# Systemic treatment of NSCLC: perioperative and metastatic settings

22/10/2026

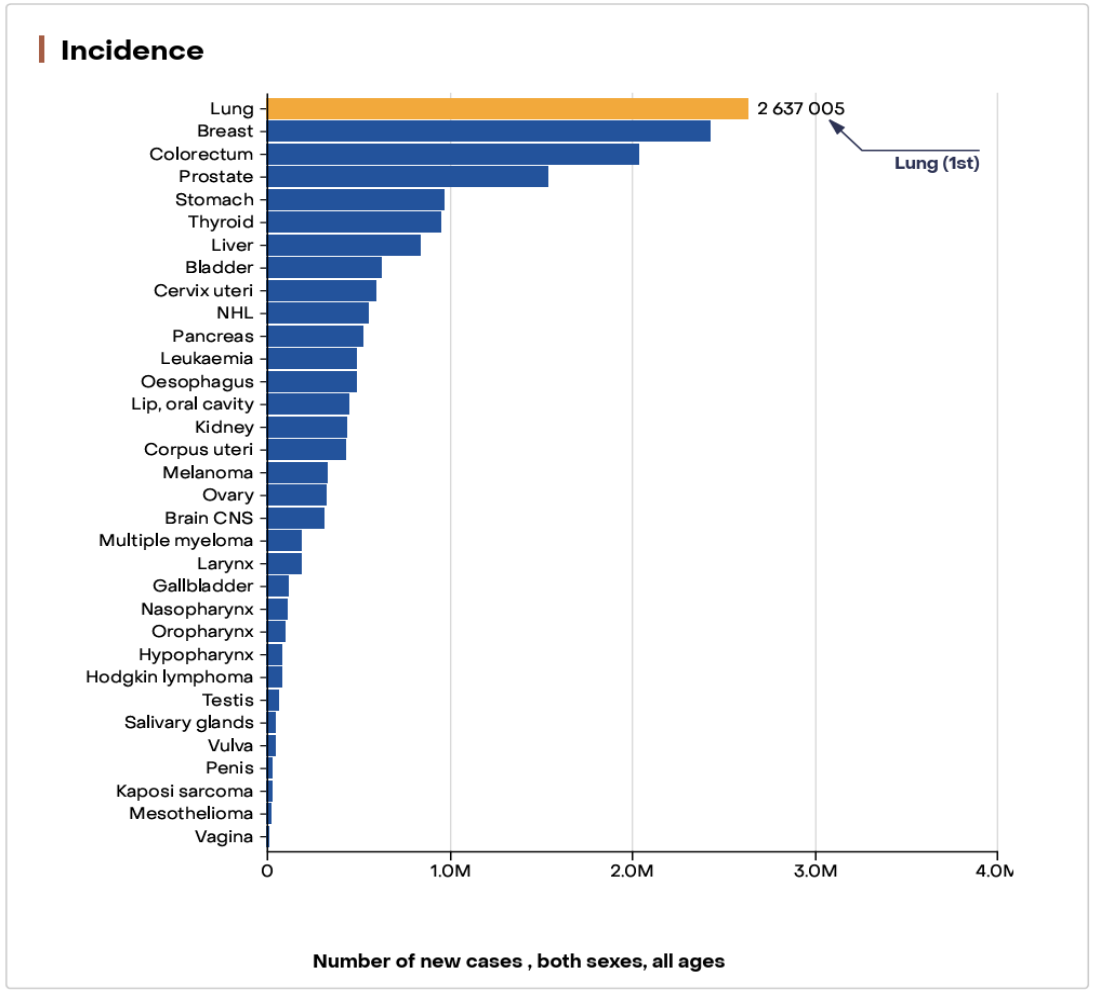
Dr Alia Harba
5th year Medical Oncology Resident, Sorbonne University, Paris- France

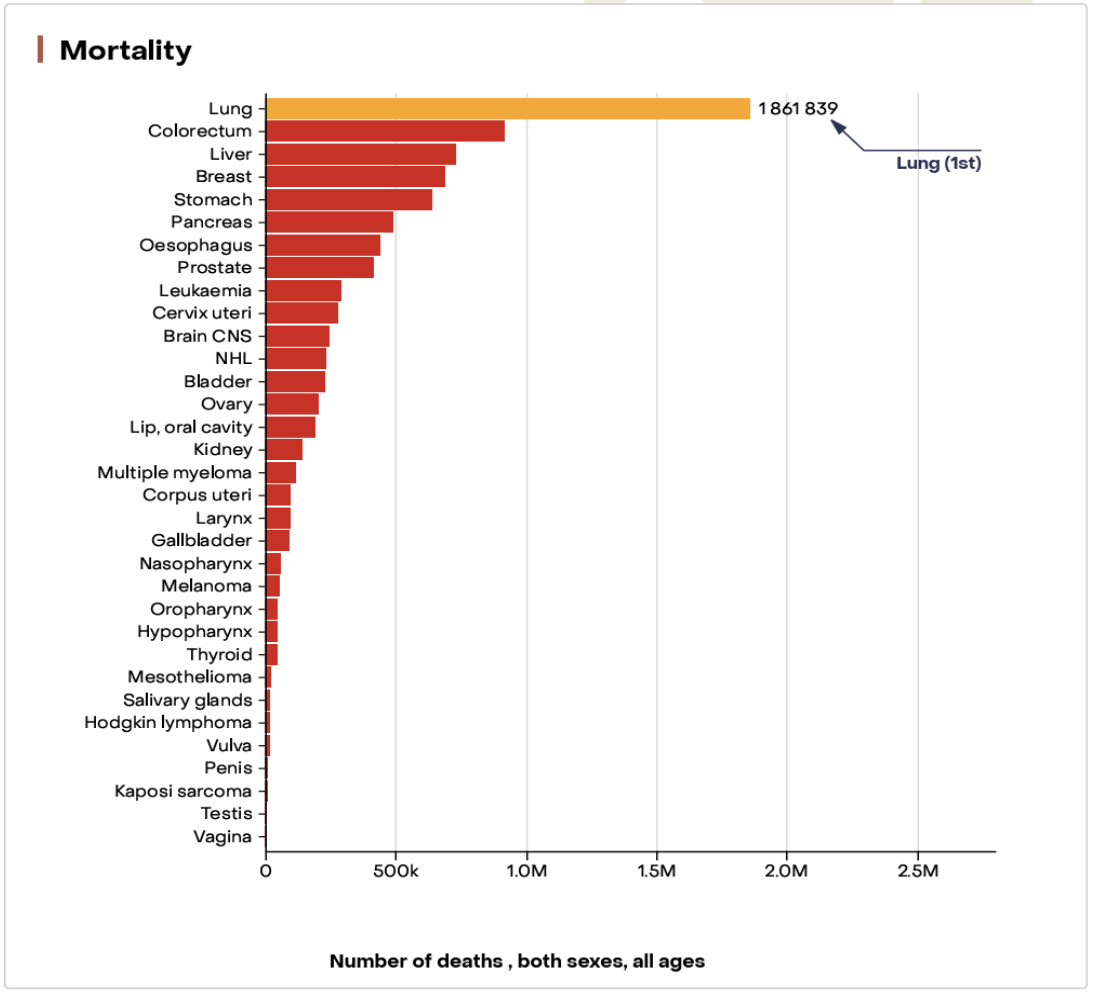
SANTÉ SORBONNE UNIVERSITÉ

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

UMPSF
Aide, Formation, Santé

# Global epidemiology




5-year survival rate: 25-30% across all stages and 15% for metastatic disease (2021)

*GLOBOCAN 2022,* SEER 2015-2021, INCA 2024, Gouliaev et al. *European Clinical Respiratory Journal 2024*

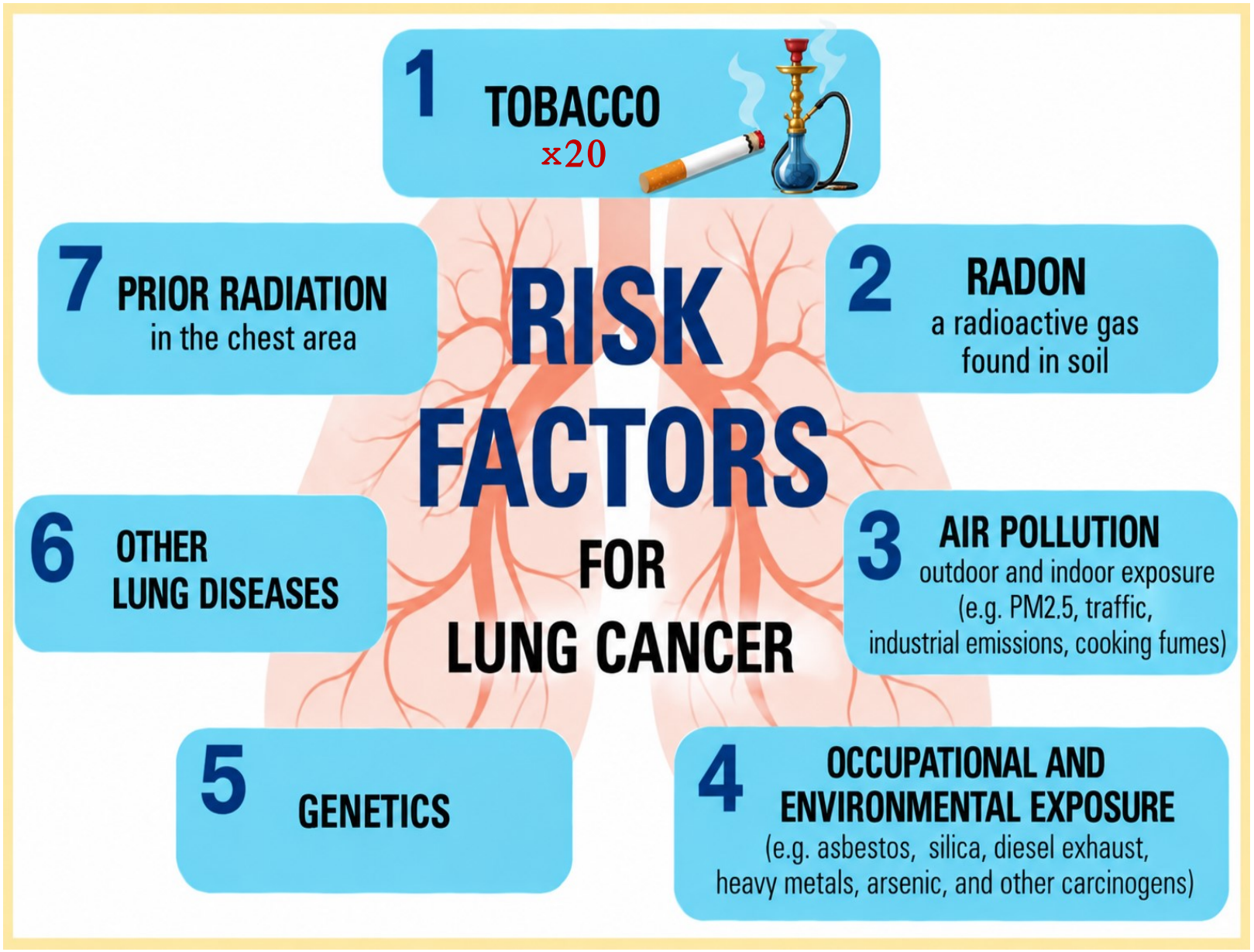
# In Syria

## 2021-2022

| Patients With Lung Cancer | | Total |
|---|---|---|
| Category | | 1670 (100) |
| Age (y) | Mean (±SD) | 59.8 (±10.3) |
| | Median (range) | 61 (16-94) |
| Histopathology | NSCLC | 1264 (75.7) |
| | SCLC | 256 (15.3) |
| | Other | 150 (9) |
| Smoking | Current smoker | 992 (61.4) |
| | Former smoker | 343 (21.3) |
| | Never smoked | 280 (17.3) |
| | Missed | 55 |
| | Valid | 1615 |
| Stage | 1 | 8 (0.8) |
| | 2 | 96 (9.2) |
| | 3 | 240 (23.2) |
| | 4 | 691 (66.8) |
| | Missed | 635 |
| | Valid | 1035 |

*M. Saifo et al. Journal of Thoracic Oncology 2023*

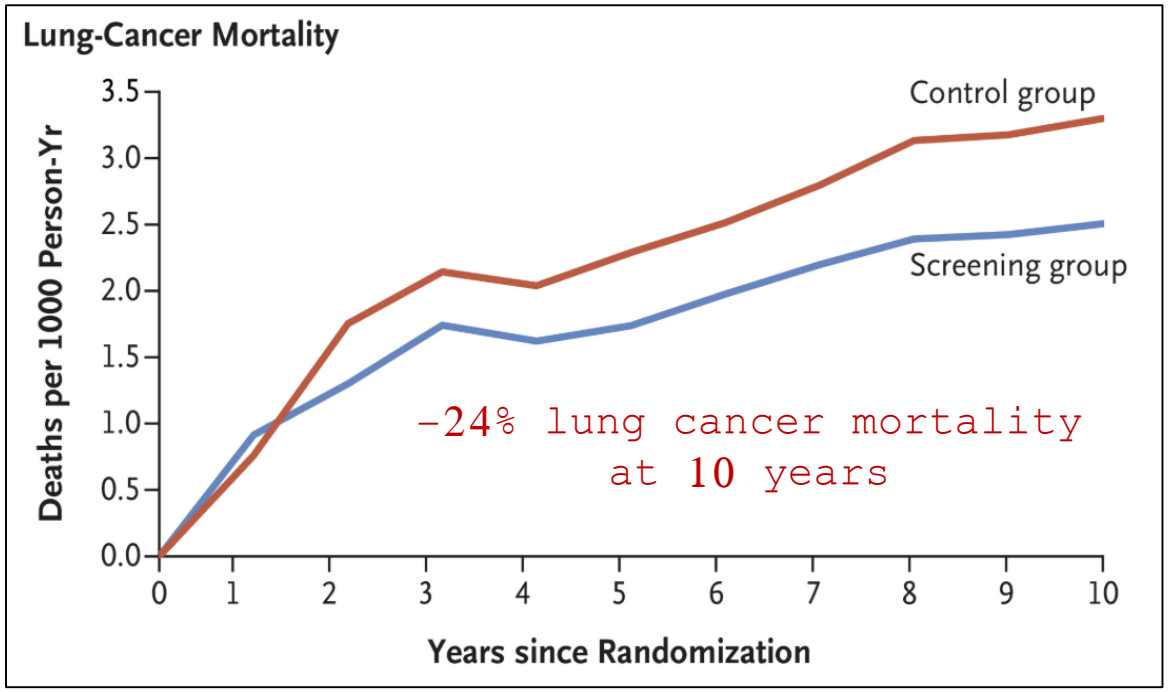
# Risk Factors



# Screening

## NELSON Trial

- Belgium + Netherlands
- 13,195 men (primary analysis) and 2594 women current smokers
- >15 cigarettes/day for >25 years, or >10 cigarettes/day for >30 years
- CT screening at T0 (baseline), year 1, year 3, and year 5.5 or no screening.
- Minimum Follow up of 10 years




*Harry J. de Koning et al. NEJM 2020*

## National Lung Screening Trial

- USA
- 53,000 participants aged 55-74,
- ≥30 pack-years, current smokers or quit <15 years
- Comparison: low-dose CT vs chest X-ray, annually for 3 years
- **-20% reduction in lung cancer mortality compared to chest X-ray**

## France

**IMPULSION pilot (INCa, may 2026):**

- 20,000 participants, 5 regions
- 50-74 y, smokers or quit <15 y, ≥20 pack-years
- LDCT at year 0 and 1, then every 2 y, with smoking cessation

# Staging

- **Contrast CT** chest-abdomen-pelvis
- **Brain imaging, systematic:** MRI or contrast CT
- *Chest MRI if vascular, nerve or wall invasion suspected*

+ evaluate patient fitness / comorbidities
Geriatric screening if >70 years

## Localised (stage I-III)

- **PET-CT** if surgery or curative radiotherapy is planned
  - **Suspicious nodes:** EBUS / (histology + N stage in one procedure); mediastinoscopy if negative
  - **No suspicious node:** biopsy the primary (guided bronchoscopy or CT-guided transthoracic biopsy)
- **Operable?** PFT with DLCO ± $VO_2$max, cardiac assessment

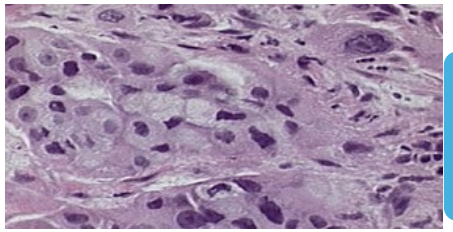
## Metastatic (stage IV)

- **Biopsy the most accessible metastatic site**
- **No PET-CT, except if oligometastatic:** PET-CT + biopsy of the metastasis

Get enough tissue from the site that gives the highest stage

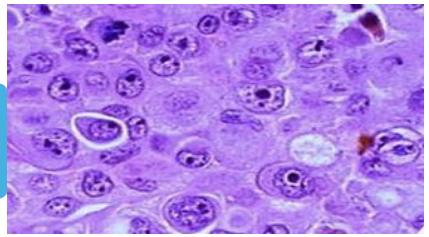
# Metastatic NSCLC: first-line decision

Stage IV NSCLC



Non -Squamous (mainly adenocarcinoma)

Squamous Cell



Molecular Testing : EGFR/ALK/ROS/BRAF/RET/MET/KRASG12C / NTRK/HER2

Never or former light smoker <15 packyears OR age < 50 years

mNSCLC with no oncogenic alteration

Negative molecular test

Oncogenic alteration → targeted therapy

According to PD-L1

PD-L1 ≥50%

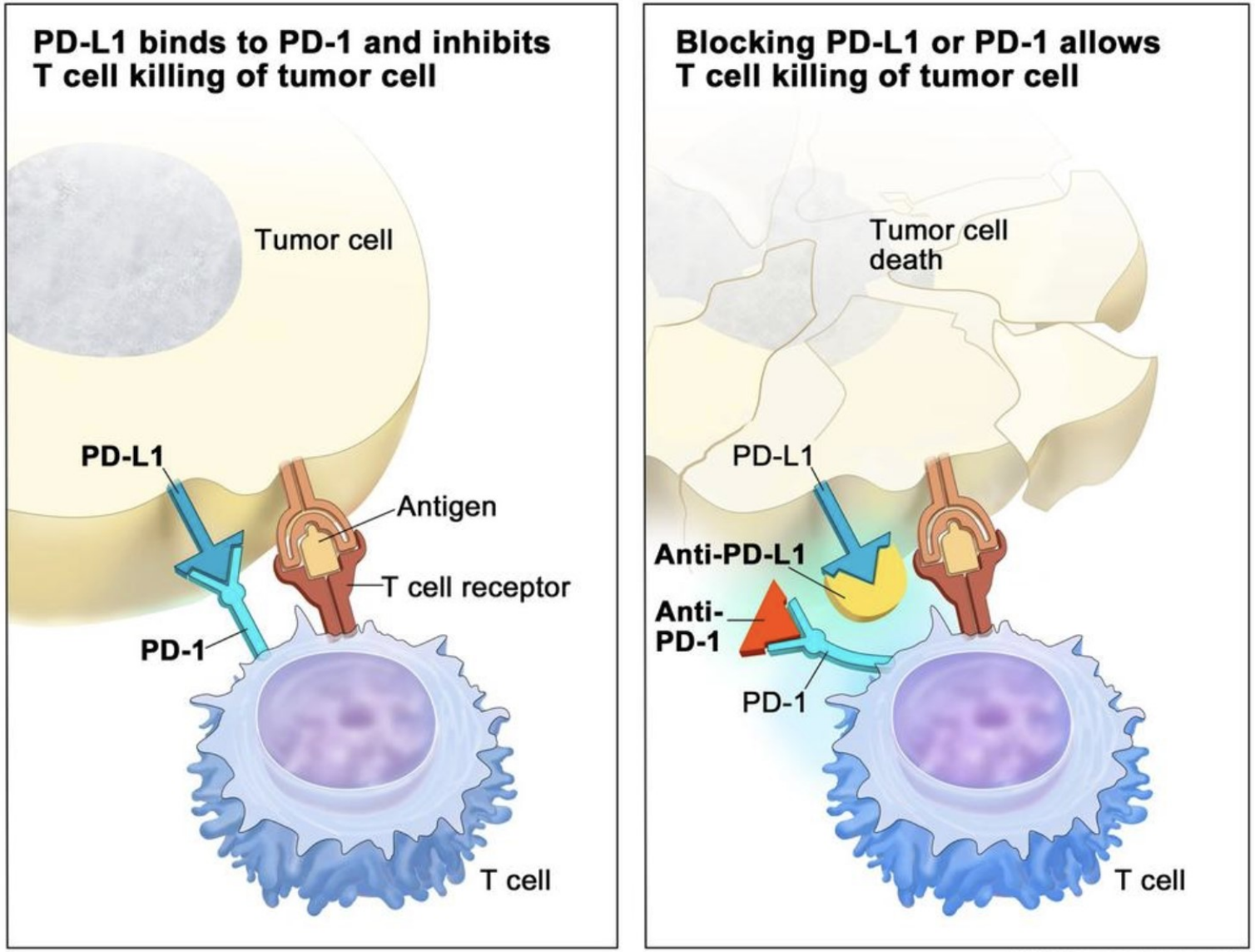
PD-L1 1-49%

PD-L1 <1%

ICI alone or ICI + chemotherapy

ICI + chemotherapy

# Immune checkpoint inhibitors (ICI): mechanism




**Anti-PD-1**

pembrolizumab, nivolumab, cemiplimab

**Anti-PD-L1**

atezolizumab, durvalumab

# ICI vs chemotherapy – PDL1 ≥ 50%

M Reck ESMO 2016

## KEYNOTE-024 Study Design (NCT02142738)

All NSCLC histology included

**Key Eligibility Criteria**
- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

R (1:1)
N = 305

- Pembrolizumab 200 mg IV Q3W (2 years)
- Platinum-Doublet Chemotherapy (4-6 cycles)

**Key End Points**

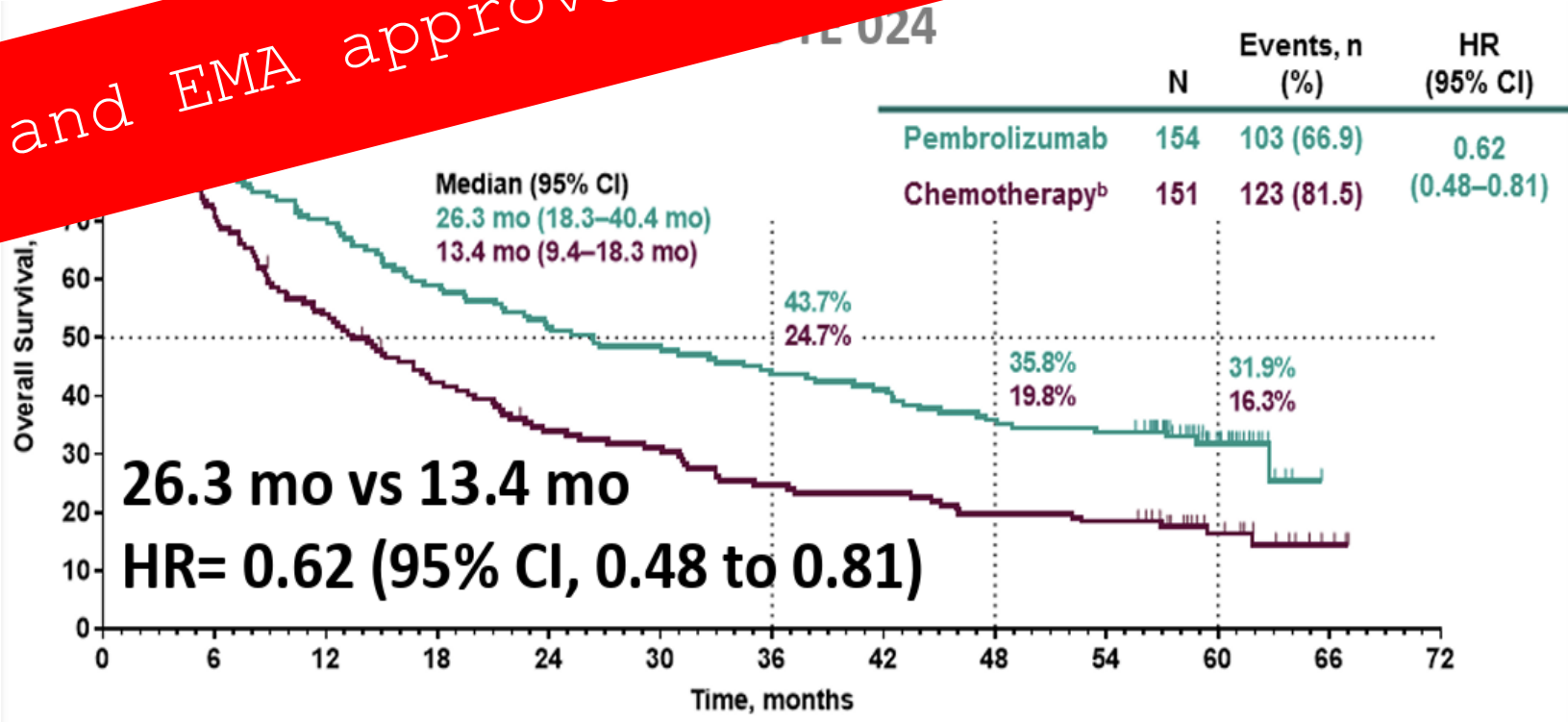
Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

Exploratory: DOR

*To be eligible for crossover, progressive disease (PD) had to be confirmed by blind… and all safety criteria had to be met.

FDA and EMA approved




*M. Reck, NEJM 2016*

# ICI + chemo vs chemo alone: KEYNOTE-189 and KEYNOTE-407

| | KEYNOTE-189: non-squamous | KEYNOTE-407: squamous |
|---|---|---|
| Design | Phase III, double-blind, 2:1, N = 616 | Phase III, double-blind, 1:1, N = 559 |
| Population | Untreated metastatic, no molecular alteration , any PD-L1 | |
| Regimen | Pembrolizumab or placebo + (pemetrexed-platinum × 4) then pemetrexed ± pembrolizumab | Pembrolizumab or placebo + carboplatin + (nab-)paclitaxel × 4, then pembrolizumab or placebo |
| ORR | With Pembrolizumab : 47.6% vs without : 18.9% | With Pembrolizumab: 58.4% vs without: 35% |
| Median PFS | 9.0 vs 4.9 months · HR 0.52 | 8.0 vs 5.1 months · HR 0.61 |
| Median OS | 22 vs 10.7 months · HR 0.56 | 17.2 vs 11.6 months · HR 0.71 |

*L. Gandhi et al. NEJM 2018; L. Paz-Ares et al. NEJM 2018*

# ICI + chemotherapy: benefit across PD-L1 subgroups

| | KEYNOTE-189: non-squamous | | KEYNOTE-407: squamous | |
|---|---|---|---|---|
| PD-L1 | PFS HR | OS HR | | |
| ≥50% ( = 50% of tumors e… PD… | | | 0.37 | 0.64 |
| 1–49% | 0.57 | 0.65 | 0.56 | 0.57 |
| <1% | 0.67 | 0.65 | 0.68 | 0.61 |

FDA and EMA approved, whatever the PD-L1

*M. Garassino et al. JCO 2023 (KEYNOTE-189, 5-year); L. Paz-Ares et al. NEJM 2018 (KEYNOTE-407)*

# First-line immunotherapy according to PD-L1

## PD-L1 ≥50%

- Pembrolizumab alone (200mg every 3 weeks)
- or chemo-pembrolizumab if high tumour burden

## PD-L1 1-49% and PD-L1 <1%

Chemo-pembrolizumab

Regimen according to histology (below)

### Non-squamous · KEYNOTE-189, every 3 weeks

| Drug | Dose | Day |
|---|---|---|
| *Induction: 4 cycles* | | |
| Pemetrexed | 500 mg/m² | D1 |
| Cisplatin (or carboplatin) | 75 mg/m² (AUC 5) | D1 |
| Pembrolizumab | 200 mg flat dose | D1 |
| *Maintenance: up to 2 years of pembrolizumab* | | |
| Pemetrexed | 500 mg/m² | D1 |
| Pembrolizumab | 200 mg flat dose | D1 |

### Squamous · KEYNOTE-407, every 3 weeks

| Drug | Dose | Day |
|---|---|---|
| *Induction: 4 cycles* | | |
| Paclitaxel (or nab-paclitaxel) | 200 mg/m² (100 mg/m²) | D1 (D1, 8, 15) |
| Carboplatin | AUC 6 | D1 |
| Pembrolizumab | 200 mg flat dose | D1 |
| *Maintenance: up to 2 years* | | |
| Pembrolizumab | 200 mg flat dose | D1 |

~72,000 € / patient / year on average (France)

# PULSE: pembrolizumab less often?

- **Low-dose pembrolizumab, India (phase III, ASCO 2026):** 50 mg + chemo vs chemo alone, **mOS 13.5 vs 10.5 months**

- **Phase III trial: Pulse**

  - Non-squamous NSCLC, **maintenance** pembrolizumab
  - Randomised 1:1: **200 mg every 6 weeks** vs 200 mg every 3 weeks
  - Primary endpoint: **overall survival** (non-inferiority, HR ≤1.25)
  - N = 1,166 · France, Spain, Belgium · recruiting since 2023
  - Also: PK, toxicity, quality of life, **cost**

**Rationale:** long half-life, PD-1 receptors saturated > 3 weeks

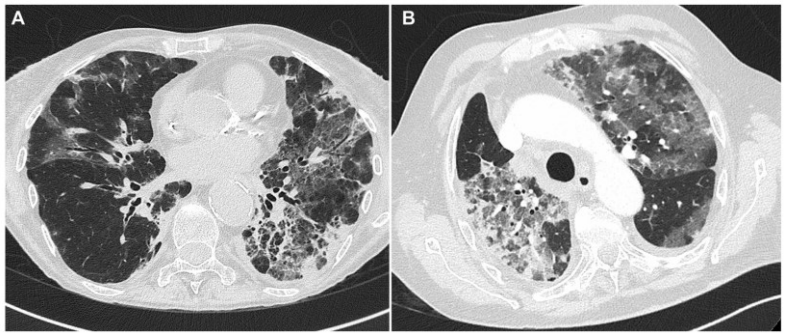
*PULSE, NCT05692999 (ELCC 2024, 106TiP); N. Menon, ASCO 2026; REFINE-Lung, NCT05085028*

# Immunotherapy toxicity: focus on pneumonitis

- 3-5% of patients ; median onset ~2-3 months after initiation of ICI
- Risk Factors: pre-existing ILD, prior thoracic RT, COPD, systemic treatment combinations
- Clinical signs: New dyspnoea, cough, hypoxaemia. May be asymptomatic (radiological only)

  New respiratory symptoms on or after ICI = pneumonitis until proven otherwise

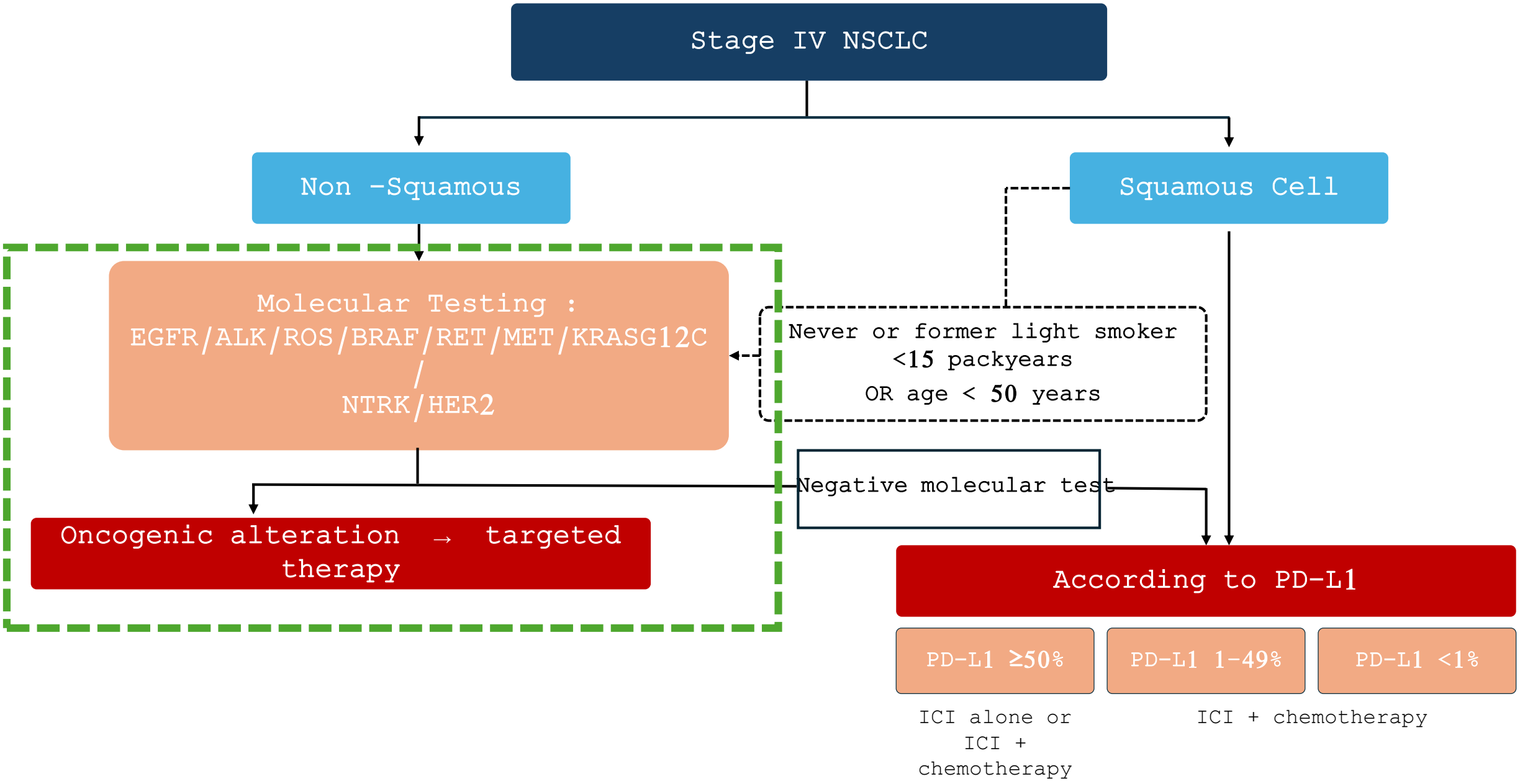
- CT patterns: **ground glass (>50%)**, NSIP, HP-like, diffuse alve




- Work up:
  - Rule out infection: cultures, viral panel, fungal markers
  - Rule out disease progression
  - Bronchoscopy with BAL: Lymphocyte-predominant alveolitis (CD
  excludes inf
- Treatment

| | |
|---|---|
| 1 | **Asymptomatic:** monitor, consider holding ICI |
| 2 | **Symptomatic, no hypoxaemia:** hold ICI; prednisone 1 mg/kg/d PO 4-6 weeks.<br>Resume when grade 1 or less |
| 3-4 | **Hypoxaemia / ICU:** stop ICI; IV methylprednisolone 1-2 mg/kg/d; taper over ≥6 weeks.<br>If no improvement: IgIV, Infliximba, MMF<br>MDT discussion before resuming ICI treatment |

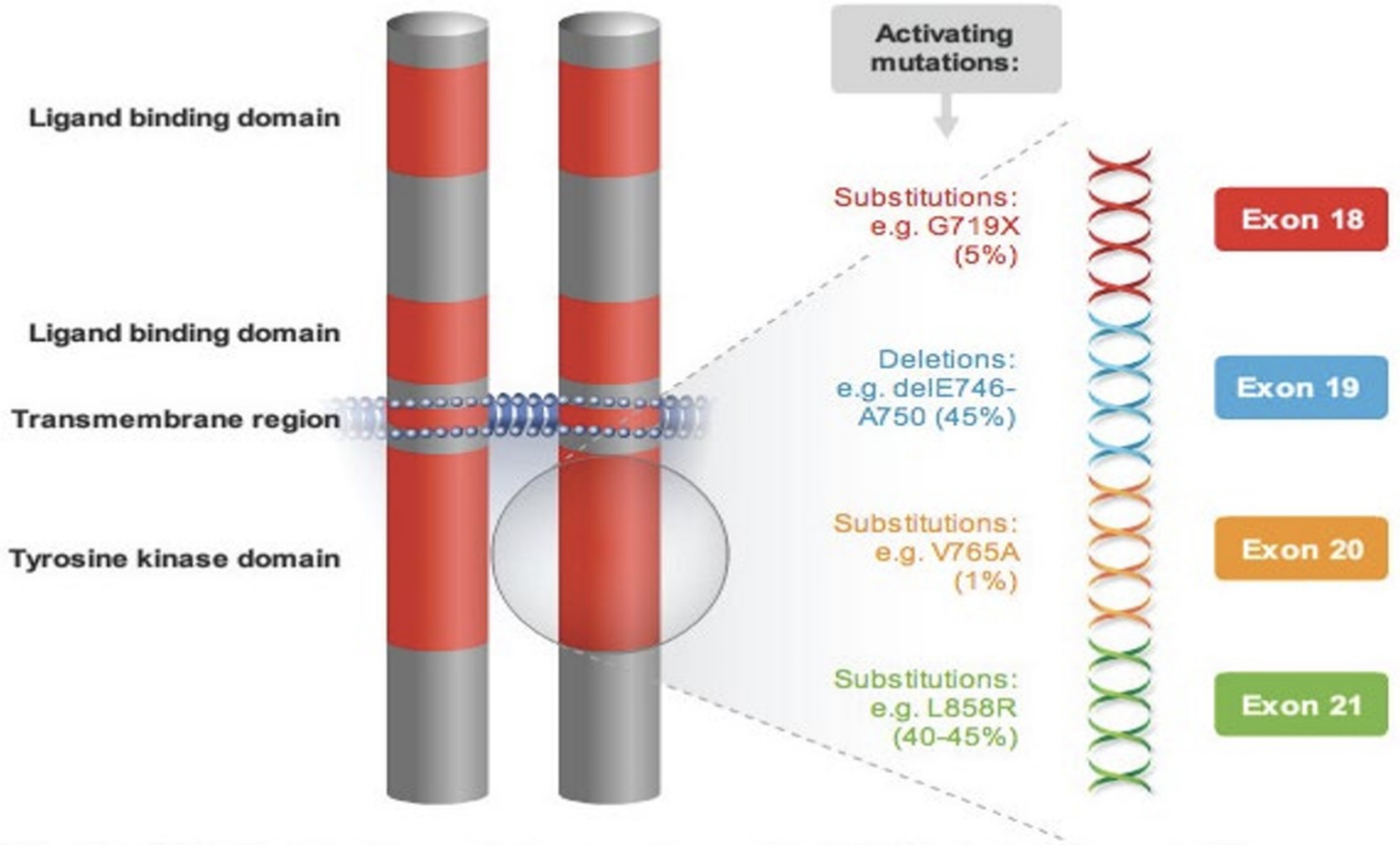
# Metastatic NSCLC: first-line decision



# EGFR-mutant NSCLC

## EGFR mutations

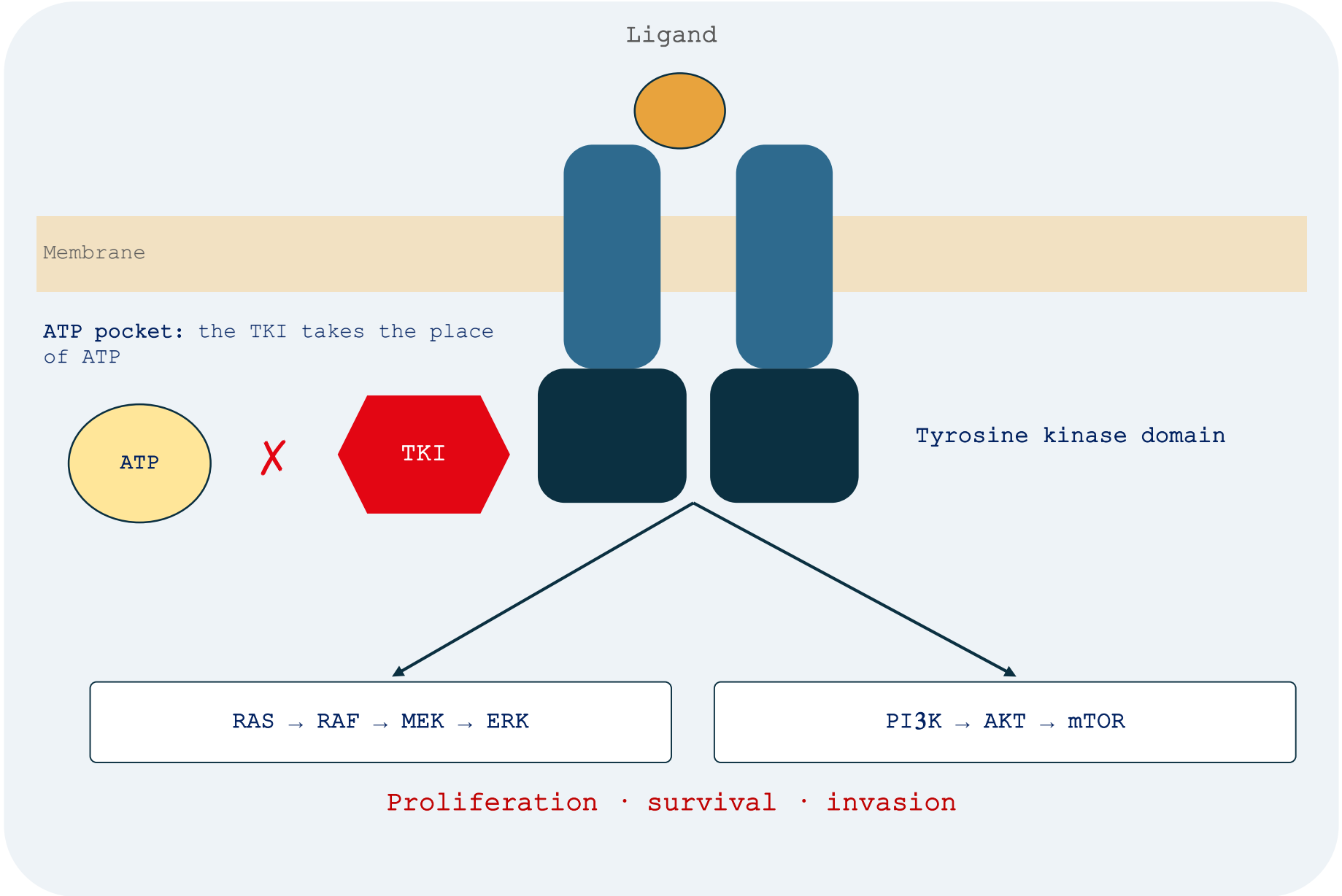
- ~10-15% in Europe, up to ~50% in East Asia
- Never / light smokers, women
- Brain metastases ~20% at diagnosis
- **Common:** exon 19 deletion, exon 21 L858R (~85-90%)
- Uncommon: exon 20 insertion, G719X, L861Q, S768I




* T790M <5% at initial EGFR mutations, however it is the major resistance mutation (50%) after treatment with reversible TKIs

*Sharma SV et al., Nat Rev Cancer 2007*

# Tyrosine kinase inhibitors: mechanism



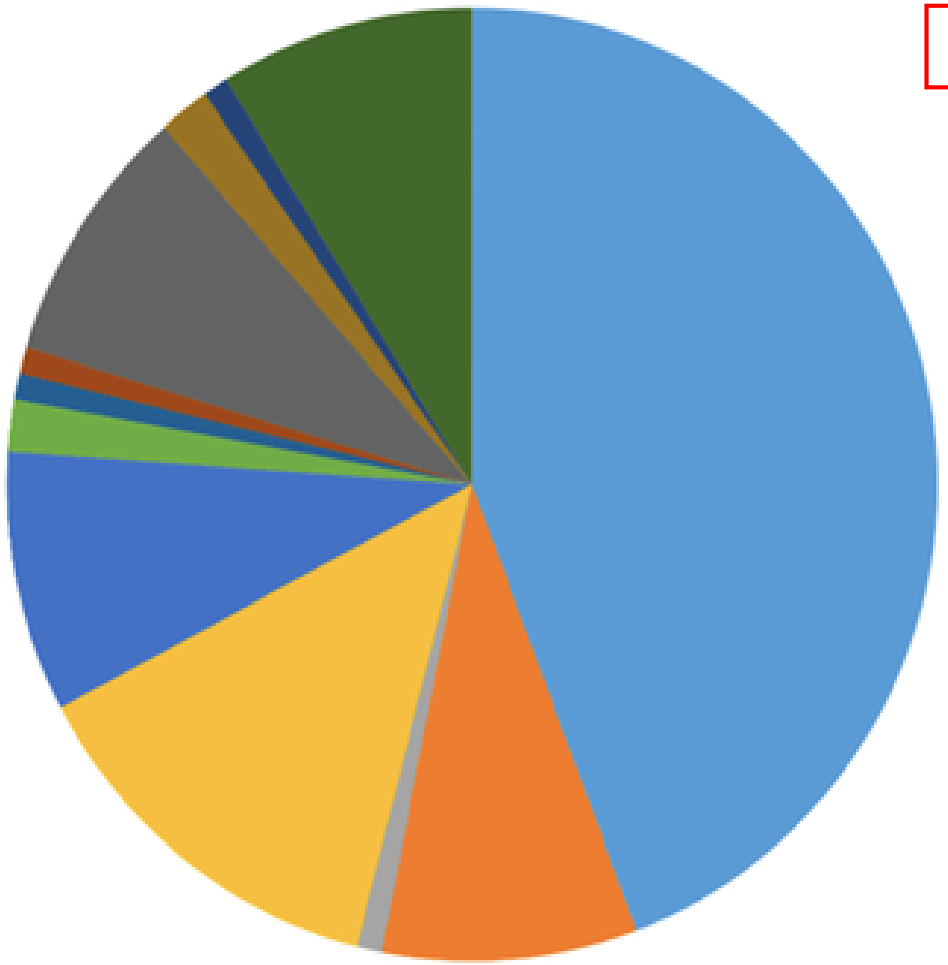
# EGFR-mutant NSCLC: 1st and 2nd generation TKIs

| Trial | Gen. | Regimen | ORR | mPFS (HR) | mOS (HR) | Price / box |
|---|---|---|---|---|---|---|
| IPASS (EGFRm) | 1G | Gefitinib vs carboplatin-paclitaxel | 71% vs 47% | 9.5 vs 6.3 mo (0.48) | 21.6 vs 21.9 mo (1.00) | ~755€ |
| EURTAC | 1G | Erlotinib vs platinum doublet | 58% vs 15% | 9.7 vs 5.2 mo (0.37) | 19.3 vs 19.5 mo (1.04) | ~850€ |
| LUX-Lung 7 | 2G vs 1G | Afatinib vs gefitinib | 70% vs 56% | 11.0 vs 10.9 mo (0.73) | 27.9 vs 24.5 mo (0.86) | ~1,580€ |
| ARCHER 1050 | 2G vs 1G | Dacomitinib vs gefitinib | 75% vs 72% | 14.7 vs 9.2 mo (0.59) | 34.1 vs 26.8 mo (0.76) | |

**1st/2nd-generation TKIs vs chemotherapy:** ORR ~60–75%, mPFS ~10–14 months

*Mok NEJM 2009; Fukuoka JCO 2011; Rosell Lancet Oncol 2012; Sequist JCO 2013; Yang Lancet Oncol 2015; Paz-Ares Ann Oncol 2017; Mok JCO 2018*

# Acquired Resistance to EGFR TKIs



- T790M ~ 50%
- EGFR amplification ~ 10%
- Other EGFR alterations ~ 1%
- HER2 amplification ~ 15%
- MET amplification ~ 10%
- PI3K mutation ~ 2%
- BRAF mutation ~1%
- SCLC transformation ~10%
- EMT ~2%
- SCC transformation ~1%
- Other unconfirmed ~10%

EGFR dependent

Bypass signal activation

Histologic transformation

# FLAURA Trial: Osimertinib

**Patients with locally advanced or metastatic NSCLC**

**Key inclusion criteria**

- ≥18 years*
- WHO performance status 0 / 1
- Exon 19 deletion / L858R (enrolment by local# or central‡ EGFR testing)
- No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS metastases allowed

Stratification by **mutation status** (Exon 19 deletion / L858R) and **race** (Asian / non-Asian)

**Randomised 1:1**

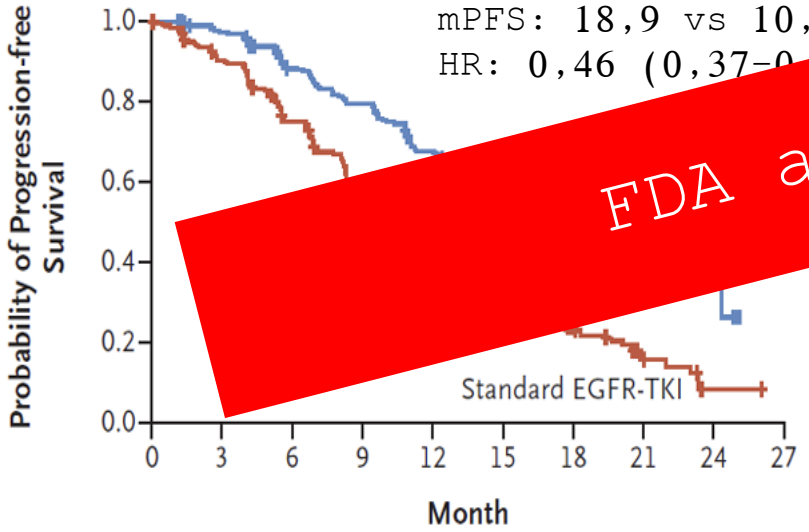
- **Osimertinib** (80 mg p.o. qd) (n=279)
- EGFR-TKI SoC §; **Gefitinib** (250 mg p.o. qd) or **Erlotinib** (150 mg p.o. qd) (n=277)

RECIST 1.1 assessment every 6 weeks¶ until objective

Crossover was allowed for patients in the **SoC** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

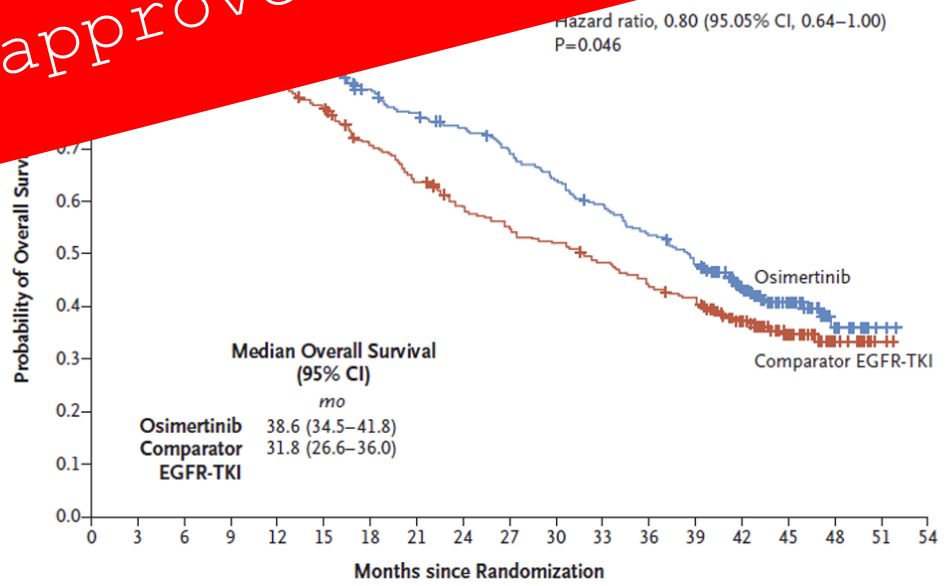
FDA and EMA approved

mPFS: 18,9 vs 10,2 Mo
HR: 0,46 (0,37–0,




No. at Risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 279 | 262 | 233 | 210 | 178 | 139 | 71 | 26 | 4 | 0 |
| Standard EGFR-TKI | 277 | 239 | 197 | 152 | 107 | 78 | 37 | 10 | 2 | 0 |



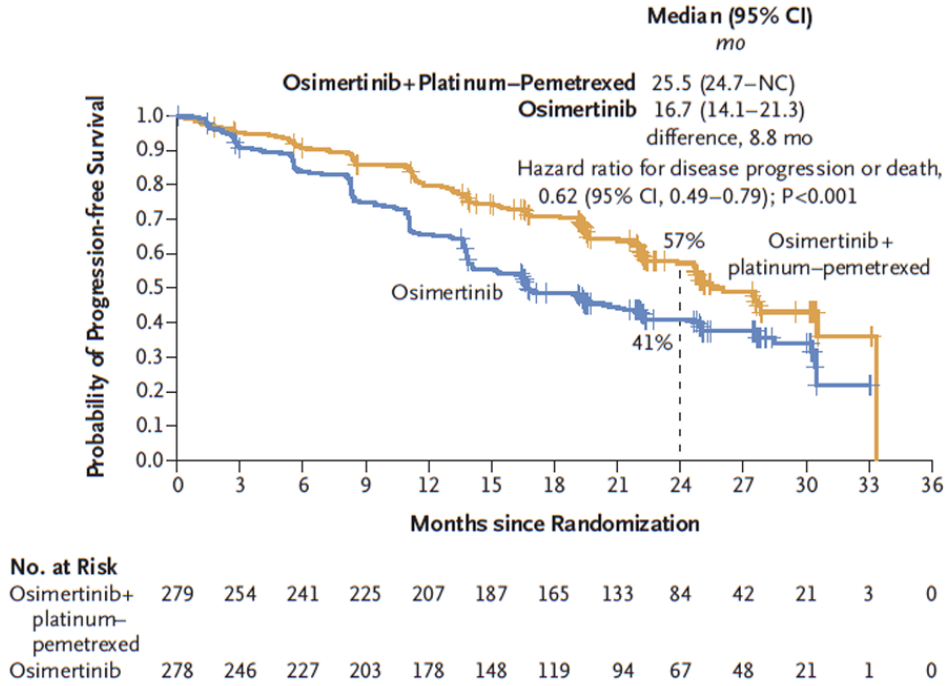

No. at Risk

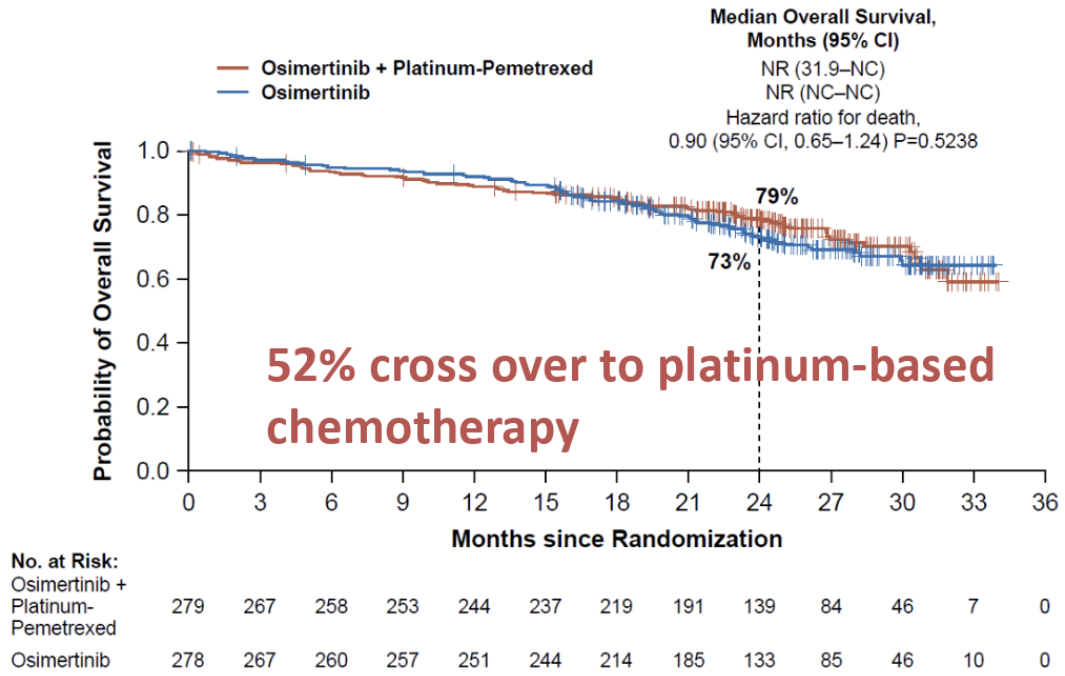
| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 279 | 276 | 270 | 254 | 245 | 236 | 217 | 204 | 193 | 180 | 166 | 153 | 138 | 123 | 86 | 50 | 17 | 2 | 0 |
| Comparator EGFR-TKI | 277 | 263 | 252 | 239 | 219 | 205 | 182 | 165 | 148 | 138 | 131 | 121 | 110 | 101 | 72 | 40 | 17 | 2 | 0 |

Soria NEJM 201

# FLAURA2 (D. Planchard, NEJM 2023)

- phase III, open-label, randomised 1:1, N = 557
- Untreated advanced **EGFR-mutated** NSCLC (**Ex19del or L858R**)
- Osimertinib + pemetrexed + cisplatin/carboplatin × 4 cycles, then




**Consider intensification in poor-prognosis disease:** brain metastases, L858R, TP53 co-mutation, detectable ctDNA

# EGFR-mutant NSCLC: 1st line options

**A. Osimertinib upfront**

Osimertinib
mPFS 18.9 mo (FLAURA)
~€4,900 / month

~90,000 €
per patient

**B. Osimertinib + chemo**

Osimertinib + platinum-pemetrexed
mPFS 25.5 mo (FLAURA2)
+ pemetrexed maintenance

~120,000€
per patient

If osimertinib is unaffordable / low-income countries (not ESMO / NCCN recommended)

**C. Sequential**

Gefitinib/Erlotinib/ Afatinib
mPFS 11 mo (LUX-Lung 7)
~€1,700 / month

→

Osimertinib if T790M+
~55% of patients
mPFS 10.1 mo (AURA3)

~45,000€
per patient

# ALK-rearranged NSCLC: first line

## ALK rearrangement

- ~3–5%
- Young, never / light smokers, adenocarcinoma
- Median PFS> 7 years

| Trial | TKI vs comparator | ORR | mPFS (HR) | OS |
|---|---|---|---|---|
| **ALEX** | Alectinib (2G) vs crizotinib (1G) | 83% vs 76% | 34.8 vs 10.9 mo (0.43) | 81.1 vs 54.2 mo (0.78)<br>7-year OS 48.6% |
| **ALTA-1L** | Brigatinib (2G) vs crizotinib (1G) | 74% vs 62% | 24.0 vs 11.0 mo (0.48) | HR 0.81 (NS) |
| **CROWN** | **Lorlatinib** (3G, active on resistance mutations to 2nd-generation TKIs) vs crizotinib | 76% vs 58% | NR (> 7 years) vs 9.1 mo (0.19)<br>5-year PFS 60% vs 8% | NR, immautr |

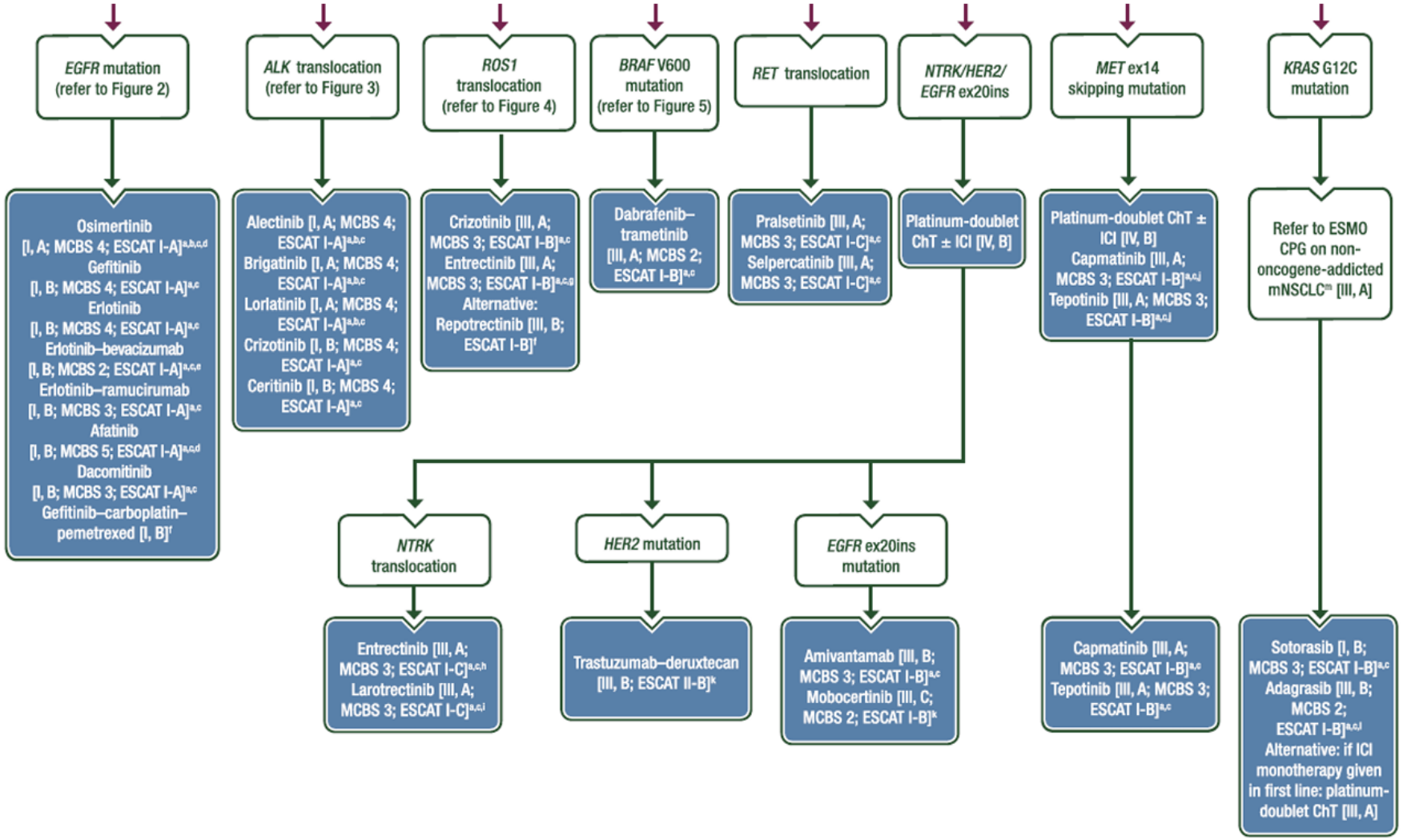
- **Specific toxicities:** alectinib: myalgia, CPK; brigatinib: early pulmonary events, CPK, lipase
- **Lorlatinib:** hypercholesterolaemia, weight gain, mood and cognitive effects

Price / Box: ~3500 -3800€ for all three drugs

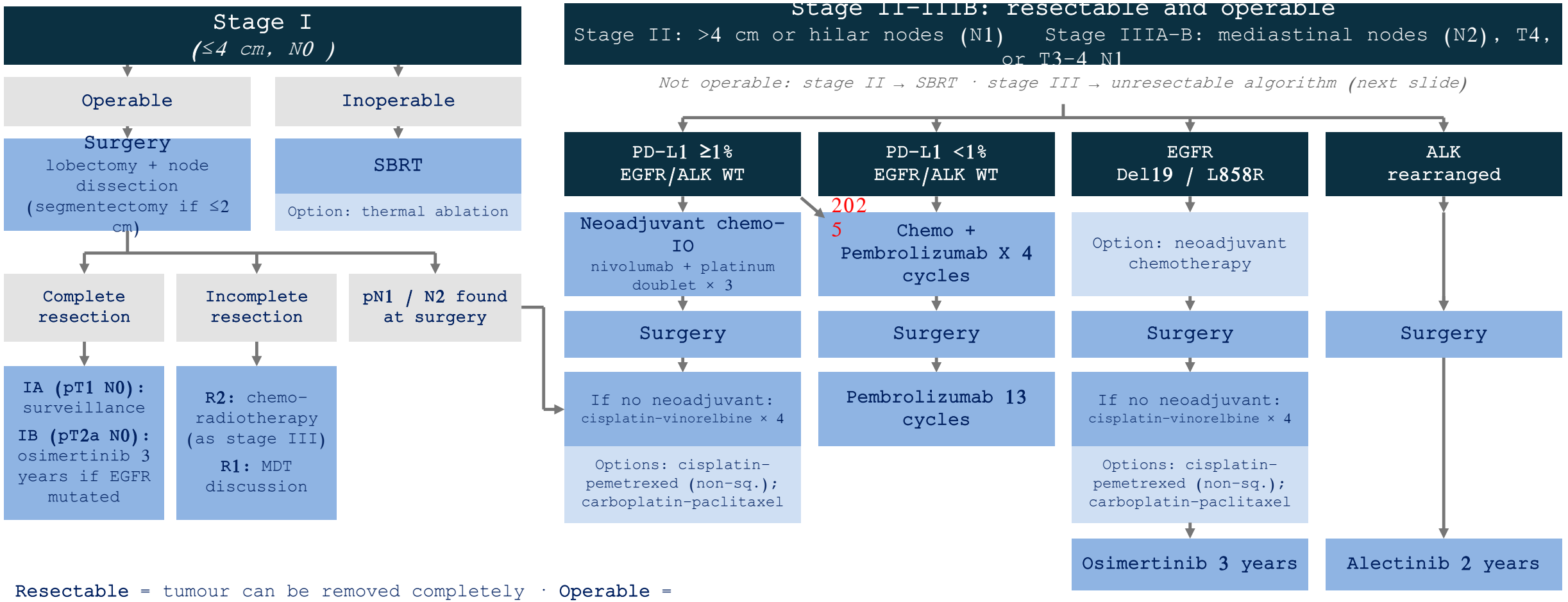
*Mok ESMO 2025 (ALEX final OS); Camidge JTO 2021 (ALTA-1L); Solomon JCO 2024 (CROWN 5-year)*

# Oncogenic-driven mutations in NSCLC

## Stage IV NSCLC : ESMO Clinical Practice Guideline



# Stage I–IIIB NSCLC

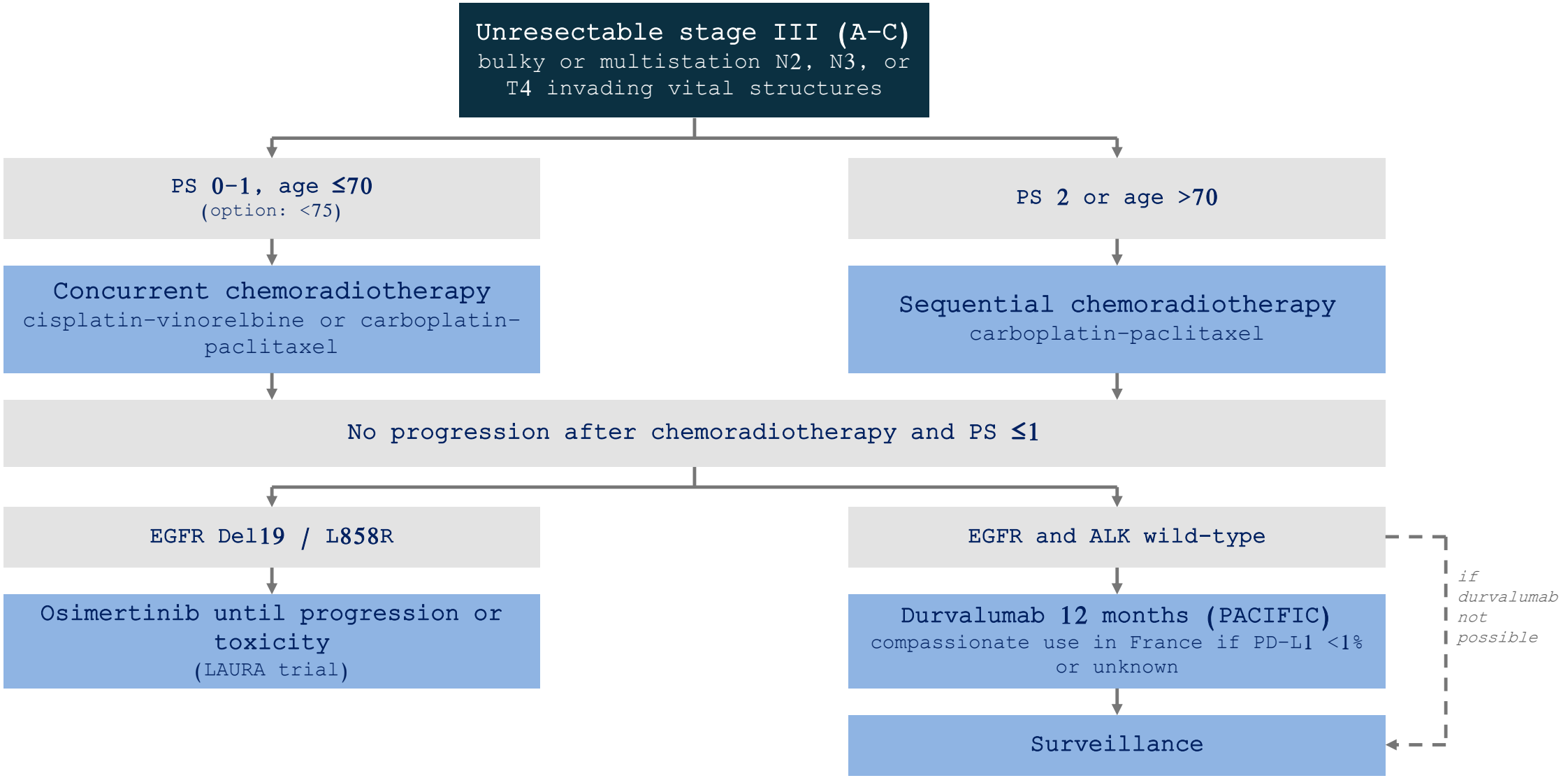



**Resectable** = tumour can be removed completely · **Operable** = patient fit for surgery

- Resectability is decided in a multidisciplinary tumour board (invasive mediastinal staging (EBUS))
- Test EGFR and ALK even in localized disease!

*Adapted from French regional guidelines 2025; ESMO; IASLC TNM 9th edition*

# Unresectable stage III NSCLC




*Adapted from French regional guidelines 2025; Antonia NEJM 2018 (PACIFIC); Lu NEJM 2024 (LAURA); IASLC TNM 9th edition*

# Take-home messages



1. **Tobacco control:** awareness campaigns, smoke-free public places, cessation support

2. **Test before treating:** Develop molecular testing (EGFR, ALK, ROS1…) and IHC (PD-L1, ALK)

3. **Explore strategies to improve access to immunotherapy and Targeted therapy**

4. **Establish multidisciplinary tumor boards (MDTs) to promote collaborative, evidence-based treatment decisions.**

# Thank you for your attention!

Contact:
aliaharba@gmail.com

# Other approved first-line IO regimens

| Regimen | Trial | Population | mOS (HR) | FDA | EMA | France |
|---|---|---|---|---|---|---|
| Atezolizumab | IMpower110 | PD-L1 high (TC ≥50% / IC ≥10%) | 20.2 vs 13.1 mo (0.59) | ✓ | ✓ | ✓ Reimbursed |
| Cemiplimab | EMPOWER-Lung 1 | PD-L1 ≥50% | 22.1 vs 14.3 mo (0.68) | ✓ | ✓ | ✓ Reimbursed |
| Cemiplimab + chemotherapy | EMPOWER-Lung 3 | All PD-L1, all histologies | 21.9 vs 13.0 mo (0.71) | ✓ | ✓ | ✗ Not reimbursed |
| Atezolizumab + bevacizumab + carboplatin-paclitaxel | IMpower150 | Non-squamous | 19.2 vs 14.7 mo (0.78) | ✓ | ✓ | ✗ Not reimbursed |
| Atezolizumab + carboplatin-nab-paclitaxel | IMpower130 | Non-squamous | 18.6 vs 13.9 mo (0.79) | ✓ | ✓ | ✗ Not reimbursed |
| Nivolumab + ipilimumab | CheckMate 227 | PD-L1 ≥1% | 17.1 vs 14.9 mo (0.79) | ✓ | ✗ | ✗ No EU approval |
| Nivolumab + ipilimumab + 2 cycles chemo | CheckMate 9LA | All PD-L1, all histologies | 15.6 vs 10.9 mo (0.66) | ✓ | ✓ | ✗ Not reimbursed |
| Durvalumab + tremelimumab + chemotherapy | POSEIDON | All PD-L1, all histologies | 14.0 vs 11.7 mo (0.77) | ✓ | ✓ | ✗ Not reimbursed |

*Herbst NEJM 2020; Sezer Lancet 2021; Gogishvili Nat Med 2022; Socinski NEJM 2018; West Lancet Oncol 2019; Hellmann NEJM 2019; Paz-Ares Lancet Oncol 2021; Johnson JCO 2023; HAS; OMEDIT IDF 2024*

# Perioperative setting: approvals

| Trial | Regimen | Indication (stage)* | FDA (USA) | EMA (EU) | France |
|---|---|---|---|---|---|
| CheckMate 816 | Neoadjuvant nivolumab + chemo × 3 | IB ≥4 cm–IIIA† | ✓ all PD-L1 | ✓ PD-L1 ≥1% | Reimbursed (PD-L1 ≥1%) |
| KEYNOTE-671 | Perioperative pembrolizumab | II–IIIB (N2) | ✓ all PD-L1 | ✓ all PD-L1 | HAS favourable (SMR moderate) |
| CheckMate 77T | Perioperative nivolumab | IIA >4 cm–IIIB (N2) | ✓ all PD-L1 | ✓ PD-L1 ≥1% | Pending |
| AEGEAN | Perioperative durvalumab | IIA–IIIB (N2) | ✓ all PD-L1 | ✓ all PD-L1 | Pending |
| IMpower010 | Adjuvant atezolizumab 1 y | II–IIIA† after adjuvant chemo | ✓ PD-L1 ≥1% | ✓ PD-L1 ≥50% | Not reimbursed |
| KEYNOTE-091 | Adjuvant pembrolizumab 1 y | IB ≥4 cm–IIIA† after adjuvant chemo | ✓ all PD-L1 | ✓ all PD-L1 | Not reimbursed |
| ADAURA | Adjuvant osimertinib 3 y | IB–IIIA†, EGFR ex19del / L858R | ✓ | ✓ | Reimbursed |
| ALINA | Adjuvant alectinib 2 y | IB ≥4 cm–IIIA†, ALK+ | ✓ | ✓ | Reimbursed (2025) |
| PACIFIC | Durvalumab 12 months after CRT | Unresectable III, no progression after CRT | ✓ all PD-L1 | ✓ PD-L1 ≥1% | Reimbursed (PD-L1 ≥1%) |
| LAURA | Osimertinib after CRT until progression | Unresectable III, EGFR ex19del / L858R | ✓ | ✓ | Reimbursed |

** Resectable NSCLC except PACIFIC and LAURA; IO trials excluded EGFR / ALK. Stage per AJCC 8th edition, † AJCC 7th edition. CRT = concurrent chemoradiotherapy*

# PD-L1 ≥50%: ICI alone or ICI + chemotherapy?

## FDA pooled analysis

- Exploratory pooled analysis of first-line trials
- Chemo-IO (n = 455) vs IO alone (n = 1,298)
- **mPFS 9.6 vs 7.1 months**
- **mOS 25.0 vs 20.9 months**
- Trend favouring chemo-ICI, not randomised

## PAULIEN (phase III)

- Pembrolizumab + chemo × 4 vs pembrolizumab
- N = 84, randomised 1:1
- **ORR 33% vs 23% (NS)**
- **PFS HR 0.91 · OS HR 0.89**
- Enrolment halted for futility

**In practice:** pembrolizumab alone

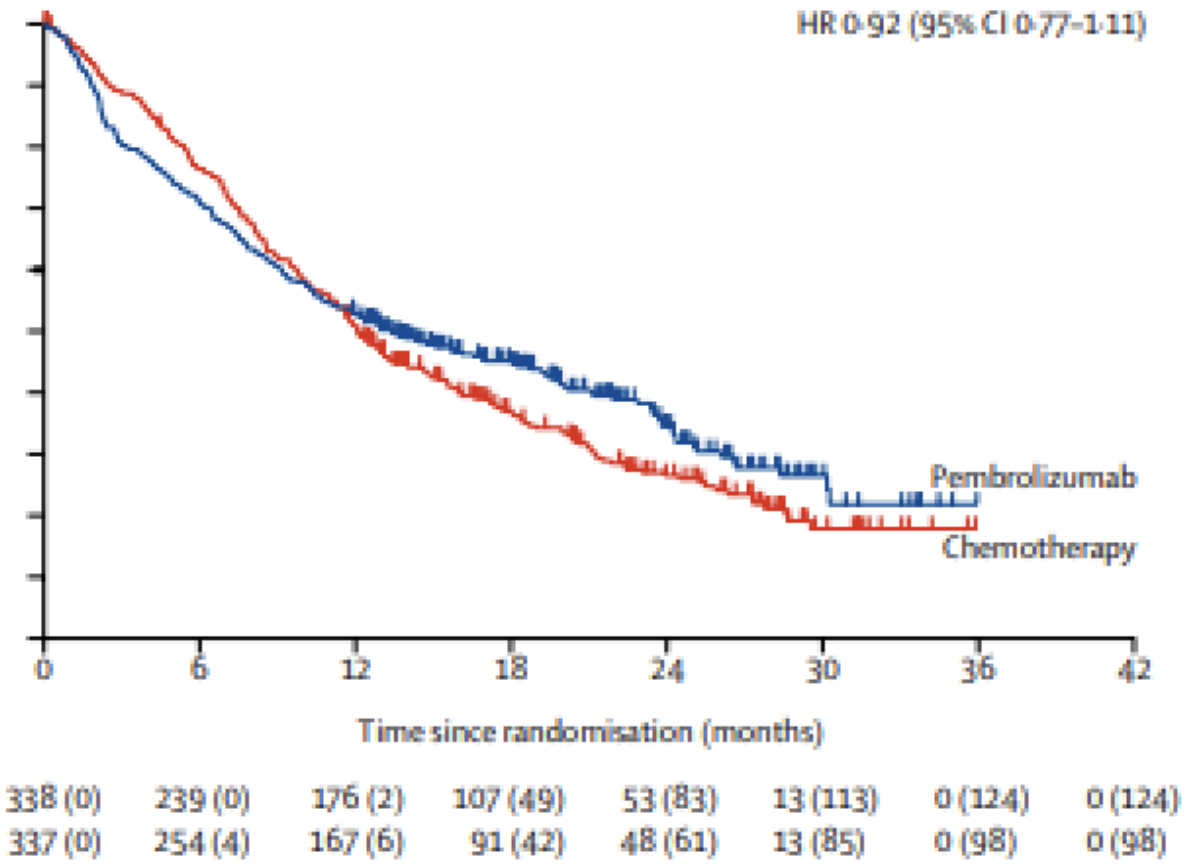
Chemo + ICI if high tumour burden (>5 metastases, liver metastases, symptomatic) and fit patient

*FDA pooled analysis (Akinboro, ASCO 2022); PAULIEN*

# Non-metastatic NSCLC: benefit and timing of each drug

| | Before surgery | | After surgery | Trial: key results vs control |
|---|---|---|---|---|
| Neoadjuvant | **Nivolumab** + platinum chemo × 3 | SURGERY → | | **CheckMate 816**<br>EFS HR 0.63 · pCR 24% vs 2% · OS HR 0.72 |
| Perioperative | **Pembrolizumab / nivolumab / durvalumab** + platinum chemo × 3–4 | SURGERY → | Same IO alone, ~1 year | **KEYNOTE-671:** EFS HR 0.59 · OS HR 0.72<br>**CheckMate 77T:** EFS HR 0.58<br>**AEGEAN:** EFS HR 0.68 |
| Adjuvant IO | | SURGERY → | Platinum chemo × 4 → **atezolizumab or pembrolizumab** 1 year | **IMpower010:** DFS HR 0.66 (stage II–IIIA, PD-L1 ≥1%)<br>**KEYNOTE-091:** DFS HR 0.76 |
| EGFR mutated | | SURGERY → | ± chemo → **osimertinib** 3 years | **ADAURA**<br>DFS HR 0.20 · OS HR 0.49 · 5-year OS 88% vs 78% |
| ALK rearranged | | SURGERY → | **Alectinib** 2 years | **ALINA**<br>DFS HR 0.24 · 2-year DFS 94% vs 63% |
| Unresectable stage III | **Concurrent chemoradiotherapy** | → | **Durvalumab** 12 months<br>EGFR: **osimertinib** | **PACIFIC:** PFS HR 0.52 · OS HR 0.68 · 5-y OS 43% vs 33%<br>**LAURA:** PFS 39.1 vs 5.6 months (HR 0.16) |

# PD-L1 1-49%: can ICI alone be enough?




## KEYNOTE-042

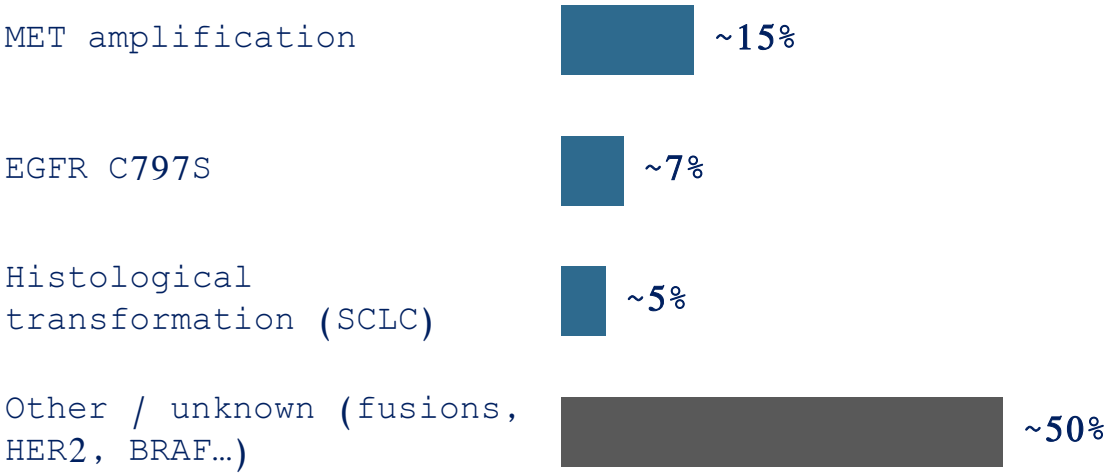
- Phase III, open-label, randomised 1:1, N = 1,274
- Untreated, PD-L1 ≥1%, no EGFR / ALK, squamous and non-squamous
- Pembrolizumab vs platinum chemotherapy
- OS HR **0.92 (0.77-1.11)** in PD-L1 1-49%
- Overall benefit driven by PD-L1 ≥50%

No: pembrolizumab alone is not enough
→ chemo + ICI

*T. Mok et al. Lancet 2019*

# EGFR: resistance to osimertinib and next line

## Resistance mechanisms (after first-line osimertinib)



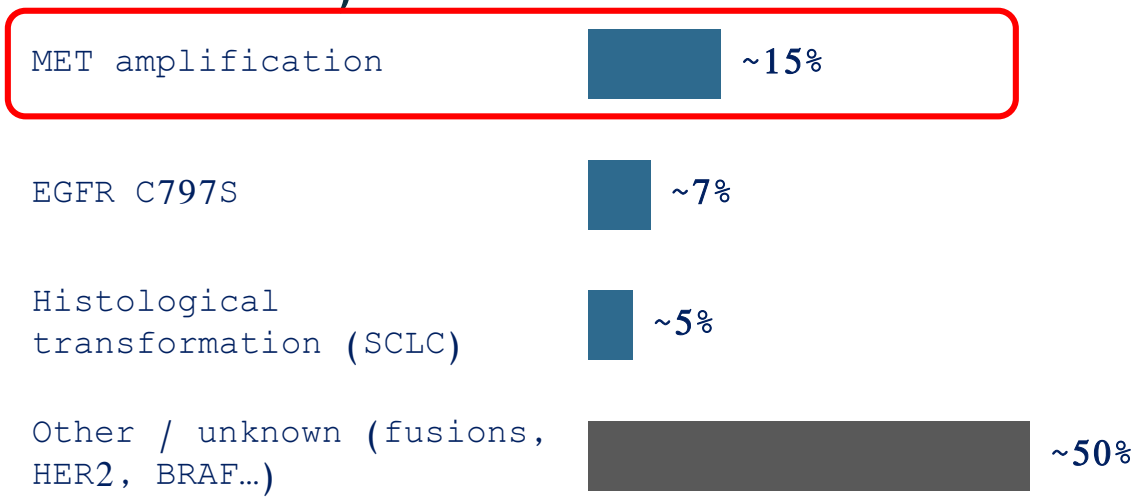

**Platinum-pemetrexed chemotherapy**

Standard after osimertinib; IO adds little in EGFR-mutant disease

*Ramalingam ESMO 2018 & Chmielecki Nat Commun 2023 (FLAURA resistance*

# EGFR: resistance to osimertinib and next line

## Resistance mechanisms (after first-line osimertinib)



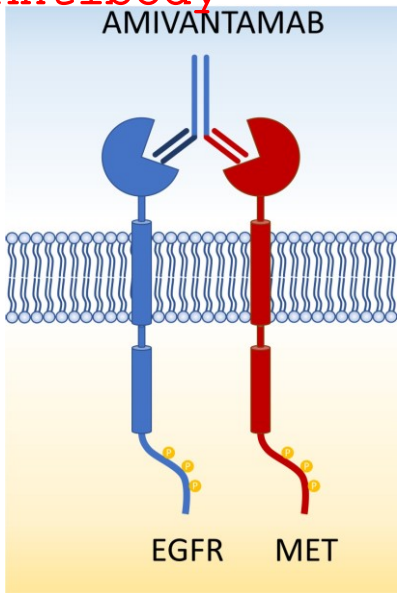

**Platinum-pemetrexed chemotherapy**

Standard after osimertinib; IO adds little in EGFR-mutant disease

**Amivantamab + carboplatin-pemetrexed**

MARIPOSA-2: mPFS 6.3 vs 4.2 mo (HR 0.48) vs chemo

Bispecific Antibody



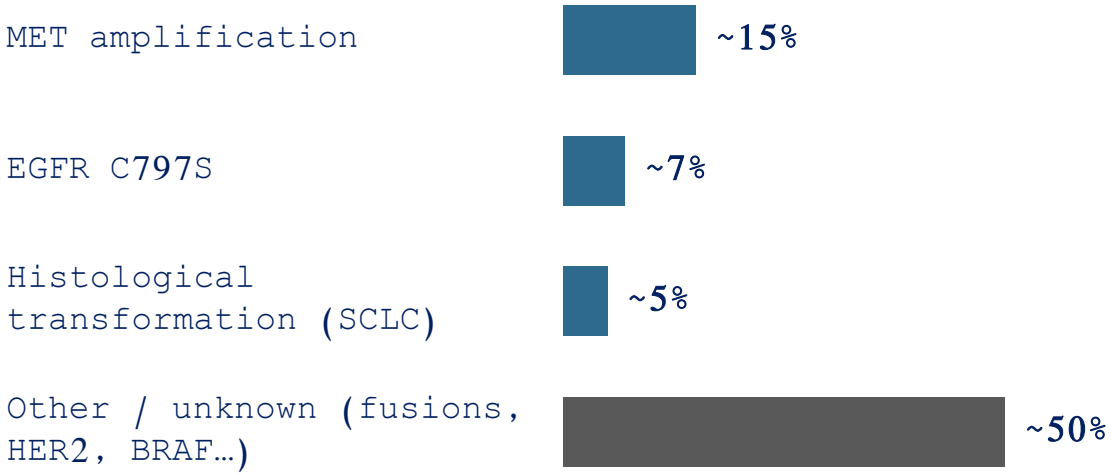

Main toxicities: infusion-related reactions (58%), neutropenia (57%, grade ≥3 45%), rash and paronychia (EGFR-related), **venous thromboembolism** (anticoagulant prophylaxis recommended)

G3 toxicities: 50%
Cost : 6000€ / 3 weeks vs ~ 100€ for chemo

*Ramalingam ESMO 2018 & Chmielecki Nat Commun 2023 (FLAURA resistance); Passaro Ann Oncol 2024 (MARIPOSA-2)*

# EGFR: resistance to osimertinib and next line

## Resistance mechanisms (after first-line osimertinib)




**Platinum-pemetrexed chemotherapy**

Standard after osimertinib; IO adds little in EGFR-mutant disease

**Amivantamab + carboplatin-pemetrexed**

MARIPOSA-2: mPFS 6.3 vs 4.2 mo (HR 0.48) vs chemo

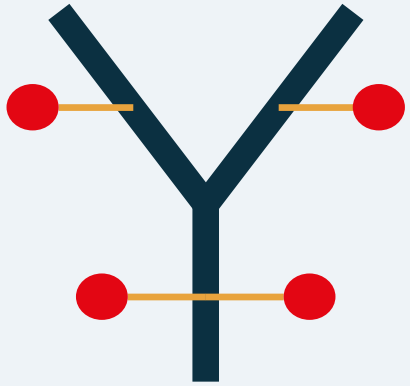
**Datopotamab deruxtecan (TROP2 ADC)**

FDA accelerated approval 2025 after EGFR TKI + platinum: ORR 45%, mPFS 6.5 mo

Antibody Drug Conjugate (ADC

*Ramalingam ESMO 2018 & Chmielecki Nat Commun 2023 (FLAURA resistance); Passaro Ann Oncol 2024 (MARIPOSA-2); FDA 2025 (Dato-DXd)*

Antibody



Linker Payload

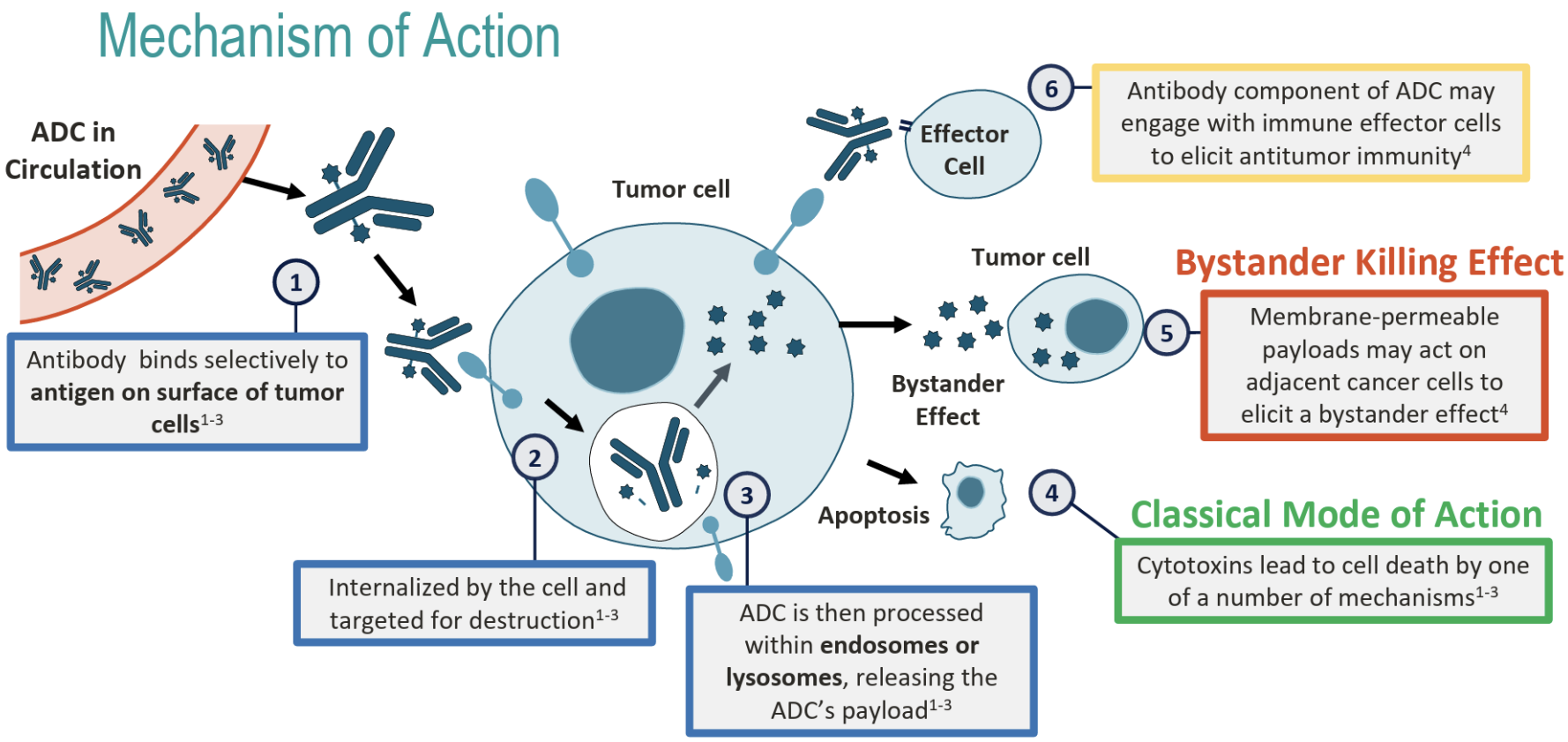
DAR = number of payloads per antibody

## Antibody

IgG1 against an antigen overexpressed on tumour cells: HER2, TROP2, c-MET, HER3

## Payload

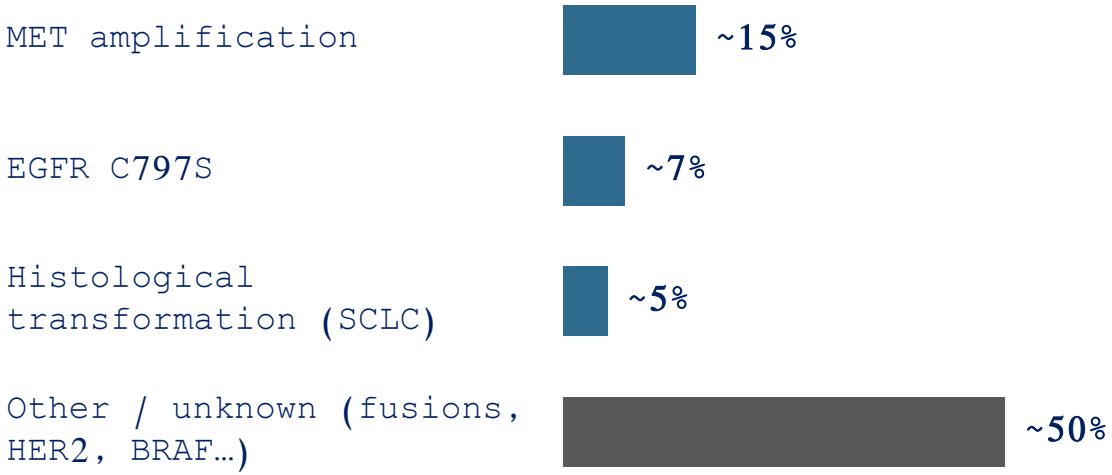
Topoisomerase-I inhibitors or microtubule inhibitors




*Adapted from D. Planchard, ADCs en 2ème ligne (Gustave Roussy)*

# EGFR: resistance to osimertinib and next line

## Resistance mechanisms (after first-line osimertinib)




**Platinum-pemetrexed chemotherapy**

Standard after osimertinib; IO adds little in EGFR-mutant disease

**Amivantamab + carboplatin-pemetrexed**

MARIPOSA-2: mPFS 6.3 vs 4.2 mo (HR 0.48) vs chemo

**Datopotamab deruxtecan (TROP2 ADC)**

FDA accelerated approval 2025 after EGFR TKI + platinum: ORR 45%, mPFS 6.5 mo

Antibody Drug Conjugate (ADC

Main toxicities: stomatitis (~50%), nausea (~35%), ocular events (~20%), ILD (~8%)

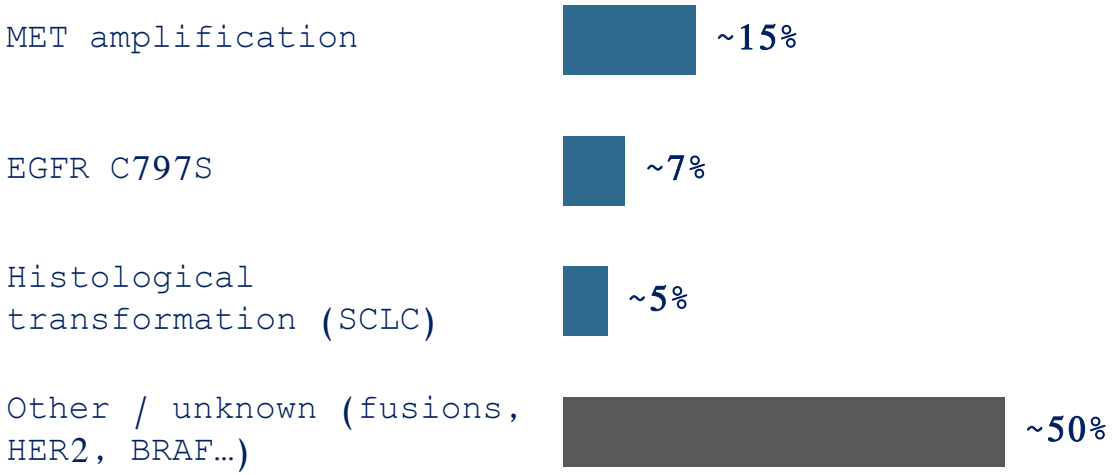
G3 toxicities: 50%

Cost : 20 000€ / 3 weeks

*Ramalingam ESMO 2018 & Chmielecki Nat Commun 2023 (FLAURA resistance); Passaro Ann Oncol 2024 (MARIPOSA-2); FDA 2025 (Dato-DXd)*

# EGFR: resistance to osimertinib and next line

## Resistance mechanisms (after first-line osimertinib)




### Amivantamab + carboplatin-pemetrexed

MARIPOSA-2: mPFS 6.3 vs 4.2 mo (HR 0.48) vs chemo

### Platinum-pemetrexed chemotherapy

Standard after osimertinib; IO adds little in EGFR-mutant disease

### Datopotamab deruxtecan (TROP2 ADC)

FDA accelerated approval 2025 after EGFR TKI + platinum: ORR 45%, mDOR 6.5 mo

### Mechanism-driven

MET amplification: osimertinib + MET inhibitor (trials); SCLC transformation: platinum-etoposide

**Re-biopsy at progression!**

**Be clear with patients about the actual benefit..**

*Ramalingam ESMO 2018 & Chmielecki Nat Commun 2023 (FLAURA resistance); Passaro Ann Oncol 2024 (MARIPOSA-2); FDA 2025 (Dato-DXd)*