UNIVERSITÀ CATTOLICA del Sacro Cuore

Comprehensive Cancer Center

BEST HOSPITALS 2022

Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

UNIVERSITÀ CATTOLICA del Sacro Cuore

Gemelli | ART

MRO . ART

# Modern Radiation Oncology. Innovation in personalised oncology: back to the future

## 33° RESIDENTIAL COURSE

Act 4 ART

**Scientific Coordinators:** *Vincenzo Valentini, Maria Antonietta Gambacorta, Luca Indovina*
**Honorary Presidents:** *Carlos A. Perez, Mario Ciallini*

## 9 | 10 | 11 October 2023

**Fondazione Policlinico Universitario A. Gemelli IRCCS**
**Largo A. Gemelli, 8 - Roma - Aula Brasca**

aifm

AITRO

EFOMP

Associazione Italiana Radioterapia e Oncologia clinica

Endorsed by ESTRO

SESSION 6: *BACK TO THE FUTURE: NSCLC*

# OLD AND NEW DRUGS: needs learned for modern treatments

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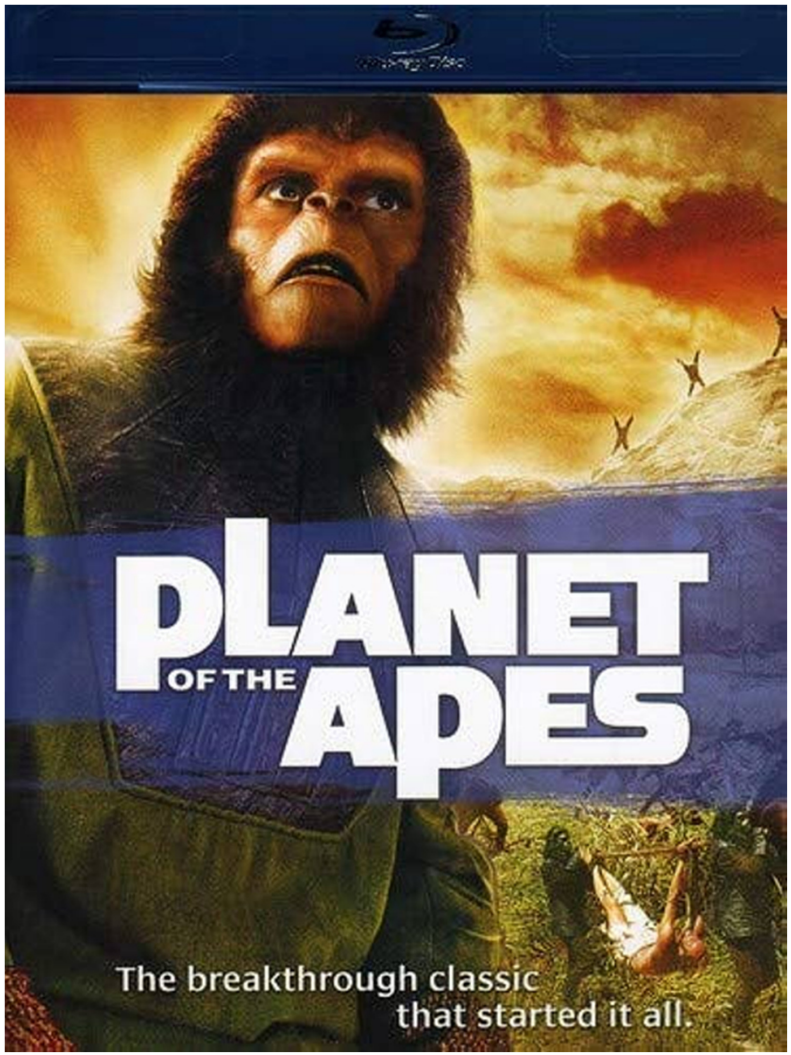
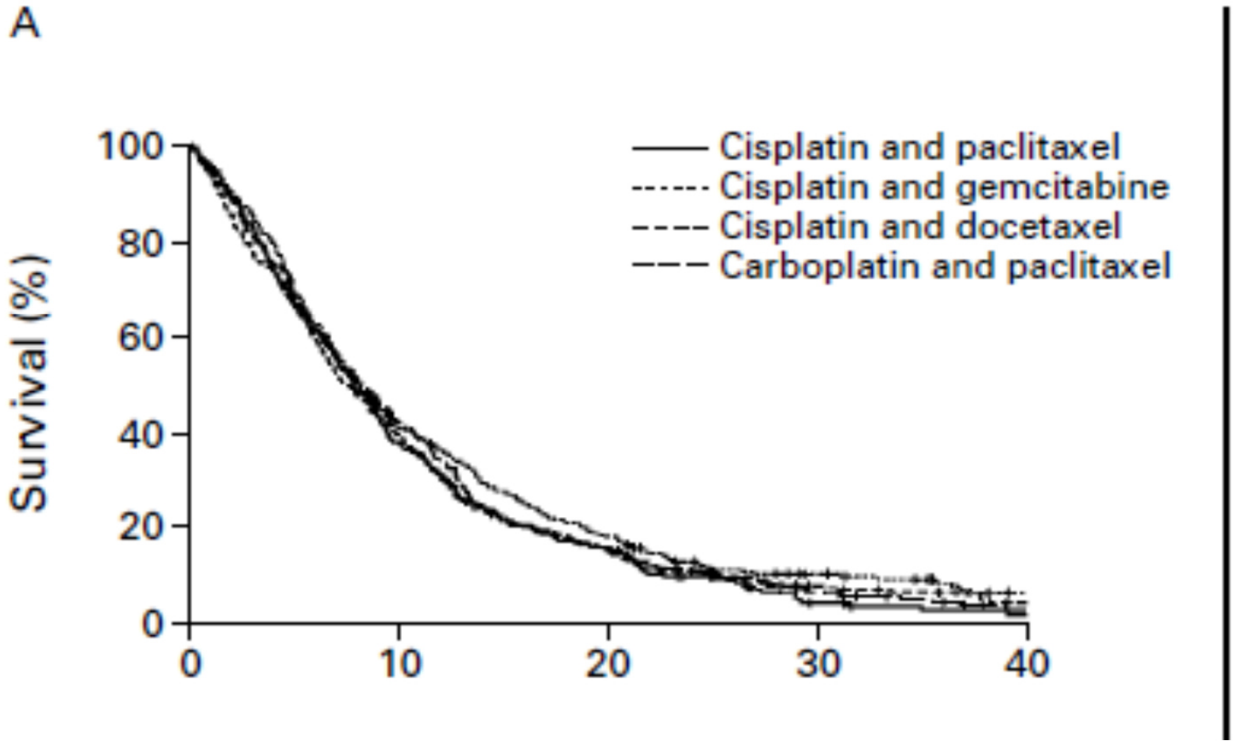
*Roma, 10 Ottobre 2023*

# In the beginning was chemotherapy



# ……and chemotherapy was for alls

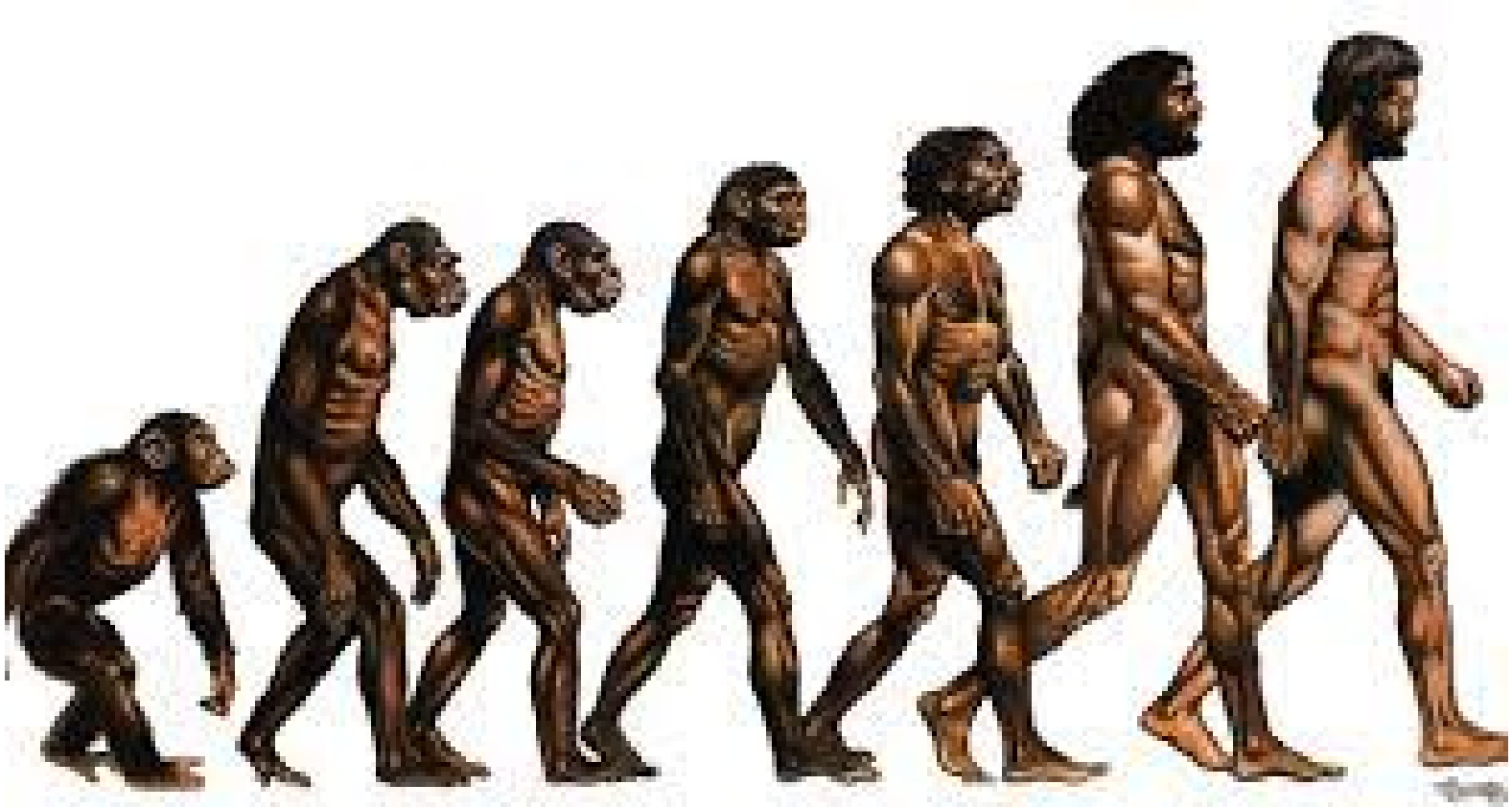
# …and oncologists saw it was not good….



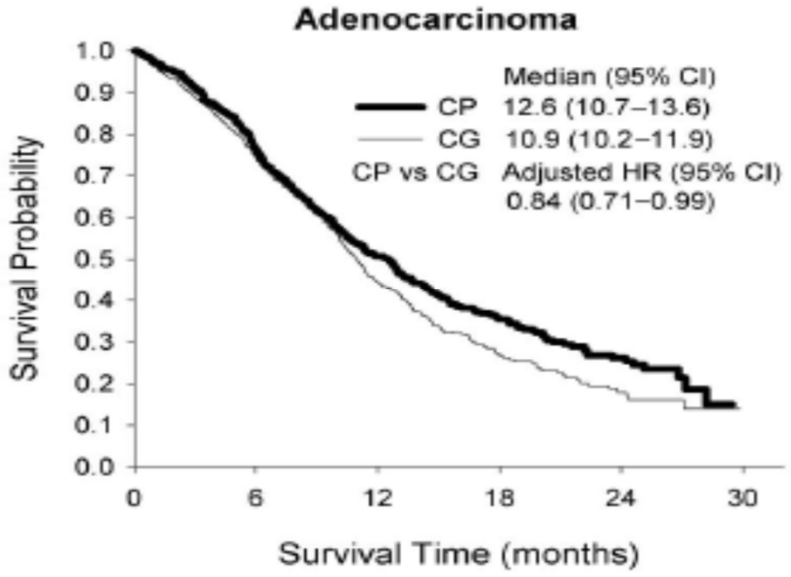

**5-yrs OS < 5%**

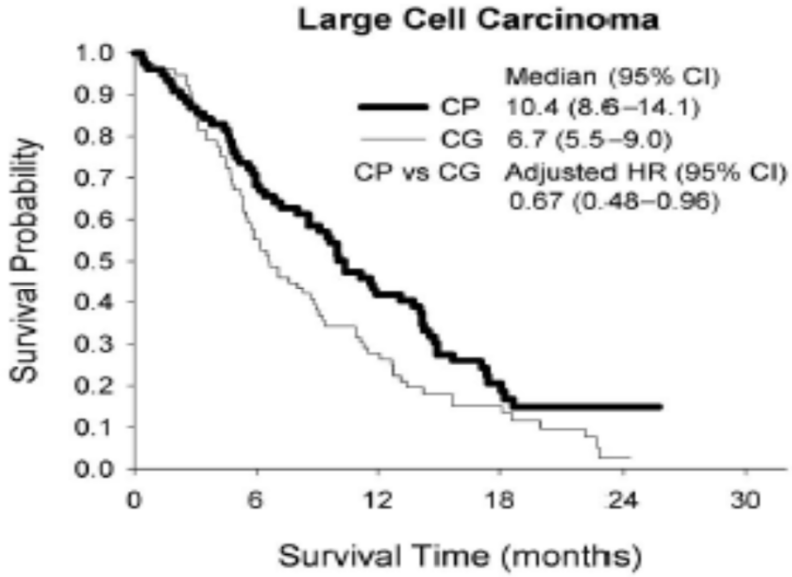
Schiller et al, NEJM 2002

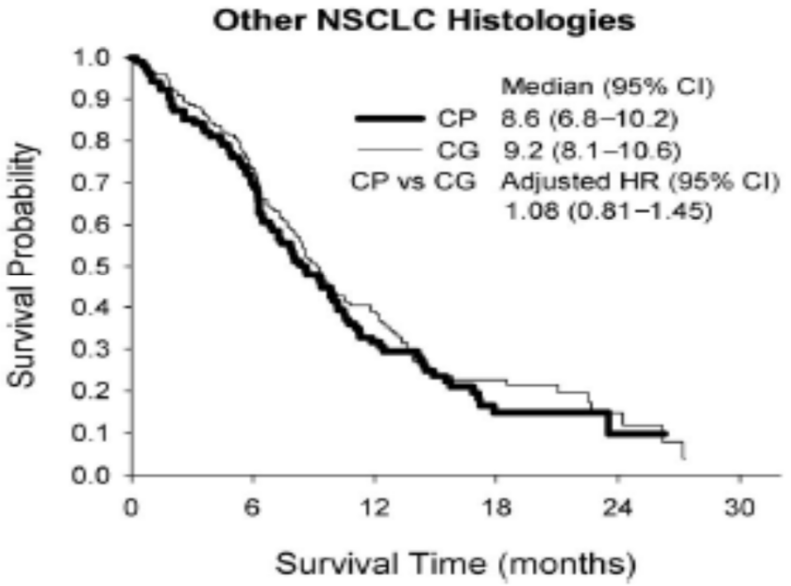
# …..the next step in the evolution

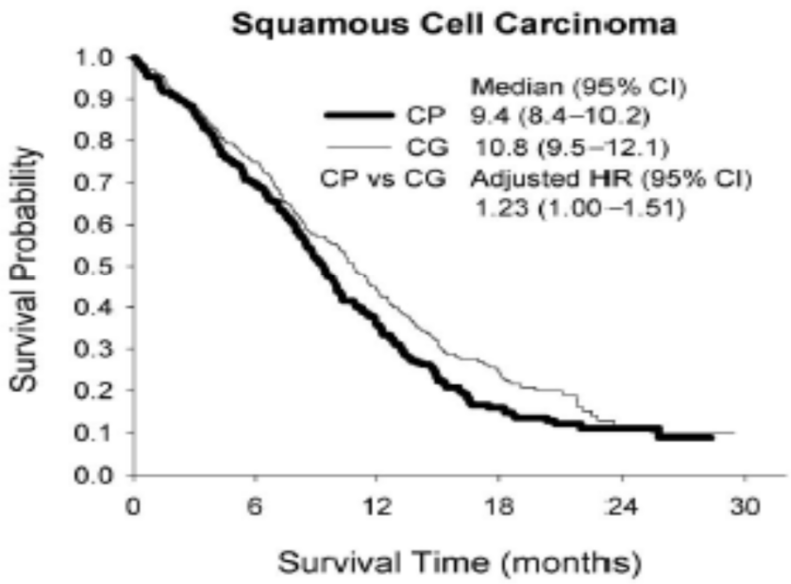


# ….different hystologies ….different responce



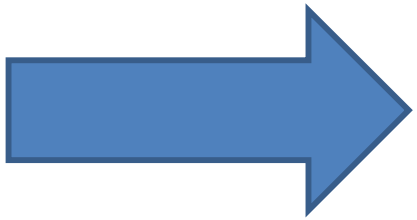



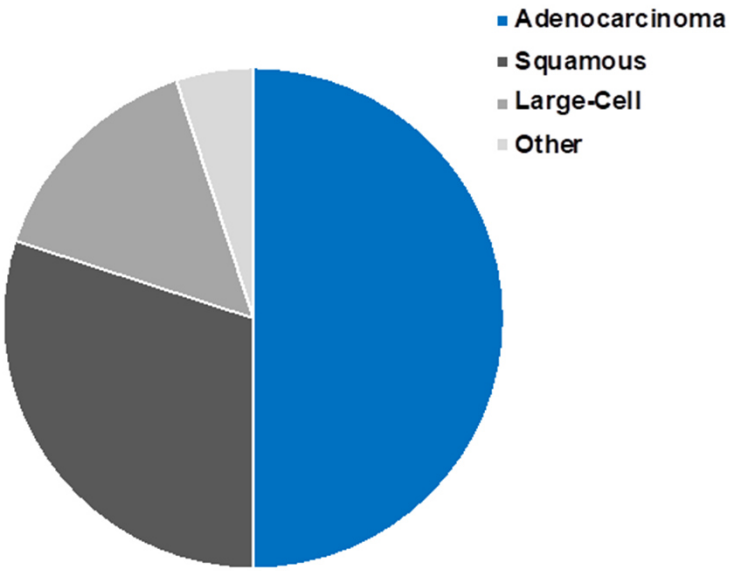

Scagliotti et al, JCO 2008

# …..the evolving view in NSCLC

**1995**

**2007**

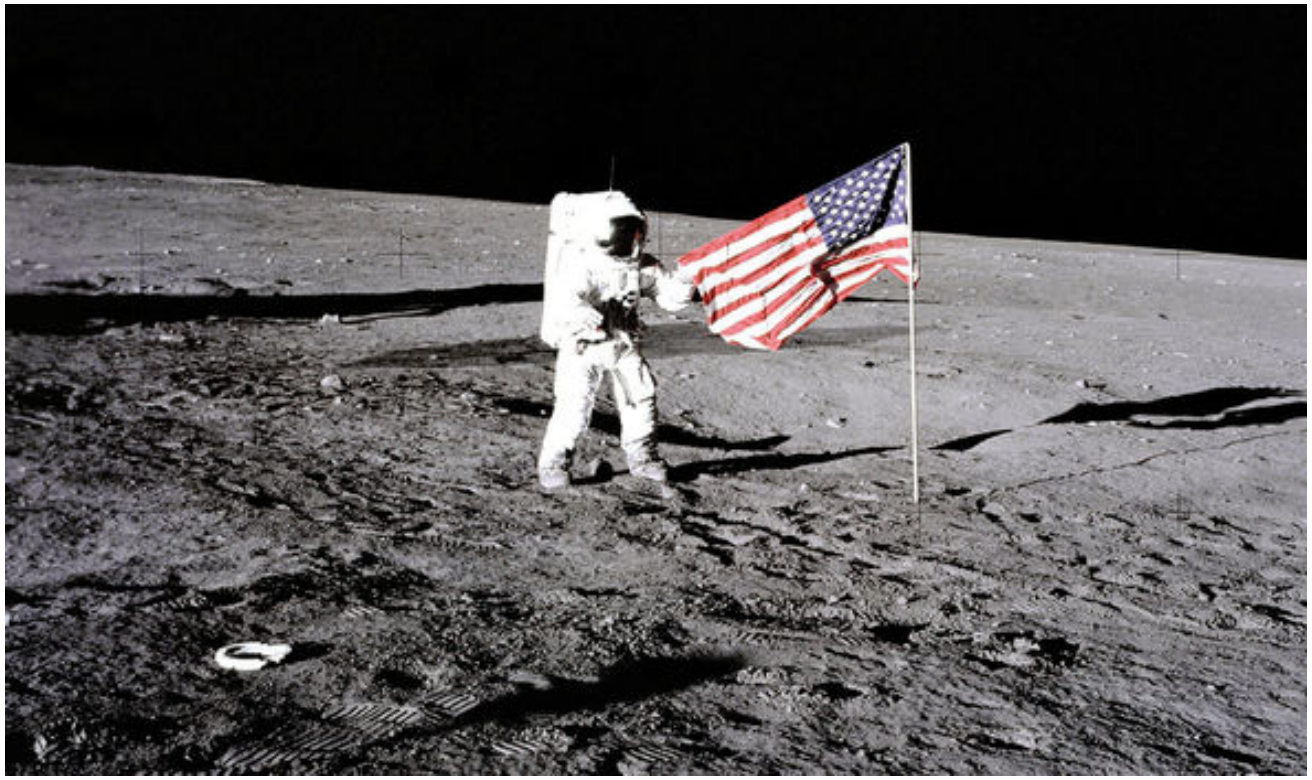





**TUMOR MORPHOLOGY**

**TUMOR HYSTOLOGY**

# the evolving view of NSCLC

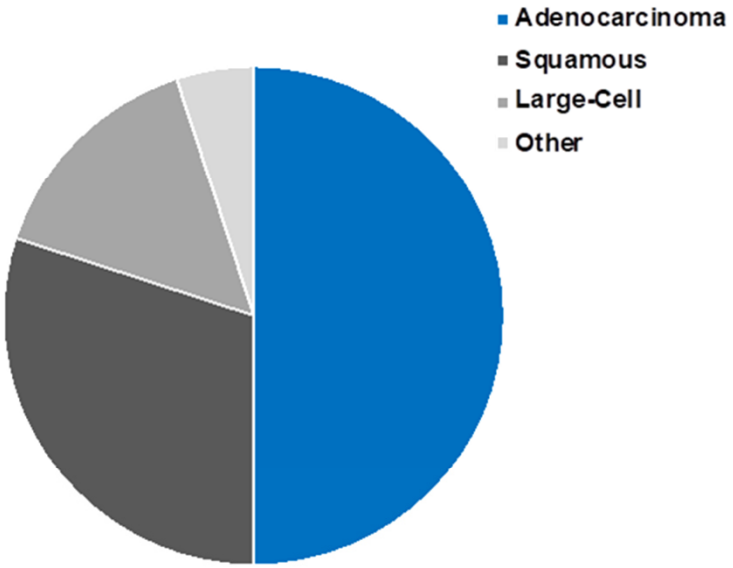


# ….the next step

**1995**

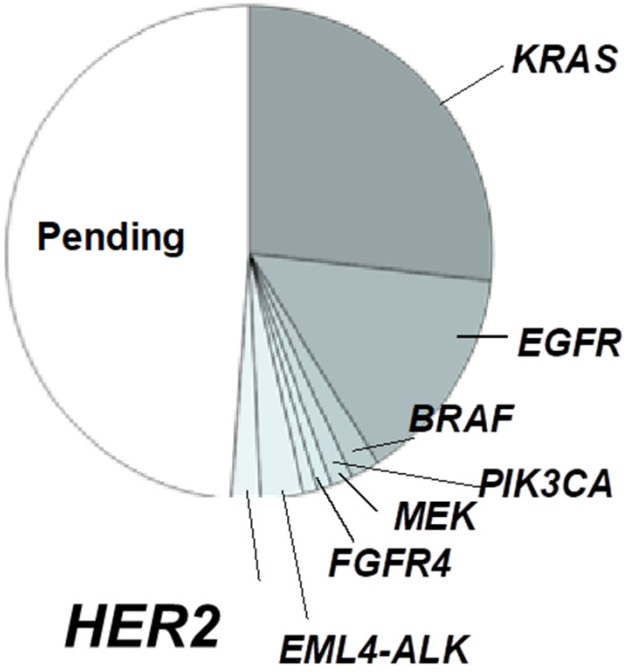
**TUMOR MORPHOLOGY**

**2007**



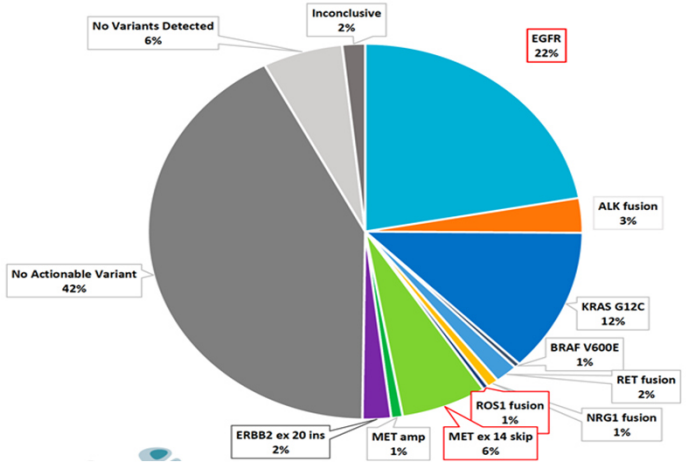

**TUMOR HYSTOLOGY**

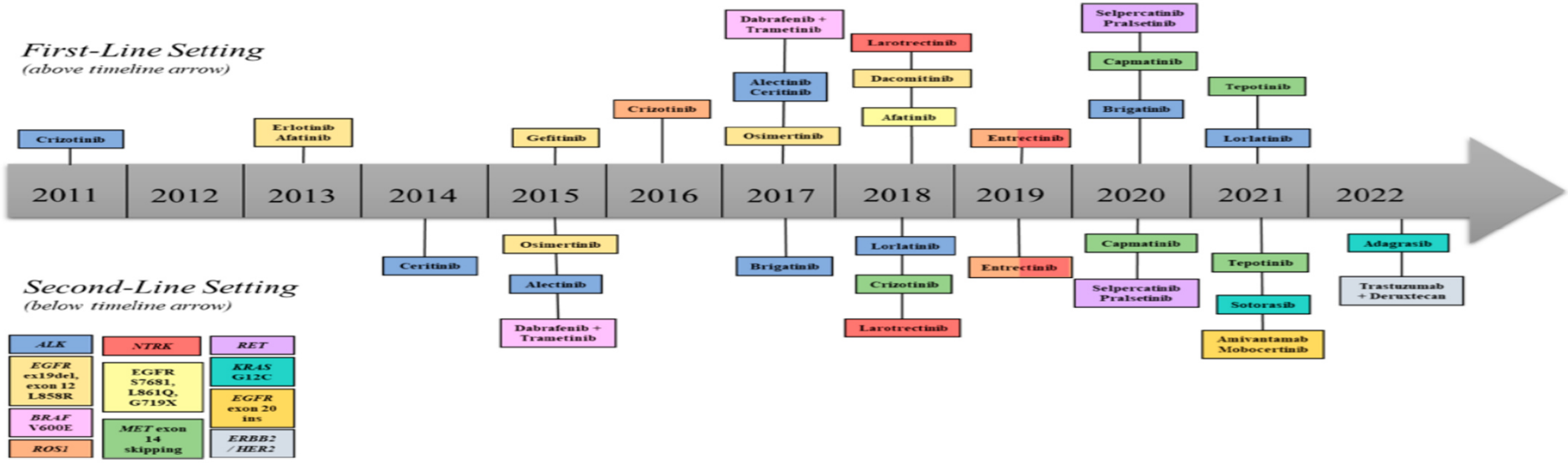
**2009**

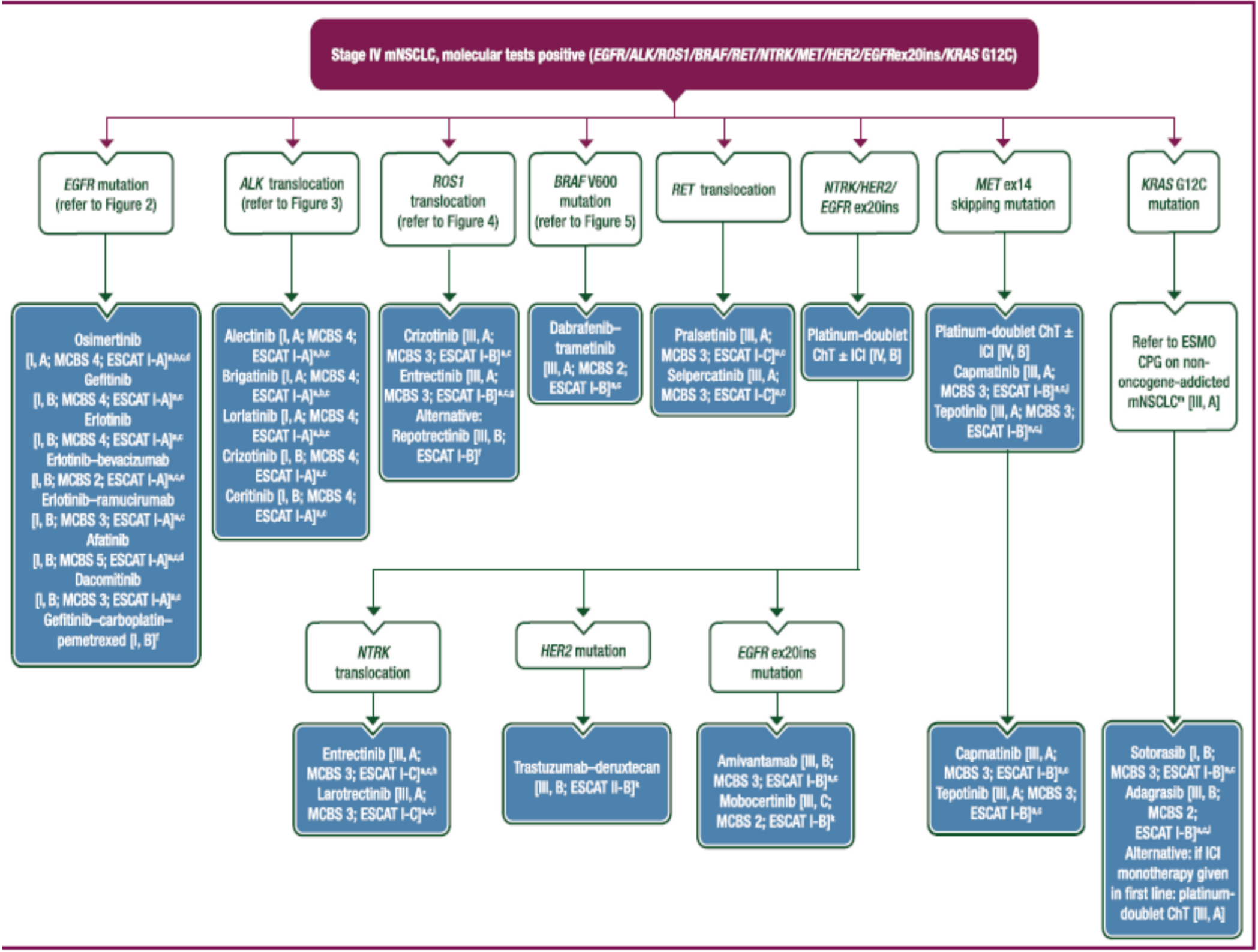



**TUMOR GENOMIC**

# ONCOGENE ADDICTED NSCLC



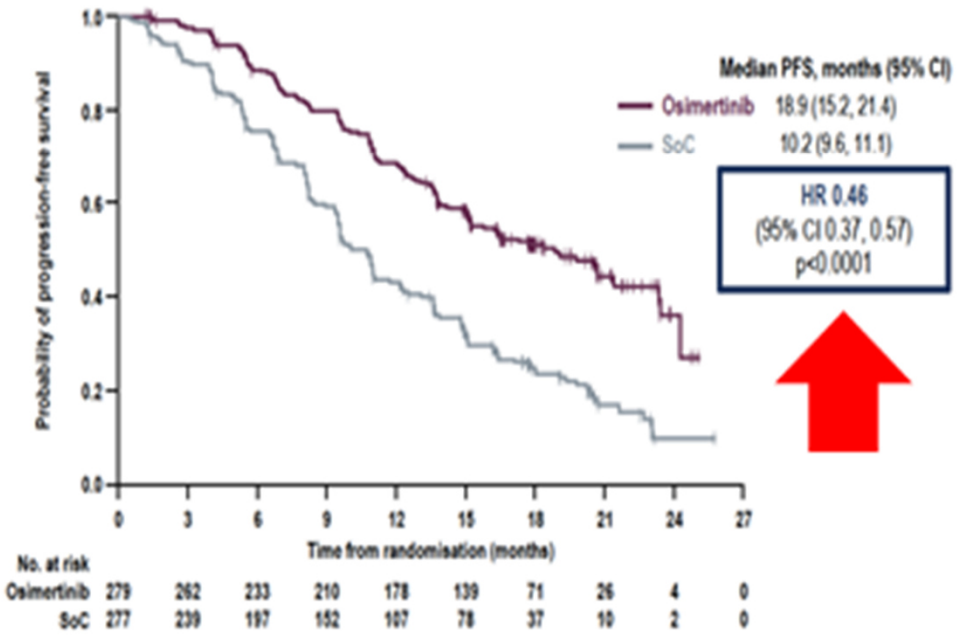




Stage IV mNSCLC, molecular tests positive (EGFR/ALK/ROS1/BRAF/RET/NTRK/MET/HER2/EGFRex20ins/KRAS G12C)
EGFR mutation (refer to Figure 2)
ALK translocation (refer to Figure 3)
ROS1 translocation (refer to Figure 4)
BRAF V600 mutation (refer to Figure 5)
RET translocation
NTRK/HER2/ EGFR ex20ins
MET ex14 skipping mutation
KRAS G12C mutation
Osimertinib [I, A; MCBS 4; ESCAT I-A][a,b,c,d]
Gefitinib [I, B; MCBS 4; ESCAT I-A][a,c]
Erlotinib [I, B; MCBS 4; ESCAT I-A][a,c]
Erlotinib–bevacizumab [I, B; MCBS 2; ESCAT I-A][a,c,e]
Erlotinib–ramucirumab [I, B; MCBS 3; ESCAT I-A][a,c]
Afatinib [I, B; MCBS 5; ESCAT I-A][a,c,d]
Dacomitinib [I, B; MCBS 3; ESCAT I-A][a,c]
Gefitinib–carboplatin–pemetrexed [I, B][f]
Alectinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Brigatinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Lorlatinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Crizotinib [I, B; MCBS 4; ESCAT I-A][a,c]
Ceritinib [I, B; MCBS 4; ESCAT I-A][a,c]
Crizotinib [III, A; MCBS 3; ESCAT I-B][a,c]
Entrectinib [III, A; MCBS 3; ESCAT I-B][a,c,g]
Alternative: Repotrectinib [III, B; ESCAT I-B][r]
Dabrafenib–trametinib [III, A; MCBS 2; ESCAT I-B][a,c]
Pralsetinib [III, A; MCBS 3; ESCAT I-C][a,c]
Selpercatinib [III, A; MCBS 3; ESCAT I-C][a,c]
Platinum-doublet ChT ± ICI [IV, B]
Platinum-doublet ChT ± ICI [IV, B]
Capmatinib [III, A; MCBS 3; ESCAT I-B][a,c,j]
Tepotinib [III, A; MCBS 3; ESCAT I-B][a,c,j]
Refer to ESMO CPG on non-oncogene-addicted mNSCLC[m] [III, A]
NTRK translocation
HER2 mutation
EGFR ex20ins mutation
Entrectinib [III, A; MCBS 3; ESCAT I-C][a,c,h]
Larotrectinib [III, A; MCBS 3; ESCAT I-C][a,c,i]
Trastuzumab–deruxtecan [III, B; ESCAT II-B][k]
Amivantamab [III, B; MCBS 3; ESCAT I-B][a,c]
Mobocertinib [III, C; MCBS 2; ESCAT I-B][k]
Capmatinib [III, A; MCBS 3; ESCAT I-B][a,c]
Tepotinib [III, A; MCBS 3; ESCAT I-B][a,c]
Sotorasib [I, B; MCBS 3; ESCAT I-B][a,c]
Adagrasib [III, B; MCBS 2; ESCAT I-B][a,c,j]
Alternative: if ICI monotherapy given in first line: platinum-doublet ChT [III, A]

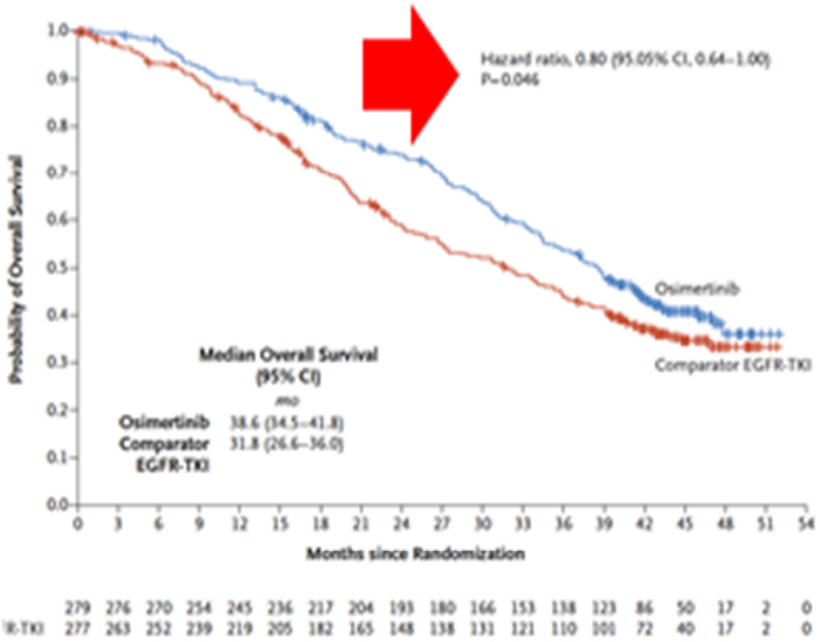
# EGFR -EX 19 del/ EX 20 (T790M)/ EX21 (L858R)

## FLAURA: OSIMERTINIB *vs.* SoC

### Primary End-Point [PFS]




### Key Secondary End-point [OS]




**OS: key secondary endpoint**

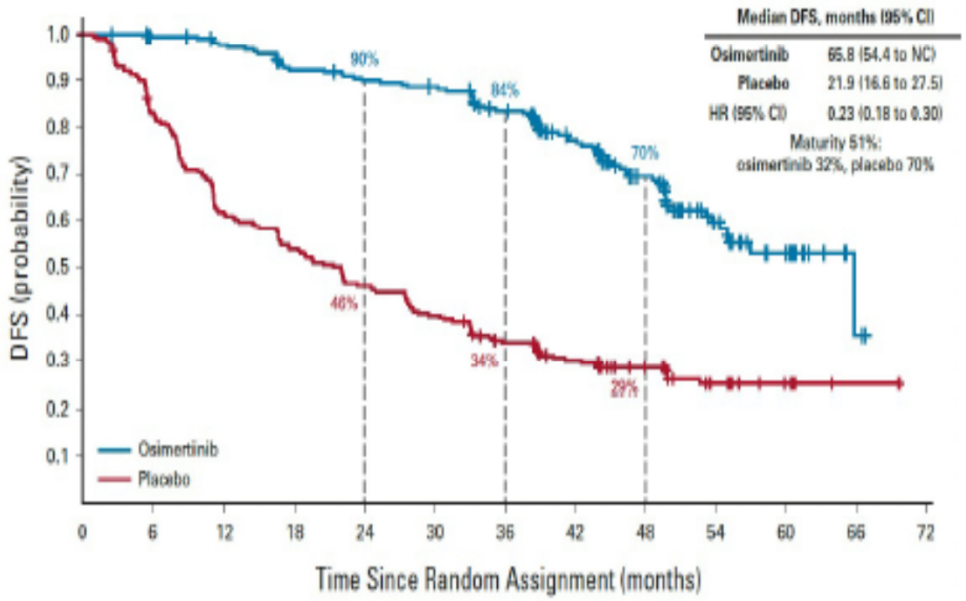
- Final OS analysis planned at approximately 318 deaths
- Statistical sign. @ *p<0.0495*, (O'Brien-Fleming)
- Alpha (interim OS) *0.0015*
- Ongoing pts: 61 patients (22%) with OSI *vs.* 13 patients (5%) with SoC

*Ramalingam S et al, ESMO 2017*
*Ohe Y et al, ESMO-ASIA 2017*
*Soria JC et al, NEJM 2017*
*Ramalingam S et al, NEJM 2019*

**ORR: 80%**

# Adjuvant Osimertinib for *mEGFR* Resected NSCLC (ADAURA)

**Disease-Free-Survival (Stage II-IIIA)**

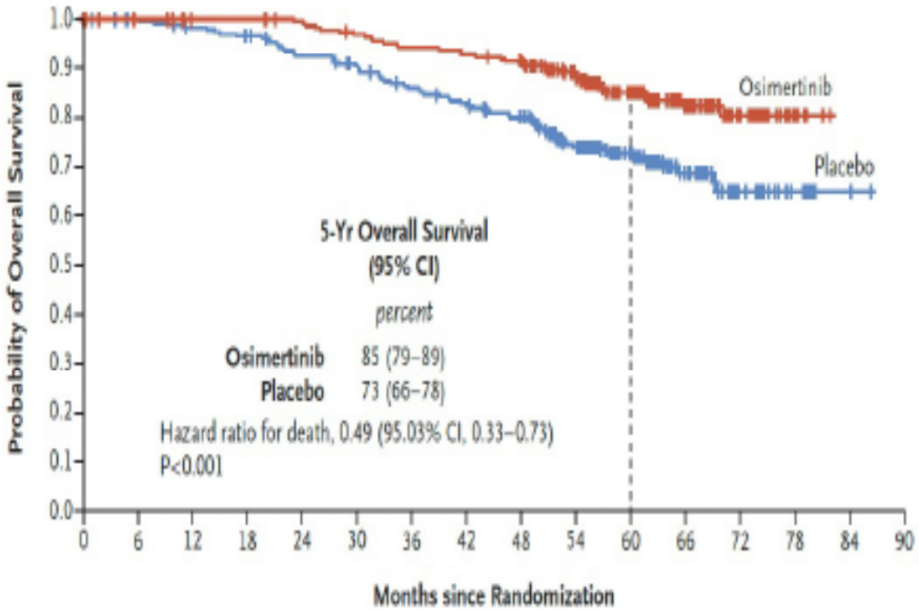



No. at risk:

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 233 | 222 | 216 | 202 | 196 | 192 | 174 | 138 | 90 | 45 | 20 | 2 | 0 |
| Placebo | 237 | 191 | 141 | 124 | 106 | 91 | 74 | 61 | 41 | 23 | 11 | 1 | 0 |

**Overall Survival (Stage II-IIIA)**

**5-yrs OS: 85%**




| No. at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 233 | 229 | 224 | 224 | 221 | 214 | 208 | 205 | 200 | 170 | 115 | 69 | 33 | 9 | 0 |
| Placebo | 237 | 232 | 226 | 221 | 210 | 202 | 190 | 182 | 171 | 138 | 94 | 53 | 25 | 8 | 2 | 0 |

*Herbst R et al, JCO 2023*

*Tsuboi M et al, NEJM 2023*

# EGFR EX 20 INSERTION

**MOBOCERTINIB**

| Outcome | PPP cohort (n = 114) | EXCLAIM cohort (n = 96) |
|---|---|---|
| IRC-assessed confirmed objective response[b] | | |
| Patients, No. (%) [95% CI] | 32 (28) [20-37] | 24 (25) [17-35] |
| Complete response | 0 | 0 |
| Partial response | 32 (28) | 24 (25) |
| Stable disease[c] | 57 (50) | 49 (51) |
| Not evaluable | 12 (11) | 10 (10) |
| Confirmed disease control rate, No. (%) [95% CI][d] | 89 (78) [69-85] | 73 (76) [66-84] |

**mPFS : 7,3 mo**

Zhou et al. JAMA Oncol.
Ramalingam Annals of Oncology (2022)

**AMIVANTANAB**

| Response per RECIST | Efficacy Population (n = 81) |
|---|---|
| ORR, % (95% CI)[a] | 40 (29 to 51) |
| CBR, % (95% CI)[b] | 74 (63 to 83) |
| Best response, No. (%) | |
| CR | 3 (4) |
| PR | 29 (36) |
| SD | 39 (48) |
| PD | 8 (10) |
| NE | 2 (2) |
| mPFS, mo (95%CI) | 8.3 (6.5, 10.9) |
| mOS, mo (95%CI) | 22.8 (14.6, NR) |

Park et al. JCO,

# ALK TRANSLOCATION

## ESMO Guidelines and Summary


| | ALECTINIB [ALEX] | BRIGATINIB [ALTA-1L] | LORLATINIB [CROWN] |
|---|---|---|---|
| PFS HR | 0.43 | 0.48 | 0.27 |
| mPFS* (ms) | 34.8 | 24 | NR |
| 2y-PFS (%) | 57 | 56 | 68 |
| ORR (%) | 83 | 74 | 76 |
| iORR (%) | 81 | 78 | 83 |
| OS HR | 0.67 | 0.81 | 0.72 |
| mOS (ms) | NR | NR | NR |
| 4y-OS (%) | 65.3 | 68 | NR |
| Maturity (Events) | 37% | 34% | 18% |
| Grade 3-5 AEs (%) | 52 | 70 | 72 |
| Discontinuation (%) | 14.5 | 13 | 7 |

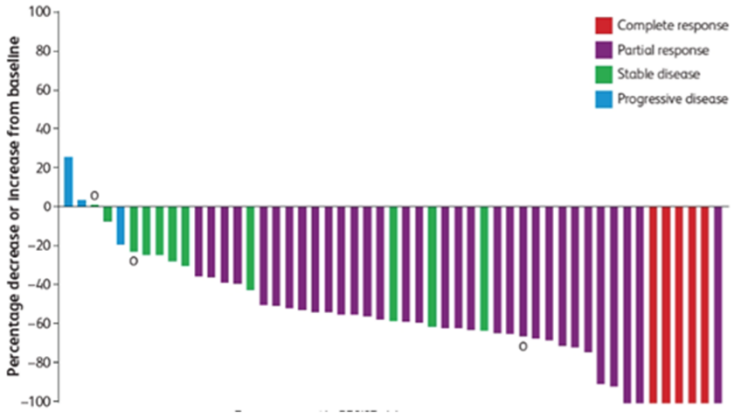
*Hendriks L et al, Ann Oncol IN PRESS*

*Mok T et al, Ann Oncol 2020*
*Tiseo M et al, ELCC 2022*
*Solomon BJ et al, AACR 2022 and JCO 2022*

# ROS-1 REARRANGEMENT

## CRIZOTINIB

**PROFILE 1001 STUDY**

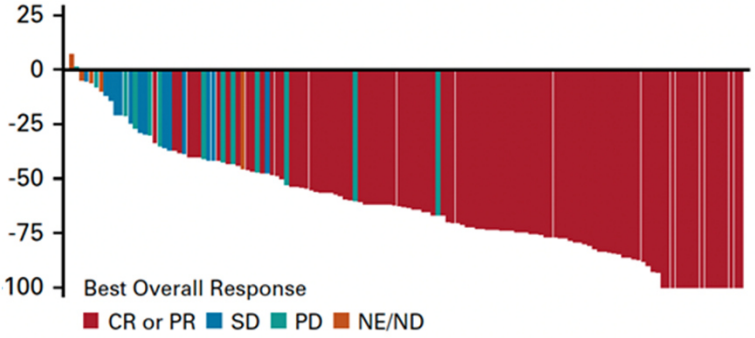



**ORR 72%**

*Shaw A et al, Ann Oncol 2019*

## ENTRECTINIB

**ALKA-372-001 STARTRK-1 STARTRK-2**



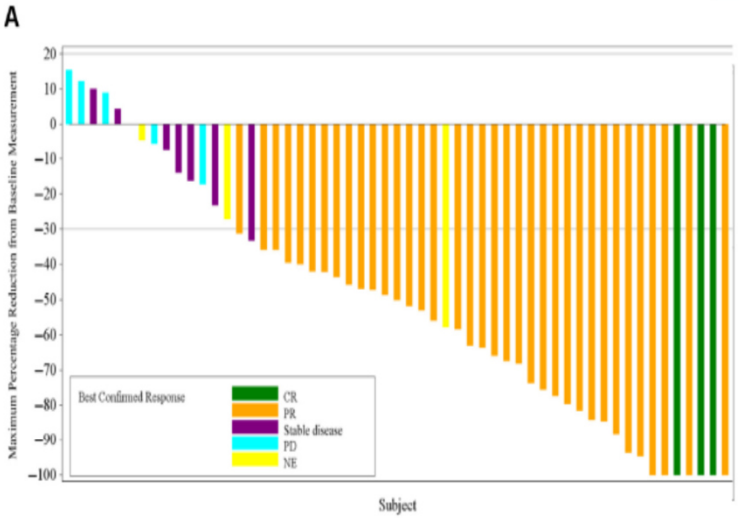

**ORR 77%**

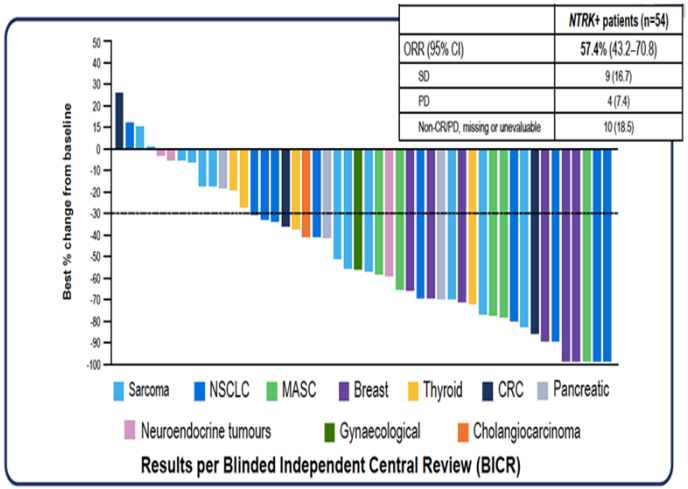
*Dziadziuszko et al, J Clin Oncol 2021*

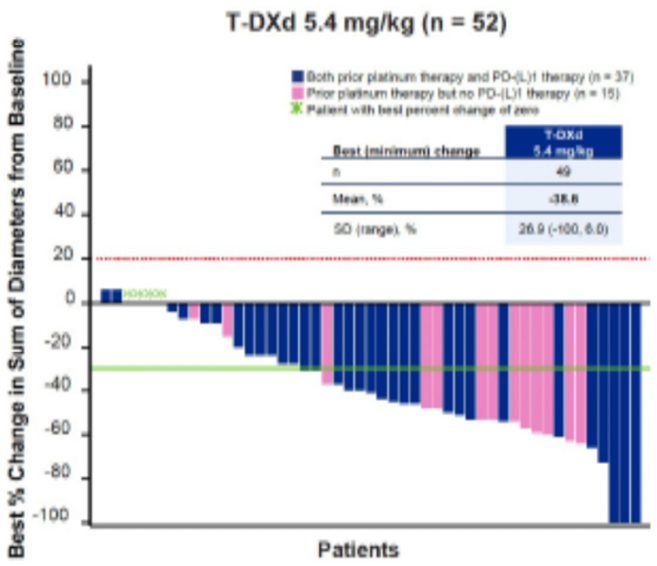
## BRAF Mutation [4-5%] : Dabrafenib + Trametinib

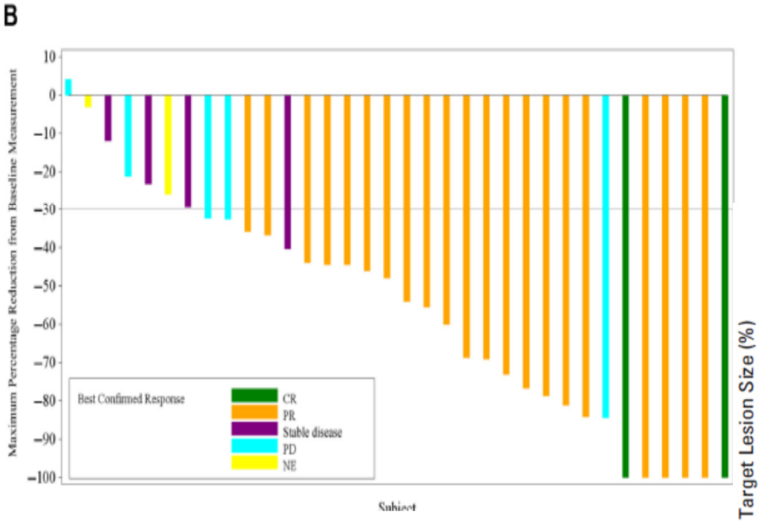
## NTRK Fusion [2-3%] : Entrectinib & Larotrectinib

## HER2 Mutation [2-3%] : Trastuzumab Deruxtecan

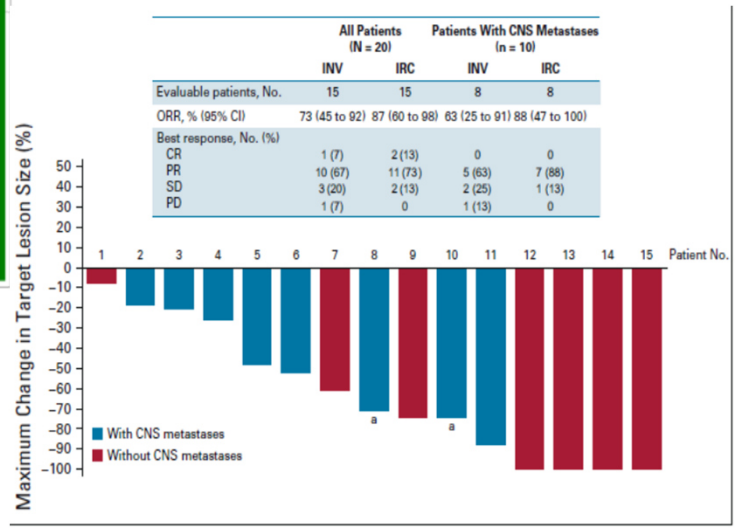



**ORR 57.4**
**[95% CI 43.3-70.8]**




**ORR 64.0%**
**[95% CI 46–69]**

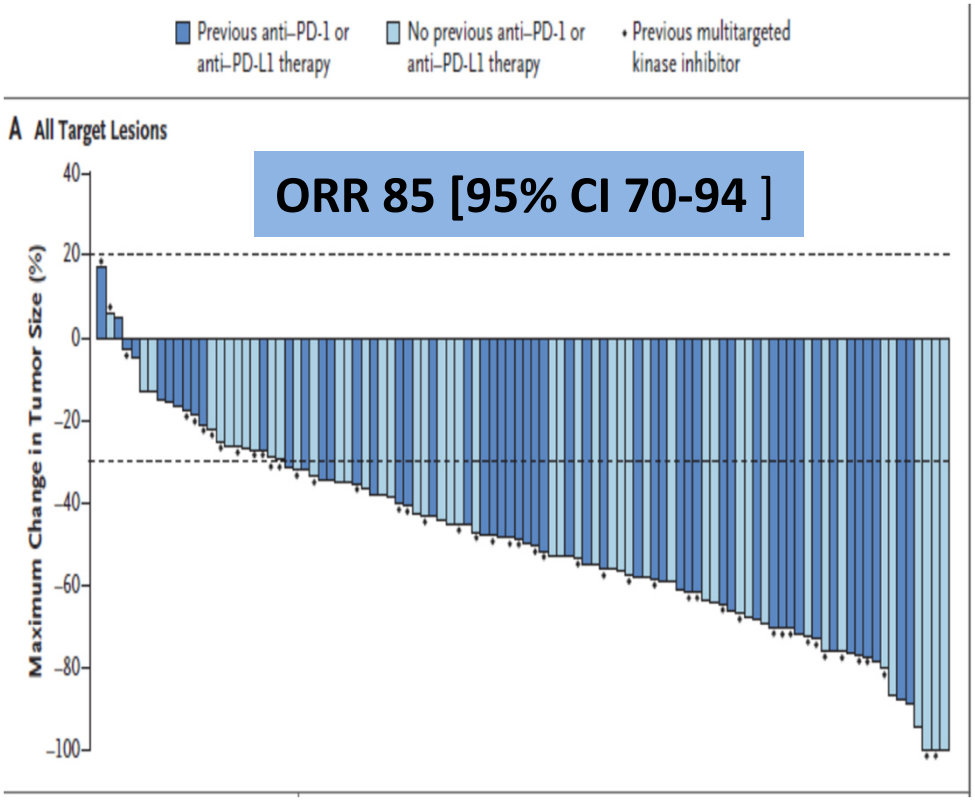
**ORR 57.7**
**[95% CI 43.2-71.3]**

*Planchard D et al, Lancet Oncol 2017*

*Goto K et al, ESMO 2022*

# RET REARRANGEMENT

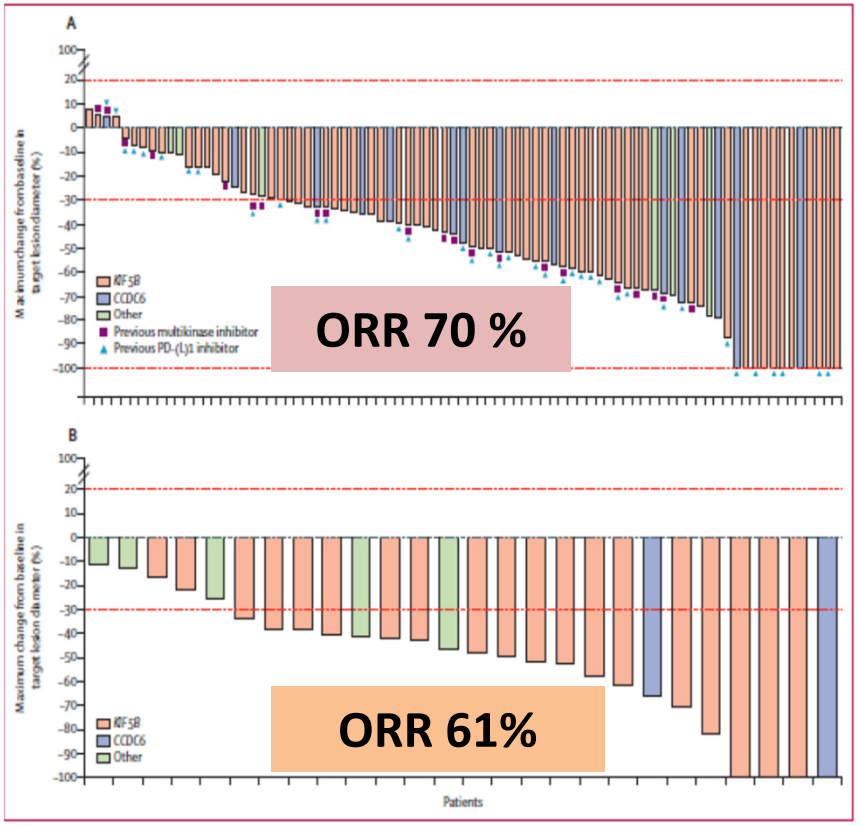
**Phase I-II SELPERCATINIB: NSCLC [105 pts]**




**ORR 85 [95% CI 70-94 ]**

Drilon, NEJM 2020

**Phase I-II PRALSETINIB: NSCLC [233 pts]**




**ORR 70 %**

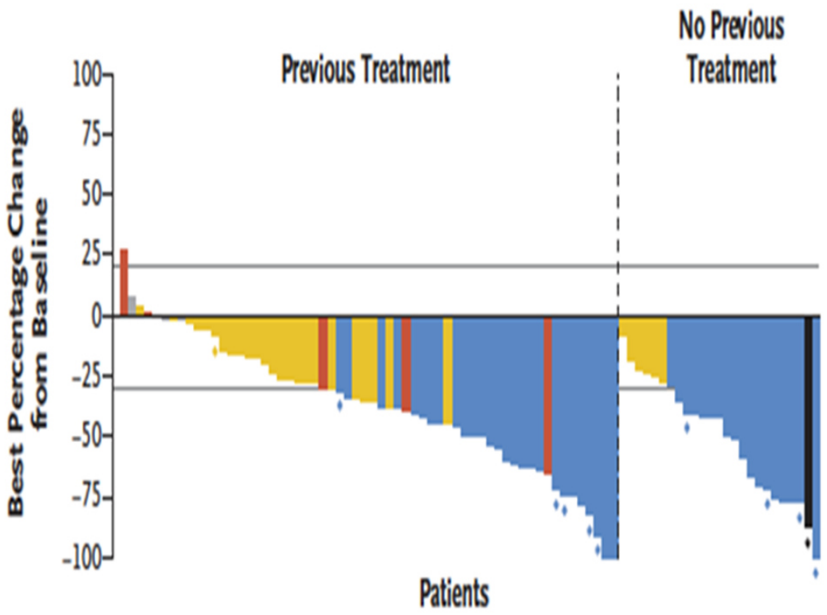
**ORR 61%**

Gainor et al, Lancet Oncol 2021

# MET EXON 14 SKIPPING MUTATION

## CAPMATINIB

### GEOMETRY NULTI-COHORT PHASE II STUDY

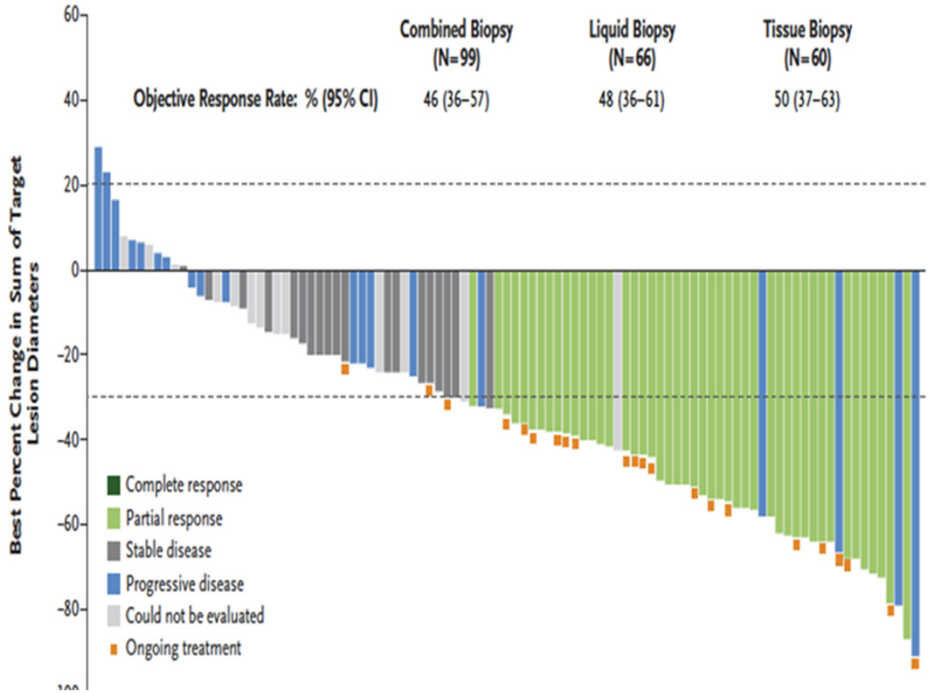



**ORR 68%**

*Wolf J et al, NEJM 2020*

## TEPOTINIB

### VISION PHASE II STUDY

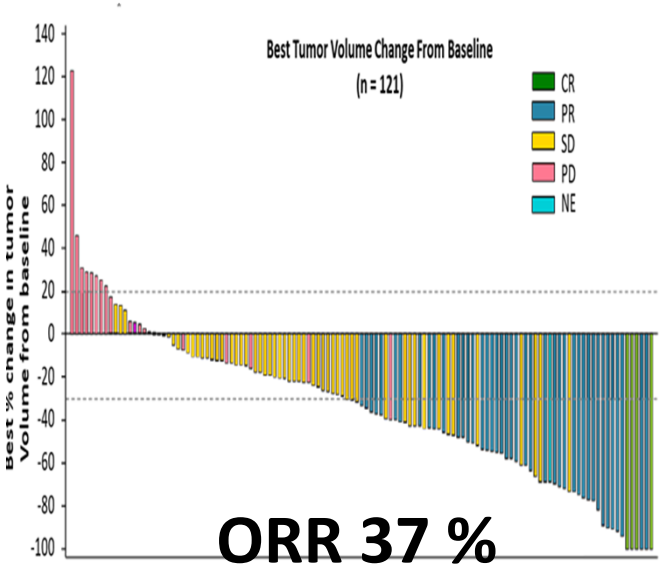



**ORR 48-56%**

*Paik PK et al, NEJM 2020*

# KRAS G12C MUTATION

## Phase II SOTORASIB: NSCLC [124 pts]

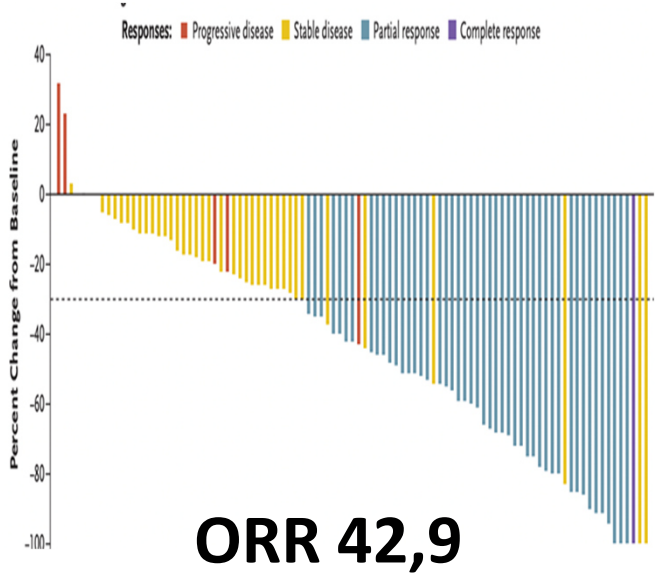



**ORR 37 %**

| Response assessed by central review | Sotorasib 960 mg, N = 124* |
|---|---|
| **Confirmed objective response rate – % (95% CI)** | **37.1 (28.6, 46.2)** |
| **Best overall response – n (%)** | |
| Complete response | 4 (3.2) |
| Partial response | 42 (33.9) |
| Stable disease | 54 (43.5) |
| Progressive disease | 20 (16.1) |
| Not evaluable | 2 (1.6) |
| Missing scan | 2 (1.6) |
| **Disease control rate – % (95% CI)** | **80.6 (72.6, 87.2)** |
| **Kaplan-Meier estimate of response -- % (95% CI)** | |
| At 3 months | **90.5 (76.7 – 96.3)** |
| At 6 months | **70.8 (54.3 – 82.2)** |
| At 9 months | **57.3 (40.4 – 71.0)** |

***Skoulidis F et al, NEJM 2021***

## Phase II ADAGRASIB: NSCLC [116 pts]

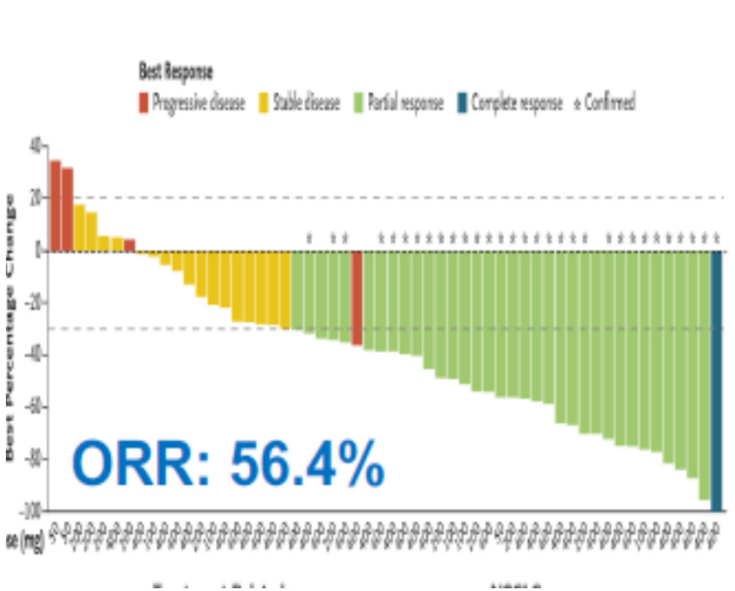



**ORR 42,9**

| | |
|---|---|
| Objective response‡ | |
| No. of patients | 48 |
| Percent (95% CI) | 42.9 (33.5–52.6) |
| Best overall response — no. (%) | |
| Complete response | 1 (0.9) |
| Partial response | 47 (42.0) |
| Stable disease | 41 (36.6) |
| Progressive disease | 6 (5.4) |
| Not evaluable | 17 (15.2) |
| Disease control | |
| No. of patients | 89 |
| Percent (95% CI) | 79.5 (70.8–86.5) |
| Median duration of response (95% CI) — mo | 8.5 (6.2–13.8) |
| Median progression-free survival (95% CI) — mo | 6.5 (4.7–8.4) |
| Median overall survival (95% CI) — mo§ | 12.6 (9.2–19.2) |

***Janne P et al, NEJM 2022***

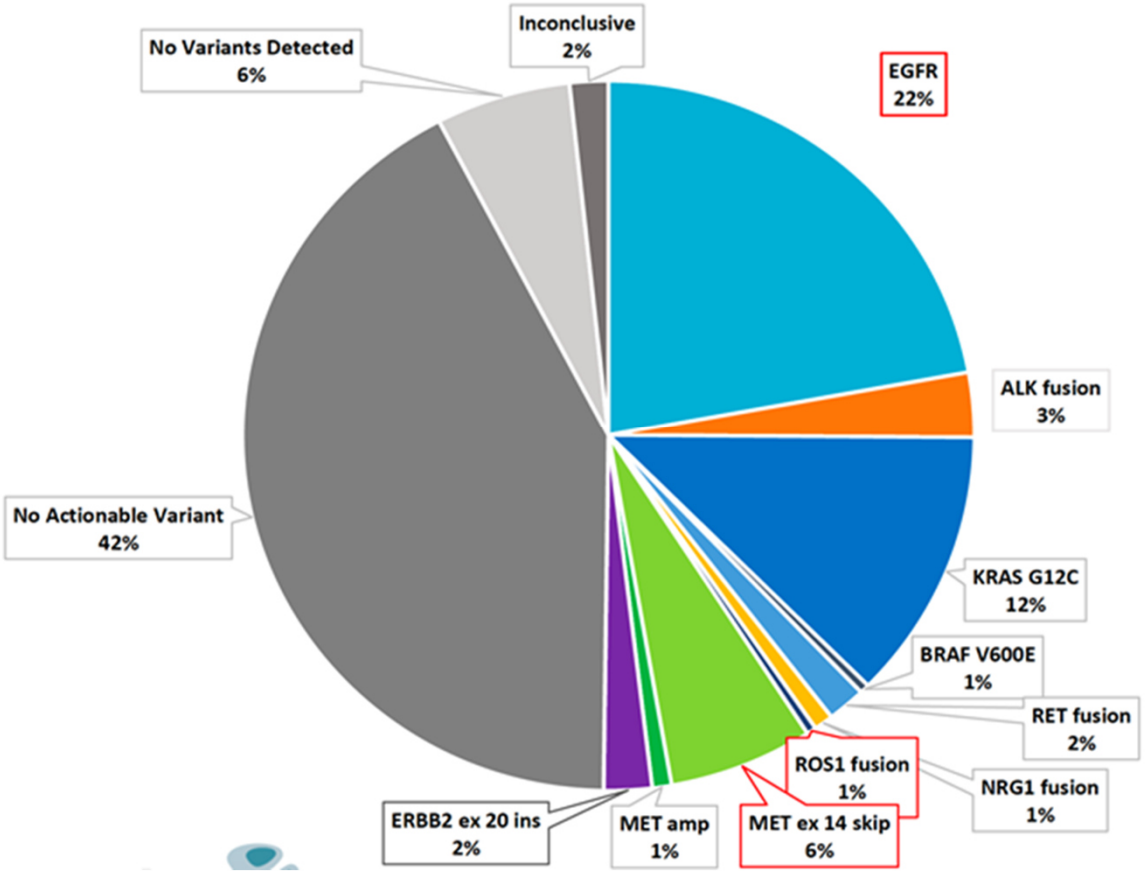
## Phase II DIVARASIB: NSCLC [60 pts]




***Sacher A et al, NEJM 2023***

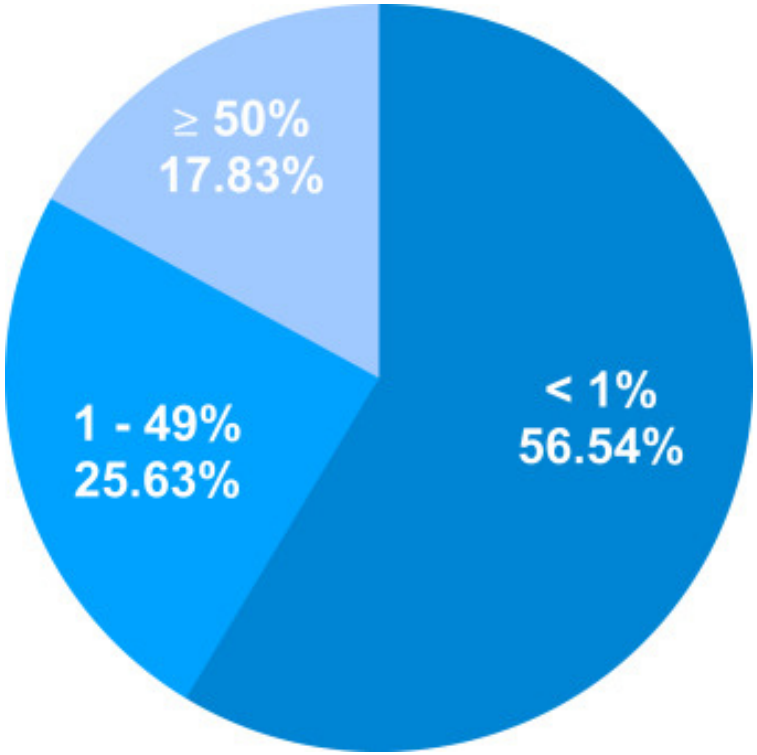
# THE IMMUNOTHERAPY ERA

**2009**



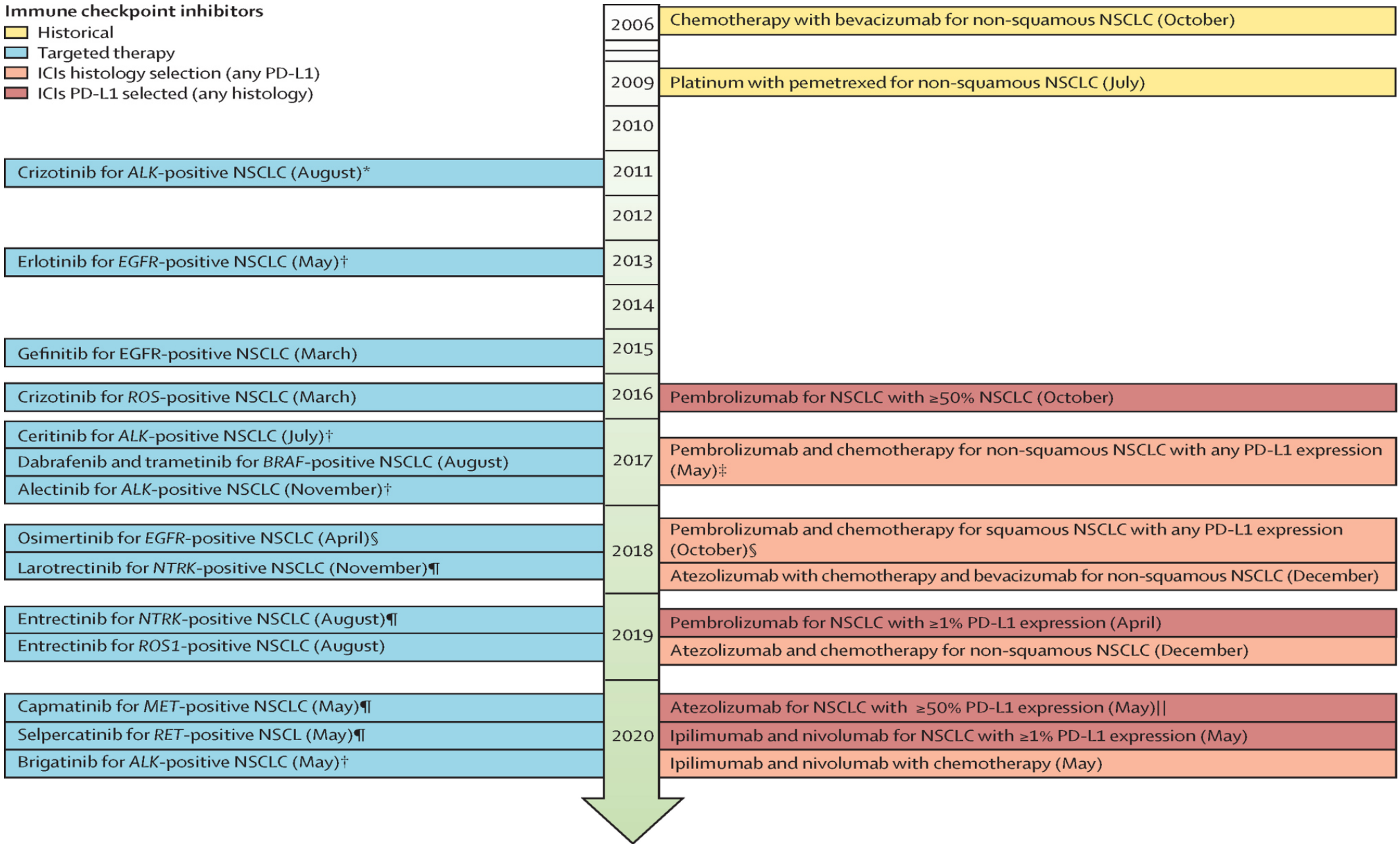

**TUMOR GENOMIC**

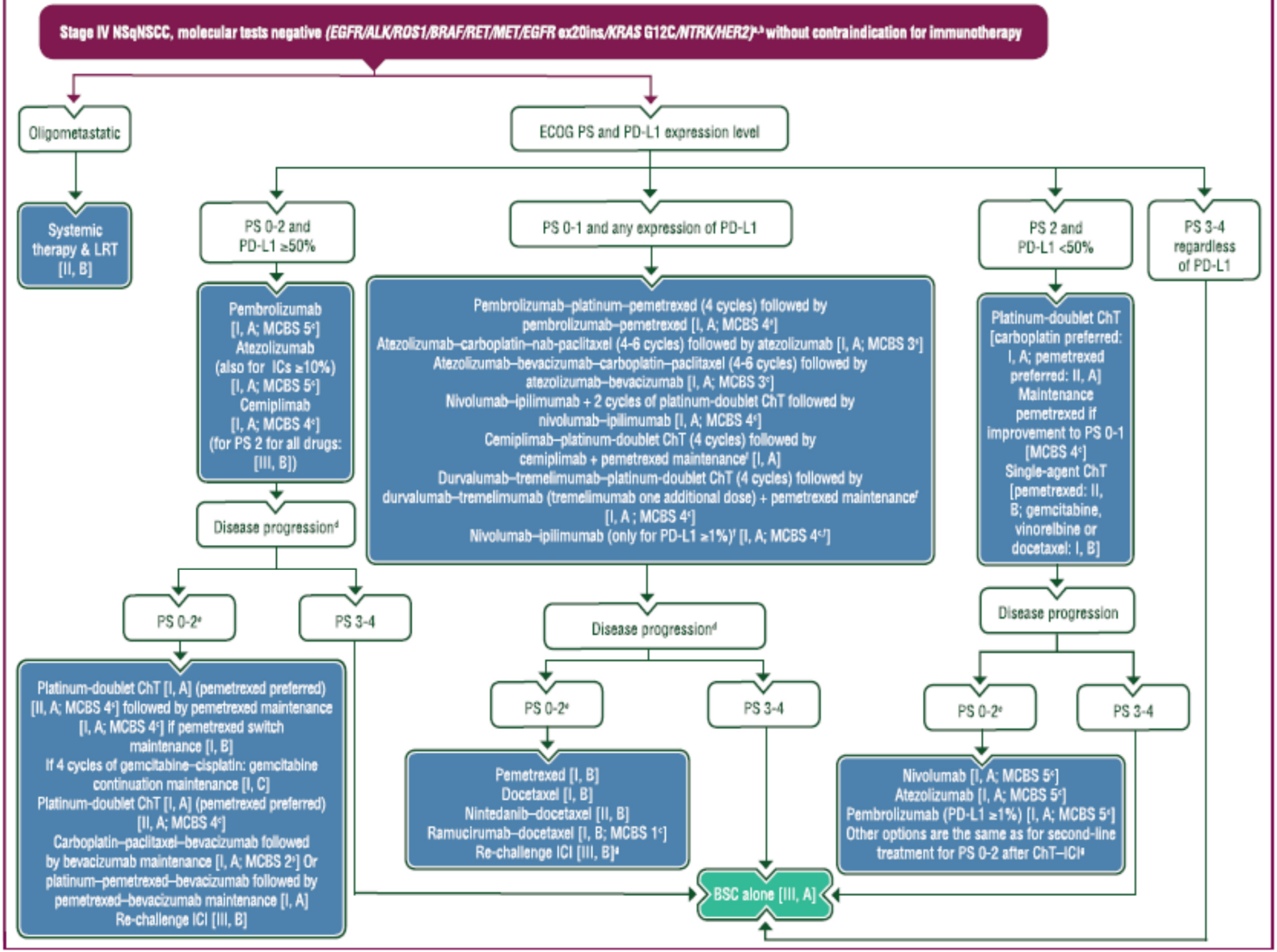
**2012**




**TUMOR PDL-1 TESTING**

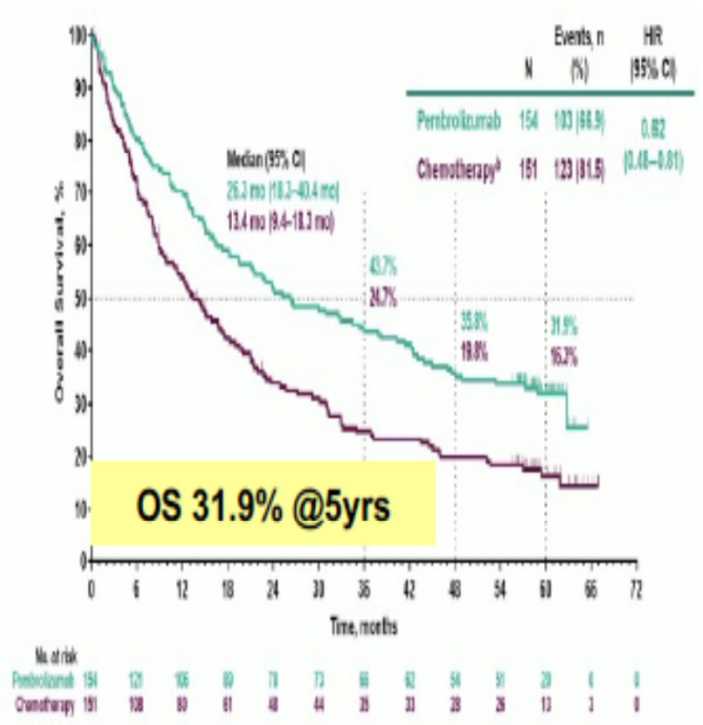
# EVOLUTION OF IMMUNOTHERAPY



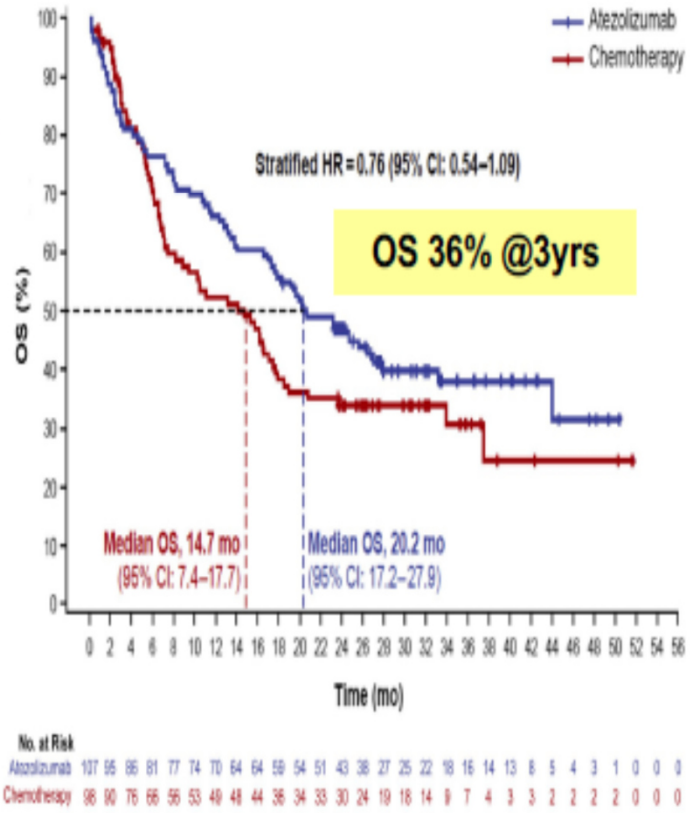

Stage IV NSqNSCC, molecular tests negative (EGFR/ALK/ROS1/BRAF/RET/MET/EGFR ex20ins/KRAS G12C/NTRK/HER2)[a,b] without contraindication for immunotherapy
Oligometastatic
Systemic therapy & LRT [II, B]
ECOG PS and PD-L1 expression level
PS 0-2 and PD-L1 ≥50%
Pembrolizumab [I, A; MCBS 5[c]]
Atezolizumab (also for ICs ≥10%) [I, A; MCBS 5[c]]
Cemiplimab [I, A; MCBS 4[c]]
(for PS 2 for all drugs: [III, B])
Disease progression[d]
PS 0-2[e]
Platinum-doublet ChT [I, A] (pemetrexed preferred) [II, A; MCBS 4[c]] followed by pemetrexed maintenance [I, A; MCBS 4[c]] if pemetrexed switch maintenance [I, B]
If 4 cycles of gemcitabine–cisplatin: gemcitabine continuation maintenance [I, C]
Platinum-doublet ChT [I, A] (pemetrexed preferred) [II, A; MCBS 4[c]]
Carboplatin–paclitaxel–bevacizumab followed by bevacizumab maintenance [I, A; MCBS 2[c]] Or platinum–pemetrexed–bevacizumab followed by pemetrexed–bevacizumab maintenance [I, A]
Re-challenge ICI [III, B]
PS 3-4
PS 0-1 and any expression of PD-L1
Pembrolizumab–platinum–pemetrexed (4 cycles) followed by pembrolizumab–pemetrexed [I, A; MCBS 4[c]]
Atezolizumab–carboplatin–nab-paclitaxel (4-6 cycles) followed by atezolizumab [I, A; MCBS 3[c]]
Atezolizumab–bevacizumab–carboplatin–paclitaxel (4-6 cycles) followed by atezolizumab–bevacizumab [I, A; MCBS 3[c]]
Nivolumab–ipilimumab + 2 cycles of platinum-doublet ChT followed by nivolumab–ipilimumab [I, A; MCBS 4[c]]
Cemiplimab–platinum-doublet ChT (4 cycles) followed by cemiplimab + pemetrexed maintenance[f] [I, A]
Durvalumab–tremelimumab–platinum-doublet ChT (4 cycles) followed by durvalumab–tremelimumab (tremelimumab one additional dose) + pemetrexed maintenance[f] [I, A ; MCBS 4[c]]
Nivolumab–ipilimumab (only for PD-L1 ≥1%)[f] [I, A; MCBS 4[c,f]]
Disease progression[d]
PS 0-2[e]
Pemetrexed [I, B]
Docetaxel [I, B]
Nintedanib–docetaxel [II, B]
Ramucirumab–docetaxel [I, B; MCBS 1[c]]
Re-challenge ICI [III, B][a]
PS 3-4
PS 2 and PD-L1 <50%
Platinum-doublet ChT [carboplatin preferred: I, A; pemetrexed preferred: II, A] Maintenance pemetrexed if improvement to PS 0-1 [MCBS 4[c]]
Single-agent ChT [pemetrexed: II, B; gemcitabine, vinorelbine or docetaxel: I, B]
Disease progression
PS 0-2[e]
Nivolumab [I, A; MCBS 5[c]]
Atezolizumab [I, A; MCBS 5[c]]
Pembrolizumab (PD-L1 ≥1%) [I, A; MCBS 5[c]]
Other options are the same as for second-line treatment for PS 0-2 after ChT–ICI[a]
PS 3-4
PS 3-4 regardless of PD-L1
BSC alone [III, A]

# NON SMALL CELL LUNG CANCER NON ONCOGENE-ADDICTED PDL-1 > 50%

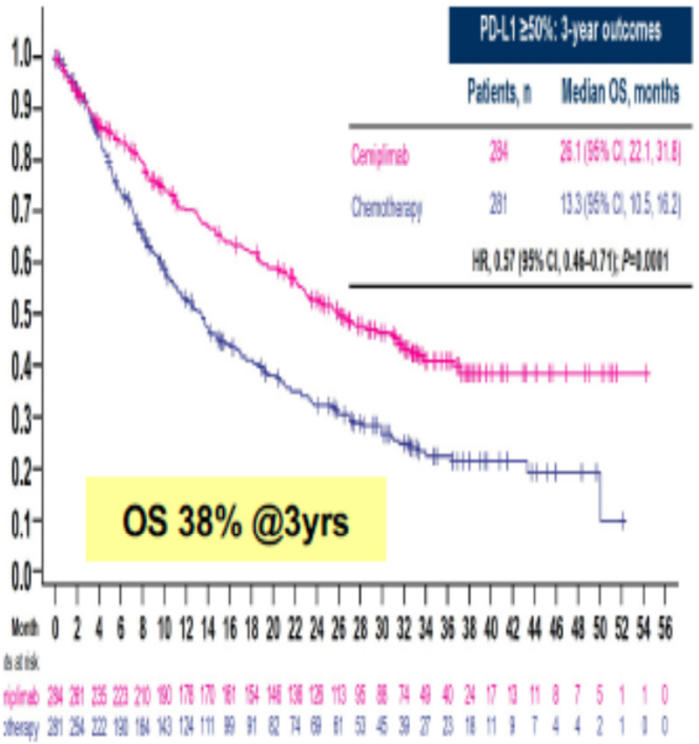
## KN 024: Pembrolizumab




## IMpower 110: Atezolizumab




## EMPOWER-L1: Cemiplimab




| | KEYNOTE-024 | IMpower-110 (Subgroup) | EMPOWER-Lung 1 |
|---|---|---|---|
| *Median follow-up* | 60 months | 31 months | 37 months |
| *Median PFS (mo)* | 7.7 (vs 5.5) - HR 0.50 | 8.2 (vs 5.0) - HR 0.59 | 8.1 (vs 5.3) - HR 0.51 |
| *TRAEs G3-5* | 27 (vs 53) | 14 (vs 55) | 18 (vs 39) |

*Reck M et al, J Clin Oncol 2021*

*Jassem J et al, J Thor Oncol 2022*

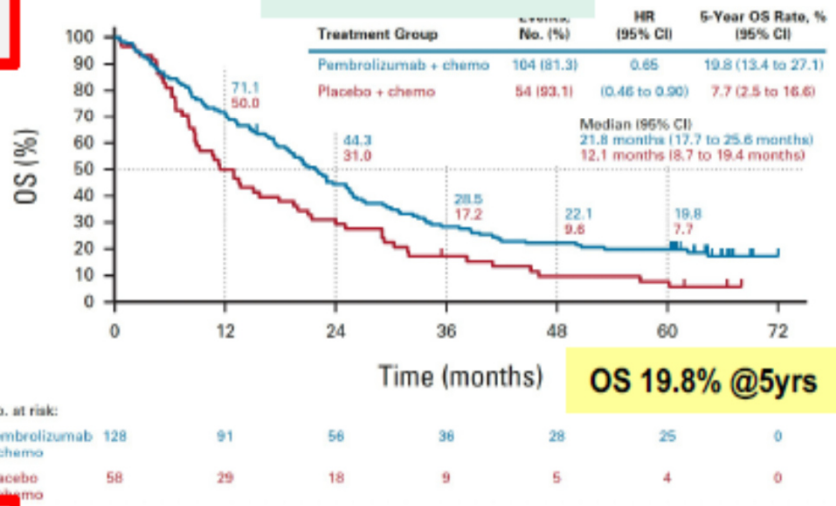
*Özgüroğlu M et al, ESMO 2022*

# NON ONCOGENE ADDICTED NSCLC /PDL-1< 50%

## Chemo-Pembro vs. Pembro in PD-L1 <50%: RCTs

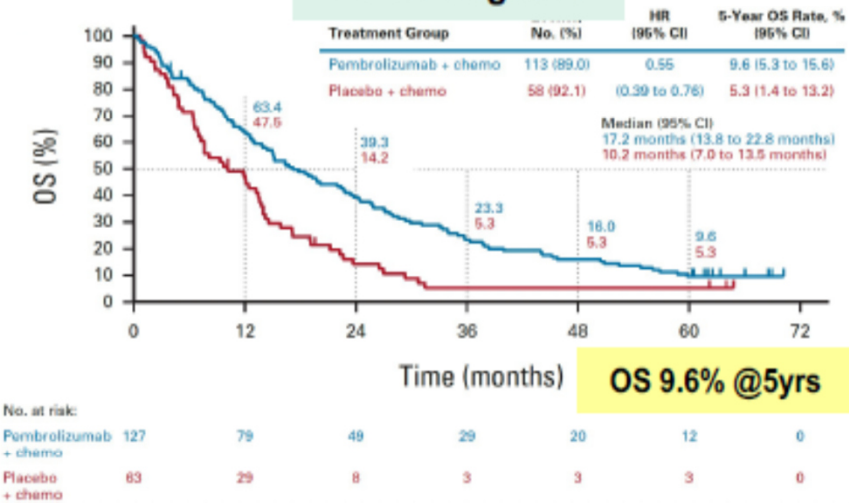
**KN 189: Non-Squamous**

### PD-L1 1-49%



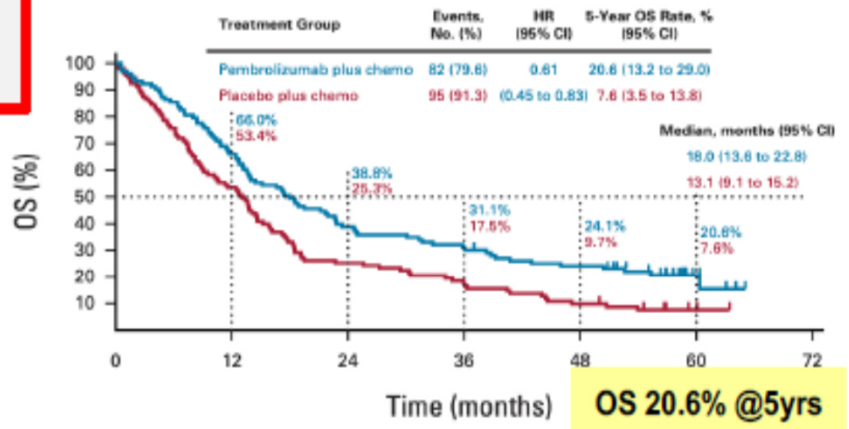

**OS 19.8% @5yrs**

### PD-L1 Negative

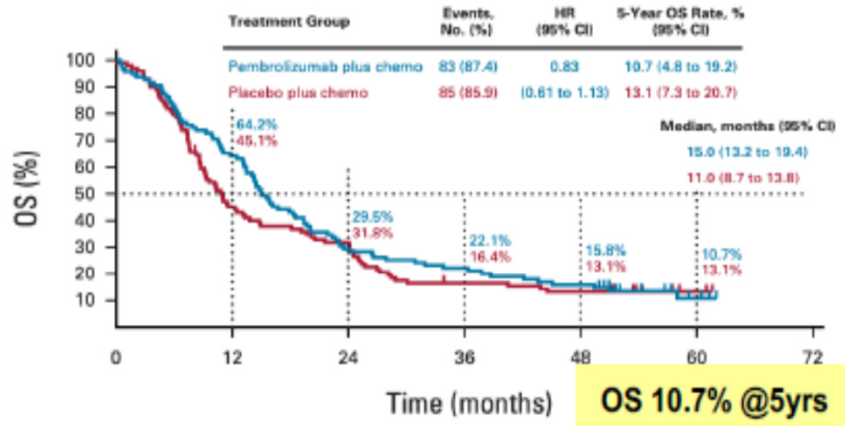



**OS 9.6% @5yrs**

**KN 407: Squamous**




**OS 20.6% @5yrs**

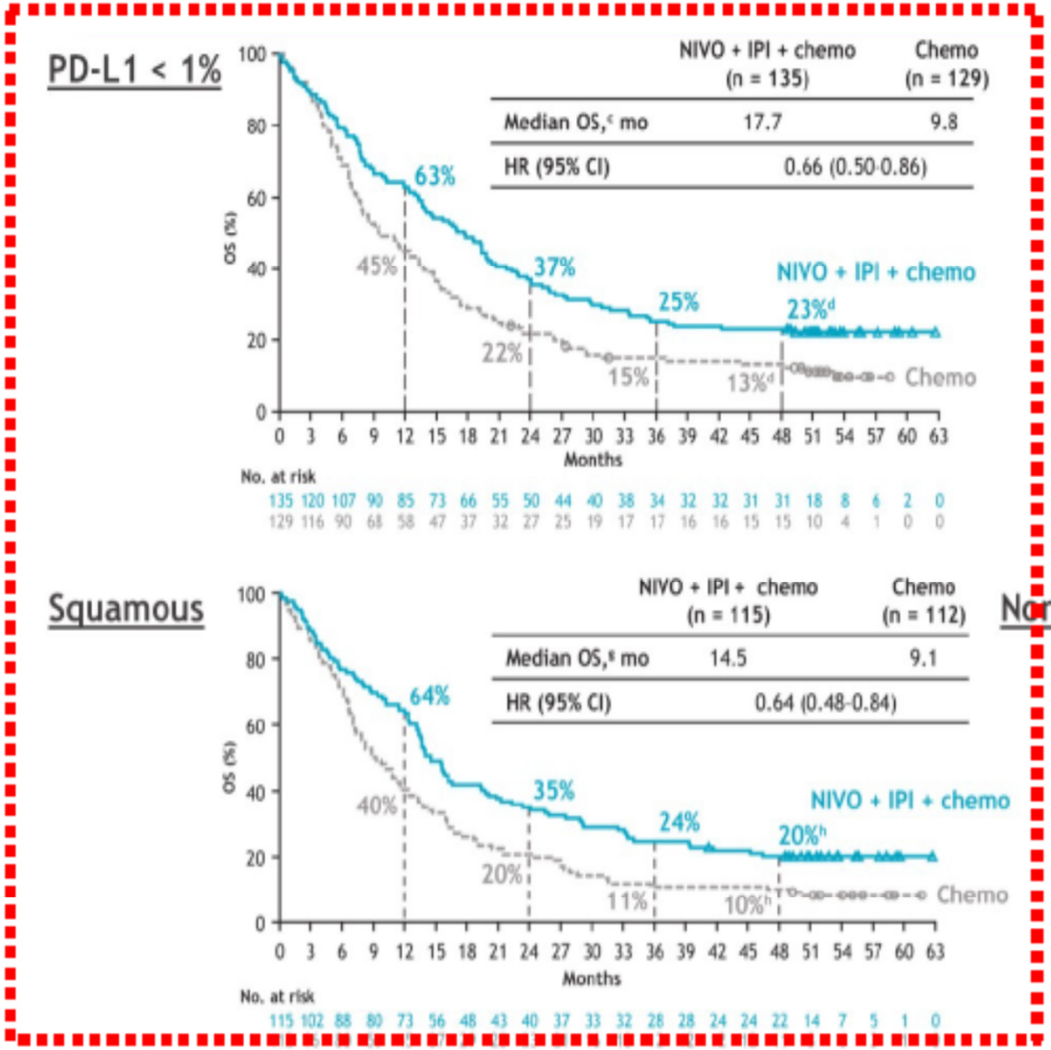


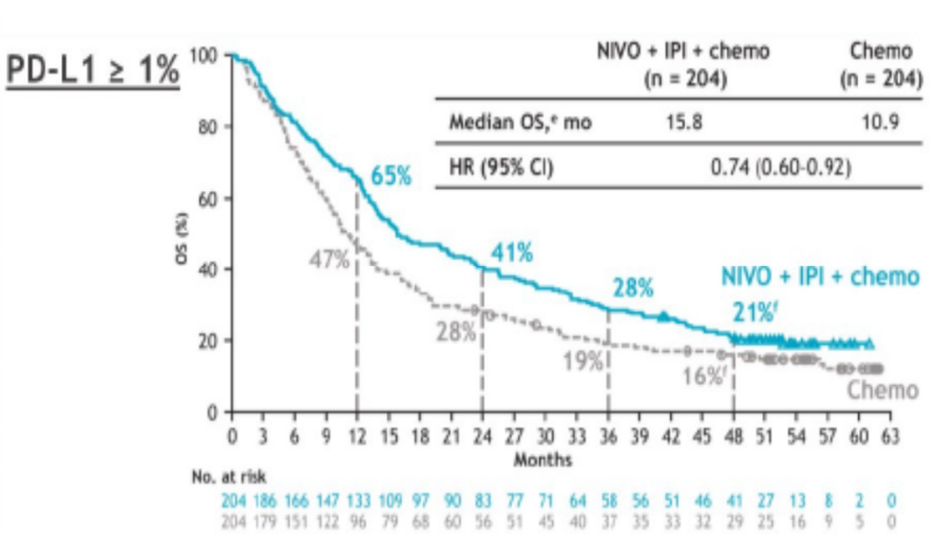

**OS 10.7% @5yrs**

*Garassino M et al, JCO 2023; Novello S et al, JCO 2023*

# NSCLC NON ONCOGENE ADDICTED PDL-1< 50%

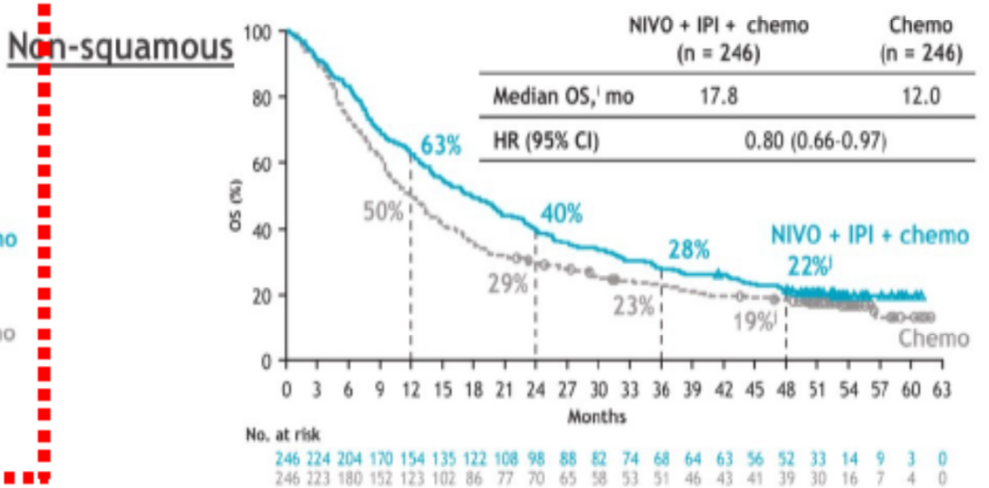
## 'Short' Chemo + NIVO-IPI: 4-yrs OS according to PD-L1 and Histology









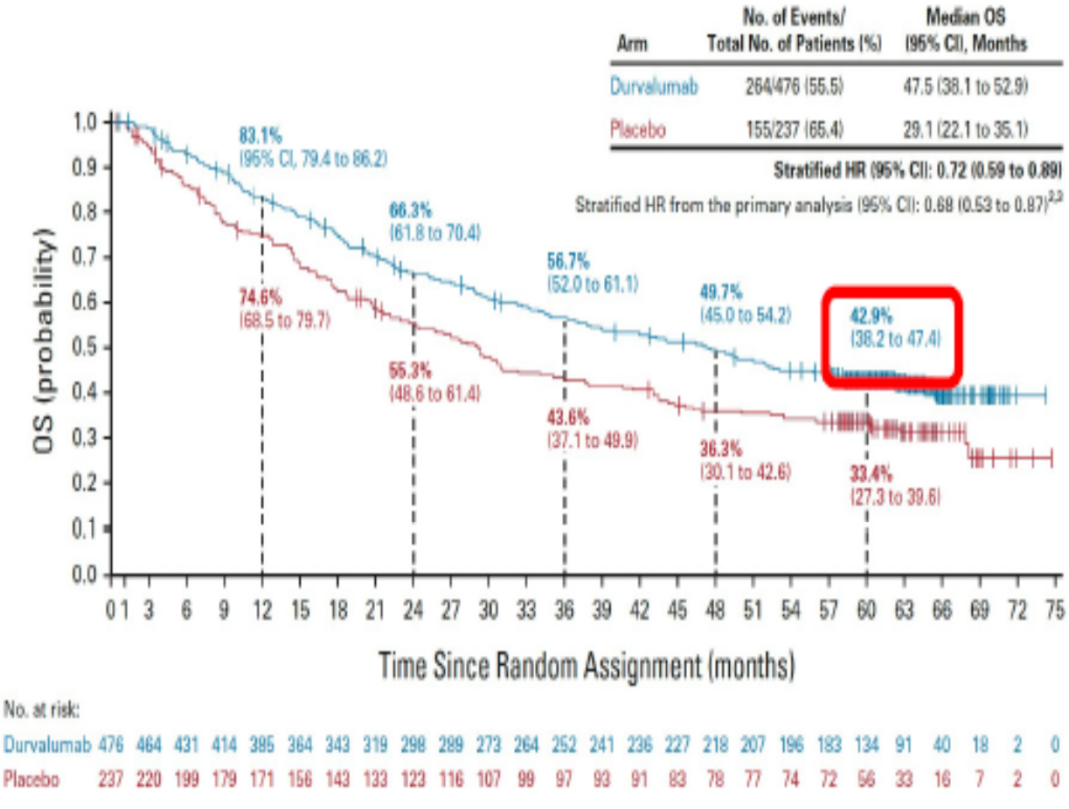

Database lock: February 13, 2023; minimum/median follow-up for OS: 47.9/54.5 months.
95% CIs for NIVO + IPI + chemo and chemo, respectively: [c]13.7-20.3 and 7.7-13.5; [d]16-30 and 8-20; [e]13.8-22.2 and 9.5-13.2; [f]16-27 and 11-22; [g]13.1-19.3 and 7.2-11.6; [h]13-28 and 5-16; [i]14.1-20.7 and 9.9-13.9; [j]17-27 and 14-24.



*Carbone D et al, ASCO 2023*

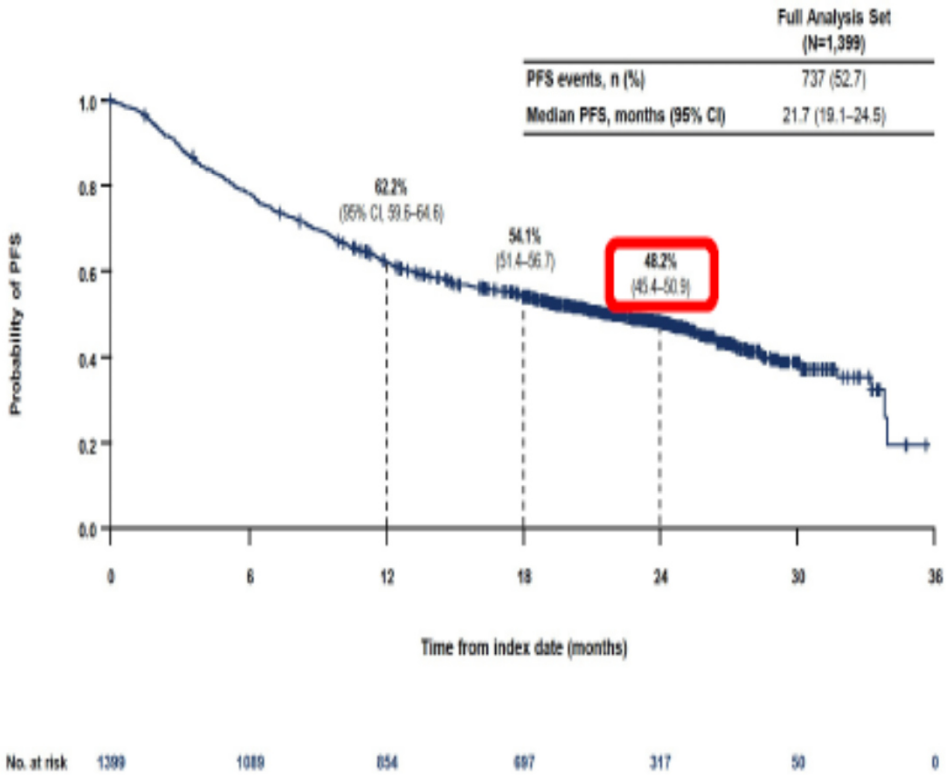
# UNRESECTABLE St. III: Durvalumab Maintainance (RCT and RWD)

## PACIFIC RCT: 5-yrs OS




*Spiegel DR et al, J Clin Oncol 2022*

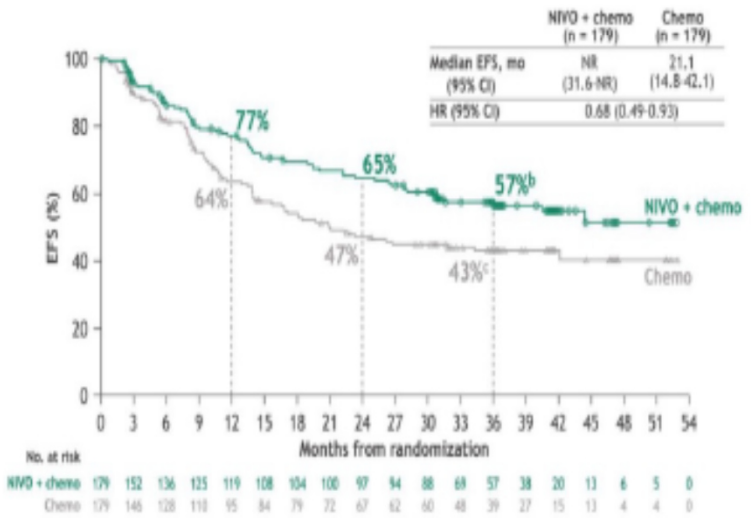
## REAL-PACIFIC: PFS




*Girard N et al, J Thor Oncol 2023*

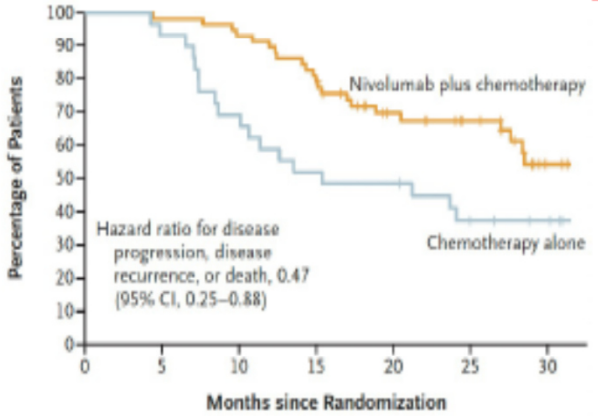
# Neoadjuvant RCTs with Anti-PD1/PD-L1: Early Data

## CM 816: A Ph. 3, Open Label – Median F.U. 41.4 mo. -



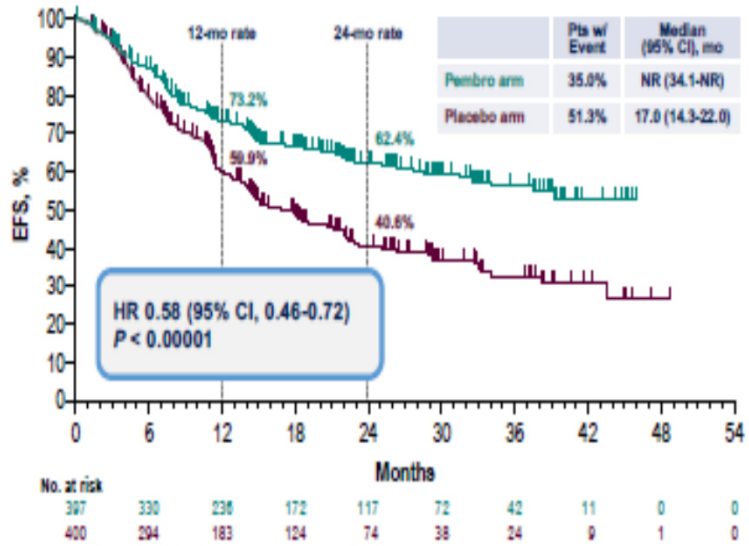

*Forde T et al, NEJM 2022, Girard N et al, ELCC 2023*

## NADIM-2: A Ph. 2R, Open Label – Median F.U. 26.1 mo. -



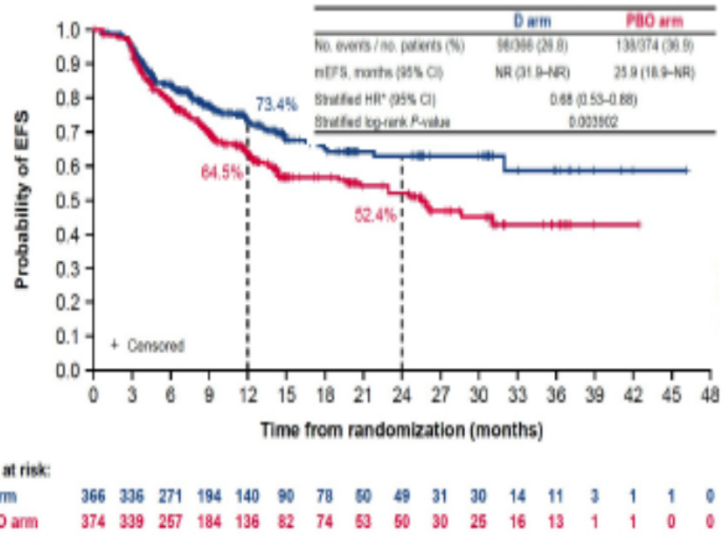

*Provencio M et al, NEJM 2023*

## KN 671: A Ph. 3, Placebo-controlled Study – Median F.U 25.2 mo. -




*Wakalee H et al, ASCO 2023 & NEJM 2023*

## AEGEAN: A Ph. 3, Placebo-controlled Study – Median F.U 11.7 mo. -




*Heymach J et al, AACR 2023*

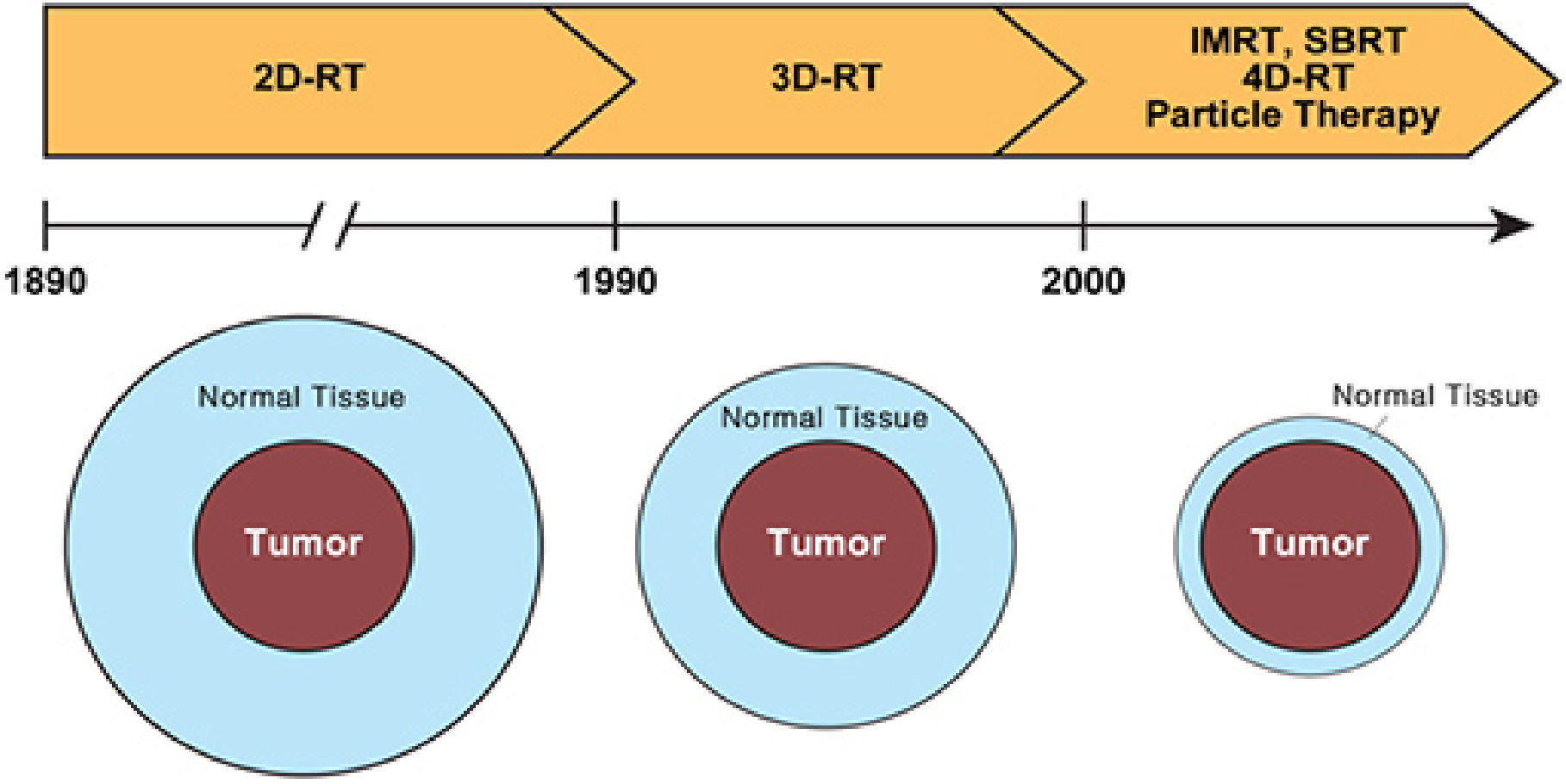
# UNMET NEEDS

- NEW COMBINATION THERAPIES
- RESISTANCE MECHANISMS
- MANAGEMENT OF TOXIC EFFECTS
- CORRECT SEQUENCES
- MORE TARGET AND MORE TARGETED THERAPIES TO COM

# WHERE WE ARE NOW

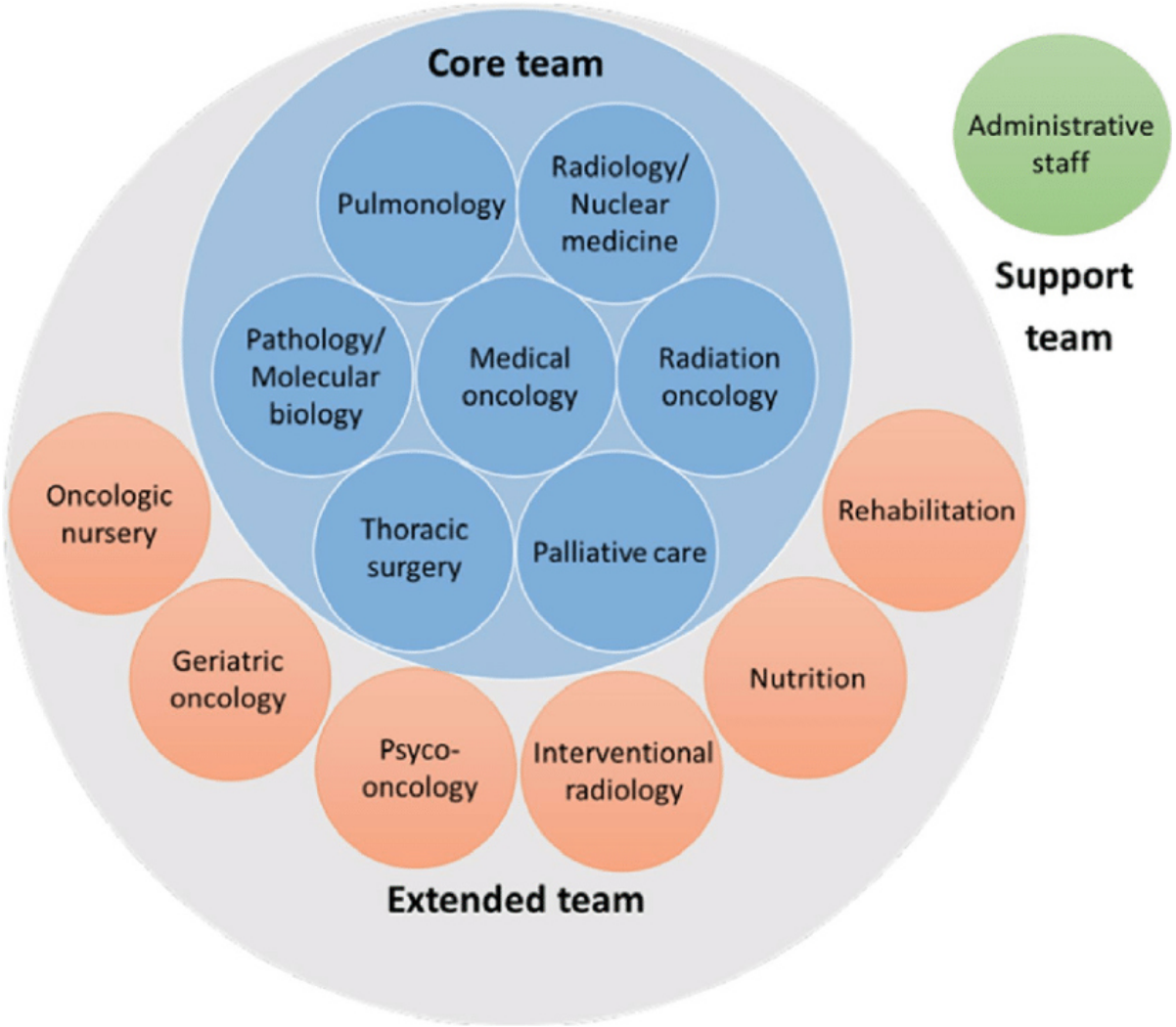
| Addiction | Biomarker | Current Options | Data Source | Median OS (months) | Estimated OS @5 yrs |
|---|---|---|---|---|---|
| *YES* | *ALK+* | *Alectinib*<br>*Brigatinib* | Phase 3<br>Phase 3 | *N.R.* | 62% |
| *YES* | *ROS1+* | *Crizotinib*<br>*Entrectinib* | Phase 1b<br>Pooled Ph.1b | *48 mo.* | 45% |
| *YES* | *EGFR+* | *Osimertinib* | Phase 3 | *40 mo.* | 35-40% |
| *YES* | *BRAF+* | *Dabrafenib + Trametinib* | Phase 2 | *18-20 mo.* | 22% |
| *NO* | *PD-L1 >50%* | *PEMBRO*<br>*Atezolizumab*<br>*Cemiplimab* | Phase 3<br>Phase 3<br>Phase 3 | *24 mo.* | 30-35% |
| *NO* | *PD-L1 1-49%* | *4 Chemo + PEMBRO*<br>*2 Chemo + NIVO-IPI* | Phase 3<br>Phase 3 | *19 mo.* | 20% |
| *NO* | *PD-L1 <1%* | *4 Chemo + PEMBRO*<br>*2 Chemo + NIVO-IPI* | Phase 3<br>Phase 3 | *16 mo.* | 10% |

# EVOLUTION OF MODERN RADIOTHERAPY




Modern radiotherapy is characterized by minimizing the volume of normal tissue being unnecessarily irradiated

# WIND OF CHANGE



# MANAGEMENT OF CNS DISEASE

Practical Radiation Oncology® (2022) 12, 265–282

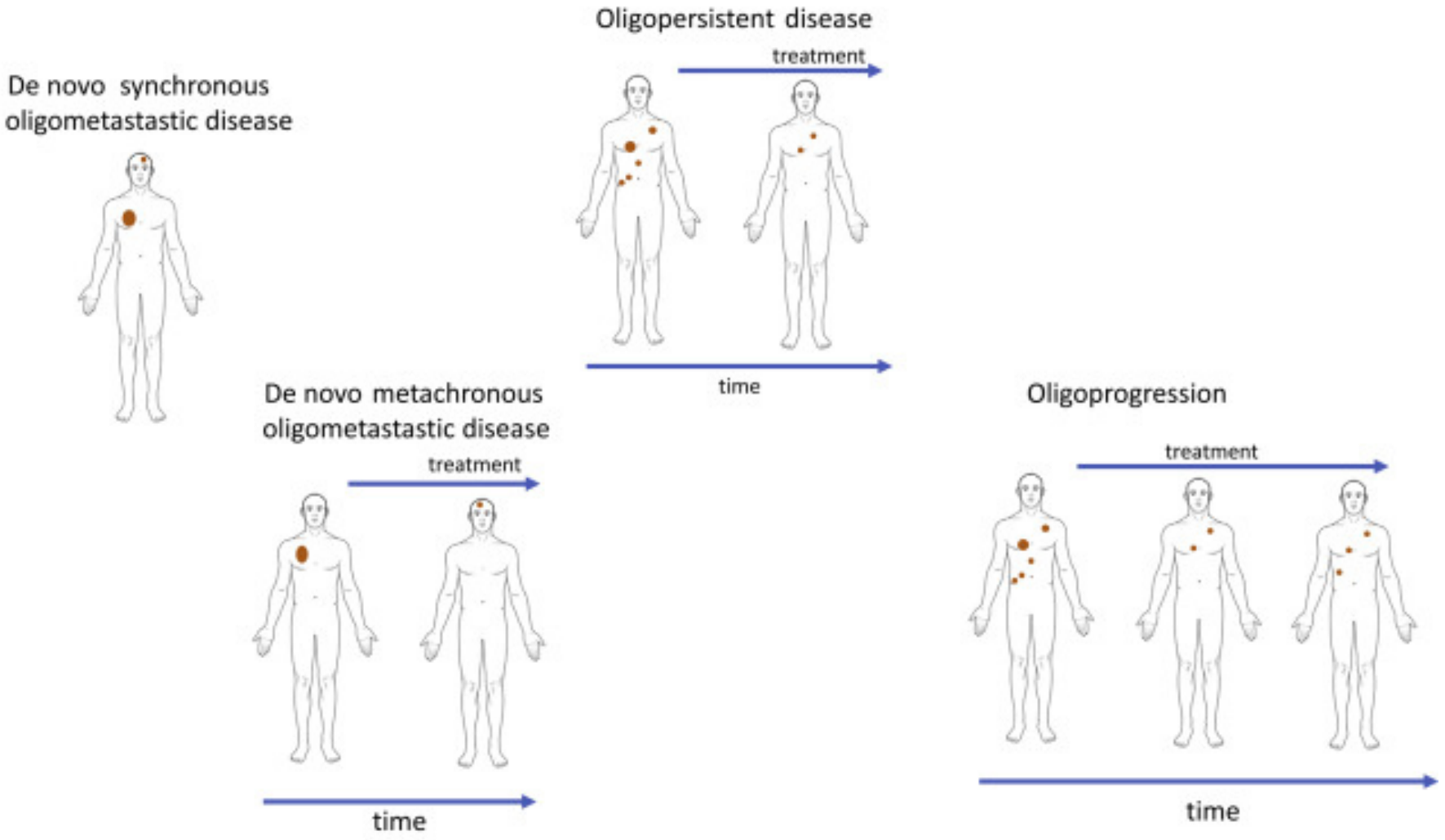


Clinical Practice Guideline

## Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline


Vinai Gondi, MD,[a,*] Glenn Bauman, MD,[b] Lisa Bradfield, BA,[c] Stuart H. Burri, MD,[d] Alvin R. Cabrera, MD,[e] Danielle A. Cunningham, MD,[f] Bree R. Eaton, MD,[g] Jona A. Hattangadi-Gluth, MD,[h] Michelle M. Kim, MD,[i] Rupesh Kotecha, MD,[j] Lianne Kraemer,[k] Jing Li, MD, PhD,[l] Seema Nagpal, MD,[m] Chad G. Rusthoven, MD,[n] John H. Suh, MD,[o] Wolfgang A. Tomé, PhD,[p] Tony J.C. Wang, MD,[q] Alexandra S. Zimmer, MD,[r] Mateo Ziu, MD,[s] and Paul D. Brown, MD[f]

# OLIGOMETASTATIC DISEASE



rapid communications

# Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

David A. Palma, MD, PhD[1]; Robert Olson, MD, MSc[2]; Stephen Harrow, MBChB, PhD[3]; Stewart Gaede, PhD[1]; Alexander V. Louie, MD, PhD[4]; Cornelis Haasbeek, MD, PhD[5]; Liam Mulroy, MD[6]; Michael Lock, MD[1]; George B. Rodrigues, MD, PhD[1]; Brian P. Yaremko, MD, PEng[1]; Devin Schellenberg, MD[7]; Belal Ahmad, MD[1]; Sashendra Senthi, MD, PhD[8]; Anand Swaminath, MD[9]; Neil Kopek, MD[10]; Mitchell Liu, MD[11]; Karen Moore, MSc[3]; Suzanne Currie, MSc[3]; Roel Schlijper, MD[2]; Glenn S. Bauman, MD[1]; Joanna Laba, MD[1]; X. Melody Qu, MD, MPH[1]; Andrew Warner, MSc[1]; and Suresh Senan, MBBS, PhD[5]

Research

JAMA Oncology | Original Investigation

# Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer

## A Phase 2 Randomized Clinical Trial

Puneeth Iyengar, MD, PhD; Zabi Wardak, MD; David E. Gerber, MD; Vasu Tumati, MD; Chul Ahn, PhD; Randall S. Hughes, MD; Jonathan E. Dowell, MD; Naga Cheedella, MD; Lucien Nedzi, MD; Kenneth D. Westover, MD, PhD; Suprabha Pulipparacharuvil, PhD; Hak Choy, MD; Robert D. Timmerman, MD

JNCI: Journal of the National Cancer Institute, 2023, 115(6), 742–748
https://doi.org/10.1093/jnci/djac015
Advance Access Publication Date: 30 January 2022
Article

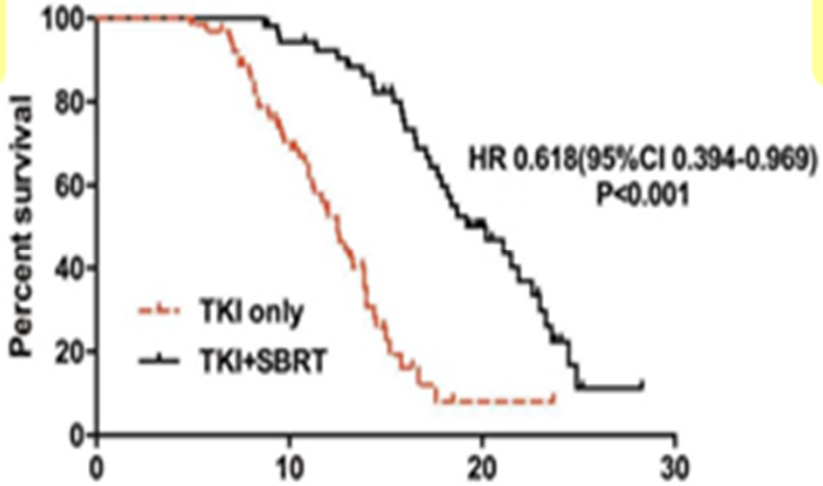
# Randomized Trial of First-Line Tyrosine Kinase Inhibitor With or Without Radiotherapy for Synchronous Oligometastatic *EGFR*-Mutated Non-Small Cell Lung Cancer

Xiao-Shan Wang, MD,[1,‡] Yi-Feng Bai, MD,[1,‡] Vivek Verma, MD,[2] Rui-Lian Yu, MD,[1] Wei Tian, MS,[1] Rui Ao, MD,[1] Ying Deng, MD,[1] Xue-Qiang Zhu, MD,[1] Hao Liu, MD,[1] Hai-Xia Pan, MD,[1] Lan Yang, MD,[1] Han-Song Bai, MD,[3] Xing Luo, MD,[3] Yan Guo, MS,[3] Ming-Xiu Zhou, MD,[3] Yue-Mei Sun, MD,[4] Zi-Can Zhang, MD,[4] Si-Min Li, MD,[3,5] Xue Cheng, MD,[3] Bang-Xian Tan, MD,[3] Liang-Fu Han, MD,[6] Ying-Yi Liu, MD,[7] Kai Zhang, MD,[8] Fan-Xin Zeng, PD,[9] Lin Jia, MD,[10] Xin-Bao Hao, MD,[11] You-Yu Wang, MD,[1] Gang Feng, MD,[1] Ke Xie, MD,[1] You Lu, MD,[12] Ming Zeng, MD, PhD[1,*]

# Oligometastatic *EGFR*+ Disease: Room for STRT?

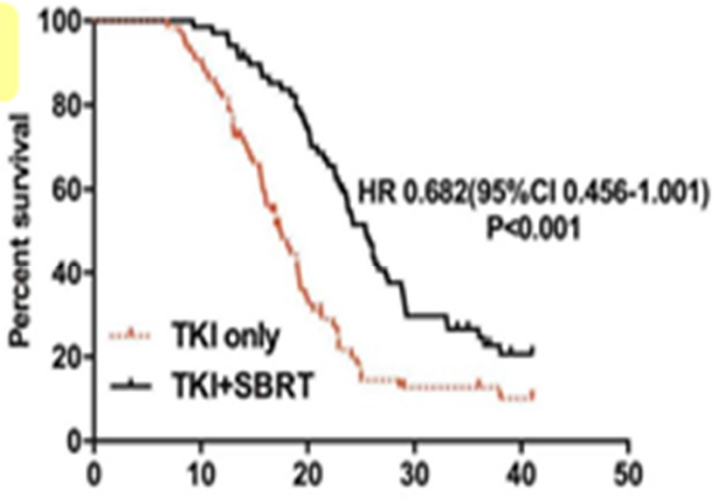
**Phase III (Asian); Oligomestatic (no more than 5 organs, no more than 2 lesion/organ); GEF/ERL or ICO; SBRT: 25-40 Gy/5frz; Primary: PFS**

**PFS**




| Number at risk | | | | |
|---|---|---|---|---|
| TKI only | 65 | 52 | 10 | 0 |
| TKI+SBRT | 68 | 61 | 35 | 3 |

**OS**




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| TKI only | 65 | 58 | 19 | 3 | 0 | 0 |
| TKI+SBRT | 68 | 65 | 47 | 19 | 0 | 0 |

- Independent at Multivariate (PFS): ECOG; Number of Met. Sites (cut-off: 3); SBRT
- Inpependent at Multivariate (OS): ECOG, Numbers of Met. Sites; T-stage; SBRT; Mutation Type (HR 0.09!!!)

*Wang XS et al, ASCO 2020*

ETOP·IBCSG
PARTNERS

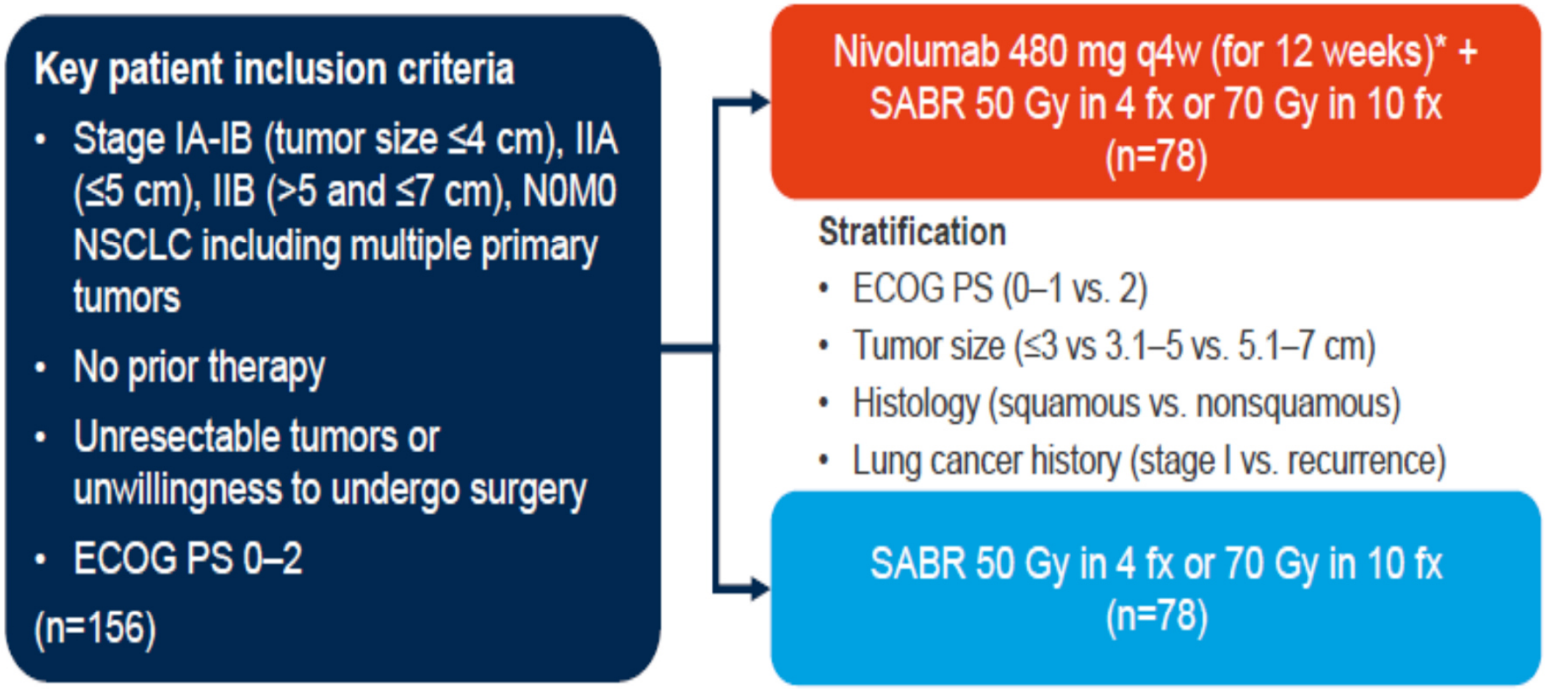
Foundation for International Cancer Research

# IASLC 2023 World Conference on Lung Cancer

September 9–12 2023

# OA12.04: Nivolumab After Stereotactic Ablative Radiotherapy for Early-Stage Non-Small Cell Lung Cancer: Randomized I-SABR Trial – Chang JY, et al

- **Study objective**
  - To evaluate the efficacy and safety of adding nivolumab to SABR in patients with node-negative NSCLC in the phase 2 I-SABR study




**Primary endpoint**

- 4-year EFS

**Secondary endpoints**

- OS, safety

*Administered on same day or 36 hours after 1st fx.

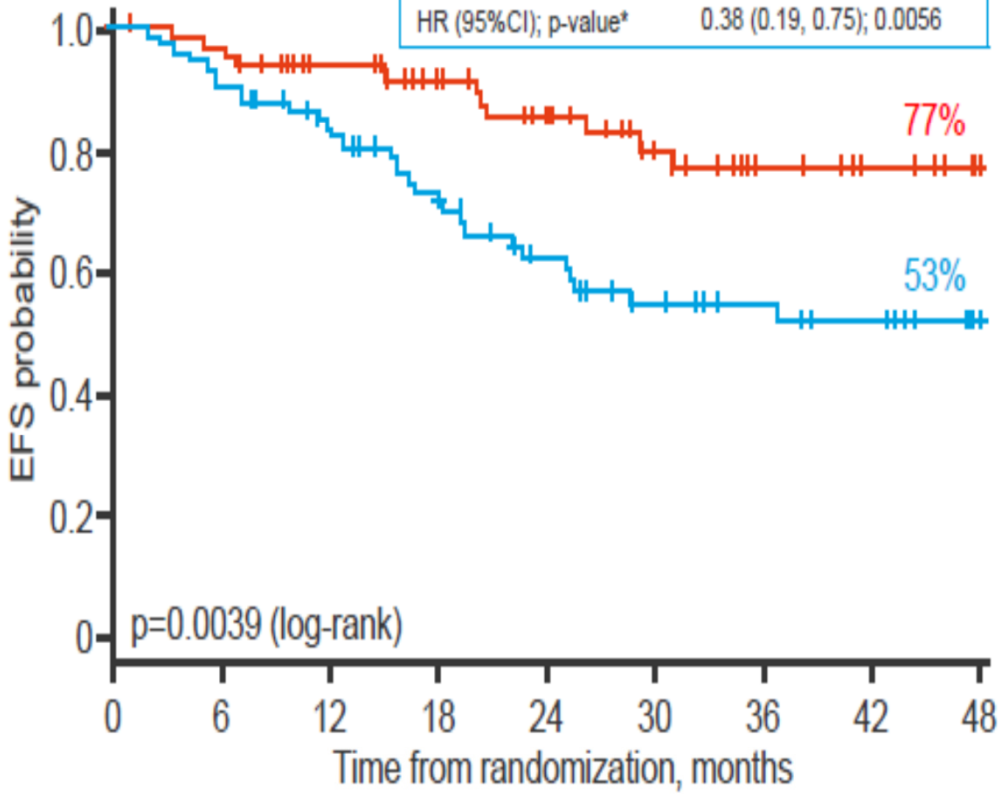
# OA12.04: Nivolumab After Stereotactic Ablative Radiotherapy for Early-Stage Non-Small Cell Lung Cancer: Randomized I-SABR Trial – Chang JY, et al

- Key results

## Event-free survival

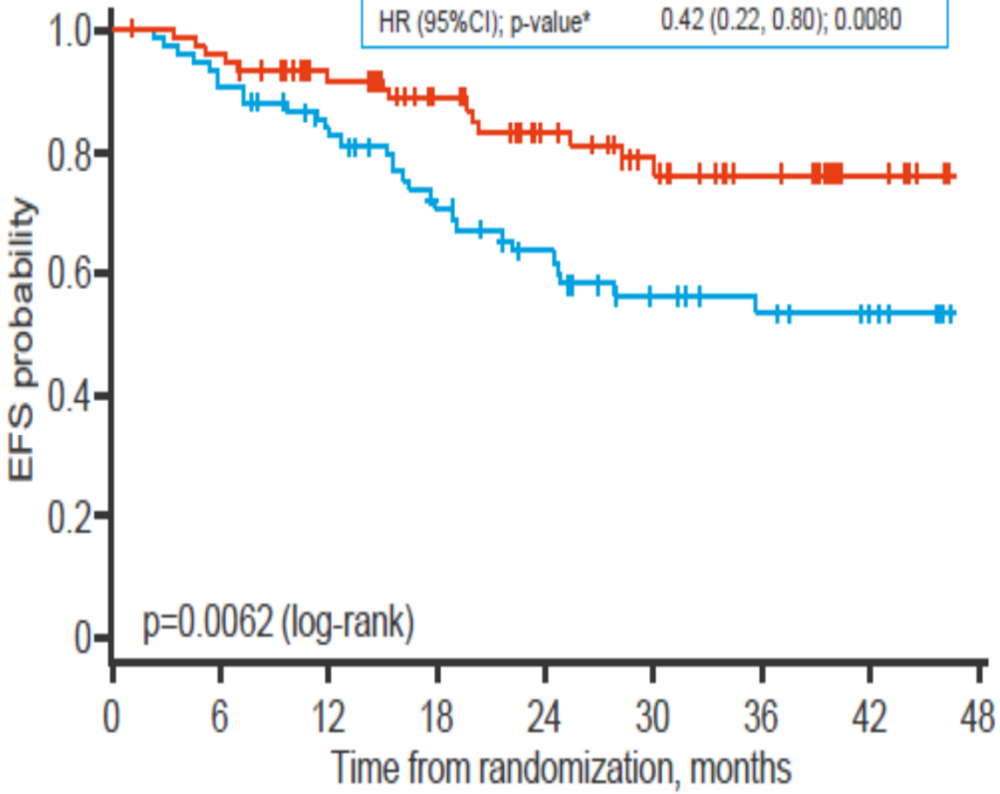
### Per protocol

| | I-SABR (n=66) | SABR (n=75) |
|---|---|---|
| Events, n | 11 | 30 |
| HR (95%CI); p-value* | 0.38 (0.19, 0.75); 0.0056 | |




### ITT

| | I-SABR (n=75) | SABR (n=75) |
|---|---|---|
| Events, n | 14 | 30 |
| HR (95%CI); p-value* | 0.42 (0.22, 0.80); 0.0080 | |




No. at risk (events)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| I-SABR | 66 (0) | 54 (4) | 38 (4) | 18 (3) | 7 (0) | 75 (0) | 62 (5) | 43 (6) | 22 (3) |
| SABR | 75 (0) | 59 (11) | 34 (14) | 22 (4) | 11 (1) | 75 (0) | 59 (11) | 34 (14) | 22 (4) |

*Cox model.

Chang JY, et al. J Thorac Oncol 2023;18(suppl 9):Abstr OA12.04

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Clinical Practice Guideline

# Treatment of Oligometastatic Non-Small Cell Lung Cancer: An ASTRO/ESTRO Clinical Practice Guideline

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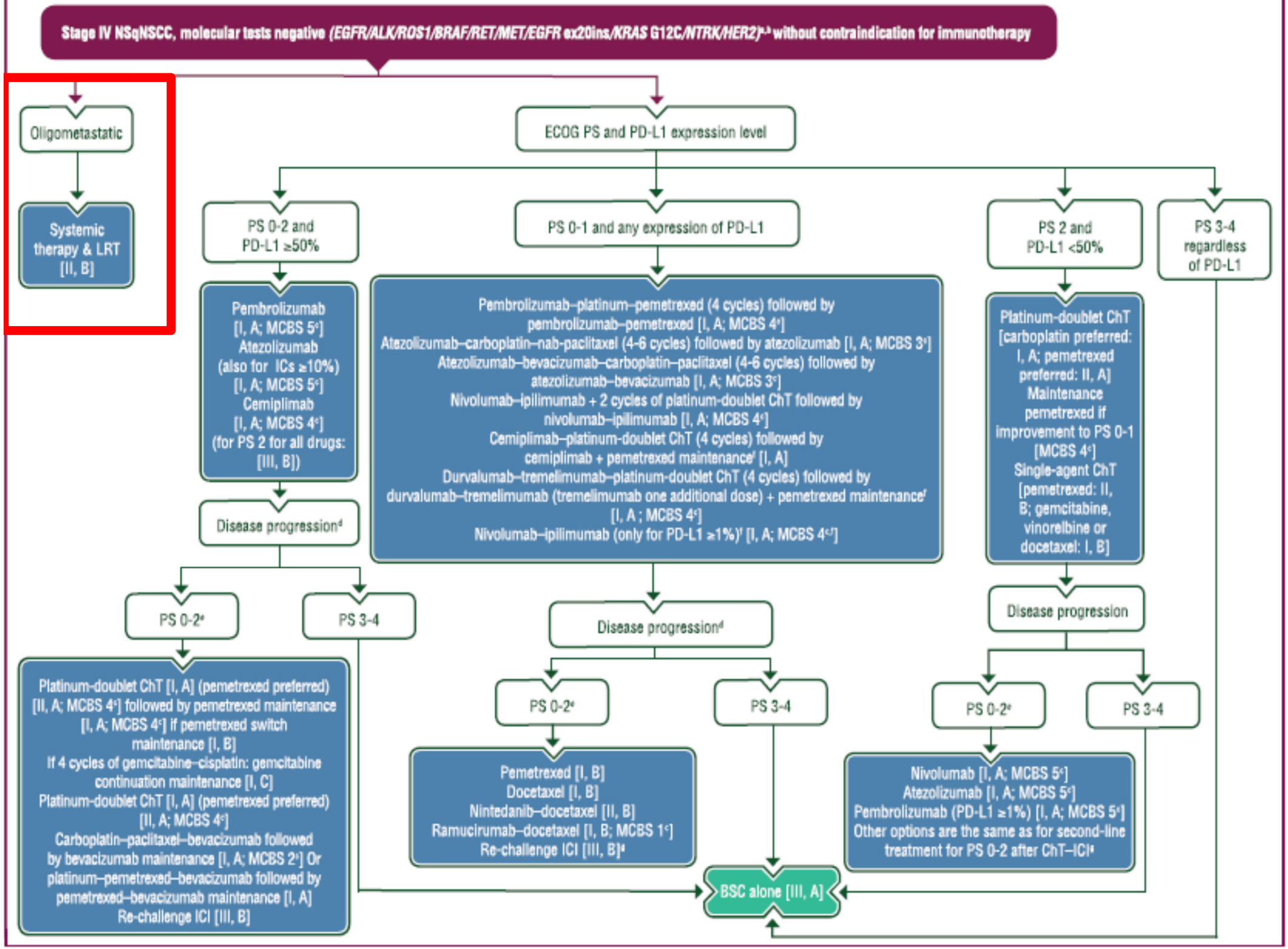
Stage IV NSqNSCC, molecular tests negative (EGFR/ALK/ROS1/BRAF/RET/MET/EGFR ex20ins/KRAS G12C/NTRK/HER2)[a,b] without contraindication for immunotherapy
Oligometastatic
Systemic therapy & LRT [II, B]
ECOG PS and PD-L1 expression level
PS 0-2 and PD-L1 ≥50%
PS 0-1 and any expression of PD-L1
PS 2 and PD-L1 <50%
PS 3-4 regardless of PD-L1
Pembrolizumab [I, A; MCBS 5[c]]
Atezolizumab (also for ICs ≥10%) [I, A; MCBS 5[c]]
Cemiplimab [I, A; MCBS 4[c]]
(for PS 2 for all drugs: [III, B])
Pembrolizumab–platinum–pemetrexed (4 cycles) followed by pembrolizumab–pemetrexed [I, A; MCBS 4[c]]
Atezolizumab–carboplatin–nab-paclitaxel (4-6 cycles) followed by atezolizumab [I, A; MCBS 3[c]]
Atezolizumab–bevacizumab–carboplatin–paclitaxel (4-6 cycles) followed by atezolizumab–bevacizumab [I, A; MCBS 3[c]]
Nivolumab–ipilimumab + 2 cycles of platinum-doublet ChT followed by nivolumab–ipilimumab [I, A; MCBS 4[c]]
Cemiplimab–platinum-doublet ChT (4 cycles) followed by cemiplimab + pemetrexed maintenance[f] [I, A]
Durvalumab–tremelimumab–platinum-doublet ChT (4 cycles) followed by durvalumab–tremelimumab (tremelimumab one additional dose) + pemetrexed maintenance[f] [I, A ; MCBS 4[c]]
Nivolumab–ipilimumab (only for PD-L1 ≥1%)[f] [I, A; MCBS 4[c,f]]
Platinum-doublet ChT [carboplatin preferred: I, A; pemetrexed preferred: II, A] Maintenance pemetrexed if improvement to PS 0-1 [MCBS 4[c]] Single-agent ChT [pemetrexed: II, B; gemcitabine, vinorelbine or docetaxel: I, B]
Disease progression[d]
Disease progression
PS 0-2[e]
PS 3-4
Platinum-doublet ChT [I, A] (pemetrexed preferred) [II, A; MCBS 4[c]] followed by pemetrexed maintenance [I, A; MCBS 4[c]] if pemetrexed switch maintenance [I, B]
If 4 cycles of gemcitabine–cisplatin: gemcitabine continuation maintenance [I, C]
Platinum-doublet ChT [I, A] (pemetrexed preferred) [II, A; MCBS 4[c]]
Carboplatin–paclitaxel–bevacizumab followed by bevacizumab maintenance [I, A; MCBS 2[c]] Or platinum–pemetrexed–bevacizumab followed by pemetrexed–bevacizumab maintenance [I, A]
Re-challenge ICI [III, B]
Pemetrexed [I, B]
Docetaxel [I, B]
Nintedanib–docetaxel [II, B]
Ramucirumab–docetaxel [I, B; MCBS 1[c]]
Re-challenge ICI [III, B][a]
Nivolumab [I, A; MCBS 5[c]]
Atezolizumab [I, A; MCBS 5[c]]
Pembrolizumab (PD-L1 ≥1%) [I, A; MCBS 5[c]]
Other options are the same as for second-line treatment for PS 0-2 after ChT–ICI[a]
BSC alone [III, A]

# TAKE HOME MESSAGE

IMMUNOTHERAPY


TARGET THERAPY

RADIOTHERAPY

# DON’T STOP WORK TOGETHER

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