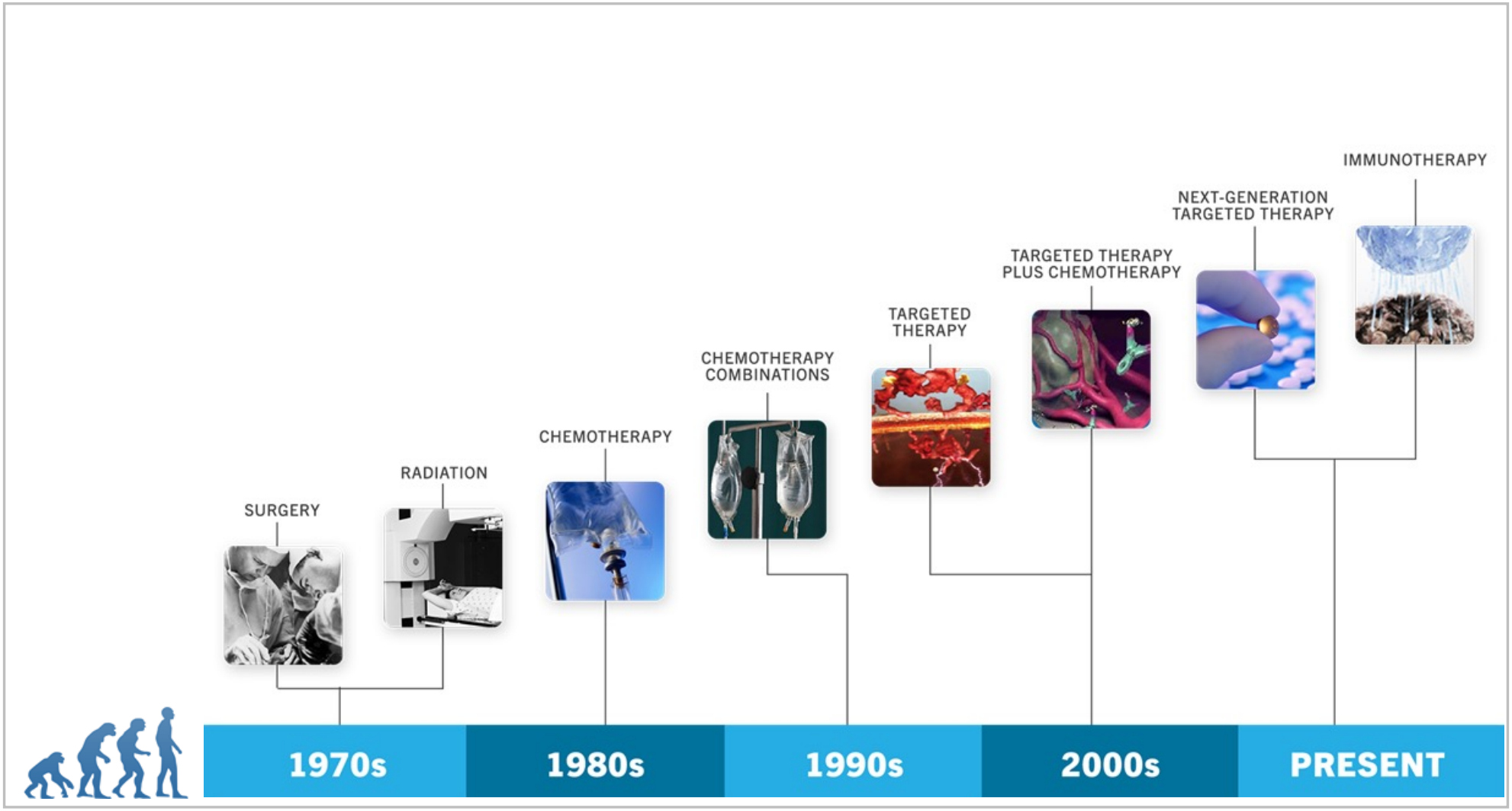
Il trattamento dei pazienti affetti da NSCLC in stadio IV

Michele Fiore

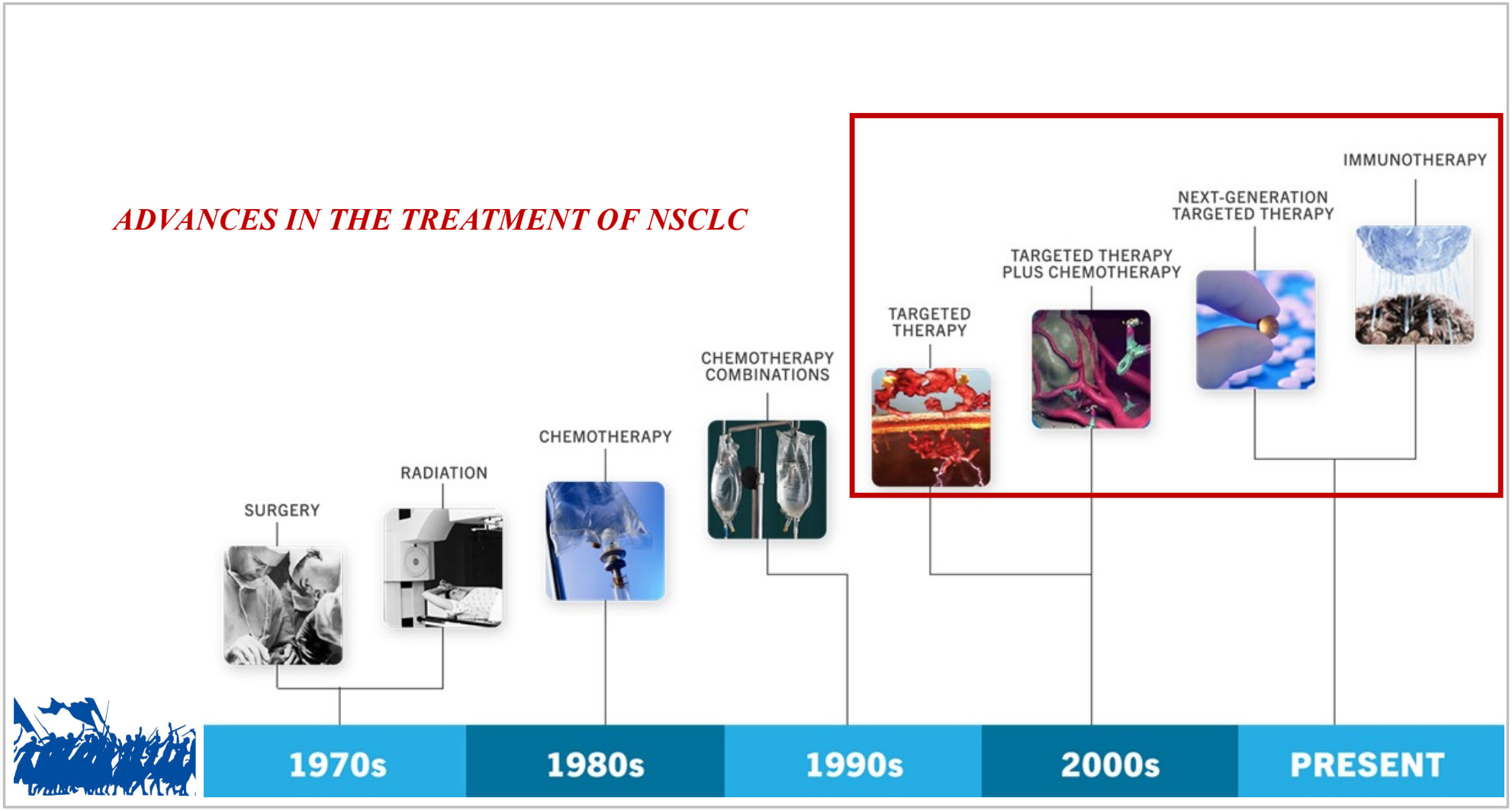
Radiation Oncology

Campus Bio-Medico University of Rome

LUNG EVOLUTION

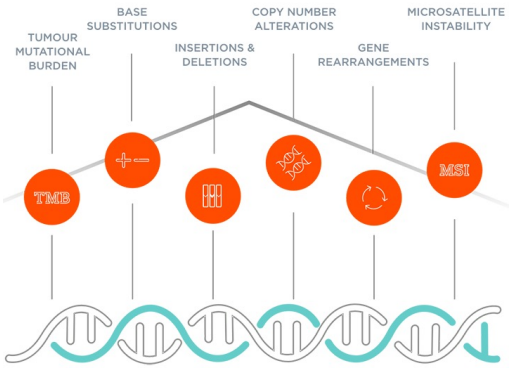


LUNG R-EVOLUTION



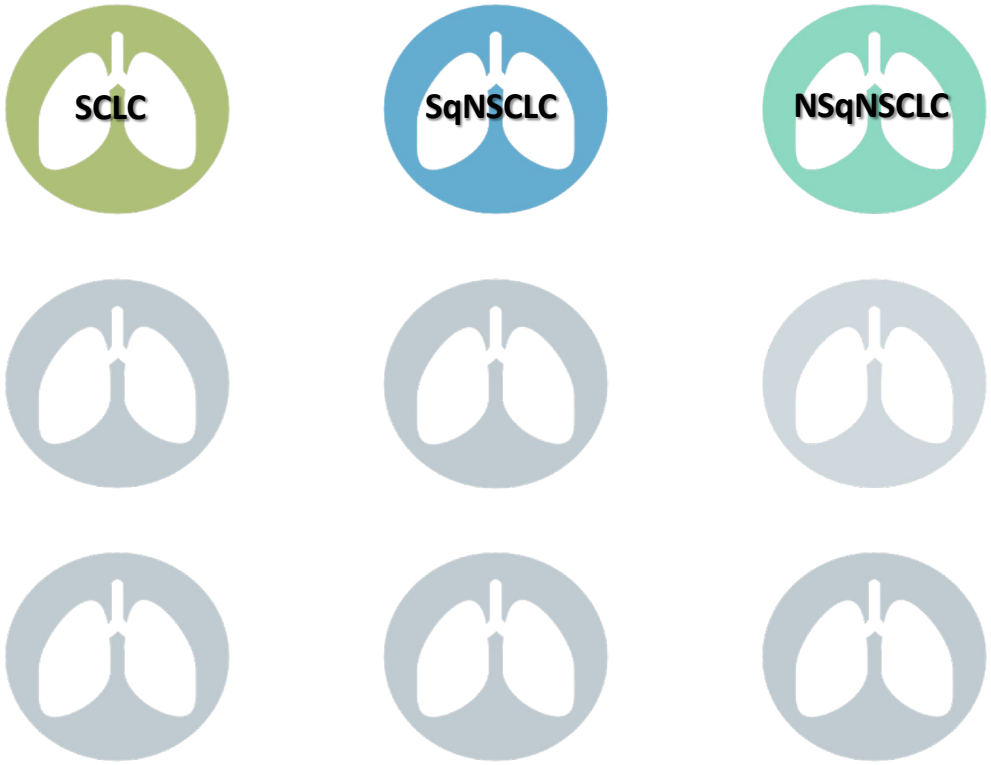
LUNG R-EVOLUTION

Tumor biology and molecular diagnostics



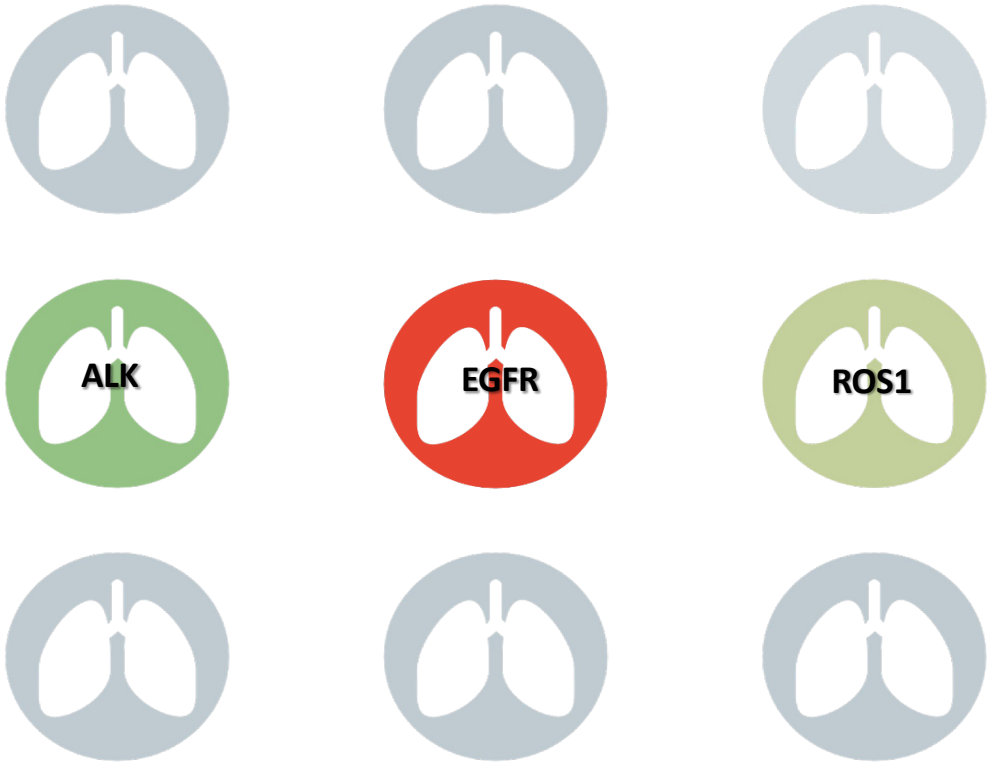
LUNG R-EVOLUTION

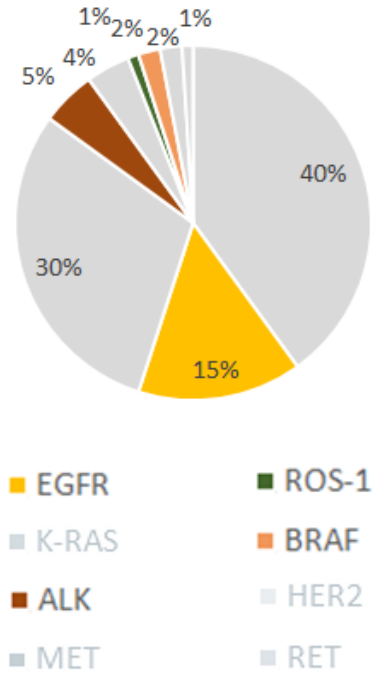
HISTOTYPE



LUNG R-EVOLUTION

MUTATIONS





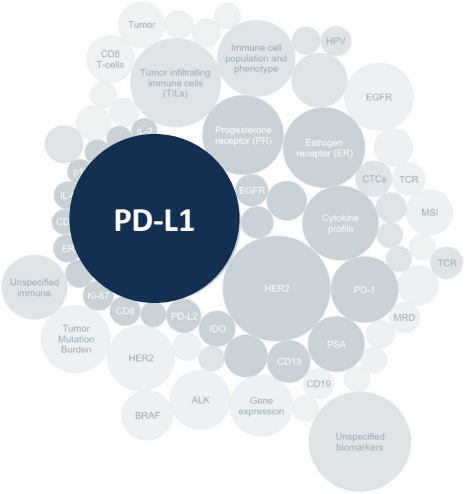
LUNG R-EVOLUTION

BIOMARKERS

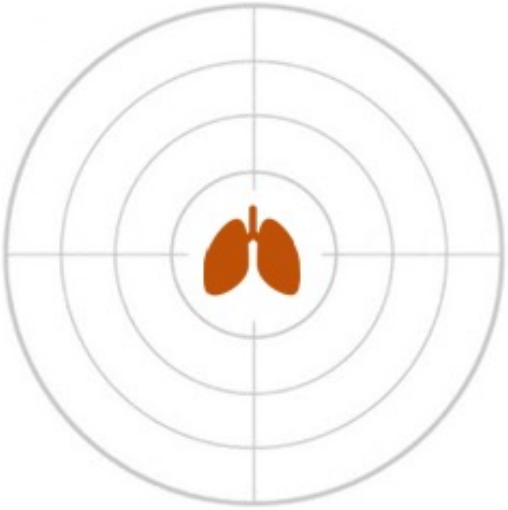
PDL1

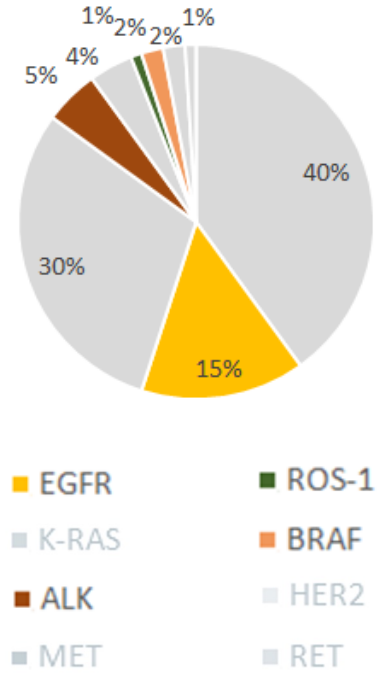
Others

None



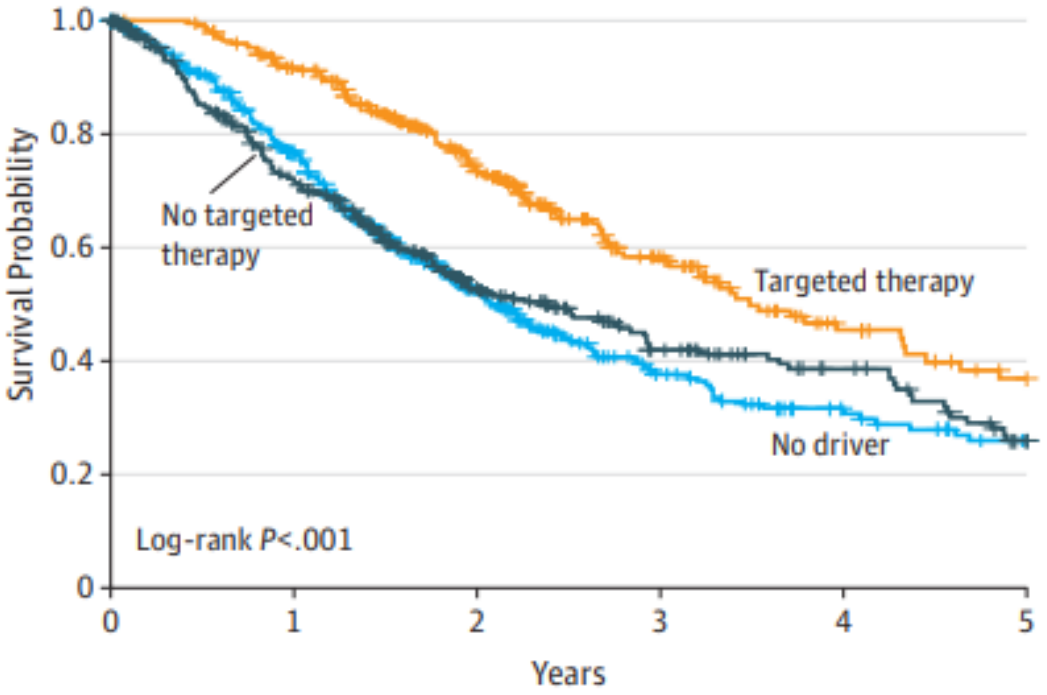
Oncogene-Addicted Non-Small-Cell Lung Cancer

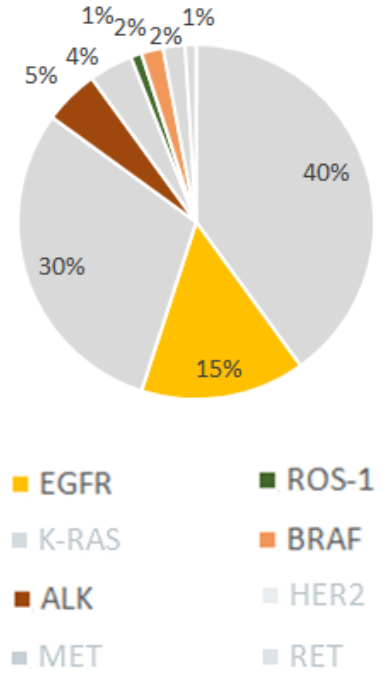




Several different driver mutations have been identified and many studies have clearly shown that upfront TKI monotherapy may improve the overall outcome of these patients.

Oncogene-Addicted Non-Small-Cell Lung Cancer

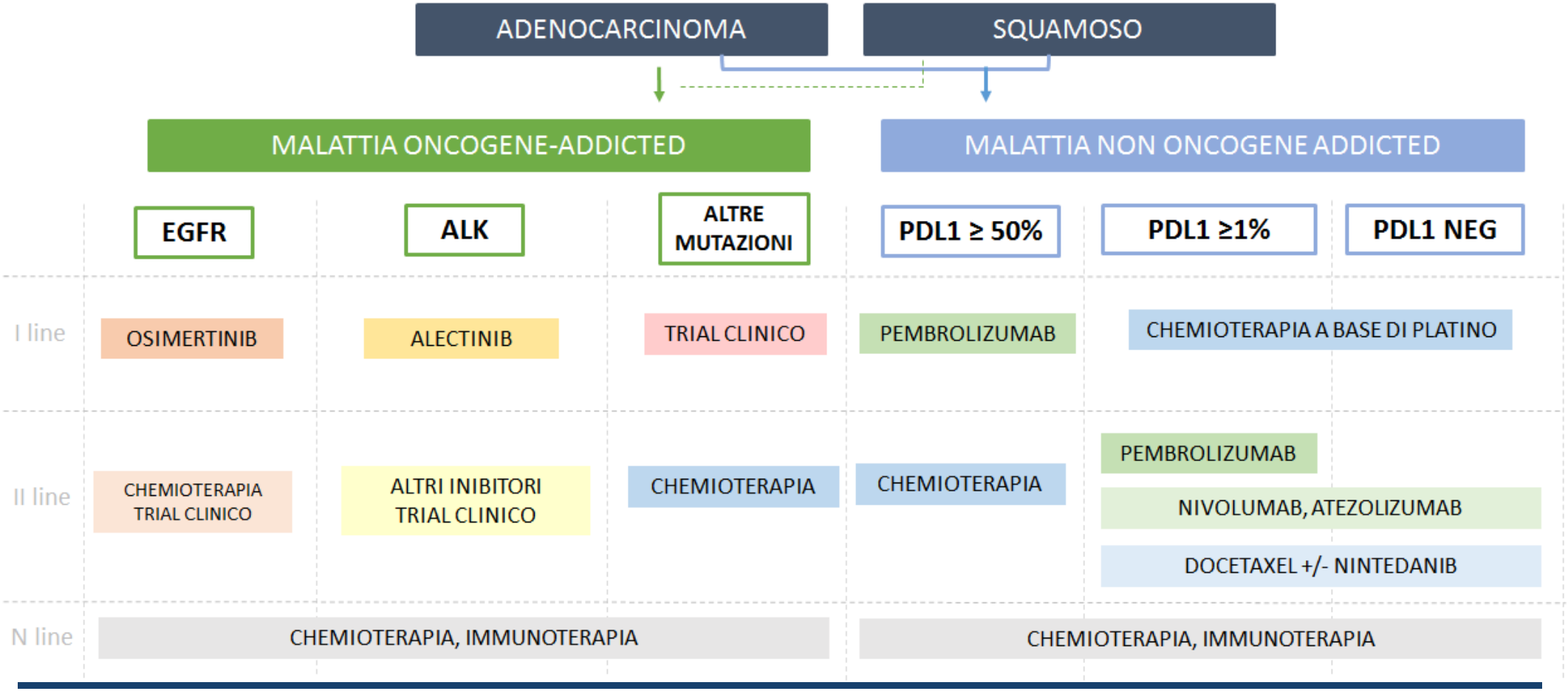




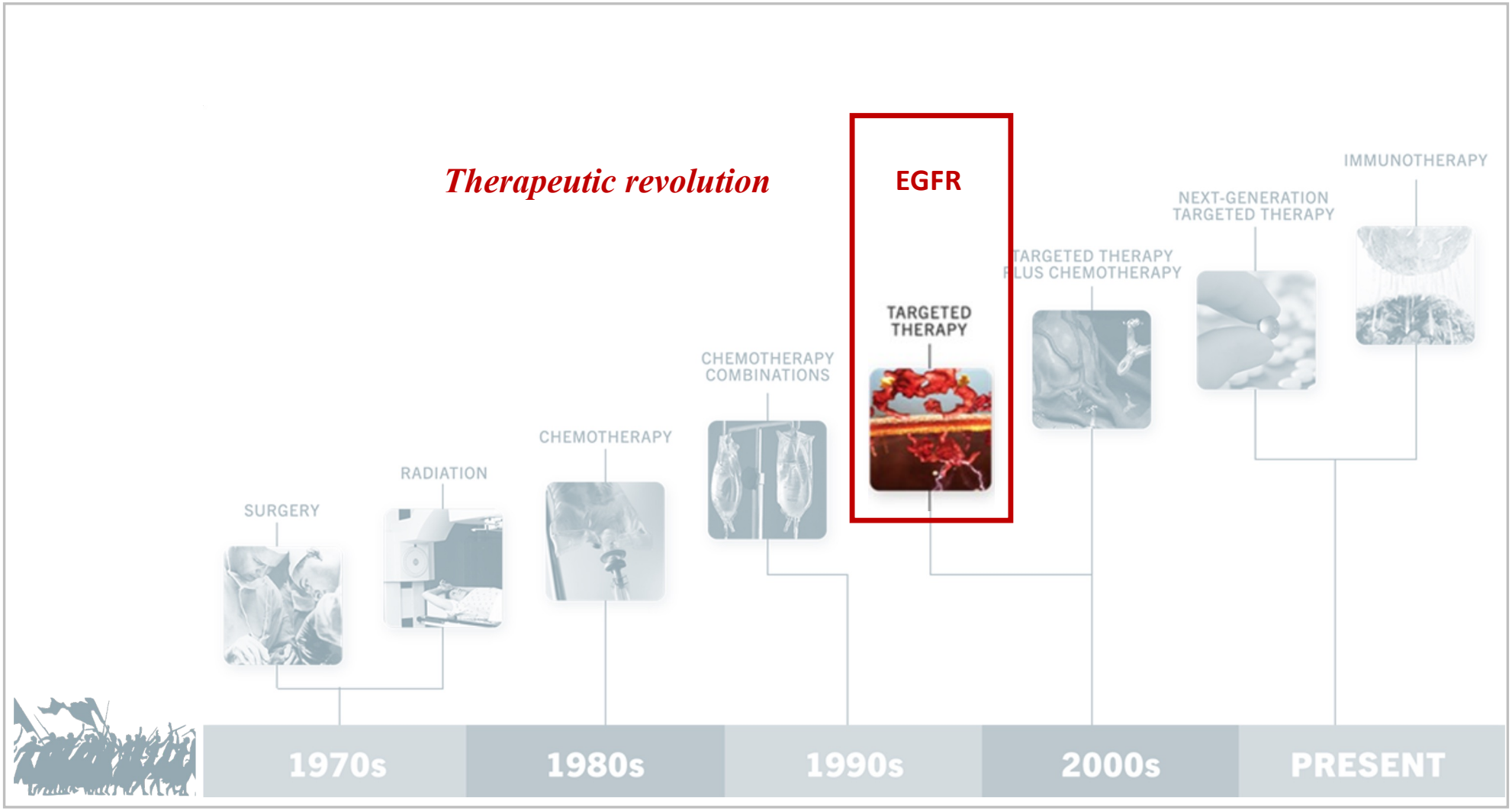
Kris MG, et al. JAMA 2014; 11(19):1998-2006

TRATTAMENTO DEL NSCLC AVANZATO

IL PRESENTE

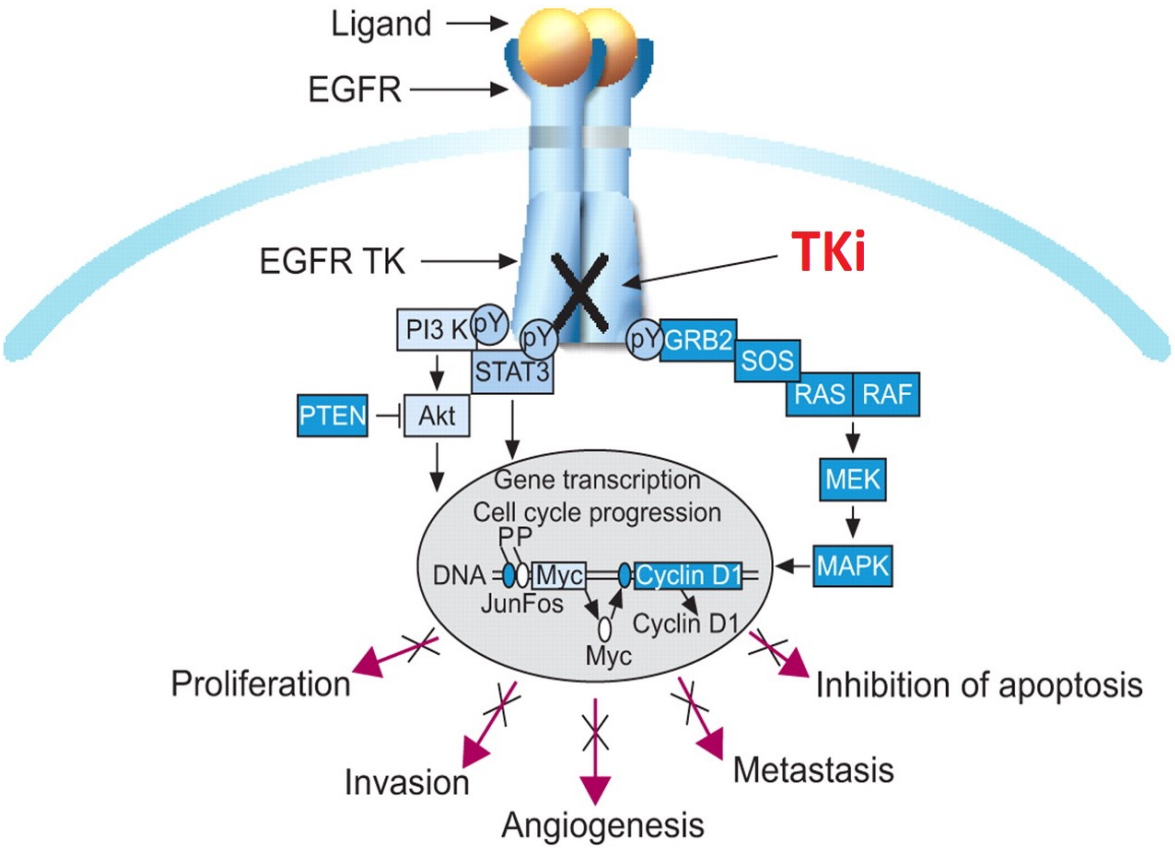


LUNG R-EVOLUTION



ONCOGENE-ADDICTED NSCLC

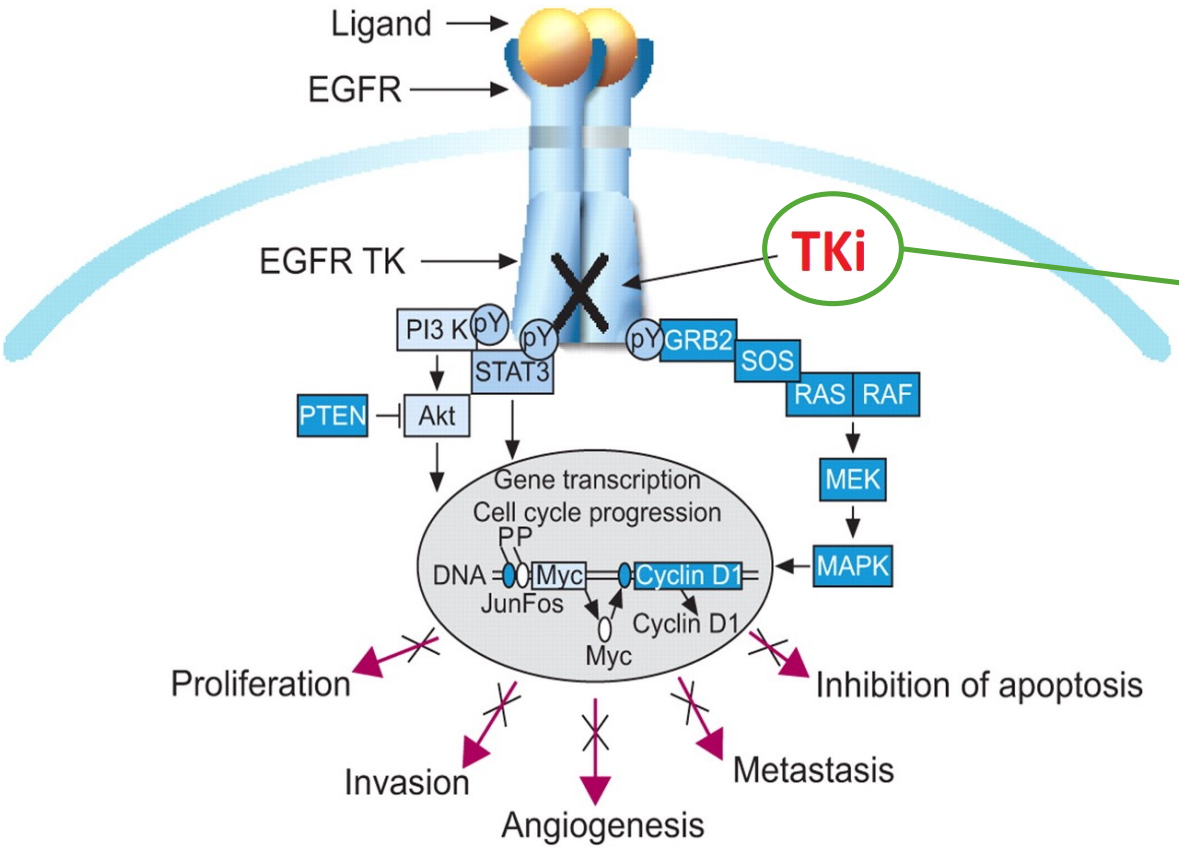
EGFR



Armour A.A., Watkins C.L.. European Respiratory Review 2010 - Bethune G. J Thorac Dis 2010

ONCOGENE-ADDICTED NSCLC

EGFR



GEFITINIB
ERLOTINIB
AFATINIB
DACOMITINIB
OSIMERTINIB

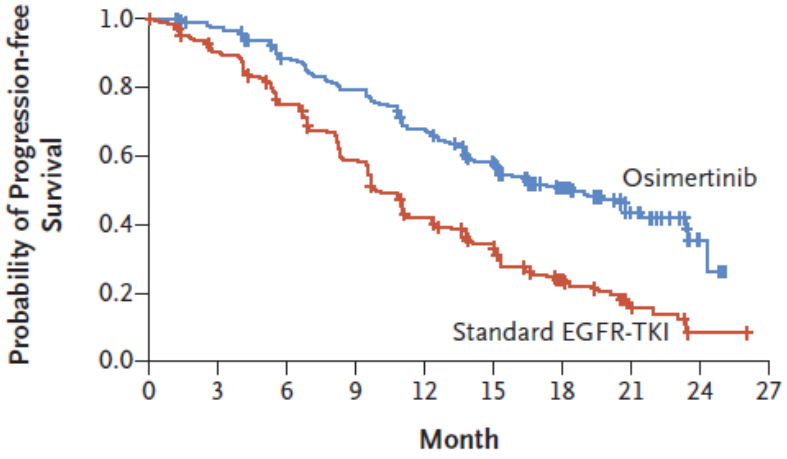
Armour A.A., Watkins C.L.. European Respiratory Review 2010 - Bethune G. J Thorac Dis 2010

EGFR

ONCOGENE-ADDICTED NSCLC

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001

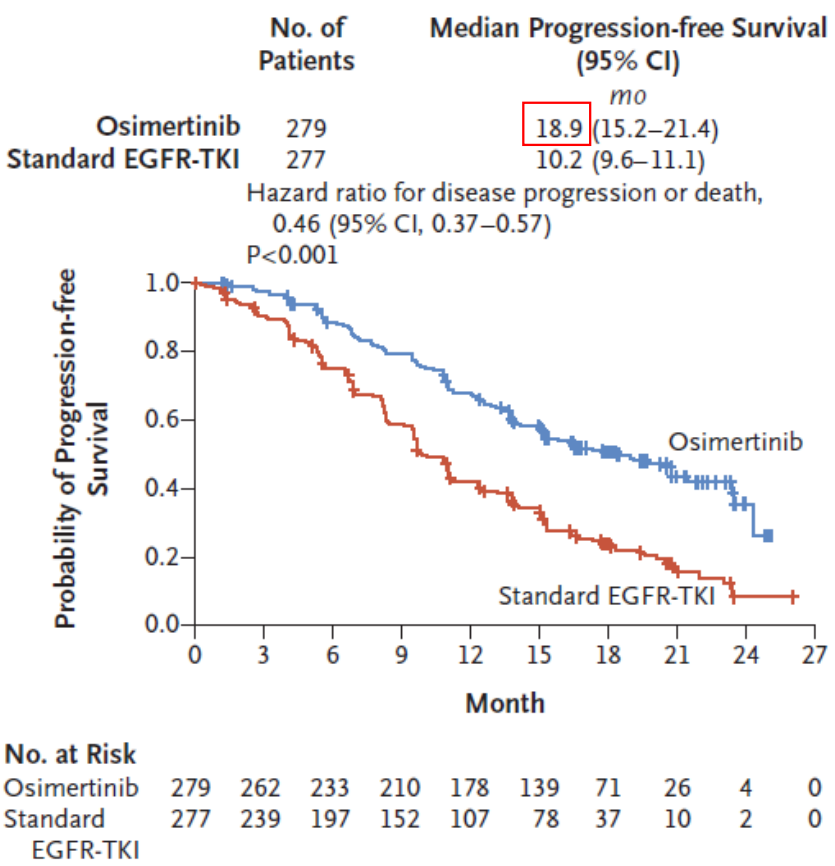


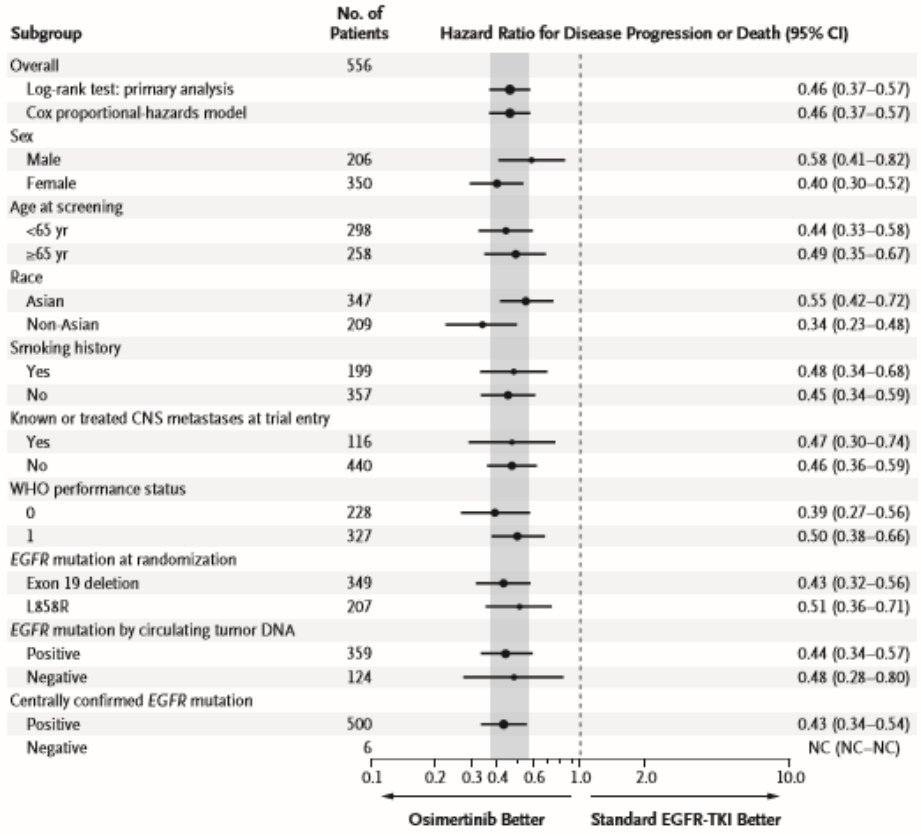
No. at Risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

Soria JC. Et al. NEJM 2018; 378(2):113-125

EGFR

ONCOGENE-ADDICTED NSCLC

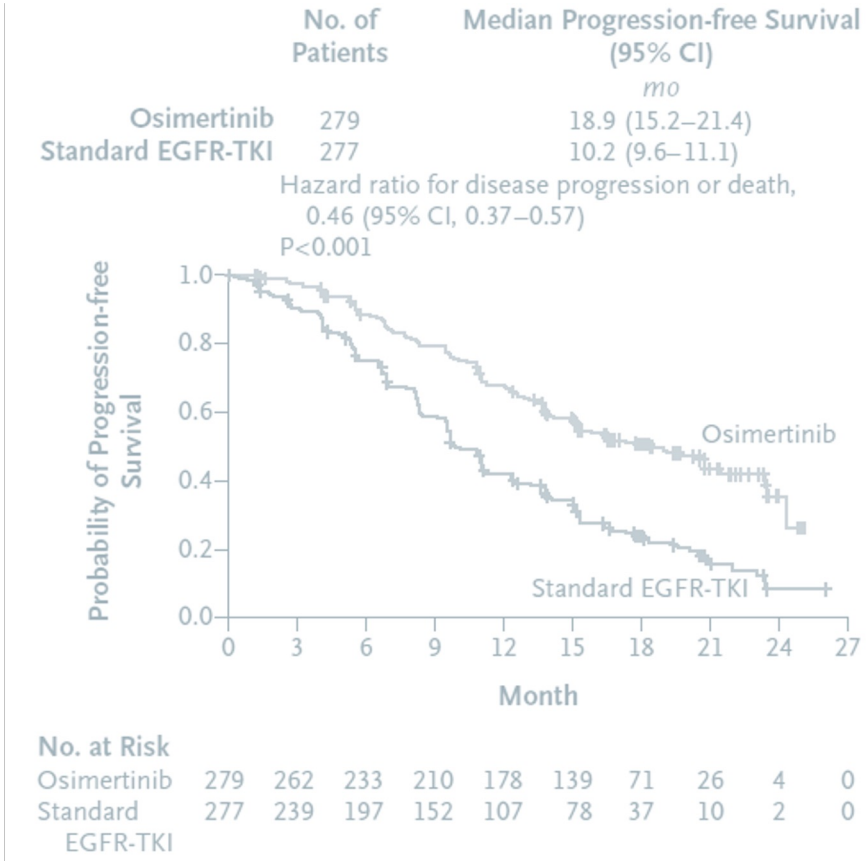


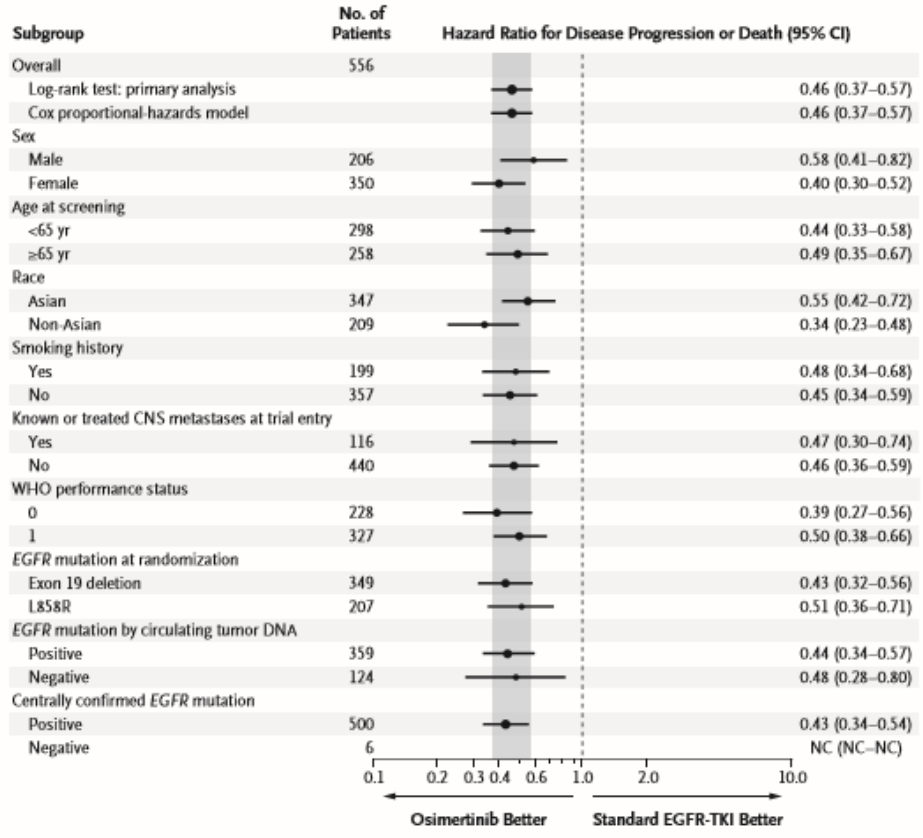


Soria JC. Et al. NEJM 2018; 378(2):113-125

EGFR

ONCOGENE-ADDICTED NSCLC





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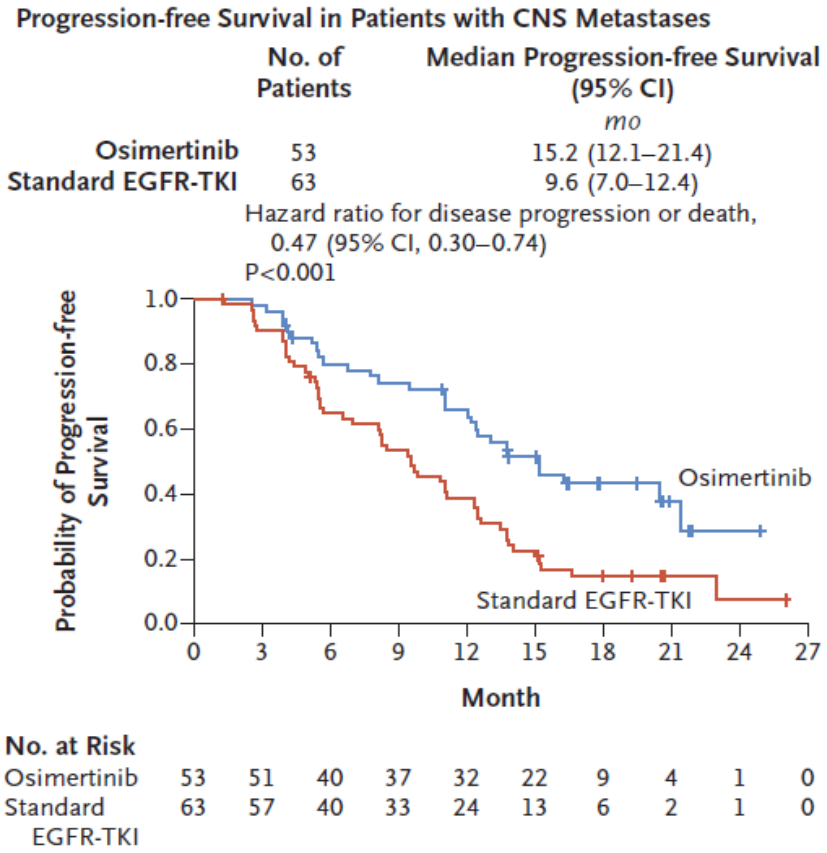
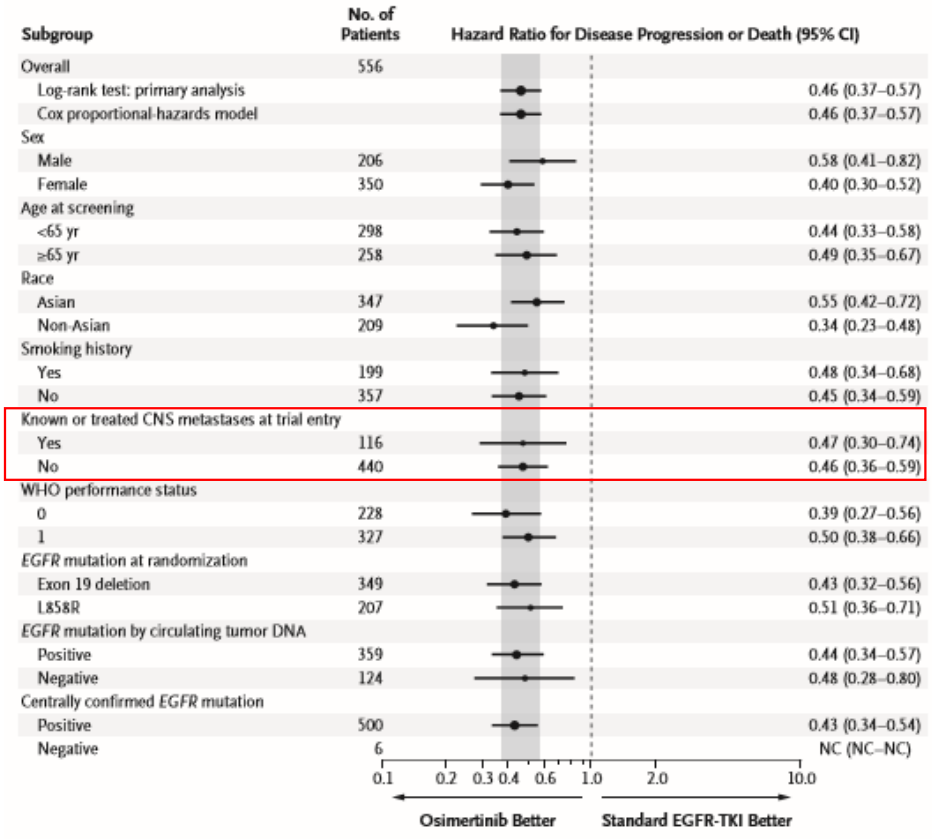
EGFR

ONCOGENE-ADDICTED NSCLC

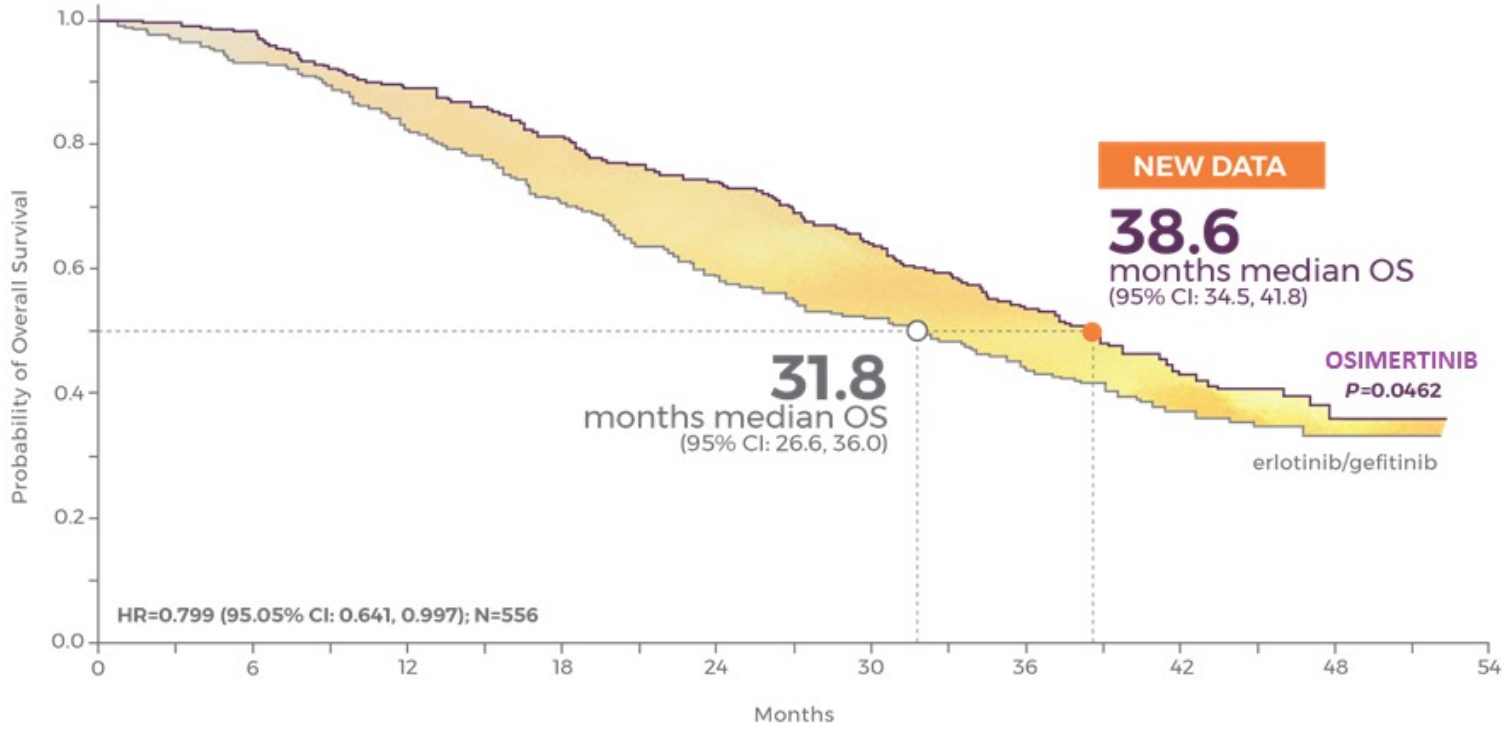




Soria JC. Et al. NEJM 2018; 378(2):113-125

ONCOGENE-ADDICTED NSCLC

EGFR



BARCELONA 2019 ESMO congress

Data cut-off: 25 June 2019

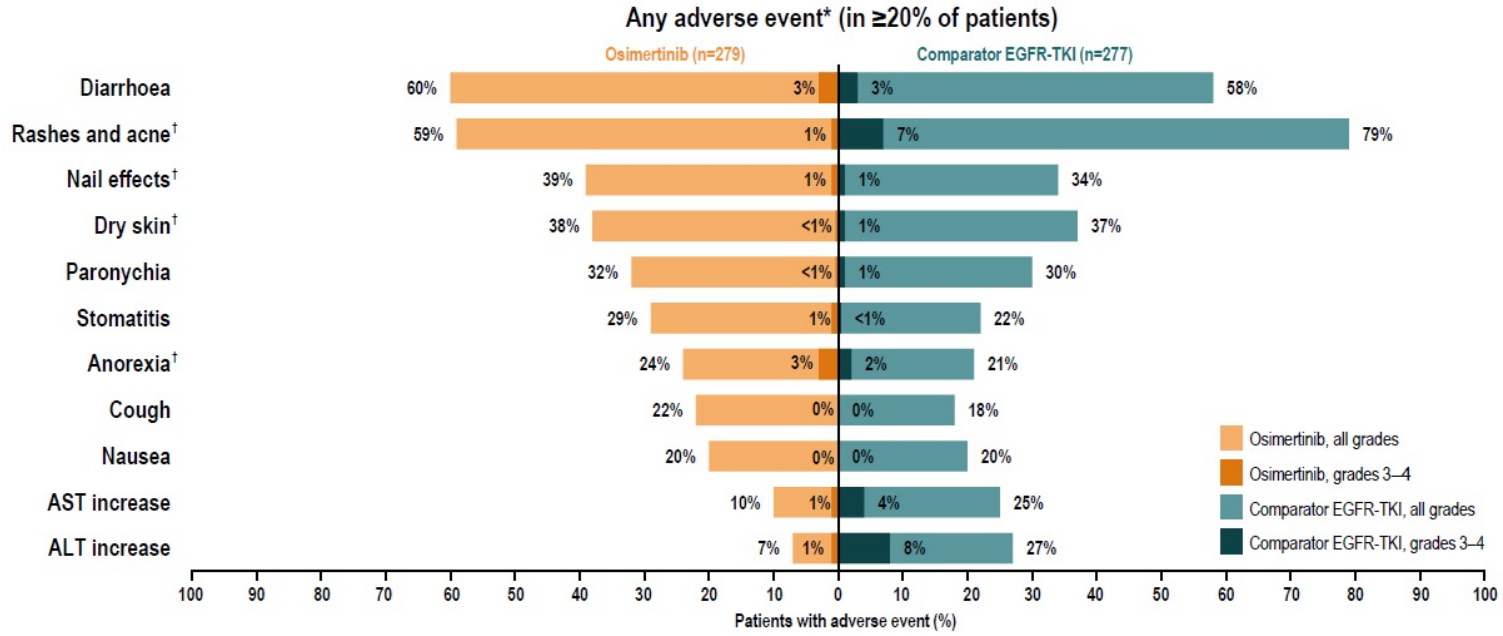
*As assessed by the investigator; Patients with multiple events in the same category counted only once in that category; Patients with events in more than one category counted once in each of those categories; †Grouped term

ONCOGENE-ADDICTED NSCLC

EGFR

SAFETY SUMMARY

- Median duration of exposure: osimertinib, 20.7 months; comparator EGFR-TKI, 11.5 months
- Grade ≥3 possibly causally related AEs: osimertinib, 51 patients (**18%**); comparator EGFR-TKI, 79 patients (**29%**)



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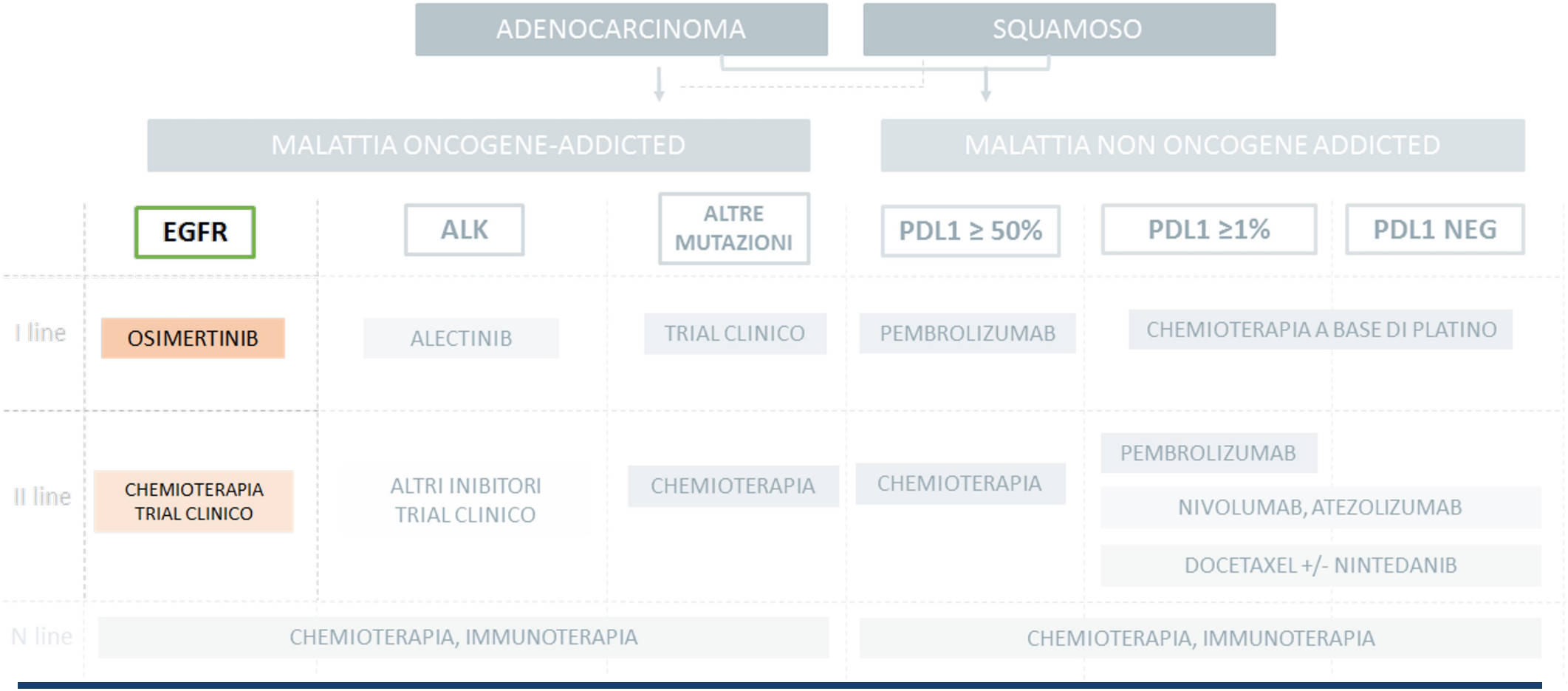
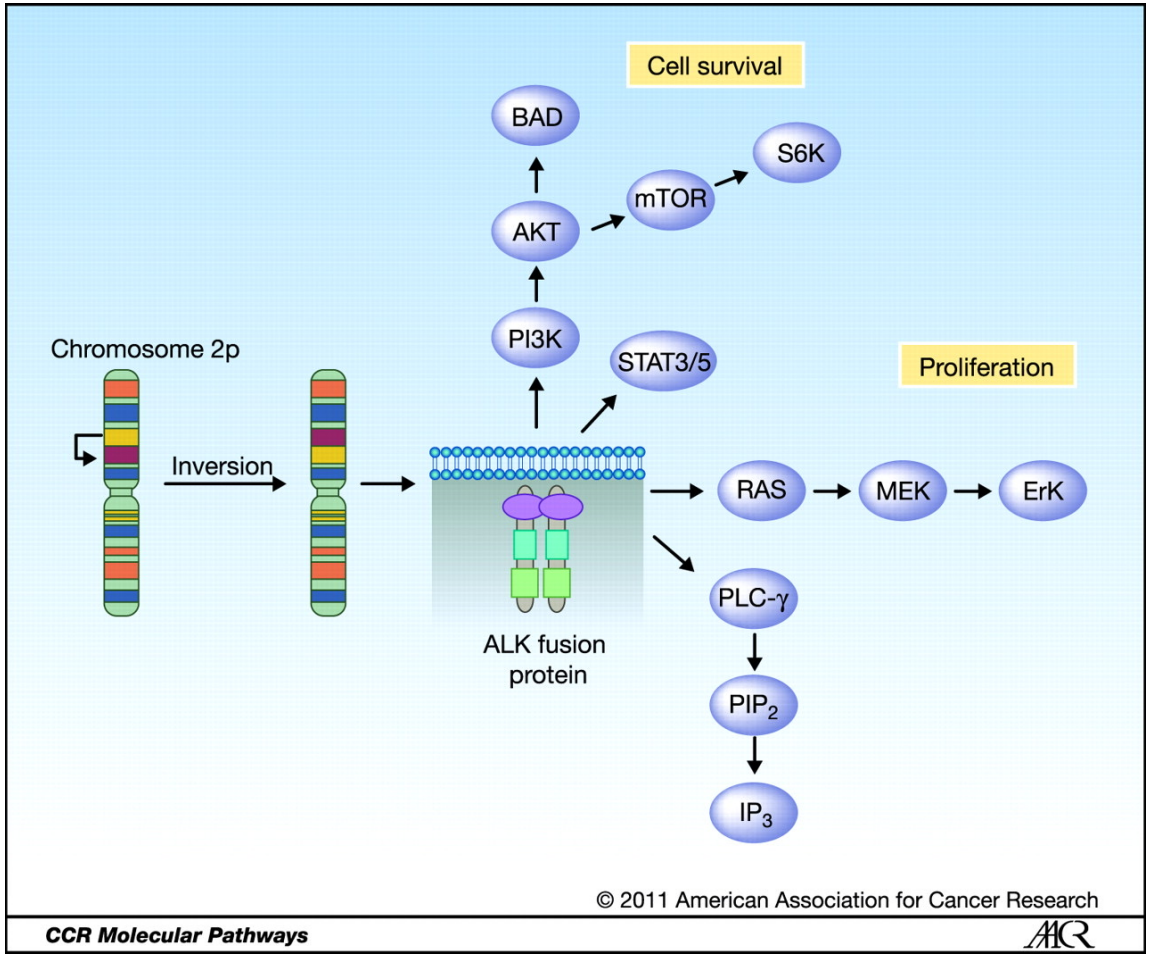
EGFR

ONCOGENE-ADDICTED NSCLC



ONCOGENE-ADDICTED NSCLC

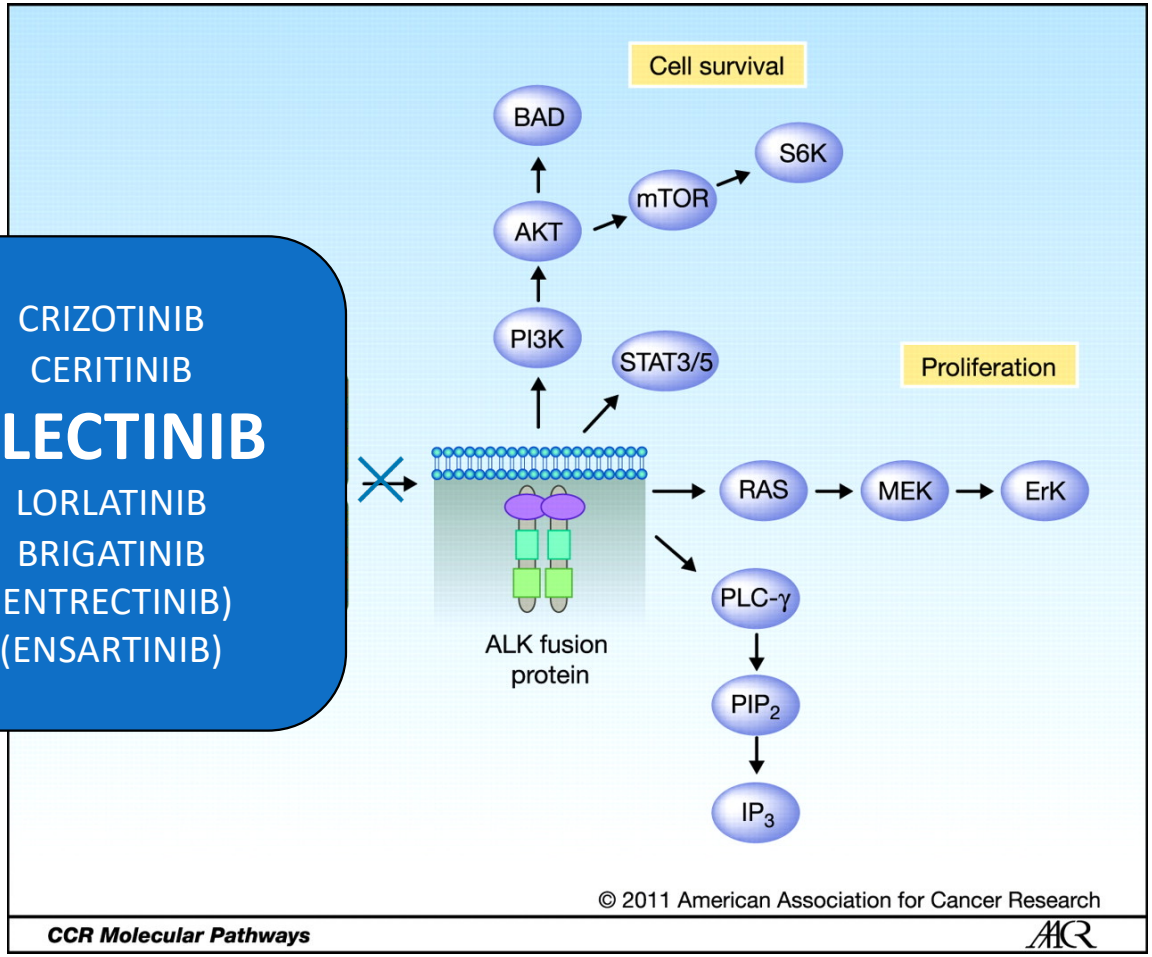
ALK



ONCOGENE-ADDICTED NSCLC

ALK

CRIZOTINIB
CERITINIB
ALECTINIB
LORLATINIB
BRIGATINIB
(ENTRECTINIB)
(ENSARTINIB)



ONCOGENE-ADDICTED NSCLC

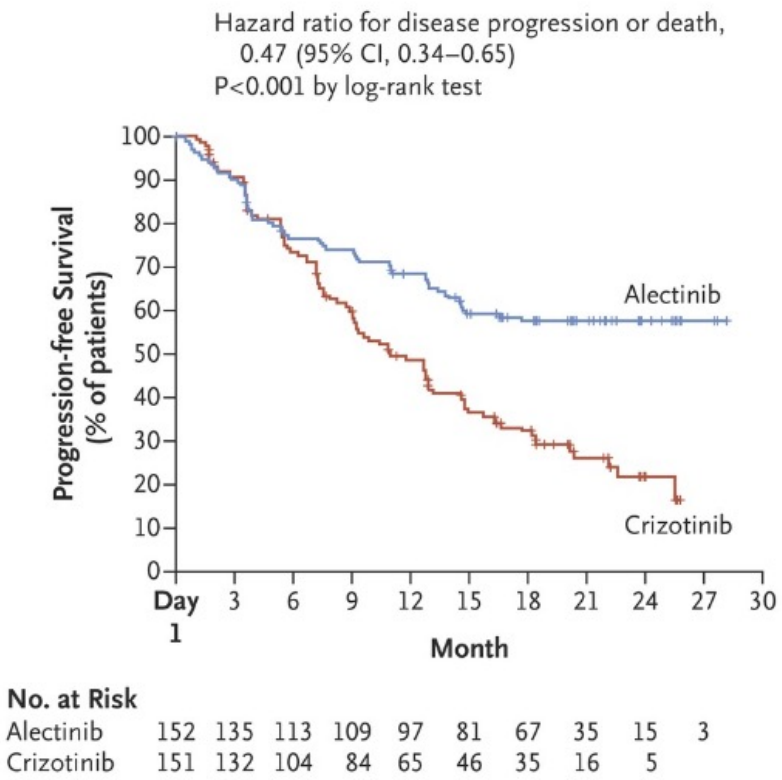
ALK

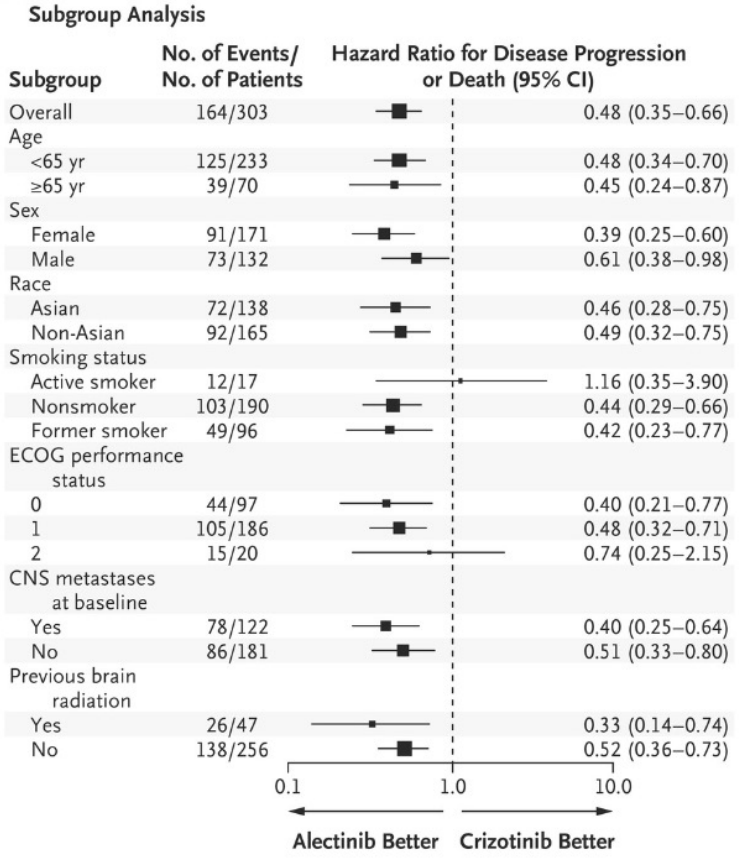
Drug name	Study	Phase	Population	vs	ORR	PFS	OS
Crizotinib	PROFILE 1007	III	Platinum-based chemotherapy pretreated (n = 347)	Pemetrexed or docetaxel	65% versus 20%	7.7 versus 3.0 months	20.3 (95% CI 18.1–not reached) versus 22.8 months
Crizotinib	PROFILE 1014	III	Previously untreated (n = 343)	Platinum plus pemetrexed	74% versus 45%	10.9 versus 7.0 months	Median OS was not reached in either group
Ceritinib	ASCEND4	III	Previously untreated (n = 376)	Platinum plus pemetrexed	72·5% vs 26%	16.6 vs 8.1 months	NA
Ceritinib	ASCEND5	III	Platinum-based chemotherapy and crizotinib pretreated (n = 231)	Pemetrexed or docetaxel	39% vs 7%	5·4 vs 1.6 months	18.1 vs 20.1 months not statistivaly significant.
Alectinib	Global study	II	Crizotinib preteated	Single arm	50%	8.9 months (95% CI, 5.6–11.3 months)	NA
Alectinib	ALEX	III	Previously untreated (n = 303)	Crizotinib	82.9% vs 75.2%	**34.8** vs 10.9 months	NA
Alectinib	J-ALEX	III	Previously untreated	Crizotinib	85% vs 70%	20.3 vs 10·2	NA
Brigatinib	NCT01449461	I/II	Previously Treated with crizotinib and naive (n = 79)	Brigatinib (30–300 mg)	71% in crizotinib-pretreated and 100% in crizotinib-naive group	13.4 months in pretreated crizotinib	NA
Brigatinib	ALTA	II	Previously treated with crizotinib and/or chemotherapy (n = 222)	Brigatinib 90 g vs 180 mg	48% (90 mg), 53% (180 mg)	9.2 and 16.7 months	NA
Lorlatinib	NCT01970865	II	6 cohorts including pts naive (275 in tot)	Lorlatinib	90% (naive)	NA	NA

Addeo A, et al. Critical reviews in Oncology/Hematology, 2018; 122:150-156

ONCOGENE-ADDICTED NSCLC

ALK

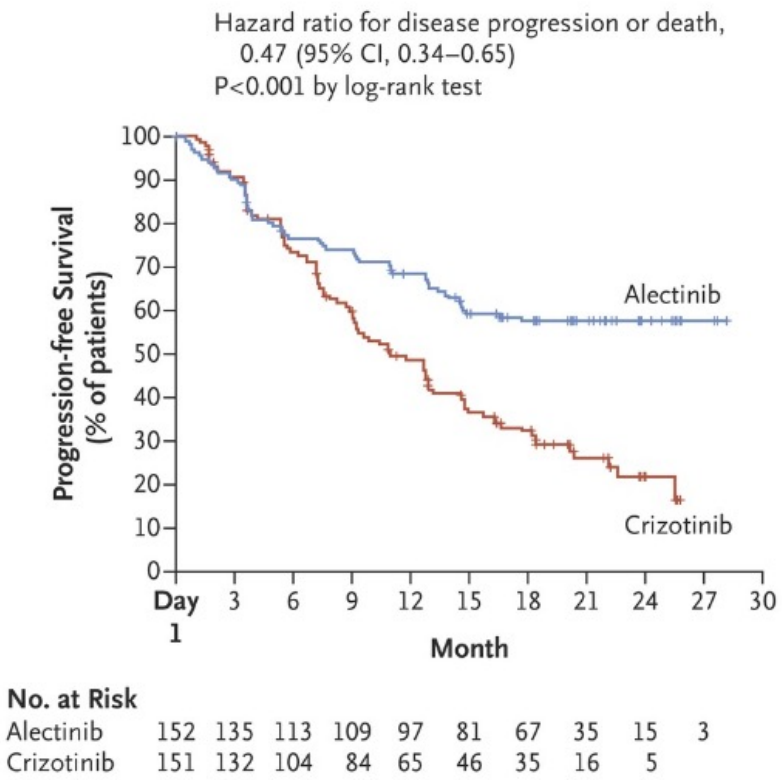


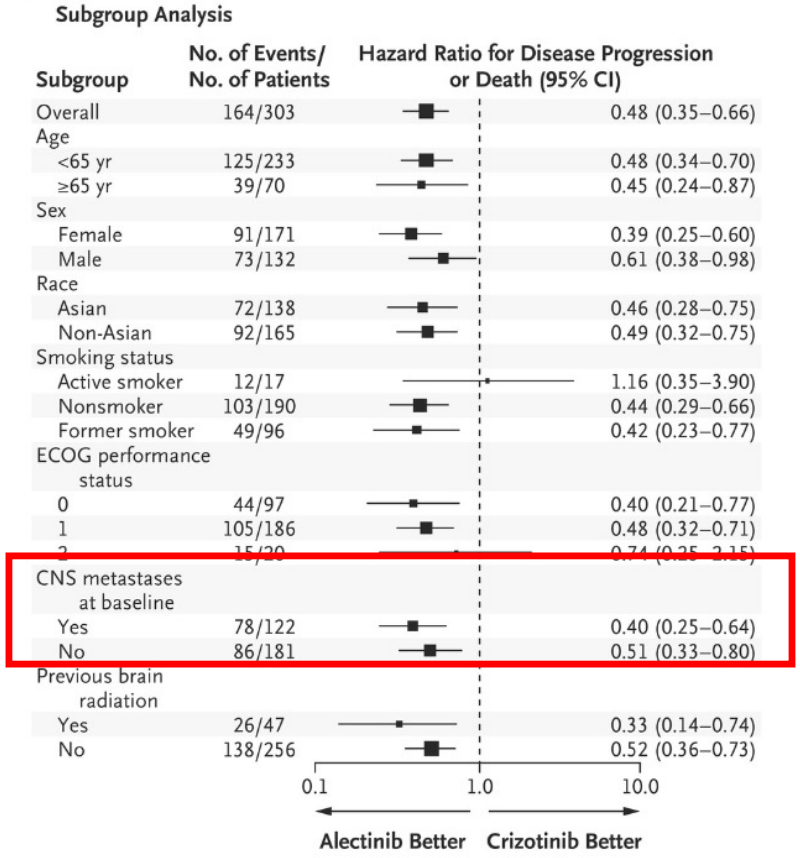


Peters S, et al. NEJM 2017; 377(9):829-838

ONCOGENE-ADDICTED NSCLC

ALK





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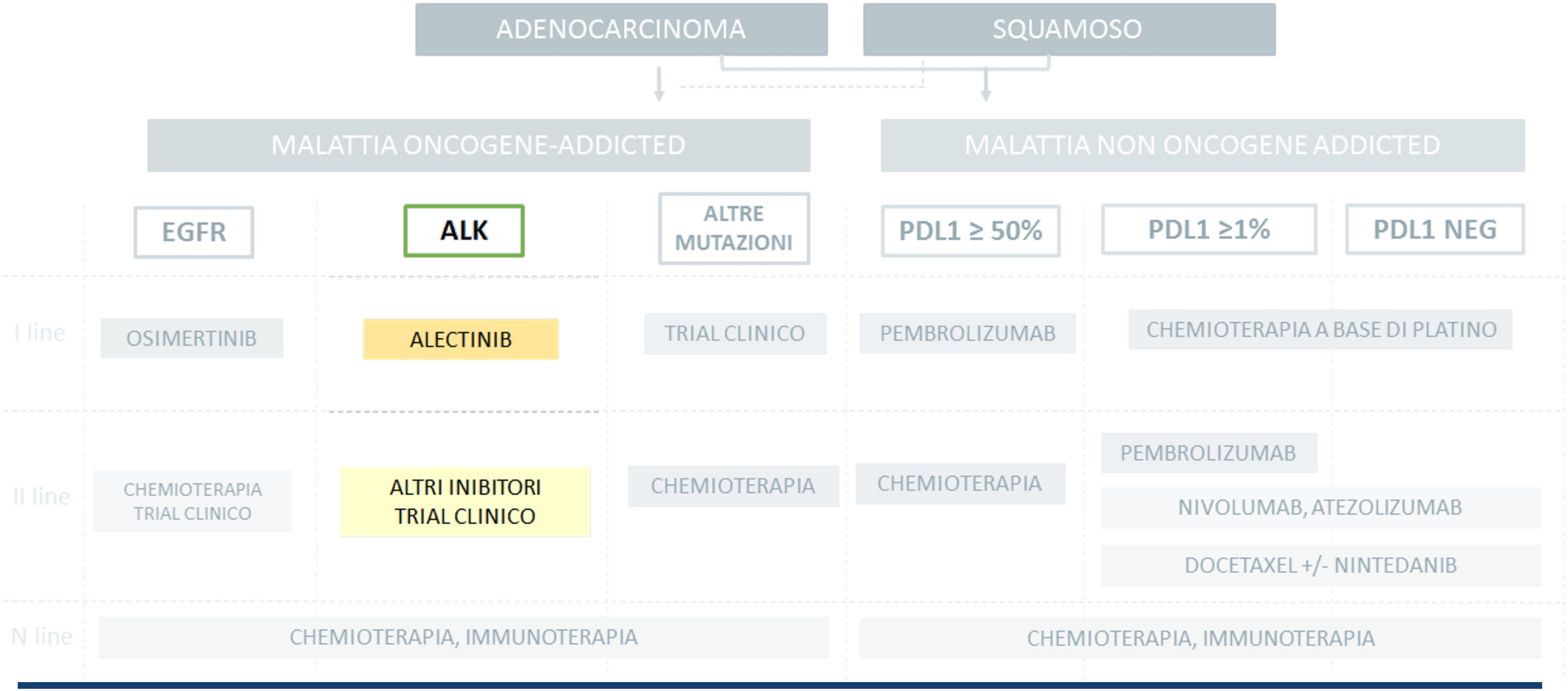
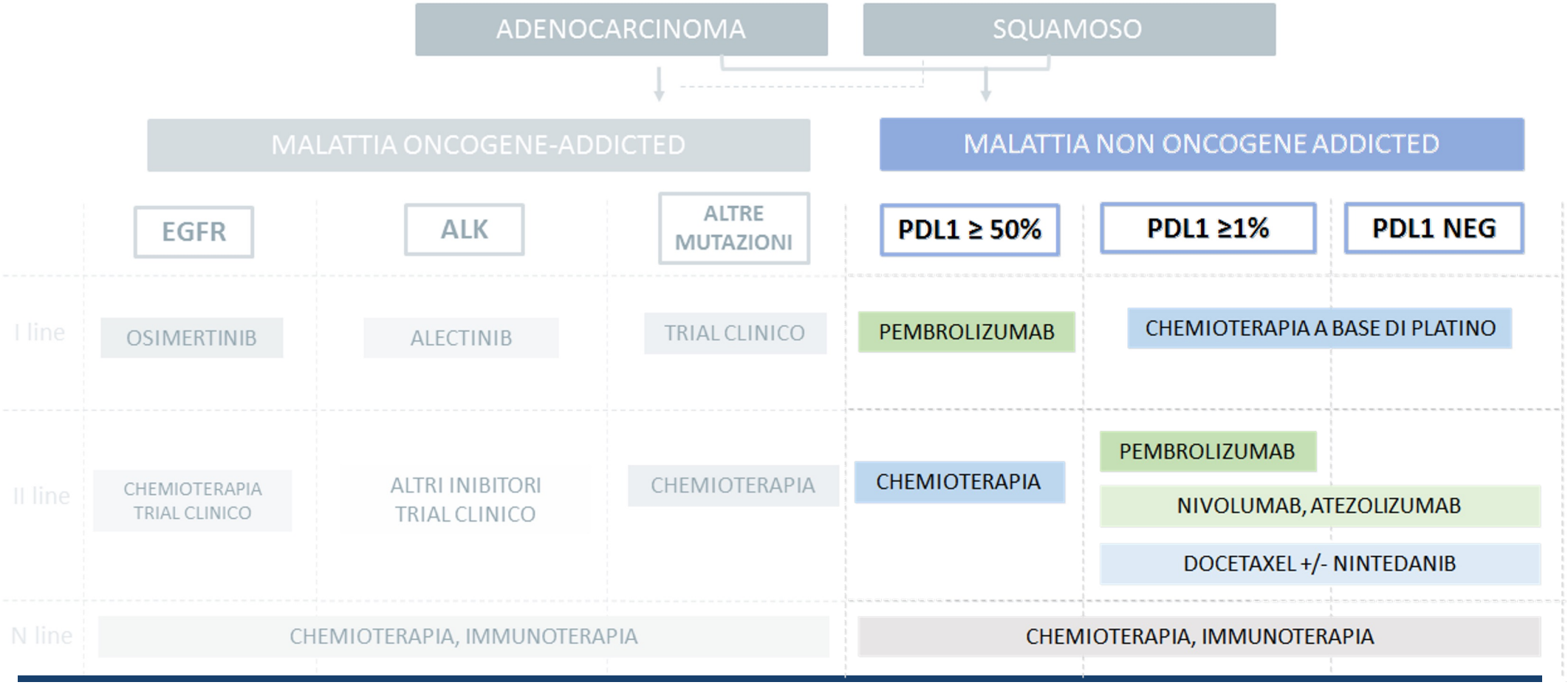
ONCOGENE-ADDICTED NSCLC

ALK



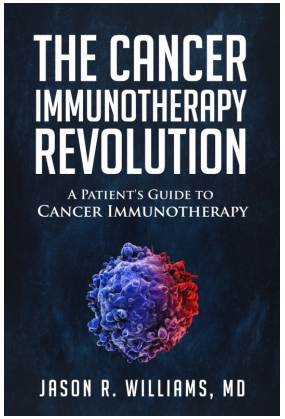
NON ONCOGENE-ADDICTED NSCLC

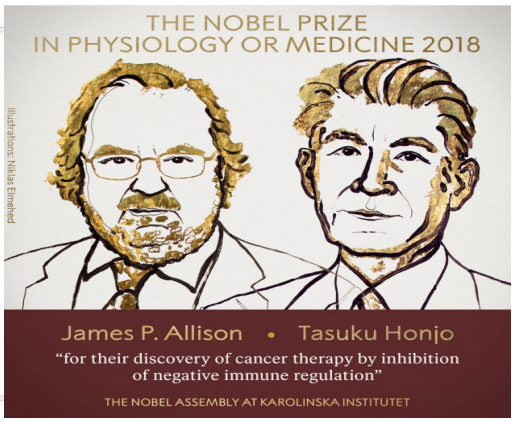


NON ONCOGENE-ADDICTED NSCLC

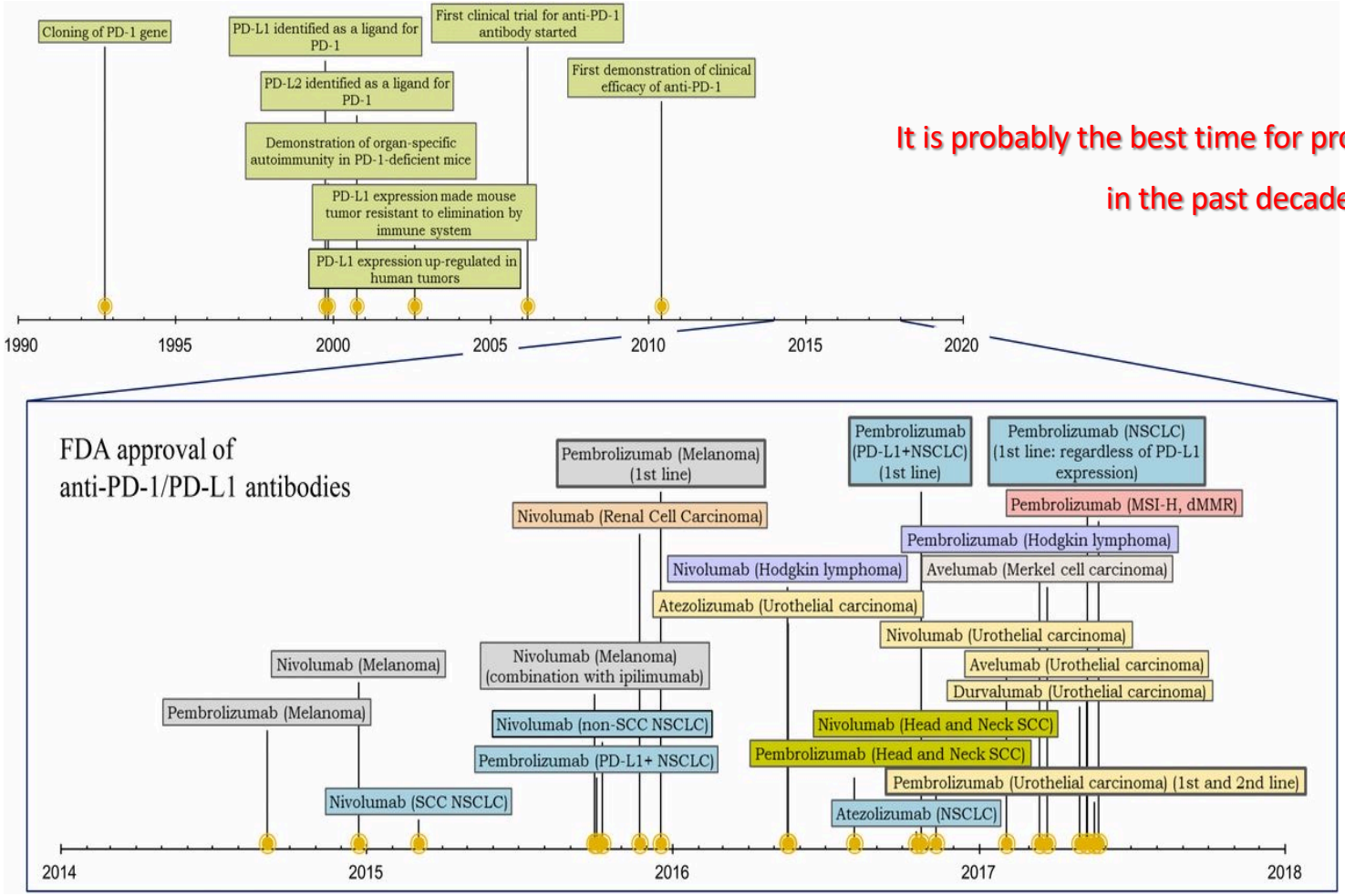
The era of immunotherapy

A SCIENTIFIC REVOLUTION



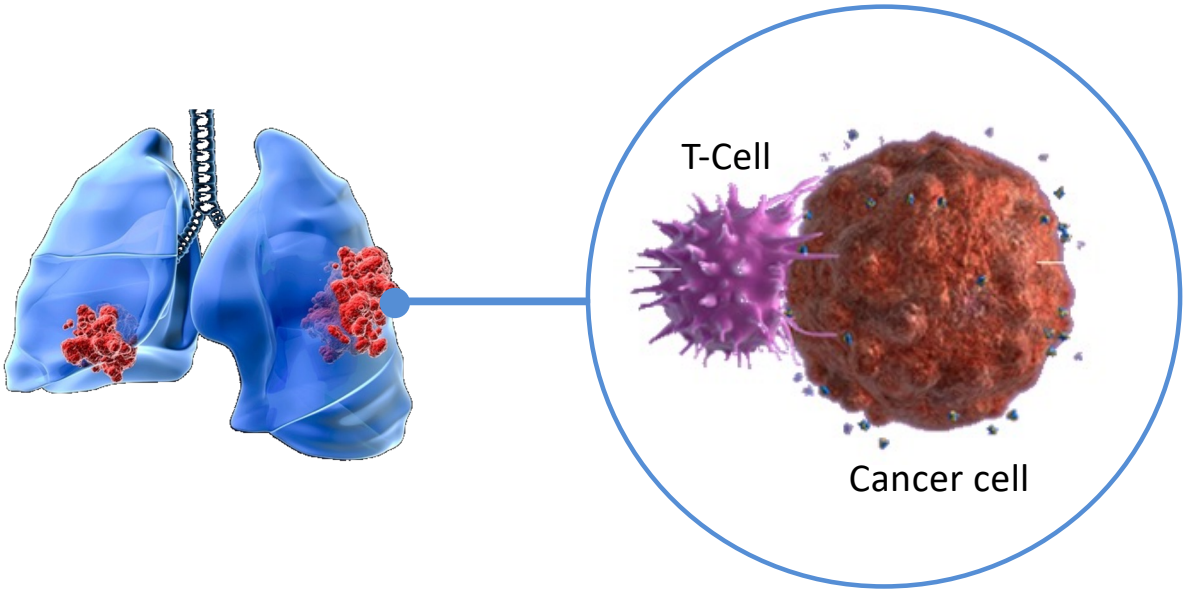


A THERAPEUTIC REVOLUTION



It is probably the best time for progress in oncology in the past decades!

A CONCEPTUAL REVOLUTION



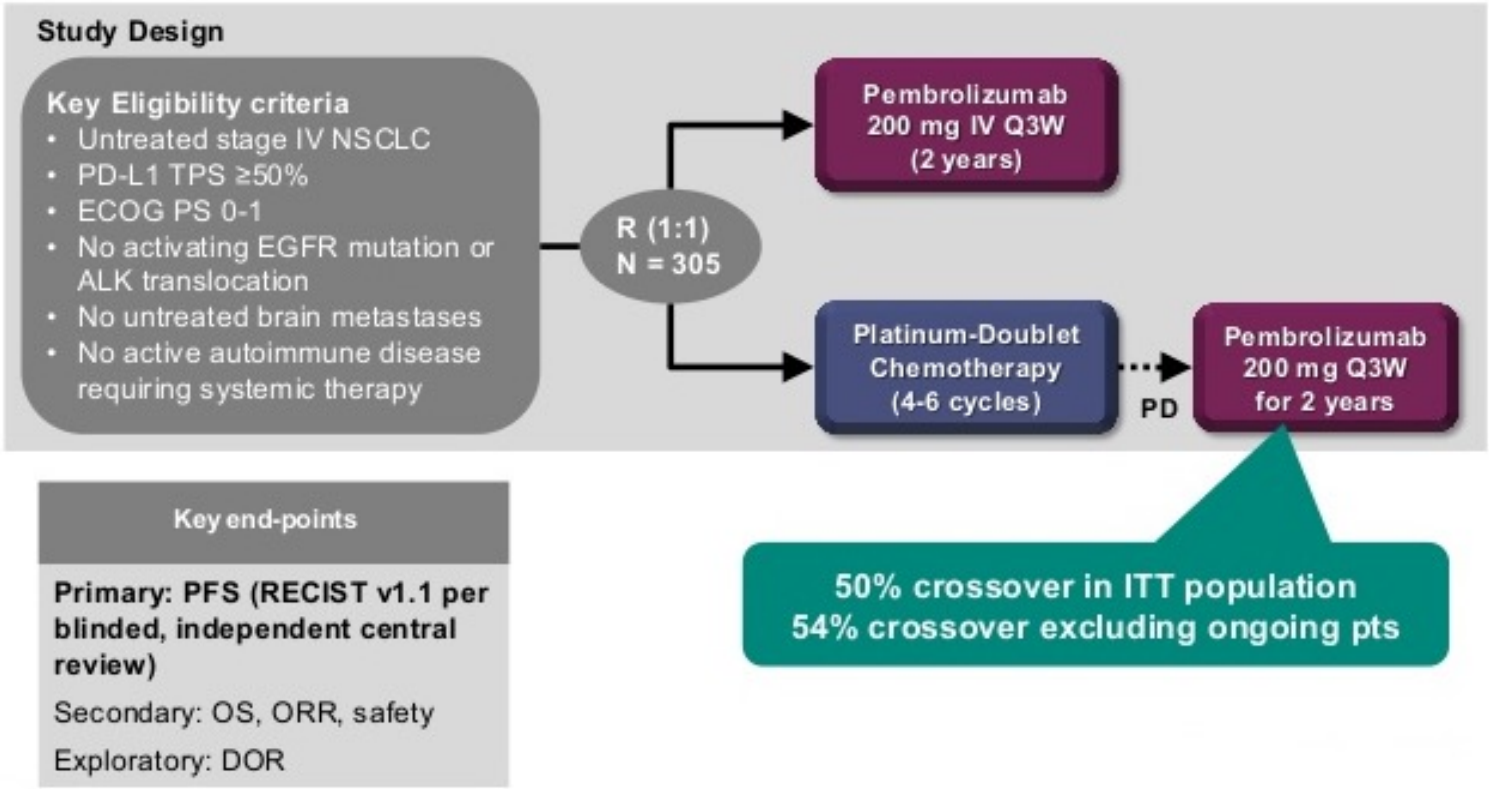
Lung cancer is an "immunogenic" tumor that can respond to immunotherapy treatment

IMMUNOTHERAPY IN NSCLC

IMMUNOTHERAPY IN NSCLC

PEMBROLIZUMAB

Keynote 024

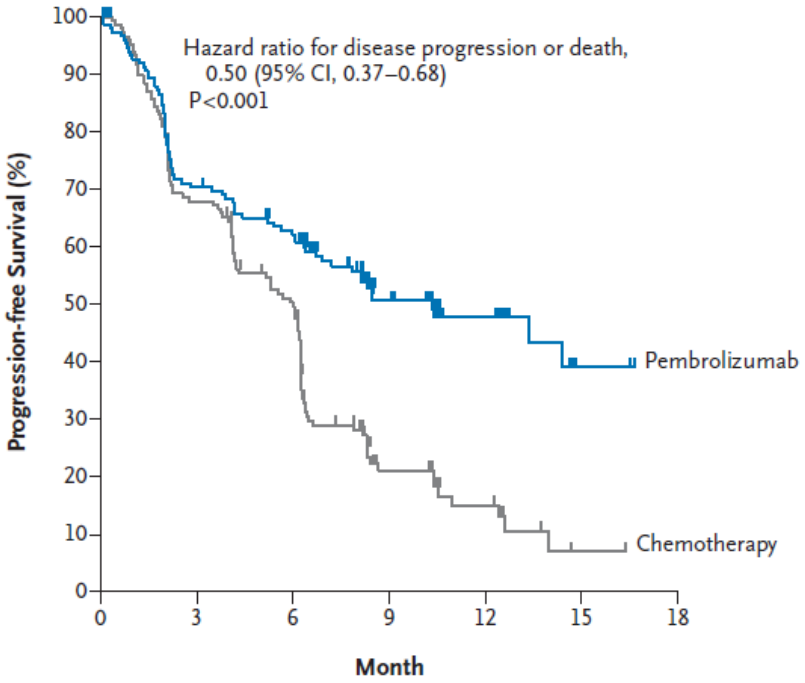


Reck M, et al. NEJM 2016; 375(19):1823-1833

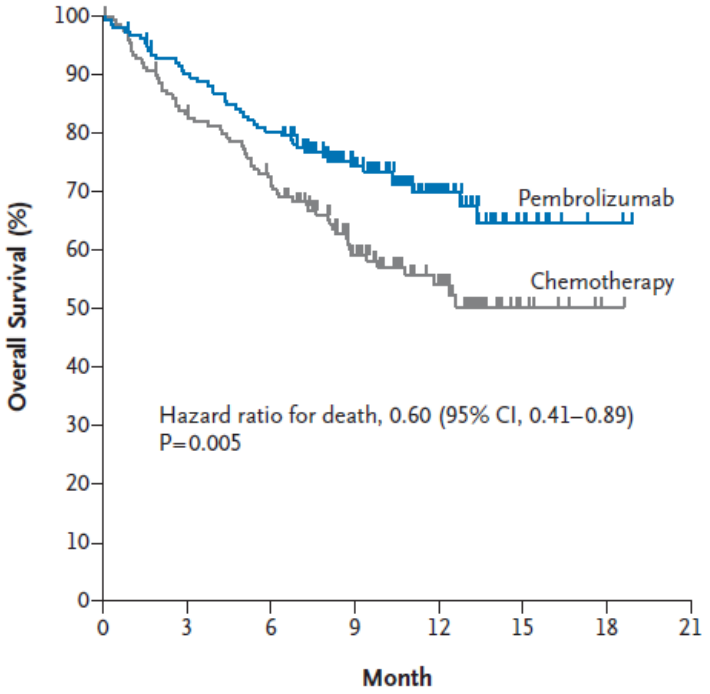
IMMUNOTHERAPY IN NSCLC

PEMBROLIZUMAB

Keynote 024



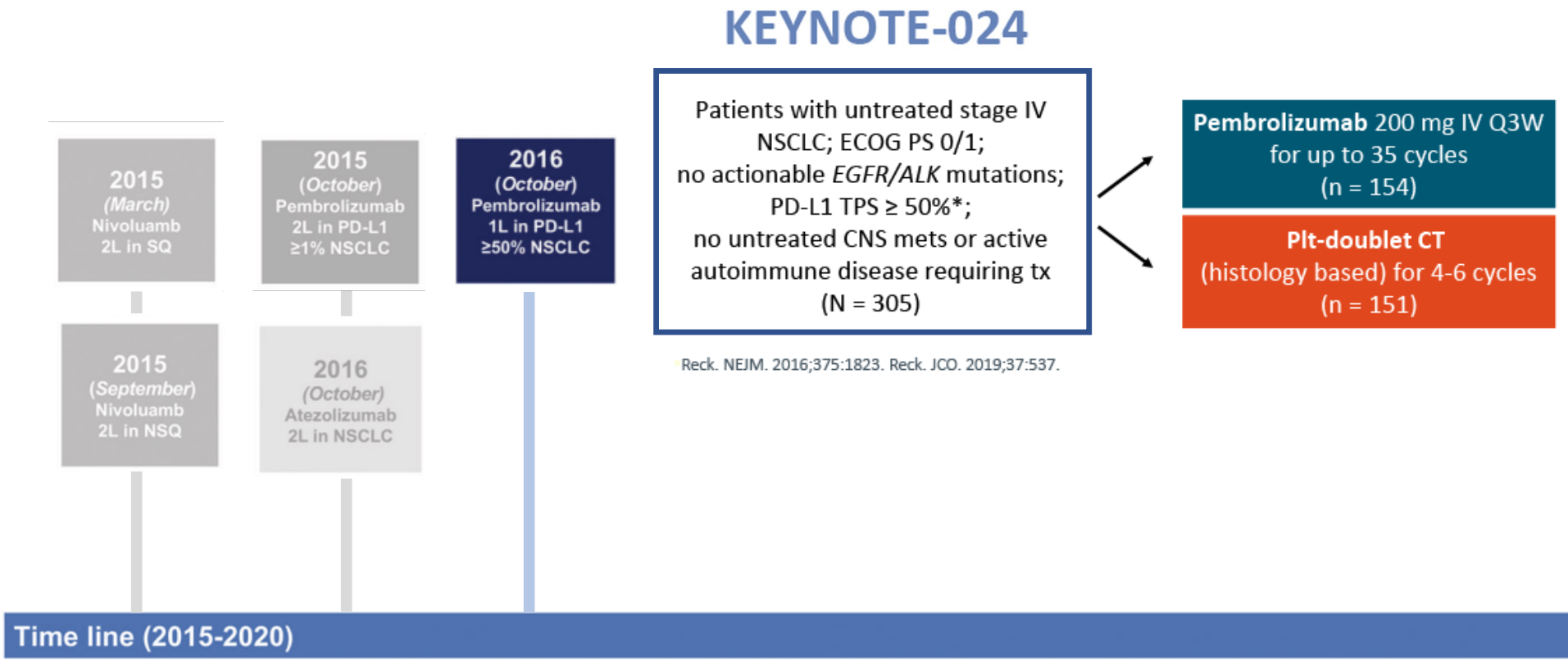
No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0



No. at Risk								
Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

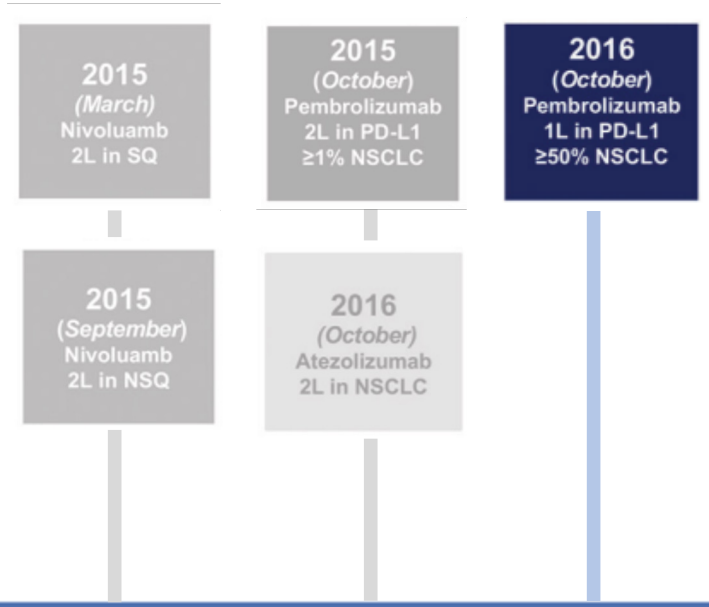
Reck M, et al. NEJM 2016; 375(19):1823-1833

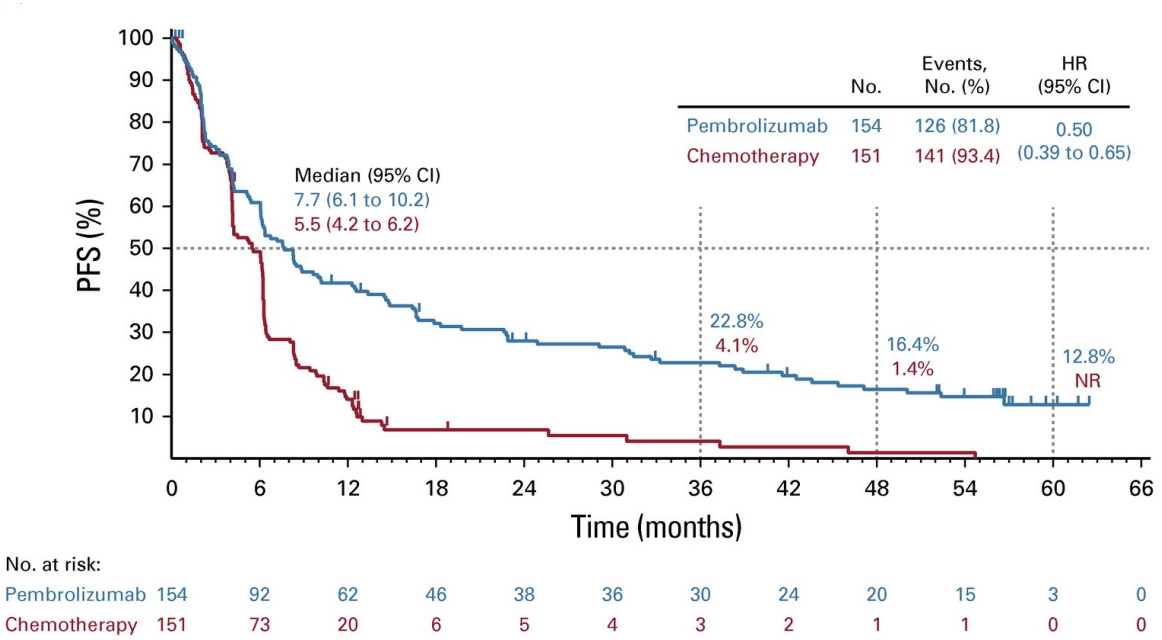
THE ERA OF IMMUNOTHERAPY



Zhou F, et al. Cell Mol Immunol. 2021; 18(2):279-293

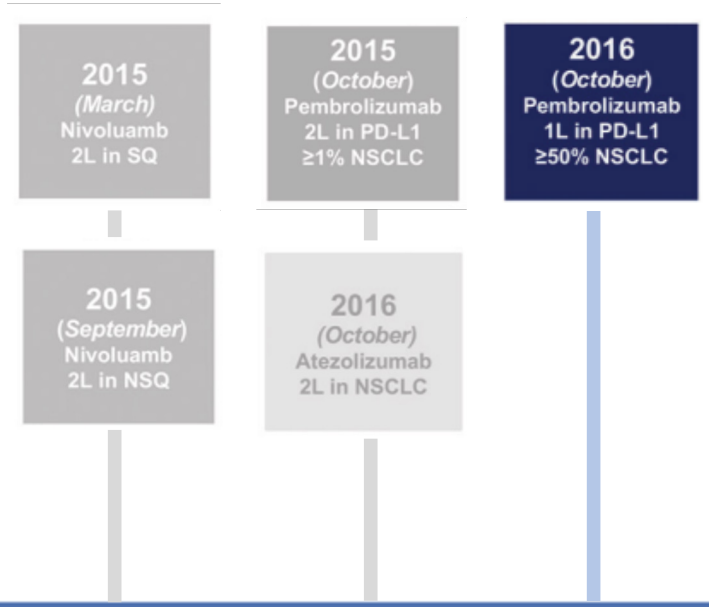
THE ERA OF IMMUNOTHERAPY

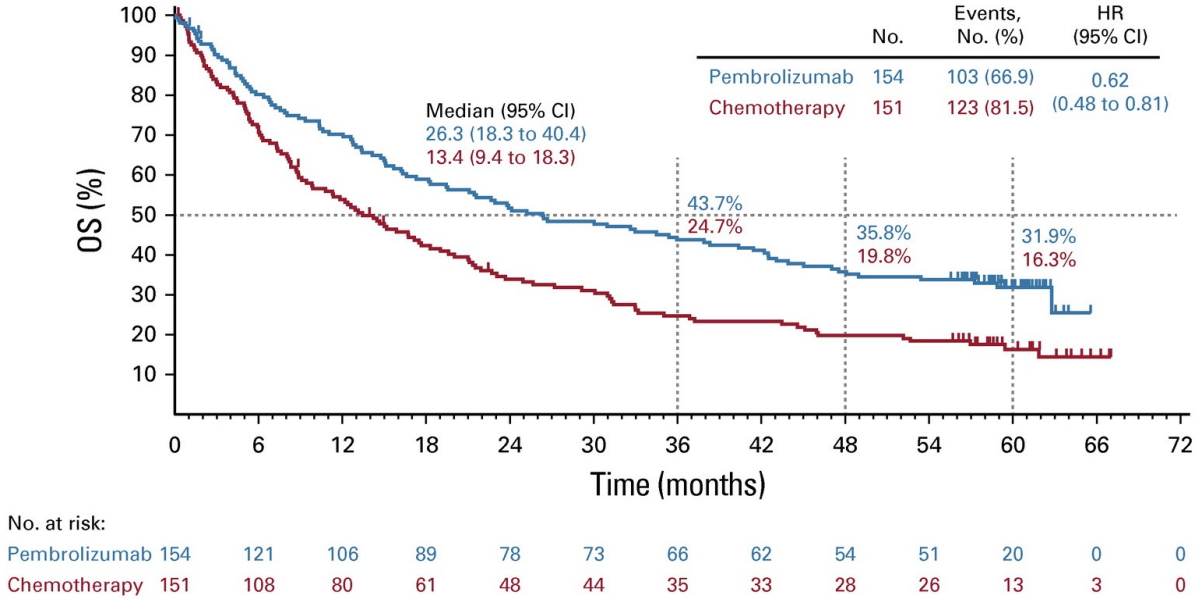




Reck M, et al. J Clin Oncol. 2021; 39(21):2339-2349

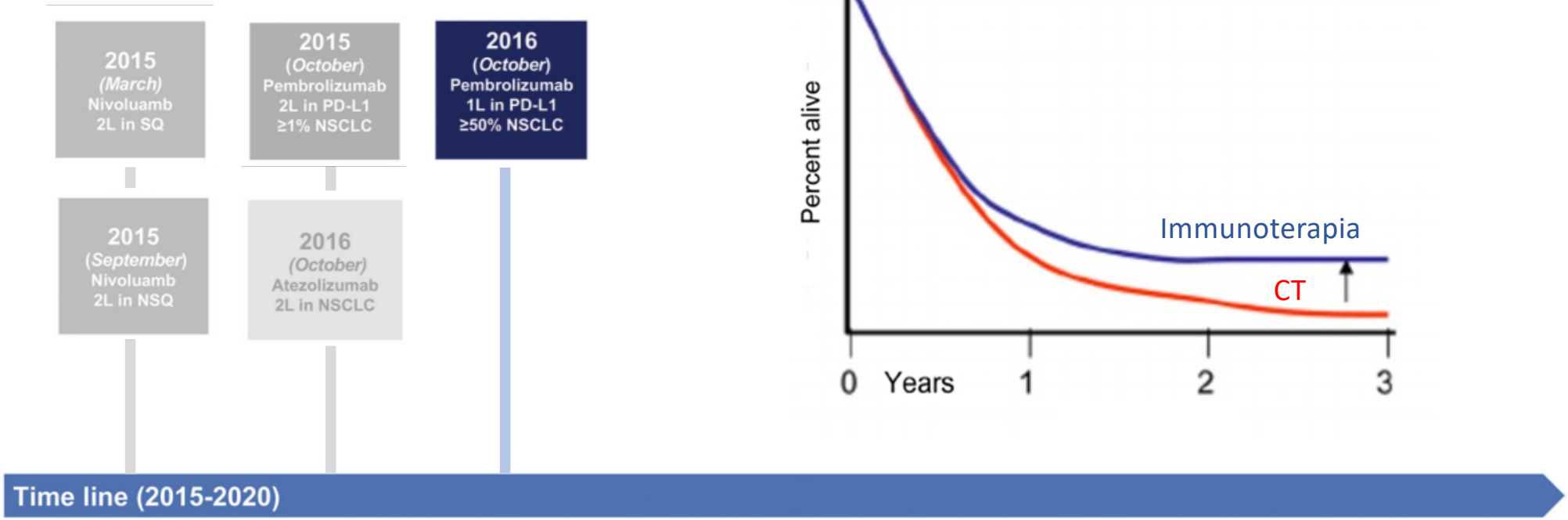
THE ERA OF IMMUNOTHERAPY



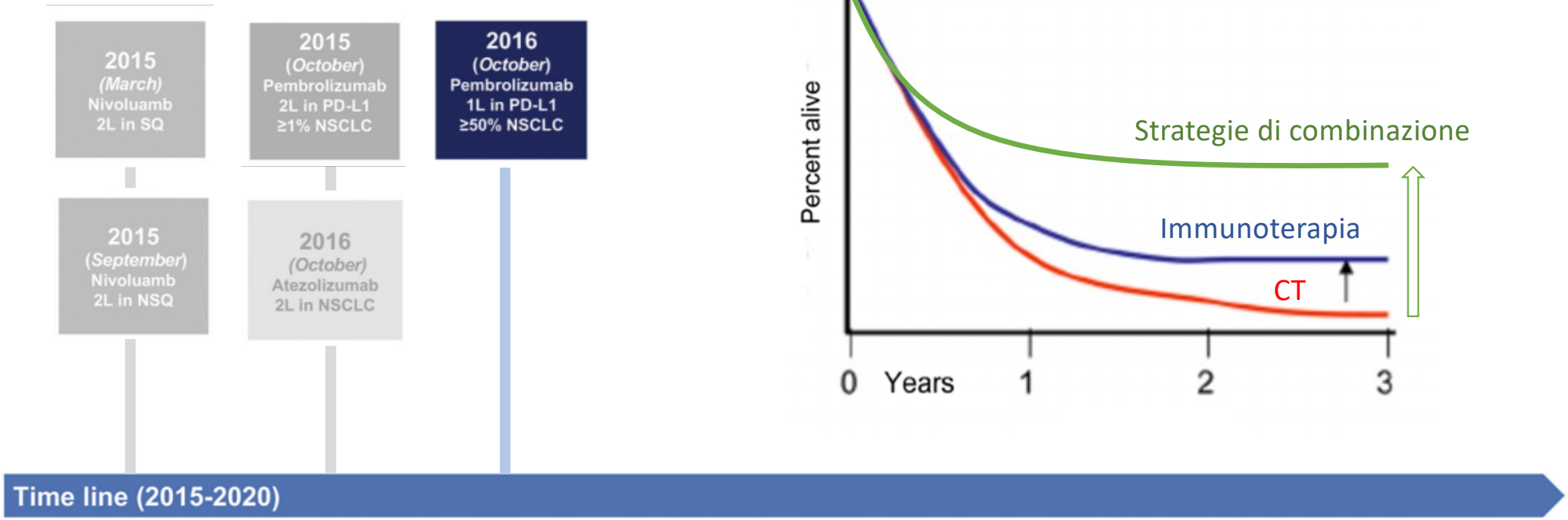


Reck M, et al. J Clin Oncol. 2021; 39(21):2339-2349

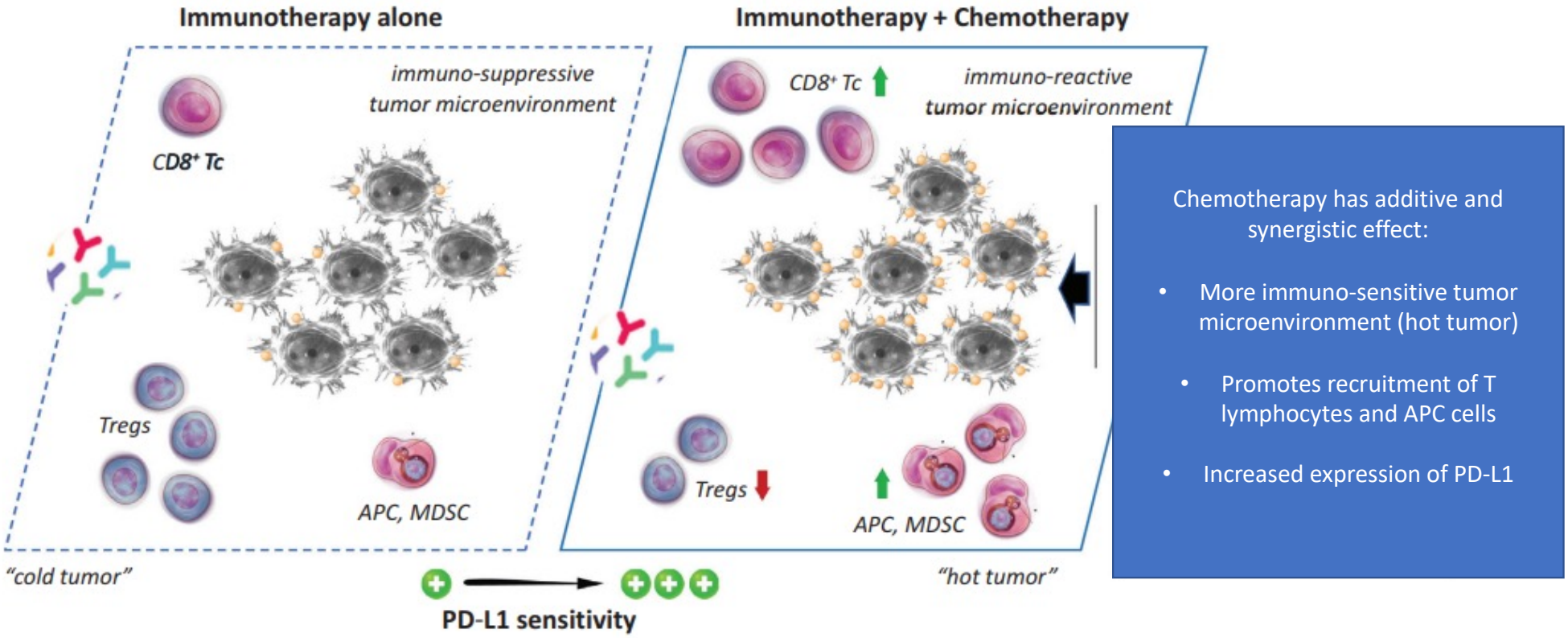
THE ERA OF IMMUNOTHERAPY



THE ERA OF IMMUNOTHERAPY



IMMUNOTHERAPY AND CHEMOTHERAPY

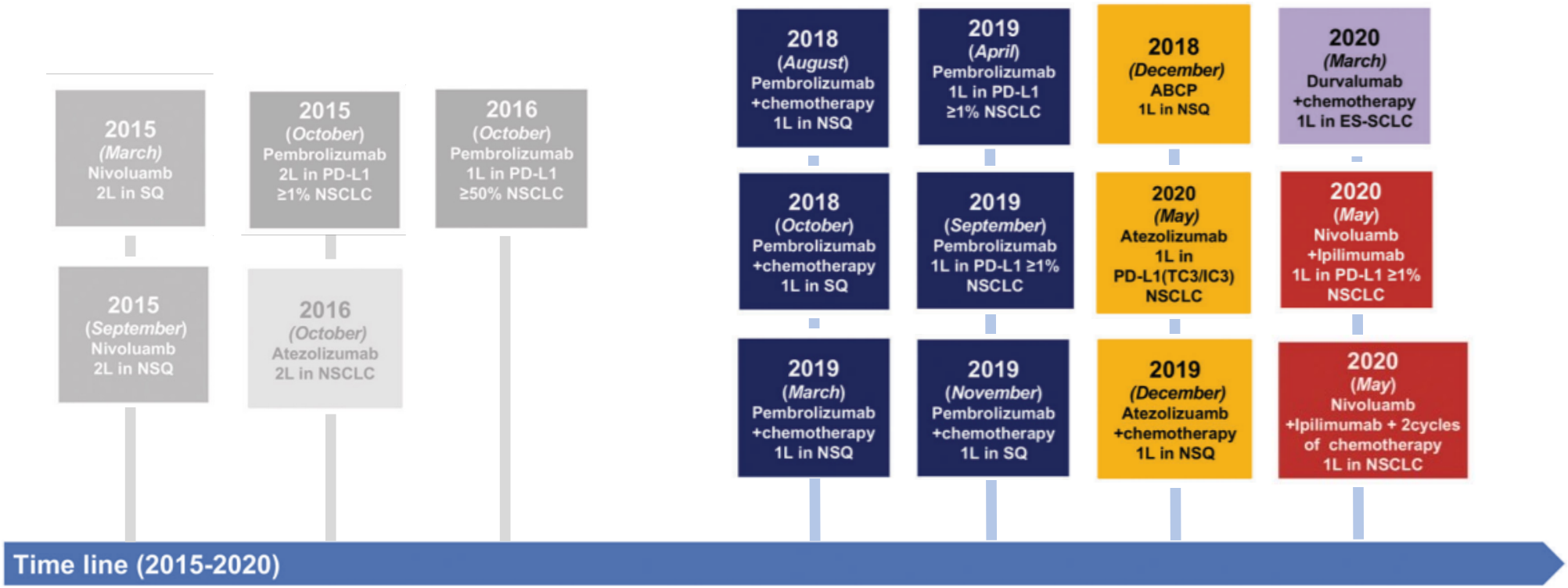


Chemotherapy has additive and synergistic effect:

- More immuno-sensitive tumor microenvironment (hot tumor)
- Promotes recruitment of T lymphocytes and APC cells
- Increased expression of PD-L1

Bailly C, et al. Combined cytotoxic chemotherapy and immunotherapy of cancer: modern times. NAR Cancer. 2020

STRATEGIES OF COMBINATION

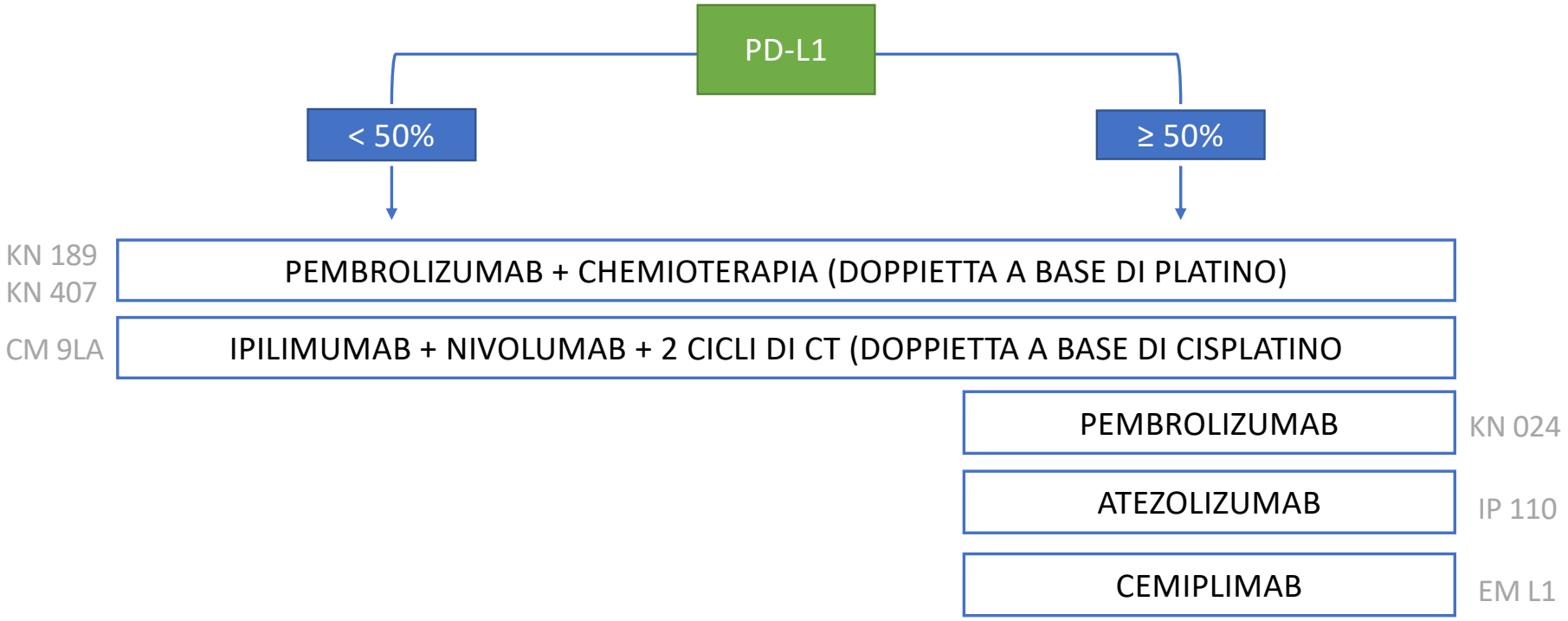


Zhou F, et al. Cell Mol Immunol. 2021; 18(2):279-293

FIRST-LINE STUDIES WITH BENEFIT IN OS

	TRIAL	DETAILS	HISTOLOGY	PD-L1	mOS (months)
SINGLE AGENT	KEYNOTE 024	Pembrolizumab vs Platinum-based ChT	NSCLC	PD-L1 ≥50%	26.3 vs 13.4
	IMpower110	Atezolizumab vs Platinum-based ChT	NSCLC	PD-L1 ≥50%	20.2 vs 13.1
	EMPOWER-Lung1	Cemiplimab vs Platinum-based ChT	NSCLC	PD-L1 ≥50%	26.1 vs 13.3
COMBINATION STRATEGIES	KEYNOTE 189	Pembrolizumab + Platinum-pemetrexed vs Placebo + Platinum-pemetrexed	NS-NSCLC	All comers	22.0 vs 10.6
	KEYNOTE 407	Pembrolizumab + Carboplatin and paclitaxel vs Placebo + Carboplatin and paclitaxel	Squamous NSCLC	All comers	17.1 vs 11.6
	IMpower130	Atezolizumab + Carboplatin plus nab-paclitaxel vs Carboplatin plus nab-paclitaxel	NS-NSCLC	All comers	18.6 vs 13.9
	EMPOWER-Lung3	Cemiplimab + Platinum-based ChT vs Cht alone	NSCLC	All comers	21.9 vs 13
	GEMSTONE 302	Sugemalimab + ChT vs Platinum-doublet ChT	NSCLC	All comers	25.4 vs 16.9
	Poseidon	Durvalumab + Tremelimumab + ChT vs Platinum-doublet ChT	NSCLC	All comers	14.0 vs 11.7
	CheckMate 227	Nivolumab + Ipilimumab vs Platinum doublet ChT	NSCLC	PD-L1 ≥ 1%	17.1 vs 13.9
	CheckMate 9LA	Nivolumab+Ipilimumab and Platinum doublet ChT vs Platinum doublet ChT	NSCLC	All comers	15.9 vs 10.9

FIRST-LINE TREATMENT IN NSCLC NON-ONCOGENE ADDICTED



FIRST-LINE TREATMENT IN NSCLC NON-ONCOGENE ADDICTED

PD-L1

< 50%

KN 189
KN 407 — PEMBROLIZUMAB + CHEMIOTERAPIA

CM 9LA — IPILIMUMAB + NIVOLUMAB + 2 CICLI DI CT

≥ 50%

AIFA AGENZIA ITALIANA DEL FARMACO

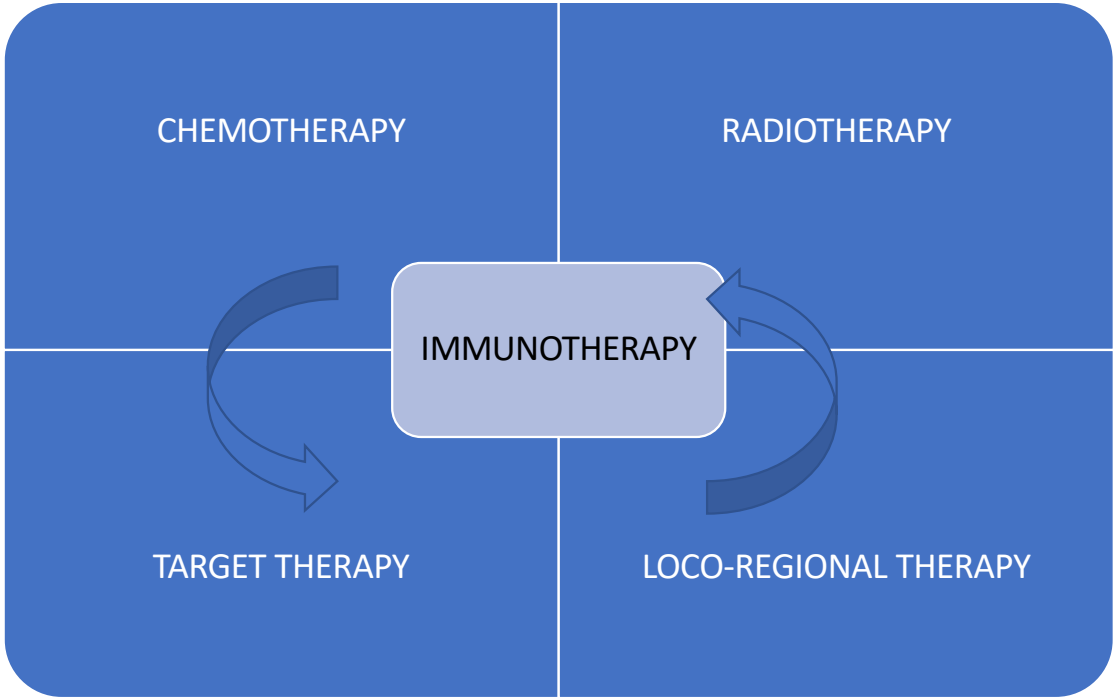
PEMBROLIZUMAB — KN 024

ATEZOLIZUMAB — IP 110

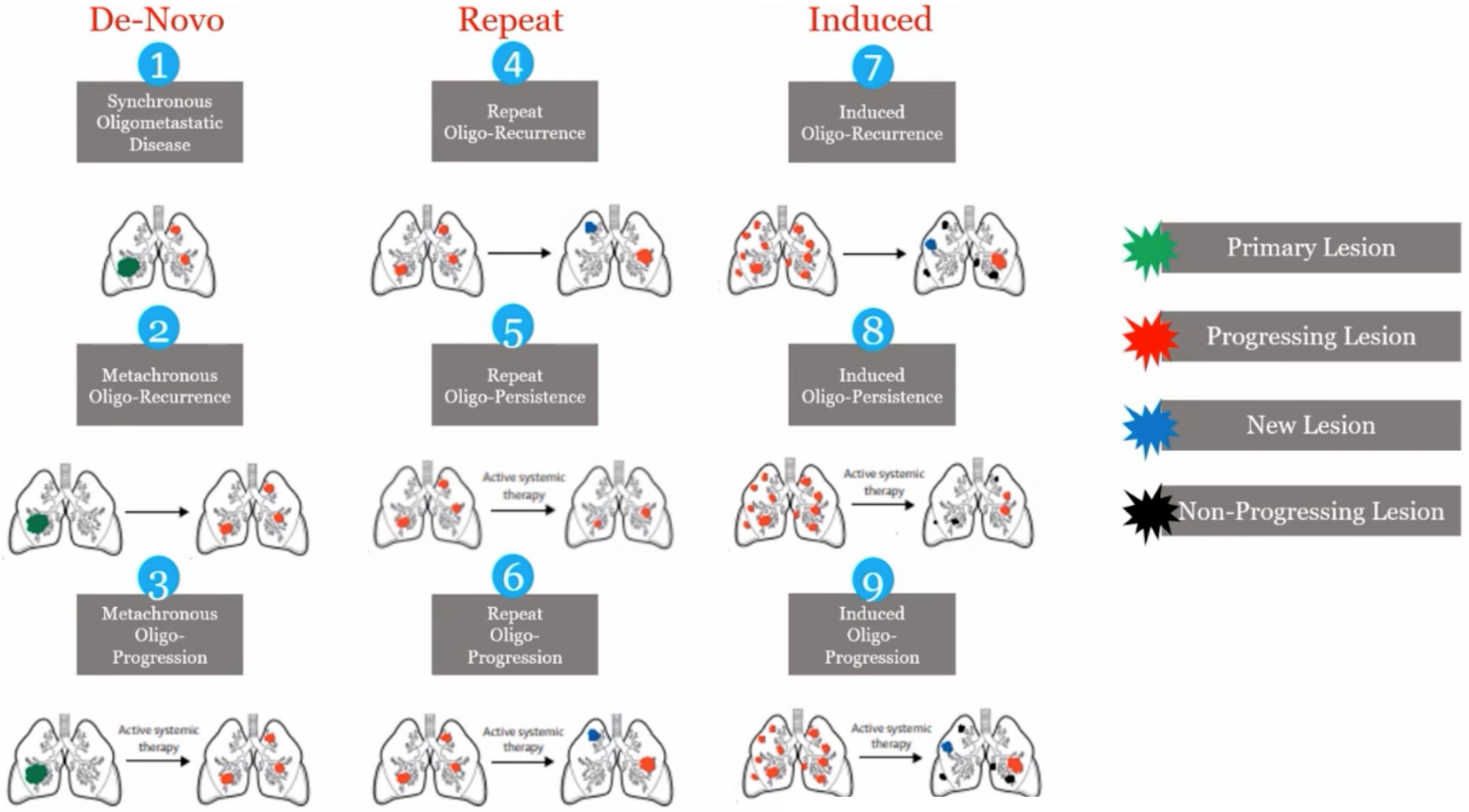
CEMIPLIMAB — EM L1

WHAT'S NEXT?

COMBINATION STRATEGIES



Oligometastatic Disease: Nine Clinical Scenarios



Guckenberger M, et al. Lancet Oncol 2020; 21: e18–28

Oligometastatic NSCLC

1. Do patients with OM NSCLC benefit from local therapies?
2. When should local therapy be administered?
3. The choice of the target (volume and dose)

Do patients with OM NSCLC benefit from local therapies?

"BETTER-THAN-EXPECTED" SURVIVAL after local treatment (RETROSPECTIVE DATA)

Inoue T et al, Jpn J Clin Oncol 2010: 41 pts with <5 M+ (25 NSCLC)
Median survival 24 months; PFS 10 months, 3y OS 39%, 3y PFS 20%

Collen et al, Annals of Oncol 2014: 26 pts with <5 M+
Median survival 23 months, PFS 11.2 months

Owen D et al. Radiat Oncol 2015: 63 pts with LUNG NODULES (40 from NSCLC)
Median survival 35 months, PFS 10.7 months

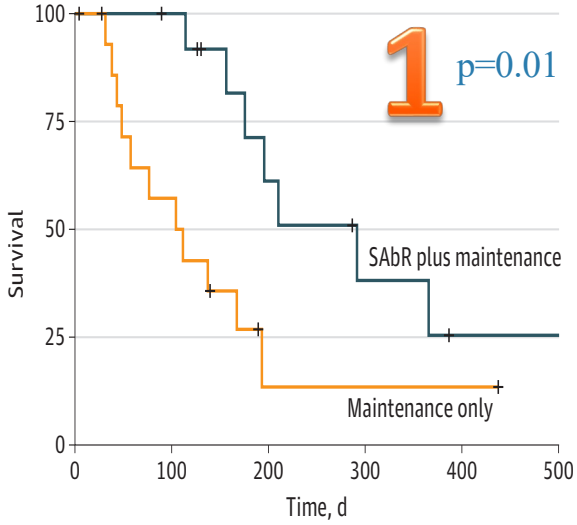
Do patients with OM NSCLC benefit from local therapies?

Prospective Trials and RANDOMIZED DATA on LCT in oligoMets
NON ONCOGENE-ADDICTED NSCLC

Trial	N° patients	PFS (months)	Notes
De Ruysscher D *J Thorac Oncol 2012*	39	12.1	OS: 13.5months
Hughes RT *Int J Radiat Oncol Biol Phys 2017*	26	11.2	Closed early
Gomez D (RANDOM PHASE II) Lancet Oncology 2016	49/94	11.9 vs 3.9	**Time to new site failure** **11.9 vs 5.7** IDMC closed
Iyengar P (RANDOM PHASE II) JAMA Oncol. 2018	29/30	9.7 vs 3.5	IDMC closed

Do patients with OM NSCLC benefit from local therapies?

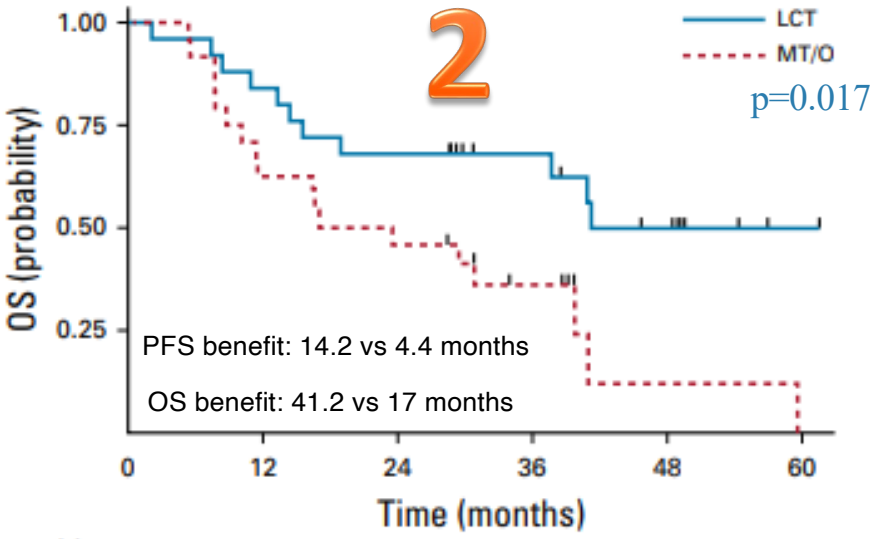
Randomized evidences for LCT in Oligometastatic NSCLC



No. at risk

SAbR plus maintenance	14	12	6	3	1
Maintenance only	15	8	1	1	1

Iyengar et al., *JAMA Oncol* 2018



No. at risk

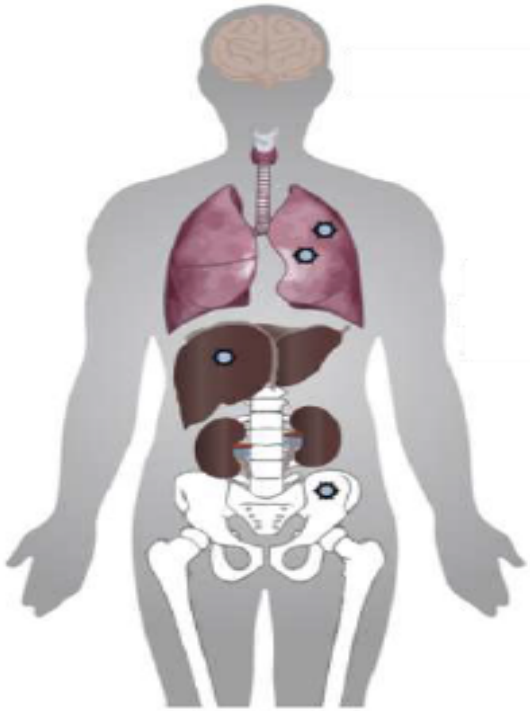
LCT:	25	21	17	12	7	1
MT/O:	24	15	11	6	1	0

Gomez et al., *J Clin Oncol* 2019

2018

ASTRO
TARGETING CANCER CARE

60TH ANNUAL MEETING
Translating Discovery to Cure
ASTRO'S

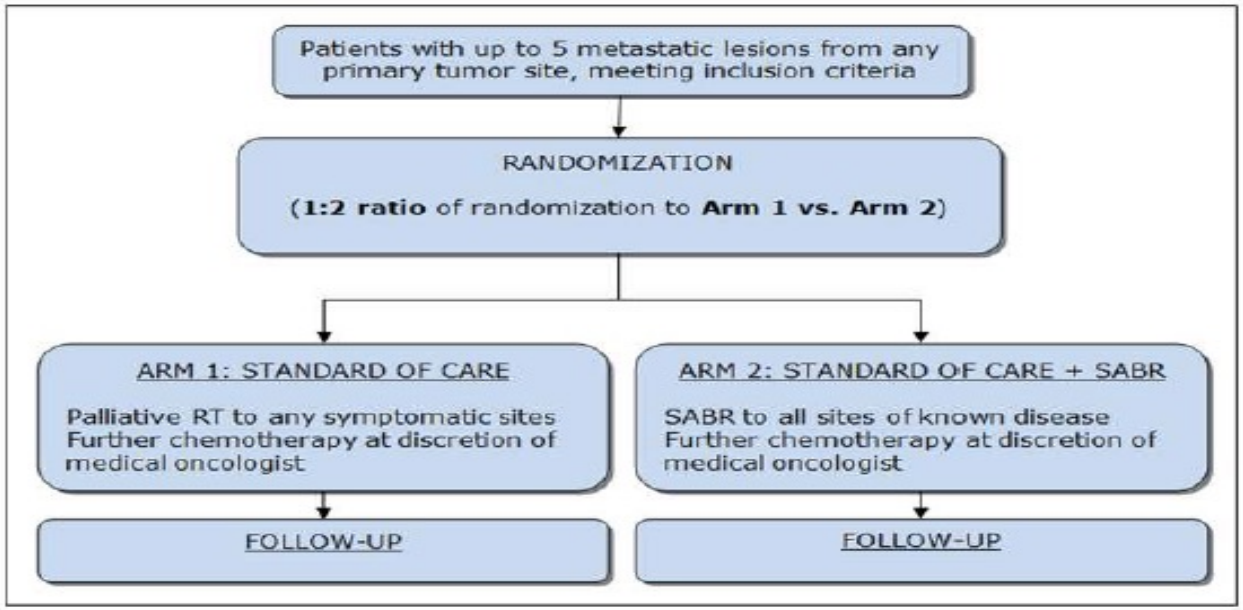


SABR-COMET: Stereotactic Radiation for the Comprehensive Treatment of Oligometastatic Cancers – Results of a Randomized Study

D. Palma, R. Olson, S. Harrow, S. Gaede, A. Louie, C. Haasbeek, L. Mulroy, M. Lock, G. Rodrigues, B. Yaremko, D. Schellenberg, B. Ahmad, G. Griffioen, S. Senthi, A. Swaminath, N. Kopek, M. Liu, K. Moore, S. Currie, G. Bauman, A. Warner, S. Senan

Western
UNIVERSITY · CANADA

SABR-COMET Schema

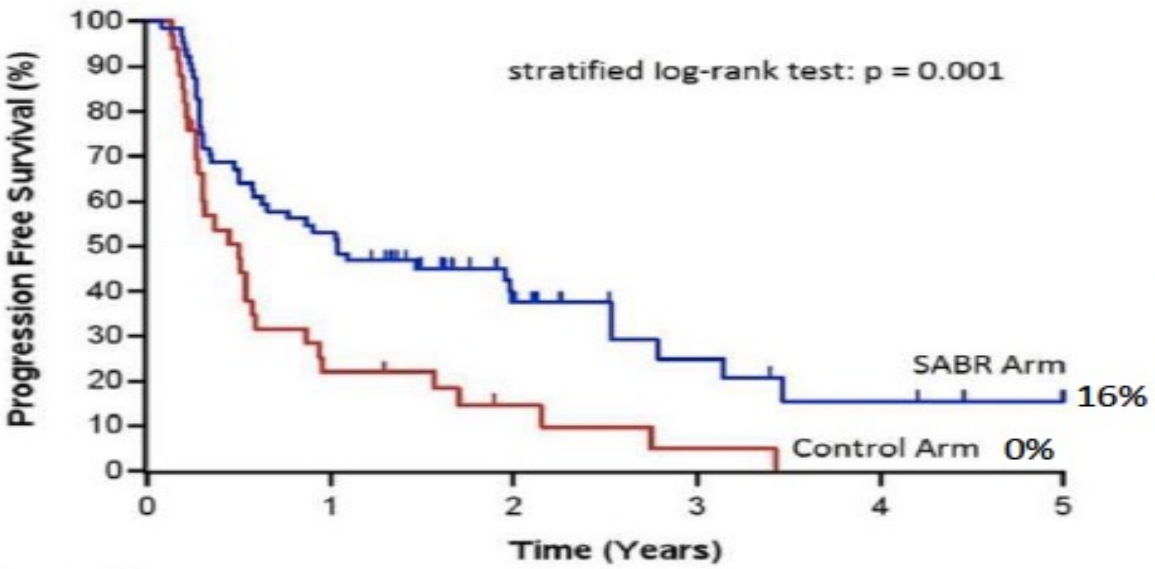


Baseline Characteristics

Between February 2012 and August 2016, **99 patients** were randomized at centres in Canada, Scotland, Netherlands and Australia

Characteristic	All Patients (n=99)
Age – median, (min, max)	68 (43, 89)
Sex – n(%)	
Male	59 (59.6)
Female	40 (40.4)
Site of Original Primary Tumor – n(%)	
Breast	18 (18.2)
Colorectal	18 (18.2)
Lung	18 (18.2)
Prostate	16 (16.2)
Other	29 (29.3)

Progression-Free Survival



Number at risk:						
Control	33	7	3	1		
SABR	66	34	15	6	3	1

Median PFS

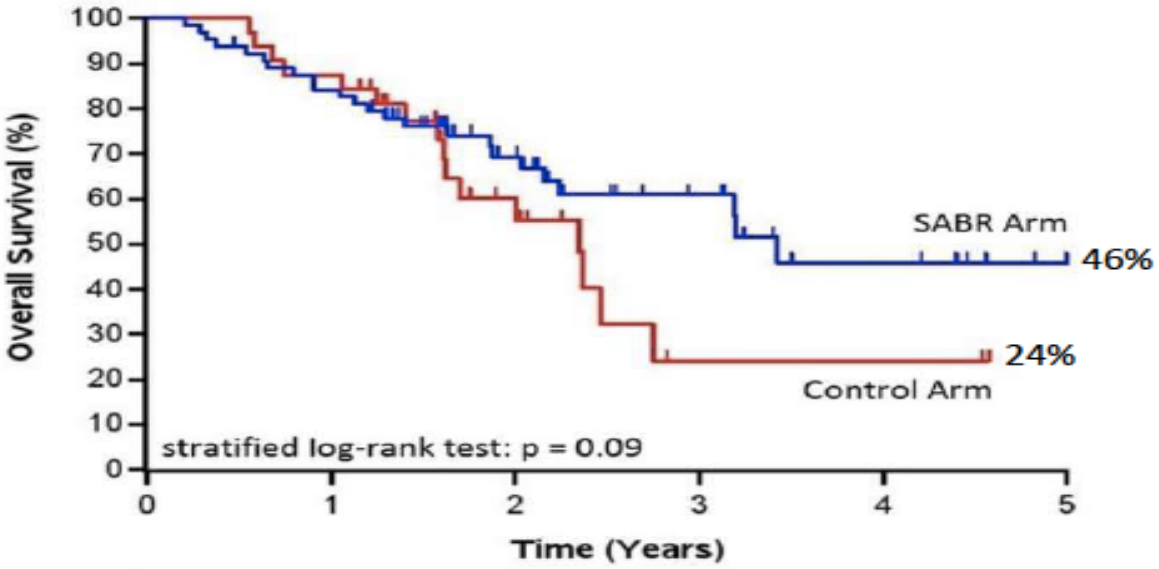
Control Arm: 6 months
(95% CI: 3.4-7.1 months)

SABR Arm: 12 months
(95% CI: 6.9-30 months)

8 patients on SABR Arm received salvage SABR after progression

Palma DA, et al. Lancet 2019; 393(10185):2051-2058

Overall Survival



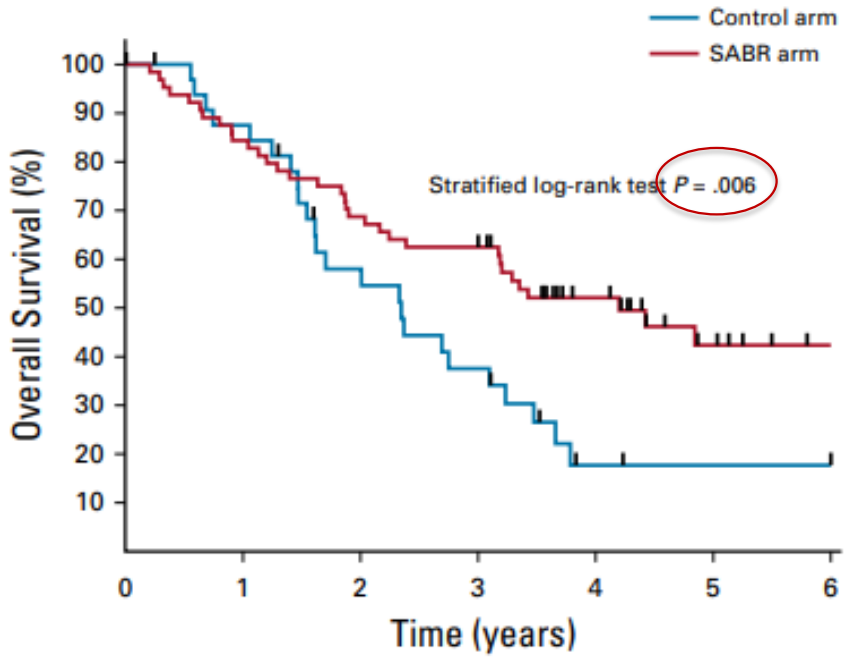
Median OS

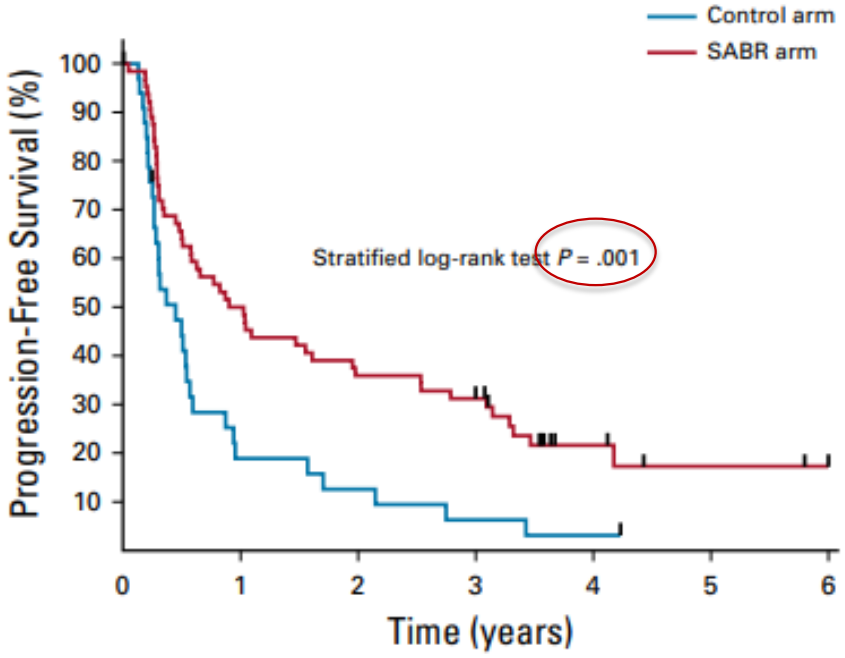
Control Arm: 28 months
(95% CI: 19-33 months)

SABR Arm: 41 months
(95% CI: 26 months to 'not reached')

Palma DA, et al. Lancet 2019; 393(10185):2051-2058

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



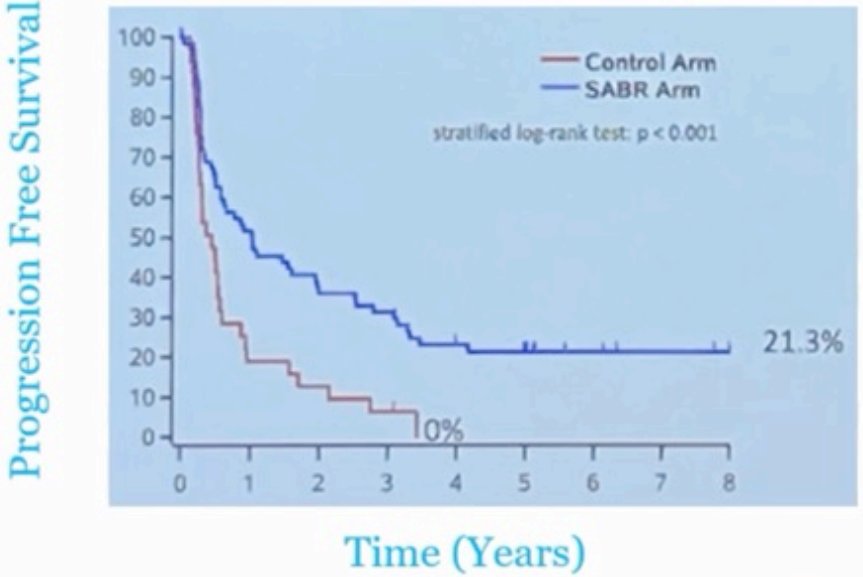


Palma DA, et al. J Clin Oncol 2020; 38:2830-2838

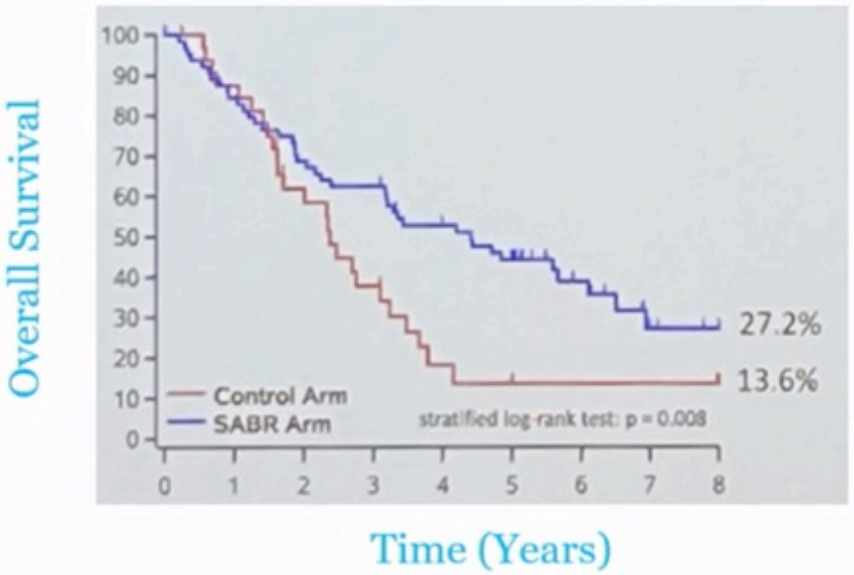
Stereotactic Radiation for the Comprehensive Treatment of Oligometastases (SABR-COMET): Extended Long-Term Outcomes

Median follow-up was 5.7 years

mPFS 12 vs 5.4 mths
in favour of local therapy



mOS 53 vs 28 mths
in favour of local therapy

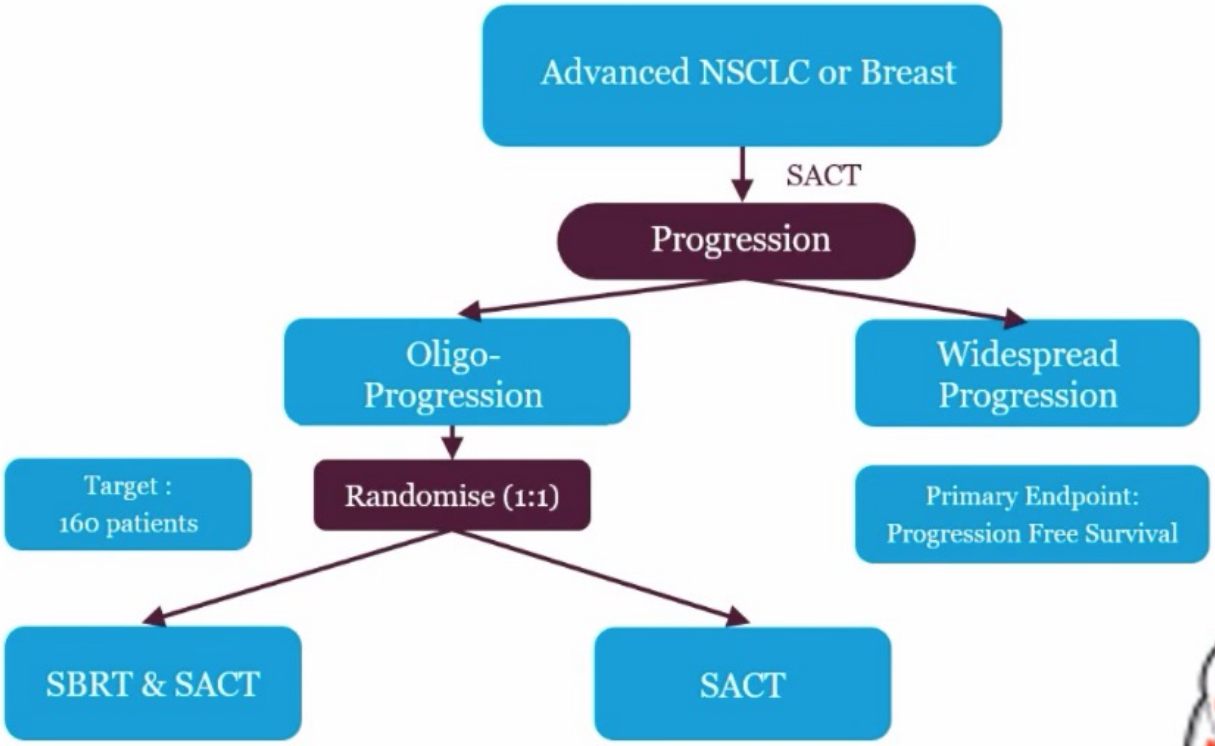


No new grade 3-5 toxicity

No impact on QoL

Harrow S, et al. IJROBP 2022 Nov 15 114(4):611-616

CURB: Ph II
Consolidative Use of RT to Block OPD



Stratification Factors:

- No. of OPD lesions: 1 vs 2-5
- Immunotherapy vs other SACT
- NSCLC vs Breast
- Driver Mutation / Hormone status

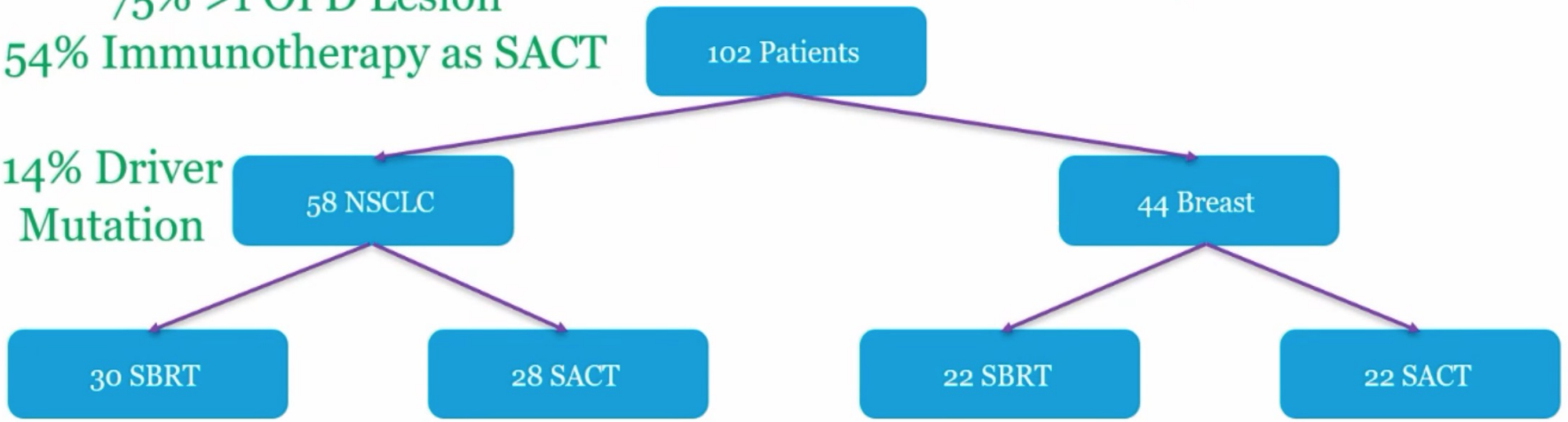
Induced Oligo-Progression

Tsai et al ASTRO 2021

CURB: Ph II: Interim Analysis
Consolidative Use of RT to Block OPD

75% >1 OPD Lesion
54% Immunotherapy as SACT

14% Driver Mutation



Median PFS 10 vs 2 months
HR 0.38
p=0.004
26% G≥2 Toxicity in SBRT arm

Median PFS 18 vs 17 weeks

Tsai et al ASTRO 2021

Final Analysis of Consolidative Use of Radiotherapy to Block (CURB) Oligoprogression Trial - A Randomized Study of Stereotactic Body Radiotherapy for Oligoprogressive Metastatic Lung and Breast Cancers

Most (75%) had >1 site of oligoprogression and 47% had >5 total lesions

Median PFS was 3.2 months in SOC arm vs. 7.2 months in SBRT arm (p=0.002).

Stratified analysis showed that NSCLC patients derived substantial PFS benefit from SBRT (2.2 months in SOC vs. 10 months in SBRT arm; p=0.002), whereas breast cancer patients did not (4.2 vs. 4.4 months, p=0.2).

No difference in OS between arms has yet been seen in either cohort.

The study was closed to accrual after a preplanned interim analysis crossed a prespecified efficacy threshold.

Tsai CJ, et al. Int J Radiat Oncol Biol Phys 2022;114(3):1-e612

Do patients with OM NSCLC benefit from local therapies?

Prospective Trials on LCT in oligoMets
ONCOGENE-ADDICTED NSCLC

Trial	N° patients	PFS2 (months)	Notes
Weickhardt AJ, et al. *J Thorac Oncol 2012;7:1807–14* (University of Colorado Cancer Center)	65 (27 EGFR+; 38 ALK+)	6.2	Range, 3.7-8 m
Yu HA, et al. J *Thorac Oncol 2013;8:346–51* (Memorial Sloan-Kettering Cancer Centre)	18 (EGFR+)	10	The median time from local therapy **until a change in systemic therapy** was 22 months (95% CI:6 to 30 months)
Gan GN, et al. *Int J Radiat Oncol Biol Phys. 2014; 88(4):892-8* (University of Colorado Cancer Center)	33 (ALK+) 14/33 suitable for SBRT	/	Median overall time on crizotinib among those treated with SBRT(14/33) versus those who progressed but were not suitable for SBRT was **28** and **10.1 months**, respectively.

Consolidative Local Ablative Therapy Improves the Survival of Patients With Synchronous Oligometastatic NSCLC Harboring EGFR Activating Mutation Treated With First-Line EGFR-TKIs

Aim: to investigate whether consolidative local ablative therapy (LAT) can improve the survival of patients with stage IV EGFR mutant NSCLC who have oligometastatic disease treated with first-line EGFR–tyrosine kinase inhibitor (TKI) therapy

145 patients were enrolled:

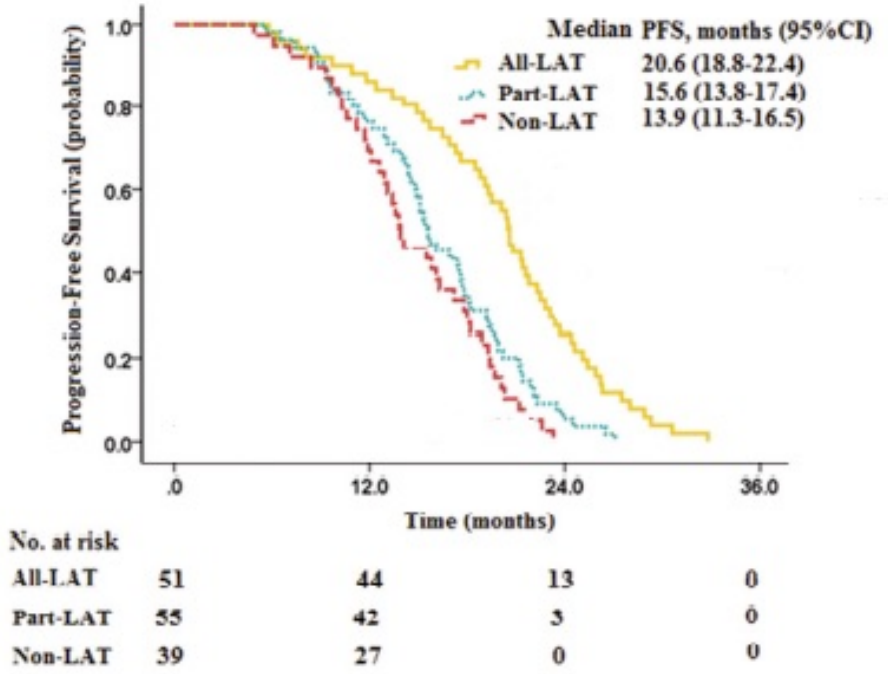
51 (35.2%) received consolidative LAT to all oligometastatic sites (all-LAT group),

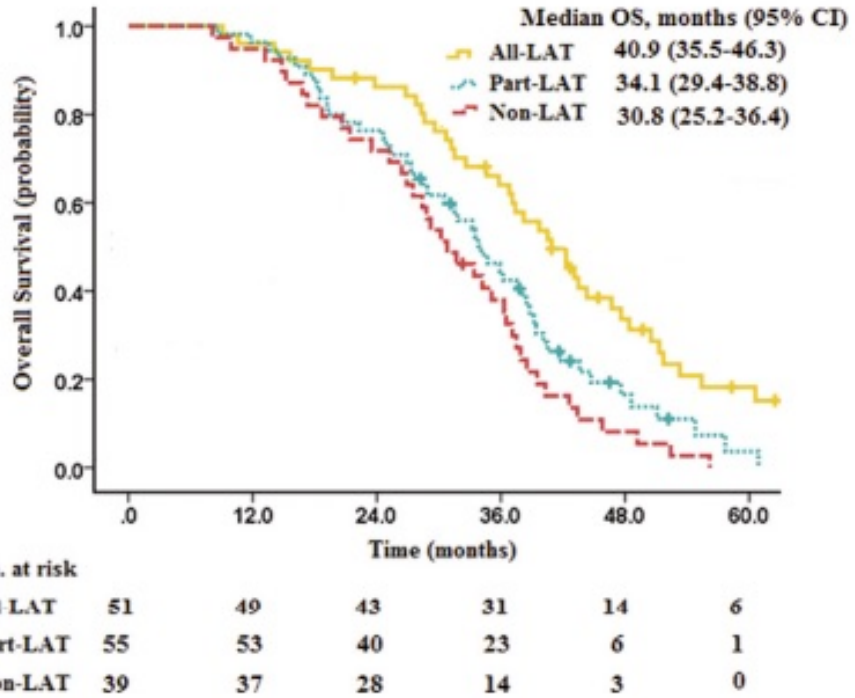
55 (37.9%) received consolidative LAT to either primary tumor or oligometastatic sites (part-LAT group)

39 (26.9%) did not receive any consolidative LAT (non-LAT group)

Xu Q et al, J Thorac Oncol. 2018;13(9):1383-1392

The median follow-up time was 38 months (range, 9.0 to 66.8 months). For the entire cohort, the median PFS (mPFS) was 17.3 months (95% CI: 15.7–18.9) and median OS (mOS) was 35.9 months





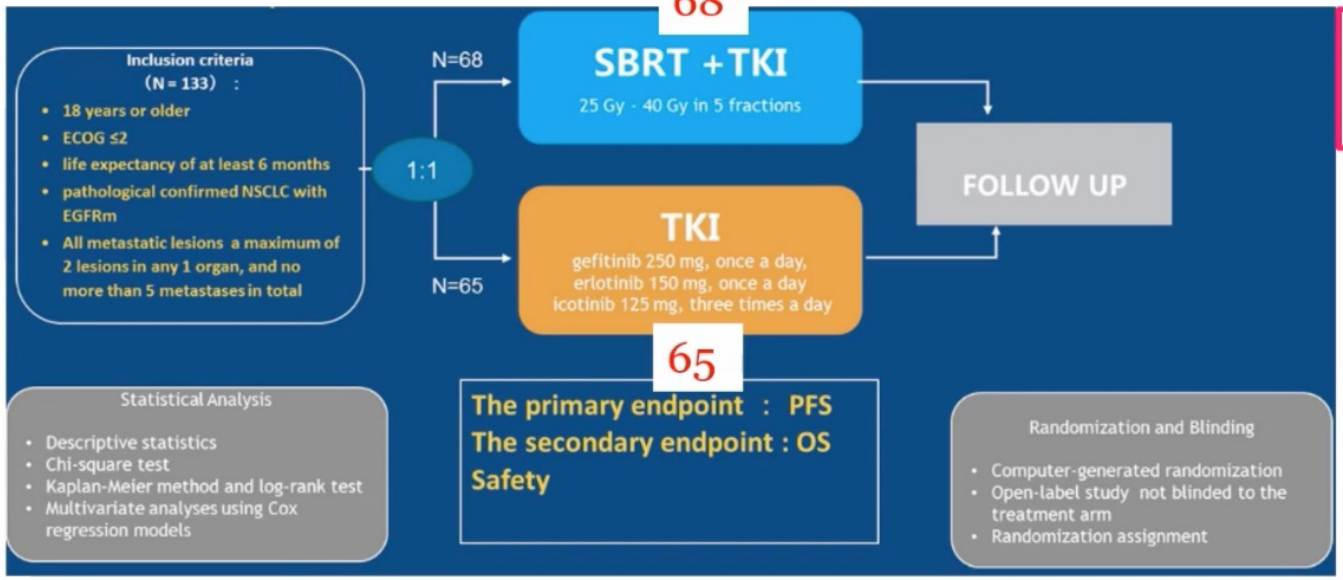
The difference was statistically significant between All-LAT group and Part-LAT or Non-LAT group but was not significant between the part-LAT and non-LAT groups

Xu Q et al, J Thorac Oncol. 2018;13(9):1383-1392

ASCO 2021

First-line tyrosine kinase inhibitor with or without aggressive upfront local radiation therapy in patients with EGFRm oligometastatic non-small cell lung cancer: Interim results of a randomized phase III, open-label clinical trial (SINDAS) (NCT02893332)

SINDAS: Ph II in Synchronous OMD in EGFR+



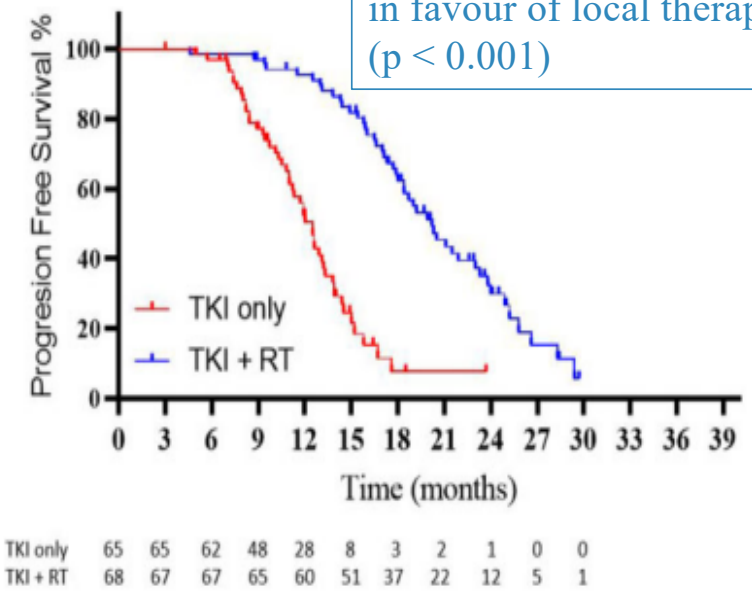
≤5 metastases (& primary +/- LNs)
≤2 in any one organ
No brain metastases

Wang et al JNCI 2022;

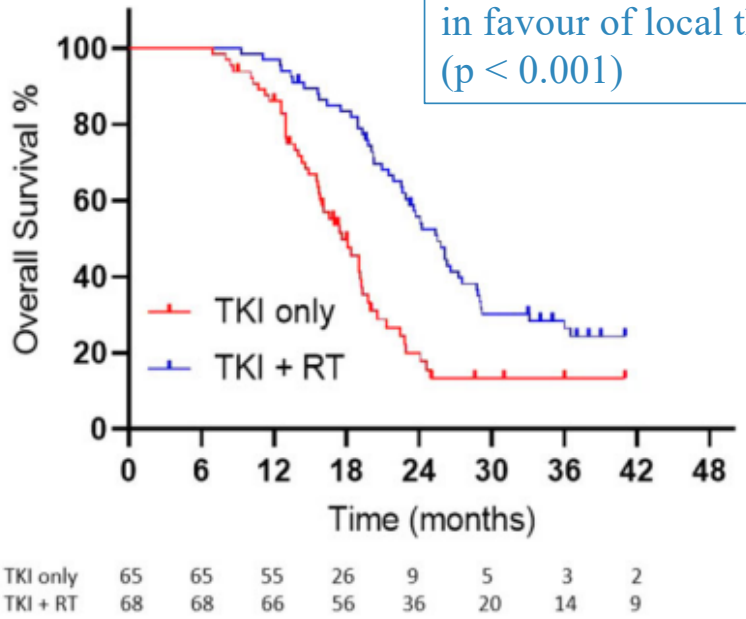
Randomized Trial of First-Line Tyrosine Kinase Inhibitor With or Without Radiotherapy for Synchronous Oligometastatic *EGFR*-Mutated Non-Small Cell Lung Cancer

The median follow-up was 23.6 months

mPFS was 20.2 vs 12.5 months in favour of local therapy ($p < 0.001$)



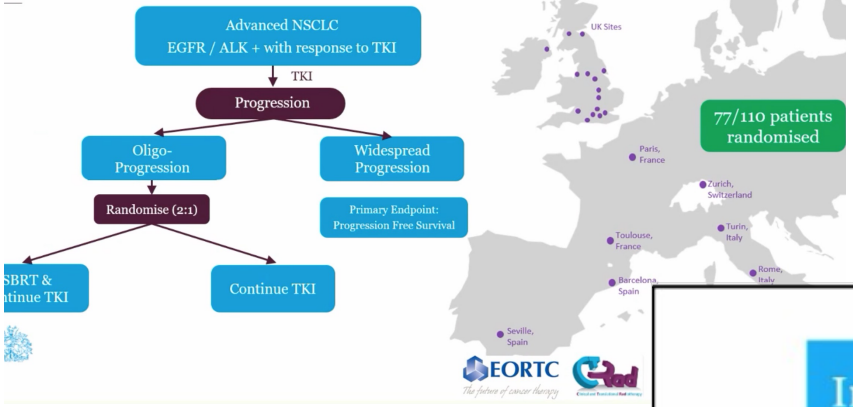
mOS was 25.5 vs 17.4 months in favour of local therapy ($p < 0.001$)



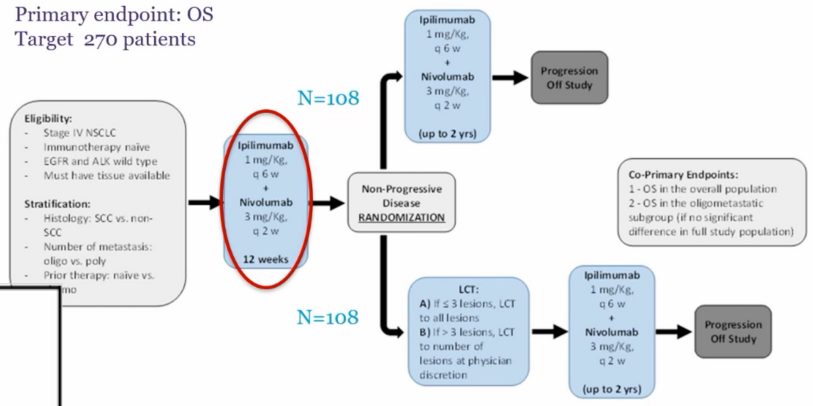
Treatment yielded no grade 5 events and a 6% rate of symptomatic grade 3-4 pneumonitis in the TKI with RT arm

Wang XS, et al. JNCI J Natl Cancer Inst. 2022; 114(5): djac015

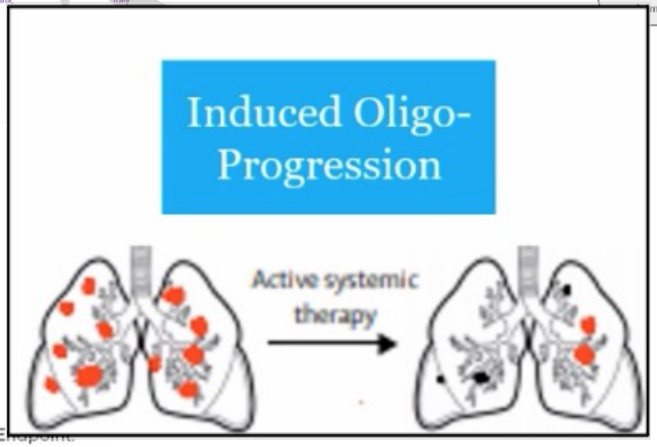
HALT Ph II/III



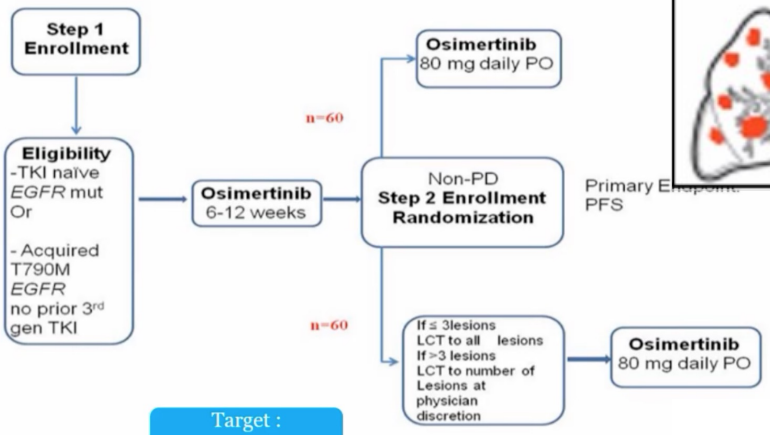
LONESTAR: Ph III



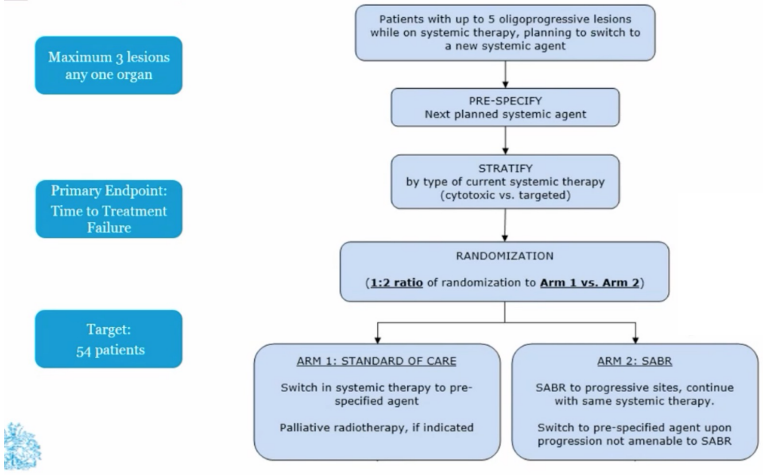
Induced Oligo-Progression



North Star Trial: Ph II



STOP Trial: Ph II



Oligometastatic NSCLC

1. Do patients with OM NSCLC benefit from local therapies?
2. When should local therapy be administered?
3. The choice of the target (volume and dose)

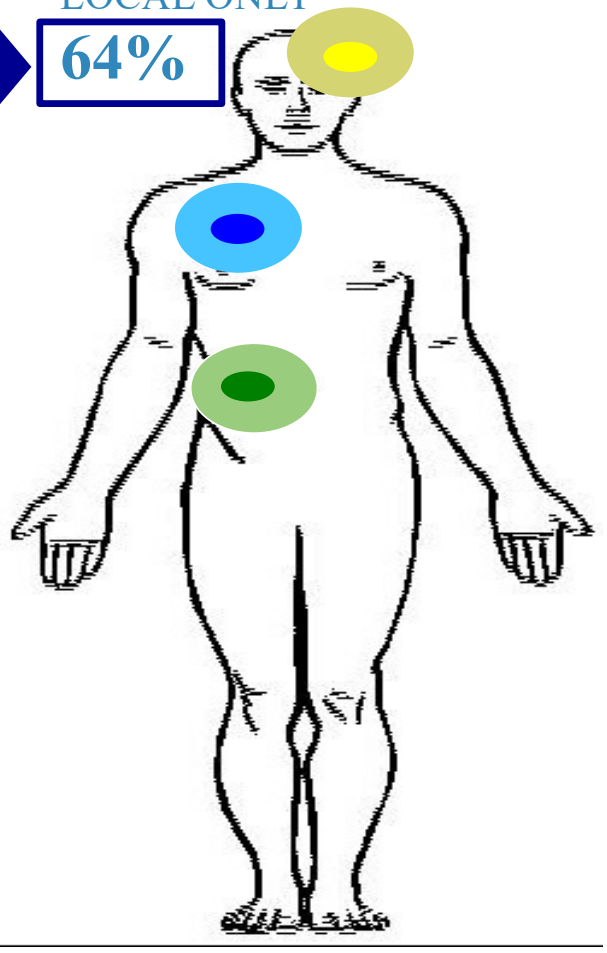
WILD TYPE NSCLC

PROGRESSION after first line chemotherapy:

University of Colorado Cancer Center

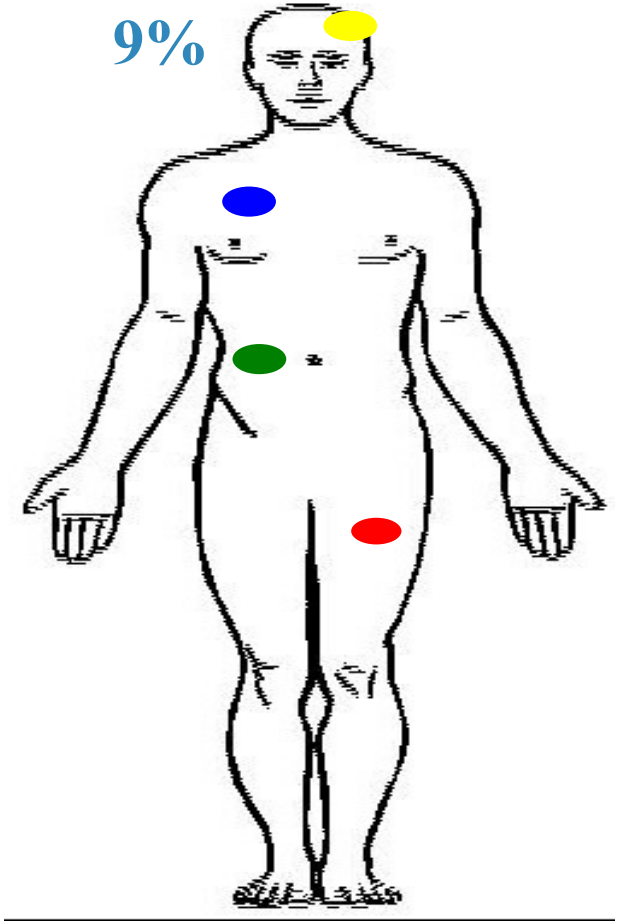
LOCAL ONLY

64%



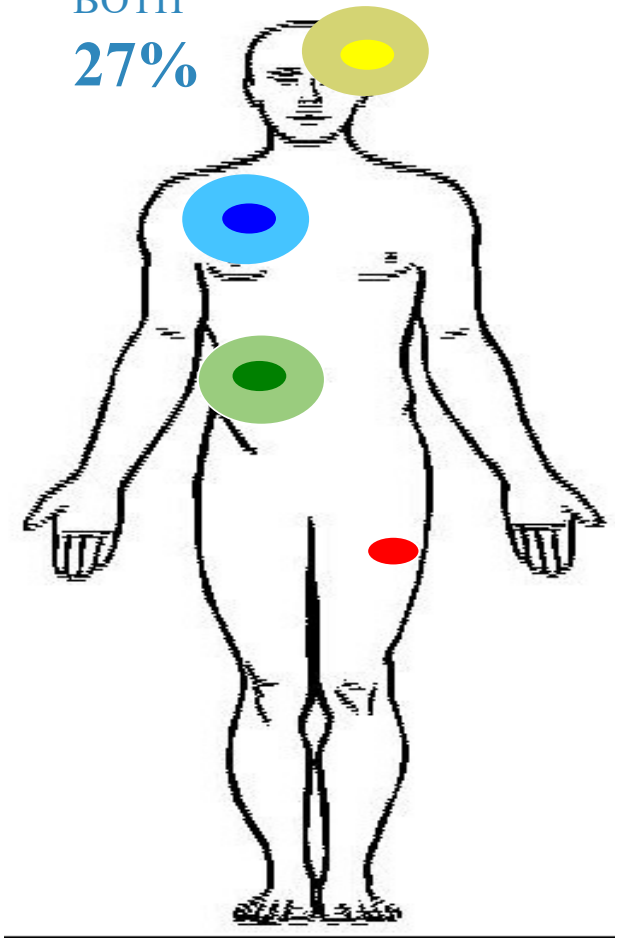
DISTANT ONLY

9%



BOTH

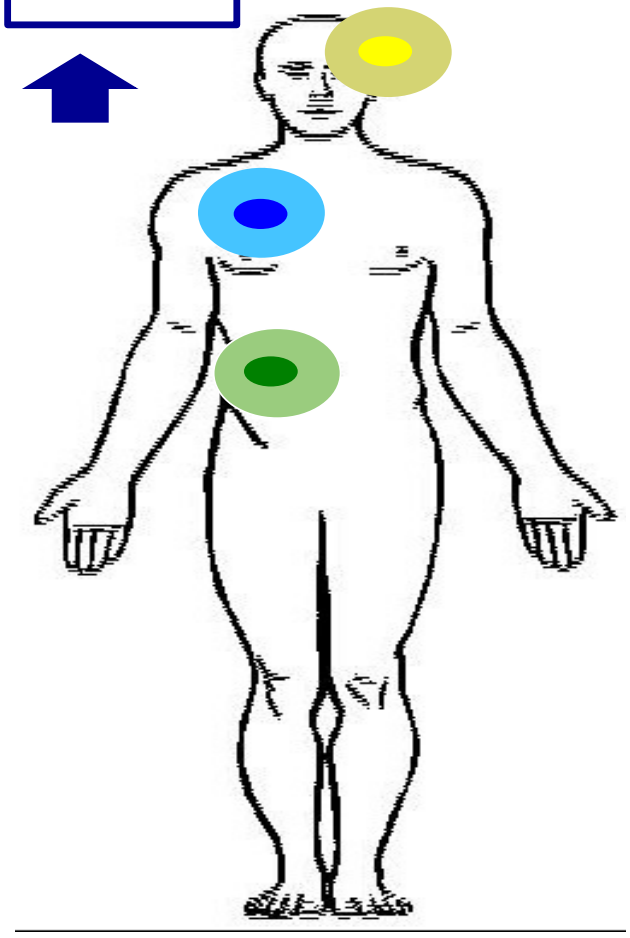
27%



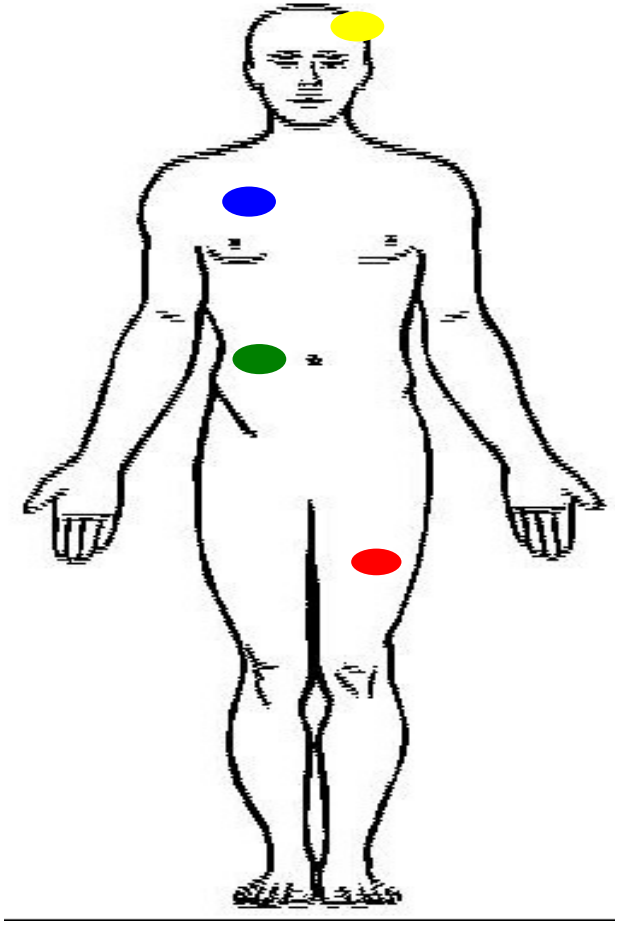
Rusthoven KE, et al. Acta Oncologica 2009; 48:578-583

PROGRESSION in EGFR-MUTATED patients after TKI:

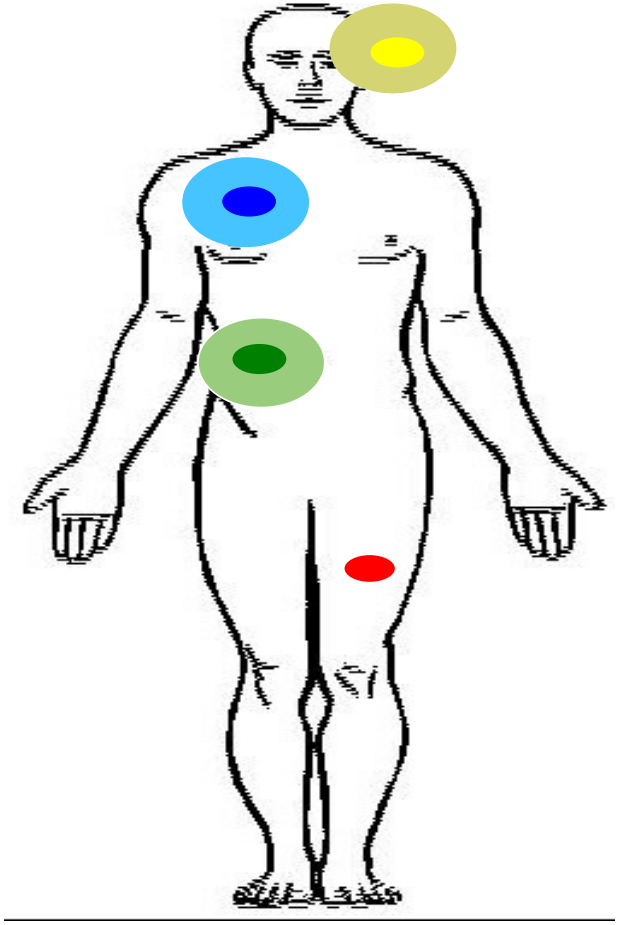
ISOLATED ORIGINAL **63.6%**



ISOLATED NEW **21.2%**



ORIGINAL + NEW **15.2%**



Deng L, et al. Int J Radiat Oncol Biol Phys 2016; 96(2): S131–S132

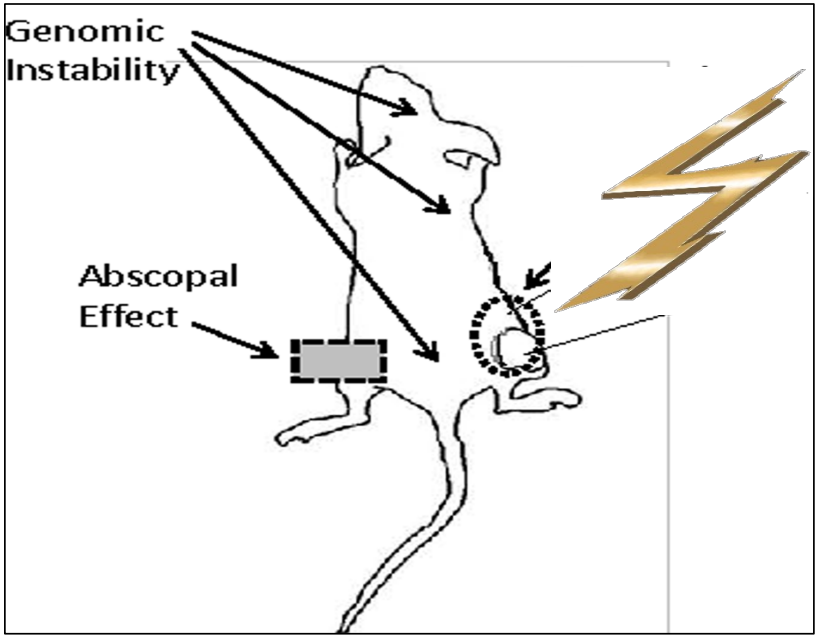
2 When should local therapy be administered?

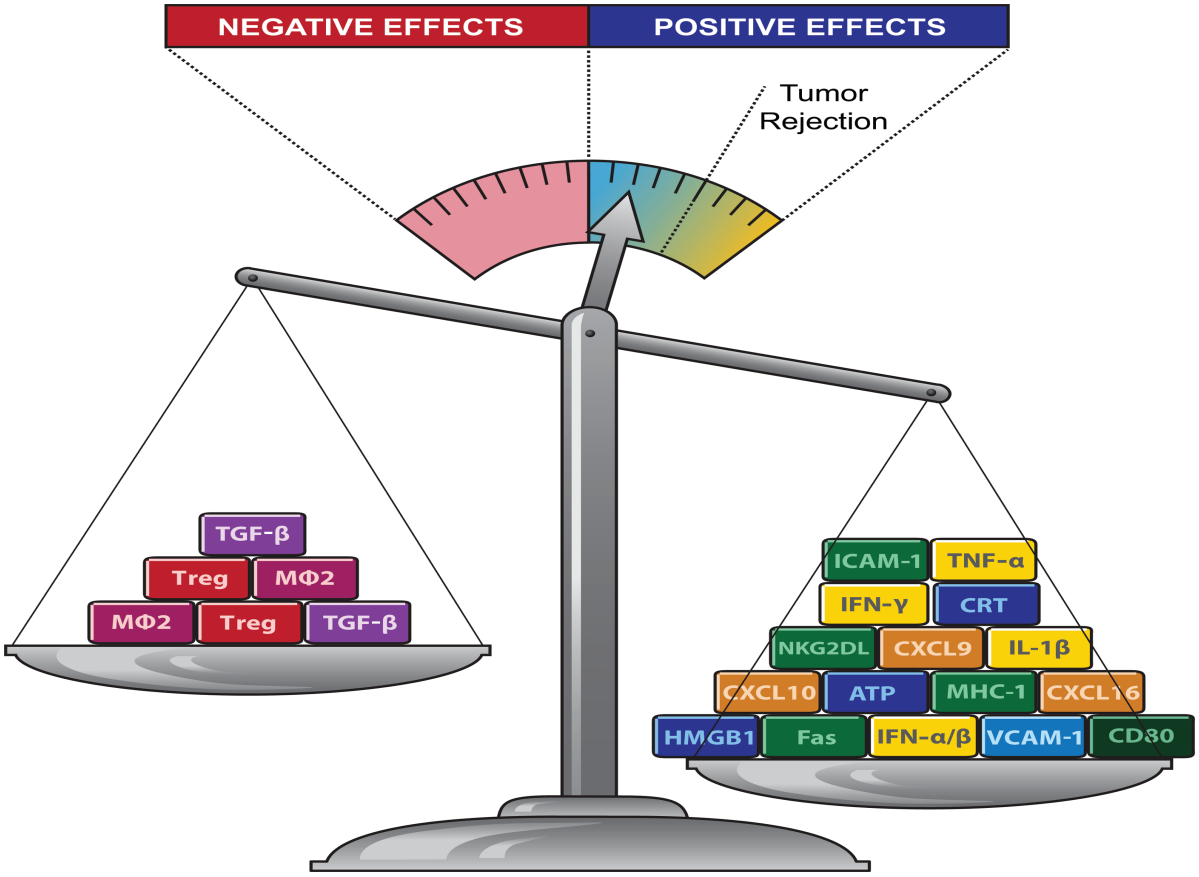
ADVANTAGES

UPFRONT LOCAL THERAPY may:

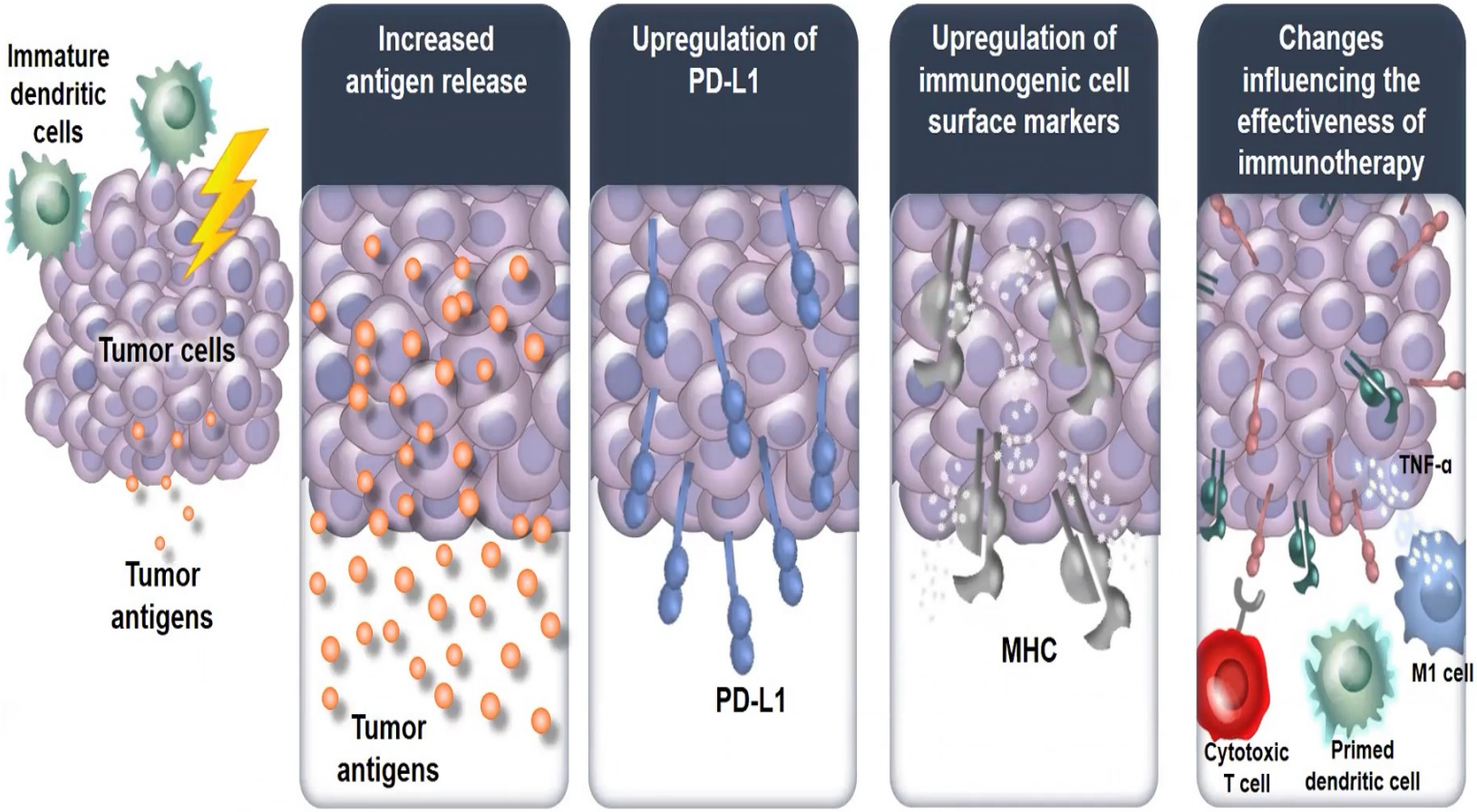
- ✓ Debulk a tumor to optimize subsequent systemic therapy
- ✓ Capture patients who might be missed should they have primary disease progression on systemic therapy
- ✓ Enhance tumor antigenicity to improve effects of immunotherapy

RADIOTHERAPY: IMMUNOSUPPRESSIVE AND PROIMMUNOGENIC EFFECTS





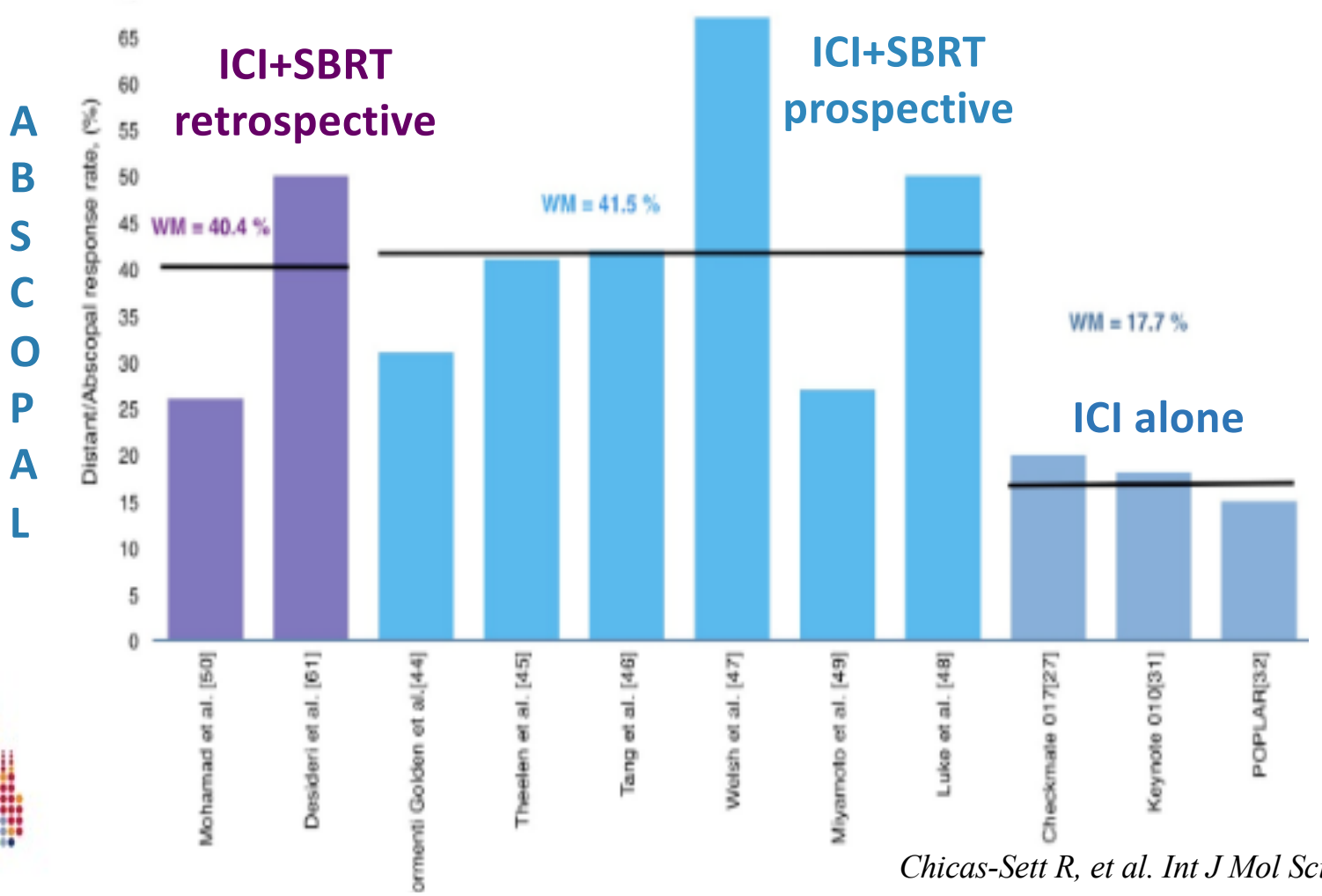
Radiotherapy Induces Multiple Immunomodulatory Changes in the Tumor Microenvironment that may Influence the Effectiveness of Immunotherapy



M1, tumor-associated macrophage; MHC, major histocompatibility complex; PD-L1, programmed cell death ligand-1; TNF-α, tumor necrosis factor alpha.

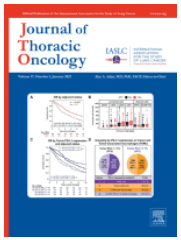
1. Daly ME, et al. *J Thorac Oncol*. 2015;10(12):1685-1693; 2. Kaur P, Asea A. *Front Oncol*. 2012;2:191; 3. Deng L, et al. *J Clin Invest*. 2014;124(2):687-695.

Combination of SBRT + Immune Checkpoint Inhibitor Increases Distant / Abscopal response



Chicas-Sett R, et al. Int J Mol Sci 2019; 20(9):2173

A Phase 1 Trial of Concurrent or Sequential Ipilimumab, Nivolumab, and Stereotactic Body Radiotherapy in Patients With Stage IV NSCLC Study

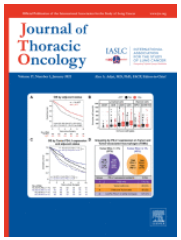


This randomized phase 1 trial combined nivolumab and ipilimumab with sequential or concurrent multisite SBRT in patients with stage IV NSCLC to evaluate safety and obtain preliminary activity data.

Methods

Treatment-naive patients with **widely metastatic NSCLC were randomized** to **concurrent** (SBRT with immunotherapy) or **sequential** (SBRT followed by immunotherapy) treatment. A maximum of four treatment fields received SBRT. Nivolumab and ipilimumab were continued until clinical progression, development of toxicity, or after 2 years.

Bestvina CM, et al. J Thorac Oncol. 2022;17(1):130-140



Results

A total of 37 patients were assessable. No dose-limiting toxicity occurred in the concurrent cohort (n = 18). The sequential cohort required a dose reduction in the central lung group owing to two grade 4 pneumonitis events (2 of 19).

Overall best response was as follows: 5.4% (2 of 37) CR, 40.5% (15 of 37) PR, 16.2% (6 of 37) SD, and 37.8% (14 of 37) PD. Median progression-free survival was 5.8 months (95% confidence interval: 3.6–11.4 mo), with median follow-up of 17.0 months. Median overall survival was not reached.

Conclusions

Concurrent nivolumab, ipilimumab, and SBRT were not more toxic than sequential therapy, and multisite SBRT was well tolerated in widely metastatic patients. Multimodality therapy resulted in durable metastasis control and encouraging early overall survival.

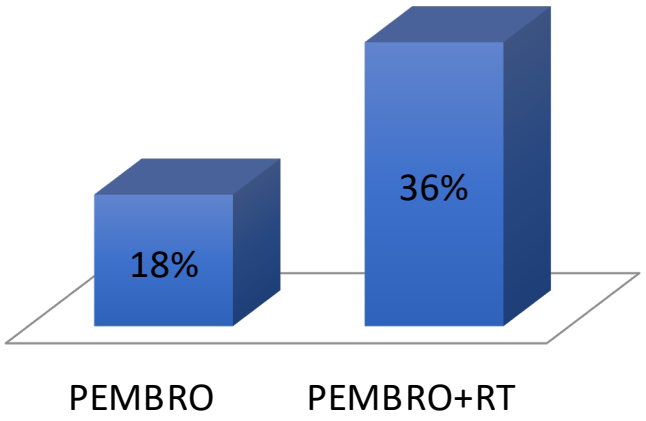
Bestvina CM, et al. J Thorac Oncol. 2022;17(1):130-140

2018 ASCO® ANNUAL MEETING

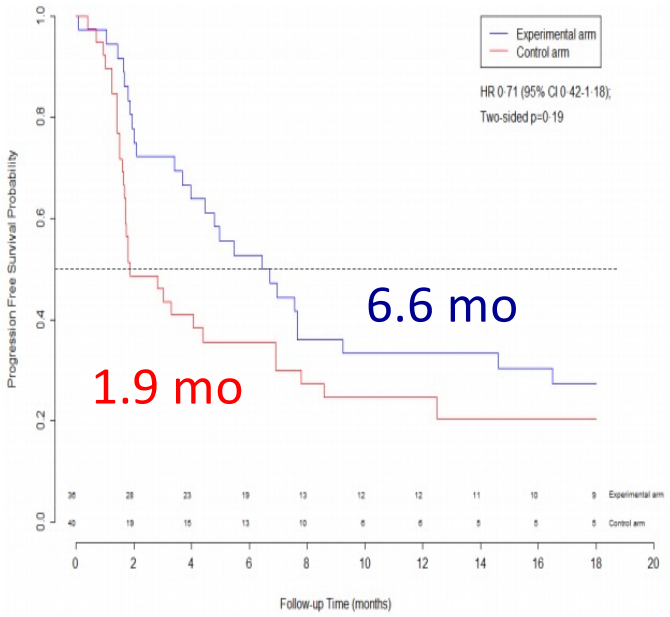
The PEMBRO-RT study:

Phase II trial of SBRT followed by Pembrolizumab vs Pembrolizumab

OVERALL RESPONSE RATE



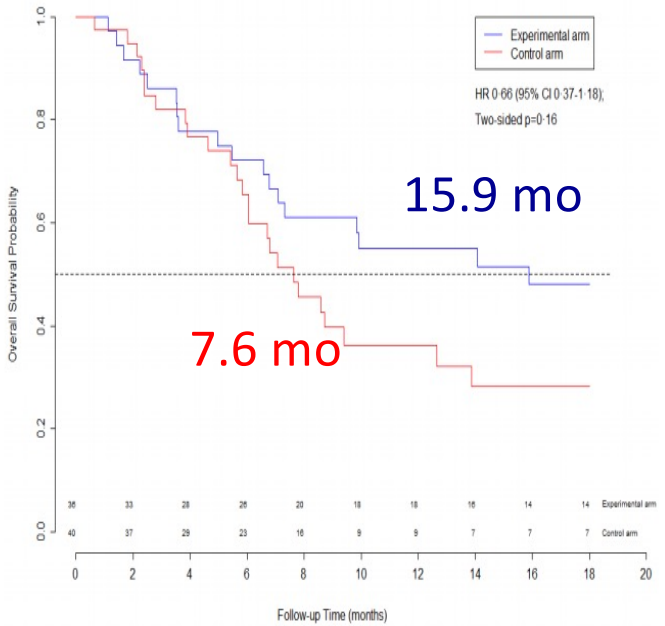
PFS



- mPFS was 1.9 months (95% CI 1.7-6.9) in the control arm vs 6.6 months (95% CI 4.0-14.6) in the experimental arm.

Accepted Jama Oncolog

OS

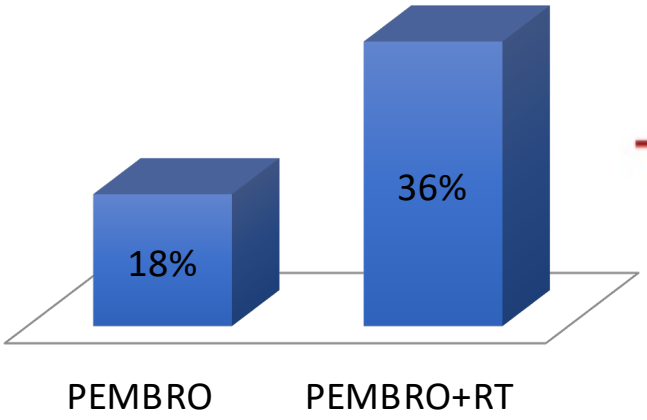


- mOS was 7.6 months (95% CI 6.0-13.9) in the control arm vs 15.9 months (95% CI 7.1-NA) in the experimental arm.

Accepted Jama Oncology

Theelen W, et al. JAMA Oncology 2019; 5(9):1276-1282

OVERALL RESPONSE RATE



Response to Treatment

	Experimental arm n = 36	Control arm n = 40
Best overall response		
Complete response	3	1
Partial response	14	8
Stable disease	9	10
Progressive disease	10	21
Objective response rate (ORR) at 12 weeks		
Overall*	36% (13/36)	18% (7/40)
PD-L1 TPS 0%	22% (4/18)	4% (1/25)
PD-L1 TPS 1-49%	38% (3/8)	38% (3/8)
PD-L1 TPS ≥50%	60% (6/10)	60% (3/5)
Disease Control Rate (DCR) at 12 weeks**	64% (23/36)	40% (16/40)

*p = 0.07; **p = 0.043

Theelen W, et al. JAMA Oncology 2019; 5(9):1276-1282

Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials
PEMBRO-RT + MDACC

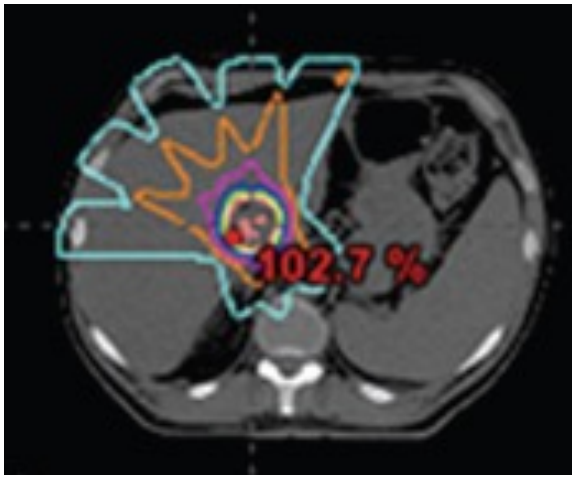
Findings	PEMBRO	SBRT+PEMBRO	
Pts	76	72	
FUP	33 months (IQR 32.4–33.6)		
Irradiate site	Lung metastasis [39%], intrathoracic lymph nodes [21%], and lung primary disease [17%]		
Abscopal Response Rate	19.7% (15 of 76)	41.7% (30 of 72)	odds ratio [OR] 2·96, 95% CI 1-42–6.20; p=0.0039)
mPFS	4.4m IQR 2.9–5.9)	9.0m (6.8–11.2)	hazard ratio [HR] 0.67, 95% CI 0.45–0.99; p=0.045
mOS	8.7 months (6.4–11.0)	19.2 months (14.6–23.8)	HR 0.67, 0.54–0.84; p=0.0004

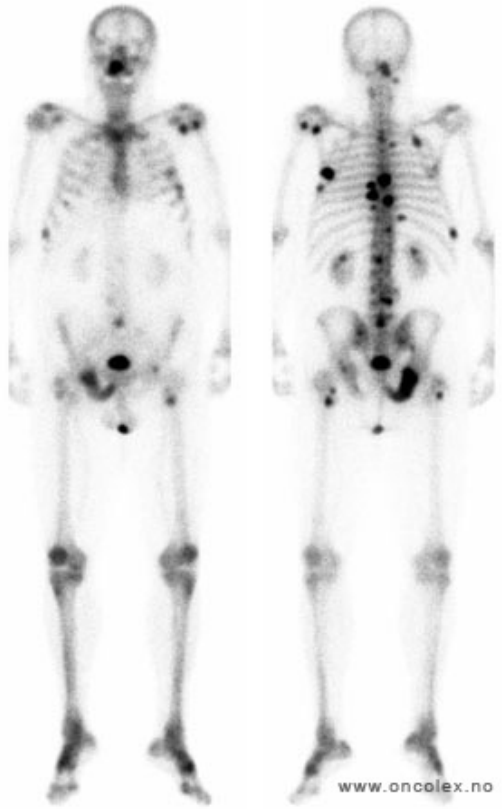
Theelen W, et al. The Lancet Respirarory Medicine 2021; 9(5):467-475

Oligometastatic NSCLC

1. Do patients with OM NSCLC benefit from local therapies?
2. When should local therapy be administered?
3. The choice of the target (volume and dose)

3 THE CHOICE OF TARGET



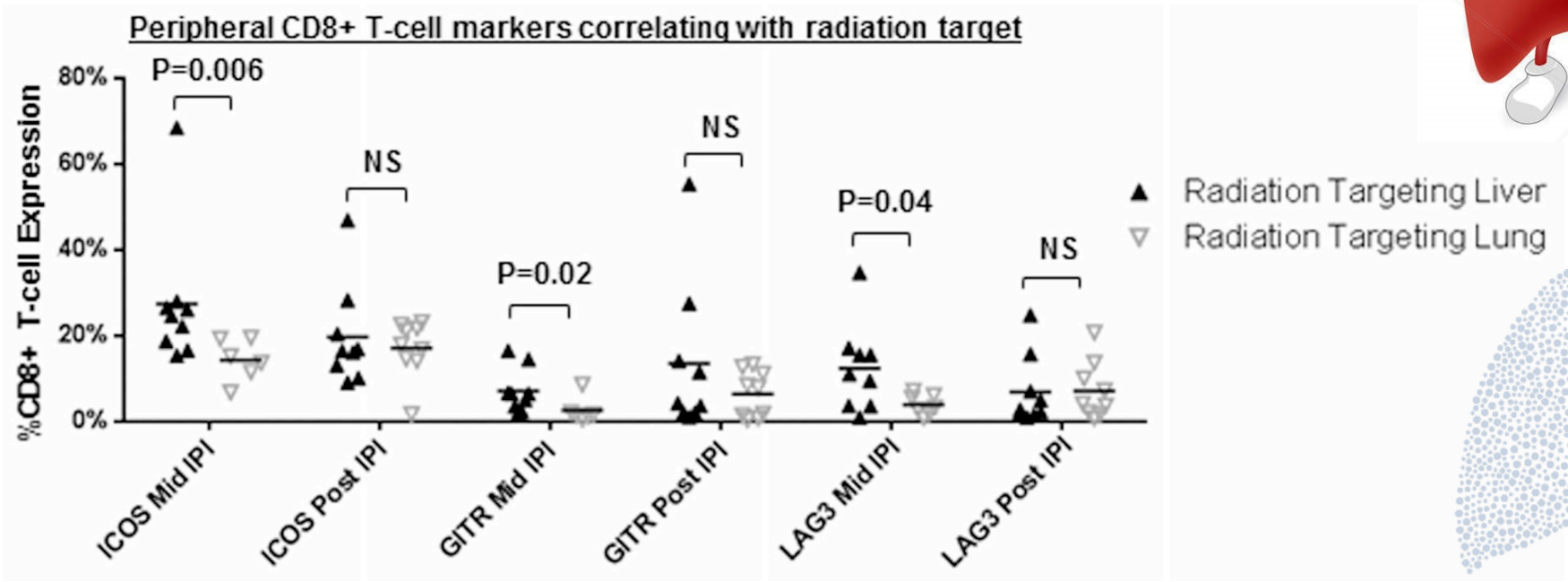


- Not all targets are immunogenically equal
- Most case of abscopal effects have involved visceral organs rather than bone

Kang J, et al. J Immunother Cancer 2016, 4:51

Fujisaki J, et al. Nature 2011; 474:216-9

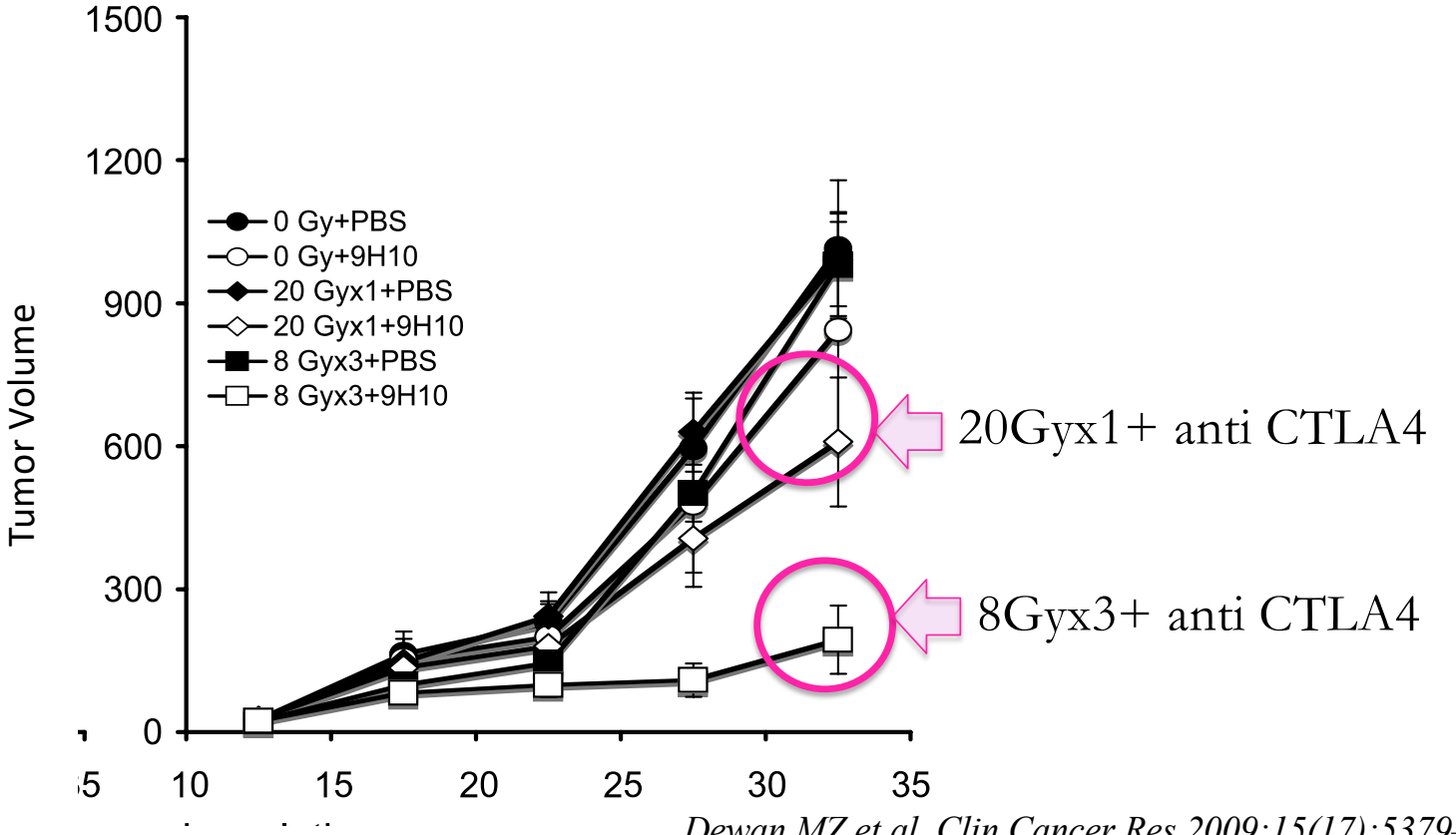
Ipilimumab with stereotactic ablative radiation therapy: Phase I results and immunologic correlates from peripheral T-cells



Hepatic irradiation increases early systemic immune activation relative to lung radiation, as indicated by increasing proportions of T-cells expressing antigens with pro-immune function and compensatory increases in antigens with inhibitory functions.

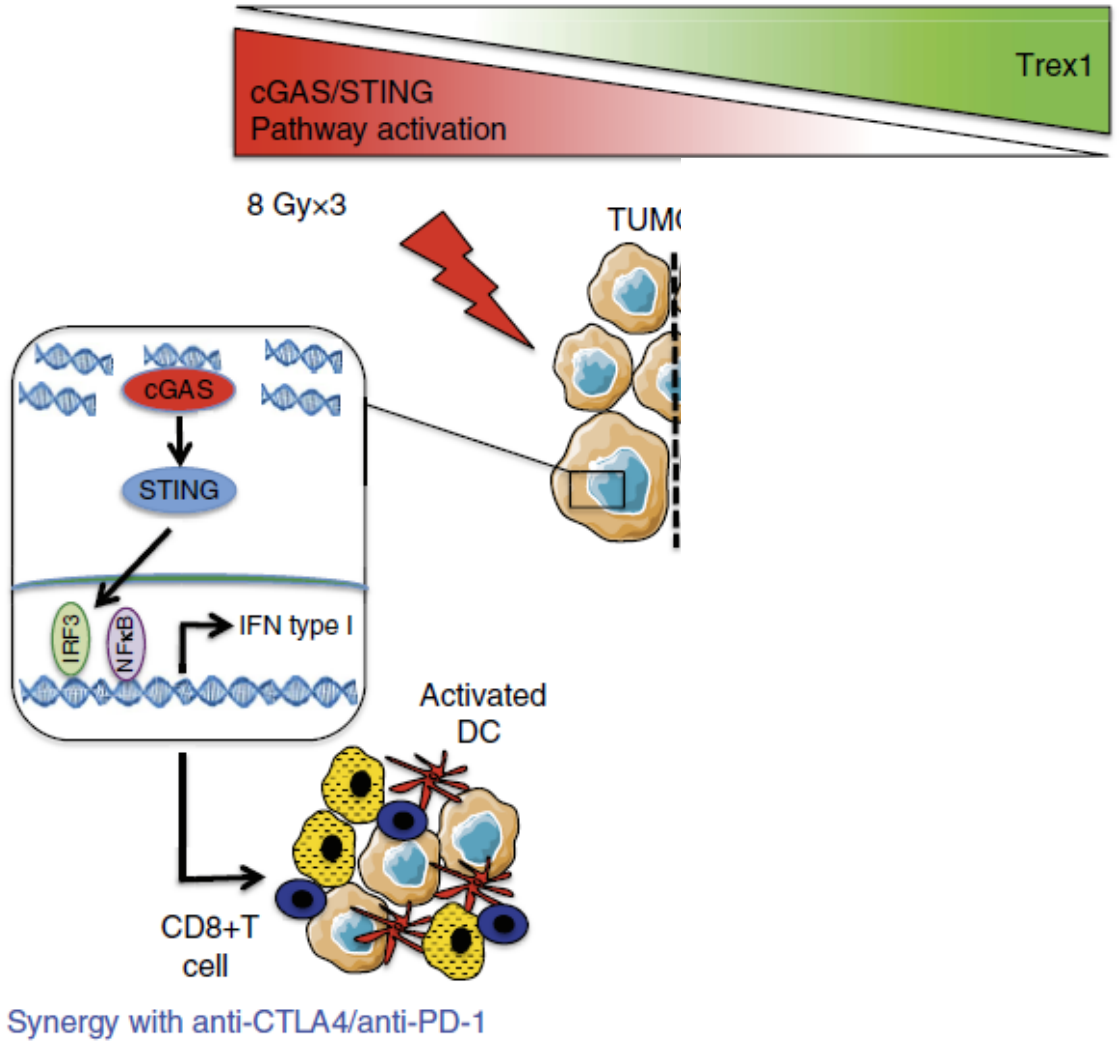
Tang C, et al. Clin Cancer Res. 2017; 23(6): 1388–1396

Fractionated but not single dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody



An abscopal effect, defined as a significant growth inhibition of the tumor outside the field occurred only in mice treated with the combination of 9H10 and fractionated radiotherapy ($p<0.01$)

Dewan MZ et al. Clin Cancer Res 2009;15(17):5379–88



Vanpouille-Box C, et al. Nat Commun 2017;8:15618

Concluding Remarks

- Many revolutionary advances have recently been made in the management of stage IV NSCLC.
- In comparison to TKIs alone, a combination of TKIs and radiation has been shown in numerous clinical studies to improve survival outcomes.
- Immunotherapy is now at the forefront of treatment in oncogenic driver negative NSCLC.
- Preclinical and recent clinical evidences in NSCLC have shown that radiotherapy might be a potent immunomodulator, enhancing the efficacy of the immune response facilitated by immune checkpoint blockade.