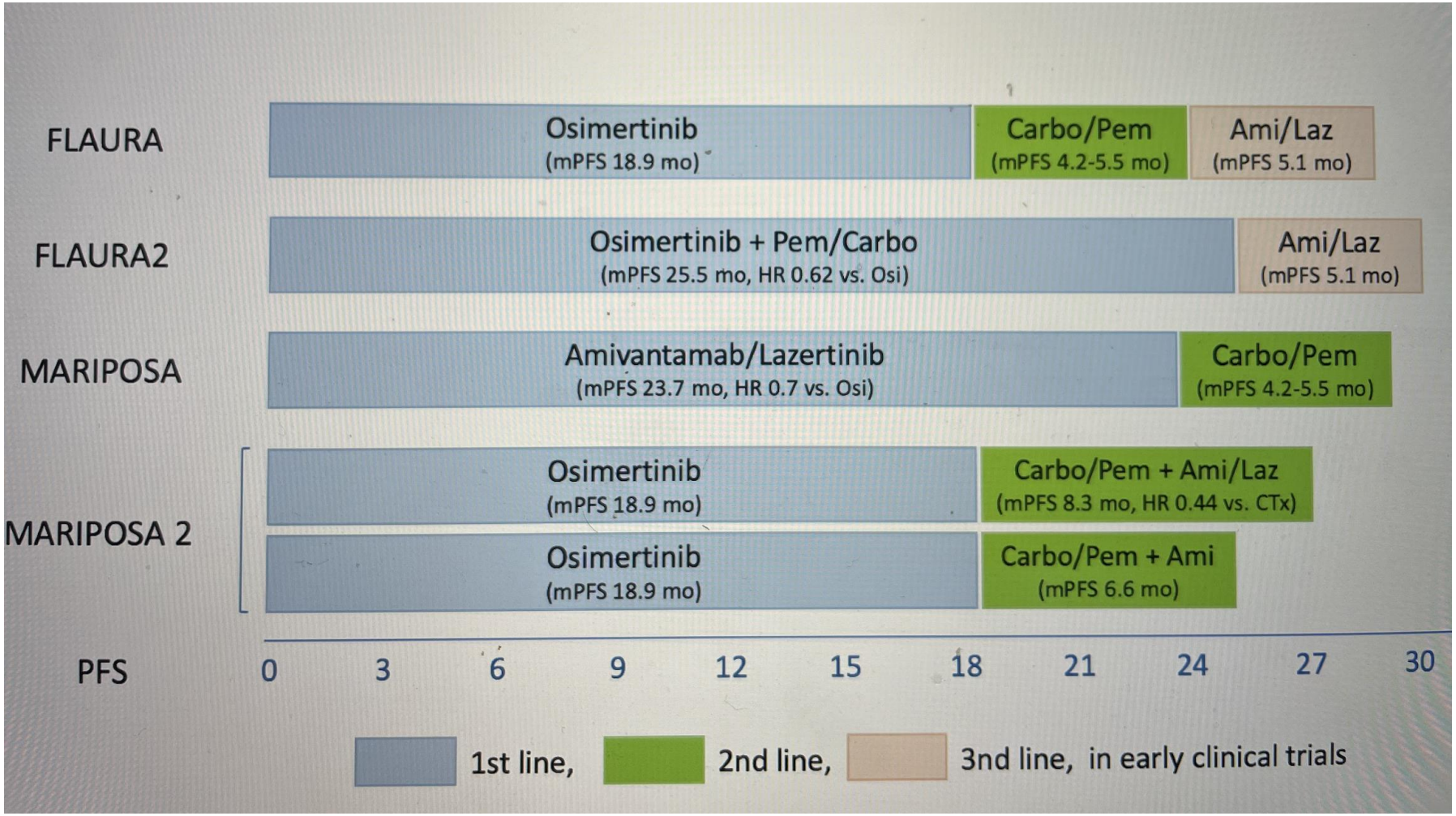


> PFS of combinations sigificantly better (comparable in all subgroups)

> Combinations more toxic. SAE frequency: 20% CT / 30% CT + ami / 52% 3-drug combi)

Passaro et al., ESMO 2023

New options for 1L therapy of EGFR-mutated lung cancer



> no urgent need to leave osimertinib 1L (my personal opinion)

> need to identify subgroups with benefit from distinct combinations

Piotrowska, Discussant, ESMO 2023, Presidential Symposium

A selection of current developments

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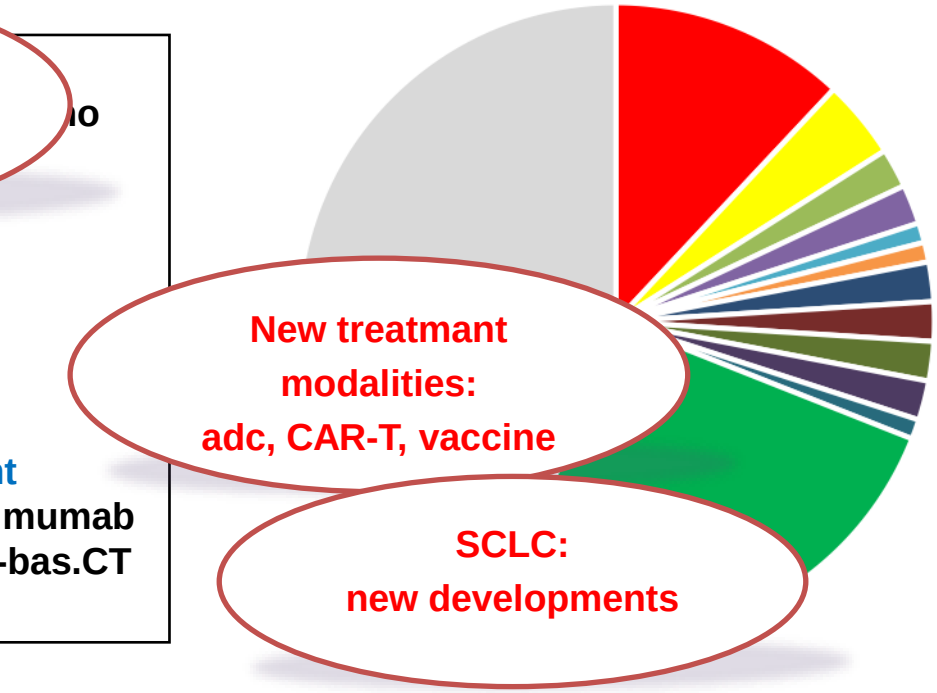

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ALINA trial: Alectinib adjvuant

ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R 1:1

N=257

Alectinib 600 mg BID 2 years → **Recurrence**

Platinum-based chemotherapy† Q3W; 4 cycles → **Recurrence**

Further treatments at investigator's choice and survival follow-up

Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

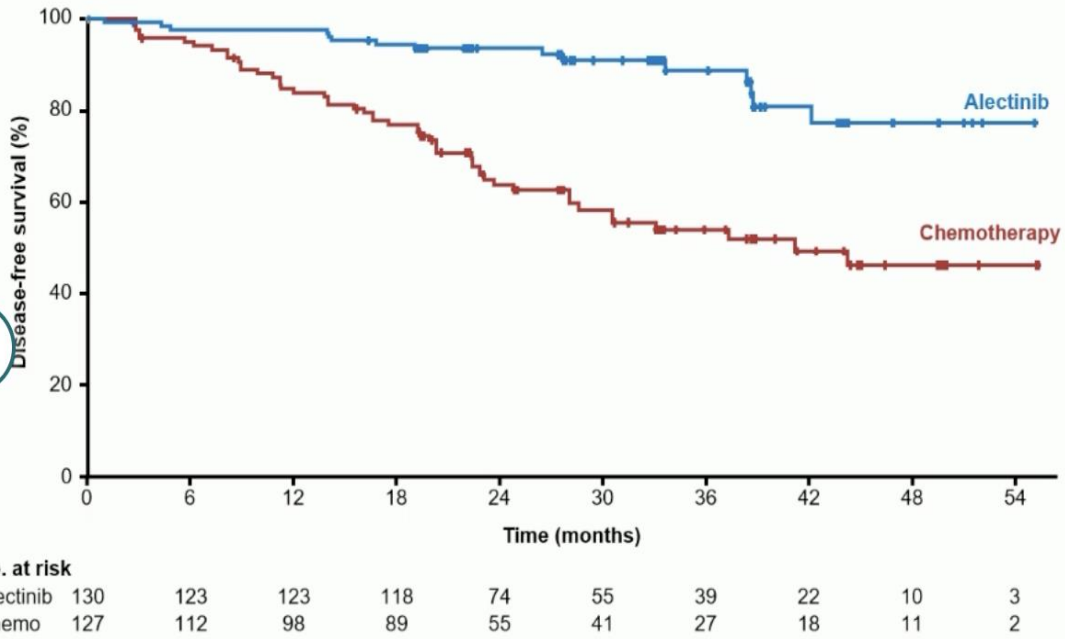
Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

Ben Solomon

ALINA: Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC)

ALINA trial: Alectinib adjvuant

Disease-free survival: ITT (stage IB–IIIA)*



	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p†<0.0001	

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

MADRID 2023 ESMO congress

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months
*Per UICC/AJCC 7th edition; †Stratified log rank; ‡2 events in the alectinib arm, 4 events in the chemo arm; one additional patient in the chemo arm died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

Ben Solomon

ALINA: Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC)

> common sense: new standard

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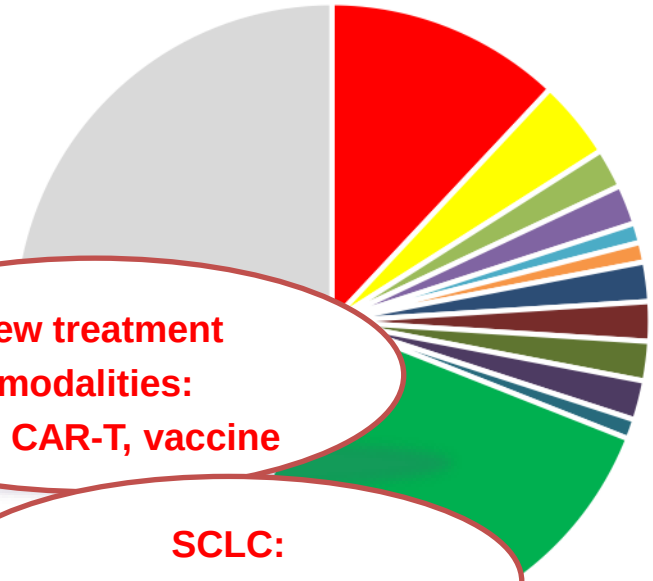

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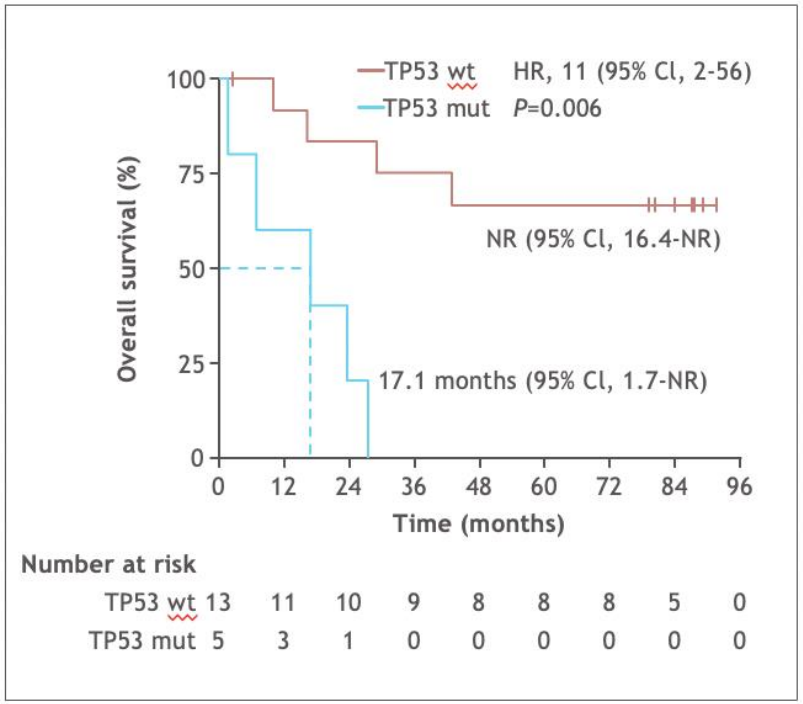
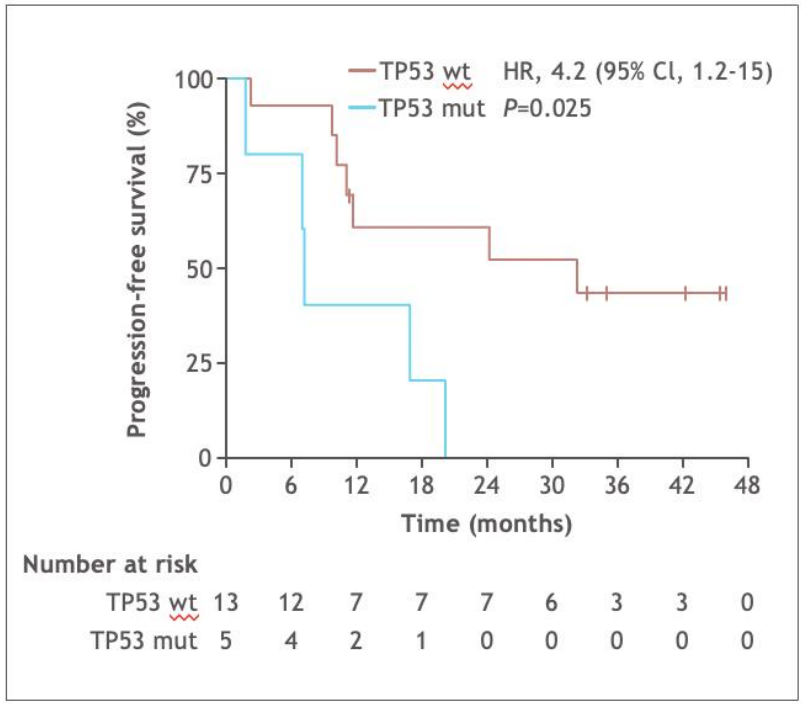
A variety of drugs available now for ROS1+ NSCLC

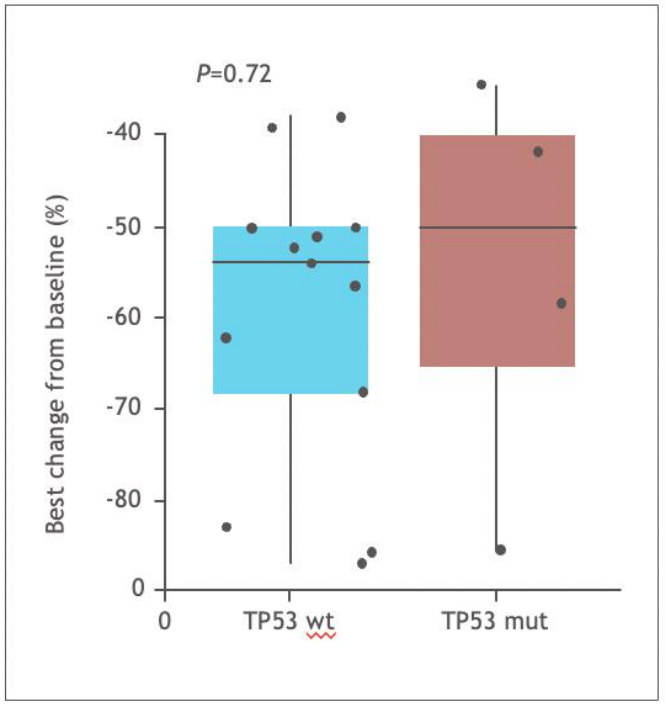
TKI	Main molecular targets	Approval (FDA/EMA)
Crizotinib	**ROS1, ALK, MET**	ALK+, **ROS1+** NSCLC
Entrectinib	**ROS1, ALK, NTRK**	**ROS1+,** NTRK+ NSCLC
Ceritinib	ALK, ROS1	ALK+ NSCLC
Lorlatinib	ALK, ROS1	ALK+ NSCLC (FDA only)
Cabozantinib	VEGFR, MET, ROS1, AXL	Renal cell carcinoma, hepatocellular ca., thyroid neoplasms
Repotrectinib	ROS1, NTRK	not approved (FDA approval)
Taletrectinib	ROS1, NTRK	not approved (FDA breakthrough designation)
Zidesamtinib (NVL-520)	ROS1, ALK, (NTRK)	not approved (early clinical evaluation)

> Off-label therapy and clinical trials should always be considered!

TP53 mutations predict worse outcome







EUCROSS phase II trial for crizotinib in advanced ROS1 NSCLC

no significant OS difference for brain mets vs. non brain mets

> No therapeutic strategy here so far (like in ALK, EGFR....)

Michels et al. JTO. 2019; Michels et al. JTO Precis Oncol. 2024

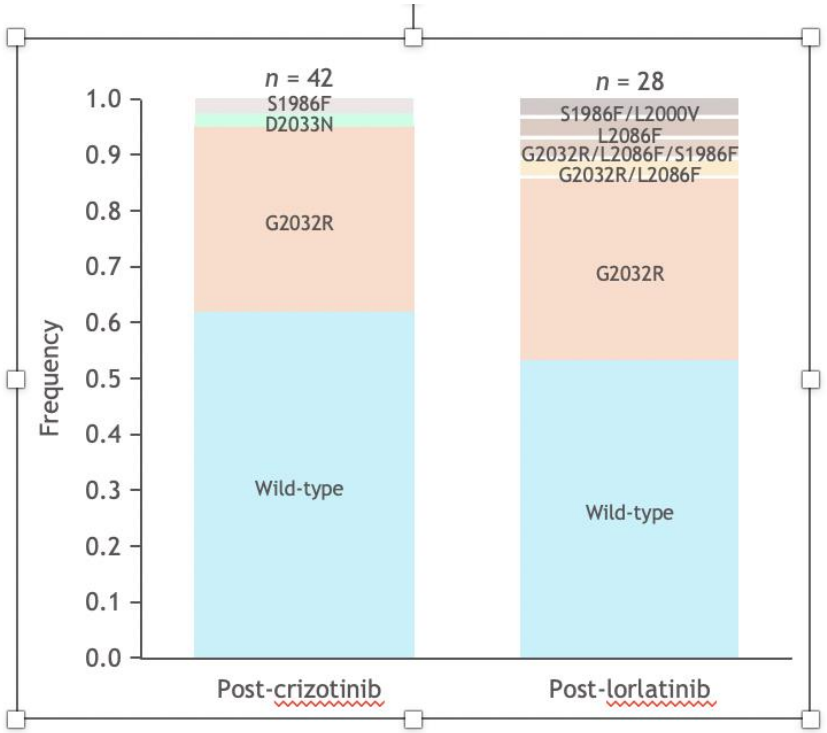
Molecular basis of resistance: ROS1 mutations

IC50 (nmol/L)	Crizotinib	Entrectinib	Lorlatinib	Repotrectinib	Cabozantinib	Ceritinib	Taletrectinib
Parental	840.5	1,801.0	>3,000	1,218.0	>3,000	1,117.0	>3,000
Nonmutant	5.4	2.7	0.7	2.0	2.8	16.4	2.6
G2032R	609.6	436.3	196.6	23.1	17.5	346.4	53.3
L2000V	37.1	25.9	2.5	10.1	7.6	124.9	29.8
L2086F	536.8	440.0	>3,000	587.9	3.6	226.9	1,265.0
S1986F/L2000V	159.4	36.1	2.4	7.2	5.1	86.9	20.3
S1986F/L2086F	469.7	344.2	>3,000	241.2	1.3	154.8	662.6
G2032R/L2086F	498.6	335.4	>3,000	248.9	5.0	573.9	744.2
S1986F/G2032R	594.4	718.5	990.6	65.1	70.1	614.7	105.4
S1986F/G2032R/L2086F	562.8	1,111.0	2,131.0	1,187.0	9.4	1,116.0	2,432.0

$IC_{50} \leq 50$ nmol/L

50 nmol/L < IC_{50} <200 nmol/L

$IC_{50} \geq 200$ nmol/L



G2032R most common resistance mutation

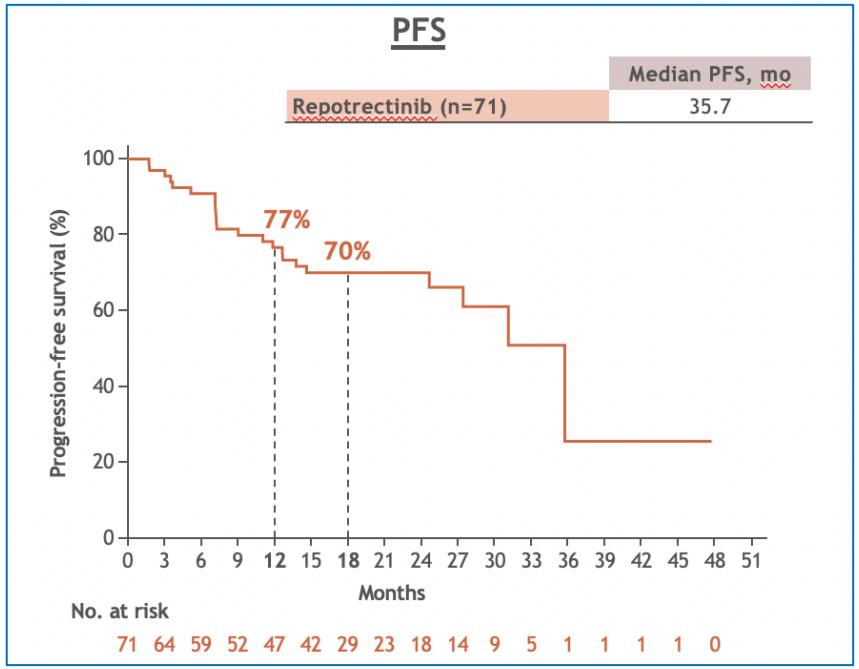
Next generation ROS1 TKIs developed against resistance mechanisms against crizotinib and entrectinib

> Off-target resistance mechanisms also described (MET amp., mutations in RAF/RAS/RAF pathway….)

Lin et al. Clin Cancer Res. 2021

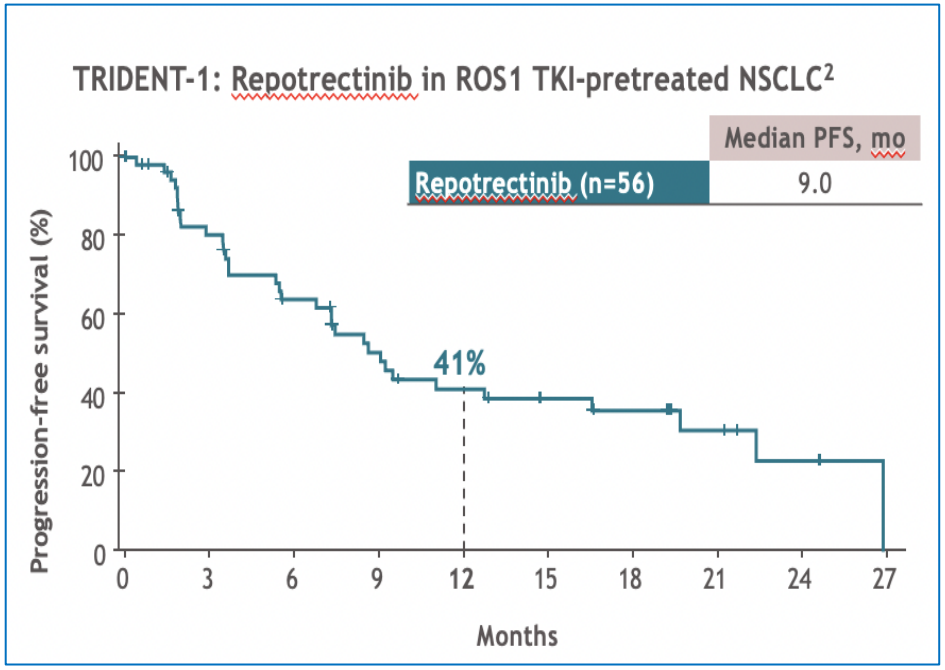
Repotrectinib in ROS1+ pts (Trident-1)

TKI-naive



ORR: **79%** (95% CI: 68-88)
mDOR: **34.1m** (95% CI: 25.6 - NE)
IC-RR: **89%**

1 prio ROS-TKI



ORR: **38%** (95% CI:25-52)
mDOR: **14.8m** (95% CI: 7.6 - NE)
IC-RR: **38%**

> Dramatic loss of efficacy if not used in 1L

Cho BC et al. Oral presentation at WCLC 2023.#OA03.06

Talectrinib in ROS1
(TRUST-I phase II)

ROS1 TKI-naïve NSCLC

	ROS1 TKI-naive NSCLC (n=67)
ORR, % (95% CI)†	92.5 (83.4-97.5)
Median DOR, months Range, months	NR 1.3-27.6
Median PFS, months Range, months	NR 0.0-29.0

Crizotinib-pretreated NSCLC

	Crizotinib-pretreated NSCLC (n=38)
ORR, % (95% CI)†	52.6 (35.8-69.0)
Median DOR, months Range, months	NR 1.4-22.2
Median PFS, months Range, months	9.8 0.0-23.5

FDA breakthrough designation

Li W et al. Oral presentation at ELCC 2023. Abstract 14MO.

NVL-520 in ROS1
(ARROS phase I)

Overall response outcomes	ROS1 TKI-pretreated NSCLC	
	≥2 prior ROS1 TKIs and ≥1 chemo (n=17)	Prior repotrectinib or lorlatinib* (n=18)
ORR, n (%)	9 (53)	9 (50)

IC-RR: 100%

ORR in G2032R: 78%

RP2D defined > phase II trial now open!

Drilon A et al. Oral presentation at EORTC-NCI-AACR (ENA) Symposium 2022. Abstract 8.

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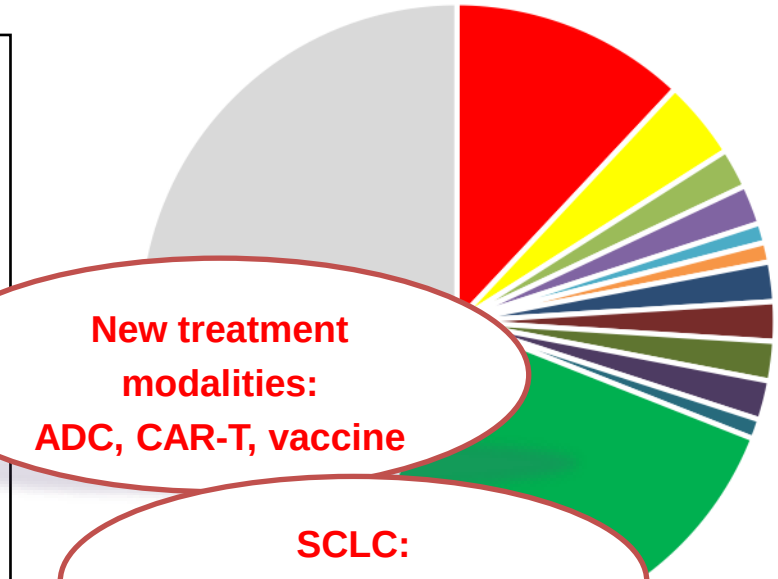

EGFR: new
combinations

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after failure of
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(KRAS: only G12C)

KRAS:
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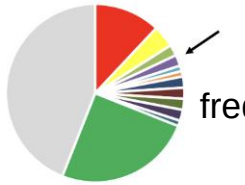
EGFR ex20 insertion mutations



frequency ca. 3%

Drug	Class	ORR	DOR	PFS	OS	Tox. (%al I/ 3,4)	Approval	
Amivantamab[1]	bispec. mab	40%	8.3	8.3	22.8	Rash (86/4) IRR (66/3) Diarrhoea (12/4)	2nd line	
Mobocertinib[2]	TKI	28%	17.5	7.3	n.r.	Diarrhoea (83/21) Nausea (43/4)	2nd line	**> to be withdrawn from market based on neg. phase III (Oct 3, 2023)**
Zipalertinib[3] CLN-081	TKI	38%	> 21m	10m	n.r.	Rash (83/0) Diarrhoea (36/0) Anemia (19/10)	FDA breakthrough designation	
Sunvozertinib[4]	TKI	39%	> 8m	12m (100 mg)	n.r.	Diarrhea (54/4) Rash 40/0) Anemia (28/4)	FDA Breakthrough designatin	**> CNS-activity**

EGFR ex20 drugs now move to 1L in combination with chemotherapy

[1]Park et al, JCO 2021; [2]Zhou et al, JAMA Onc 2021; [3]Yu et al, JCO 2022 #9007); [4]Yang et al, JCO 2021#9008), Piotrowska et al, JCO 2023

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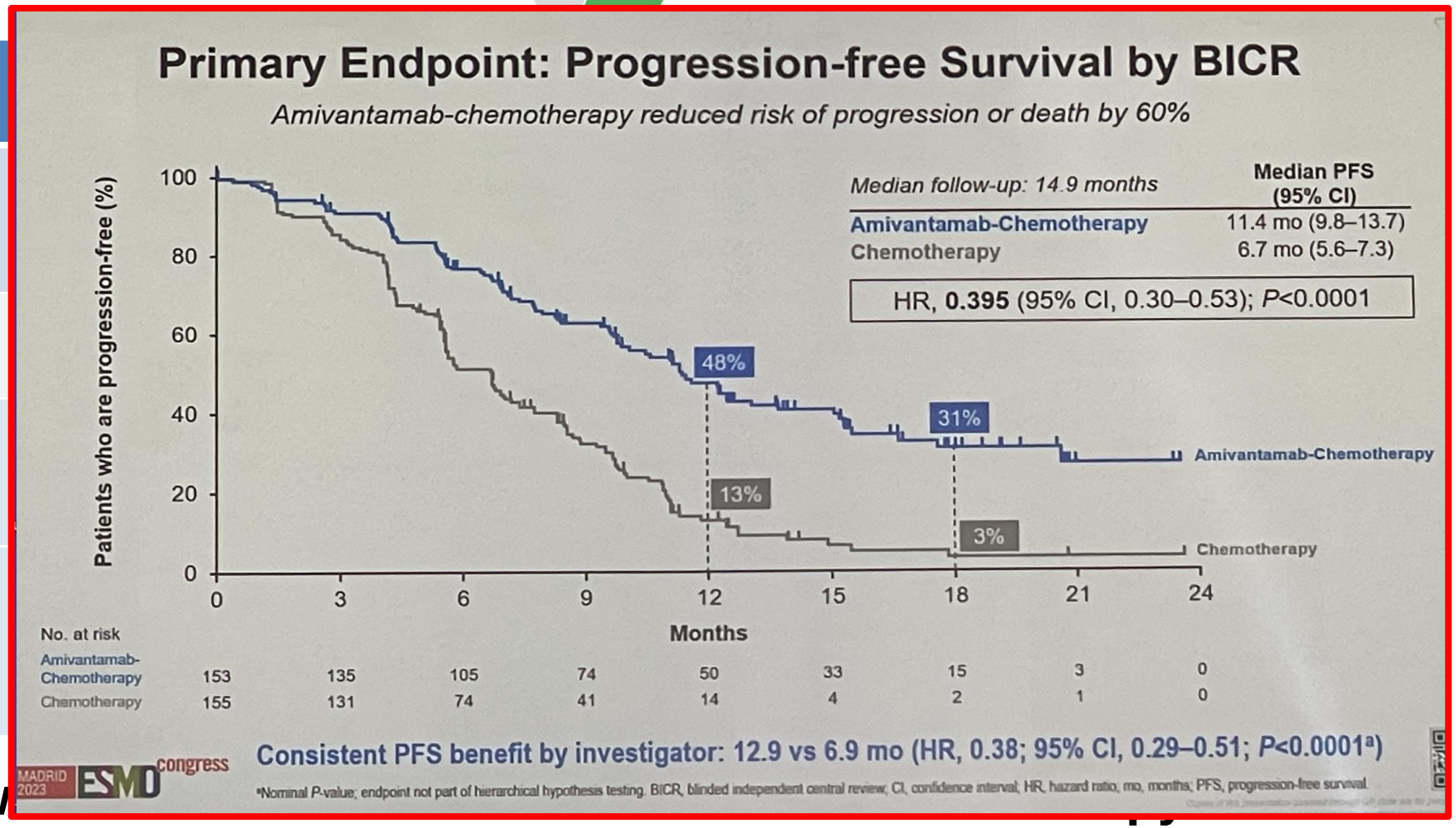


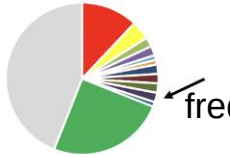
EGFR ex20 drugs now

> Papillon Trial, Presidential Symposium, N.Girard

[1]Park et al, JCO 2021; [2]Zhou et al, JAMA Onc 2021; [3]Yu et al, JCO 2022 #9007); [4]Yang et al, JCO 2021#9008), Piotrowska et al, JCO 2023

Jürgen

HER2 ex20 insertion mutations



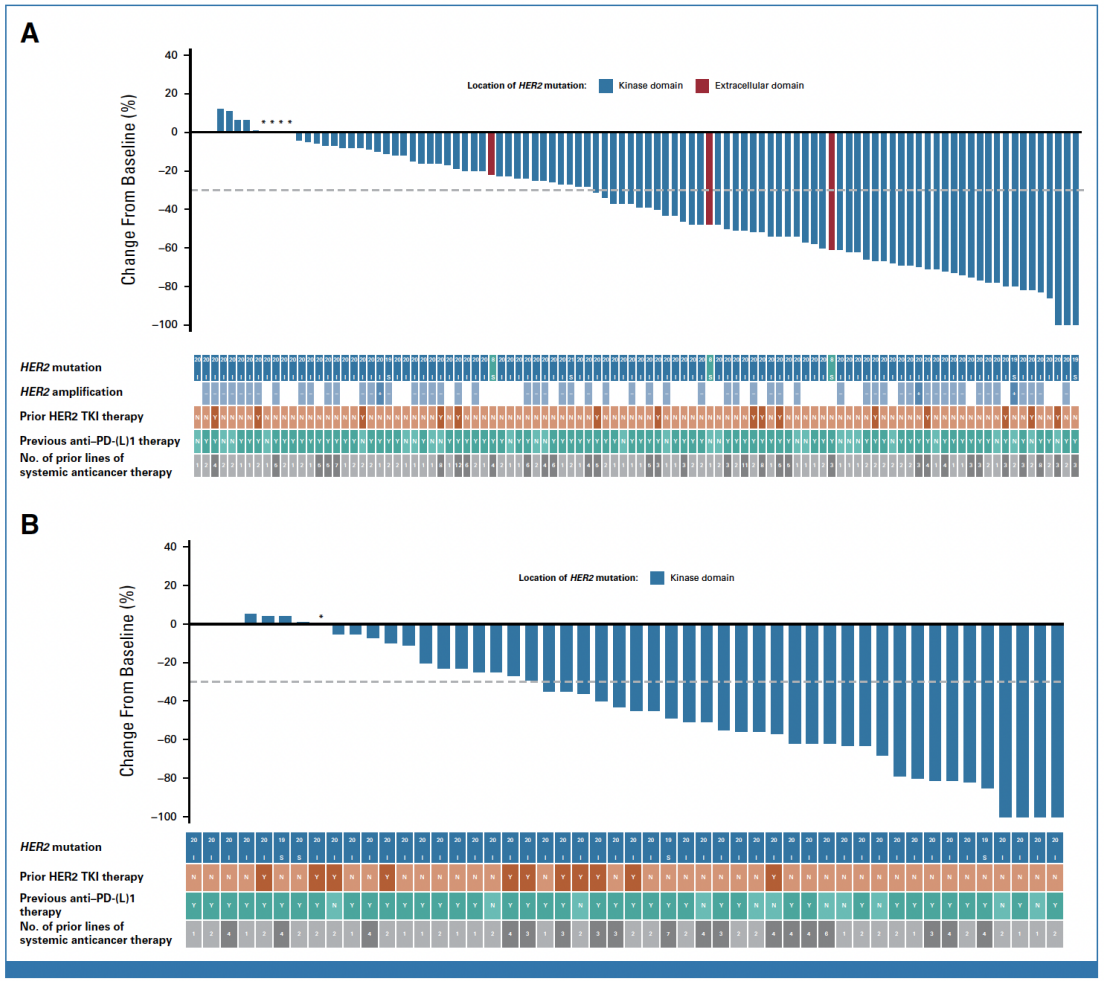
FDA approved 2nd line: trastuzumab-deruxtecan (ADC)

DESTINY-Lung01 phase I trial
ORR 55 %, PFS 8.2 m, OS 17.8 m

DESTINY-Lung02 phase II trial

T-DXd 5.4 mg/kg
ORR 49 %
mDOR: 16.8m
mOS: 19.5m
ILD all grade:13%

T-DXd 6.4 mg/kg
ORR 56 %
mDOR:NE
mOS: NE
ILD all grade: 28%



> DESTINY-Lung 04: 1L TDXd vs. IO/chemo

Li et al, NEJM 2022; Goto et al, JCO 2023

A selection of current developments

IO + IO/chemo
in early and
Intermediate stages

PD-L1 < 50% TCS:
> chemo / IO -
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PD-L1 independent
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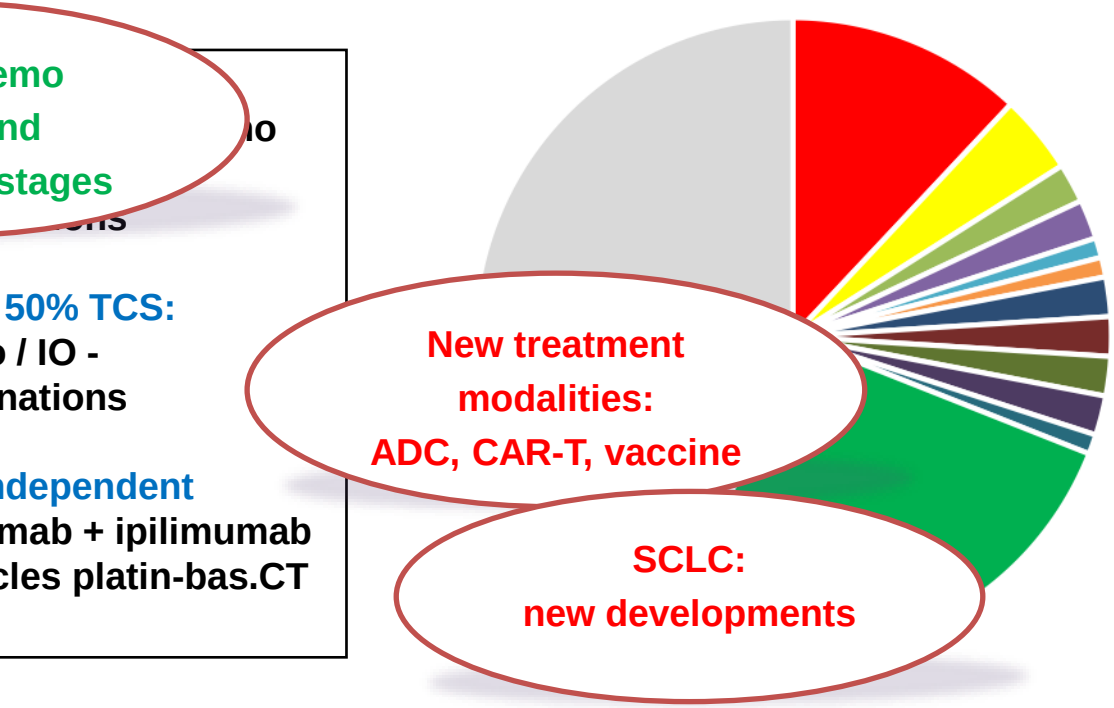

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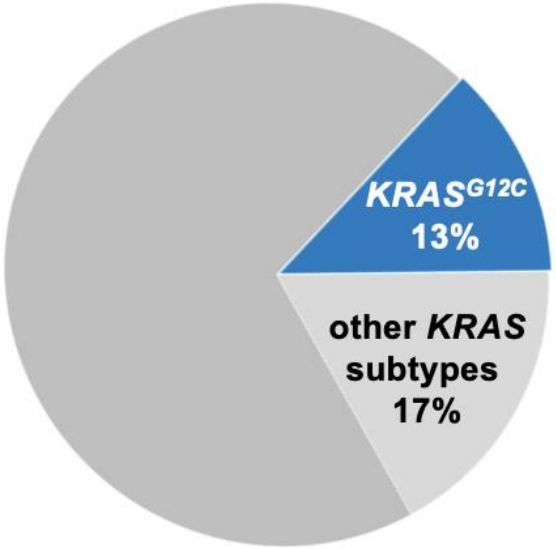
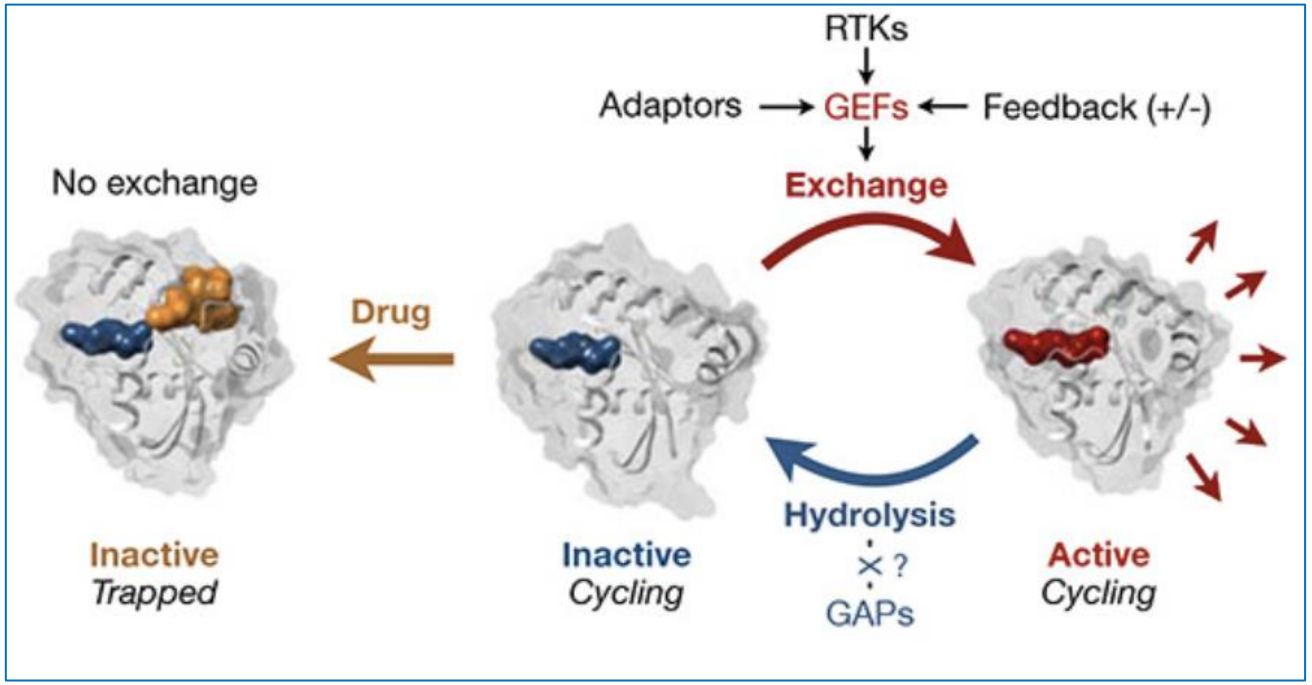




KRAS mutations:

- **ca. 30% of lung adenocarcinoma**
- **ca. 40% KRAS G12C**

1st generation of effective KRAS G12C inhibitors

- **covalent bond with C12**
- **trap KRAS in inactive state**

> KRAS genes code for GTPase molecules

Biology and mode of action of targeted drugs is different from RTK-directed therapies

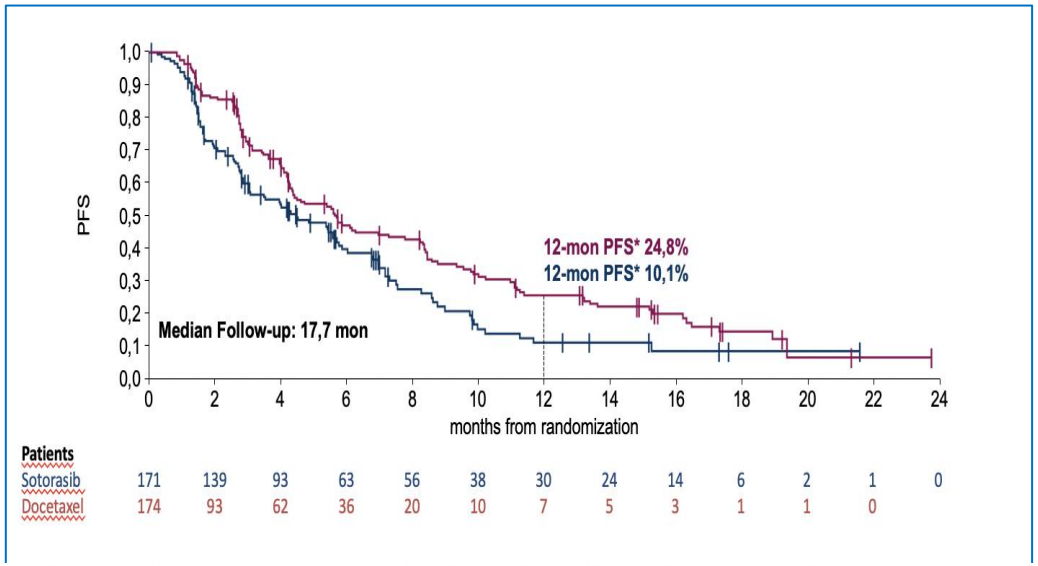
Scheffler et al, JTO 2018; Kim et al, Cell 2020

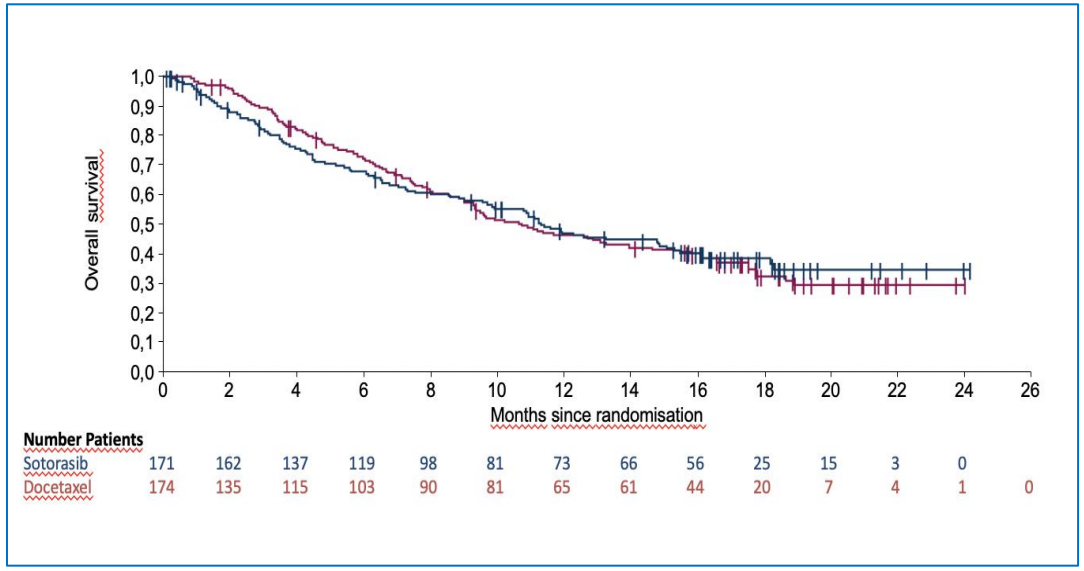
KRAS G12C

Sotorasib (1st in class) approved and standard 2L line

% (95% KI)	Sotorasib	Docetaxel
ORR	28,4 (21,5; 35,4)	13,2 (8,6; 19,2)
DCR	82,5 (75,9; 87,8)	60,3 (52,7; 67,7)

Codebreak 200 Phase III: sotorasib vs. docetaxel 2L





	Sotorasib 960 mg oral 1x daily (N=171)	Docetaxel 75 mg/m² IV Q3W (N=174)
HR (95% KI)**	0,66 (0,51; 0,86)	
P-value (1-seitig)***	P=0,002	
median PFS, (95% KI)****	5,6 (4,3; 7,8)	4,5 (3,0; 5,7)

	Sotorasib 960 mg oral 1x daily(N=171)	Docetaxel 75 mg/m² IV Q3W (N=174)
deaths, N (%)	109 (63,7)	94 (54,0)
HR (95% KI)†	1,01 (0,77; 1,33)	
P-value(1-side)‡	P=0,53	
Median OS, months (95% KI)§	10,6 (8,9; 14,0)	11,3 (9,0; 14,9)

> A scientific, but not a clinical breakthrough ?

Many KRAS G12C-inhibitors in clinical trials now in mono- or combination approaches

KRAS G12C inhibitor	Combination therapies under investigation	Trial phase	Study sponsor
Sotorasib	PD-1, PD-L1, SHP2, MEK, pan-ErbB, EGFR, mTOR, CDK4/6, chemotherapy	I/II/III	Amgen
Adagrasib	PD-L1, EGFR, pan-ErbB, SHP2	I/II/III	Mirati Therapeutics
JDQ443	PD-1, SHP2	I/II	Novartis
D-1553	Chemotherapy	I/II	InventisBio
GDC-6036	PD-1, VEGF, EGFR	I	Genentech
JNJ-74699157	NA	I	Janssen Pharmaceuticals
LY3499446	EGFR, CDK4/6	I/II	Eli Lilly and Company

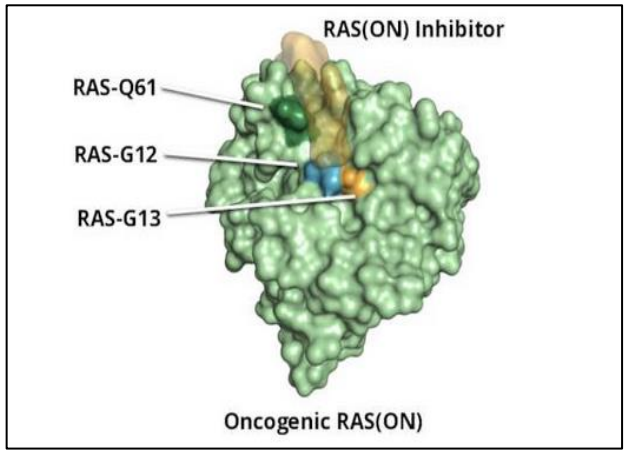
Drug	Sponsor	Properties	Status
New variant-specific agents			
ASP3082	Astellas	KRAS-G12D targeted degrader	Phase I
HRS-4642	Jiangsu Hengrui Medicine	KRAS-G12D inhibitor	Phase I in China
MRTX1133	Mirati	Non-covalent KRAS-G12D inhibitor	Phase I/II to start
RMC-9805	Revolution Medicines	KRAS-G12D molecular glue inhibitor[a]	IND-enabling
RMC-8839	Revolution Medicines	KRAS-G13C molecular glue inhibitor[a]	IND-enabling
BI-KRASG12D	Boehringer Ingelheim	Non-covalent KRAS-G12D inhibitor	Preclinical
JAB-22000	Jacobio	KRAS-G12D inhibitor	Preclinical
ERAS-4	Erasca	KRAS-G12D inhibitor	Preclinical
Pan-KRAS inhibitors			
RMC-6236	Revolution Medicines	RAS^{MULTI} molecular glue inhibitor[a]	Phase I
NA	Astellas	Pan-KRAS degrader	IND in 2023
NA	Boehringer Ingelheim	Pan-KRAS degrader	Preclinical
NA	Boehringer Ingelheim	Pan-KRAS inhibitor	Preclinical
New on-state inhibitors			
FMC-376	Frontier Medicines	KRAS-G12C inhibitor	IND-enabling
BBO-8520	BridgeBio	KRAS-G12C inhibitor	IND-enabling

> Which drug will make it to the 1L ?

> Which combination (IO essential) ?

Ostrem and Shokart, Ann Rev Cancerbio, 2022; Mullard, Nature Rev Drug Disc, 2023

KRAS(ON) inhibitors: the new kids on the block



RMC-6291: KRAS^{G12C}(ON), phase I, 63 pts.

- **23 NSCLC**
- **17 NSCLC activity analysis**
- **10 previously treated with KRAS^{G12C}i. 50% PR, 100% DCR**
- **7 not treated with KRAS$^{G12Ci.}$ 43% PR (not all confirmed)**
- **Safety: QTc prolongation grade 3 TRAE: 11%**

AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held October 11-15, 2023.; https://www.revmed.com/

A selection of current developments

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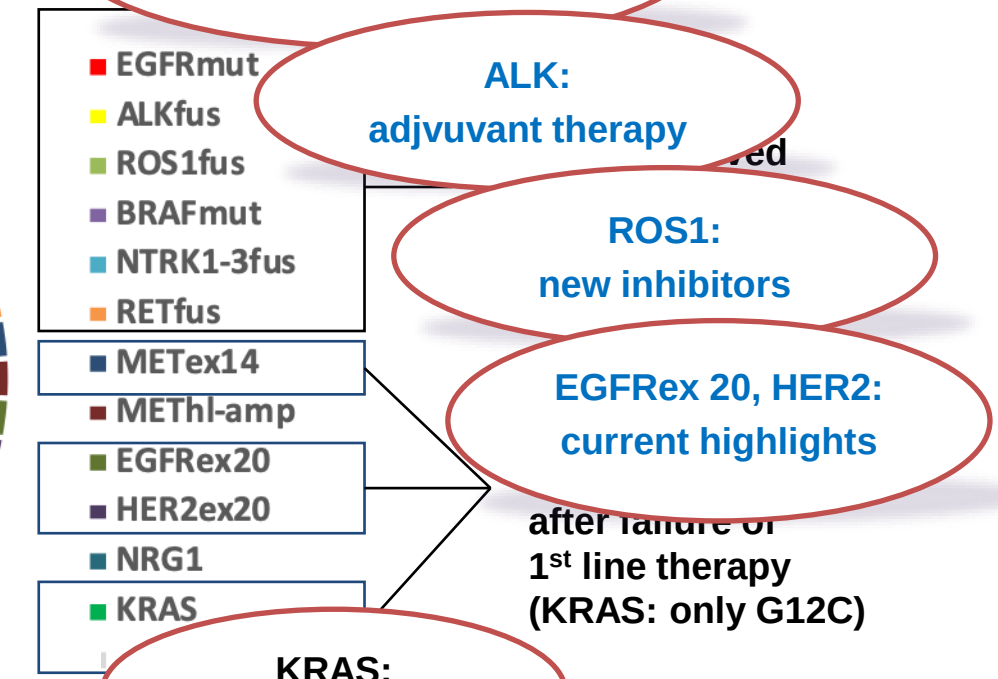

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Aktuelle EMA-Zulassungen zu systemischer neo-/adjuvanter Immuntherapie beim NSCLC

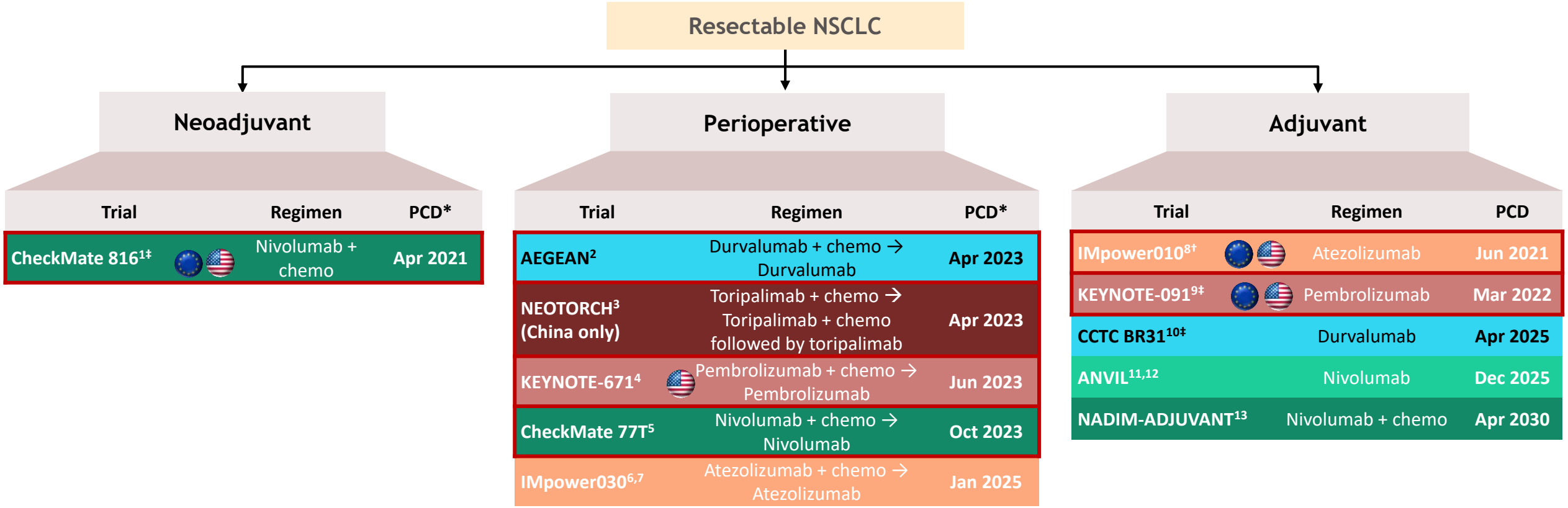
06/2023 Nivolumab + Chemotherapie **neoadjuvant** für NSCLC mit PD-L1 ≥ 1% (CheckMate-816)

04/2022 Atezolizumab **adjuvant** nach vorheriger Chemotherapie bei PD-L1 ≥ 50% (IMpower010)

10/2023 Pembrolizumab **adjuvant** nach vorheriger Chemotherapie unabhängig vom PD-L1 Status (KEYNOTE-091)

Alle Zulassungen für NSCLC Patienten mit einem hohen Rezidivdruck (ohne genaue Angabe des Stadiums >> Stadium IB - IIIA)

Ongoing Phase 3 trials with anti-PD-(L)1



*Or date of first data disclosure. †Refer to each country's local guidance for eligible patient population and specific therapeutic strategies. ‡Placebo-controlled adjuvant component.
PCD=primary completion date.

1. Forde PM et al. Oral presentation at AACR 2021. Abstract CT003. 2. Heymach JV et al. Oral presentation at AACR 2023. Abstract CT005. 3. Lu S et al. Oral presentation at ASCO Plenary April 2023. Abstract 425126. 4. Wakelee HA et al. Oral presentation at ASCO 2023. Abstract LBA100. 5. Cascone T et al. Oral presentation at ESMO 2023. Abstract LBA1. 6. Rizvi NA et al. Poster presentation at WCLC 2018. Abstract P2.17-27. 7. Clinicaltrials.gov. NCT03456063. Accessed September 27, 2023. 8. Wakelee HA. Oral presentation at ASCO 2021. Abstract 8500. 9. Paz-Ares L et al. Oral presentation at ESMO Plenary 2022. Abstract VP3-2022. 10. Clinicaltrials.gov. NCT02273375. Accessed September 27, 2023. 11. Chaft JE et al. Poster presentation at ASCO 2018. Abstract TPS8581. 12. Clinicaltrials.gov. NCT02595944. Accessed September 27, 2023. 13. Clinicaltrials.gov. NCT04564157. Accessed September 27, 2023.

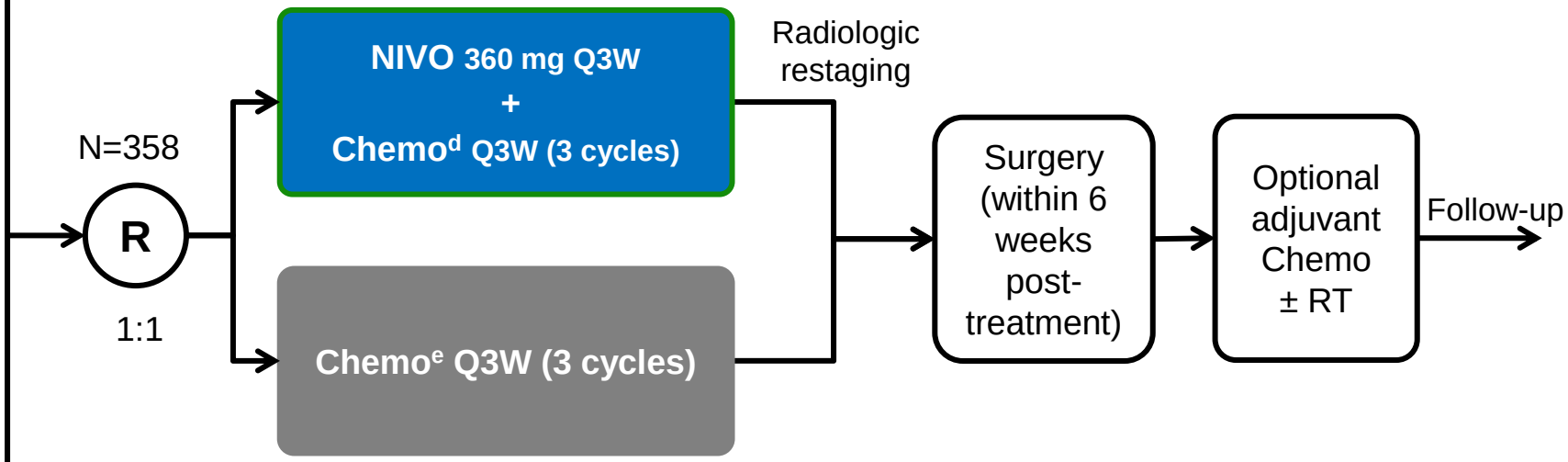
Tina Cascone & Jose Louis Campo Canaveral, BMS satellite symposium, ESMO 2023

CheckMate 816

CheckMate 816: Stage IB-IIIA
Neodjuvant nivolumab + chemotherapy vs. chemo

Key eligibility criteria
- Newly diagnosed, resectable, stage IB (≥4 cm)-IIIA NSCLC (per 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



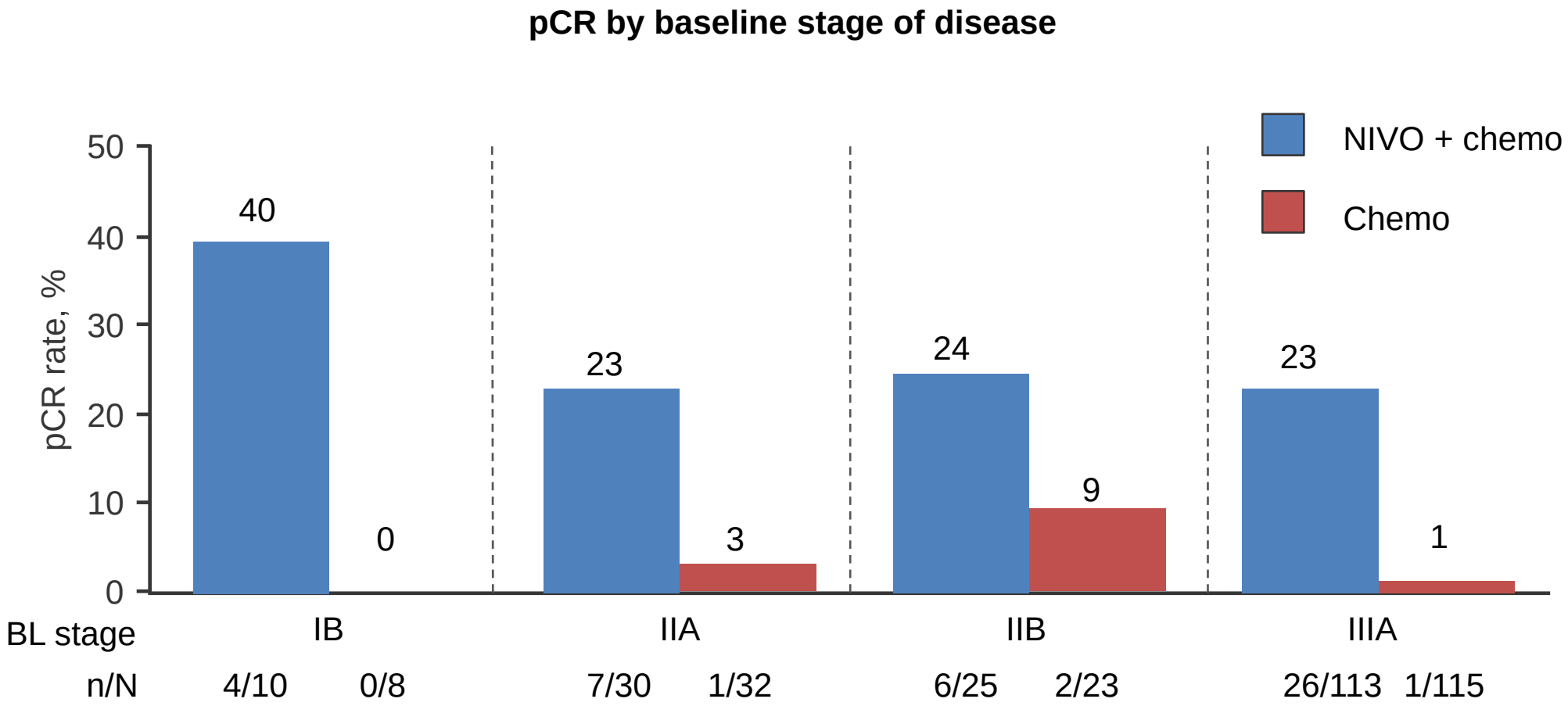
Primary endpoints
- pCR by BIPR
- EFS by BICR

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

Key exploratory endpoints included
- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

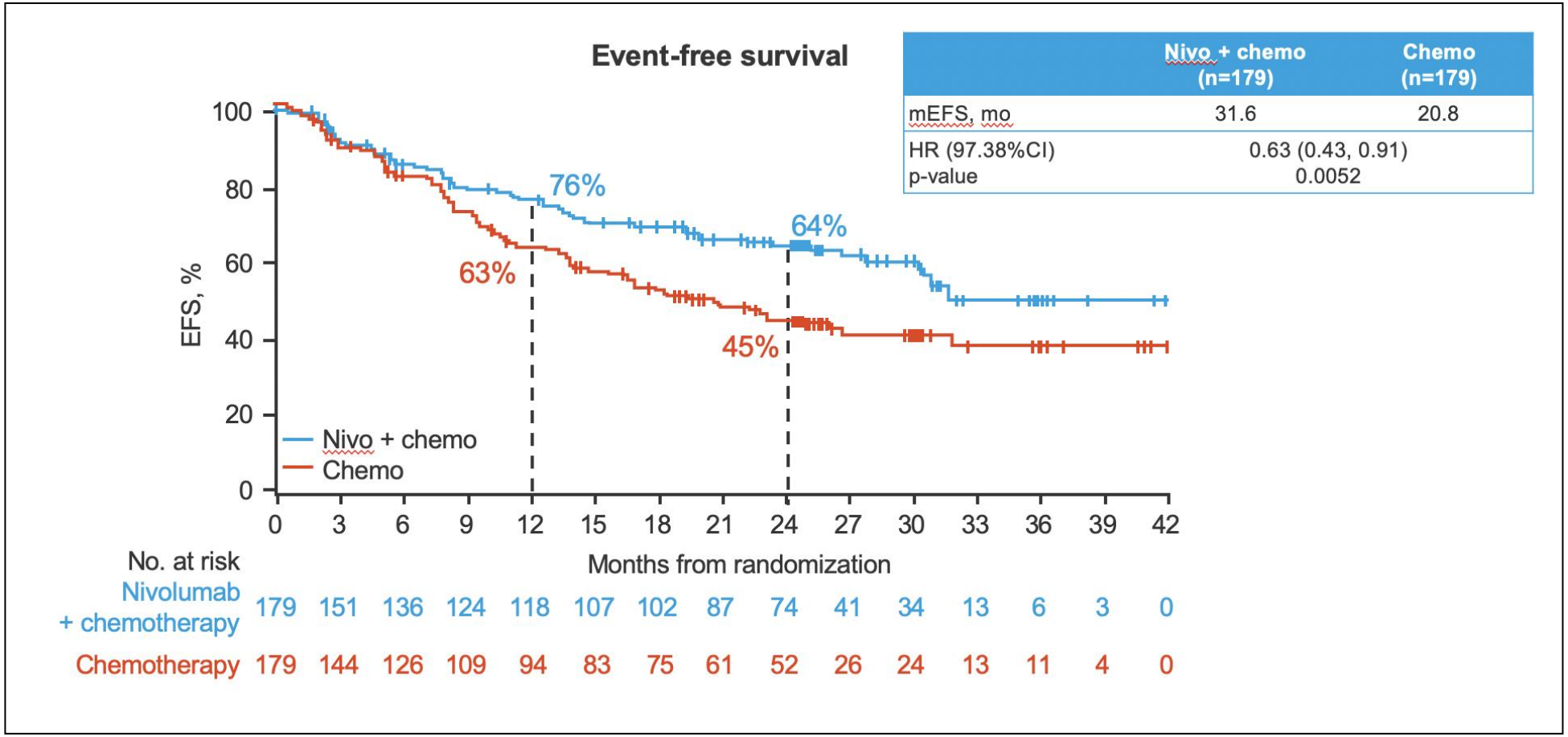
Spicer J et al. 2021 ASCO Annual Meeting, Oral Abstract Session – Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers, Abstract No. 8503

CheckMate 816: Pathological Complete Responses



Spicer J, et al. ASCO 2021 # 8503d

CheckMate 816: Event-free Survival



> deutlicher Vorteil für Nivo + chemo

Girard N, et al. AACR; 2022. Abstract nr CT012

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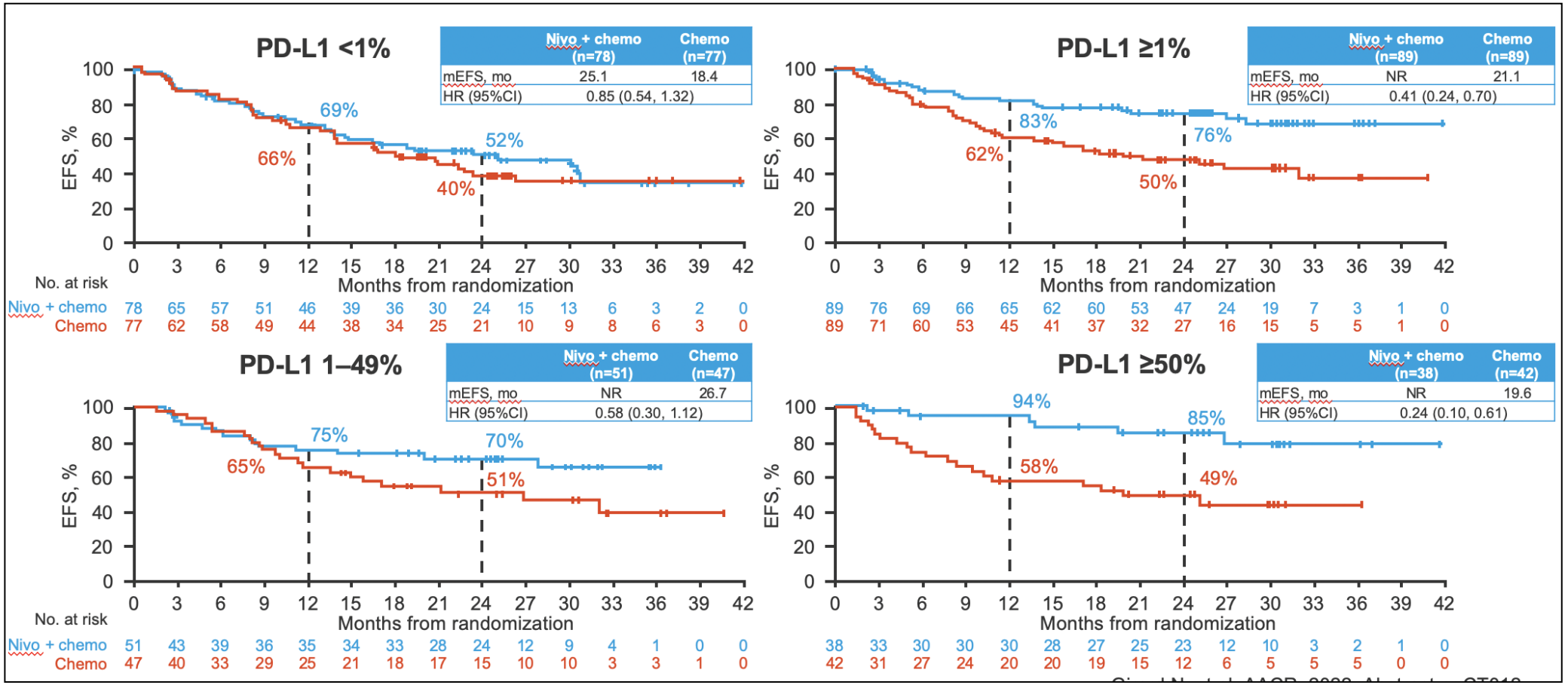


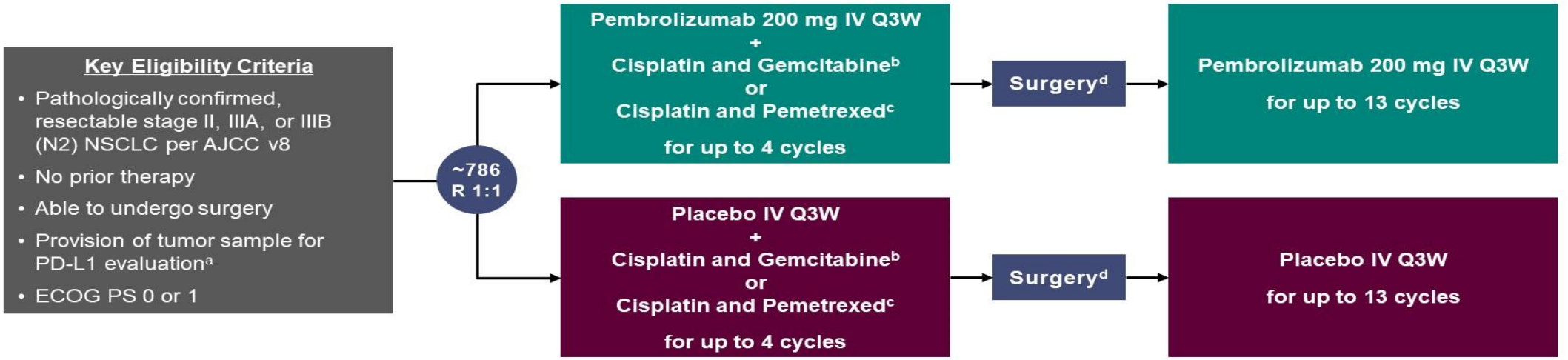
> Kombi nur in PD-L1 + signifikant überlegen

Girard N, et al. AACR; 2022. Abstract nr CT012

KEYNOTE-671

KEYNOTE-671 Perioperative ChT + Pembrolizumab vs. Neoadjuvante ChT

KEYNOTE-671 Study Design
Randomized, Double-Blind, Phase 3 Trial



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

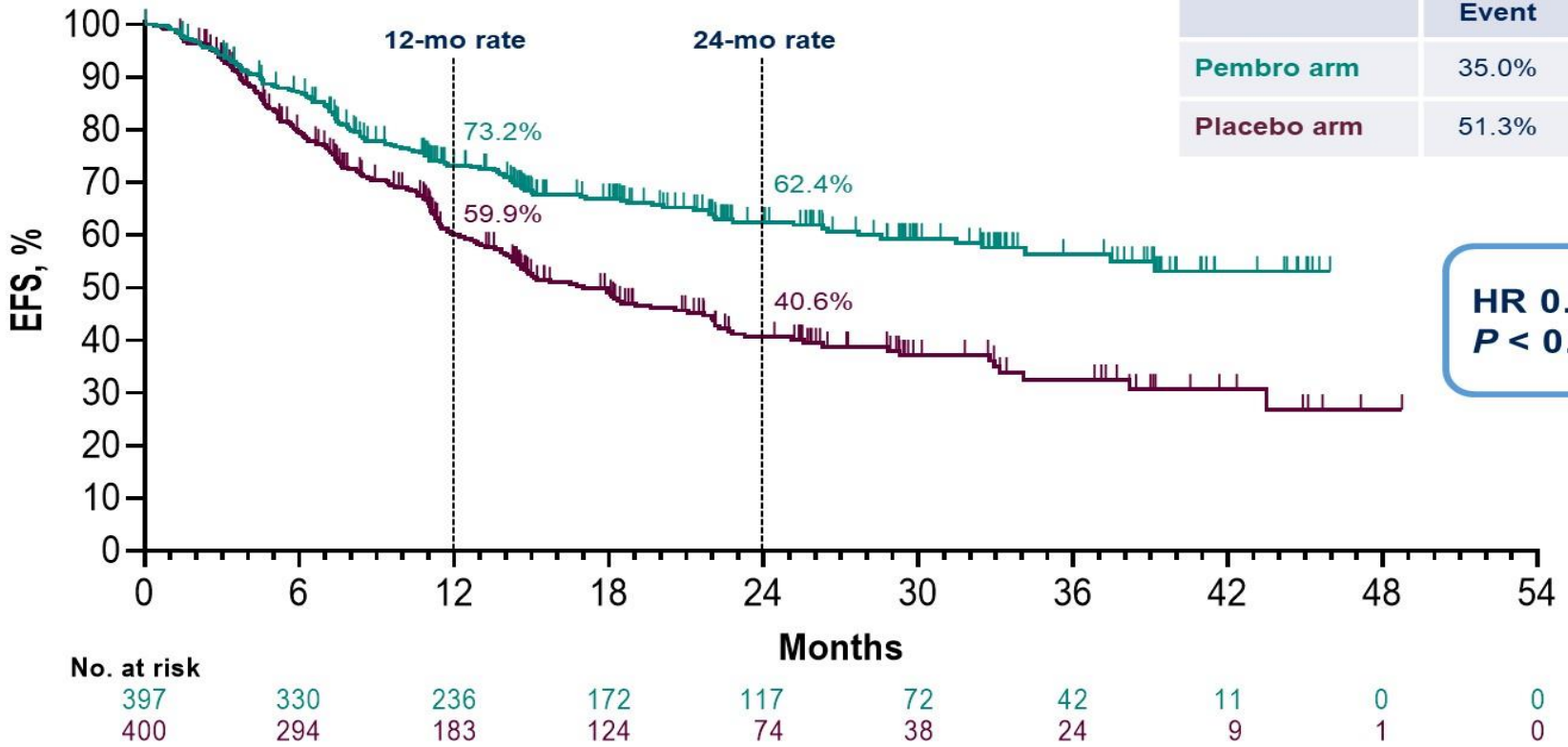
Key secondary end points: mPR and pCR per blinded, independent pathology review, and safety

[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.

Wakelee et al. ASCO 2023, NEJM 2023

KEYNOTE-671: Results

Event-Free Survival



	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)

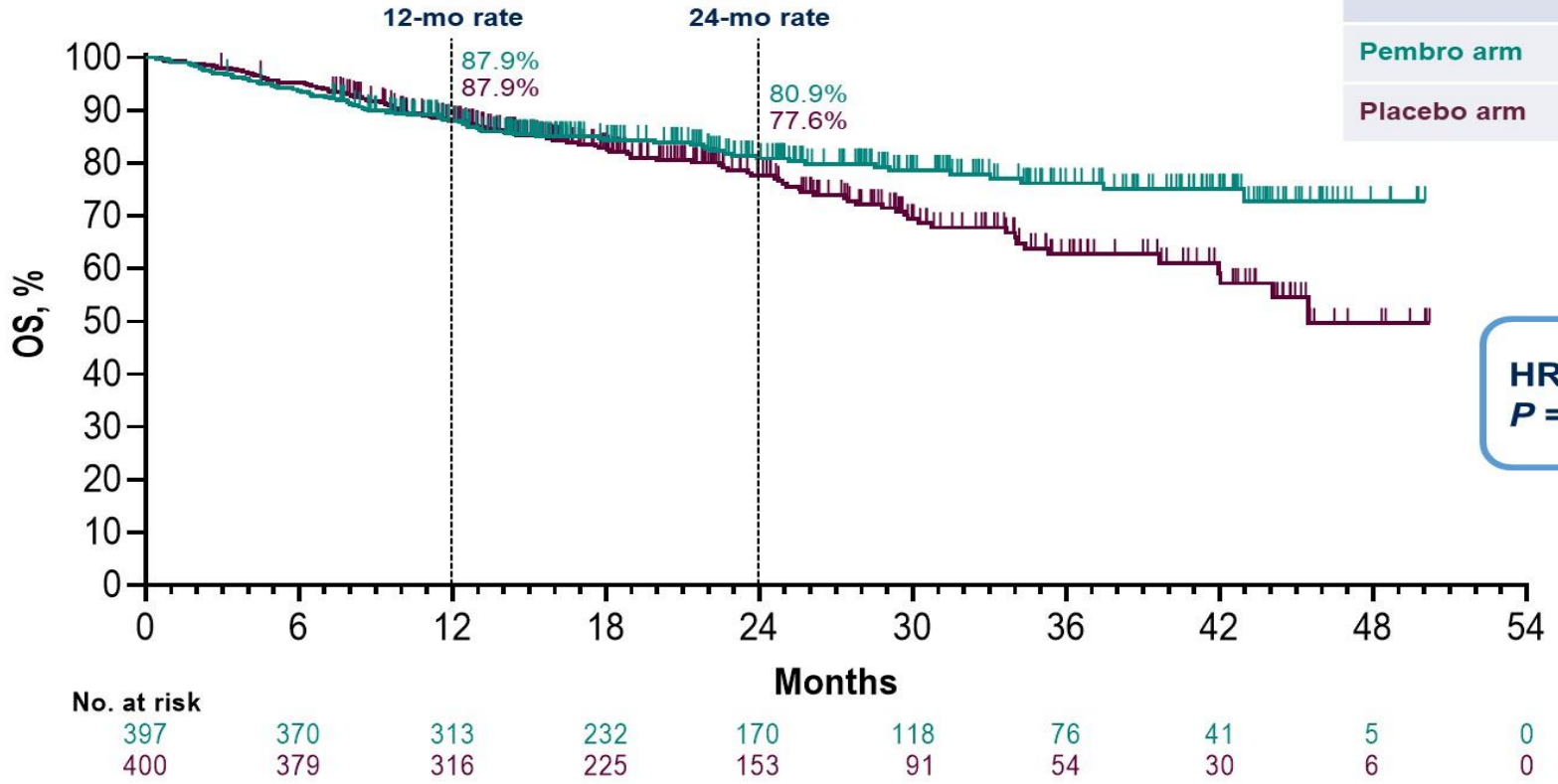
HR 0.58 (95% CI, 0.46-0.72)
***P* < 0.00001**

EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Wakelee et al. ASCO 2023, NEJM 2023

KEYNOTE-671: Results

Overall Survival



	Pts w/ Event	Median (95% CI), mo
Pembro arm	19.1%	NR (NR-NR)
Placebo arm	25.3%	45.5 (42.0-NR)

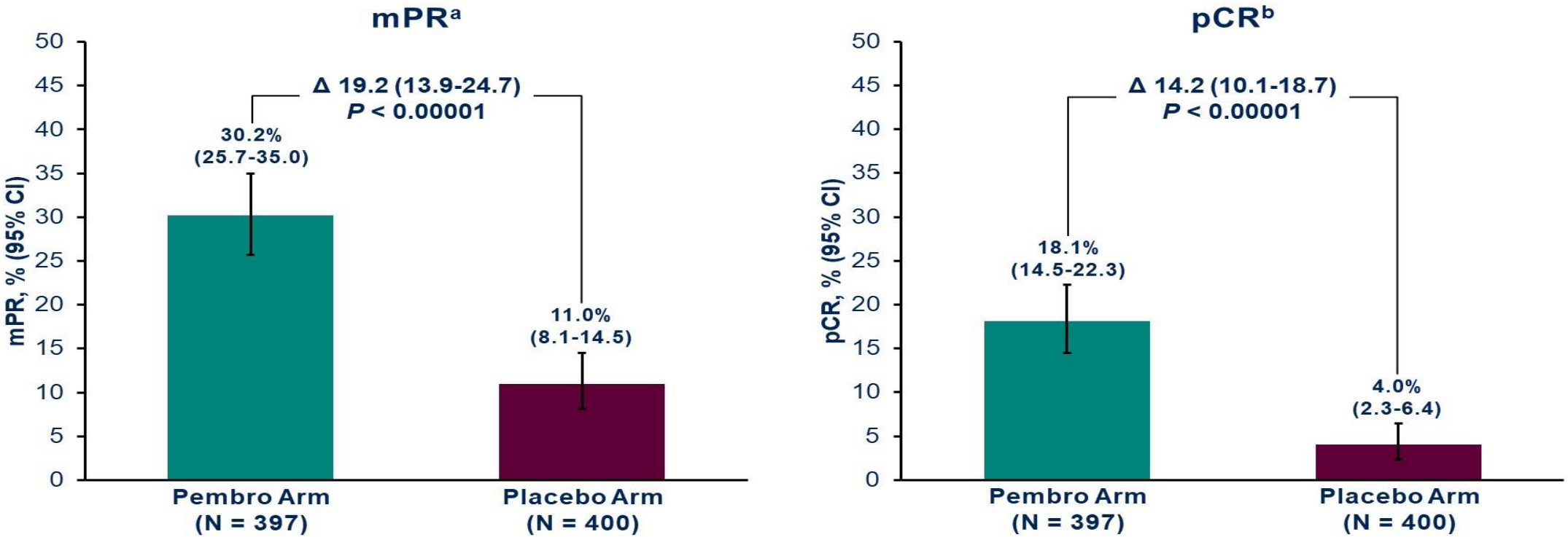
HR 0.73 (95% CI, 0.54-0.99)
***P* = 0.02124[a]**

OS defined as time from randomization to death from any cause. [a] Significance boundary not met at IA1; OS will continue to be tested according to the analysis plan. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Wakelee et al. ASCO 2023, NEJM 2023

KEYNOTE-671

Pathological Response
Assessed per Blinded, Independent Pathologist Review



[a] Per IASLC criteria, defined as ≤10% viable tumor cells in resected primary tumor and lymph nodes. [b] Per IASLC criteria, defined as absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0). Data cutoff date for IA1: July 29, 2022.

Vitale Tumorzellen:

pCR 0%, major pathologic response (MPR) < 10%, pathologic response 11-50%, 51-100% no pathologic response

Immuntherapie in frühen und intermediären Stadien des NSCLC:
aktueller Stand der Diskussion

- Überzeugende Daten der perioperativen Chemoimmuntherapie
  aber: ca. 20% erreichen die Operation nicht!

- Anhand des aktuellen Zulassungsstatus ist eine perioperative Chemoimmuntherapie
  mit Wechsel des ICI (Nivo > Pembro) möglich

- Überzeugende neoadjuvante Daten vor allem für Stadium IIIA

- Fehlende randomisierte Daten (Neoadjuvanz vs. keine Neoadjuvanz)

- Empfehlungen bleiben Bestandteil interdisziplinärer Diskussionen in Tumorboards

- Verzögerung oder Beeinträchtigung einer Resektion durch eine Immuntherapie wurde bis jetzt
  nicht nachgewiesen

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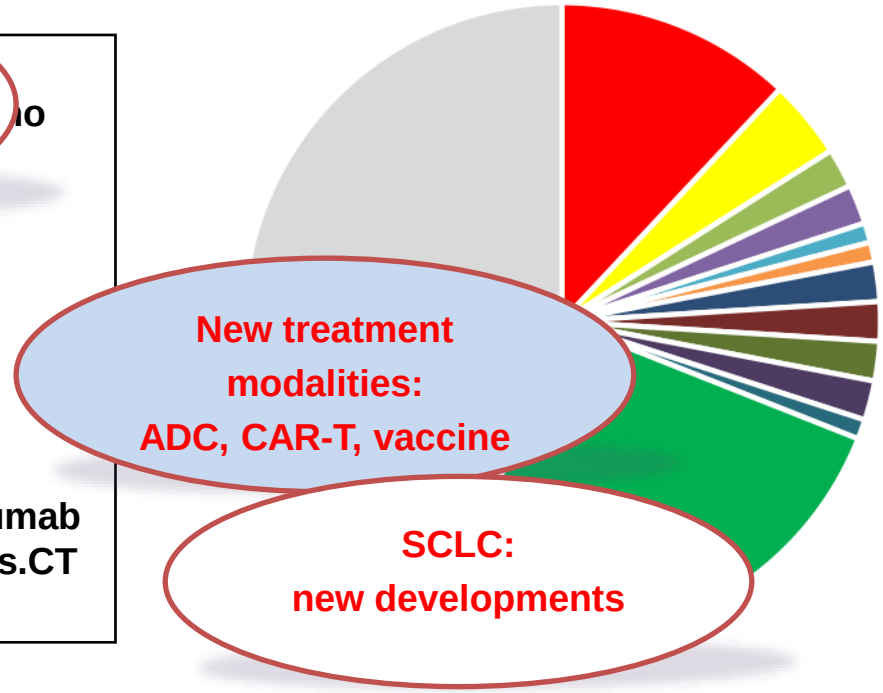

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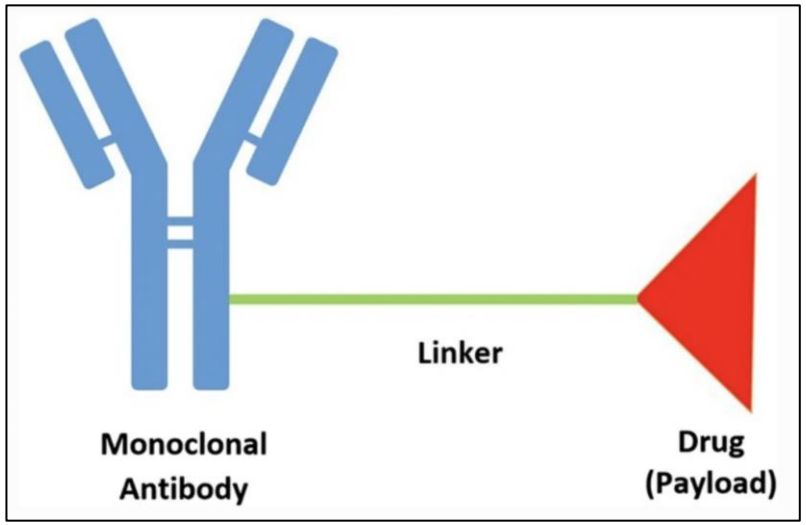
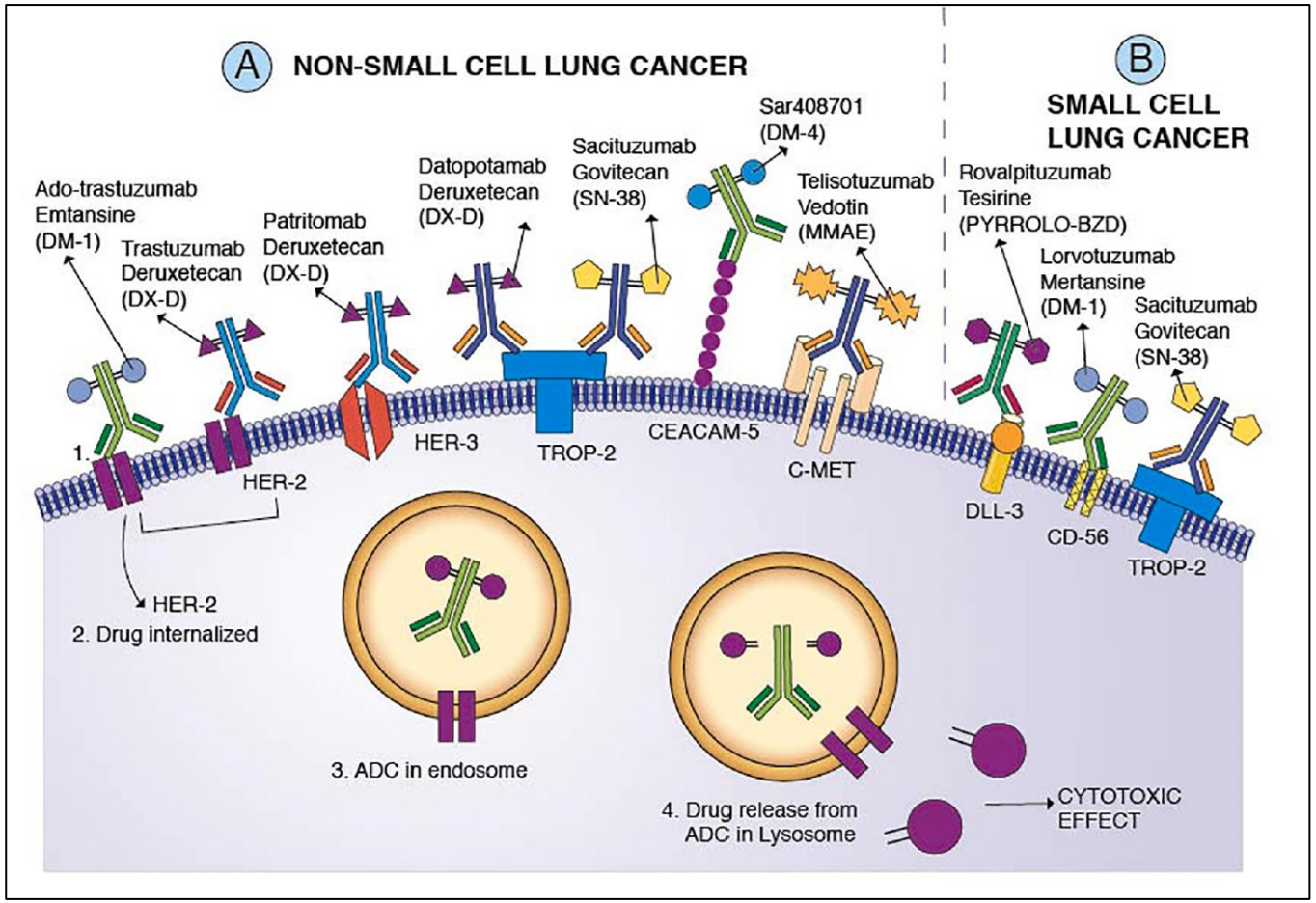
Antibody-Drug Conjugates, ADCs)
> targeted chemotherapy



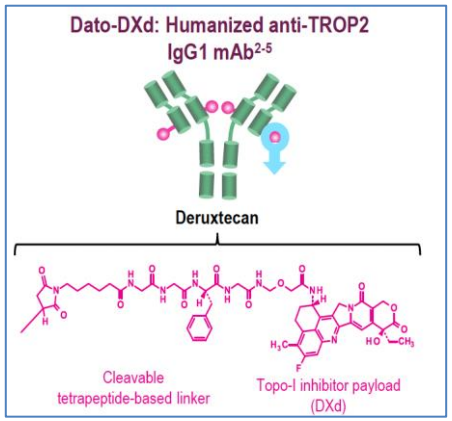


Lievano et al., Drug Saf 2021

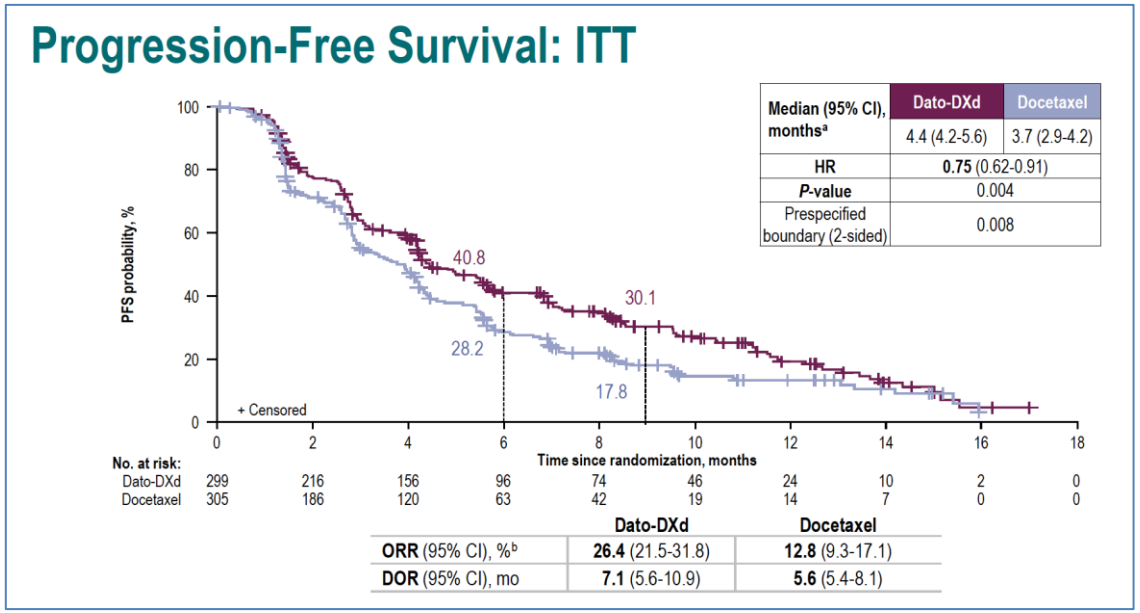
Desai et al, Lung Cancer 2022

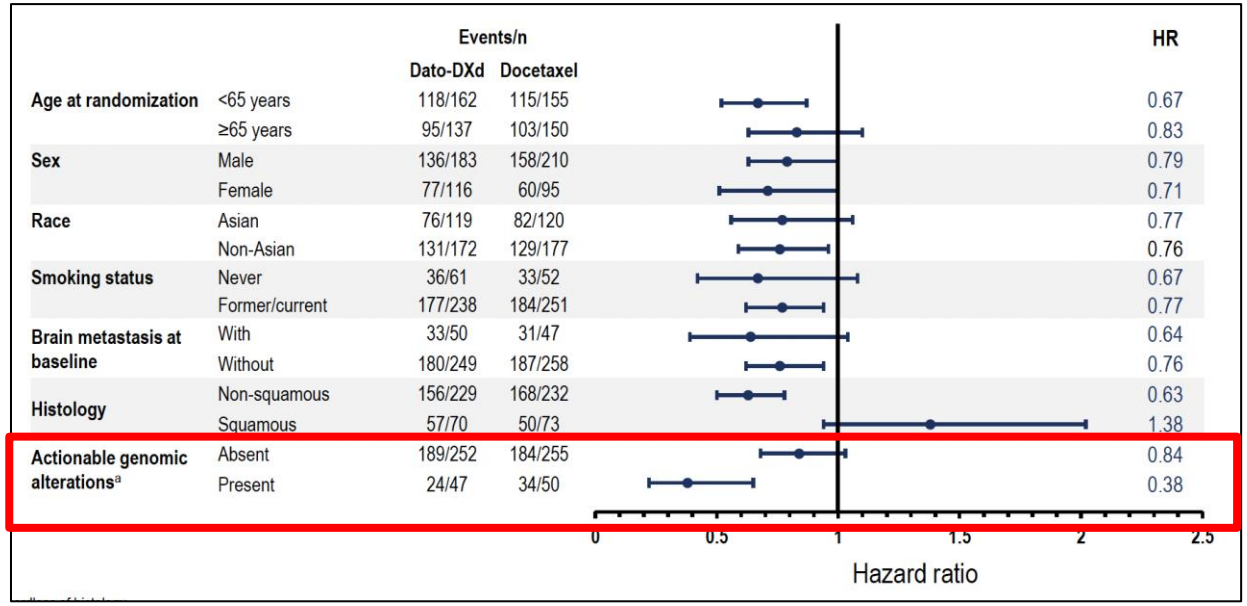
Datopotamab-deruxtecan (Dato-Dxd)

Target molecule on tumor: Trop 2



Tropion-LUNG 01 phase III vs. Docetaxel





> Dato-Dxd more effective compared to chemotherapy in pretreated patients

> Patients with driver mutations (EGFRmut) have pronounced benefit

> Current strategies: combinations

Ahn et al., ESMO 2023

ADC development in lung cancer

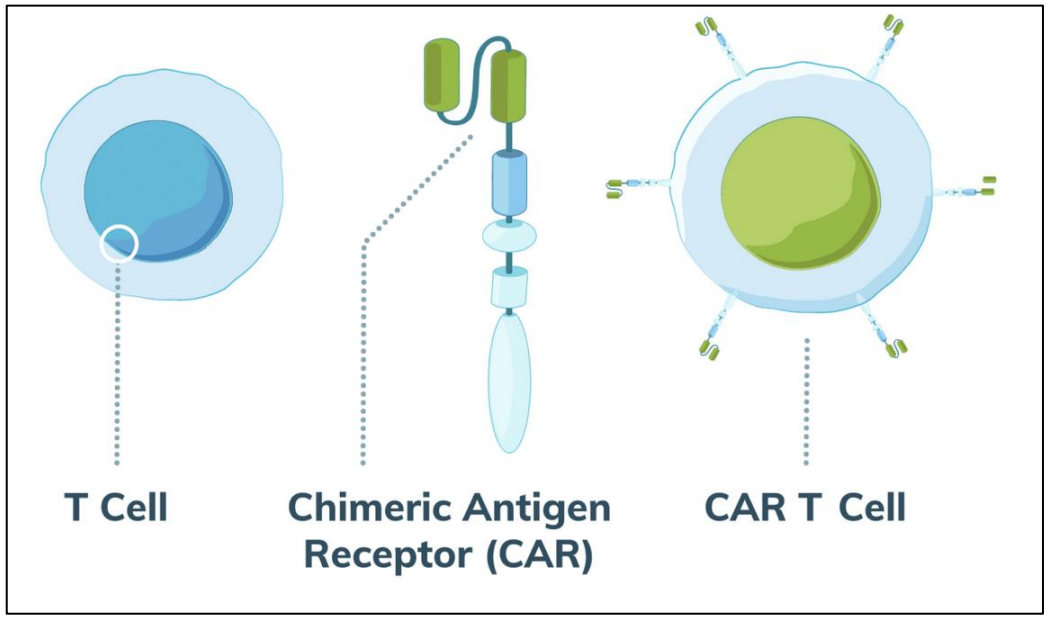
Driver mutation-specific

Driver-mutation independent

Target	Drug	Payload	Linker	RP2D and Schedule	DAR
HER2	Trastuzumab-DM1	DM1	Noncleavable (thioether)	3.6 mg/kg, once every 3 weeks	3.1
	Trastuzumab-DXd	Deruxtecan	Cleavable (tetrapeptide)	6.4 mg/kg, once every 3 weeks	8
HER3	Patritumab-DXd	Deruxtecan	Cleavable (tetrapeptide)	5.6 mg/kg, once every 3 weeks	8
TROP2	Datopotamab-DXd	Deruxtecan	Cleavable (tetrapeptide)	6 mg/kg, once every 3 weeks	4
	Sacituzumab govitecan	SN-38	Cleavable (carbonate)	10 mg/kg on day 1 and 8, once every 3 weeks	7.6
CEACAM5	Tusamitamab ravtansine	DM4	Cleavable (SPDB)	100 mg/m^2, once every 2 weeks	3.8
c-MET	Telisotuzumab vedotin	MMAE	Cleavable (valine-citrulline)	2.7 mg/kg, once every 3 weeks	3.1
B7-H3	I-DXd (DS-7300a)	Deruxtecan	Cleavable (tetrapeptide)	TBD	4
	MGC018	DUBA	Cleavable (valine-citrulline)	TBD	2.7
CD56	Lorvotuzumab mertamsine	DM1	Cleavable (disulfide)		—
AXL	Enapotamab vedotin	MMAE	Cleavable (protease)	2.2 mg/kg, once every 3 weeks	—
	Mecbotamab vedotin	MMAE	Cleavable (valine-citrulline)	TBD	—
PK7	Cofetuzumab pelidotin	Auristatin-0101	Cleavable (valine-citrulline)	TBD	4
PVRL4	Enfortumab vedotin	MMAE	Cleavable (valine-citrulline)	TBD	4
TF	Tisotumab-vedotin	MMAE	Cleavable (valine-citrulline)	TBD	4
EGFR	MRG003	MMAE	Cleavable (valine-citrulline)	2.0 mg/kg, once every 3 weeks	4
ROR2	Ozuriftamab vedotin	MMAE	Cleavable (valine-citrulline)	TBD	4
NaPi2b	Upifitamab rilsodotin	AF-HPA	Cleavable (protease)	TBD	12-15
	Lifastuzumab vedotin	MMAE	Cleavable (valine-citrulline)	TBD	3-4

Passaro et al., JCO 2023

CAR-T cells in lung cancer



> many early trials in lung cancer

> include driver-specific constructs

TABLE 1 Targeting antigens of lung cancer for CAR-T cell therapy registered in ClinicalTrials.gov

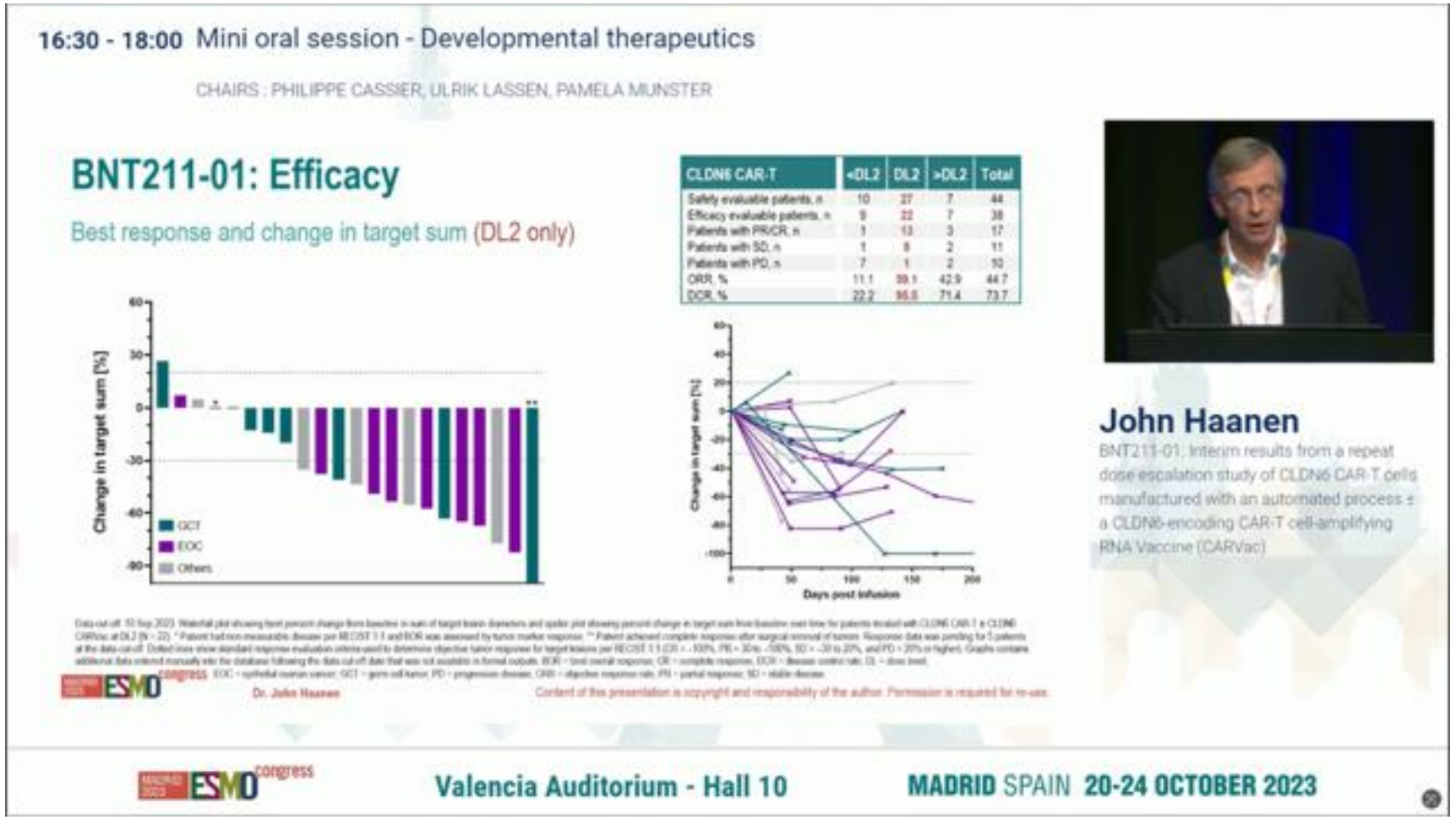
Targeted antigen	Estimated enrollment	Phase	Age (y)	Status	First posted	Sponsor	ClinicalTrial ID
CEA	40	I/II	18–75	Recruiting	Apr 16, 2020	Chongqing Precision Biotech, China	NCT04348643
CEA	75	I	18–80	Unknown	Jan 29, 2015	Southwest Hospital, China	NCT02349724
CD276	24	Early I	1–70	Not yet recruiting	Apr 29, 2021	PersonGen BioTherapeutics (Suzhou), China	NCT04864821
EGFR	11	I	18–75	Recruiting	Nov 6, 2019	Sun Yat-sen University, China	NCT05060796
EGFR	11	Early I	18–75	Recruiting	Sep 29, 2021	Second Affiliated Hospital of Guangzhou Medical University, China	NCT05060796
HER2	45	I	≥18	Recruiting	Nov 14, 2018	Baylor College of Medicine, USA	NCT03740256
HER2	18	I	≥18	Recruiting	Dec 9, 2020	Carisma Therapeutics, USA	NCT04660929
HER2	10	I/II	18–80	Unknown	Sep 5, 2013	Chinese PLA General Hospital, China	NCT01935843
MSLN	15	I/II	18–70	Terminated	Apr 24, 2012	National Cancer Institute, USA	NCT01583686
MSLN	27	I	≥18	Recruiting	Feb 15, 2017	University of Pennsylvania, USA	NCT03054298
MUC1	20	I/II	18–70	Unknown	Oct 27, 2015	PersonGen BioTherapeutics (Suzhou), China	NCT02587689
MUC1	60	I/II	18–70	Recruiting	May 16, 2018	First Affiliated Hospital of Guangdong Pharmaceutical University, China	NCT03525782
PD-L1	20	I/II	18–65	Unknown	Aug 10, 2016	Shanghai International Medical Center, China	NCT02862028
ROR1	60	I	≥18	Recruiting	Mar 11, 2016	Fred Hutchinson Cancer Research Center, USA	NCT02706392
TnMUC1	112	I	≥18	Recruiting	Jul 18, 2019	Tmunity Therapeutics, USA	NCT04025216
PD-L1 and CD80/CD86	10	Early I	≥18	Unknown	Feb 23, 2017	Second Xiangya Hospital of Central South University, China	NCT03060343
GPC3 or TGFβ	30	I	18–75	Recruiting	Jun 26, 2017	Second Affiliated Hospital of Guangzhou Medical University, China	NCT03198546
αPD1 and MSLN	10	Early I	18–70	Recruiting	Jul 28, 2020	Wuhan Union Hospital, China	NCT04489862
NY-ESO-1 or EGFR V III	73	I/II	4–70	Recruiting	Aug 20, 2018	Shenzhen BinDeBio, China	NCT03638206
MAGE-A1, MAGE-A4, MucI, GD2, and MSLN	20	I/II	18–80	Recruiting	Nov 29, 2017	Shenzhen Geno-Immune Medical Institute, China	NCT03356808
HER2, MSLN, PSCA, MUC1, GPC3, Lewis-Y, AXL, EGFR, or B7-H3	30	I	18–75	Recruiting	June 23, 2017	The Second Affiliated Hospital of Guangzhou Medical University, China	NCT03198052
HER2, MSLN, PSCA, MUC1, Lewis-Y, GPC3, AXL, EGFR, Claudin18.2/6, ROR1, GD1, or B7-H3	40	I	18–85	Recruiting	Apr 13, 2021	Second Affiliated Hospital of Guangzhou Medical University, China	NCT04842812

https://www.mesothelioma.com/treatment/immunotherapy/car-t-cell-therapy/

Chen et al, Thoracic Cancer 2022

Combination CAR-T cells and RNA vaccine

BioNTech Phase I/IIa, Zielstruktur auf den Tumorzellen: Claudin 6



> Mixed solid tumors: ORR 59%

A selection of current developments

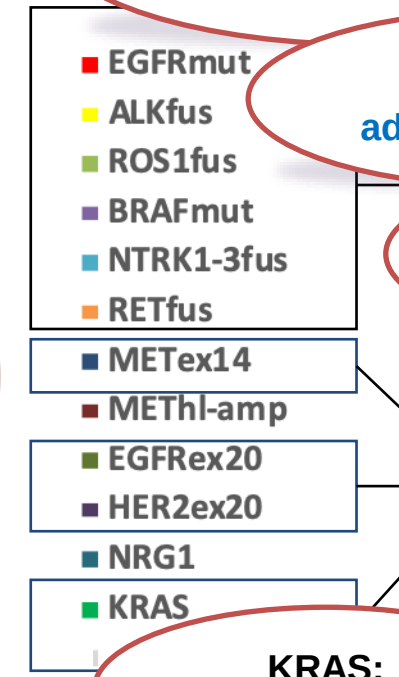
IO + IO/chemo
in early and
Intermediate stages

PD-L1 < 50% TCS:
> chemo / IO -
combinations

PD-L1 independent
> nivolumab + ipilimumab
+ 2 cycles platin-bas.CT

New treatmant
modalities:
adc, CAR-T, vaccine

SCLC:
new developments



EGFR: new
combinations

ALK:
adjvuvant therapy

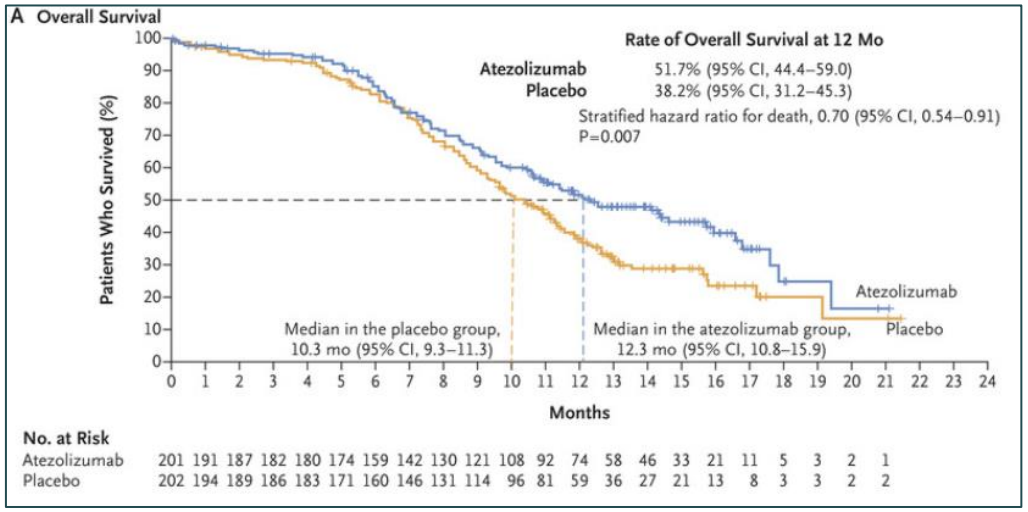
ROS1:
new inhibitors

EGFRex 20, HER2:
current highlights

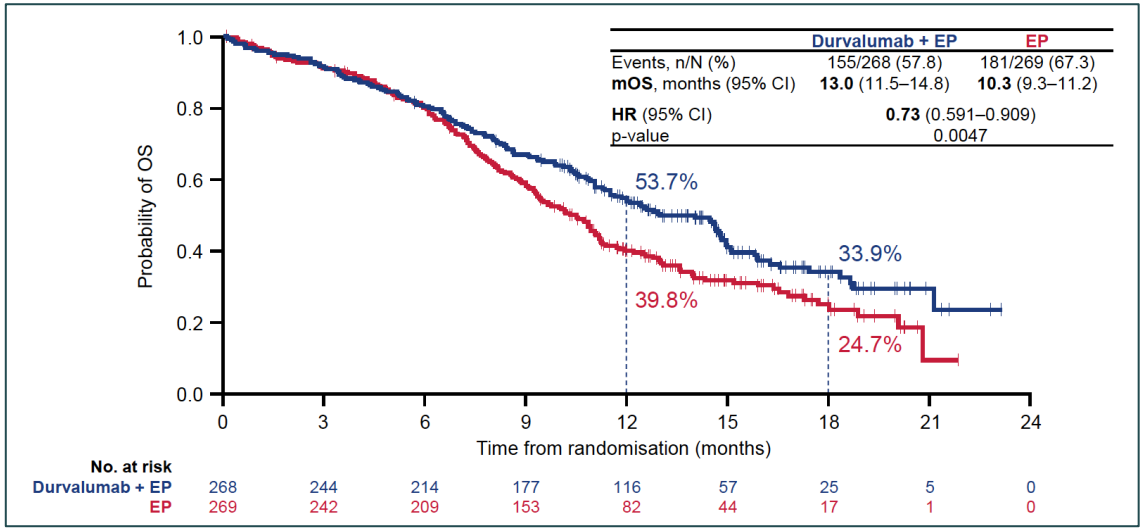
after failure of
1st line therapy
(KRAS: only G12C)

KRAS:
new inhibitors

Only one innovation in systemic therapy of SCLC for decades: Introduction of immune-checkpoint inhibitors



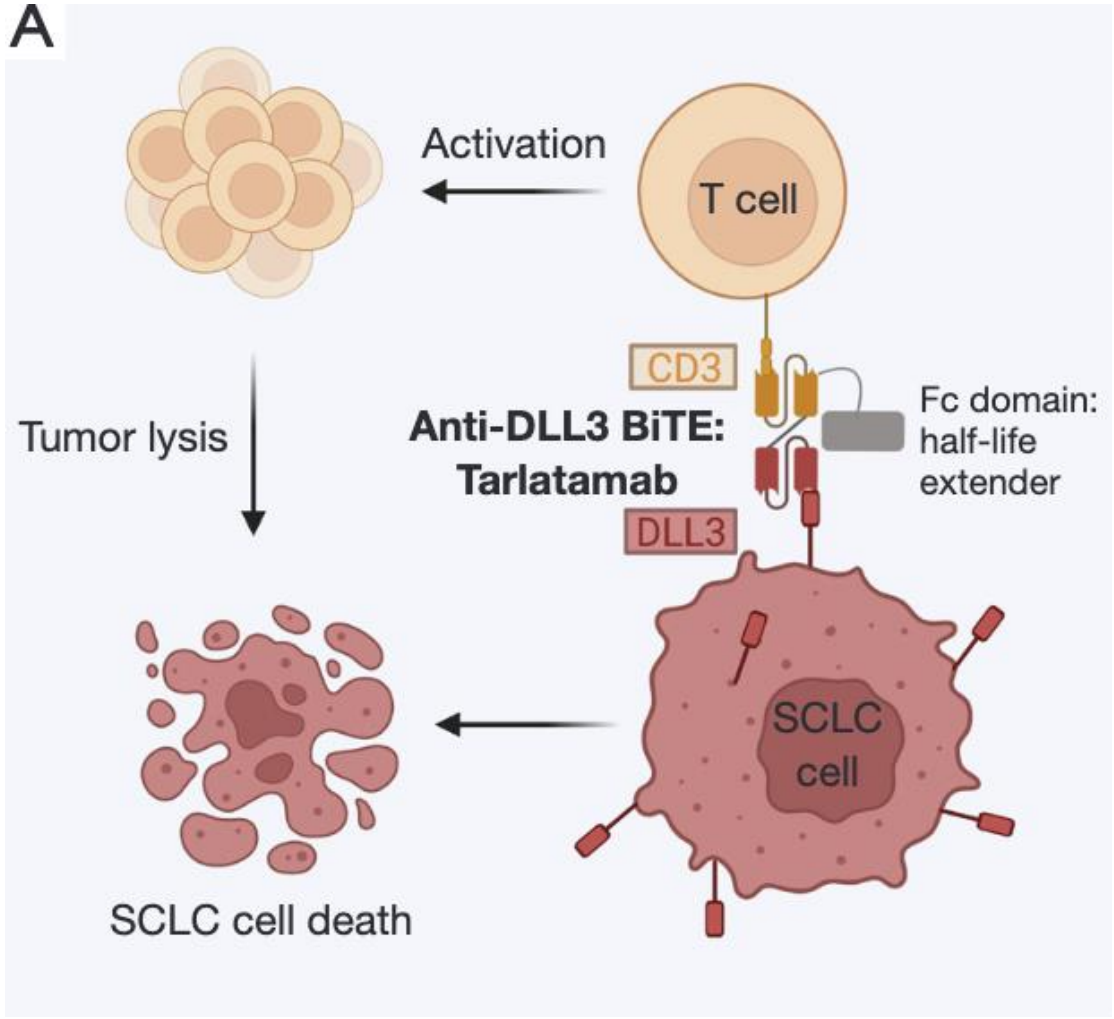
Impower 133, Horn et al, NEJM 2018



CASPIAN, Paz-Arez, Lancet 2019

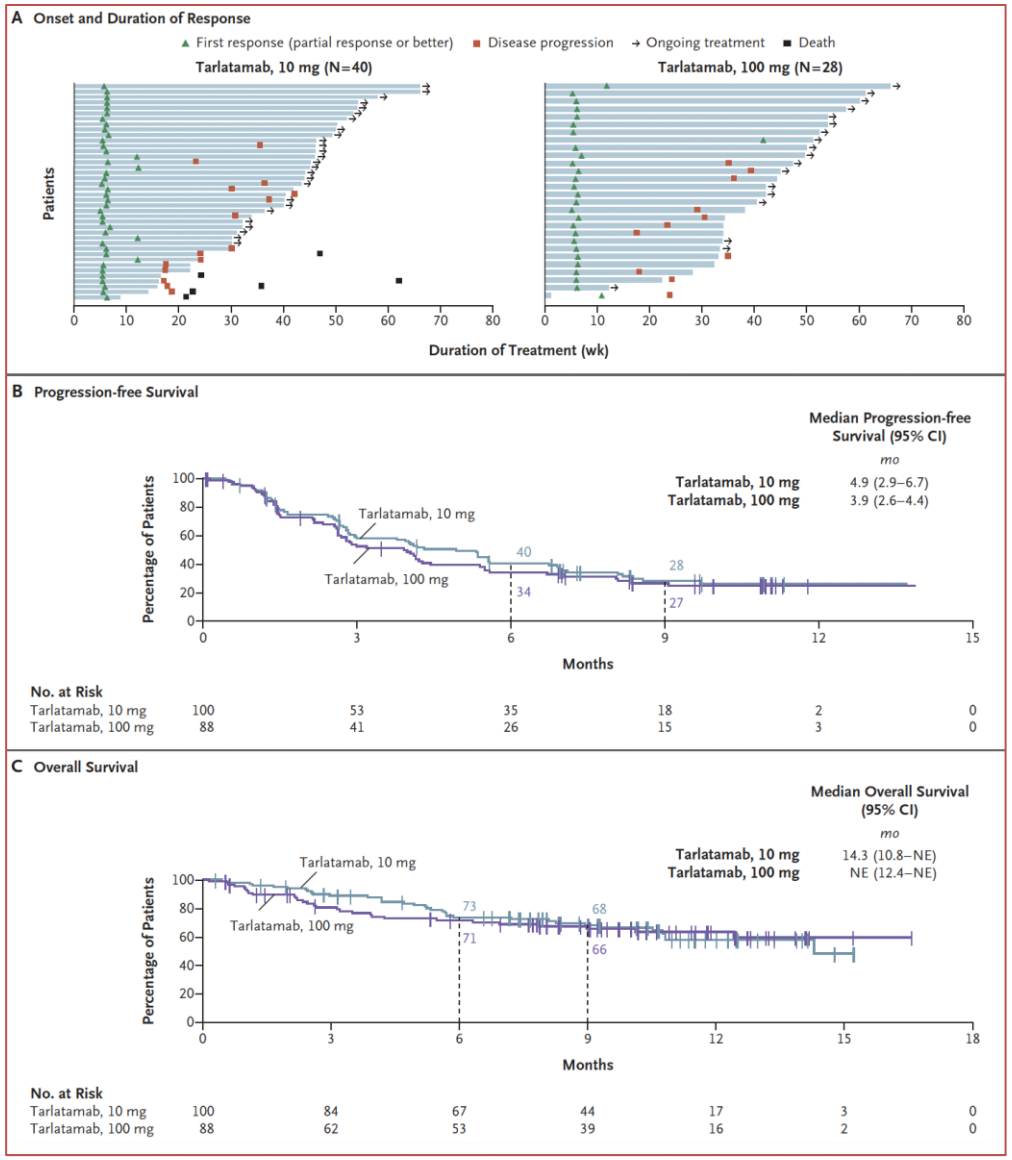
> Chemo + anti-PDL1 ICI 1st line: OS benefit 2 – 2.5 mon.

The bispecific T-cell engager (BiTE) Tarlatamab in SCLC



Apaydin and Sage, TLCR 2023

The bispecific T-cell engager (BiTE) Tarlatamab in SCLC



Ahn et al, NEJM 2023

Phase II: Tarlatamab mono in relapsed SCLC

- 220 pts.
- ORR 40% (97.5 CI 29 – 52)
- mPFS 4.9 months (95% CI 2.9-6.7)
- **mOS 14 months (10.8-NE)**

- CRS grade III 10 mg-group 1%

  100 mg-group 6%
- Treatment discontinuation due to TRAE: 3%

Conclusions

- **EGFR:** more 1L options > higher PFS, higher toxicity >> OS?
- **ALK:** 3 year adjuvant alectinib standard now
- **ROS1:** next-gen. TKIs > rebiopsy! Clinical trials!
- **EGFR ex20:** amivantamab + chemo 1L standard soon
- **HER ex20:** trastuzumab deruxtecan standard 2L, with chemo 1L soon (?)
- **KRAS:** new inhibitors (for all KRAS subtypes will come)

> **Rebiopsies! Clinical trials! Off-label treatment!**

- Neoadj. or perioperative IO/chemo new options now for stages II, IIIA (w/o EGFR, ALK)
- Adjuvant IO for all pts now (w/o EGFR, ALK)

> **Always discuss in ITB**

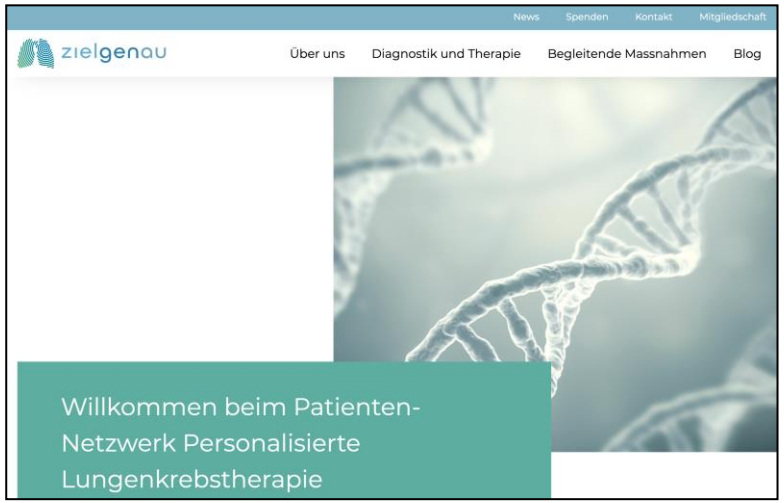
- ADCs new option for many relapsed pts. with and without driver mutations
- New immunotherapeutic strategies will come also in lung cancer (CAR-T, BiTEs, Vaccine)

- SCLC: DLL3/CD3 BiTEs, bispecific antibodies new effective drugs

> **Trials in particular in relapse after IO/chemo!**

Zielgenau e.V.

www.zielgenau.org



Unsere Ziele

Gesundheits-kompetenz

"Der gut informierte Patient lebt länger." Das ist keine Phrase, sondern Realität. Wir setzen uns dafür ein, dass Patienten Wissen aufbauen können.

Umfassende Diagnostik

Wir fordern eine flächendeckende, umfassende molekulare Diagnostik bei jedem Patienten mit nicht-kleinzelligem Lungenkrebs.

Personalisierte Therapie

Wir wollen, dass sich Therapiesituation und Überlebenschancen von Lungenkrebspatienten in Deutschland verbessern.

Patientenzentrierte Forschung

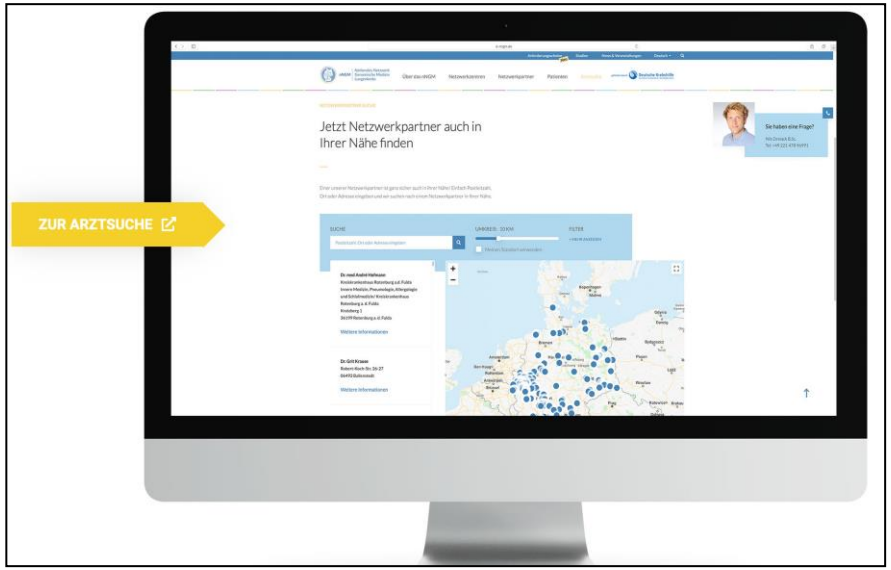
Wir brauchen neue Therapieansätze, ein besseres Nebenwirkungsmanagement und die Vernetzung von Ärzten, Patienten und Forschern.

MET CRUSADERS
Ras Kickers Lung Cancer
ALK Fusion
EGFR esisters
PATIENTS driving RESEARCH t
THE ROSI DERS

Reiner, Diagnose 2009, Testung auf Mutation 2014, Mutation ROS1, "Ich fahre gerne die weite Strecke zu meiner Klinik, da dort die Experten für meine seltene Lungenkrebsart sind."

Guido, Diagnose 02/2020, EGFR-Mutation, "In der Natur tanke ich Energie und kann gleichzeitig die Seele baumeln lassen – hier bin ich glücklich."

Bärbel, Diagnose 2008, ROS1-Mutation 2012 festgestellt, Spaziergang mit Hund 2020, "Ich habe eine chronische Erkrankung und lebe gut damit."



Danke !

- **allen Patienten und ihren Familien**

- **allen regionalen Netzwerkpartnern**

... und viele weitere Krankenkassen