Ruolo delle evoluzioni future nel NSCLC

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Potenziali conflitti d’interesse da dichiarare

Tipo di affiliazione o supporto finanziario	*Sponsor*
Speakers’s fee	AstraZeneca, MSD, Roche, Novartis
Adivosory boards	BMS

Il ruolo delle evoluzioni future nel NSCLC
Agenda

- How to increase survival in unresctable LA NSCLC?
  - New therapeutic scenarios
  - What to expect at progression from PACIFIC?
- Special populations (EGFRm)
- (Un)Resectable… Uncertain

Il ruolo delle evoluzioni future nel NSCLC
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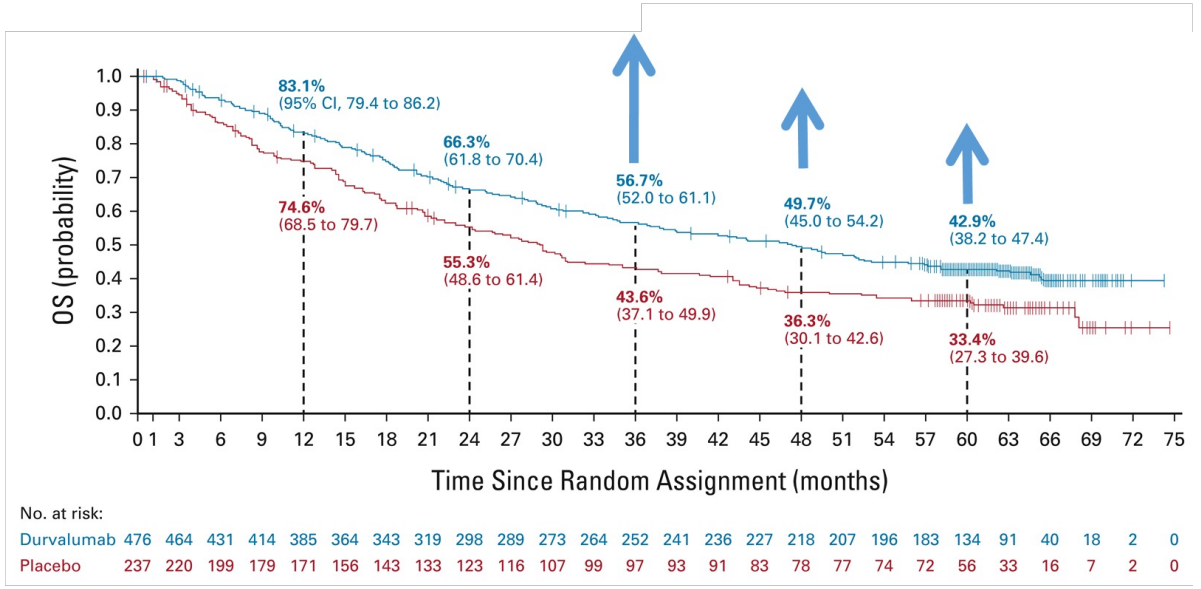
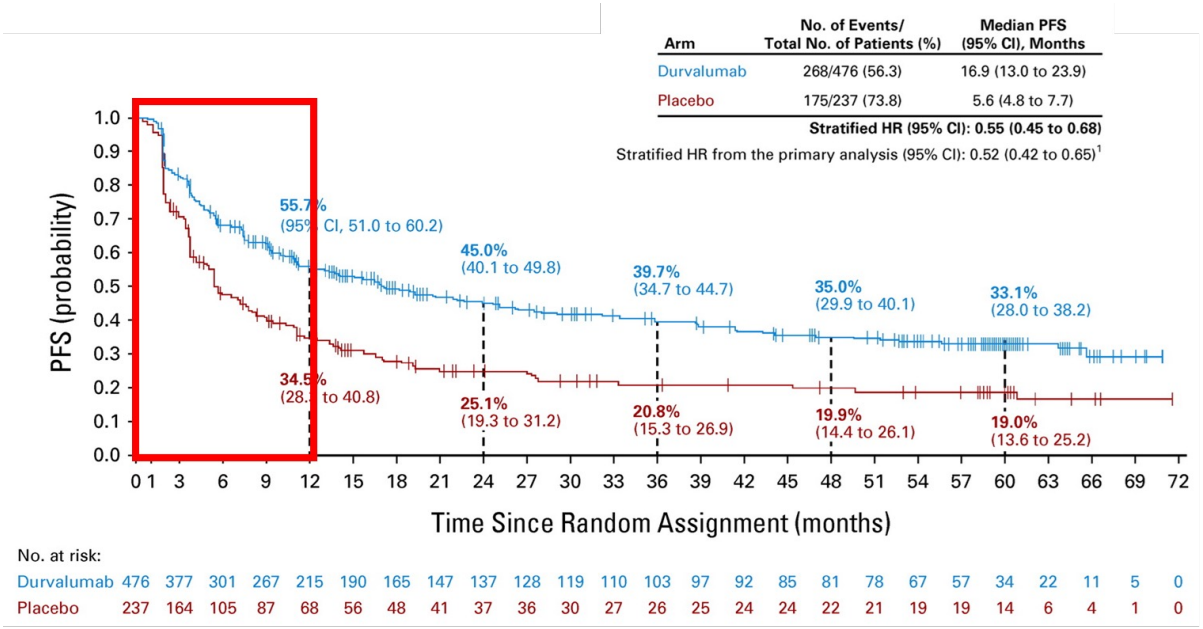
  - What to expect at progression from PACIFIC?



Spigel DR, J Clin Oncol 2022.



Spigel DR, J Clin Oncol 2022.

Months	Progressed or dead (%)
3	20.8
6	36.8
9	43.9
12	44.3

PRIMARY RESISTANCE
Progression after receiving at least 6 weeks (two cycles) but not more than 6 months of ICI treatment.

SECONDARY RESISTANCE
Progression after experiencing clinical benefit (either CR/PR or SD lasting 6 months or greater)

RESISTANCE AFTER ICI DISCONTINUATION
Related to toxicity and those unrelated, including the completion of a planned treatment regimen.

Progression after treatment discontinuation, within 12 weeks from the last ICI dose received, are considered as having secondary resistance.

Progressive disease after 12 weeks could benefit from rechallenge with ICI.

Adapted from Park K, WCLC 2022

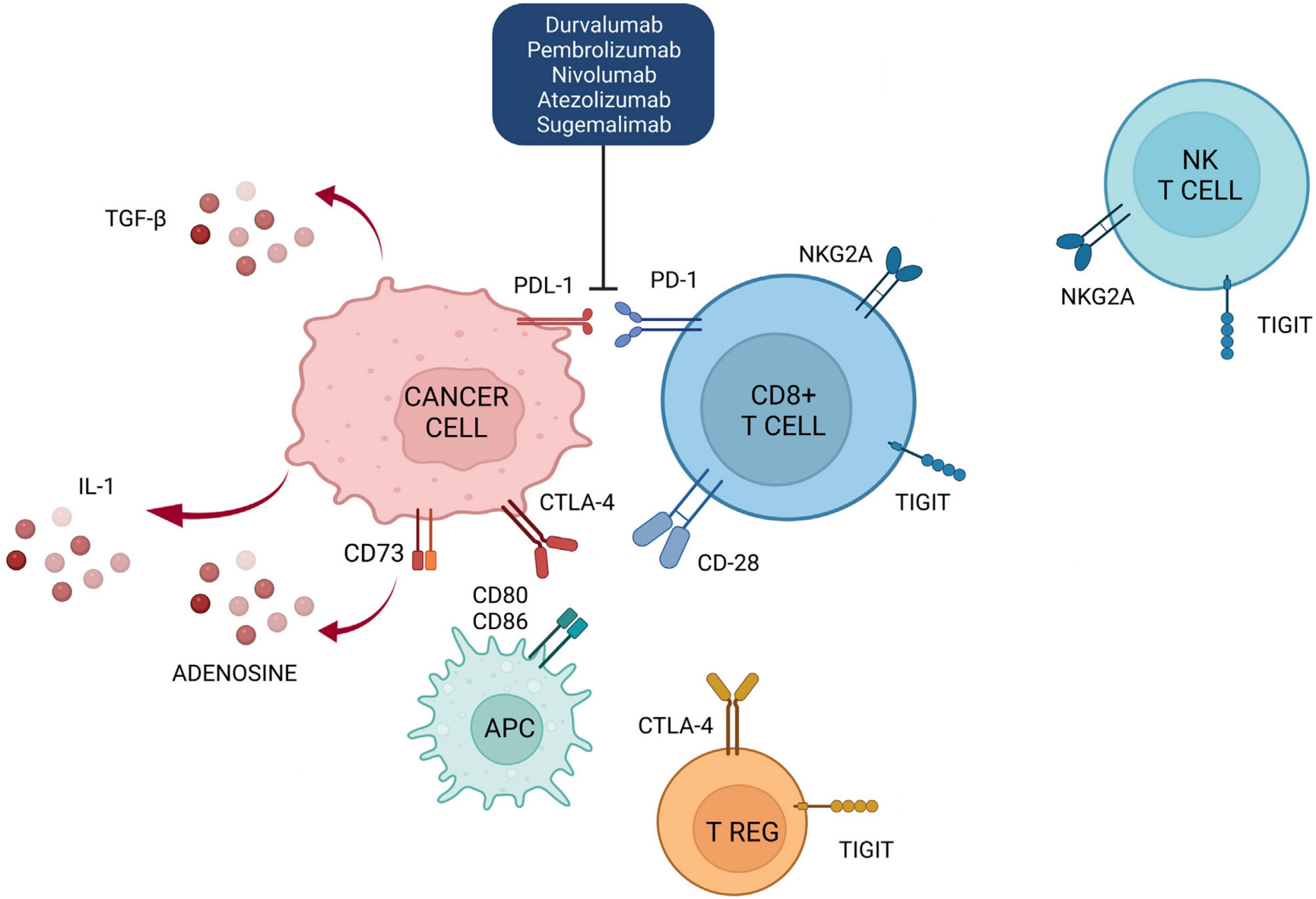
Treatment strategies in unresectable stage III NSCLC to improve efficacy:

IO timing

Trial	Phase	Treatment	G≥3 pneumonitis	ORR	1 yr PFS	Median PFS	
PACIFIC	III	Durvalumab consolidation	3.4%	28.4%	55.3%	17.2 mo	**Consolidation**
LUN 14-69	II	Pembrolizumab consolidation	6.5%	-	61.2%	18.7 mo	
Deterred (p2)	II	Atezolizumab concomitant RT /consolidation	16%	-	> 50%	13.2 mo	**IO only**
Nicolas	II	Nivolumab concomitant/consolidation	10.3%	73.4%	53.7%	12.7 mo	
KEYNOTE-799	II	Pembrolizumab concomitant/consolidation Carboplatin-Paclitaxel Sq + Non sq Cisplatin-Pemetrexed Non sq	 8% 6.9%	 71.4% 75.5%	 67.3% 69.4%	 30.6 mo NR	**Concomitant + Consolidation**
PACIFIC-2	III	Durvalumab + CRT > Durvalumab vs CRT + Placebo > Placebo		**ongoing**			
ATF-16	II	Atezolizumab > CRT > Atezolizumab	2.2%	-	66%	23.7	**Induction + Consolidation**

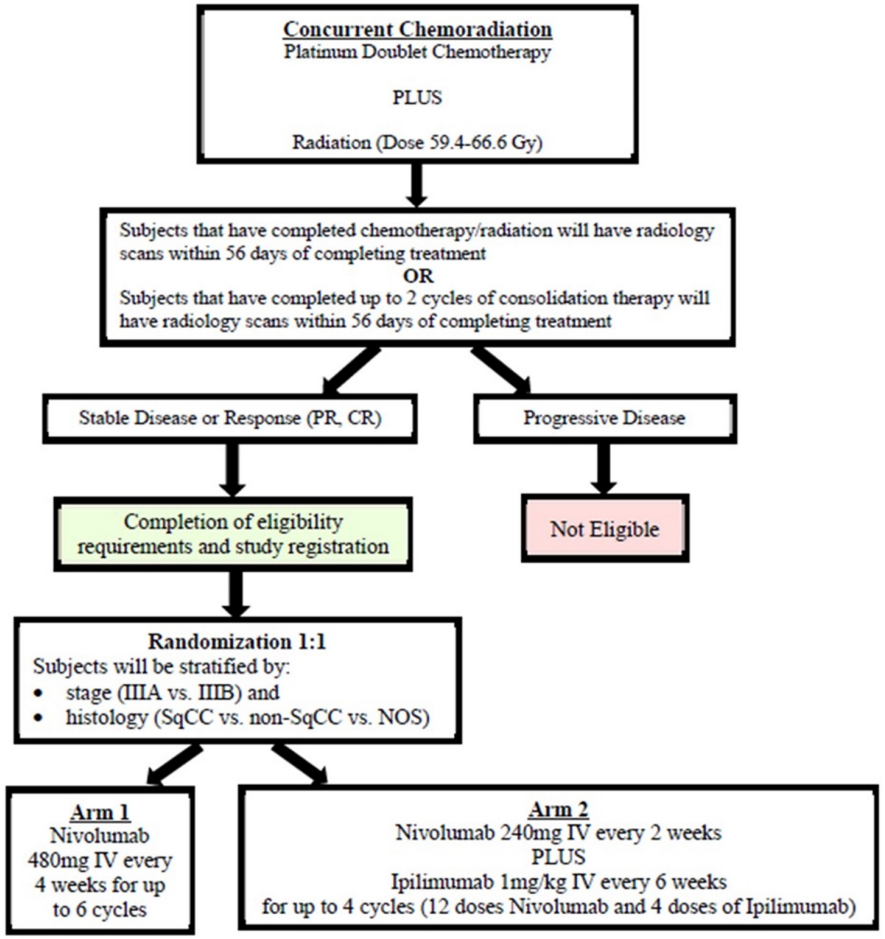
Is IO timing enough?

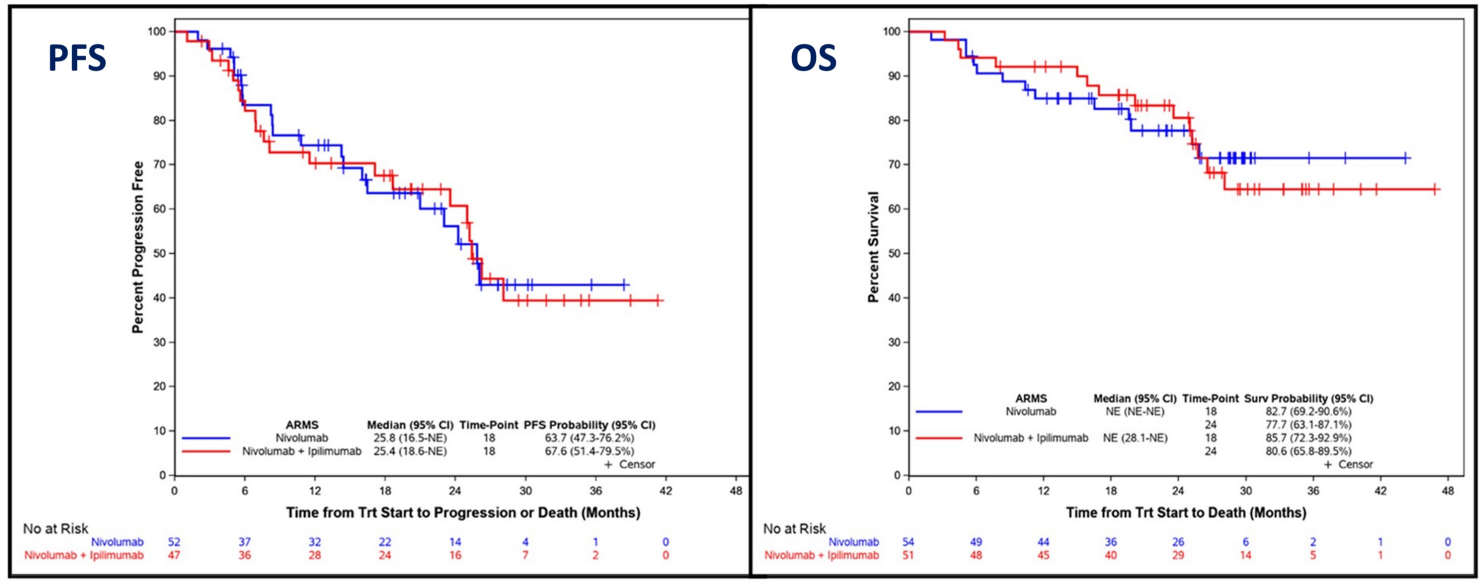
Treatment strategies in unresectable stage III NSCLC: beyond PACIFIC



Modified from: Cortiula F et al. Ann Oncol, 2022.

Consolidation Nivolumab plus Ipi or Nivo alone after chemoradiation for unresectable stage III NSCLC. BTCRC LUN 16-081.



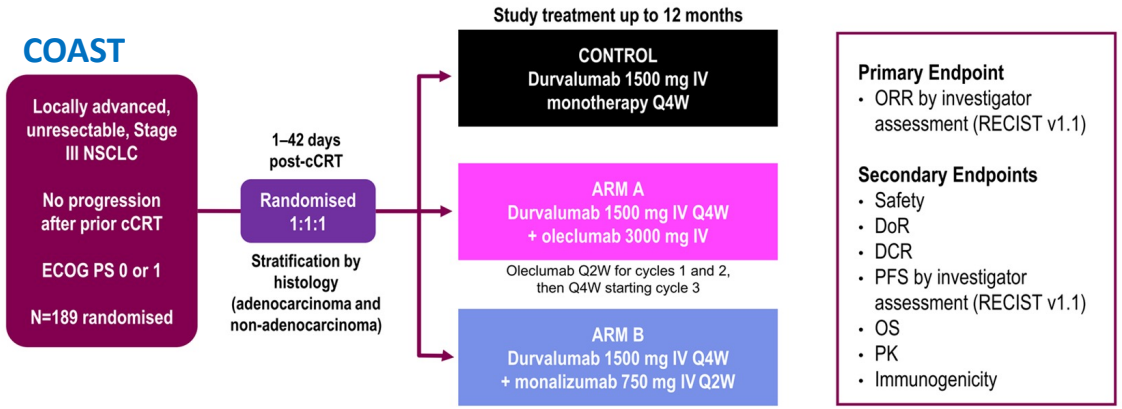


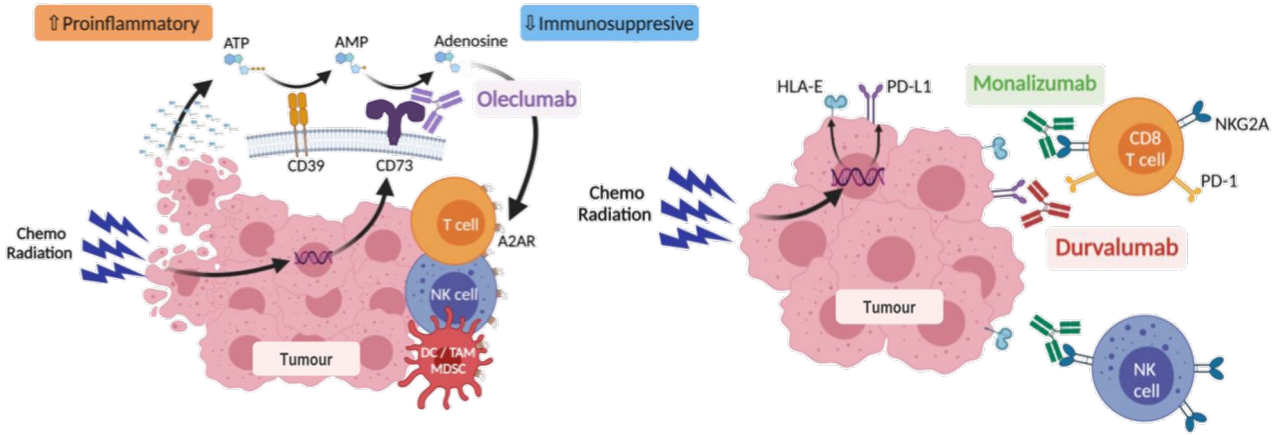
	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	27.7 (2-44.2)	29.2 (3.2-46.8)
Progression Free Survival*		
18- Month (95% CI)	63.7 (47.3-76.2)	67.6 (51.4-79.5)
P-value	<0.1	<0.1
Median, months (95% CI)	25.8 (16.5-NR)	25.4 (18.6-NR)
Overall Survival		
18- Month (95% CI)	82.7 (69.2-90.6)	85.7 (72.3-92.9)
24- Month (95% CI)	77.7 (63.1-87.1)	80.6 (65.8-89.5)
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

	Nivolumab Alone (N=54)	Nivolumab/Ipilimumab (N=51)
Any Treatment-Related AE (TRAE), n (%)	39 (72.2)	41 (80.4)
Any Grade ≥3 AE, n (%)*	21 (38.9)	27 (52.9)
Any Grade ≥3 TRAE, n (%)	10 (18.5)	14 (27.5)
TRAE Occurring in ≥ 10% Pts, n (%)		
Fatigue	17 (31.5)	16 (31.4)
Dyspnea	8 (14.8)	10 (19.6)
Rash	9 (16.7)	8 (15.7)
Hypothyroidism	7 (13)	8 (15.7)
Diarrhea	4 (7.4)	10 (19.6)
Pruritus	5 (9.3)	9 (17.7)
Arthralgia	2 (3.7)	6 (11.8)
Nausea	2 (3.7)	6 (11.8)
Pneumonitis		
Grade ≥2	12 (22.2)	16 (31.4)
Grade 3 (no Gr 4/5 pneumonitis)	5 (9.3)	9 (17.6)
Median time to Gr ≥2 Pneum, mo. (range)	11.9 (4.1-36.6)	7.3 (1.3-36.9)

IO-IO strategy in unresectable NSCLC: ongoing phase III trials

Trial	NCT	Intervention	Control	Cons.	Primary EP	Co-Target
CheckMate 73L	NCT04026412	CCRT + Nivo 360 mg q 3w → Nivo 360 mg q 3w + Ipi 1 mg/kg q 6w (A) CCRT + Nivo 360 mg q 3w → Nivo 480 mg q 4w (B)	PACIFIC (C)	12 mo	OS Arm A vs C,PFS arm A vs C	**CTLA4**
SKYSCRAPER-03	NCT04513925	cCRT → Tiragolumab 840 mg q4w + Atezolizumab 1680 mg q4w	PACIFIC	12 mo	PFS ITT & PD-L1+	**TIGIT**
KEYVIBE-006	NCT05298423	CCRT + Pembrolizumab / Vibostolimab → Pembrolizumab/ Vibostolimab	PACIFIC	12 mo	PFS (ITT, PD-L1+) OS (ITT, PD-L1+)	**TIGIT**
PACIFIC-8	NCT05211895	cCRT → Durvalumab 1500 mg IV q4w + Domvanalimab 20 mg/kg IV q4w	Durvalumab 1500 mg q4w	12 mo	PFS in PD-L1 TC ≥50%	**TIGIT**
PACIFIC-9	NCT05221840	cCRT → Durvalumab q4w + Oleclumab IV q4w (A) cCRT → Durvalumab q4w + Monalizumab IV q4w (B)	Durvalumab q4w (C)	12 mo 12 mo	PFS: A & B vs C	**CD73** **NKG2A**



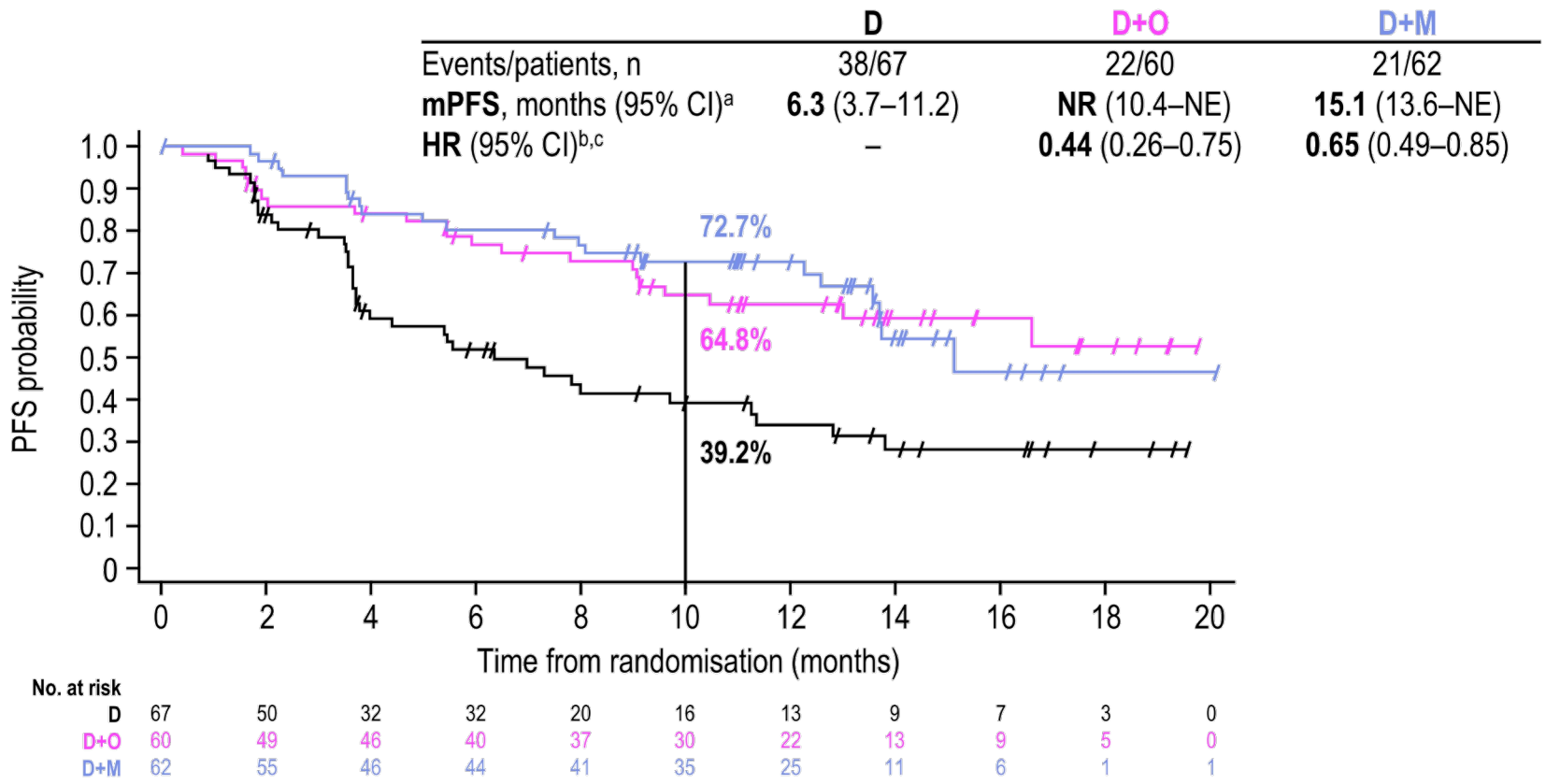


COAST: Activity and Progression free Survival

Antitumour activity by investigator assessment
(interim analysis; ITT population)

Antitumour activity	D (N=67)	D+O (N=60)	D+M (N=62)
Confirmed ORR (95% CI),[b] % [n]	**17.9 (9.6, 29.2)** [12]	**30.0 (18.8, 43.2)** [18]	**35.5 (23.7, 48.7)** [22]

ORR: Primary EP



Martinez-Marti A, ESMO 2021.
Herbst RS et al. J Clin Oncol, 2022.

COAST: safety

	Durvalumab (n = 66)		Durvalumab + Oleclumab (n = 59)		Durvalumab + Monalizumab (n = 61)	
Preferred Term	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Patients with at least 1 TEAE, No. (%)	65 (98.5)	23 (34.8)	57 (96.6)	21 (35.6)	61 (100)	16 (26.2)
Cough	12 (18.2)	0	18 (30.5)	1 (1.7)	27 (44.3)	0
Dyspnea	17 (25.8)	2 (3.0)	15 (25.4)	1 (1.7)	14 (23.0)	1 (1.6)
Asthenia	10 (15.2)	0	10 (16.9)	0	14 (23.0)	0
Pneumonitis	11 (16.7)	0	11 (18.6)	0	10 (16.4)	1 (1.6)
Pruritus	7 (10.6)	0	10 (16.9)	0	15 (24.6)	0
Hypothyroidism	10 (15.2)	0	9 (15.3)	0	12 (19.7)	0
Arthralgia	11 (16.7)	0	9 (15.3)	0	10 (16.4)	0
Diarrhea	7 (10.6)	1 (1.5)	7 (11.9)	0	12 (19.7)	0
Fatigue	7 (10.6)	0	8 (13.6)	0	9 (14.8)	0
Pyrexia	6 (9.1)	0	8 (13.6)	0	10 (16.4)	0
Rash	6 (9.1)	0	9 (15.3)	0	8 (13.1)	0
Back pain	7 (10.6)	2 (3.0)	5 (8.5)	0	9 (14.8)	0
Hyperthyroidism	8 (12.1)	0	6 (10.2)	0	6 (9.8)	0
Pneumonia	9 (13.6)	6 (9.1)	5 (8.5)	4 (6.8)	4 (6.6)	1 (1.6)
Productive cough	7 (10.6)	0	6 (10.2)	0	5 (8.2)	0
Decreased appetite	6 (9.1)	0	6 (10.2)	0	5 (8.2)	0
Constipation	10 (15.2)	0	4 (6.8)	0	2 (3.3)	0
Amylase increased	7 (10.6)	1 (1.5)	4 (6.8)	0	4 (6.6)	1 (1.6)
Insomnia	7 (10.6)	0	3 (5.1)	0	4 (6.6)	0
Nausea	8 (12.1)	0	1 (1.7)	0	5 (8.2)	0
Lymphocyte count decreased	4 (6.1)	2 (3.0)	8 (13.6)	4 (6.8)	1 (1.6)	0
Radiation pneumonitis	3 (4.5)	1 (1.5)	7 (11.9)	0	3 (4.9)	0
Hyperglycemia	2 (3.0)	0	6 (10.2)	0	3 (4.9)	0
Anxiety	0	0	1 (1.7)	0	7 (11.5)	0

TEAEs Occurring in ≥ 10% of Patients in Any Arm (all causality; as-treated population)

Safety summary (as-treated population)

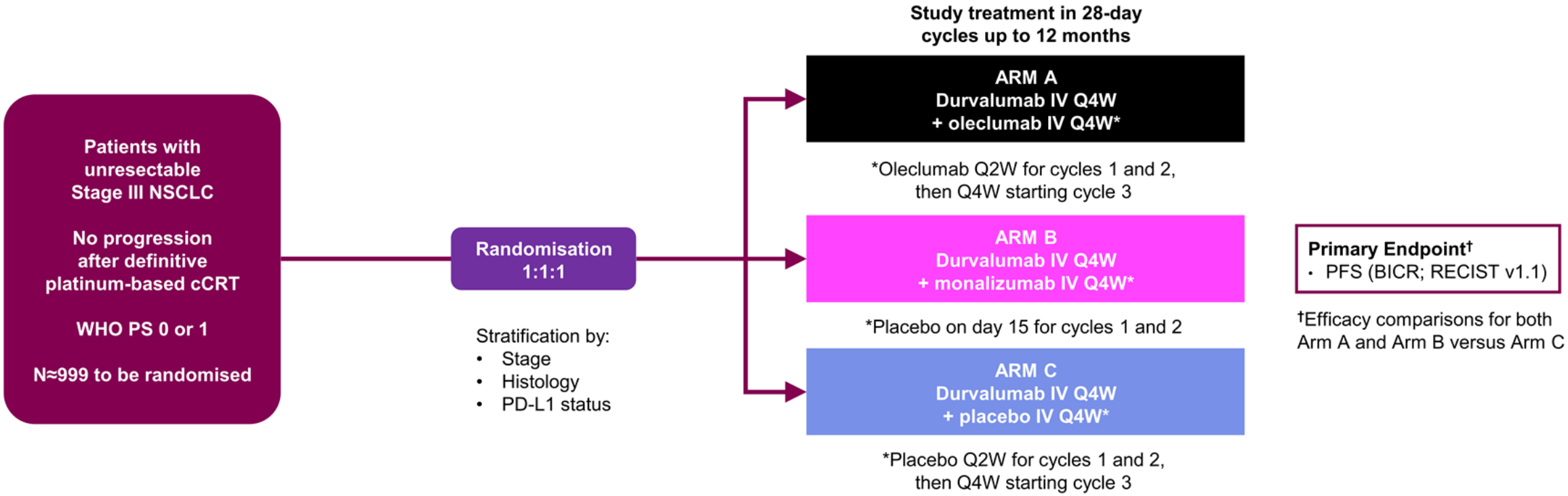
Incidence, n (%)	D (N=66)	D+O (N=59)	D+M (N=61)
Any TEAEs	65 (98.5)	57 (96.6)	61 (100)
Grade ≥3 TEAEs	26 (39.4)	24 (40.7)	17 (27.9)
Study drug-related AEs	49 (74.2)	46 (78.0)	50 (82.0)
Study drug-related SAEs	6 (9.1)	7 (11.9)	5 (8.2)
AEs leading to discontinuation	11 (16.7)	9 (15.3)	9 (14.8)
Deaths[a,b]	7 (10.6)	4 (6.8)	3 (4.9)

[a]All reported deaths within 90 days post-last dose, regardless of relationship to study drug
[b]In total, 4 deaths were related to study drug, 2 (pneumonitis and radiation pneumonitis) in the D arm, 1 (pneumonitis) in the D+O arm, and 1 (myocardial infarction) in the D+M arm

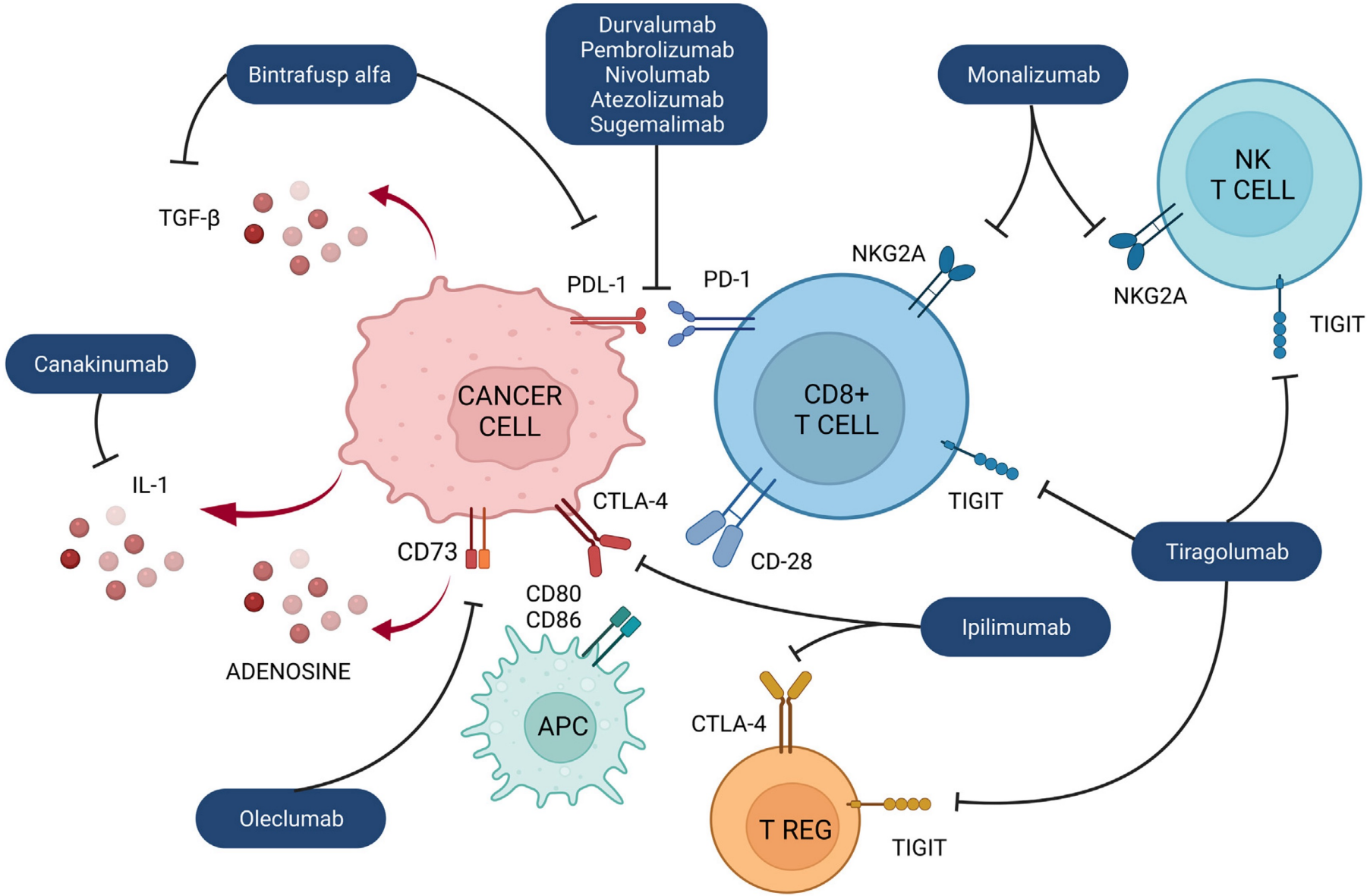
Herbst RS et al. J Clin Oncol, 2022.

PACIFIC 9:

Phase 3 study of durvalumab combined with oleclumab or monalizumab in patients with unresectable Stage III NSCLC

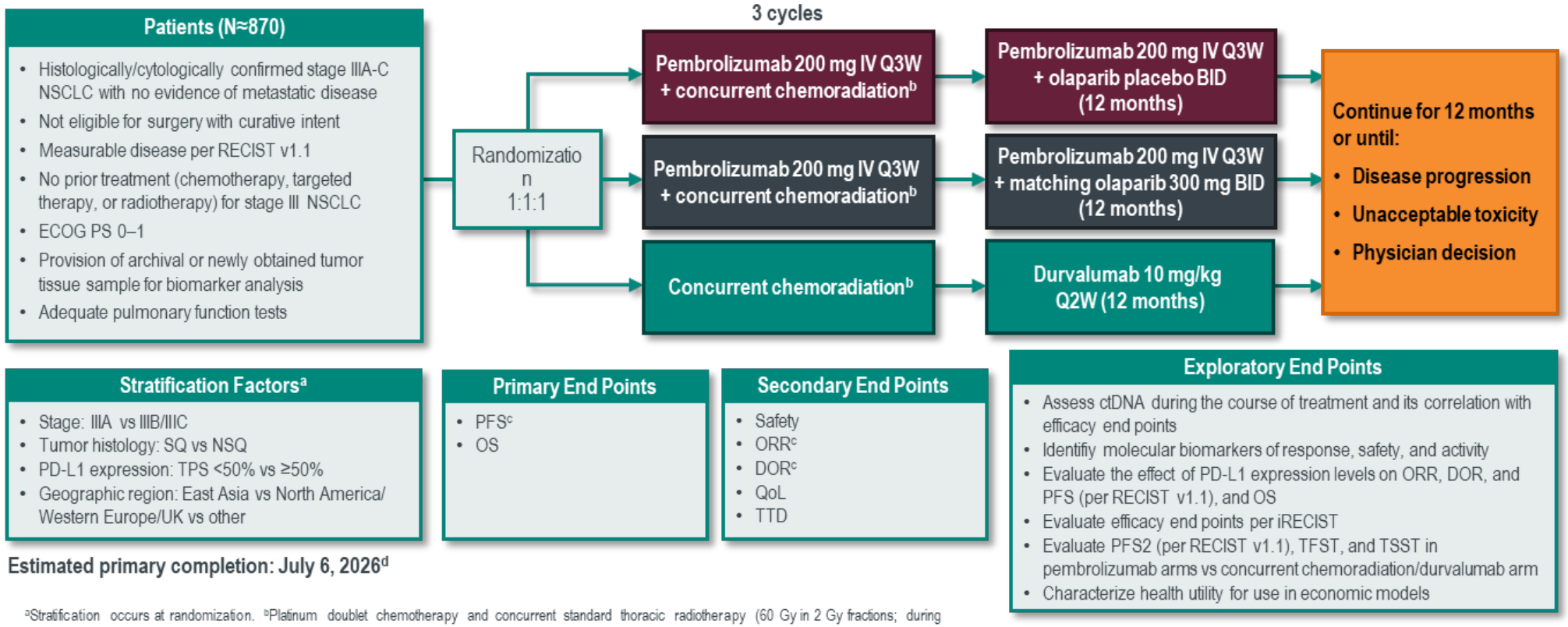


Treatment strategies in unresectable stage III NSCLC: beyond PACIFIC



Cortiula F et al. Ann Oncol, 2022.

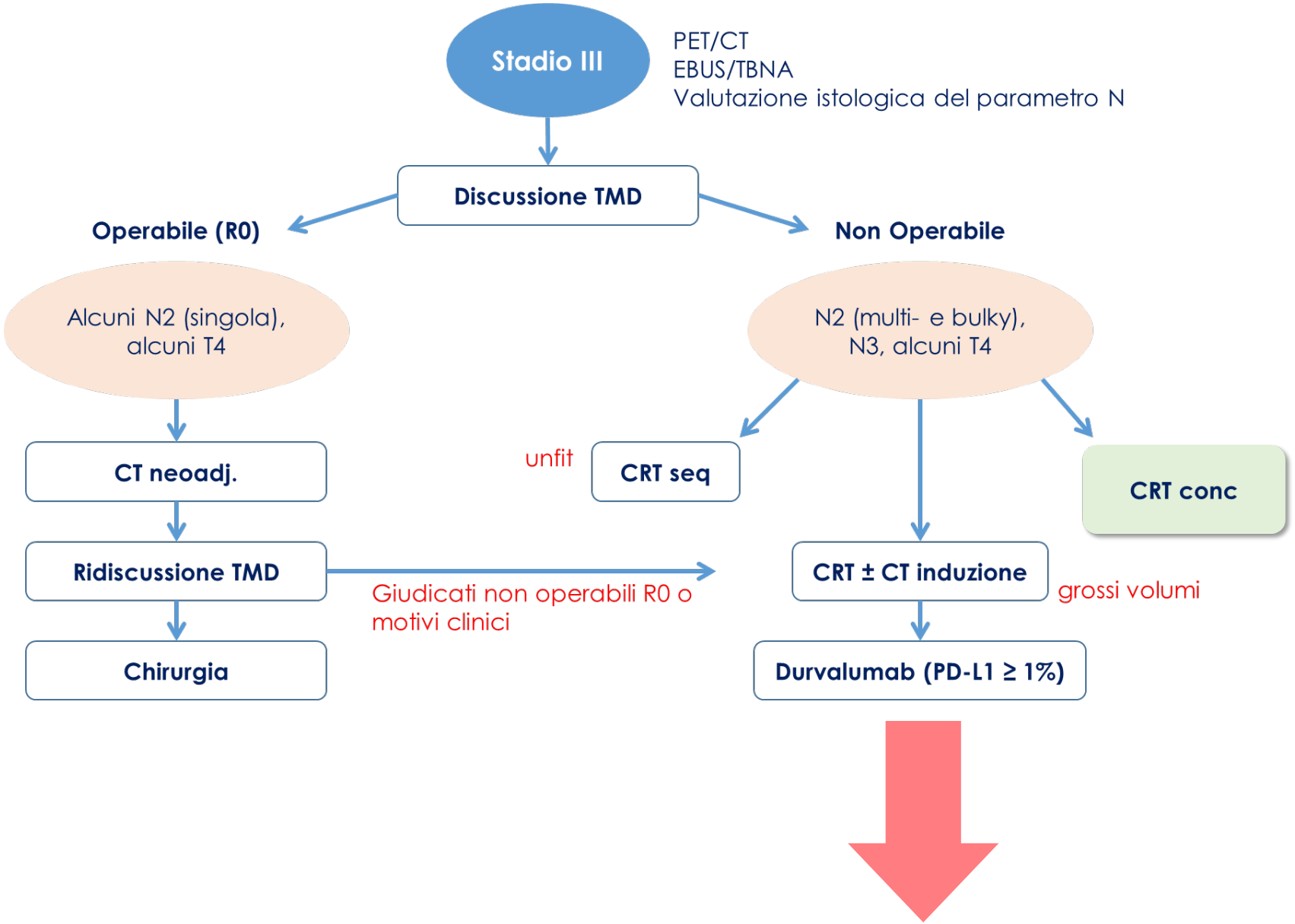
KEYLYNK-012: Phase III, randomized, double-blind, placebo-controlled study of pembrolizumab in combination with concurrent CRT followed by pembrolizumab ± olaparib vs concurrent CRT followed by durvalumab in patients with unresectable, locally advanced, stage III NSCLC - NCT04380636



[a]Stratification occurs at randomization. [b]Platinum doublet chemotherapy and concurrent standard thoracic radiotherapy (60 Gy in 2 Gy fractions; during cycles 2 and 3). Platinum doublet options (per investigator's choice) include cisplatin + pemetrexed (NSQ histology only), cisplatin + etoposide, and carboplatin + paclitaxel. [c]Assessed per RECIST v1.1 by BICR. [d]Subject to change.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04380636. Accessed: February 24, 2021. **2.** Jabbour et al. Presented at EMSO 2020. Abstract 1256TiP.

Algoritmo terapeutico dello stadio III



HOW TO TREAT AT PROGRESSION AFTER PACIFIC

Gestione delle recidive in pazienti affetti da NSCLC sottoposti a trattamento CHT-RT seguito da immunoterapia di consolidamento

Poliprogressione:
Approcci sistemici di ultima generazione

Associazione Italiana
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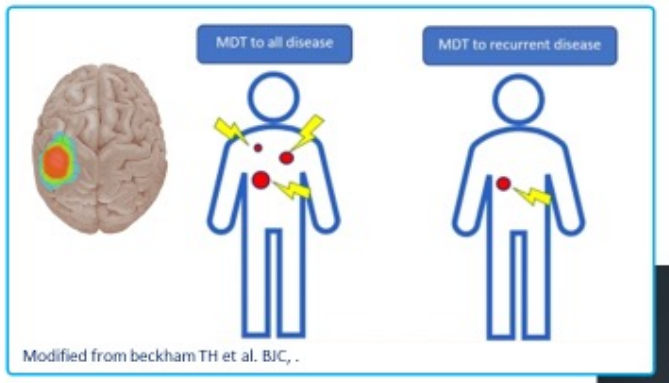

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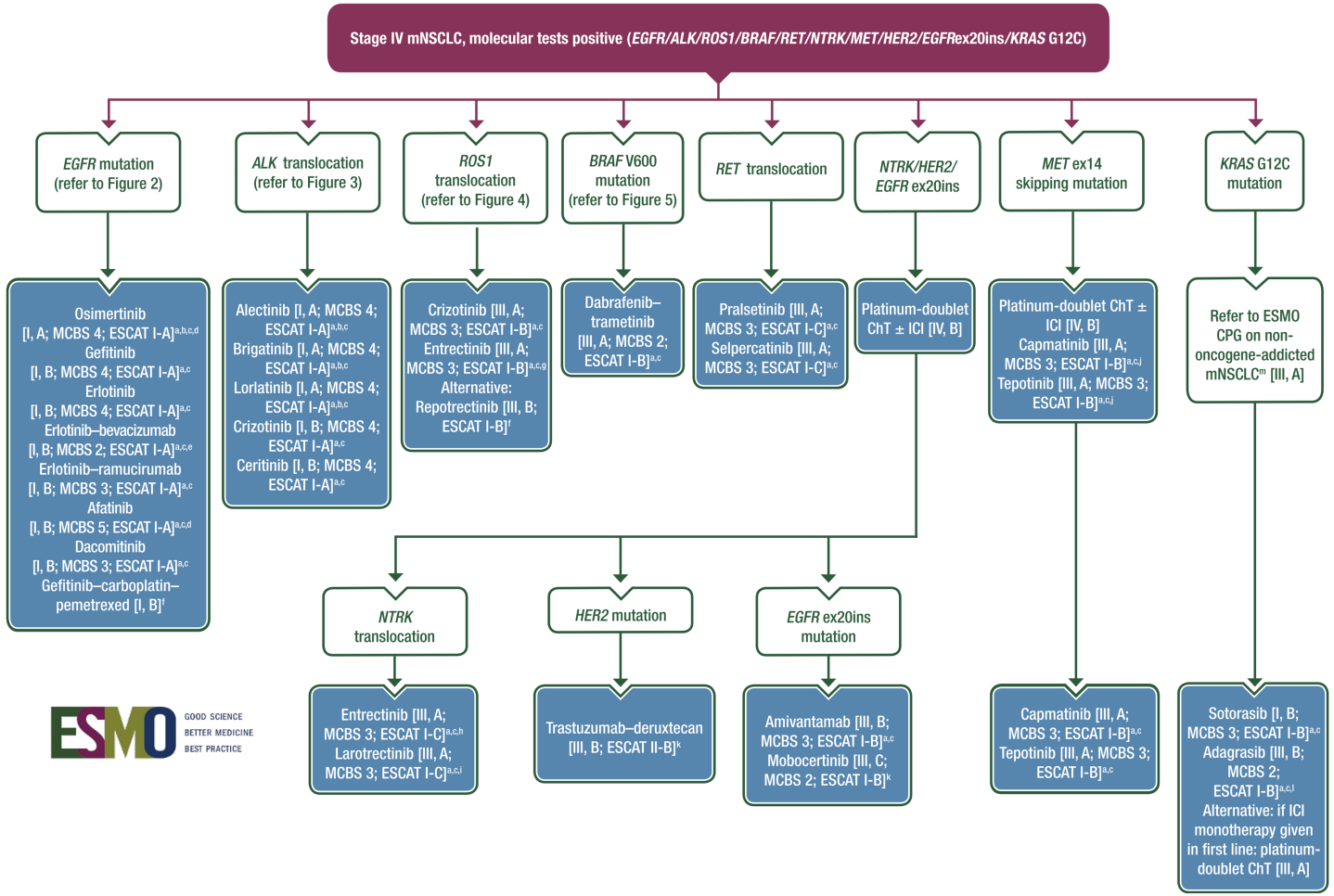
Oligoprogressive diasease

Data regarding the optimal therapeutic approach, including rechallenge, at widespread systemic progression on durvalumab are limited

What guidelines tell us…. Advanced disease

dGA: first line



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

L. E. Hendriks[1], K. M. Kerr[2], J. Menis[3], T. S. Mok[4], U. Nestle[5,6], A. Passaro[7], S. Peters[8], D. Planchard[9], E. F. Smit[10,11], B. J. Solomon[12], G. Veronesi[13,14] & M. Reck[15], on behalf of the ESMO Guidelines Committee*

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Available online 23 January 2023

Key words: ESCAT, ESMO Clinical Practice Guideline (CPG), ESMO-MCBS, oncogene-addicted metastatic non-small-cell lung cancer (mNSCLC), treatment, targeted therapy

INCIDENCE AND EPIDEMIOLOGY

Details on incidence and epidemiology are covered in the Supplementary Material Section 1, available at https://doi.org/10.1016/j.annonc.2022.12.009.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnostic procedures

Details on diagnostic procedures are covered in the Supplementary Material Section 2, available at https://doi.org/10.1016/j.annonc.2022.12.009. See Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.12.009 for a flow chart on diagnosis and testing biopsy/cytology samples in stage IV non-small-cell lung cancer (NSCLC).

Pathology and molecular biology

Biomarker testing is essential to identify subgroups of NSCLC with oncogenic drivers that can be therapeutically targeted. These drivers are mainly found in lung adenocarcinomas (LUADs). Demonstration of the specific molecular alteration is necessary to tailor treatment with the appropriate targeted therapy. The frequency of oncogenic drivers in NSCLC as well as general discussion of testing strategy and methodology, including the use of liquid biopsies, can be found in the Supplementary Material Section 3, available at https://doi.org/10.1016/j.annonc.2022.12.009.

Many parameters might determine which tests are required; pre-eminent amongst them is access to appropriate drugs.[1] Testing is mandatory for oncogenic drivers for which drugs are approved for routine usage. Broader testing may be used to support early drug access or clinical trials.[2,3] For personalised therapy approaches, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT) classifications[4] need to be considered (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.009).

Clinically-relevant *EGFR* gene mutations in NSCLC include substitutions, deletions and insertions in exons 18-21 that activate the tyrosine kinase and variably confer sensitivity or resistance to available epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) or other drugs.[3,5] The most common alterations conferring sensitivity to first- to third-generation TKIs are the exon 21 L858R substitution and exon 19 deletion mutations. At a minimum when resources or material are limited, these mutations should be evaluated. The next most common alteration is a large group of exon 20 insertions mostly resistant to current EGFR TKIs but sensitive to some emerging agents (discussed in the treatment paragraph including *EGFR* exon 20 insertions). Other mutations, including in exon 18, variably sensitise, while some mutations confer resistance and may

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☆Note: Approved by the ESMO Guidelines Committee: February 2002, last update December 2022. This publication supersedes the previously published version—*Ann Oncol* 2018;29 (Suppl 4):iv192-iv237.

No dGA… ????

PD-L1≥ 50%
…nza di alterazioni
…olari driver

→ **Pembrolizumab**
Atezolizum…
Cemip…

→ **Progressione** → **Chemioterapia a base di platino**

PD-L1 < 50% o ND
in assenza di alterazioni molecolari driver
Istologia non-squamosa

→ **…mioterapia con platino + …emetrexed + Pembrolizumab per 4 cicli;**
Nivolumab + ipilimumab + 2 cicli di chemioterapia con platino + pemetrexed

→ **Risposta o stabilità** → **Mantenimento* o follow-up**

*con pemetrexed + pembrolizumab o nivolumab + ipilimumab per due anni

→ **Progressione** → **Docetaxel +/- Nintedanib; Nivolumab⁺, Atezolizumb⁺, Pembrolizumab⁺**

P… 50% o ND
…senza di alterazioni molecolari driver
…istologia squamosa

→ **Chem… a base carboplatino + …clitaxel + Pembrolizumab …cli; Nivolumab + ipilimu… cicli di chemioterapia … platino + (nab) paclitaxel**

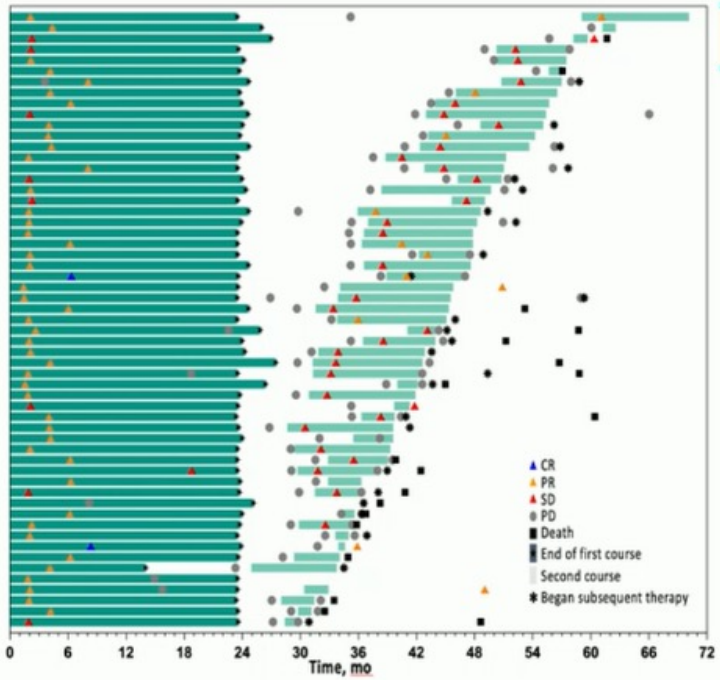
→ **Risposta o stabilità** → **Mantenimento** o follow-up**

→ **Progressione** → **Docetaxel; Nivolumab⁺, Atezolizumb⁺, Pembrolizumab⁺**

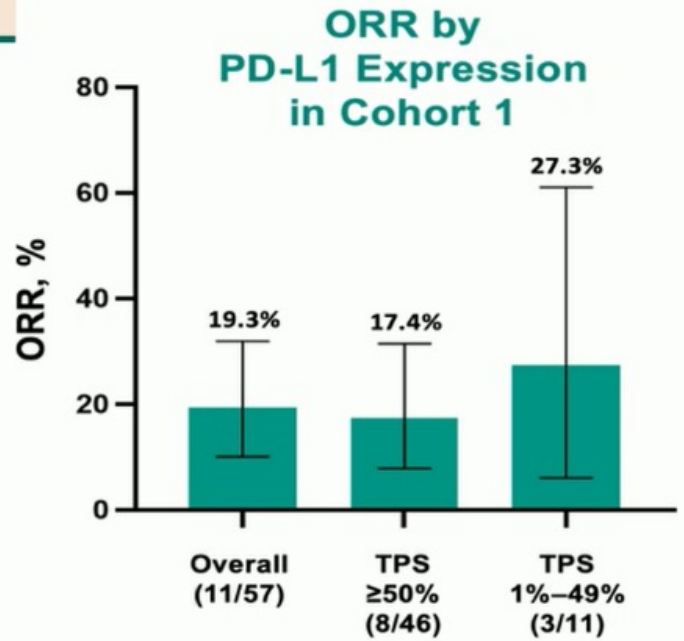
⁺in pazienti a progressione a chemioterapia (che non hanno ricevuto immunoterapia in prima linea)

ICIs rechallenge:
The Pembro lesson:encouraging data from RCT

Pooled analysis: Pembrolizumab retreatment after completion of 2 years of first-line pembrolizumab (KN-042 in PD-L1>=1%, KN-024 + KN-598 in PD-L1>=50%)



	N = 57
ORR (95% CI), %	**19% (10–32)**
DCR(95% CI), %	**74 (60–84)**
DOR ≥6 mo, %	**79%**
OS, median (95% CI), mo	27.5 (21.7–NR)
PFS, median (95% CI), mo	**10.3 (6–14)**
Treatment related AE	25%
Grade 3-4	5%
Discontinued for AE	1



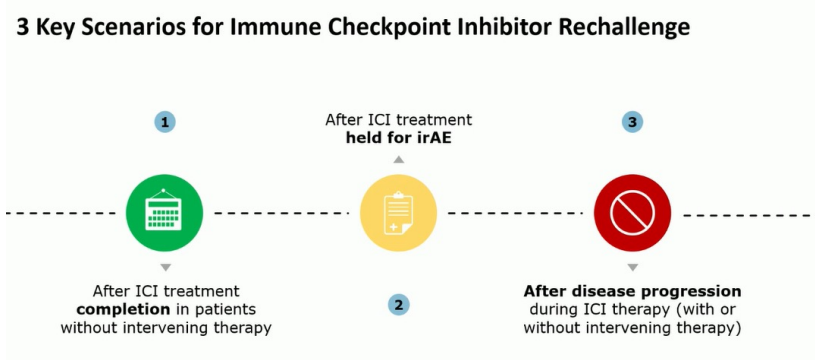
Median time from stopping pembrolizumab to restart	**12.0 months (3.8–35.6)**
Time from start of second course to data cutoff	**21.5 months (0.6–46.5)**

Rodriguez Abreu et al. WCLC, 2022.

ICIs rechallenge

Meta-analysis	Reason ICI discontinued	Overall response rate	Median PFS	Immune related adverse events
Cai et al.	All patients	20%		41% G3+ 13%
	Disease progression	8%		
	irAE or clinician decision	34%		
Inno et al.	All patients	21.8%	4.9 m	52% G3+ 22%
	Disease Progression	15%	2.9 m	57%
	irAE	44%	13.2 m	42%
Xu et al.	Disease Progression	11%		G3+ 9%
	irAE	20%		
	Completion	46%		

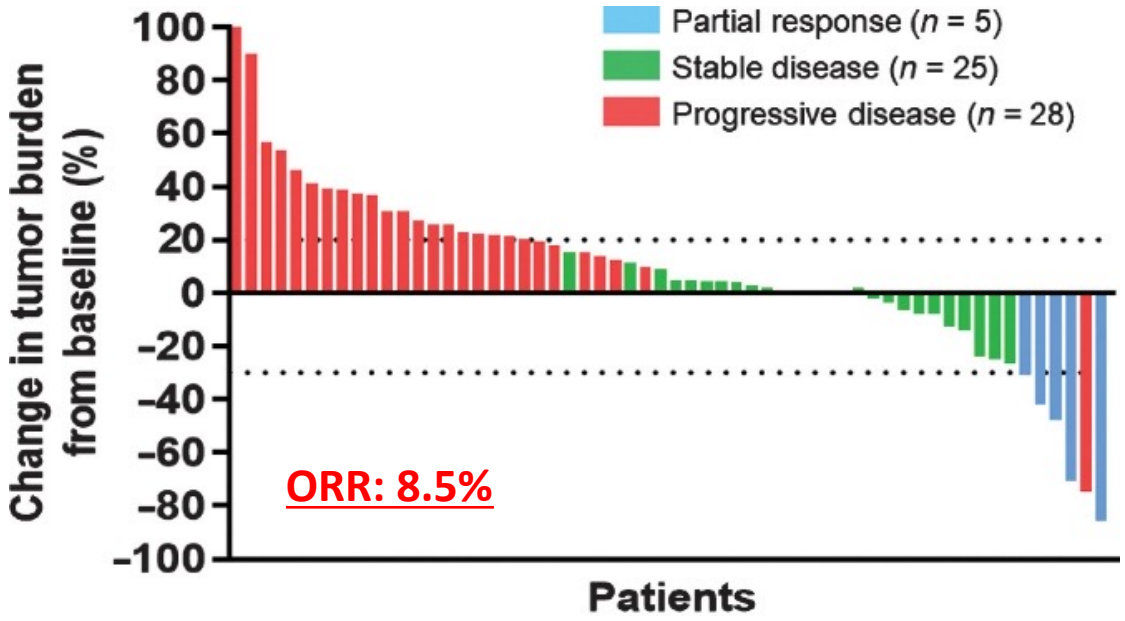
Cai et al. Transl Lung Cancer Res 2022; 11:1555-1566; Inno A, et al. Crit Rev Oncol Hem 2021; 165:103434; Xu S, et al. JTO Clin Res Rep 2022; 3:100309

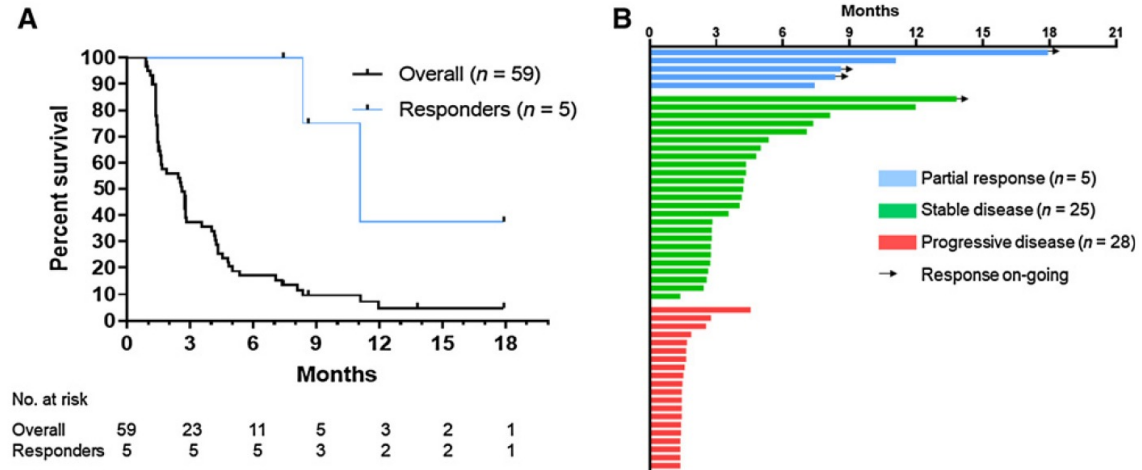


Natasha Leighl

Open questions in immunotherapy for advanced NSCLC: Duration of IO, combinations and rechallenge

Nivolumab retreatment: timing matters



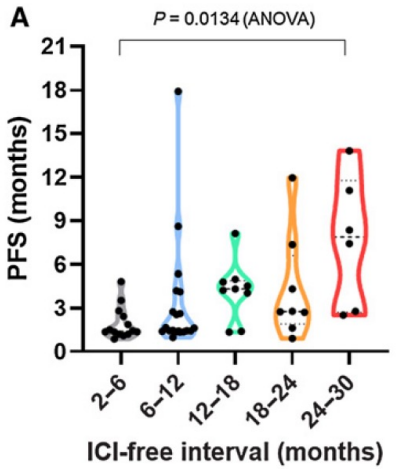


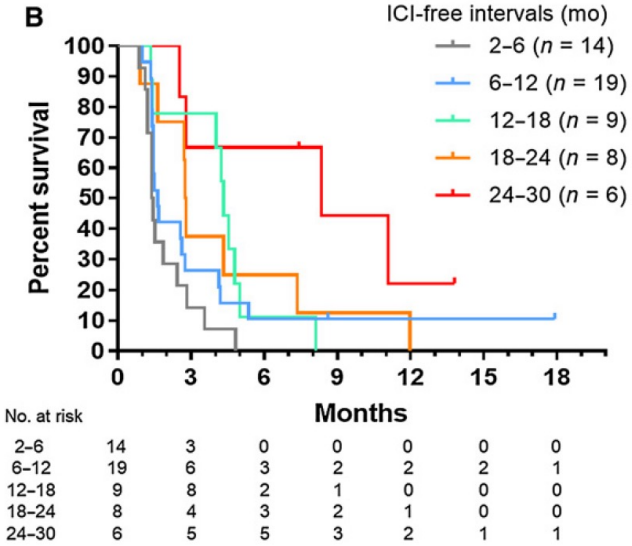
mPFS: 2.6 months
5 responders mPFS 11.1 months

Table 2. Cox-proportional hazard regression analysis for PFS.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≤70/>70)	1.10 (0.64–1.87)	0.73		
Sex (male/female)	1.25 (0.69–2.29)	0.47		
Smoking history (yes/no)	1.55 (0.75–3.18)	0.23		
ECOG PS (0/1)	0.73 (0.42–1.28)	0.28		
Histology (non-Sq/Sq)	0.45 (0.25–0.81)	0.01	0.57 (0.31–1.05)	0.07
Stage (III, IV/recurrence)	1.35 (0.72–2.53)	0.35		
PD-L1 expression at diagnosis (<50%/≥50%)	1.24 (0.89–1.70)	0.59		
Response with prior ICI (CR, PR/SD ≥ 6 months)	0.85 (0.48–1.49)	0.56		
Duration of prior ICI (≤8.1 months/>8.1 months)	1.83 (1.02–3.30)	0.04	1.27 (0.68–2.38)	0.46
ICI-free interval (≤9.2 months/>9.2 months)	2.61 (1.47–4.64)	0.001	2.02 (1.10–3.73)	0.02
History of irAE with prior ICI (yes/no)	0.51 (0.28–0.91)	0.02	0.69 (0.37–1.29)	0.24

Abbreviations: Non-Sq, non-squamous; PS, performance status; Sq, squamous.





…ICI free interval matters

Akamatsu H et al. Clin Cancer Res, 2022.

IRCCS "Giovanni Paolo II"
PugliaSalute

Phase II, two-cohorts, randomized trial comparing standard of care versus immune-based combination in relapsed stage III non-small-cell lung cancer (NSCLC) pretreated with chemoradiotherapy and durvalumab

CONDOR

Key Eligibility Criteria
- NSCLC with systemic or local relapse after curative CT-RT followed by durvalumab
- At least 2 and no more than 4 platinum-based CT cycles
- ECOG PS 0–1
- Evidence of *EGFR*, *ALK* ,*ROS1* wild type

A — Relapsed during durvalumab therapy → R → Investigator's choice single-agent CT + durvalumab

B — Relapsed during durvalumab therapy → R → Investigator's choice single-agent CT

Both A and B → Until PD

C — Relapsed after completion of durvalumab therapy → R → Investigator's choice platin-doublet + durvalumab x 4 cycles followed by maintenance durvalumab+olaparib → Until PD

D — Relapsed after completion of durvalumab therapy → R → Investigator's choice platin-doublet + durvalumab x 4 cycles followed by maintenance durvalumab

Primary endpoints:
- OS

Secondary endpoints:
- PFS
- ORR
- Safety
- PFS and OS according to biomarkers

Recruiting

FoRT Fondazione Ricerca Traslazionale

Agenda

- How to increase survival in unresctable LA NSCLC?
  - New therapeutic scenarios
  - What to expect at progression from PACIFIC?

- Special populations (EGFRm)

- (Un)Resectable… Uncertain

CONTROVERSIES IN THORACIC ONCOLOGY J Thor Oncol, 2021; 16:12.

IASLC

Consolidation Durvalumab Should Not Be Administered to Patients With Stage III *EGFR*-Mutant NSCLC

Check for updates

Jacqueline V. Aredo, MD, MS,[a] Jessica A. Hellyer, MD,[b] Joel W. Neal, MD, PhD,[c] Heather A. Wakelee, MD[c,*]

CONTROVERSIES IN THORACIC ONCOLOGY

IASLC

Durvalumab Consolidation Should Be the Standard Therapy in Stage III *EGFR*-Mutant NSCLC After Chemoradiation

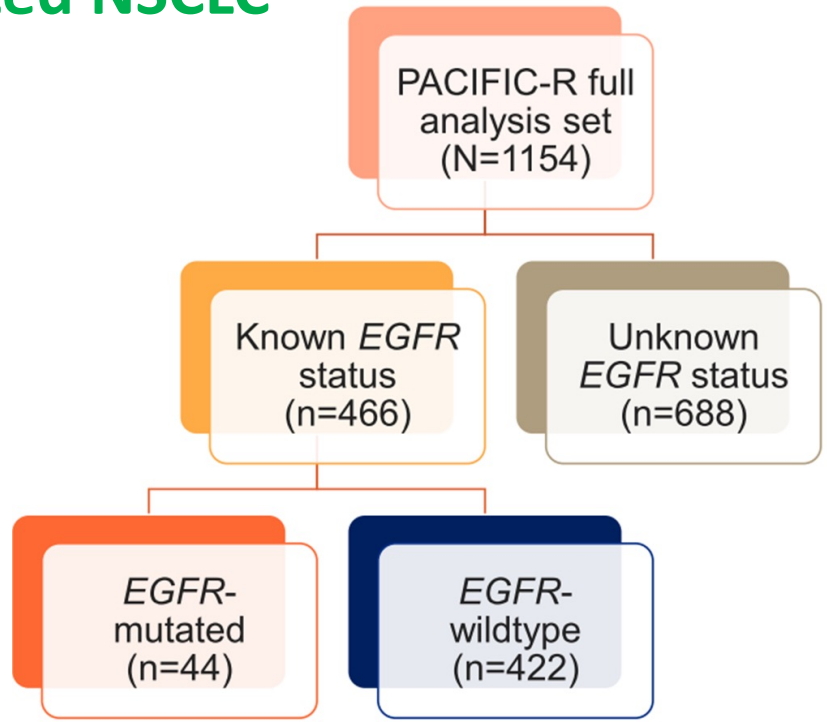
Check for updates

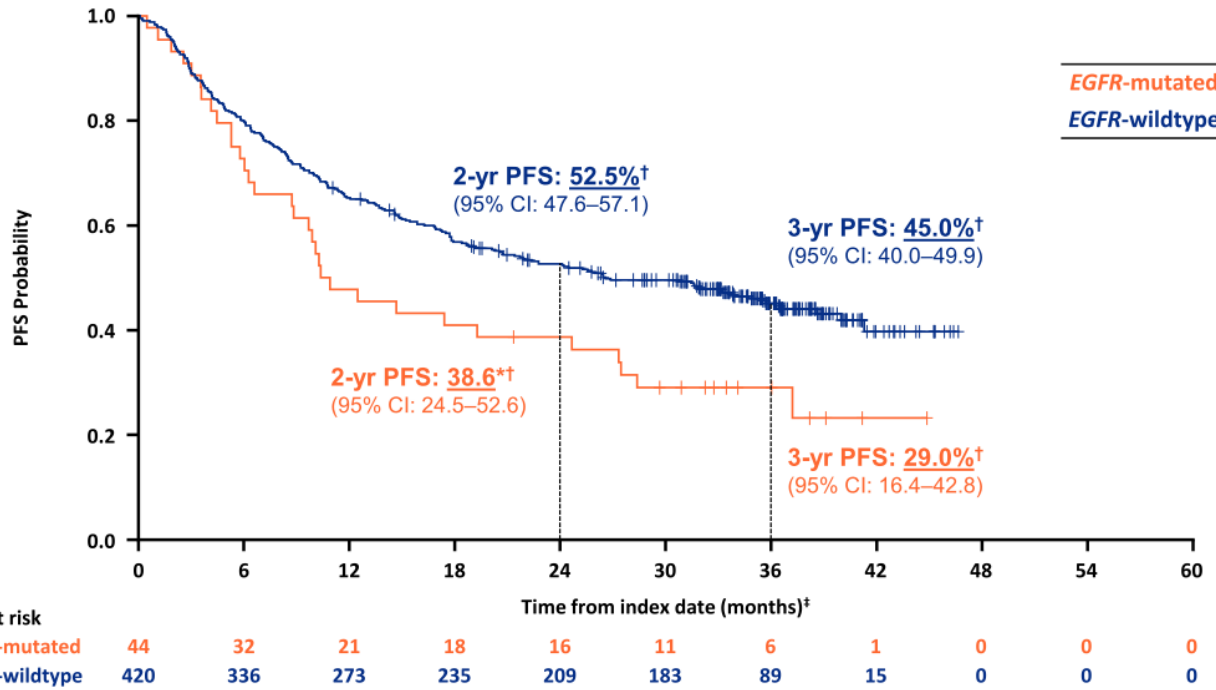
Daniel Morgensztern, MD,* Ramaswamy Govindan, MD

J Thor Oncol, 2021; 16:12.

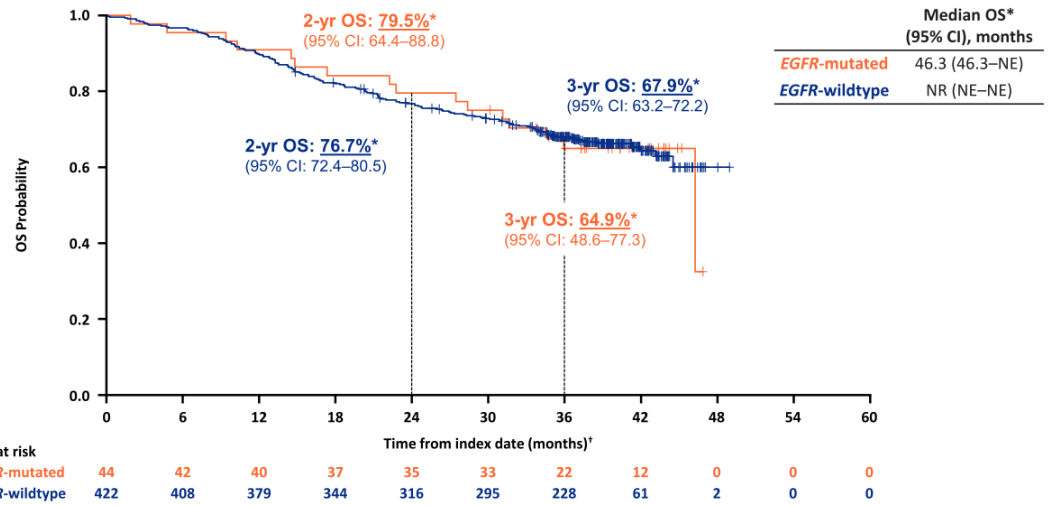
PACIFIC-R: outcomes in unresectable stage III EGFR-mutated NSCLC

- Documentation of EGFR status was not a requirement for participation in the PACIFIC EAP or PACIFIC-R
- 466 of 1154 patients (40.4%) in the PACIFIC-R full analysis set had a known EGFR status:
  - 44 of 466 (9.4%) had EGFR-mutated NSCLC
  - 422 of 466 (90.6%) had EGFR-wildtype NSCLC





	Median PFS† (95% CI), months
EGFR-mutated	10.6 (8.7–27.3)
EGFR-wildtype	26.4 (20.5–35.7)



	Median OS* (95% CI), months
EGFR-mutated	46.3 (46.3–NE)
EGFR-wildtype	NR (NE–NE)

Peters S. WCLC, 2023.

Rethinking therapy for unresctable LA NSCLC

Stage III Unresectable NSCLC

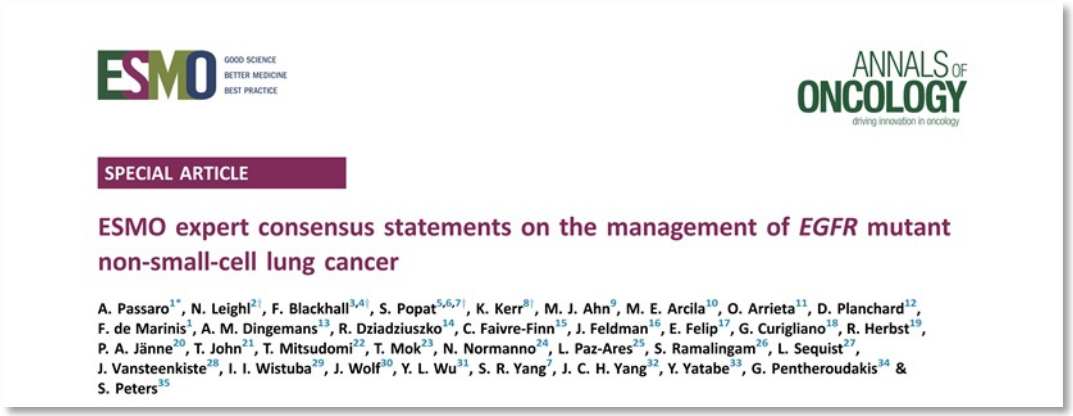
- **PD-L1**
- **CGP** EGFR, ALK, ROS1, KRAS

PD-L1 ≥ 1%, no genomic alterations

cCRT ± Durvalumab

Driver mutations ?

CLINICAL TRIAL



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO expert consensus statements on the management of *EGFR* mutant non-small-cell lung cancer

A. Passaro[1*], N. Leighl[2†], F. Blackhall[3,4†], S. Popat[5,6,7†], K. Kerr[8†], M. J. Ahn[9], M. E. Arcila[10], O. Arrieta[11], D. Planchard[12], F. de Marinis[1], A. M. Dingemans[13], R. Dziadziuszko[14], C. Faivre-Finn[15], J. Feldman[16], E. Felip[17], G. Curigliano[18], R. Herbst[19], P. A. Jänne[20], T. John[21], T. Mitsudomi[22], T. Mok[23], N. Normanno[24], L. Paz-Ares[25], S. Ramalingam[26], L. Sequist[27], J. Vansteenkiste[28], I. I. Wistuba[29], J. Wolf[30], Y. L. Wu[31], S. R. Yang[7], J. C. H. Yang[32], Y. Yatabe[33], G. Pentheroudakis[34] & S. Peters[35]

9: In patients with *EGFR*-mutant inoperable stage III NSCLC, undergoing curative-intent chemoradiotherapy, what is the role of consolidation ICI therapy?

STATEMENT: In *EGFR*-positive disease, the use of consolidation ICI therapy after curative-intent chemoradiotherapy (CT-RT), is not recommended [I,C].

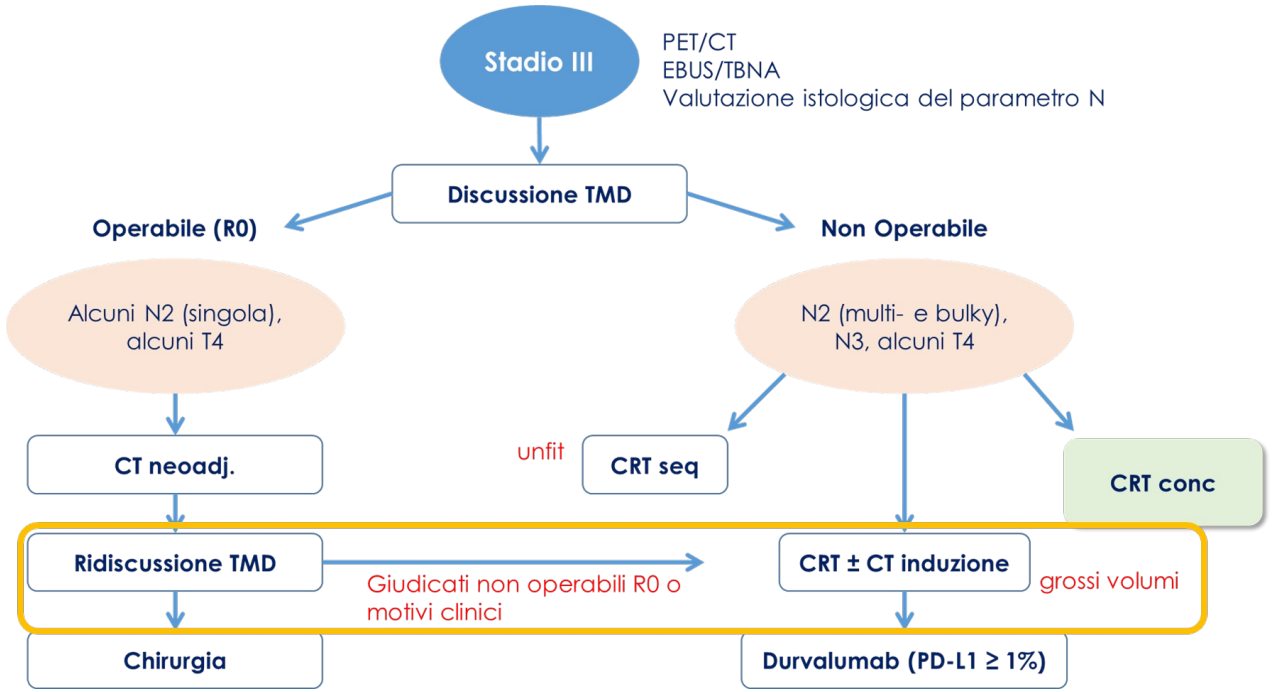
Passaro A et al. Ann Oncol, 2022.

Some ongoing trials with target approach in unresectable LA-NSCLC in patients with dGA

Study	dGA	Phase	NCT
Osimertinib Maintenance After Definitive Chemoradiation in Patients With Unresectable EGFR Mutation Positive Stage III Non–small-cell Lung Cancer: LAURA Trial in Progress	EGFR	III	NCT03521154
A Study of Lazertinib as Consolidation Therapy in Patients With Locally Advanced, Unresectable, EGFR-Mutant Non-Small Cell Lung Cancer (Stage III) Following Chemoradiation Therapy (PLATINUM)	EGFR	II	NCT05338619
Afatinib Sequenced With Concurrent Chemotherapy and Radiation in EGFR-Mutant Non-Small Cell Lung Tumors: The ASCENT Trial	EGFR	II	NCT01553942
Combination of Almonertinib and Concurrent Chemoradiotherapy in Unresectable Stage III NSCLC	EGFR	-	NCT04952168
Brigatinib Post Definitive Chemo-radiotherapy in Patients With ALK-fusion Non-small Cell Lung Cancer (BOUNCE)	ALK	II	NCT05718297

Agenda

- How to increase survival in unresctable LA NSCLC?
  - New therapeutic scenarios
  - What to expect at progression from PACIFIC?
- Special populations (EGFRm)
- (Un)Resectable… Uncertain



Efficacy data: Adjuvant and Peri-Adjuvant…: which best?

	NeoAdj	Peri-Adj				Adj
	CM816 (chemo-Nivo)	AEGEAN (chemo-Durva)	Neotorch (Chemo-Tori)	KN671 (chemo-Pembro)	CM77T (chemo-Nivo)	IMpower010 (Atezo)
Randomized	358 1:1	802 (1:1)	404 (1:1)	797 (1:1)	461 (1:1)	507 (1:1)
Endpoints	PCR, EFS	PCR, EFS	MPR, EFS (by stage)	EFS, OS	PCR, EFS	EFS
Stages	II-IIIB	II-IIIB	IIIA/B	II-IIIB	II-IIIB	IB-IIIA
Surgery (%)	83	81	82	82	78	-
pCR (%)	24	17.2	24.8	18.1	25.3	-
EFS median (months)	NR	NR	NR	NR	NR	NR
EFS 2 yrs (%)	65	63.3	67	62	70	60*
EFS HR	0.68	0.68	0.40	0.58	0.58	0.69*
OS median	NR	NR	NR	NR	NR	NR
OS 2 yrs (%)	82.7	63.3	67	62	70	84.8**
OS HR	0.62	-	-	0.73	-	0.42**

*Stage II-IIIA, PDL-1 > 1%.
**Stage II-IIIA, PD-L1 ≥ 50%, EGFR-ALK neg

Consensual definition of stage III NSCLC Resectability: EORTC-Lung Cancer Group initiative with other scientific societies

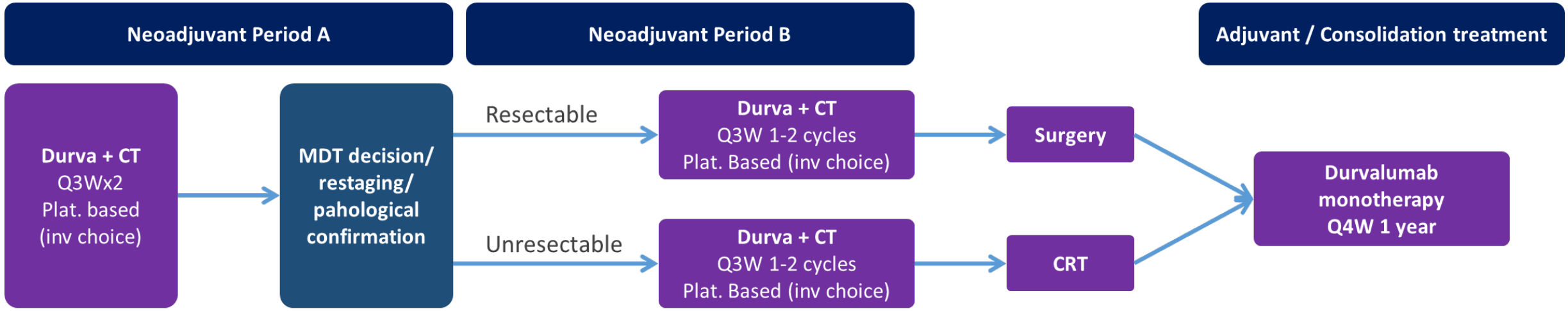
	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY¶	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE*§	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

***Multiple station N2**: case-by-case discussion; the exact number of nodes/stations cannot be defined
¶**Bulky N2**: lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of *highly selected patients*, including those patients in multidisciplinary trials with surgery as local therapy can be discussed
§Some **T4 tumours by infiltration of major structures** are potentially resectable – see Table 1

Dingemans AM, WCLC 2023.

MDT-BRIDGE (NCT05925530)

A Multicentre, Phase II, Single-Arm, Interventional Study of Neoadjuvant Durvalumab and Platinum-based CT, followed by either surgery and adjuvant Durvalumab or CRT and consolidation Durvalumab, in patients with resectable or borderline resectable Stage IIB-IIIB NSCLC



Primary EP: Resection rate is defined as the proportion of all participants who completed all intended neoadjuvant therapy, MDT re-assessment, and definitive surgical resection of the primary tumour.

Concluding remarks: a long and winding road

- PACIFIC regimen is still the standard of care in unresectable LA NSCLC (fit for cCRT and IO, PD-L1+)
- Concerns about PACIFIC in oncogene-addicted NSCLC (EGFRm)…. Waiting for LAURA
- IO timing: will add benefit?
- IO-IO combinations are under investigation in phase 3 trials: promising results from the phase 2 COAST trial: Durvalumab + Oleclumab or Monalizumab; PACIFIC-9 ongoing.
- What to do at progression? Not defined strategy. IO rechallenge may be helpuful in responders (not those with primary or secondary resistance), but no IO compound is registered in this setting. Phase 2 Condor trial may address a response.
- NeoAdjuvant and peri-operative IO may change clinical practice in potentially resectable NSCLC
- Algorithm of treatment of LA-NSCLC is under redefinition and construction (neoadjuvant IO, adjuvant IO, adjuvant Osimertinib and Alectinib)
- To test, to test, to test…