Immunoterapia adiuvante nella malattia non-oncogene addicted

Alessandro Del Conte

Centro di Riferimento Oncologico (CRO)
Oncologia Medica e dei Tumori Immunocorrelati
Pordenone - Aviano

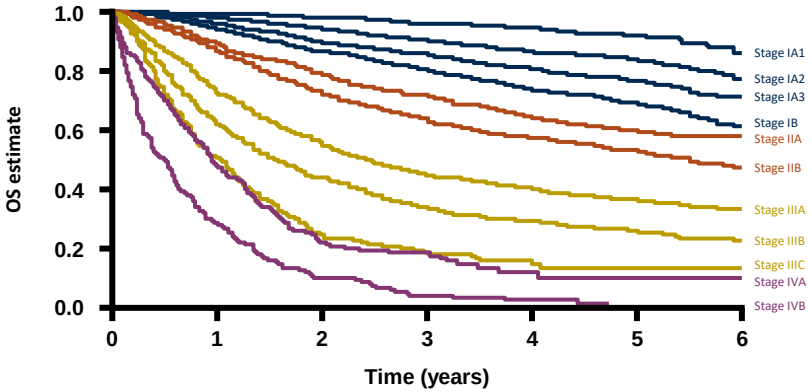
Disclosures

- **Advisory Boards / Honoraria / Speakers' fee / Consultant for**:
  - MSD
  - Astra-Zeneca
  - BMS
  - Roche
  - Boehringer Ing.

Agenda

- Terapia adiuvante con ICI
- Ruolo della fase adiuvante nella strategia peri-operatoria con ICI+CT
- Prospettive future

Sopravvivenza in paz con NSCLC resecabili stadio II-III (AJCC 8°)



5-year survival[1]

Stage I	**68–92%**
Stage II	**53–60%**
Stage III	**13–36%**
Stage IV	**0–10%**

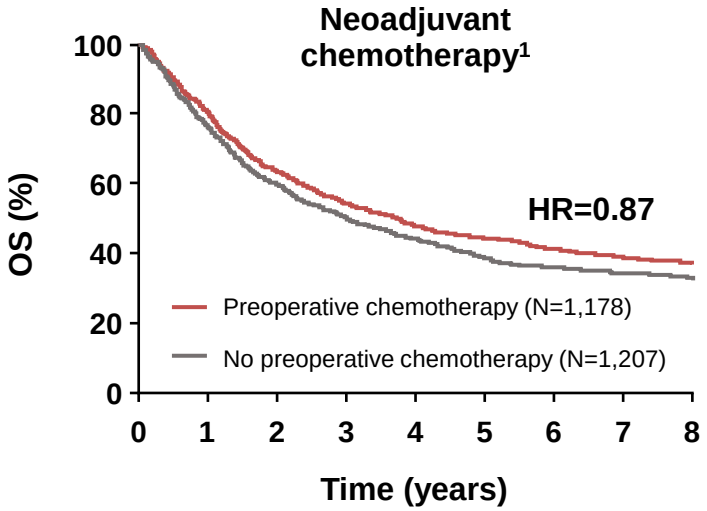
30-35%DG

- ~ 25% dei pazienti con NSCLC si presenta con malattia resecabile (St.I)[1,2]
- La chirurgia rimane il trattamento curativo d'elezione per i pazienti elegibili con NSCLC in stadio precoce[2]

- ~ 35-60% dei pazienti sviluppa una recidiva dopo la sola chirurgia[1,2]

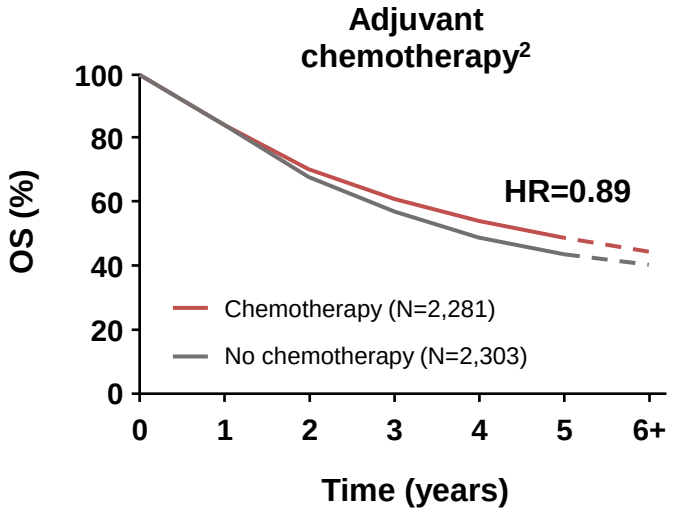
1. Goldstraw P et al. *J Thorac Oncol.* 2016;11(1):39-51
2. Howington JA, et al. Chest. 2013

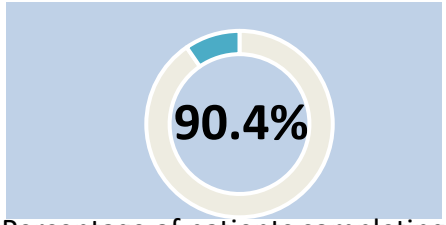
CT adiuvante e neoadiuvante incrementano significativamente OS nei pazienti con stadio I-III NSCLC



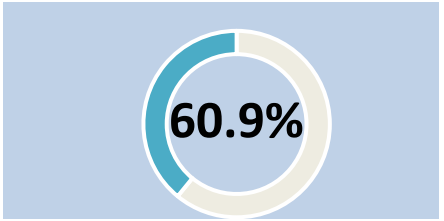
5%

improvement in 5-year OS[1,2]





Percentage of patients completing three cycles



Percentage of patients completing three cycles

Pignon JP et al. *J Clin Oncol*. 2008;26(21):3552-3559
NSCLC Meta-analysis Collaborative Group. *Lancet*. 2014;383(9928):1561-1571

The current neoadjuvant and perioperative ICI-based treatment landscape in NSCLC: phase 3 trials

Resectable NSCLC

Neoadjuvant

Trial	Regimen
CheckMate 816[1]	Nivolumab + Chemotherapy

Adjuvant

Trial	Regimen
KEYNOTE-091/PEARLS[2]	Pembrolizumab
IMpower010[3]	Atezolizumab
CCTC BR31[4]	Durvalumab
ANVIL[5]	Nivolumab
NADIM-ADJUVANT[6]	Nivolumab + Chemotherapy

Perioperative

Trial	Regimen
CheckMate 77T[7]	Nivolumab + Chemotherapy → Nivolumab
IMpower030[8]	Atezolizumab + Chemotherapy → Atezolizumab
AEGEAN[9]	Durvalumab + Chemotherapy → Durvalumab
KEYNOTE-671[10]	Pembrolizumab + Chemotherapy → Pembrolizumab
Neotorch[11]	Toripalimab + Chemotherapy → Toripalimab + Chemotherapy → Toripalimab

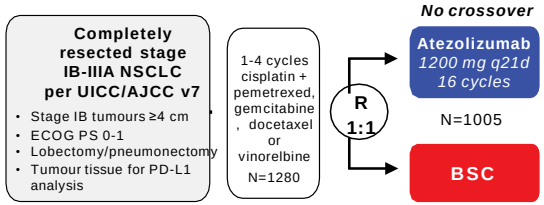
1. Forde PM et al. *N Engl J Med*. 2022. 2022;386(21):1973-1985. 2. O'Brien M et al. *Lancet Oncol.* 2022 Oct;23(10):1274-1286. 3. Felip E et al. *Lancet*. 2021;398(10308):1344-1357. 4. Clinicaltrials.gov. NCT02273375. 5. Chaft JE et al. *Journal of Clinical Oncology* 36, no. 15_suppl 2018. Abstract TPS8581. 6. Calvo V et al. *Journal of Clinical Oncology* 39, no. 15_suppl 2021. Abstract TPS8581. 7. Cascone T et al. *Journal of Clinical Oncology* 38, no. 15_suppl 2020. Abstract TPS9076. 8. Peters S et al. *Annals of Oncology*. Volume 30, Supplement 2, 2019. Abstract 82TiP. 9. Heymach JV et al. *Cancer Res* (2023) 83 (8_Supplement). Abstract CT005. 10. Wakelee H e al. *N Engl J Med*. 2023 Jun 3. 11. Lu S et al. *Journal of Clinical Oncology* 41, no. 16_suppl 2023. 8501-8501.

Adapted and Updated from ESMO Congress 2022 Industry Satellite Symposium

Adjuvant immunotherapy for NSCLC

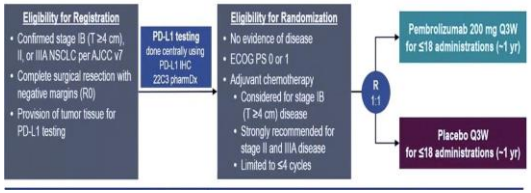
Randomized studies design

IMpower010



- Design: **open label**
- **Platinum-chemo: mandatory (96%)**
- **Adiuvant carboplatin: NO**
- Stage IIIA/N2: 40%/30%
- Squamous: 34%
- Primary endpoint: DFS II-IIIA PDL1 > 1%

PEARLS/KEYNOTE-091



- Design: placebo controlled
- Platinum-chemo: recommanded (85%)
- Adiuvant carboplatin: 30%
- Stage IIIA/N2: 30%/21%
- Squamous: 35%
- **Co-Primary endpoint: DFS Ib-IIIA PDL1 > 50%**

CCTG BR.31

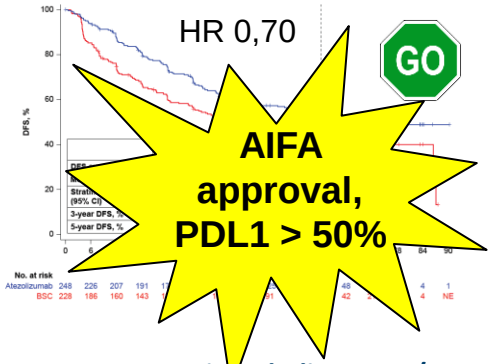
- Design: placebo controlled
- Platinum-chemo: recommanded (85%)
- Adiuvant carboplatin: 24%
- Stage IIIA/N2: 31%/23%
- Squamous: 28%
- Primary endpoint: **DFS PDL1 > 25%**

Adjuvant immunotherapy for NSCLC

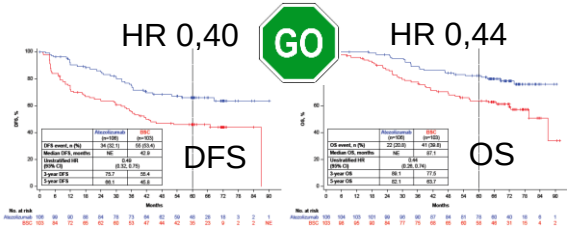
Randomized studies results

IMpower010

Stage II–IIIA, PD-L1 ≥1%

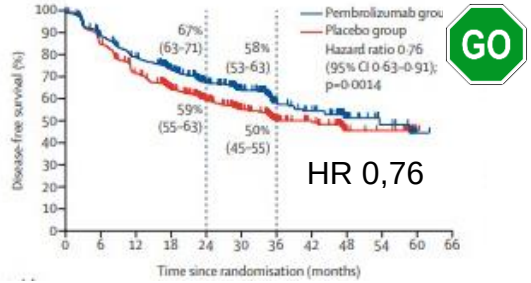


PD-L1 ≥50%: excluding EGFR/ALK

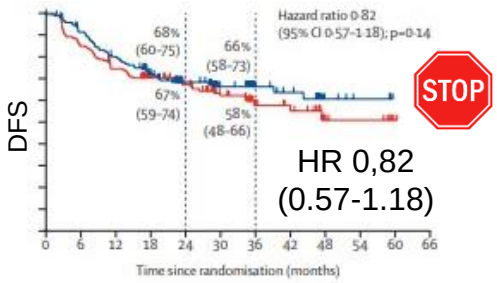


PEARLS/KEYNOTE-091

All randomized Ib–IIIA

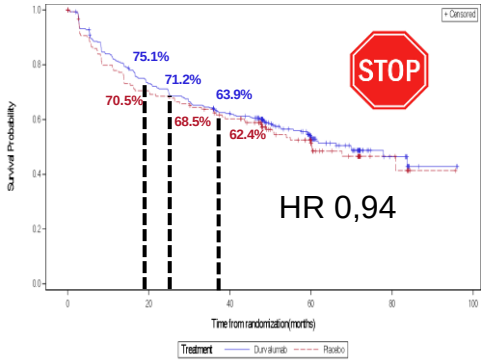


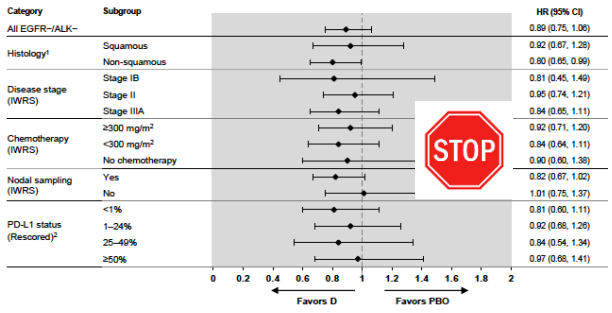
PD-L1 ≥50%: stage Ib-IIIA



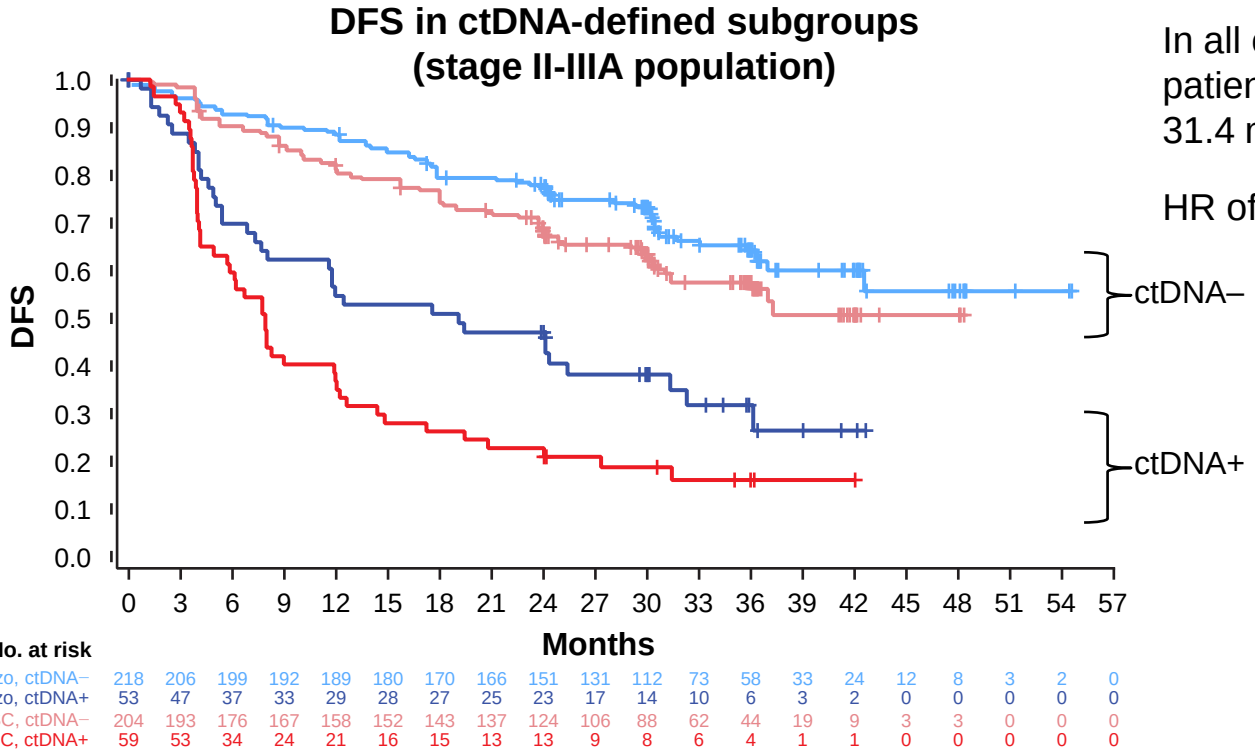
CCTG BR.31

PDL1>25% EGFR-/ALK-





ctDNA positivity was strongly prognostic, with DFS favouring atezo in both ctDNA+ and ctDNA– patients



In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an

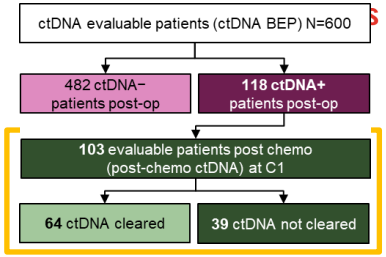
HR of 0.69 (95% CI: 0.53, 0.89)

ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

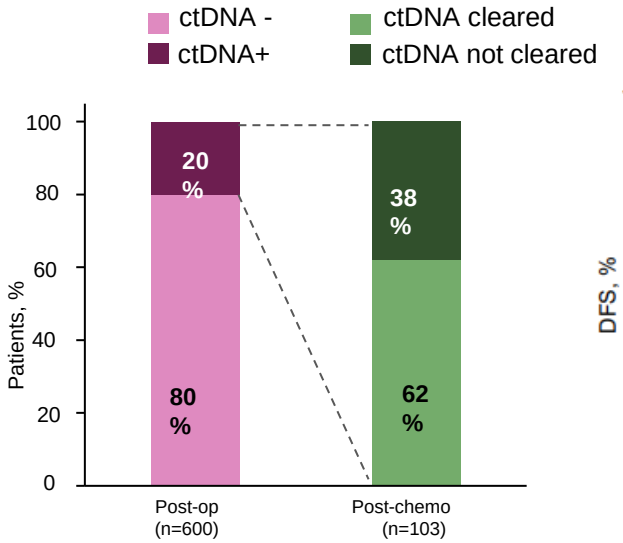
ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

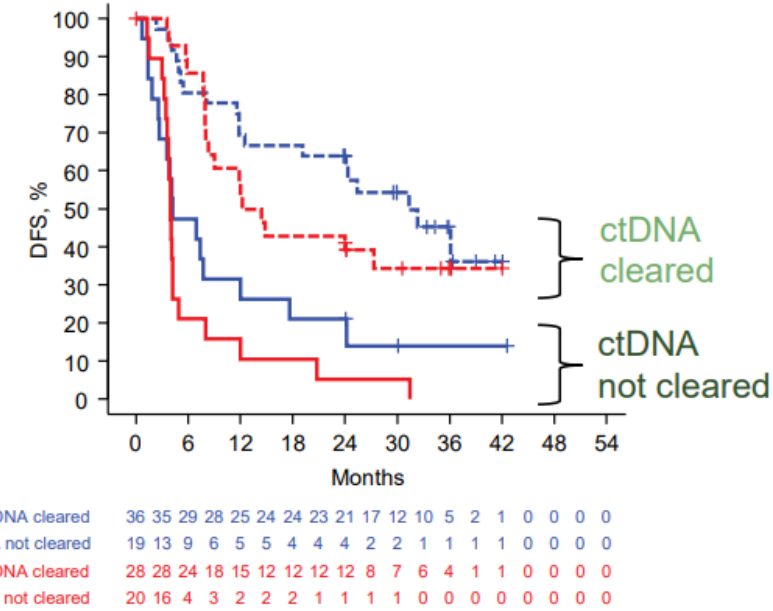
Zhou et al, Ann of Onc 2021
https://doi.org/10.1016/j.annonc.2021.10.018

DFS by treatment arm and post-chemo ctDNA clearance status



La clearance del ctDNA post-CT predice un outcome favorevole

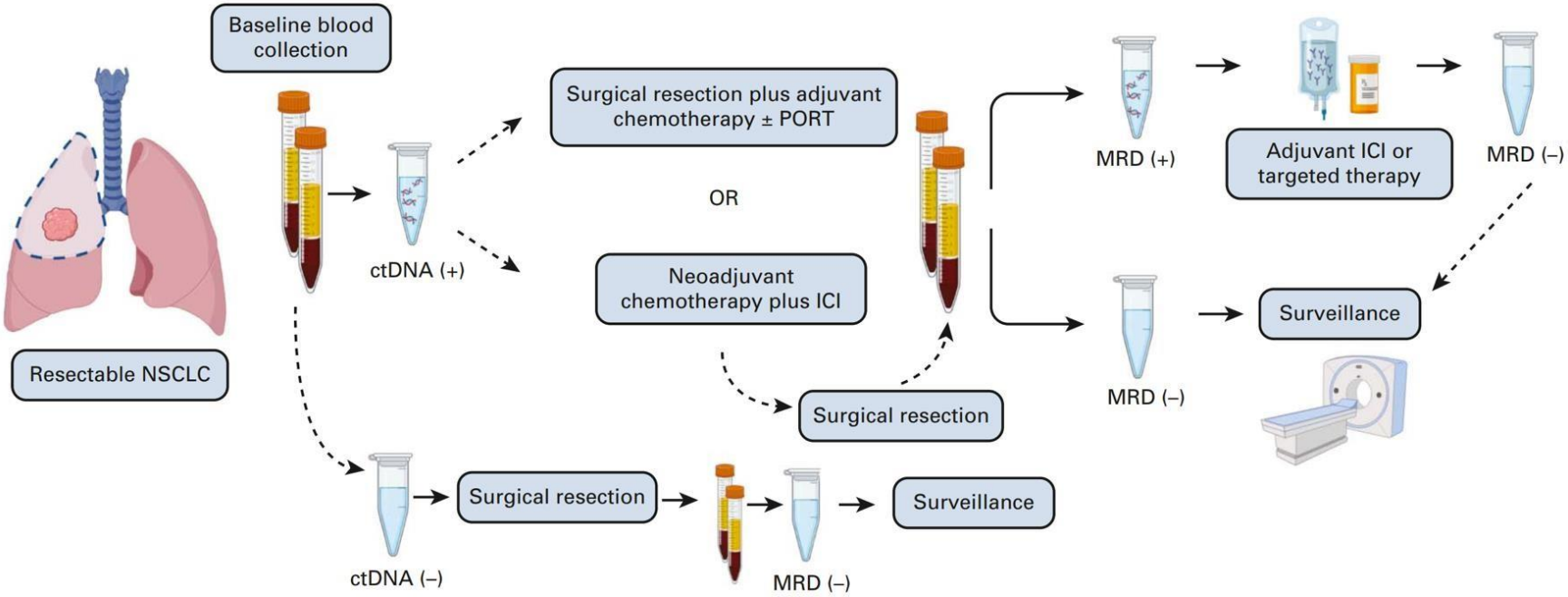




ctDNA cleared	Atezo (n=36)	BSC (n=28)
mDFS, mo	31.3	13.3
HR (95% CI)	**0.7** (0.37, 1.34)	

ctDNA not cleared	Atezo (n=19)	BSC (n=20)
mDFS, mo	4.2	3.9
HR (95% CI)	**0.67** (0.34, 1.32)	

Role of ctDNA/MRD in early-stage and locally advanced NSCLC



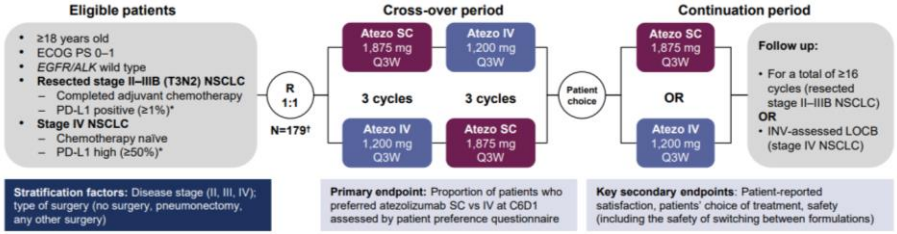
Most studies have demonstrated ctDNA/MRD as optimal predictors for recurrence and prognosis. However, whether it could help conduct personalized treatment modalities remained unclear.

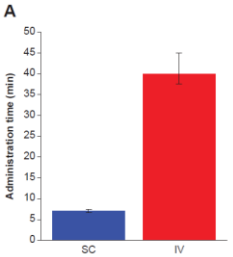
W.Z Zhong| Novel Immunotherapies WCLC 2024

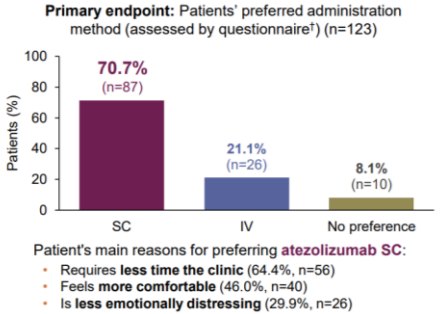
Impatto psicologico della terapia adiuvante

1 anno di terapie endovena ?
Ma non ero guarita ?

IMscin002 – Ph 2







The median administration time:

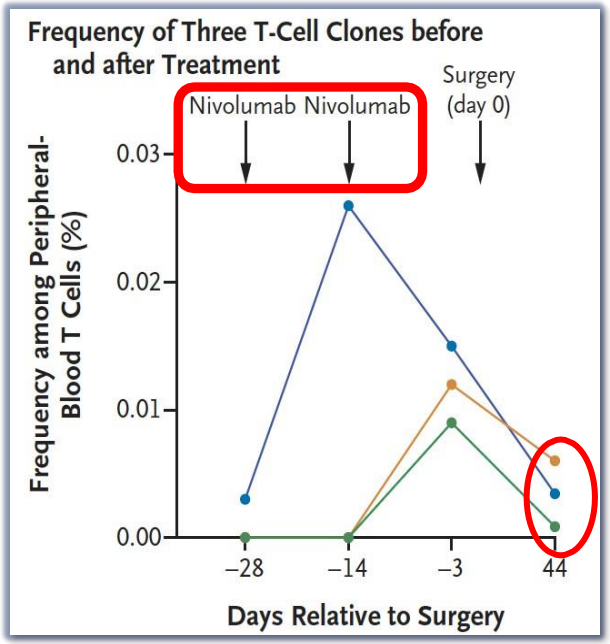
- **7.1 minutes** for atezolizumab SC
- 40 minutes for atezolizumab IV

Aggiungere l’immunoterapia solo nella fase adiuvante aumenta significativamente l’outcome ?

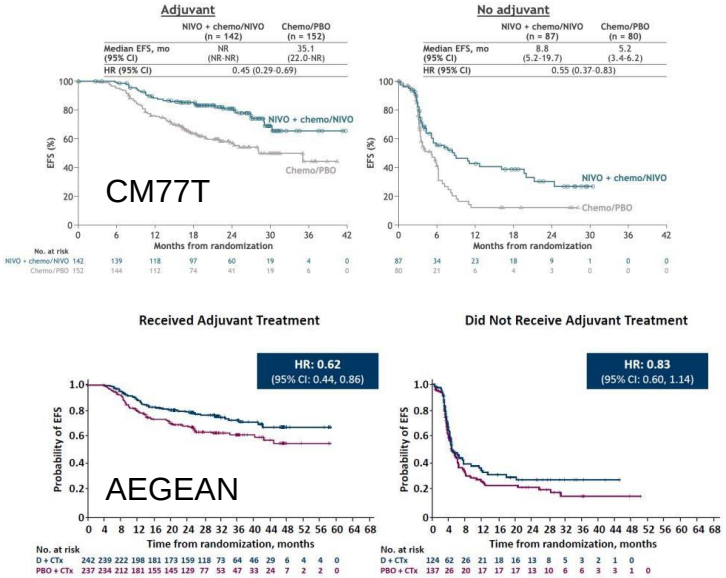
Stando ai dati degli studi, i risultati potrebbero essere considerati controversi :

- IMP 010 OK
- KN 091 forse (l’OS non è significativa)
- BR 31 e ANVIL negativi

Ha più senso aggiungere l'immunoterapia nella fase adiuvante dopo una CT-ICI neoadiuvante ?



- Neoadjuvant ICI inadequate for sustained T cell activation
- Large but <u>transient</u> expansion of shared intratumoral T-cell clones

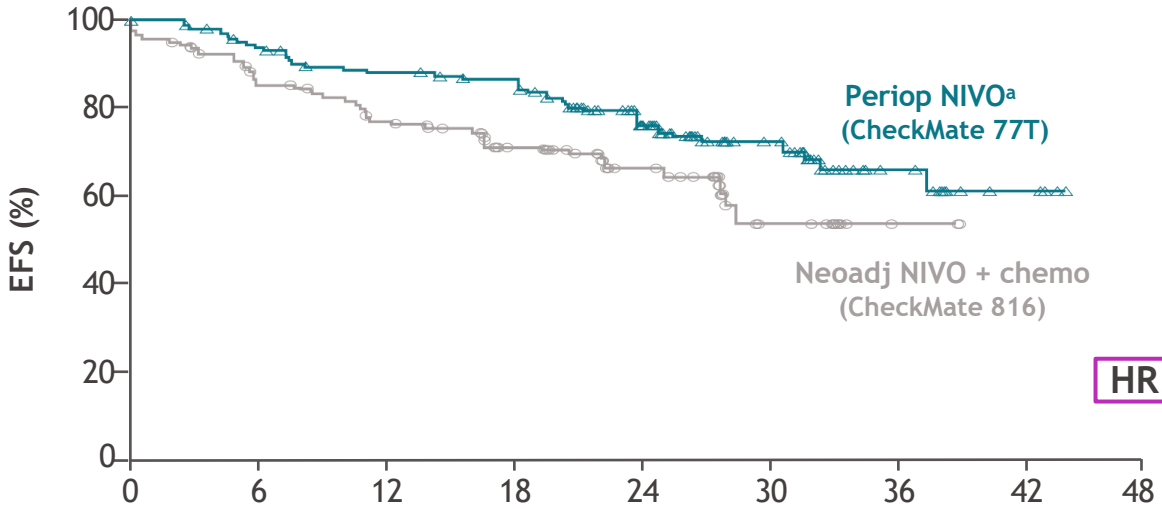


Forde NEJM 2018

Studi di fase III

Trial	Nº pts	Stage	Experimental arm	Control arm	Primary EP	Pathological Response	Primary Endpoint Result
CheckMate-816 Forde PM (2022)	358	IB-IIIA	Platinum doublet + Nivo(x3)	Platinum doublet + Placebo(x3)	pCR EFS	pCR: 24% vs 2.2% MPR: 36.9% vs 8.9%	pCR: 24% vs 2.2% mEFS: 31.6 vs 20.8 m
Keynote-671 Wakelee H (2023)	786	II-IIIB	Platinum doublet + Pembro (x4) -> adj Pembro(x13)	Platinum doublet + Placebo(x4)	EFS OS	pCR: 18.1% vs 4% MPR: 30.2% vs 11%	24-m EFS: 62.4 % vs 40.6% 24-m OS: 80.9 % vs 77.6%
AEGEAN Heymach JV (2023)	800	IIA-IIIB	Platinum doublet + Durva (x4) -> adj Durva (x12)	Platinum doublet + Placebo(x4) -> adj Placebo (x12)	pCR EFS	pCR: 17.2% vs 4.3% MPR: 33.3% vs 12.3%	mEFS: NR vs 25.9 months
NEOTORCH Lu S (2023)	406	IIIA-IIIB	Platinum doublet + toripalimab(x3) -> adj cycle x1 -> toripalimab(x13)	Platinum doublet + placebo(x3) -> adj cycle x1 -> placebo(x13)	MPR EFS	pCR: 24.8% vs 1% MPR: 48.5% vs 8.4%	MPR: 48.5% vs 8.4% mEFS: NR vs 15.1 months
CheckMate 77T Cascone T (2024)	461	IIA(>4cm)-IIIB(N2)	Nivo+CT -> Nivo q4w(x13)	Placebo+CT -> Placebo (x13)	EFS	pCR 25.3% vs 4.7% MPR 35.4% vs 12.1%	mEFS HR 0.58

Landmark EFS (BICR) from definitive surgey



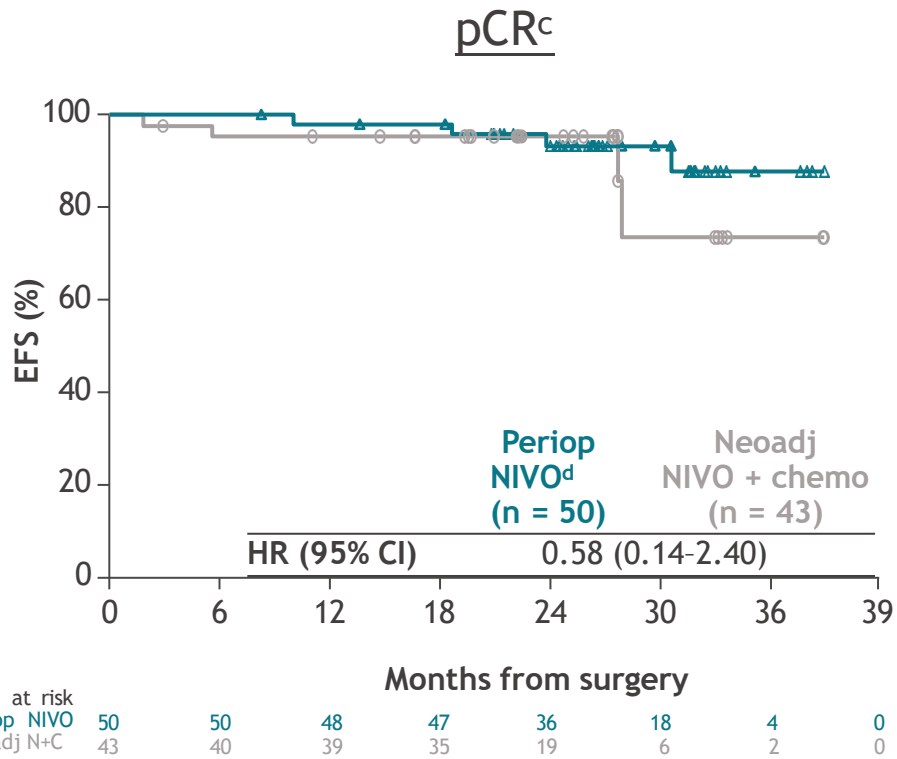
Weighted (ATE)[b]	Periop NIVO[a] (n = 139.4[c])	Neoadj NIVO + chemo (n = 147.5[c])
HR (95% CI)	0.61 (0.39-0.97)	

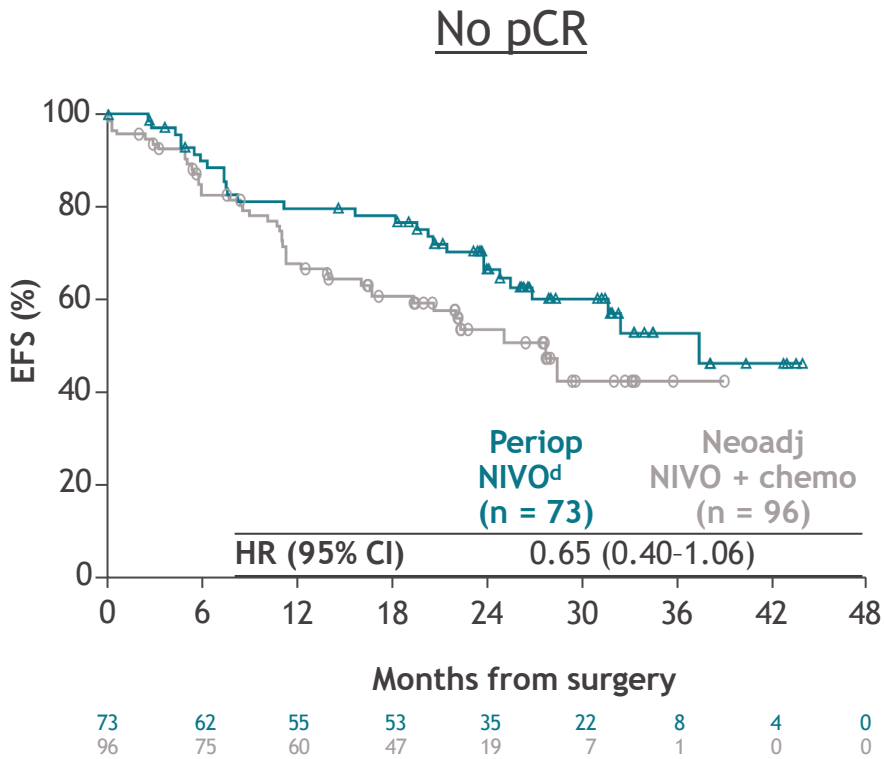
The 1st direct comparison study indicated superiority of periop NIVO to neoadj NIVO using patient data of CM77T and CM 816.

- ± 40% reduction in risk of disease recurrence or death
- Regardless of baseline stage, with greater magniture on PDL1 < 1%

Forde PM WCLC 2024 PL02.08

Landmark EFS (analysis population) by pCR status



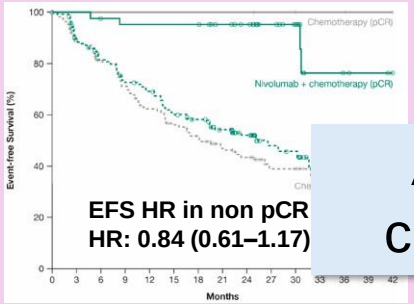


Forde PM WCLC 2024 PL02.08

Perioperative strategy improves EFS in patients without a pCR

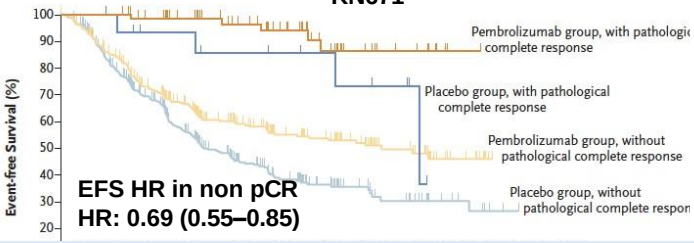
Neoadjuvant approach

CM816



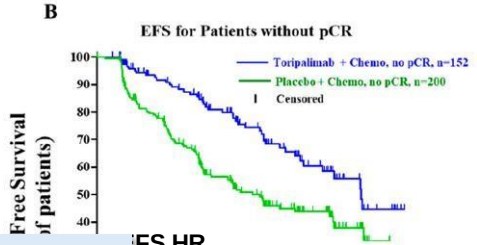
EFS HR in non pCR
HR: 0.84 (0.61–1.17)

KN671



EFS HR in non pCR
HR: 0.69 (0.55–0.85)

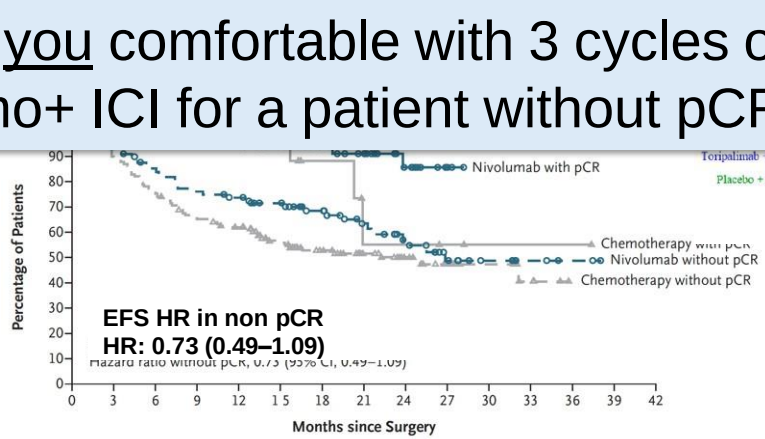
NEOTORCH



EFS HR
HR: 0.5 in non pCR
3 (0.38–0.74)

- Median EFS 24.5 versus 15.1 months
- HR= 0.53 (95%CI 0.38-0.74)

Are you comfortable with 3 cycles of chemo+ ICI for a patient without pCR?

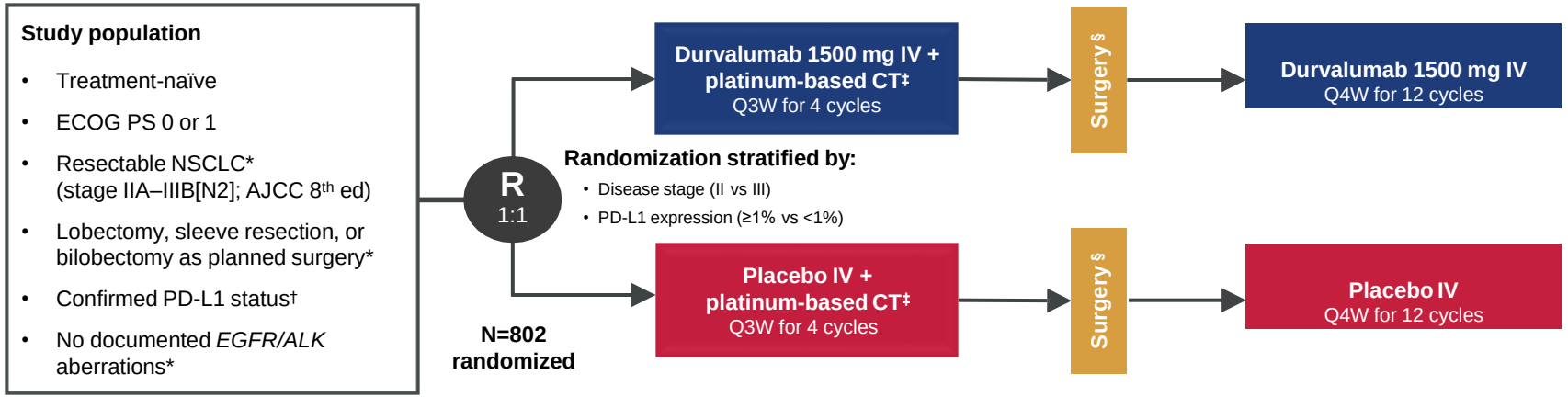


EFS HR in non pCR
HR: 0.73 (0.49–1.09)

Perioperative approach

Forde NEJM 2022, Wakelee NEJM 2023, Lu JAMA 2024, Cascone NEJM 2024

AEGEAN: a phase 3, global, randomized, double-blind, placebo-controlled study



Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented *EGFR/ALK* aberrations¶

Primary:

- pCR by central lab (per IASLC 2020[1])
- EFS using BICR (per RECIST v1.1)

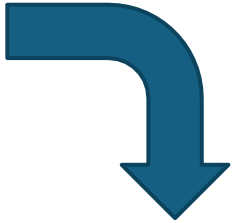
Key secondary:

- MPR by central lab (per IASLC 2020[1])
- DFS using BICR (per RECIST v1.1)
- OS

In Italia attivo da poco programma di EAP

How could we raise the bar higher?

Novel Immunotherapies



Novel agents

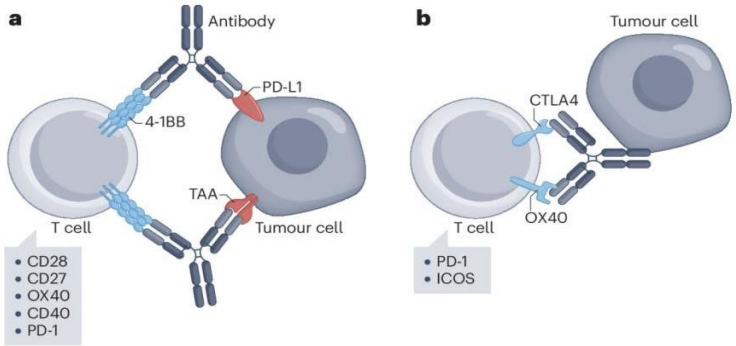
- Novel targets
- Cell based therapy
- Cancer vaccine
- Oncolytic virus

Novel combinations

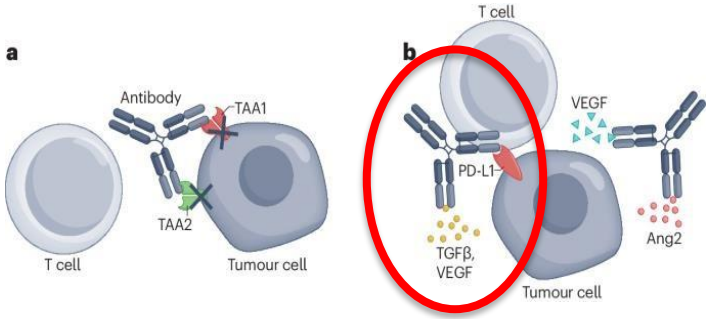
- ICI+Chemo
- ICI+antiangiogenic drug
- ICI+TKI
- ICI+novel agents

Bispecific and multispecific antibody

Bring immune cells close to tumor cells



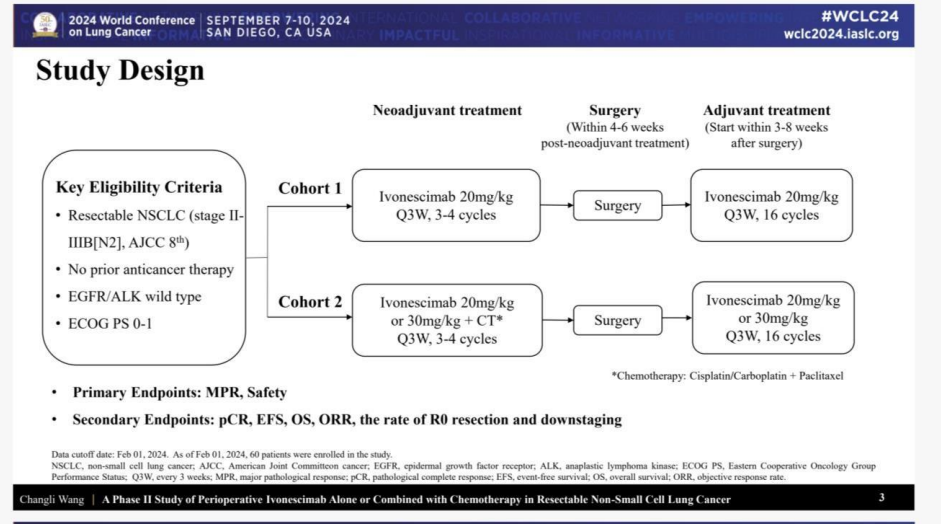
Blocking multiple signals

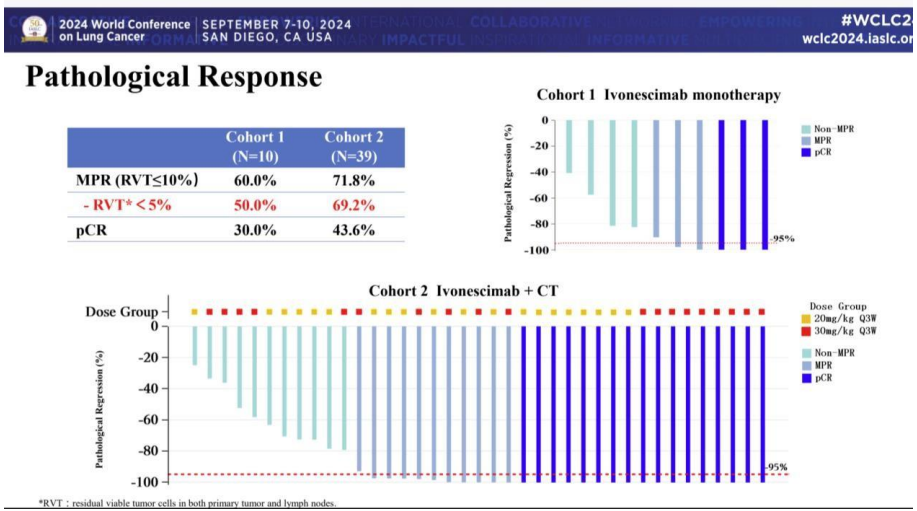


Rationale: Bind multiple target in one time to increase efficacy and decrease risk of toxicity.

Maria-Elisabeth Goebeler et al. 2024 nature reviews clinical oncology

A Phase II Study of Perioperative Ivonescimab （anti-PD-1/VEGF bispecific antibody.）Alone or Combined with Chemotherapy in Resectable Non-Small Cell Lung Cancer（pCR rate was 43.6%, MPR rate was 71.8%）





	Cohort 1 (N=10)	Cohort 2 (N=39)
MPR (RVT≤10%)	60.0%	71.8%
- RVT* < 5%	50.0%	69.2%
pCR	30.0%	43.6%

W.Z Zhong| Novel Immunotherapies WCLC 2024

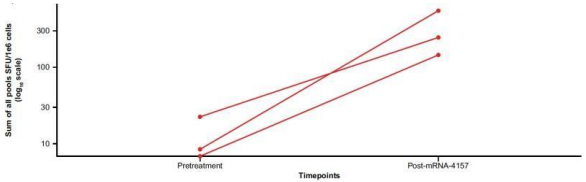
Personalized neoantigen mRNA vaccine for resected NSCLC

KEYNOTE-603
NCT03313778

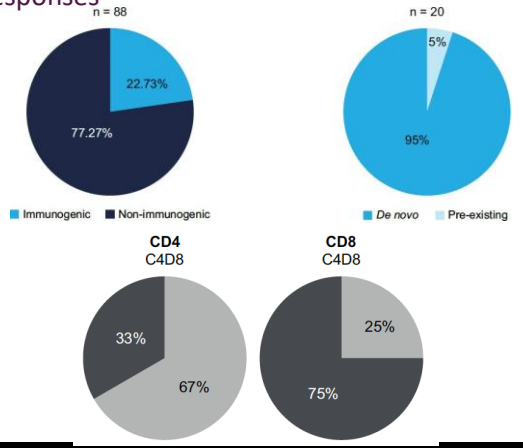
- Part A of multi-tumor Phase 1
- Adjuvant mRNA-4157 monotherapy for resected NSCLC
- 4 biomarker-evaluable pts (2 Stage IA, 2 Stage IIB)

- Most common mRNA-4157 related AEs: pyrexia (n=2), influenza like illness (n=2), and injection-site pain (n=1)
- No recurrences observed in early follow-up (15-30 months)

Neoantigen specific T cells

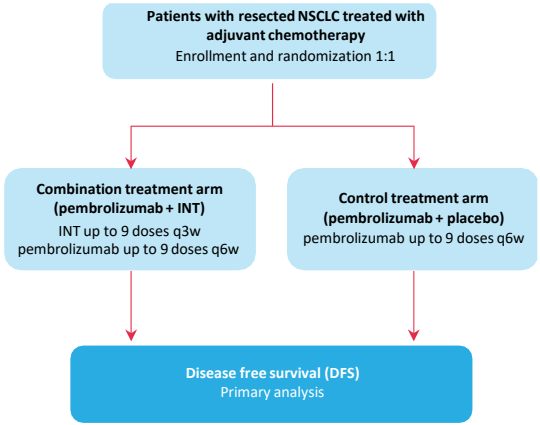


De-novo and polyfunctional CD4 and CD8 responses



INTerpath-002
NCT06077760

- mRNA-4157 (V940) with pembrolizumab
- Resected Stage II-IIIB NSCLC treated with adjuvant chemo
- Randomized Ph3, N = ~868



Slide Courtesy Dr.Vincent Lam, TTLC
2024 Gainor et al, SITC 2023
Moderna Corporate Presentation,

CONCLUSIONI

- Terapia con ICI post CT adiuvante è lo standard di terapia nei pazienti PDL1 >50%
- A breve possibilità di infusione sc…..quanto costerà ?
- L'apporto della fase ICI adiuvante nella strategia perioperatoria sembra essere maggiore nei pazienti NON in pCR
- Aperto EAP per CT-ICI perioperatoria secondo schema AEGEAN (CT+durvalumab)
- Dati preliminari interessanti con anticorpi bispecifici
- In Italia in corso studi anche con vaccini ad mRNA

Grazie per l'attenzione

alessandro.delconte@cro.it

Centro di Riferimento Oncologico (CRO)
Oncologia Medica e dei Tumori Immunocorrelati
Pordenone - Aviano