Oncologia Polmonare

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Tumori toracici

Tumori polmonari non a piccole cellule

PD-L1

- EGFR
- ALK
- KRAS
- ROS1
- HER2
- BRAF
- MET
- RET
- NTRK1,2,3
- EGFR ins20

Tumori polmonari a piccole cellule

Mesoteliom,i tumori del timo, sarcomi

Multidisciplinary Tumor Board
for the Management of Unresectable Stage III NSCLC

Radiologist | Pneumologist | Thoracic Surgeon | Medical Oncologist | Radiation Oncologist

Multidisciplinary Tumor Board
Assessment of resectability and path

RESECTABLE NSCLC

UNRESECTABLE NSCLC

Diagnostic and Pre-treatment Evaluation

- CT scan/FDG PET
- Brain MRI
- Pulmonary function testing
- Bronchoscopy/ EBUS/TBNA
- Diagnosis
- Pathological mediastinal nodes evaluation
- NGS and PD-L1 assessment are highly recommended

Conclusions

Treatment of unresectable stage III NSCLC has considerably improved over the last few years and consolidative durvalumab after concurrent chemo-radiotherapy is now firmly established as the standard of care in this setting. There is a general consensus that a complete and accurate clinical and pathological staging is mandatory in patients with stage III NSCLC, to define the optimal treatment plan.

Resectability of the tumor should be discussed in the context of a multidisciplinary team. When the patient is selected for chemo-radiotherapy, a concomitant schedule should be preferred, whenever feasible.
Radical radiotherapy should be performed taking into account for possible pulmonary, cardiac or esophageal side effects. Elderly should also be considered for concomitant treatment according to Performance Status and comborbidities. Sequential Durvalumab administration should be started as soon as possible.

New Strategies in Unresectable Stage III NSLC

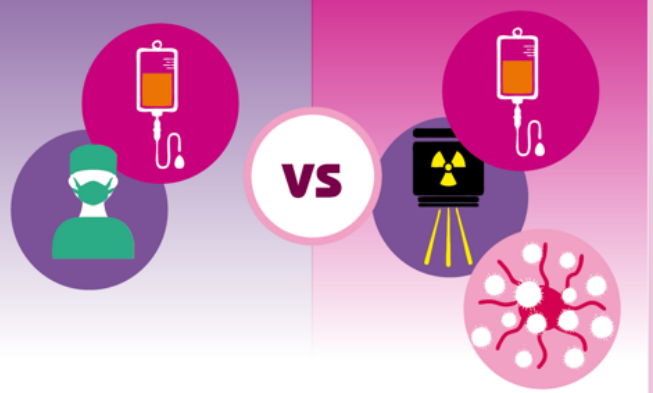
1: Combination of concomitant Immunotherapy + Chemotherapy + Radiotherapy and
2: TARGET THERAPY
3: Minimize/Avoid Severe Toxicity

Treatment

Preoperative CHEMOTHERAPY and SURGERY

VS

Concomitant or sequential CHEMOTHERAPY with RADIOTHERAPY and IMMUNOTHERAPY



Hot topics

- Concomitant or sequential **Radiotherapy**
- **Molecular NGS** to be performed at diagnosis
- **Timing between** chemo-radiation and Durvalumab
- **Management of disease** recurrence/progression during or after Durvalumab

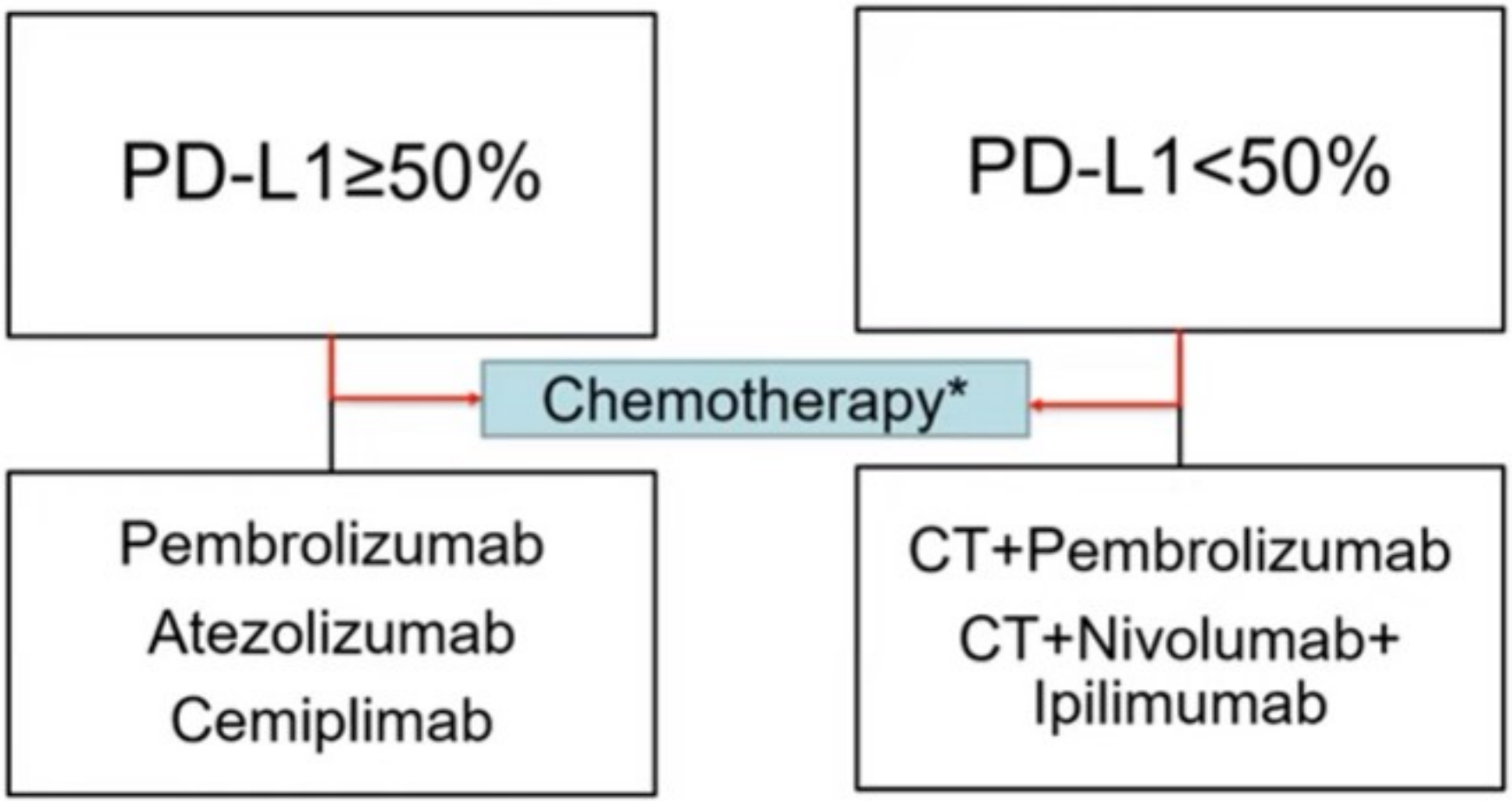
- **Immunotherapy** in patiens with oncogene addicted NSCLC
- **Treatment** in frail patients
- **Management of the Toxicity** of Chemotherapy plus Radiotherapy and Immunotherapy
- **Target therapy** in Oncogene Addicted

C Catania et al, Critical Reviews in Oncology / Hematology (2022)

Trattamenti malattia avanzata

- Immunoterapia e chemio-immunoterapia
- Target therapy
- Anticorpi coniugati

Italian algorithm in first-line non-oncogene addicted advanced NSCLC



*If not feasible I/O or CT with platinum doublets

KEYNOTE-189: study design

Key Eligibility Criteria

- Untreated stage IV nonsquamous NSCLC
- No sensitizing *EGFR* or *ALK* alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification Factors

- PD-L1 expression (TPS[a] <1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

R (2:1)

N = 410

Pembrolizumab 200 mg + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m²
Q3W for 4 cycles

Pembrolizumab 200 mg Q3W for up to 31 cycles
+
Pemetrexed 500 mg/m² Q3W

N = 206

Placebo (normal saline) + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m²
Q3W for 4 cycles

Placebo (normal saline) for up to 31 cycles
+
Pemetrexed 500 mg/m² Q3W

Crossover= 55.8%

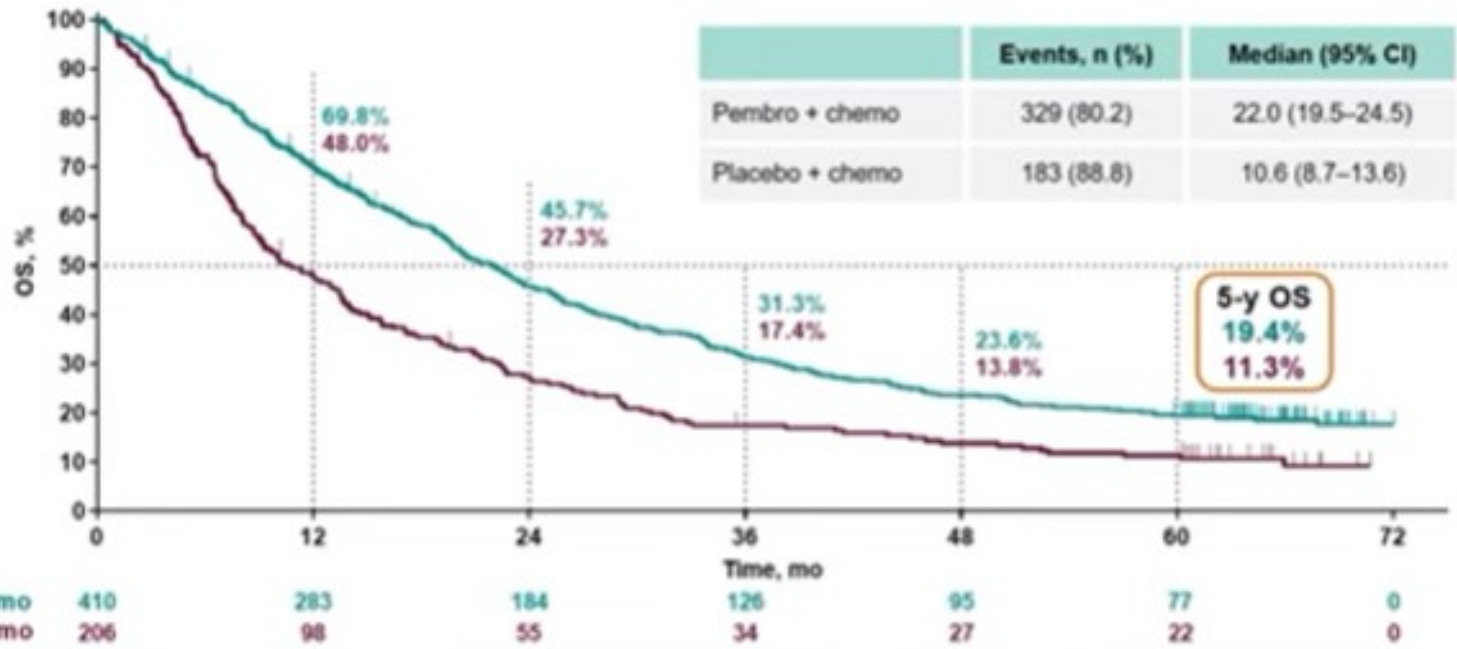
Pembrolizumab 200 mg Q3W for up to 35 cycles

PD[b]

[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

Garassino M, ESMO 2022

KN-189: 5-year OS ITT population



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

No. at risk							
Pembro + chemo	410	283	184	126	95	77	0
Placebo + chemo	206	98	55	34	27	22	0

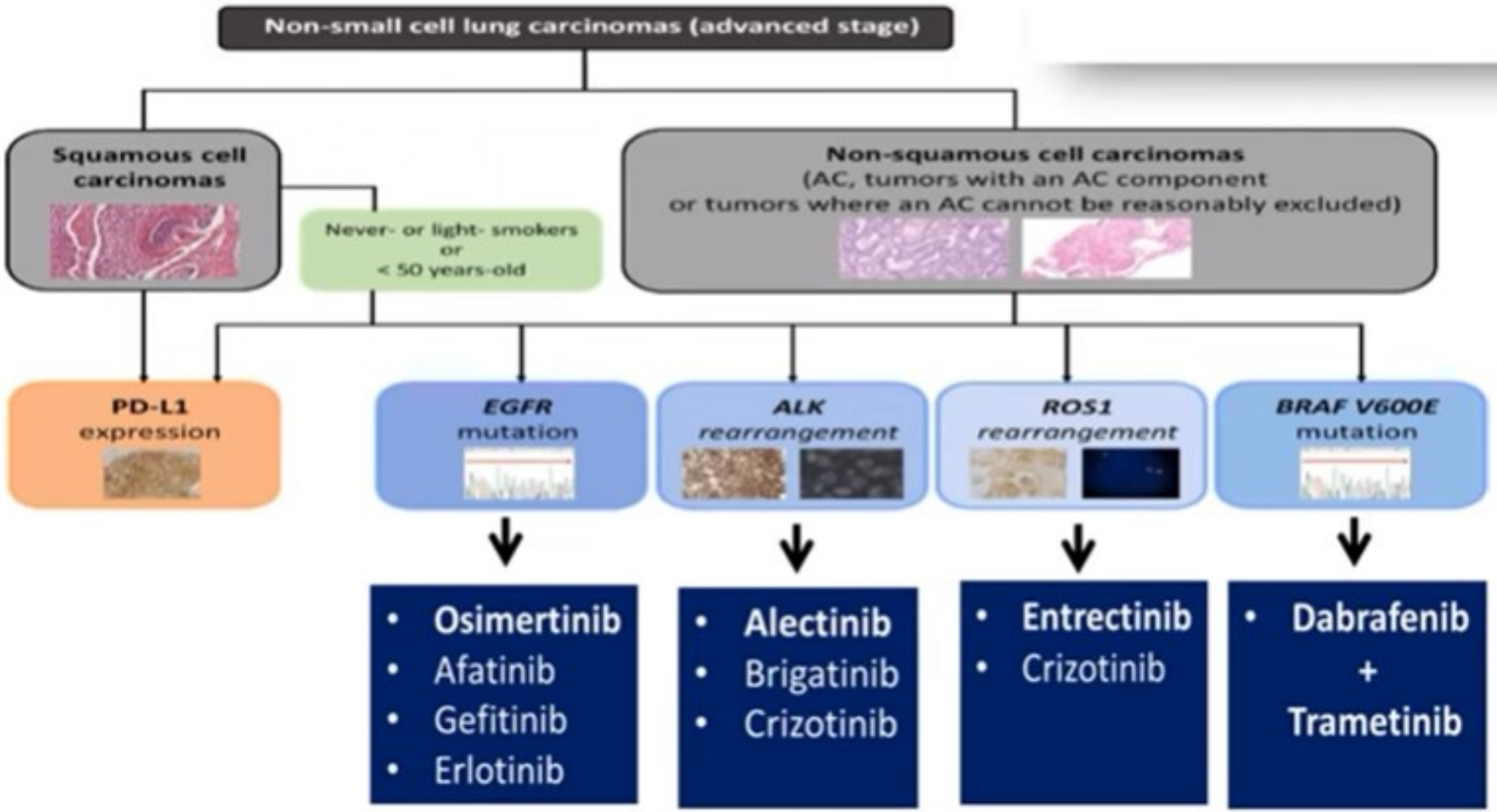
	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8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

Garassino M, ESMO 2022

Trattamenti malattia avanzata

- Immunoterapia e chemio-immunoterapia
- Target therapy
- Anticorpi coniugati

Diagnostic and Therapeutic Algorithm for AIFA Reimbursed Biomarker Testing Therapies in Italy for 1L of A-NSCLC in 2022



Precision Medicine in Advanced NSCLC today and tomorrow

ONCOGENE ADDICTED

EGFR

EGFR exon20

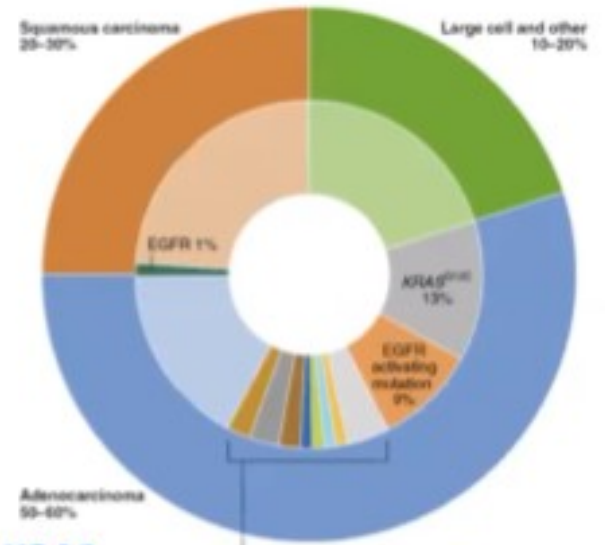
Alk

ROS1

BRAF

NTRK

RET



KRAS G12c

MET

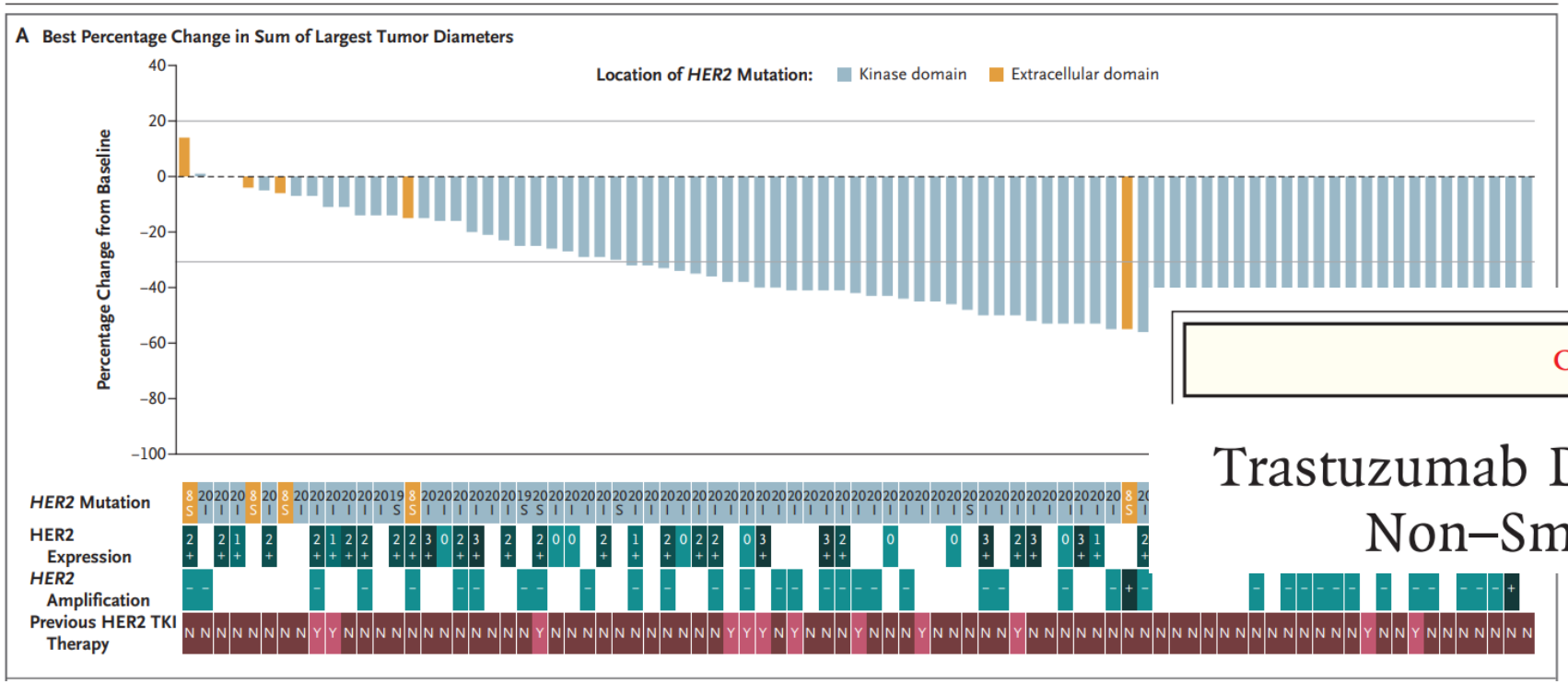
HER2

Wang M et al, Nature Medicine 2021

Linee Guida AIOM – Neoplasie del Polmone 2021

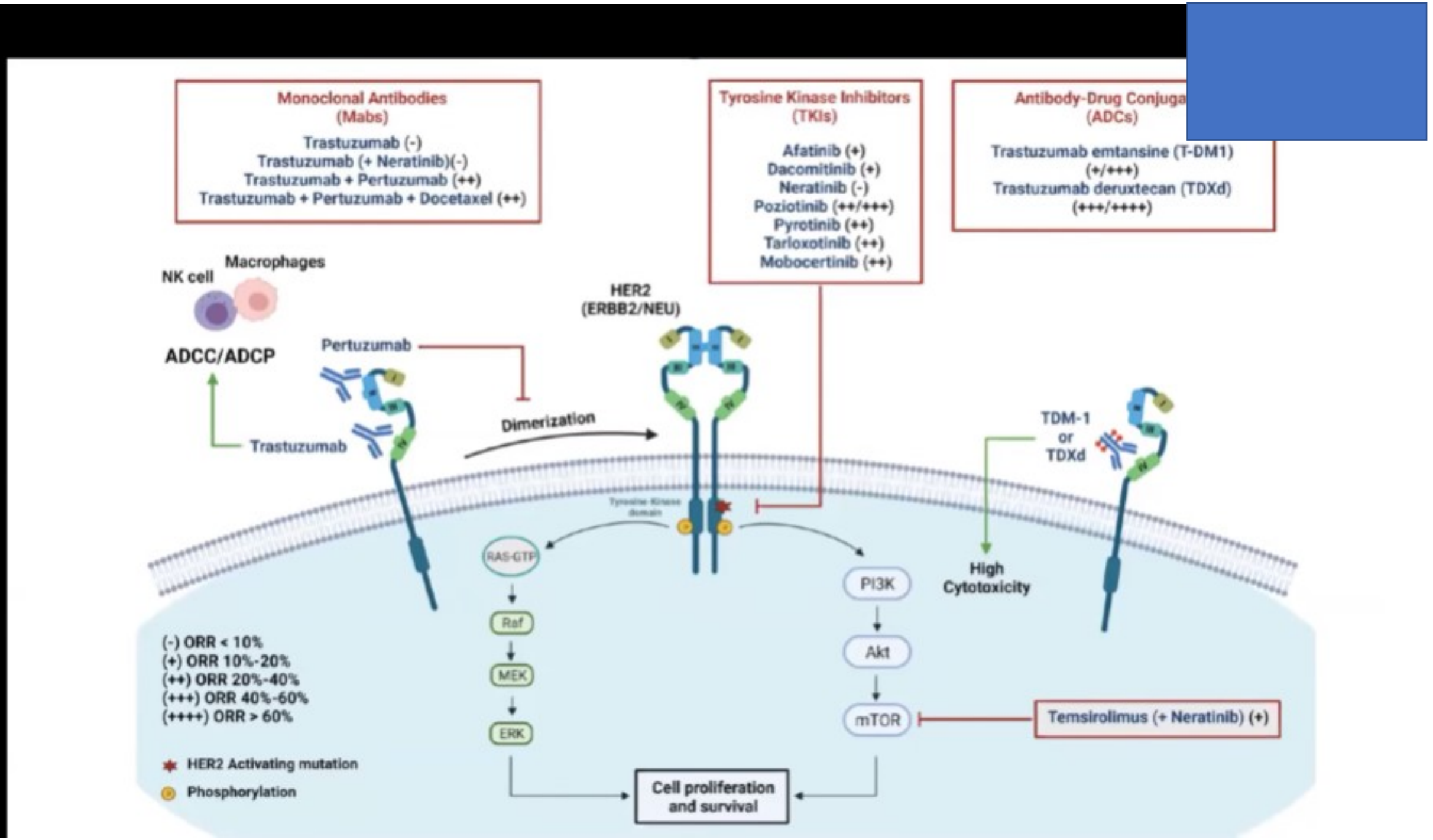
10+PDL1

Anticorpi coniugati



ORIGINAL ARTICLE

Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer


Monoclonal Antibodies
(Mabs)
Trastuzumab (-)
Trastuzumab (+ Neratinib)(-)
Trastuzumab + Pertuzumab (++)
Trastuzumab + Pertuzumab + Docetaxel (++)
Tyrosine Kinase Inhibitors
(TKIs)
Afatinib (+)
Dacomitinib (+)
Neratinib (-)
Poziotinib (++/+++)
Pyrotinib (++)
Tarloxotinib (++)
Mobocertinib (++)
Antibody-Drug Conjuga
(ADCs)
Trastuzumab emtansine (T-DM1)
(+/+++)
Trastuzumab deruxtecan (TDXd)
(+++/++++)
NK cell
Macrophages
ADCC/ADCP
Pertuzumab
Trastuzumab
Dimerization
HER2
(ERBB2/NEU)
TDM-1
or
TDXd
High
Cytotoxicity
RAS-GTP
Raf
MEK
ERK
PI3K
Akt
mTOR
Temsirolimus (+ Neratinib) (+)
Cell proliferation
and survival
(-) ORR < 10%
(+) ORR 10%-20%
(++) ORR 20%-40%
(+++) ORR 40%-60%
(++++) ORR > 60%
HER2 Activating mutation
Phosphorylation

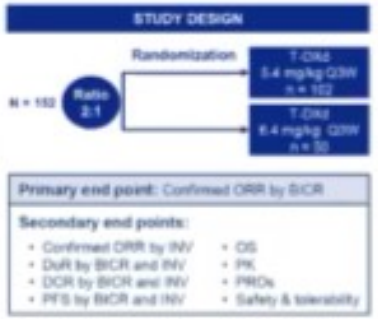
DESTINY-Lung02 Background and Study Design

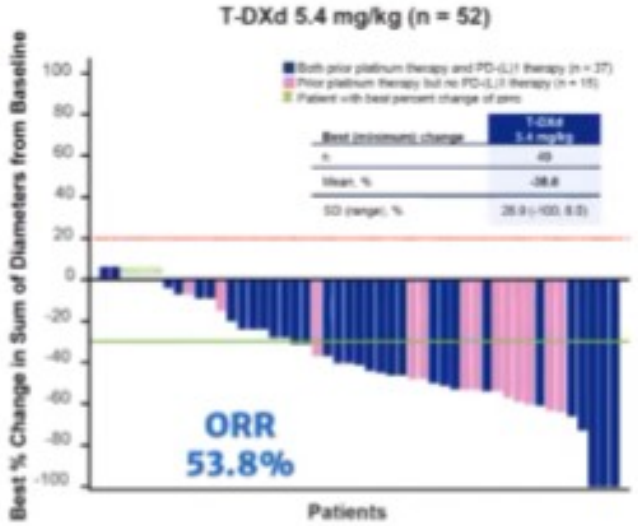
Randomized, multicenter, international, 2-arm, non-comparative, phase 2 trial (NCT04644237)

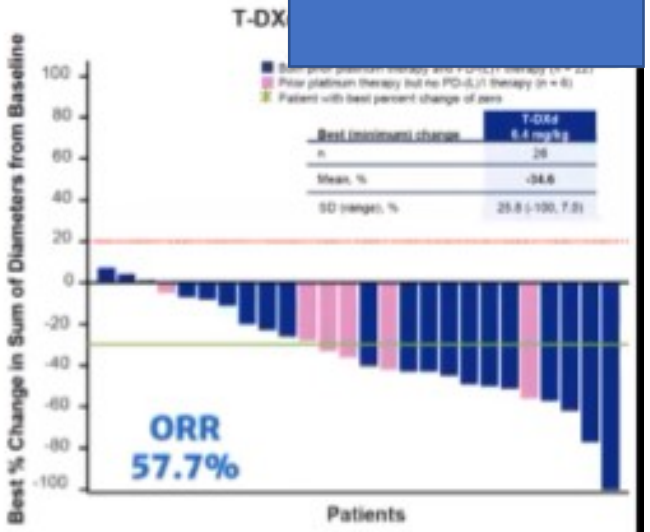
T-DXd, a HER2 antibody-drug conjugate,[1-3] in *HER2*m NSCLC

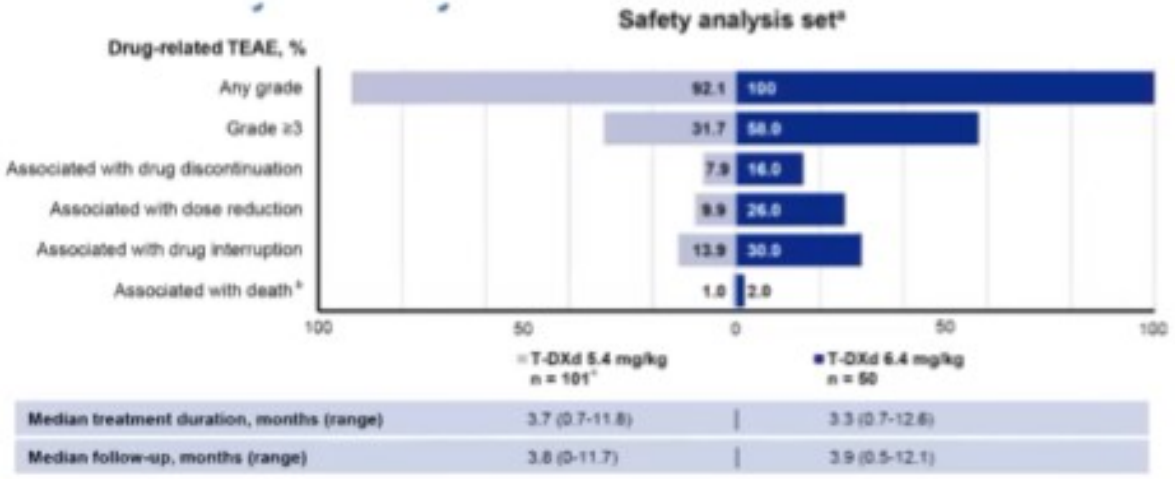
- In DESTINY-Lung01, T-DXd 6.4 mg/kg showed strong and durable clinical activity in patients with previously treated *HER2*m NSCLC, adjudicated drug-related ILD occurred in 26% of patients[4]
  - These results warranted evaluation of the benefit/risk profile of T-DXd 5.4 mg/kg and further assessment of T-DXd 6.4 mg/kg in this population
- **DESTINY-Lung02 is a randomized, phase 2 trial** assessing the efficacy and safety of 2 doses of **T-DXd (5.4 and 6.4 mg/kg)** in previously patients with metastatic *HER2*m NSCLC

The study was not powered to statistically compare the 2 arms









	T-DXd 5.4 mg/kg n = 101	T-DXd 6.4 mg/kg n = 50
Median treatment duration, months (range)	3.7 (0.7-11.8)	3.3 (0.7-12.6)
Median follow-up, months (range)	3.8 (0-11.7)	3.9 (0.5-12.1)

	Safety analysis set[b]	
Adjudicated as drug-related ILD[a]	T-DXd 5.4 mg/kg n = 101	T-DXd 6.4 mg/kg n = 50
Any grade, n (%)	**6 (5.9)**	**7 (14.0)**
Grade 1	3 (3.0)	1 (2.0)
Grade 2	2 (2.0)	6 (12.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	0	0
Cases resolved, n (%)	3 (50.0)	1 (14.3)
Median time to onset of first adjudicated ILD, days (range)	67.5 (40-207)	41.0 (36-208)

- The rate of adjudicated drug-related ILD was lower in the T-DXd 5.4 mg/kg arm compared with the 6.4 mg/kg arm
- Most cases of adjudicated drug-related ILD were low grade (grade 1/2)

Goto K et al, ESMO 2022

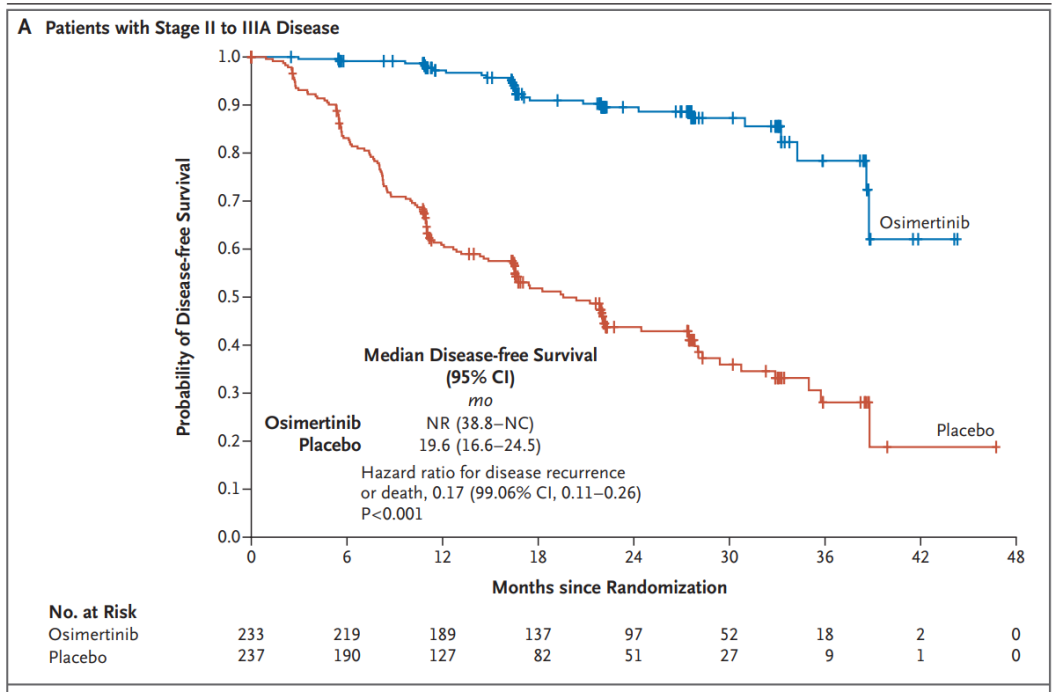
Stadiazione NSCLC malattia precoce

Regime preoperatorio

Regime postoperatorio (terapia target e immuno)

Malattia avanzata

Target therapy post-operatoria



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

PHASE III ADAURA STUDY DESIGN

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non-squamous NSCLC
Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Max. interval between surgery and randomisation:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Osimertinib 80 mg, once daily

Randomisation 1:1 (N=682)

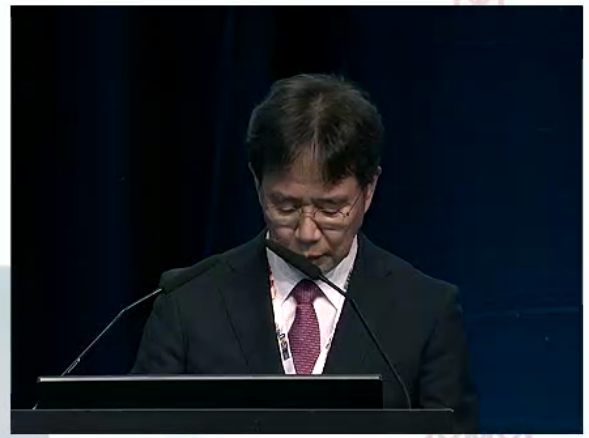
Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II / IIIA patients, designed for superiority under the assumed DFS HR of 0.70
- **Key secondary endpoints:** DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life
- **Pre-specified exploratory endpoints:** Patterns of recurrence, time to CNS disease recurrence or death (CNS DFS)



Masahiro Tsuboi
Non-metastatic NSCLC and other thoracic malignancies

PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

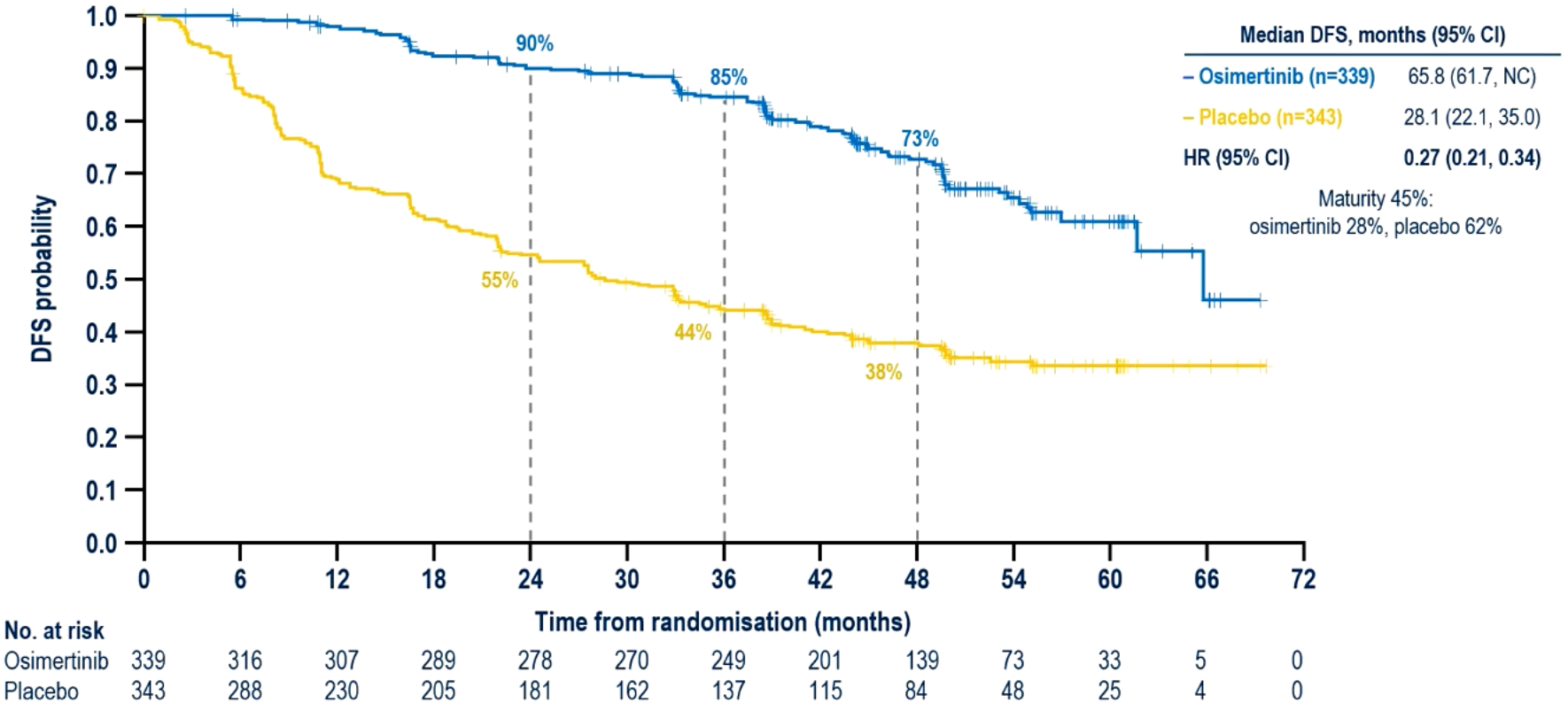
*At the time of recruitment, staging was determined by the AJCC 7th edition staging manual. †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue. §Patients received a CT scan after resection and within 28 days prior to treatment. ¶Stage IB / II / IIIA.

AJCC, American Joint Committee on Cancer; CNS, central nervous system; CT, computerized tomography; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; WHO, World Health Organization

CHAIRS : FLORIAN LORDICK, AMANDA PSYRRI

4.B - Brest Auditorium

UPDATED DFS IN THE OVERALL POPULATION (STAGE IB / II / IIIA DISEASE)



Median DFS, months (95% CI)	
– Osimertinib (n=339)	65.8 (61.7, NC)
– Placebo (n=343)	28.1 (22.1, 35.0)
HR (95% CI)	0.27 (0.21, 0.34)

Maturity 45%:
osimertinib 28%, placebo 62%

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

PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

Median follow-up: osimertinib 44.2 months (range 0 to 69), placebo 27.7 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data.

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable
Data cut-off: April 11, 2022.

Masahiro Tsuboi

Non-metastatic NSCLC and other thoracic malignancies

Stadiazione NSCLC malattia precoce

Regime preoperatorio

Regime postoperatorio (terapia target e immuno)

STADIO III NON OPERABILE

Malattia avanzata

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Resectability of the tumor should be discussed in the context of a multidisciplinary team. When the patient is selected for chemo-radiotherapy, a concomitant schedule should be preferred, whenever feasible.
Radical radiotherapy should be performed taking into account for possible pulmonary, cardiac or esophageal side effects. Elderly should also be considered for concomitant treatment according to Performance Status and comborbidities. Sequential Durvalumab administration should be started as soon as possible.

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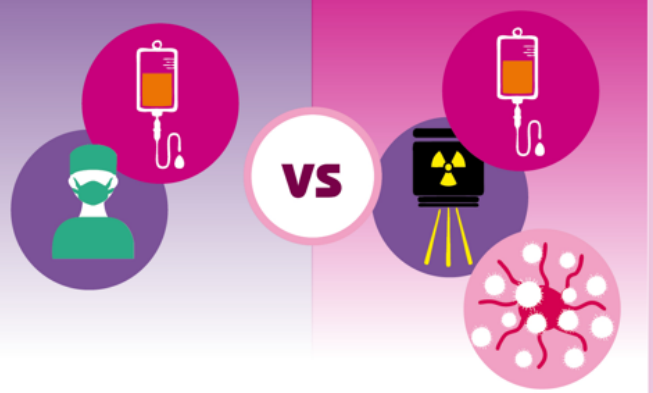
1: Combination of concomitant Immunotherapy + Chemotherapy + Radiotherapy and
2: TARGET THERAPY
3: Minimize/Avoid Severe Toxicity

Treatment

Preoperative CHEMOTHERAPY and SURGERY

VS

Concomitant or sequential CHEMOTHERAPY with RADIOTHERAPY and IMMUNOTHERAPY



Hot topics

- Concomitant or sequential **Radiotherapy**
- **Molecular NGS** to be performed at diagnosis
- **Timing between** chemo-radiation and Durvalumab
- **Management of disease** recurrence/progression during or after Durvalumab

- **Immunotherapy** in patiens with oncogene addicted NSCLC
- **Treatment** in frail patients
- **Management of the Toxicity** of Chemotherapy plus Radiotherapy and Immunotherapy
- **Target therapy** in Oncogene Addicted

C Catania et al, Critical Reviews in Oncology / Hematology (2022)

PACIFIC : Trial Design

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

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitve platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

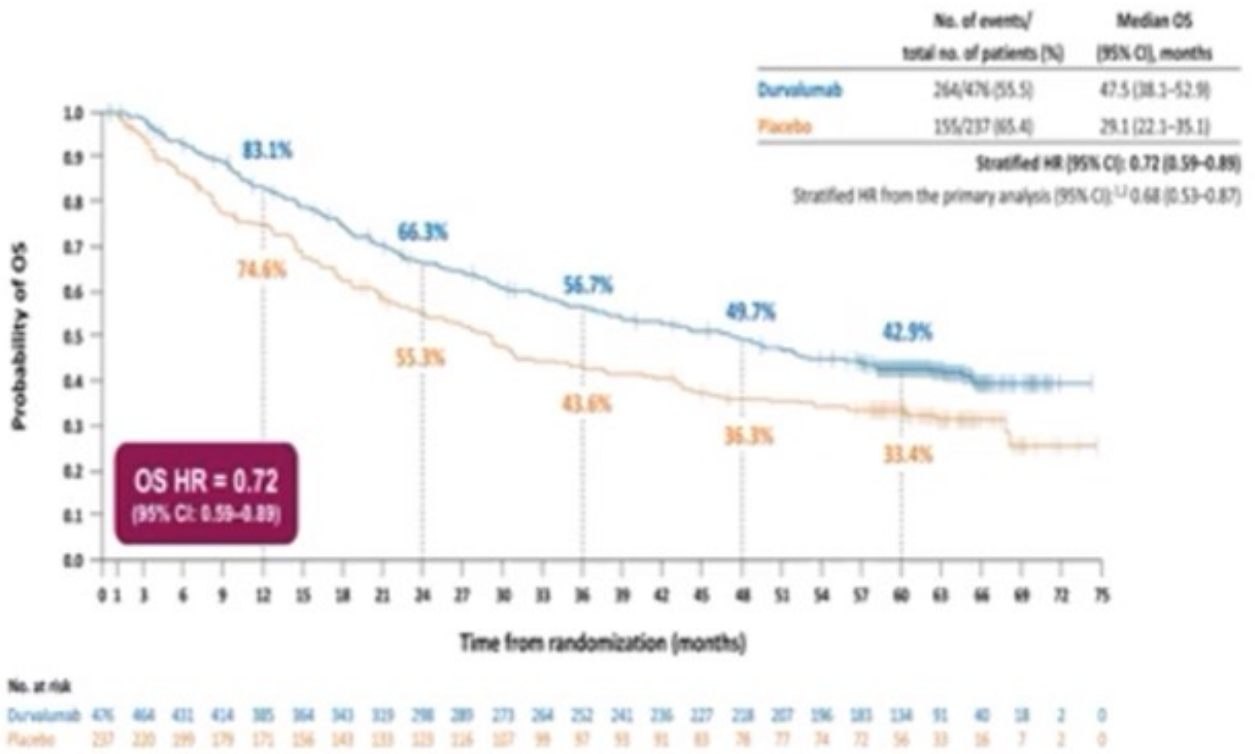
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

Stratification factors
- **Age at randomization** (<65 vs ≥65 years of age) - **Gender** (male vs female) - **Smoking history** (smoker vs non-smoker)

L Paz-Ares et al, ESMO 2017; SJ Antonia et al, NEJM 2017

PACIFIC Trial: 5-ys OS with Durvalumab after Chemoradiotherapy in Inoperable Stage III NSCLC

Updated OS (ITT)

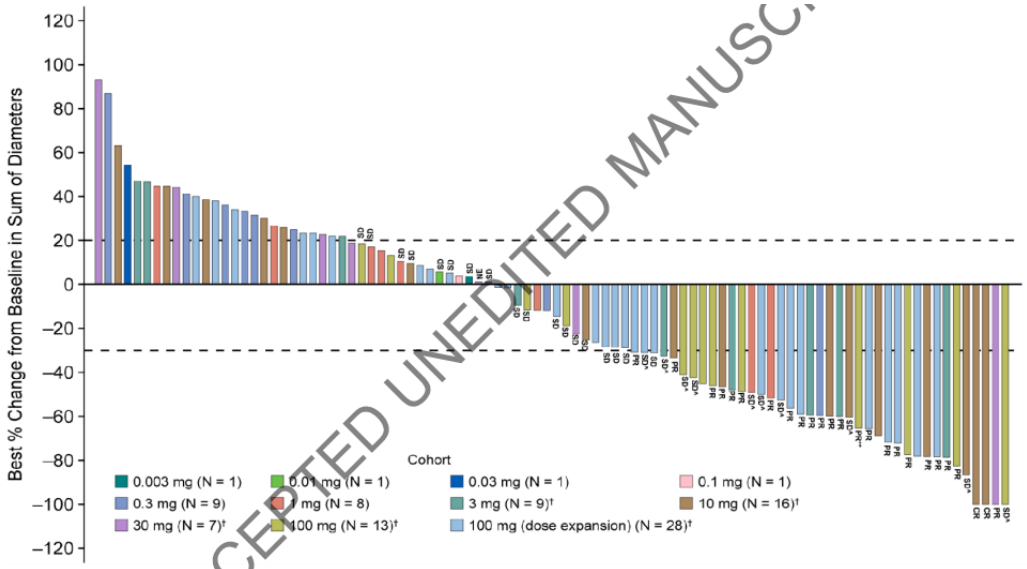


DR Spigel et al, ASCO 2021/ JCO 2022

Terapie innovative

Protocolli in apertura

Amgen 20210004 dal titolo: "A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Subjects with Relapsed Small Cell Lung Cancer and DLL3 overexpression after Platinum-based First-Line Chemotherapy (DeLLphi-304



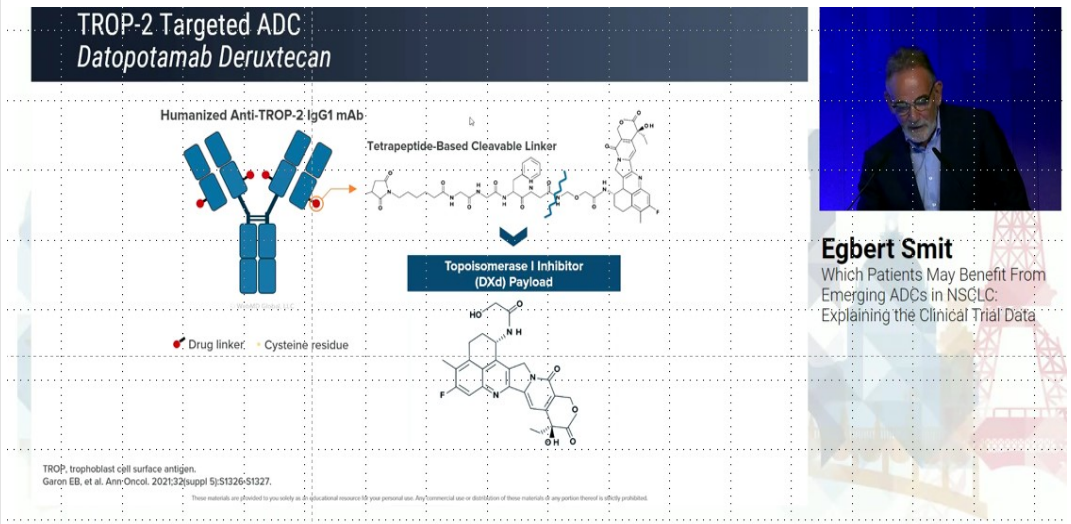
Author's Accepted Manuscript

Tarlatamab, a first-in-class DLL3-targeted bispecific T cell engager, in recurrent small-cell lung cancer: an open-label, phase 1 study

107 pazienti pretrattati hanno ricevuto tarlatanab
ORR 25%
RC 2%
PR 22%
PD 5%
Controllo della malattia 51%
Durata mediana della risposta 12 mesi

A Phase III, Randomised, Open-label, Multicentre, Global Study of Datopotamab Deruxtecan (Dato- DXd) in Combination With AZD2936 or AZD2936 Alone Versus Pembrolizumab for the First line Treatment of Patients With Locally-advanced or Metastatic NSCLC PD-L1 ≥50% Without Actionable Genomic Alterations (TROPION-Lung10)

AZD2936: anticorpo bispecifico anti-TIGIT/antiPD1



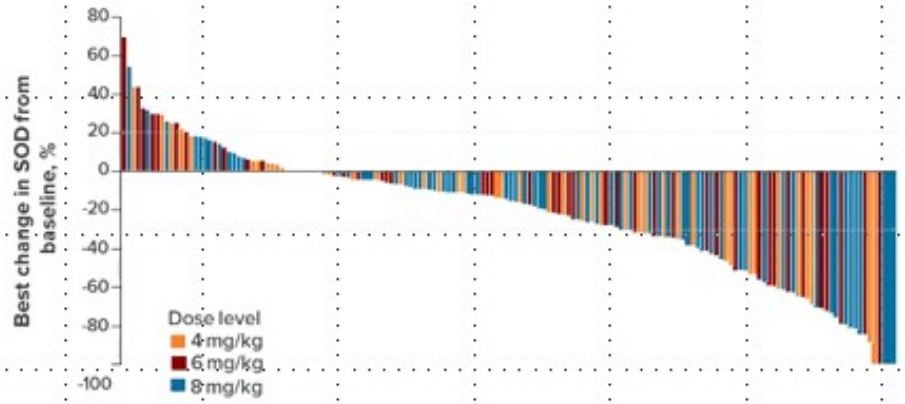
TROPION-PanTumor01: Dato-DXd
Efficacy

Best Overall Response (BICR)

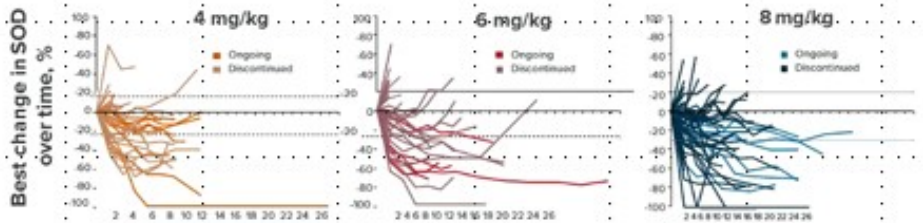
Patients	Dato-DXd Dose		
	4 mg/kg (n = 50)	6 mg/kg (n = 50)	8 mg/kg (n = 80)
ORR, n (%)	12 (24)	14 (28)	19 (24)
CR, n (%)	0	0	1 (1)
PR, n (%)	12 (24)	14 (28)	18 (23)
SD, n (%)	25 (50)	20 (40)	42 (53)
Non-CR/PD, n (%)	1 (2)	2 (4)	2 (3)
PD, n (%)	7 (14)	10 (20)	8 (10)
NE, n (%)	5 (10)	5 (10)	9 (11)
DOR, median (95% CI), months	NE (2.8-NE)	10.5 (5.6-NE)	9.4 (5.8-NE)

- Antitumor activity was observed at 4-, 6-, and 8-mg/kg doses of Dato-DXd
- Most responses were durable over time, including a median DOR of 10.5 months in the 6-mg/kg cohort

Best Change in Sum of Diameters (per BICR)



Change in Sum of Diameters of Target Lesion (per BICR) Over Time



SOD, sum of diameters.

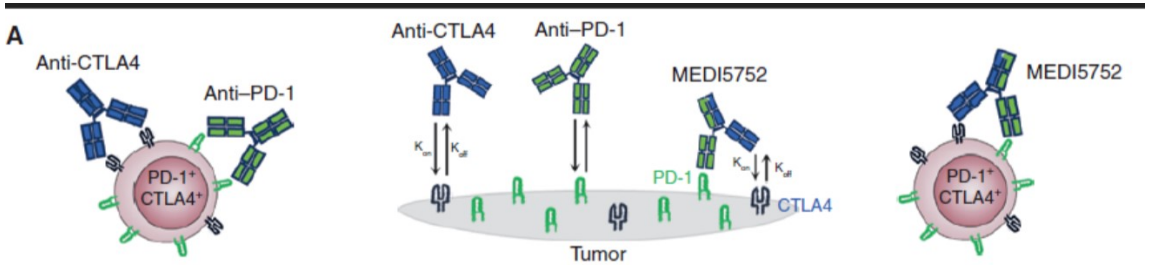
Garon EB, et al. J Thoracic Oncol. 2021;16(10 suppl):S892-S893.

Egbert Smit

Which Patients May Benefit From Emerging ADCs in NSCLC: Explaining the Clinical Trial Data

A Phase III, Two- Arm, Parallel, Randomized, Multi-Center, Open-Label, Global Study to Determine the Efficacy of Volrustomig (MEDI5752) Versus Pembrolizumab in Combination with Chemotherapy for First-Line Treatment of Patients with Metastatic Non-Small Cell Lung Cancer (mNSCLC) (eVOLVE-Lung02) (D798AC00001)

Design and Efficacy of a Monovalent Bispecific PD-1/CTLA4 Antibody That Enhances CTLA4 Blockade on PD-1^{+} Activated T Cells



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A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 Mutation

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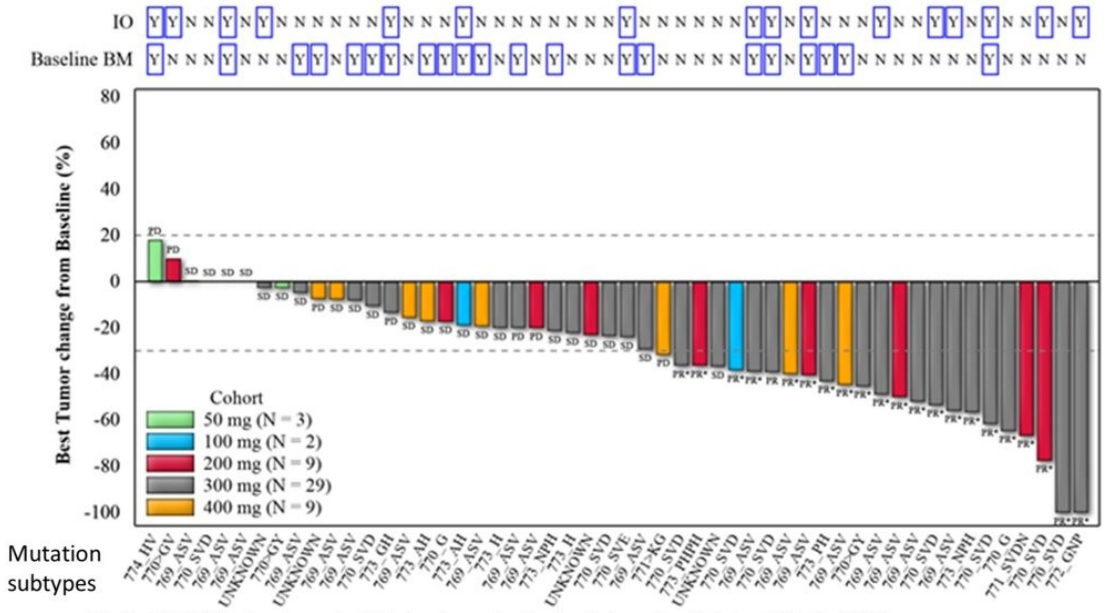
FDA Grants Breakthrough Therapy Designation to DZD9008 for EGFR Exon20Ins-Positive NSCLC

Figure 1. Anti-tumor activity in post platinum treated NSCLC with EGFR Exon20ins



IO: Anti-PD(L)1 treatment. BM: brain metastasis. Data cut-off date: 30 July, 2021.

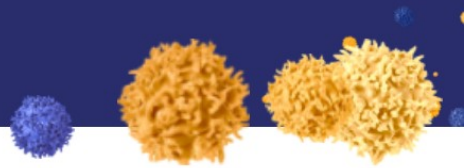
Table 2. Anti-tumor efficacy of DZD9008 in post platinum EGFR Exon20ins cohorts

Tumor Response	50 mg (N = 3)	100 mg (N = 2)	200 mg (N = 9)	300 mg (N = 29)	400 mg (N = 9)	Total (N = 52)
Confirmed ORR, n (%)	0 (0.0)	1 (50.0)	5 (55.6)	13 (44.8)	2 (22.2)	21 (40.4)
Confirmed DCR, n (%)	2 (66.7)	2 (100.0)	7 (77.8)	26 (89.7)	7 (77.8)	44 (84.6)
Median DoR, months	NA	5.9	Not reached*	5.5	9.7	5.9

A Phase 3 Study to Evaluate Zimberelimab (AB122) Combined with Domvanalimab (AB154) Compared to Pembrolizumab in Front-Line, PD-L1-High, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

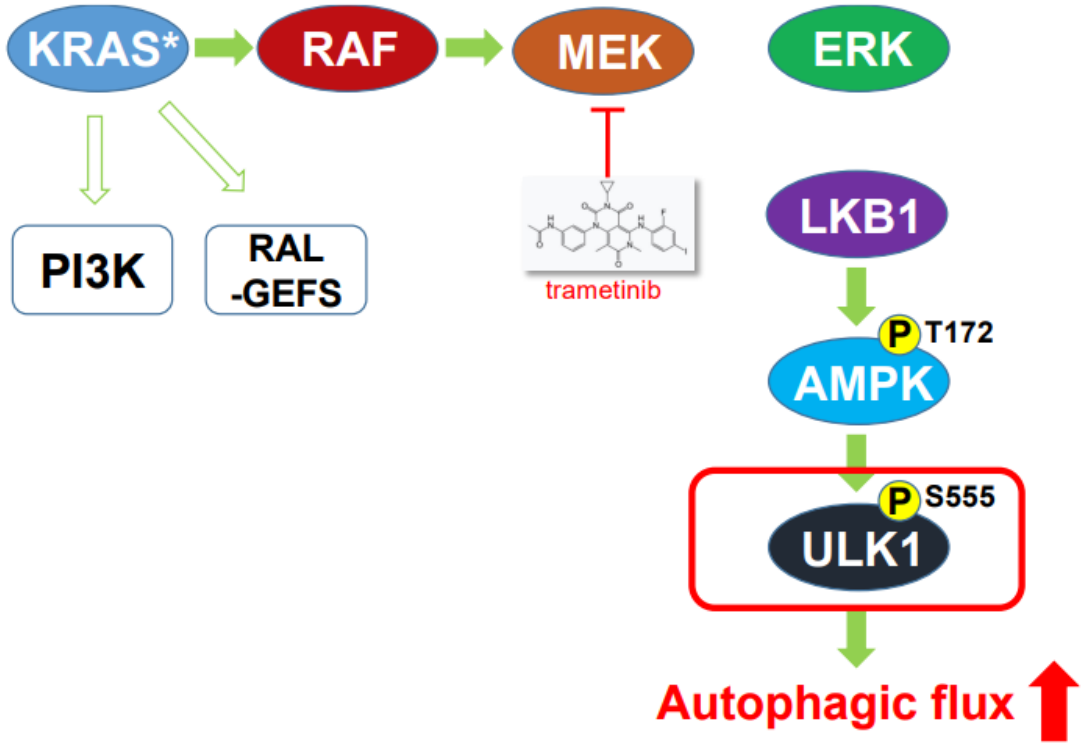
ANTI-PD-1 ZIMBERELIMAB

ANTI-TIGIT ANTIBODIES – DOMVANALIMAB



A Phase 1/2, First-in-Human Study of DCC-3116 as a Single Agent and in Combination with Trametinib or Sotorasib in Patients with Advanced or Metastatic Solid Tumors with RAS or RAF Mutations

DCC-3116, a First-in-Class Selective Inhibitor Of ULK1/2 Kinases and Autophagy, Combines with the KRAS^{G12C} Inhibitor Sotorasib Resulting in Tumor Regression in NSCLC Xenograft Models



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