
## NSCLC avanzato: malattia non-oncogene addicted

# Immunoterapia: ruolo del rechallenge

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# Disclosures

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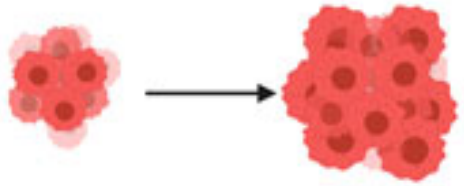
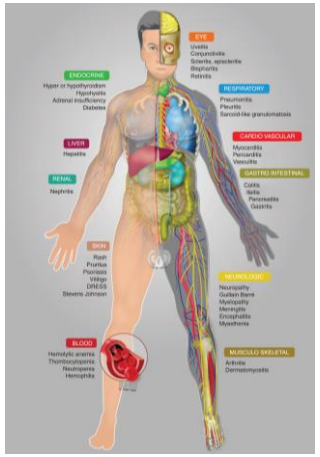
# Rechallenge con ICI

***Ritrattamento con ICI (dopo precedente beneficio clinico), in seguito a:***

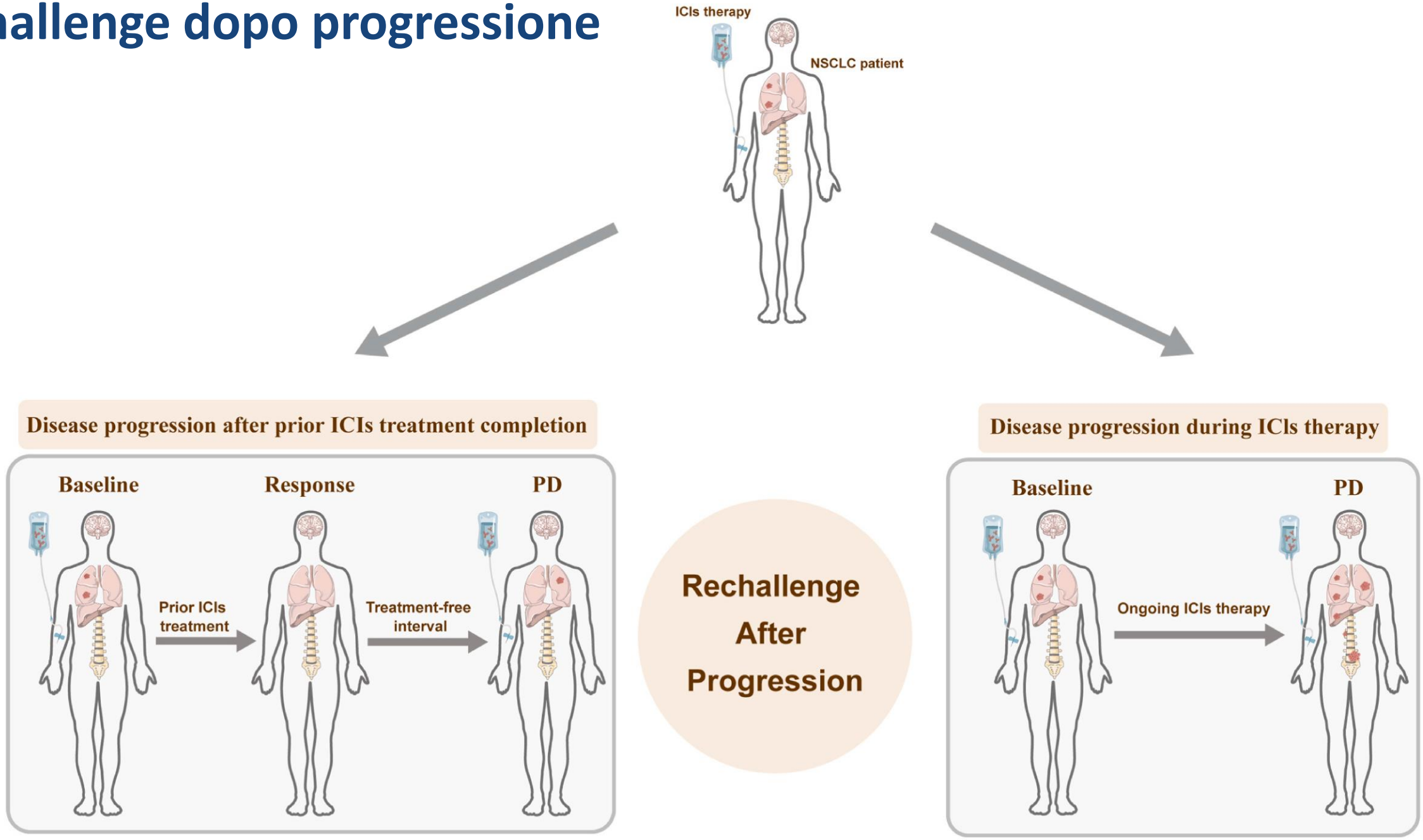
- **Progressione di malattia**



- **Tossicità immuno-correlata**



# Rechallenge dopo progressione




Gang X, et al. Cancer Lett 2024

# Rechallenge dopo il termine del trattamento

## Second-Course Pembrolizumab: Pooled Analysis Design

- Exploratory analysis of patients who had second course of pembrolizumab from 5 clinical trials[1]

Patients with stage IV nonsquamous or squamous NSCLC without *EGFR/ALK* mutations; eligible for second course of pembro (SD or better with 35 cycles of first-course pembro OR stopped first-course pembro after ≥8 cycles with confirmed CR for ≥2 cycles after CR assessment);
no receipt of anticancer treatment since last dose of pembro

**Second-Course Pembrolizumab**
**200 mg IV Q3 Wk for up to 17 cycles**

**Cohort 1** →

**Pembrolizumab* Single Agent as First Course**

PD-L1 TPS: ≥1%,[2,3] ≥50%[4,5]

Included studies: KEYNOTE-024,[4] KEYNOTE-042,[2,3] KEYNOTE-598‡[5]

**Cohort 2** →

**Pembrolizumab* + Chemotherapy† as First Course**

PD-L1 TPS: any

Included Studies: KEYNOTE-189,[6,7] KEYNOTE-407[8,9]

*Pembro 200 mg IV Q3 wk up to 35 cycles (~2 yr). †Cisplatin or carboplatin + pemetrexed in KEYNOTE-189, carboplatin + paclitaxel or nab-paclitaxel in KEYNOTE-407. ‡Only included patients from pembro + placebo arm for this analysis.

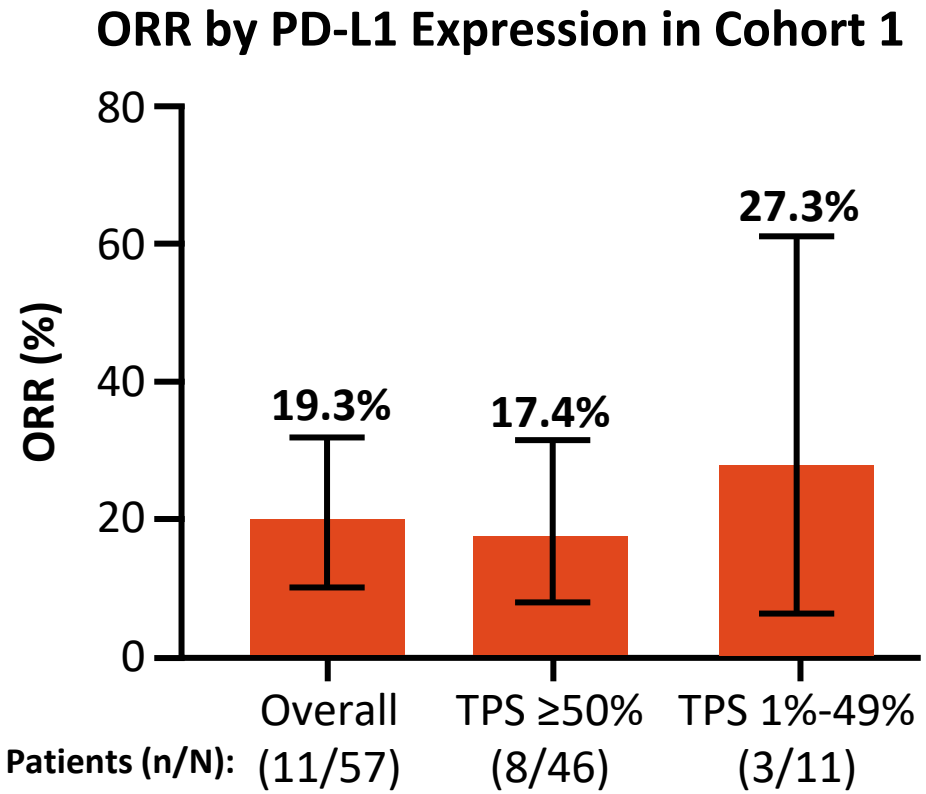
1. Rodriguez-Abreu. WCLC 2022. Abstr OA15.06. 2. Mok. Lancet. 2019;393:1819. 3. Wu. Int J Cancer. 2021;148:2313. 4. Reck. NEJM. 2016;375:1823. 5. Boyer. JCO. 2021;39:2327. 6. Gandhi. NEJM. 2018;378:2078. 7. Horinouchi. Cancer Sci. 2021;112:3255. 8. Paz-Ares. NEJM. 2018;379:2040. 9. Chen. JTO. 2021;2:1.

Rodriguez-Abreu D, et al. J Thor Oncol 2022 Suppl

# Rechallenge dopo il termine del trattamento

## Second-Course Pembrolizumab: Survival and tumor response

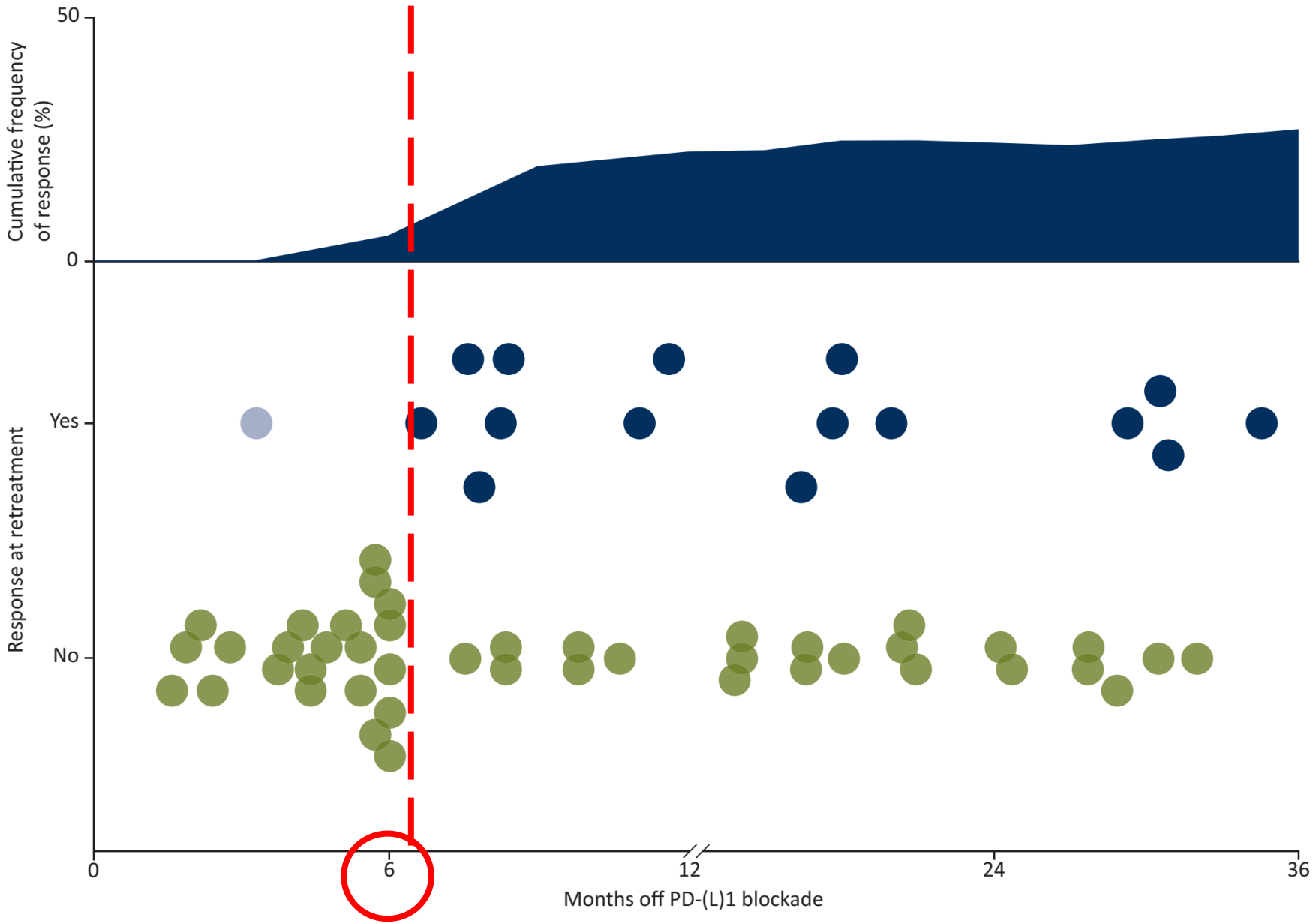
| | Cohort 1 (n = 57) | Cohort 2 (n = 14) |
|---|---|---|
| Time from stopping 1st course to 2nd-course initiation, mo (95%CI) | 12.0 (3.8-35.6) | 5.4 (0.9-18.2) |
| ORR, % (95% CI) | 19.3 (10.0-31.9) | 0 (0-23.2) |
| DCR, % (95% CI) | 73.7 (60.3-84.5) | 50.0 (23.0-77.0) |
| Best overall response, n (%) | | |
| ▪ CR | 0 | 0 |
| ▪ PR | 11 (19.3) | 0 |
| ▪ SD | 31 (54.4) | 7 (50.0) |
| ▪ PD | 8 (14.0) | 2 (14.3) |
| ▪ NA | 7 (12.3) | 5 (35.7) |
| Median DoR, mo (range) | NR (0*-20*) | -- |
| ▪ DoR ≥6 mo, % | 78.8 | -- |
| Median OS,† mo (95% CI) | 27.5 (21.7-NR) | NR (NR-NR) |
| ▪ 6 mo rate, % (95% CI) | 85.1 (72.4-92.3) | 85.1 (52.3-96.1) |
| Median PFS,† mo (95% CI) | 10.3 (5.6-14.0) | 7.7 (1.8-NR) |
| ▪ 6 mo rate, % (95% CI) | 60.8 (46.0-72.7) | 54.5 (22.9-78.0) |




*No PD at time of last disease assessment. †From start of second-course pembrolizumab.

Rodriguez-Abreu D, et al. J Thor Oncol Suppl 2022

# Timing del rechallenge dopo interruzione programmata




***Retreated pts, n=61[1,2]***

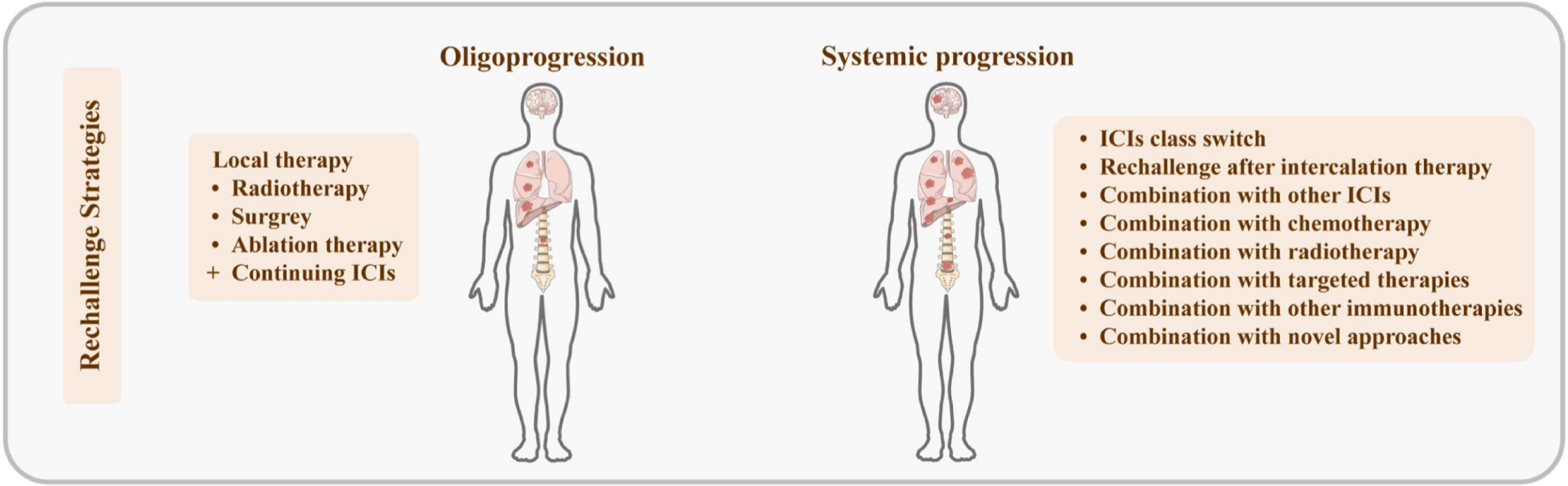
| TFI | N | RR, n (%) |
|---|---|---|
| > 6 mo | 43 | 15 (35) |
| < 6 mo | 18 | 1 (5) |

***p=0.02***


1. Herbst RS, et al. J Clin Oncol 2020;
2. Sheth S, et al. J Immunother Cancer 2020

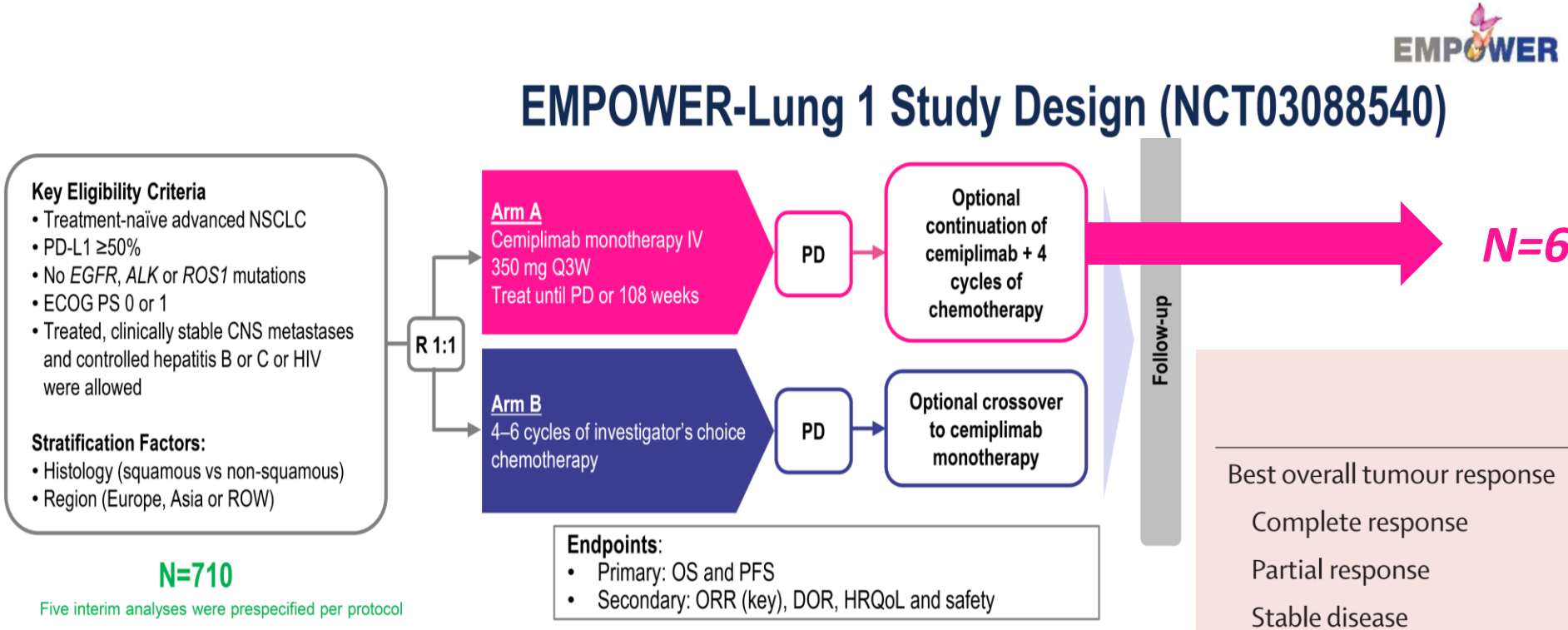

Schoenfeld AJ, et al. Ann Oncol 2021

# Pattern di progressione e strategie di rechallenge




Gang X, et al. Cancer Lett 2024

# ICI + chemioterapia




| | Initial cemiplimab monotherapy | After added chemotherapy |
|---|---|---|
| Best overall tumour response | | |
| Complete response | 0 | 3 (5%) |
| Partial response | 19 (30%) | 17 (27%) |
| Stable disease | 28 (44%) | 35 (55%) |
| Non-complete response or non-progressive disease | 0 | 0 |
| Progressive disease | 13 (20%) | 9 (14%) |
| Not evaluable | 4 (6%) | 0 |
| Objective response rate (95% CI) | 19 (30%; 19–42) | 20 (31%; 20–44) |

Data are n (%), unless otherwise indicated.

**PFS: 6.6 months***
**OS: 15.1 months***

** After added chemotherapy*

Özgüroğlu M, et al. Lancet Oncol 2023

# ICI + inibitori dell'angiogenesi: studi di fase III

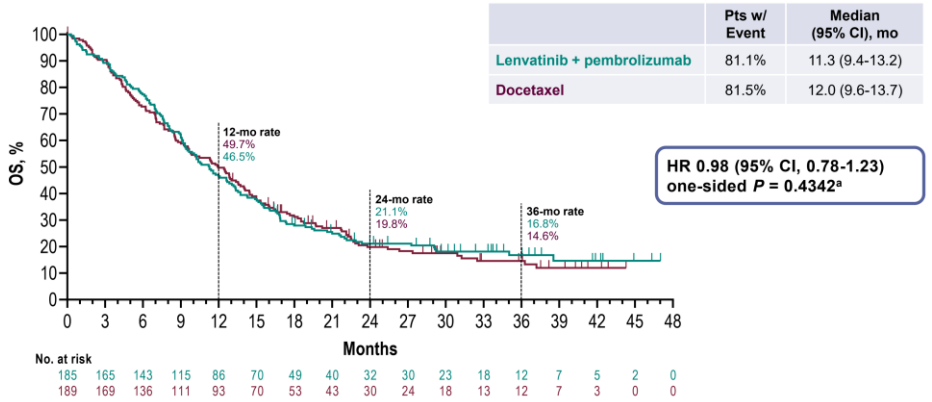
## LEAP-008[1]

**Key Eligibility Criteria**

- Histologically or cytologically confirmed stage IV NSCLC
- Progression following one anti–PD-(L)1 therapy given for ≥2 doses[a] and platinum-containing chemotherapy (sequential or combined)
- No prior use of or indication for EGFR-, ALK-, or ROS1-directed therapy
- Provision of tumor sample for PD-L1 evaluation[b]
- ECOG PS 0 or 1

~405
R 4:4:1

- Lenvatinib 20 mg orally QD + Pembrolizumab 200 mg IV Q3W (maximum 35 cycles for pembro)
- Docetaxel 75 mg/m² IV Q3W
- Lenvatinib 24 mg orally QD




| | Pts w/ Event | Median (95% CI), mo |
|---|---|---|
| Lenvatinib + pembrolizumab | 81.1% | 11.3 (9.4-13.2) |
| Docetaxel | 81.5% | 12.0 (9.6-13.7) |

HR 0.98 (95% CI, 0.78-1.23)
one-sided *P* = 0.4342[a]

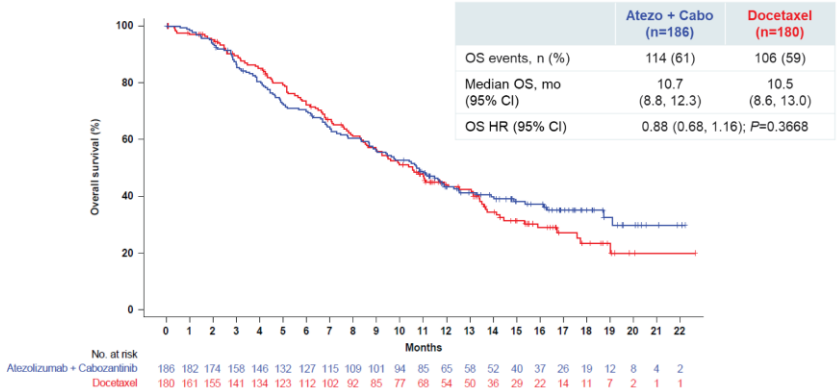
## CONTACT-01[2]

- Histologically or cytologically confirmed NSCLC (nonsquamous and squamous)
- ECOG PS 0-1
- Progression on or after immune checkpoint inhibitor and platinum-based chemotherapy
- Any PD-L1 status[a]
- Absence of sensitizing *EGFR* mutation or *ALK* fusion oncogene

N=366

R 1:1

- Atezolizumab 1200 mg Q3W + Cabozantinib 40 mg QD → PD or loss of clinical benefit
- No crossover allowed
- Docetaxel (75 mg/m² Q3W) → PD




| | Atezo + Cabo (n=186) | Docetaxel (n=180) |
|---|---|---|
| OS events, n (%) | 114 (61) | 106 (59) |
| Median OS, mo (95% CI) | 10.7 (8.8, 12.3) | 10.5 (8.6, 13.0) |
| OS HR (95% CI) | 0.88 (0.68, 1.16); *P*=0.3668 | |

## SAPPHIRE[3]

**Key Eligibility Criteria**

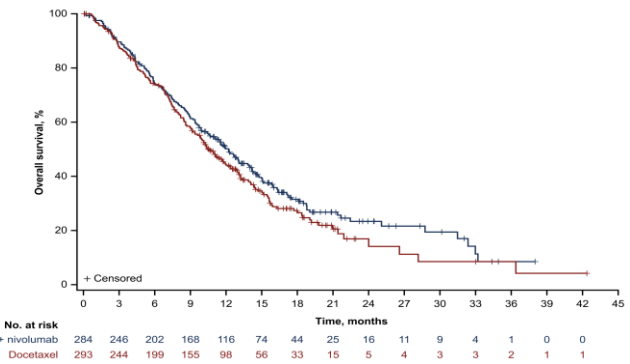
- Unresectable, locally advanced, or metastatic NSQ NSCLC
- No EGFR, ROS1, or ALK alterations
- One or two prior regimens with most recent including CPI (≥4 months) with or after PBC
- Discontinuation of prior CPI <90 days prior to randomization
- ECOG PS 0 or 1
- No active brain metastases[a]

R 1:1

- Sitravatinib (100 mg QD) + Nivolumab (240 mg Q2W or 480 mg Q4W) n=284[b]
- Docetaxel (75 mg/m² Q3W) n=293[b]

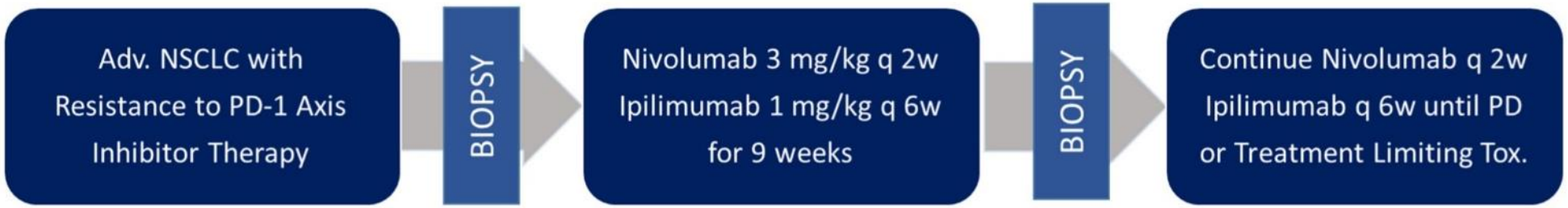
**Stratification Factors**

- Prior treatment regimens in the advanced setting: 1 vs 2
- Baseline ECOG PS: 0 vs 1
- Treated and/or stable brain metastases at baseline: presence vs absence




1. Leighl N, et al. ESMO IO Congress 2023; 2. Neal J, et al. J Clin Oncol 2024;42(20):2393-2403. 3; Borghaei H, et al. Ann Oncol. 2024;35(1):66-76.

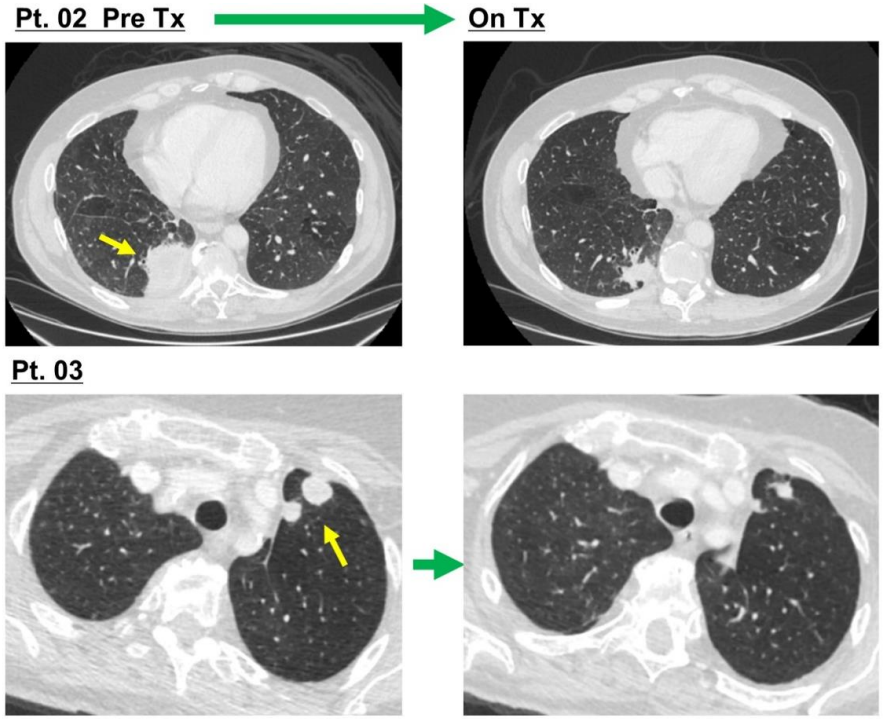
# Combo ICI: anti-PD1+ anti-CTLA-4




**Cohort 1 Primary Resistance:**[1] **n= 10, if ≥ 1 response or SD ≥ 24 weeks by irRC, enroll an additional 30 pts**
**Cohort 2 Acquired Resistance:**[2] **n= 10 (Exploratory Cohort)**

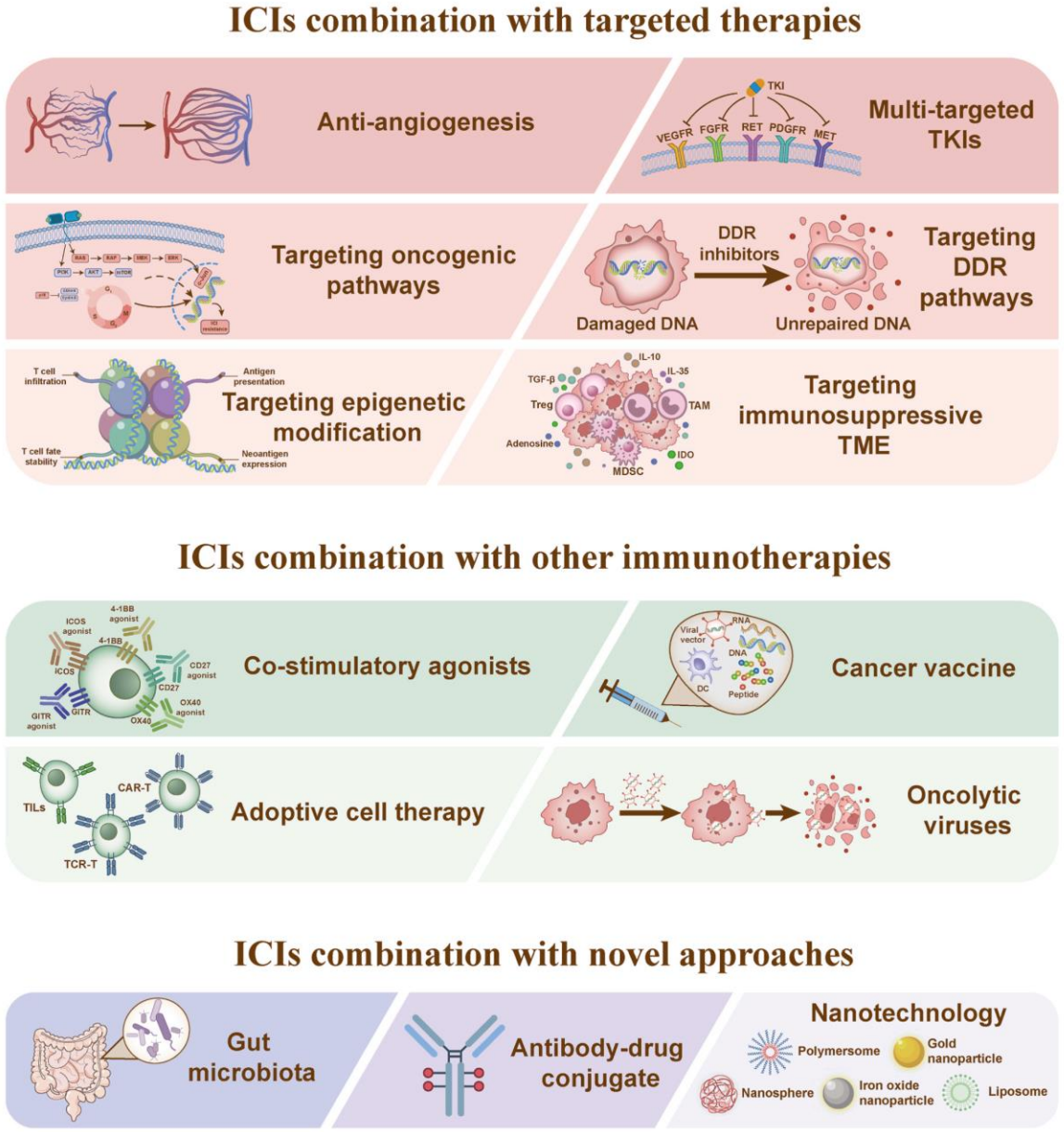
1. *Defined as PD or SD <24 wks*
2. *Defined as CR/PR or SD ≥24 wks*

| Outcomes | Cohort 1 | Cohort 2 |
|---|---|---|
| RR, % | 0 | 10 |
| DCR, % | 20 | 60 |
| mPFS, mo | 1.8 | 7.6 |
| mOS, mo | 6.8 | 31.8 |




Gettinger SN, et al. ASCO 2023

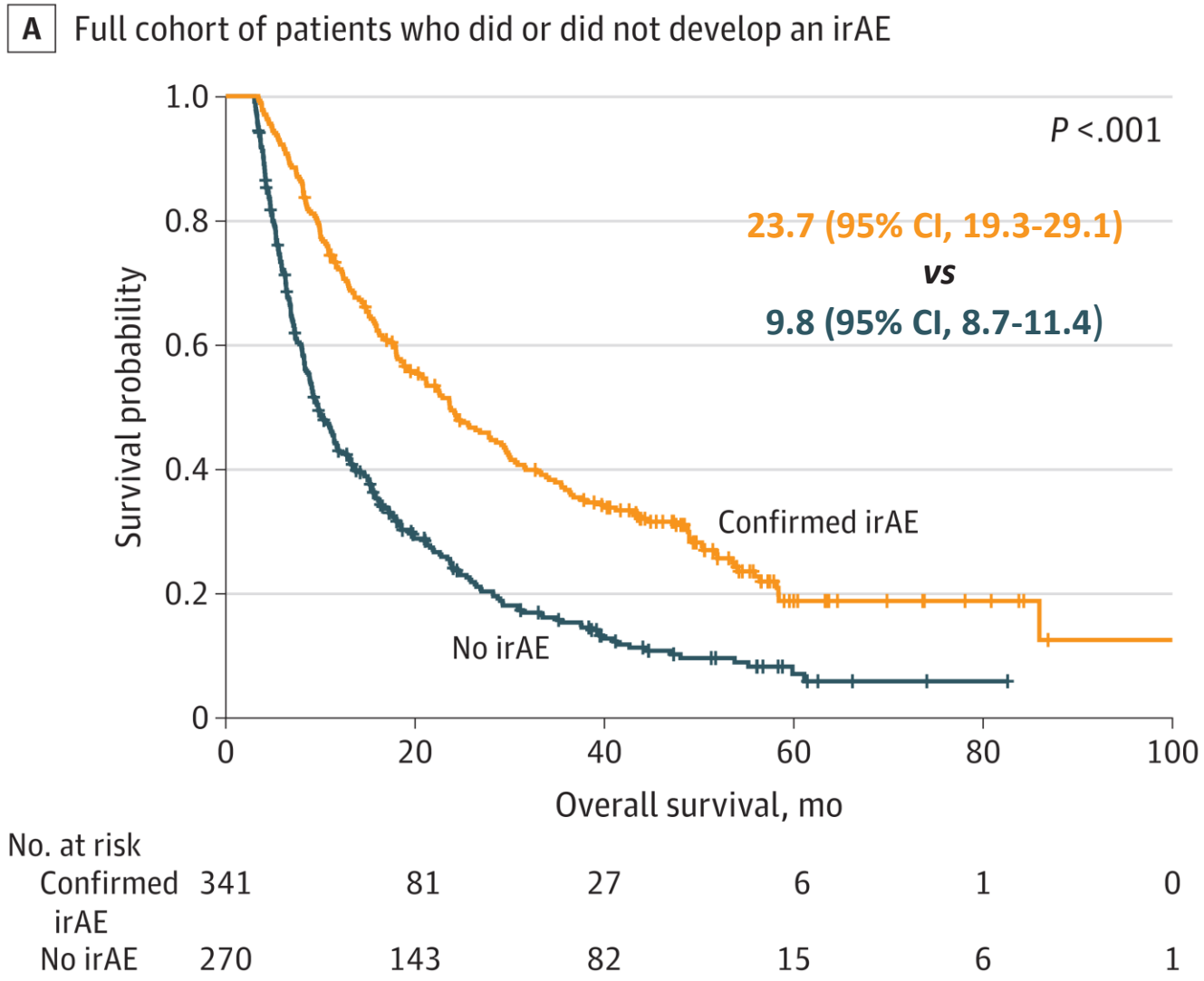
# Rechallenge dopo progressione: prospettive future




Gang X, et al. Cancer Lett 2024

# Rechallenge dopo tossicità: Impatto prognostico degli irAEs nel NSCLC

- Large retrospective study of 803 pts with NSCLC treated with ICI
- Only clinically meaningful irAEs were considered (i.e. irAEs mandating delay or discontinuation of ICI therapy and/or systemic corticosteroids for management of toxic effects
- To mitigate immortal time-bias from patients with a poor prognosis who may have died before
- developing an irAE, a 12-week cutoff was used for OS (611 pts included)
- Developing irAEs remained associated with OS in the total cohort after Cox proportional hazards regression with known prognostic characteristics (hazard ratio, 0.53 [95% CI, 0.40-0.70]; *P* < .001).




Cook S, et al. JAMA Netw Open 2024;7(1):e2352302.

# Rechallenge dopo irAEs

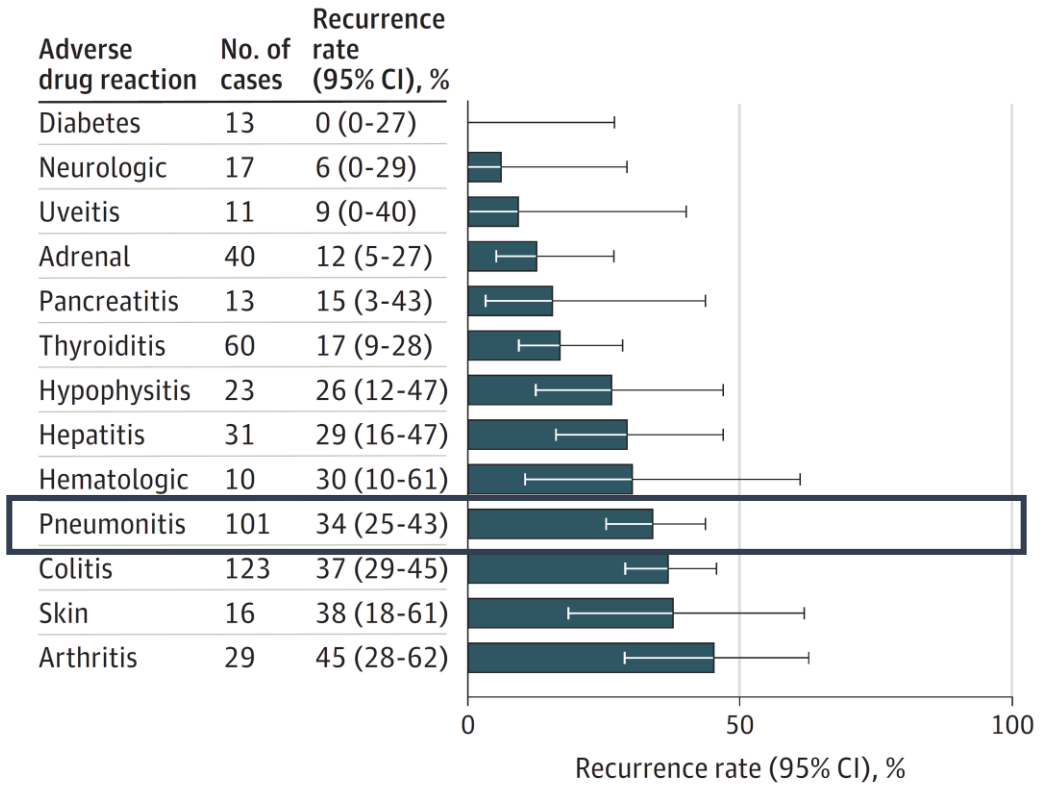
*Summary of retrospective studies on rechallenge ICIs after irAEs*

| | Santini[1] | Simonaggio[2] | Abu-Sbeih[3] | Naidoo[4] | Pollack[5] | Delaunay[6] |
|---|---|---|---|---|---|---|
| **N irAEs** | 68 various | 93 various | 167 colitis | 43 pneumonitis | 80 various | 64 pneumonitis |
| **tumor** | NSCLC | Multiple | Multiple | Multiple | Melanoma | Multiple |
| **Retreat.** | 38 | 40 | 167 | 12 | 80 | 10 |
| **New/Recurr.** | 52% (40% G≥3) | 55% (60% G≥3) | 34% (10% G≥3) | 25% (0% G≥3) | 18% (0% G≥3) | 30% (0% G≥3) |

**≈20-50% New/Recurrent irAEs**

*Pharamcovigilance study (VigiBase)[7]*
*Data on 452 informative rechallenge*

**Figure 2. Rate of Recurrence According to the Initial Immune-Related Adverse Event**

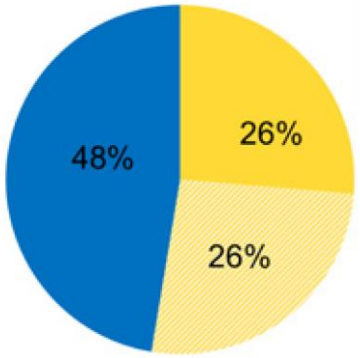



1. Santini FC, et al. Cancer Immunol Res 2018;6(9):1093-1099. 2. Simonaggio A, et al. JAMA Oncol 2019;5(9):1310–7.
3. Abu-Sbeih H, et al. J Clin Oncol 2019;37(30):2738-2745. 4. Naidoo J, et al. J Clin Oncol 2017;35(7):709-717. 5. Pollack MH, et al. Ann Oncol 2018;29(1):250-255.
6. Delaunay M, et al. Eur Respir J 2017;50(2):1700050. 7. Dolladille C, et al. JAMA Oncol 2020;6(6):865-871.

# Safety and Efficacy of Re-treating with Immunotherapy after Immune-Related Adverse Events in Patients with NSCLC

**Table 2.** Characteristics of initial irAEs ***N=38*** ***N=30***

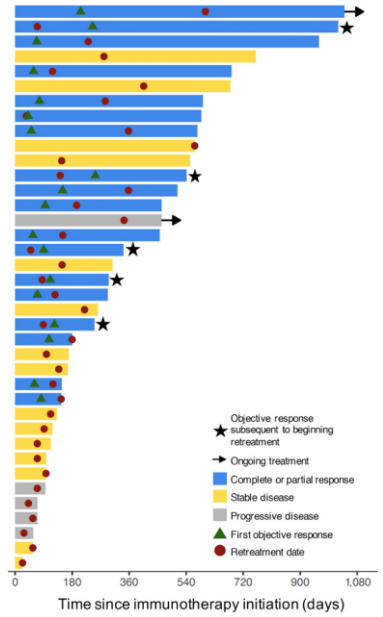
| | Retreatment | Discontinuation | *P* |
|---|---|---|---|
| Grade of the first irAE, *N* (%) | | | 0.01 |
| Grades 1 and 2 | 25 (66) | 10 (33) | |
| Grades 3 and 4 | 13 (34) | 20 (67) | |
| Type of irAE; *N* (%) | | | 0.62[a] |
| Pneumonitis | 6 (16) | 7 (23) | |
| Colitis | 7 (18) | 5 (17) | |
| Rash/pruritus | 5 (13) | 6 (20) | |
| ALT or AST increase | 3 (8) | 4 (13) | |
| Arthralgia/myalgia | 5 (13) | 1 (3) | |
| Nephritis | 2 (5) | 2 (7) | |
| Pancreatic enzymes elevation | 4 (11) | 0 (0) | |
| Meningitis/headache | 2 (5) | 1 (3) | |
| Endocrine disorders[b] | 2 (5) | 1 (3) | |
| Ventricular arrhythmias | 1 (3) | 0 (0) | |
| Fatigue | 1 (2) | 0 (0) | |
| ITP | 0 (0) | 1 (3) | |
| Other | 0 (0) | 2 (7) | |
| Hospitalizations, *N* (%) | 8 (21) | 16 (53) | 0.01 |
| Time interval to irAE: | | | |
| Days, median (range) | 69 (14–577) | 73 (2–452) | 0.77 |
| No. infusions before the irAE: | | | |
| No., median (range) | 4.5 (1–42) | 5.5 (1–27) | 0.51 |
| Corticosteroid used, *N* (%) | 29 (76) | 29 (97) | 0.03 |
| Intravenous | 3 (10) | 12 (40) | |
| Oral | 23 (80) | 16 (53) | |
| Other[c] | 3 (10) | 2 (6) | |
| Steroids > 4 weeks, *N* (%) | 10 (34) | 15 (65)[d] | 0.04 |
| Anti-TNF used in the first toxicity, *N* (%) | 0 (0) | 3 (9) | 0.05 |
| irAE resolved to, *N* (%) | | | 0.03 |
| Grades 0 and 1 | 37 (97) | 23 (79) | |
| Grade > 2 | 1 (3) | 6 (21) | |
| Death related to irAE; *N* (%) | 0 | 2 | |

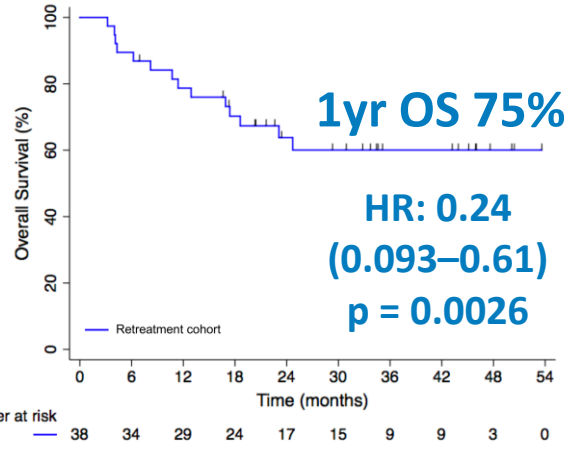



Recurrent irAE
New irAE
No subsequent irAE

| Recurrent irAE | Same irAE N (%) | New irAE N (%) |
|---|---|---|
| Total | 10 (50) | 10 (50) |
| Type irAE: | | |
| Pneumonitis | 1 (10) | 2 (20) |
| Colitis | 2 (20) | 3 (30) |
| ALT/AST elevation | 1 (10) | 2 (20) |
| Arthralgia/Myalgia | 3 (30) | 1 (10) |
| Rash/Pruritus | 1 (0) | 1 (10) |
| Neuropathy | 0 (0) | 1 (10) |
| Ventricular arrhythmias | 1 (10) | 0 (0) |
| Nephritis | 1 (10) | 0 (0) |
| Grades of the recurrent irAE | | |
| Grade 1 and 2 | 4 (40) | 8 (80) |
| Grade 3 and 4 | 6 (60) | 2 (20) |
| Corticosteroid | | |
| Oral | 7 (70) | 4 (40) |
| Intravenous | 2 (20) | 2 (20) |
| Steroids > 4 weeks | 5/9 (55) | 5/6 (83) |
| Anti-TNF | 0 (0) | 2 (20) |
| irAEs resolved to: | | |
| Grades 0 and 1 | 9 (90) | 8 (80) |
| Grades >= 2 | 1 (10) | 2 (20) |
| Deaths related to irAE | 0 (0) | 2 (20) Pneumonitis Colitis |

**RR: 13%**




**1yr OS 75%**

**HR: 0.24 (0.093–0.61) p = 0.0026**

Santini FC, et al. Cancer Immunol Res 2018;6(9):1093-1099.

# Rechallenge dopo irAEs G3-G4: cosa dicono le linee guida


**Quesito 13 GRADE. Nei pazienti affetti da tumori solidi che hanno sospeso la terapia con ICI per un evento avverso immunocorrelato G3-G4, alla risoluzione dell'evento il ripristino del trattamento con ICI (rispetto all'interruzione definitiva) è raccomandato?**

**RACCOMANDAZIONE:** Nei pazienti affetti da tumori solidi che hanno sospeso la terapia con ICI per un evento avverso immunocorrelato G3-G4, il ripristino del trattamento con ICI non dovrebbe essere preso in considerazione come opzione terapeutica di prima intenzione.*

**Questa raccomandazione non si applica ai pazienti con determinate tossicità immunocorrelate, in cui il rechallenge può essere considerato, e per le quali si rimanda ai rispettivi capitoli:*

- *tossicità cutanea G3 non SJS/TEN (vedi paragrafo 4.3);*
- *tossicità endocrine (vedi capitolo 5);*
- *diarrea/colite di grado 3, in pazienti trattati con anti-PD-1/PD-L1 (vedi paragrafo 6.1.3);*
- *eventi avversi muscoloscheletrici di grado 3, in casi selezionati (vedi paragrafo 11.3);*
- *tossicità pancreatica (vedi paragrafo 6.3.3);*
- *tossicità pericardica (vedi paragrafo 10.4).*

**Forza della raccomandazione: CONDIZIONATA A SFAVORE**

# Conclusioni

- **Dopo termine regolare del trattamento:**
  - Il rechallenge di anti-PD1 a progressione dopo interruzione programmata è fattibile e attivo (soprattutto se TFI ≥ 6 mesi per escludere resistenza acquisita)
- **In caso di progressione durante il trattamento:**
  - La combinazione di anti-PD1 + chemioterapia a progressione da singolo agente anti-PD1 è una strategia promettente
  - Il rechallenge con anti-PD1/anti-CTLA4 e anti-PD1/anti-angiogenici non ha dimostrato al momento chiari vantaggi
  - Altre strategie di rechallenge con nuove combinazioni costituiscono al momento un approccio sperimentale
- **Dopo tossicità immuno-correlata:**
  - Il rechallenge può essere preso in considerazione caso per caso, tenendo conto della tipologia e del grado di tossicità riportato, della risposta precedentemente ottenuta e delle alternative terapeutiche disponibili

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