Image generated by DALL-E

Progress in Targeted Therapies for Early-Stage NSCLC

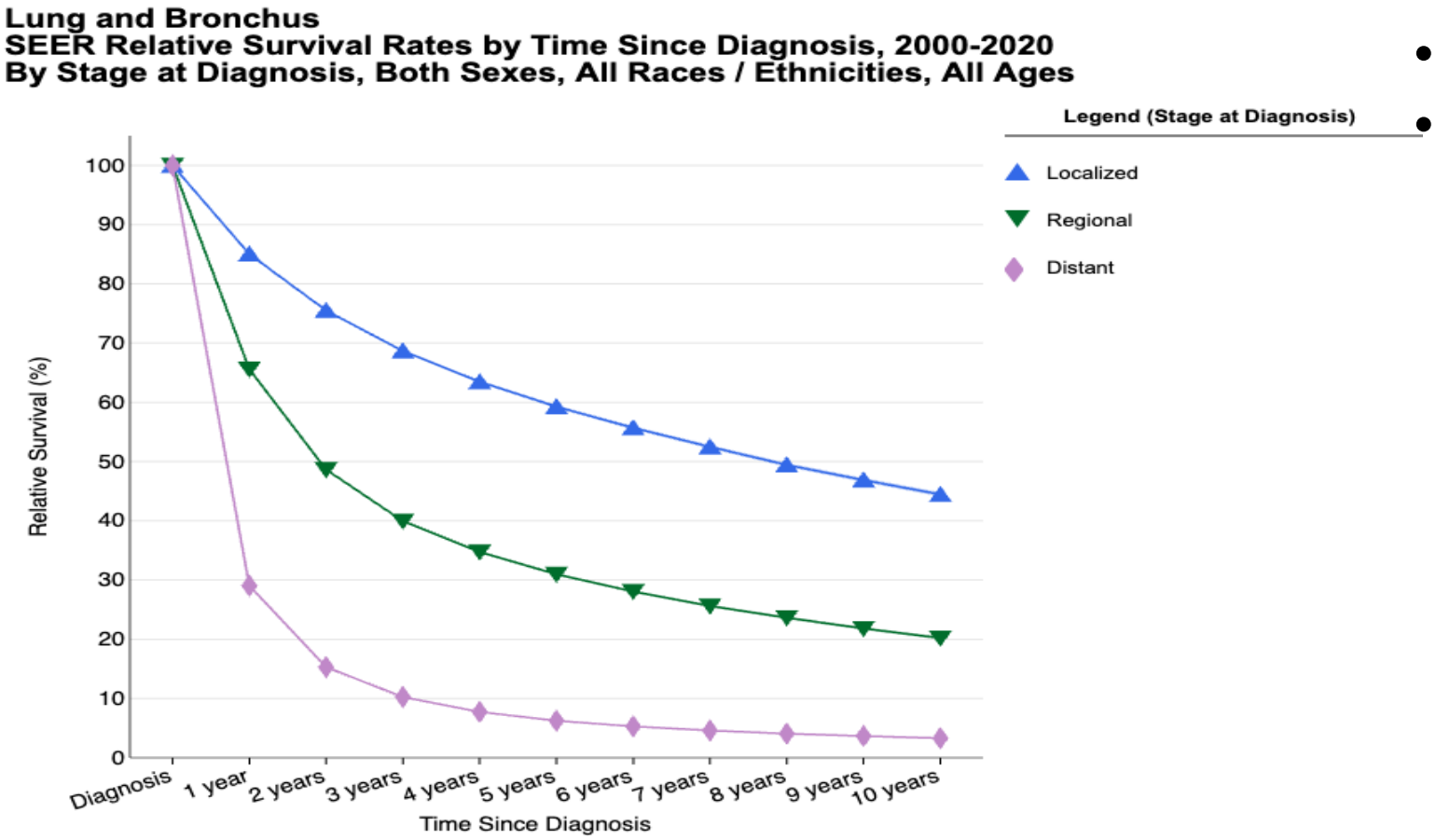
Lyudmila Bazhenova, MD

Professor of Medicine,

Lung Cancer Unit Leader

Director Hematology and Oncology Training Program

How do we increase survival in early-stage lung cancer?

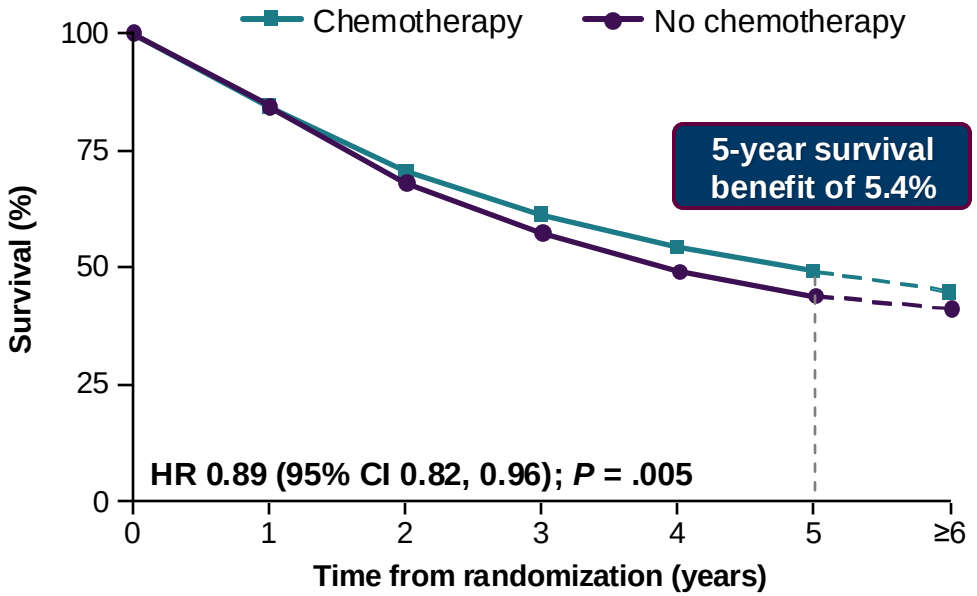


- Increase screening rates
- Improve efficacy of neoadjuvant/adjuvant therapy

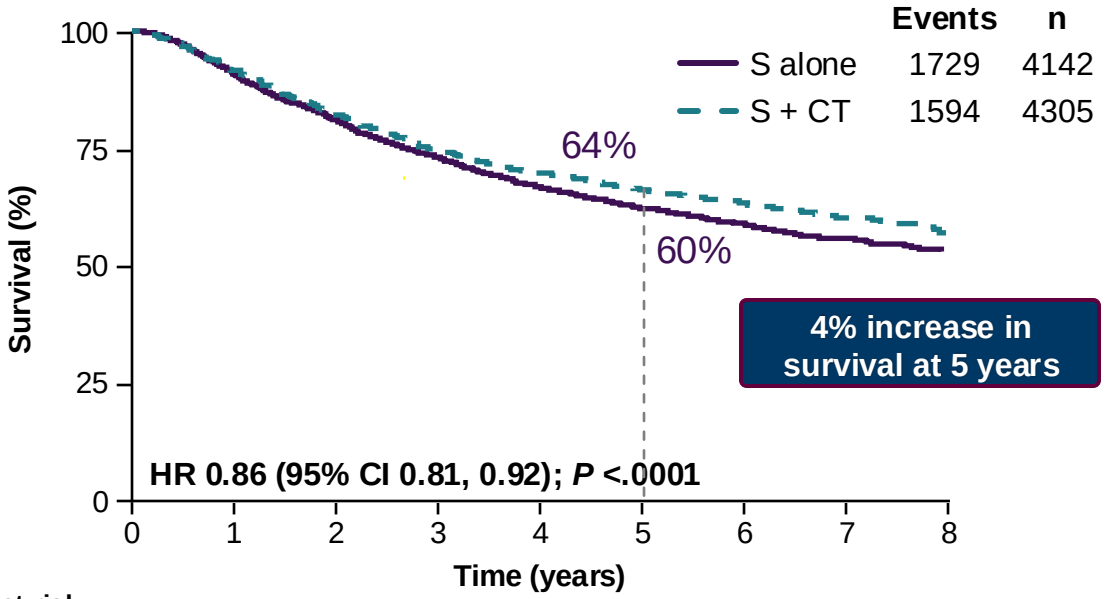
SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2024 Apr 17. [updated: 2024 Nov 5; cited 2024 Nov 14]. Available from: https://seer.cancer.gov/statistics-network/explorer/. Data source(s): SEER Incidence Data, November 2023 Submission (1975-2021), SEER 22 registries (excluding Illinois and Massachusetts). Expected Survival Life Tables by Socio-Economic Standards.

Adjuvant Platinum-Based Doublet Chemotherapy is Standard of Care in Patients with Resected Stage II–III NSCLC and Select Patients with Stage IB Disease[1]

LACE pooled analysis of 5 randomized adjuvant cisplatin trials performed since 1995 (n = 4584)[2]



Meta-analysis of randomized adjuvant chemotherapy trials performed since 1965 (n = 8447)[3]



Number at risk

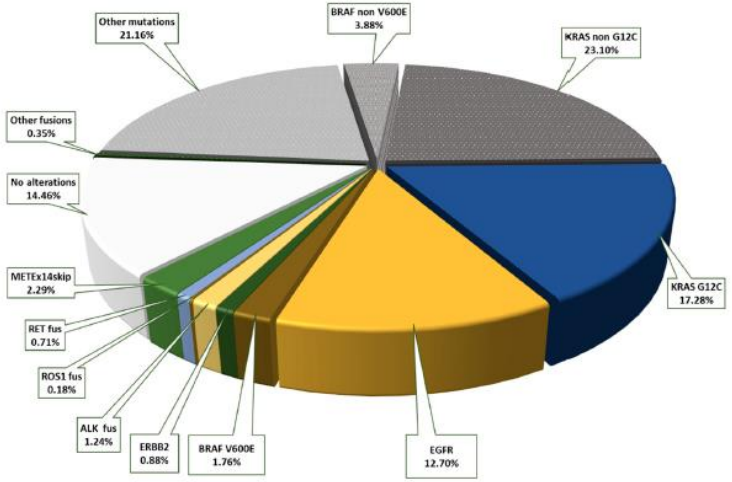
S alone	4142	3648	3102	2584	2083	1601	841	407	148
S + CT	4305	3809	3261	2746	2278	1785	936	473	165

Results from large randomised trials[4,5] and meta-analyses[2,3] have shown a statistically significant OS benefit (~5% at 5 years) only in patients with stage II-III disease

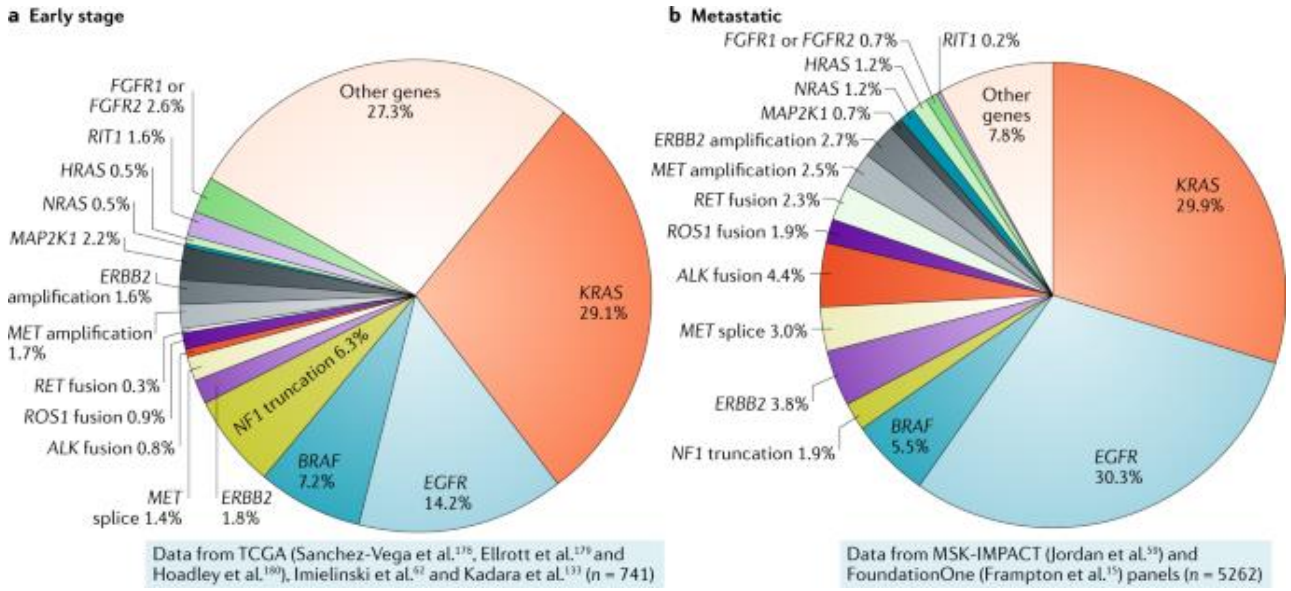
1. Kris MG et al. *J Clin Oncol*. 2017;35:2960-2974; 2. Pignon JP et al. *J Clin Oncol*. 2008;26:3552-3559; 3. NSCLC Meta-analyses Collaborative Group. *Lancet*. 2010;375:1267-1277; 4. Arriagada R et al. *N Engl J Med*. 2004;350:351-360; 5. Winton T et al. *N Engl J Med*. 2005;352:2589-2597.

Driver mutation in early-stage lung cancer

Retrospective Single center N=2066. 47% early stage



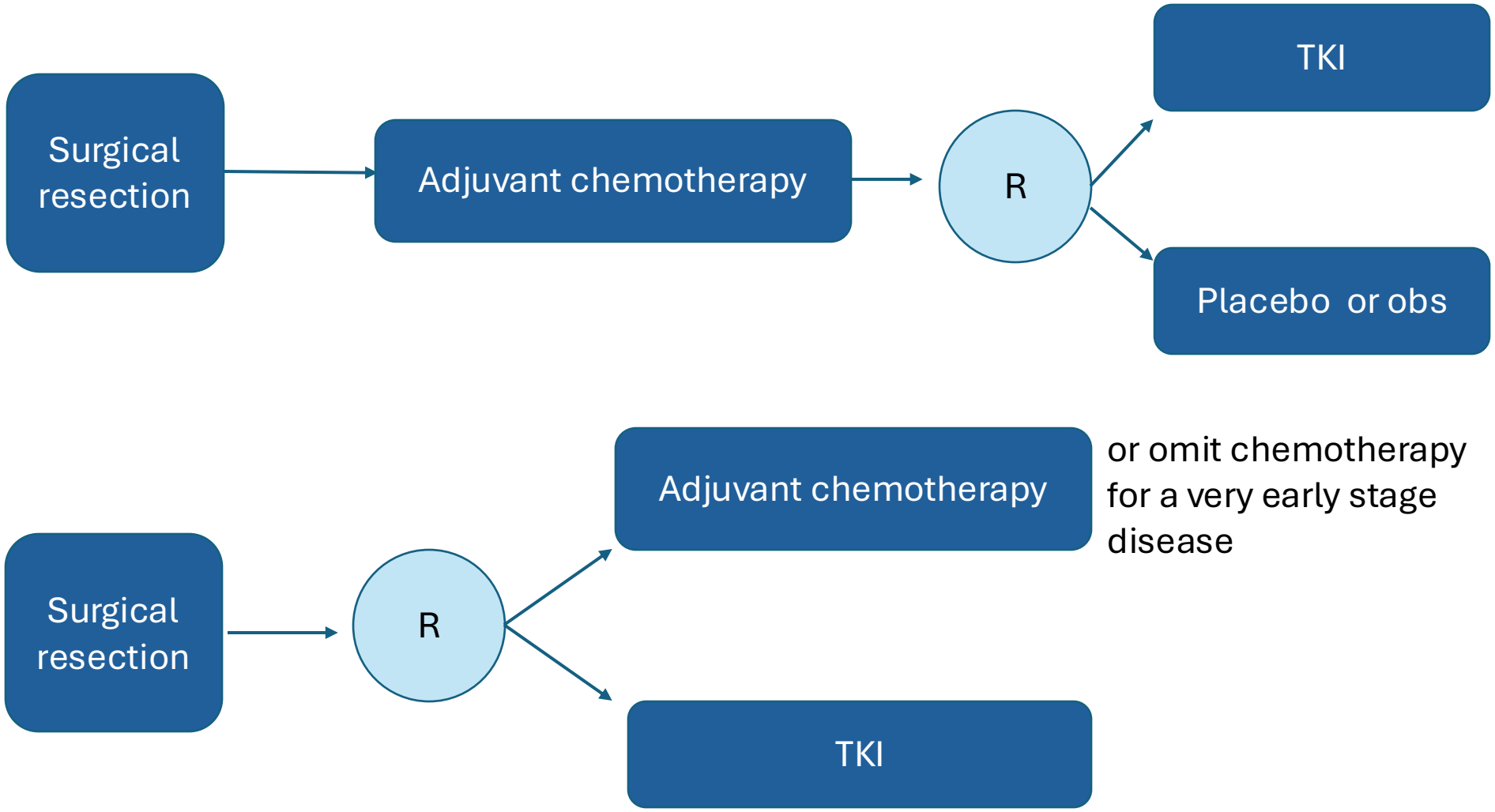
Combined analysis of whole-exome sequencing data from TCGA and other databases.



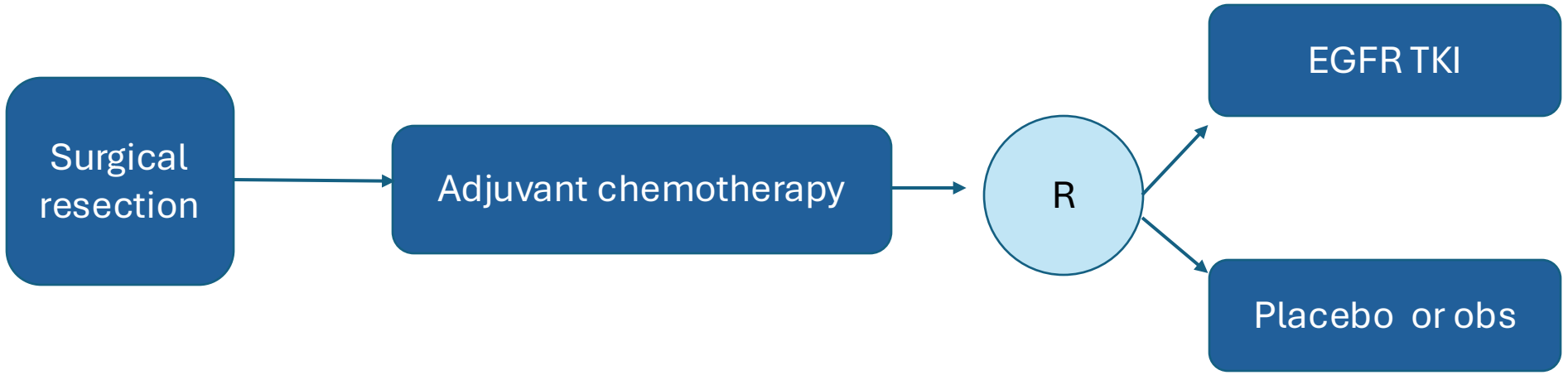
Overall similar frequencies between early and advanced stages
Prognostic value of each specific alteration is being debated.

Stephan-Falkenau et al International J of Molecular sciences 2022; Skoulidis et al Nat Reviews Cancer 2018

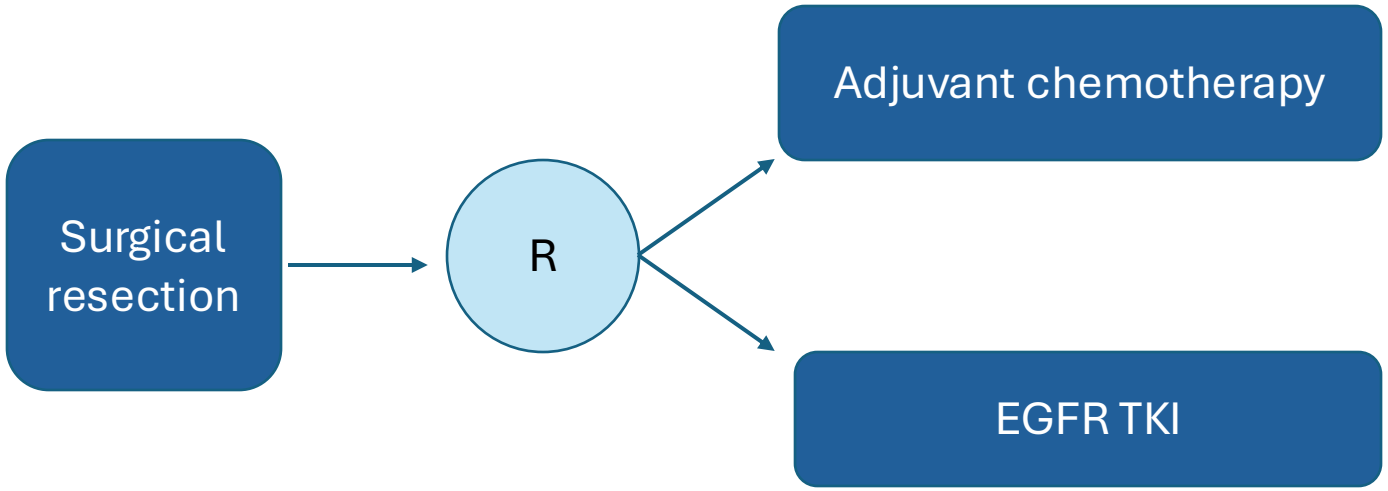
Potential approach to randomized adjuvant TKI studies



Potential approach to randomized adjuvant TKI studies



RADIANT[1]
BR 19 [2]
ADAURA[3,4]



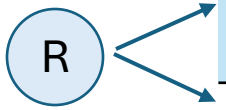
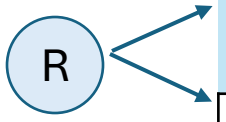
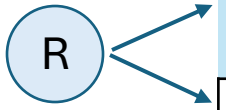
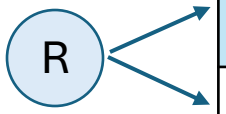
EVAN[5,6]
ADJUVANT/CTONG 1104[7,8,9]
EVIDENCE [10]
IMPACT[11]

Very early stage

CORIN[12]

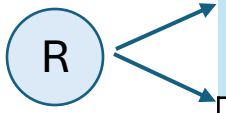
[1] Kelly K et al. *J Clin Oncol.* 2015;33:4007–4014; [2] Goss GD et al. *J Clin Oncol* 2013;31:3320–3326; [3] Wu Y-L et al. *N Engl J Med.* 2020; 383:1711-1723 [4] Herbst et al JCO 2023 [5] Yue D et al. *Lancet Respir Med.* 2018;6:863–873 [6] Yue et al JCO 2022 [7] Zhong WZ et al. *Lancet Oncol* 2018;19:139–148; [8]Wu et al, ASCO 2020. [9]Zhong et al JCO 2021 [10] He et all Lancet Resp Medicine 2021; [11] Tada et al. JCO 2021. 12 Ou et al Lancet 2023

DFS but not OS benefit in phase III randomized trials of TKI vs chemotherapy

Study (phase) Stage	Study design		Endpoints	Results
EVAN (II)[1,2] N=102 IIIA		Erlotinib x 2y	**2Y DFS** mDFS,OS	2y DFS 81.4% vs 44.6% RR 1.823 , p=0.0054 mDFS 42.4 m vs 21 m , HR 0.268 ; p<0.0001;
		cis/vinorelbine x 4		mOS 84.2 vs 61.1 HR 0.37;p 0.003
ADJUVANT /CTONG1104 (III)[3,4,5] N=222 II-IIIA		Gefitinib x 2 y	**mDFS** OS, 3 and 5y DFS, 5y OS	mDFS 30.8 vs 19.8, HR 0.56 p=0.001 3yDFS 31% vs 28% HR 0.84, p=0.74
		Cis/vinorelbine x 4		mOS 75.5m and 62.8m, HR 0.92; P 0.674
EVIDENCE (III)[6] N=322 II-IIIA		Icotinib x 2 y	**mDFS** OS, 3 and 5 y DFS	mDFS 47 vs 22.1, HR 0.36, P<0.0001 3y PFS 69.3% vs 32.5%
		Cis/vinorelbine(peme) x 4		OS immature. HR 0.91, 5y DFS not reported ?
IMPACT (III)[7] N=232 II-III		Gefitinib x 2 y	**mDFS** OS	mDFS 35.5 vs 25.0 HR 0.92, P .63
		Cis/vinorelbine x 4		5 Y OS 78%, 75%, HR 1.03, p 0.89

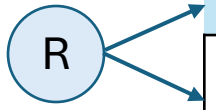
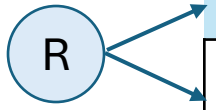
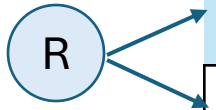
[1] Yue D et al. *Lancet Respir Med.* 2018;6:863–873 [2] Yue et al JCO 2022 [3] Zhong WZ et al. *Lancet Oncol* 2018;19:139–148; [4]. Wu et al, ASCO 2020. [5] Zhong et al JCO 2021 [6] He et all Lancet Resp Medicine 2021, [7] Tada et al. JCO 2021

Randomized trials of TKI vs observation without chemotherapy

Study (phase) Stage	Study design		Endpoints	Results
CORIN (II)[1] N=102 IB (7th edition)		Icotinib x 1y	**3Y DFS** mDFS,OS	3y DFS 96% vs 84% , p=0.041 mDFS NR
		observation		mOS not mature

[1] Ou et al Lancet 2023.

Randomized TKI vs observation trials post adjuvant chemotherapy

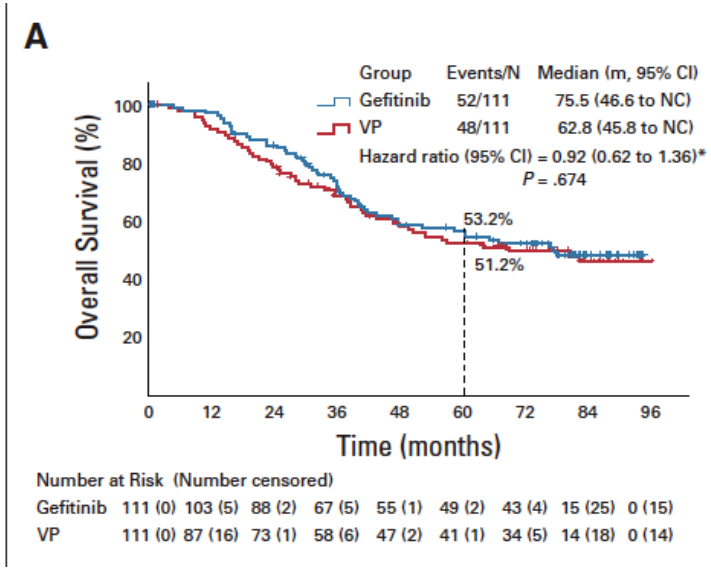
Study (phase)	Study design	Endpoints	Results
BR 19 (III)*[1] N=15 EGFR mt IB-IIIA	 Gefitinib x 2 y Placebo	**mDFS** OS, 3 and 5 y DFS	*EGFR mt mDFS HR,1.84; p 0.40* favoring placebo *EGFR mt mOS HR, 3.16, p 0.15* favoring placebo
RADIANT (III)**[2] N=161 EGFR mt IB-IIIA	 Erlotinib x 2 y Placebo	**mDFS** OS, DFS and OS EGFR mt	EGFR mt mDFS 46.4 v 28.5 m HR 0.61; 95% 0.38 to 0.98; P .039 (NSS) mOS not reported
ADAURA (III)[3,4,5] N=682 EGFR mt IB- IIIA	 Osimertinib x 3 y Placebo	**mDFS II-IIIA** DFS in all, OS	mDFS II-IIIA 65.8 vs 21.9. HR 0.23 (99% CI, 0.11-0.26); *P* <.001 mDFS all 65.8 vs 28.1 HR 0.27 (99.12% CI, 0.14-0.30); p<0.001 5Y OS 85% vs 73% HR 0.49 p <0.001

*phase III unselected. 15 patients with EGFR m ** phase III with EGFR overexpression and amplification, 161 with EGFR mt

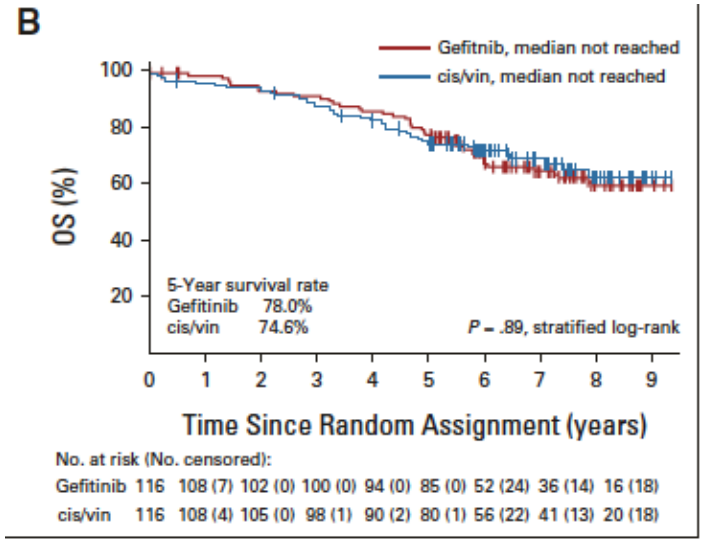
[1] Goss GD et al. *J Clin Oncol* 2013;31:3320–3326 [2] Kelly K et al. *J Clin Oncol.* 2015;33:4007–4014; [3] Wu Y-L et al. *N Engl J Med.* 2020; 383:1711-1723; [4] Herbst et al JCO 2023, [5] Tsuboi et al NEJM 2023

OS in phase III trials

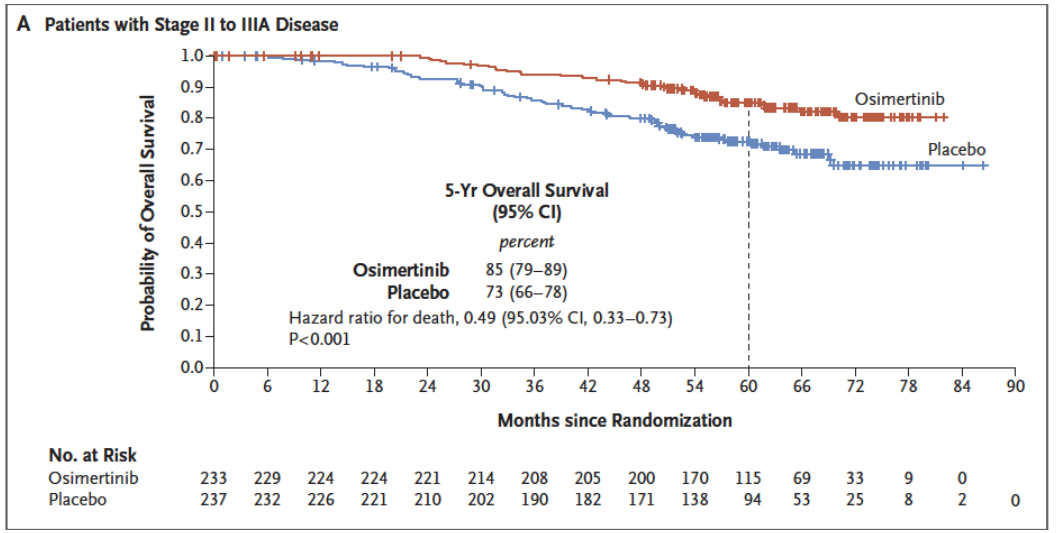
ADJUVANT[1]



IMPACT[2]

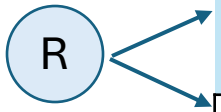


ADAURA[2]



[1]Zhong et al JCO 2021; [2]Tada et al. JCO 2021; [3] Tsuboi et al NEJM 2023

Randomized trials of TKI vs chemotherapy

Study (phase) Stage	Study design		Endpoints	Results
ALINA[1] N=257 IB- IIIA		Alectinib x 2y	**DFS II-IIIA, then all** mOS, CNS DFS	2y DFS II –IIIA 93.8% vs 63% , HR 0.24 p=0.001 2t DFS All 93.6% vs 63.7% HR 0.24 p -0.001
		Chemotherapy x 4		mOS not mature

[1] . [1]Wu et al NEJM 2024

Challenges and future directtions

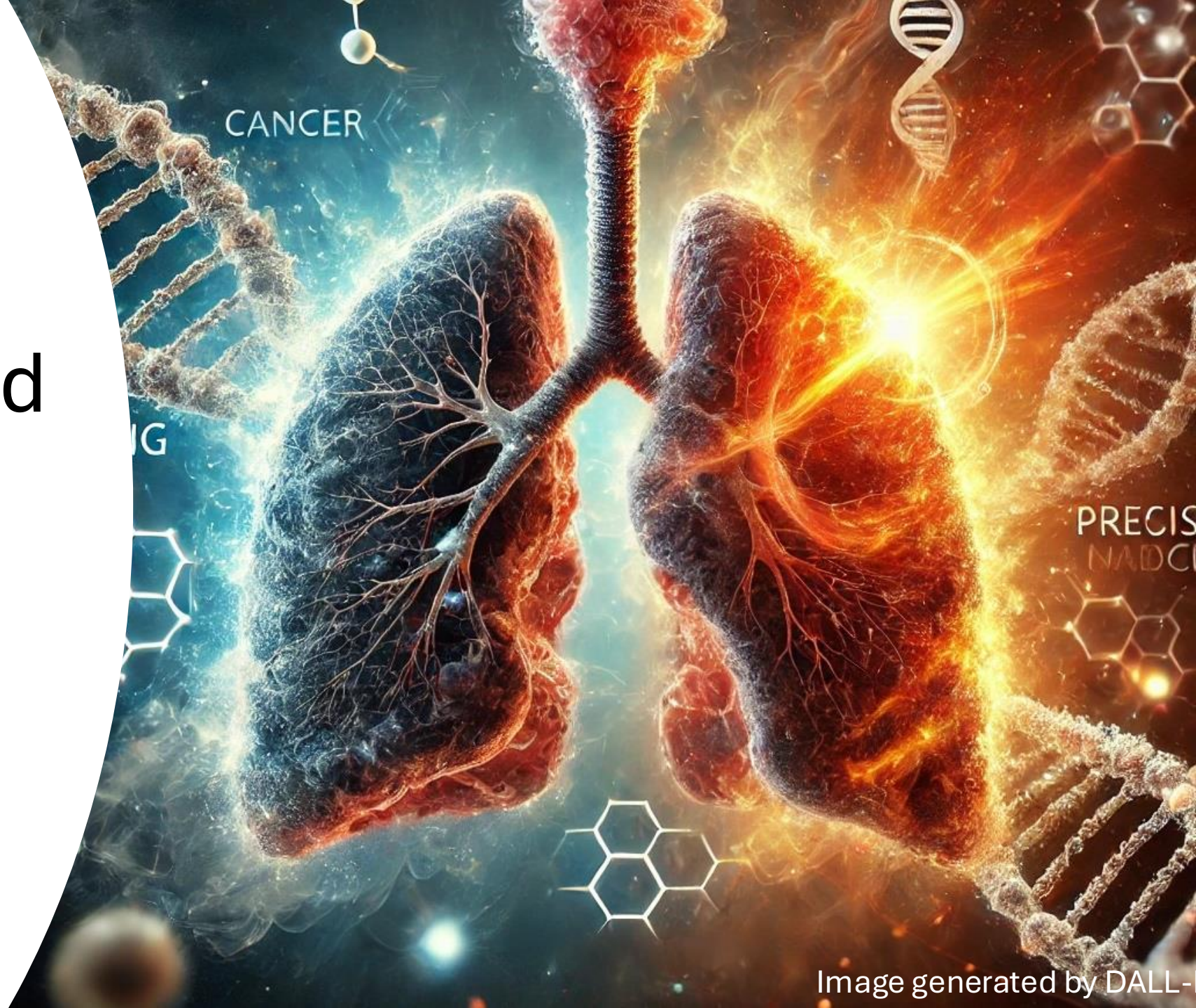


Image generated by DALL-

Questions left post ADAURA and ALINA

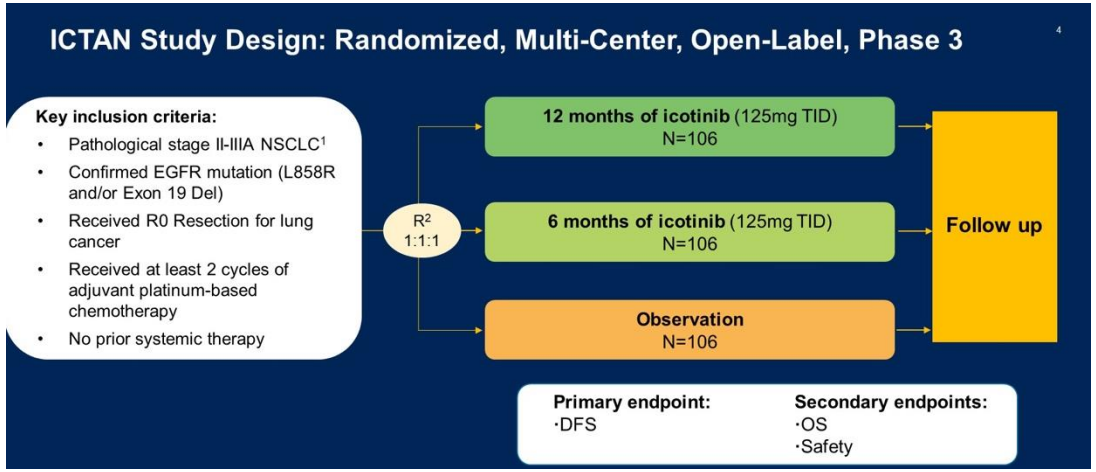
- What is an optimal duration of adjuvant targeted therapy
- Is chemotherapy necessary for all patients
- How do we manage long term toxicity of adjuvant targeted therapy
- Is there a benefit in neoadjuvant approach
- What about other rare mutations
- Very early stages (IA1, IA2, IA3, IB)
- MRD

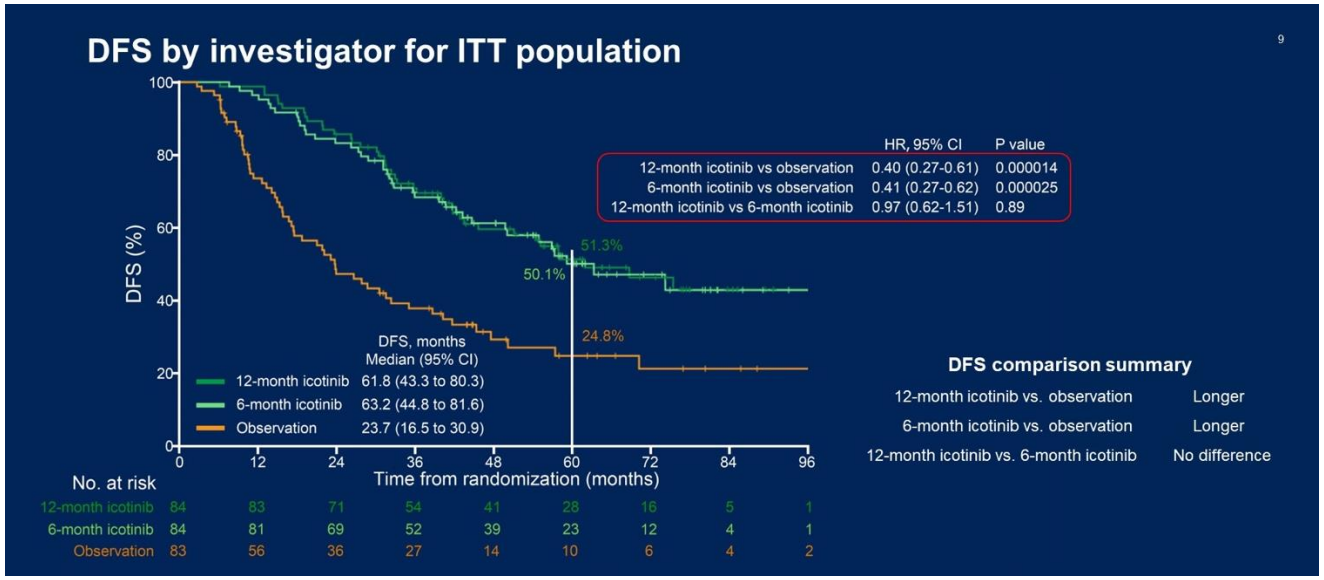
Next questions to answer

- What is an optimal duration of adjuvant targeted therapy
- Is chemotherapy necessary for all patients
- How do we manage long term toxicity of adjuvant targeted therapy
- Is there a benefit in neoadjuvant approach
- What about other rare mutations
- Very early stages (IA1, IA2, IA3, IB)
- MRD

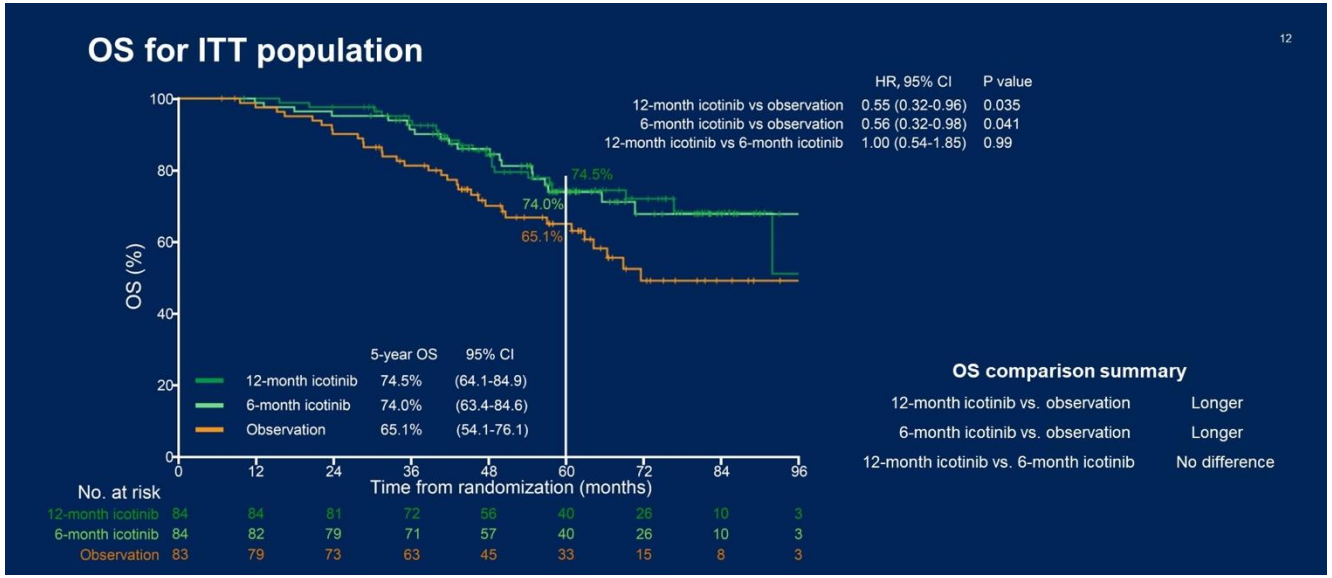
Duration of therapy

ICTAN, GASTO1003



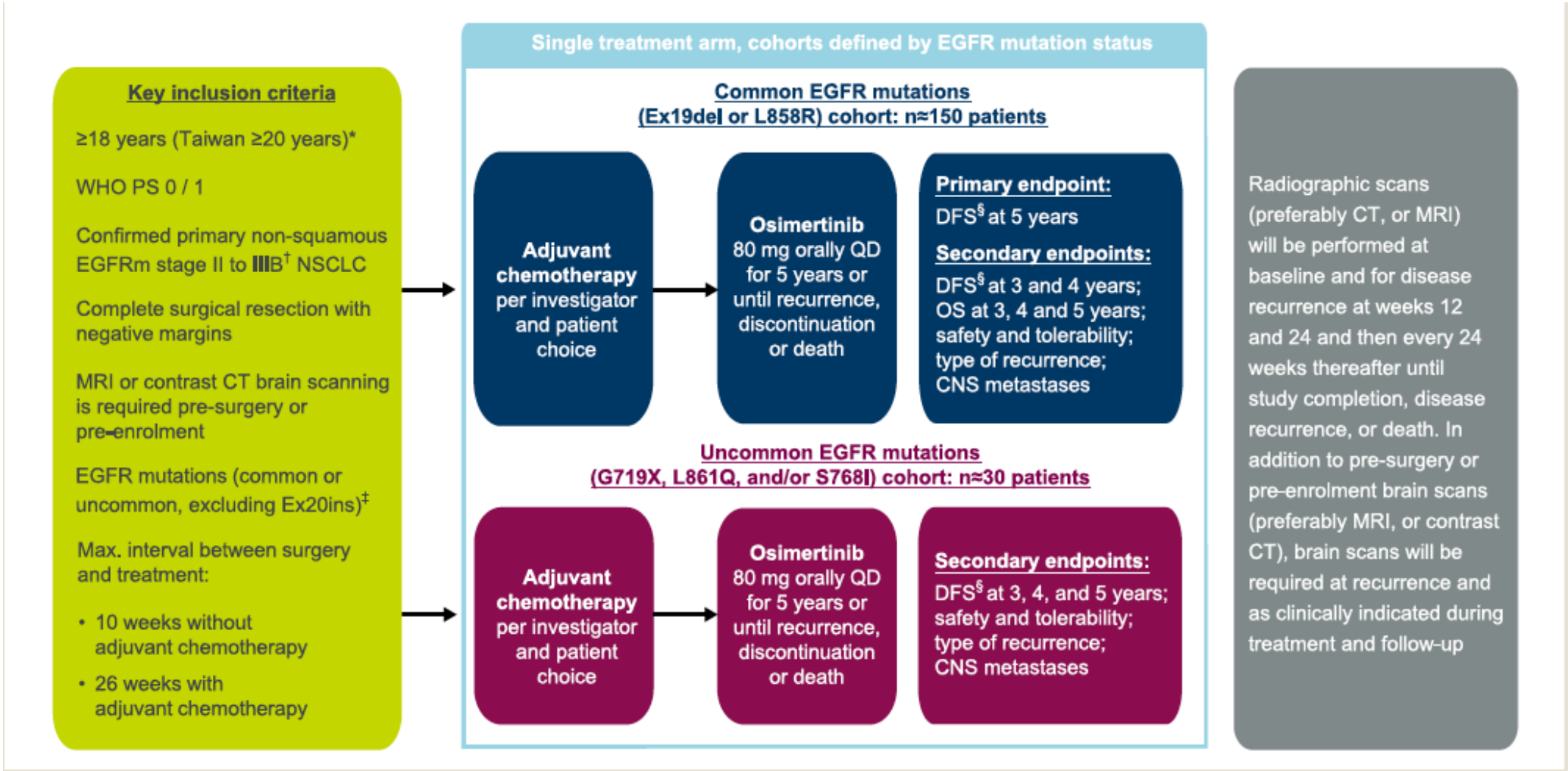


No difference in outcomes between stage II and III



Wang et al ASCO 2024

Extending duration. TARGET trial NCT05526755



Soo et al Clinical Lung Cancer 2024

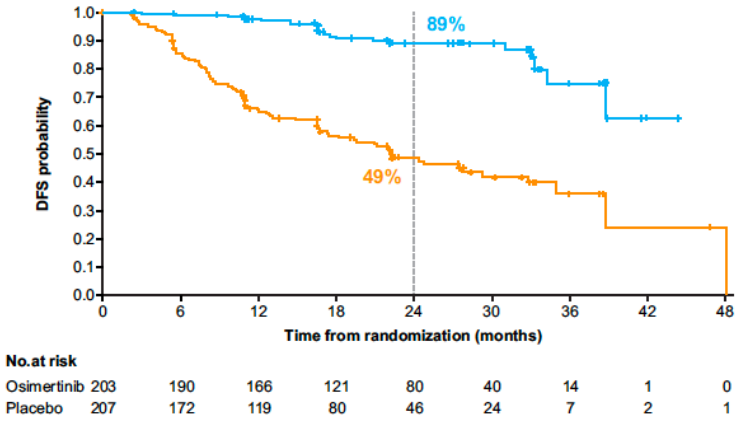
66% of patients completed adjuvant Osimertinib in ADAURA
41% completed placebo

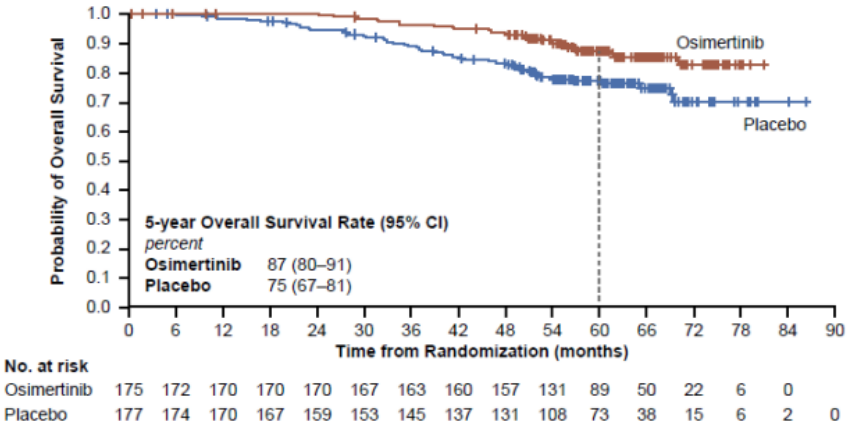
Next questions to answer

- What is an optimal duration of adjuvant targeted therapy
- Is chemotherapy necessary for all patients
- How do we manage long term toxicity of adjuvant targeted therapy
- Is there a benefit in neoadjuvant approach
- What about other rare mutations
- Very early stages (IA1, IA2, IA3, IB)
- MRD

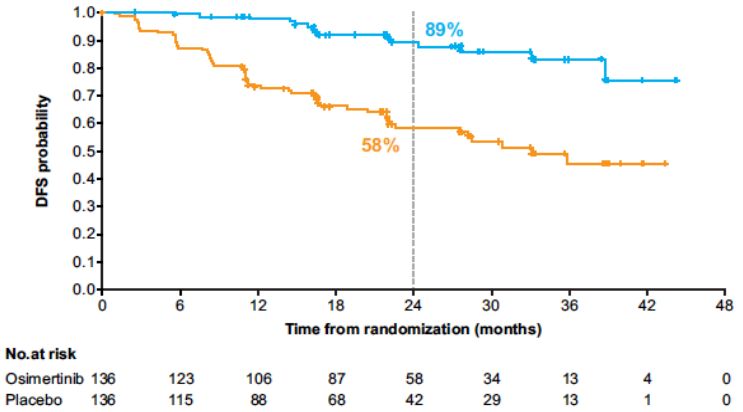
Outcomes by Receipt of Adjuvant Chemotherapy

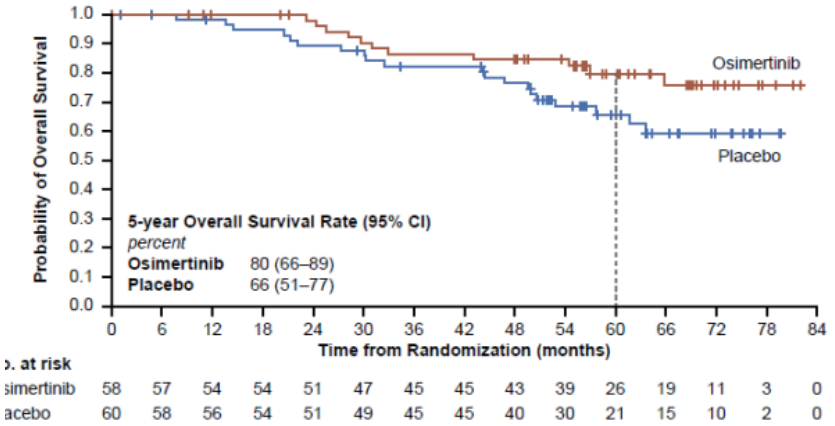
Received adjuvant chemotherapy





Did not receive adjuvant chemotherapy





Stage II-IIIA best survival in the group receiving chemotherapy and TKI

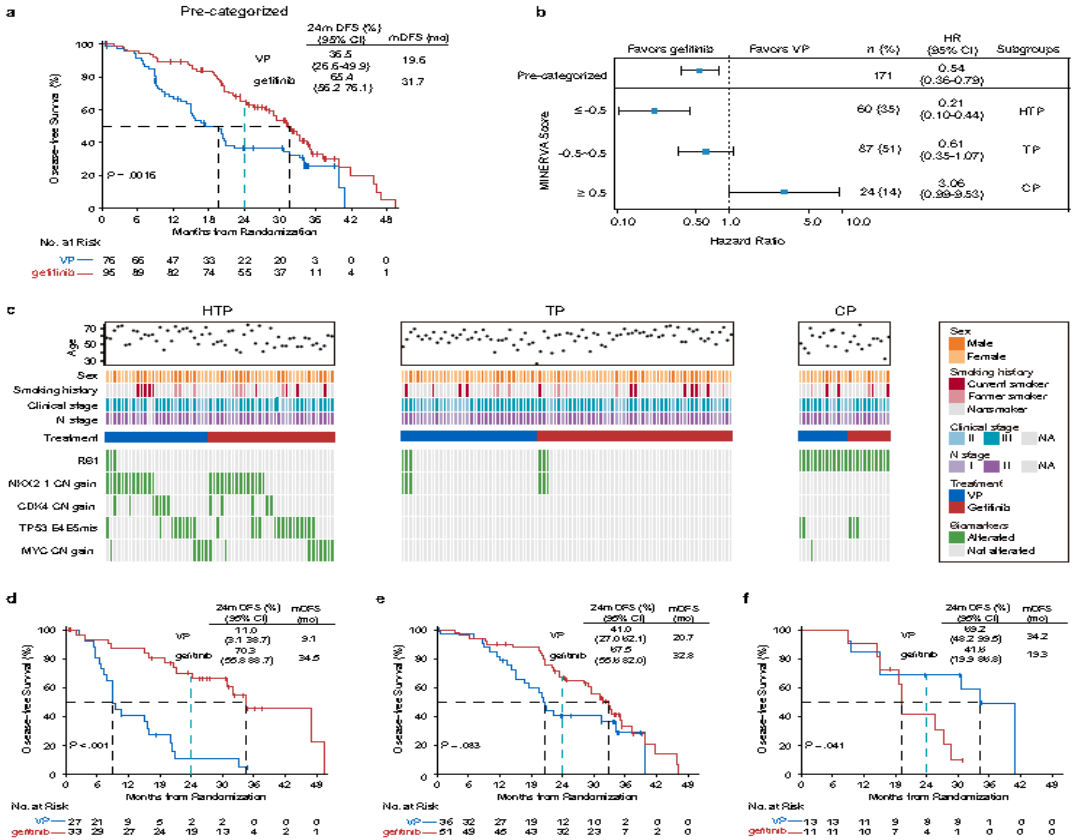
Treatment	5Y OS %
No chemotherapy placebo	66
Chemotherapy Placebo	75
No chemotherapy osimertinib	80
Chemotherapy osimertinib	87

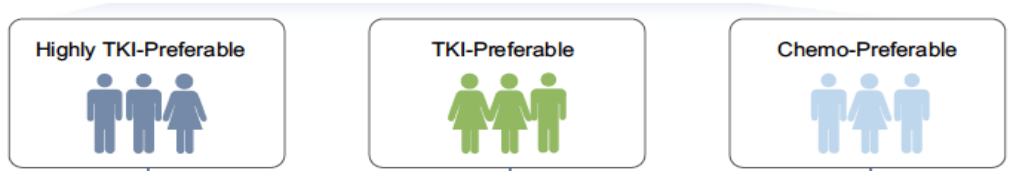
DFS patterns were similar by stage.

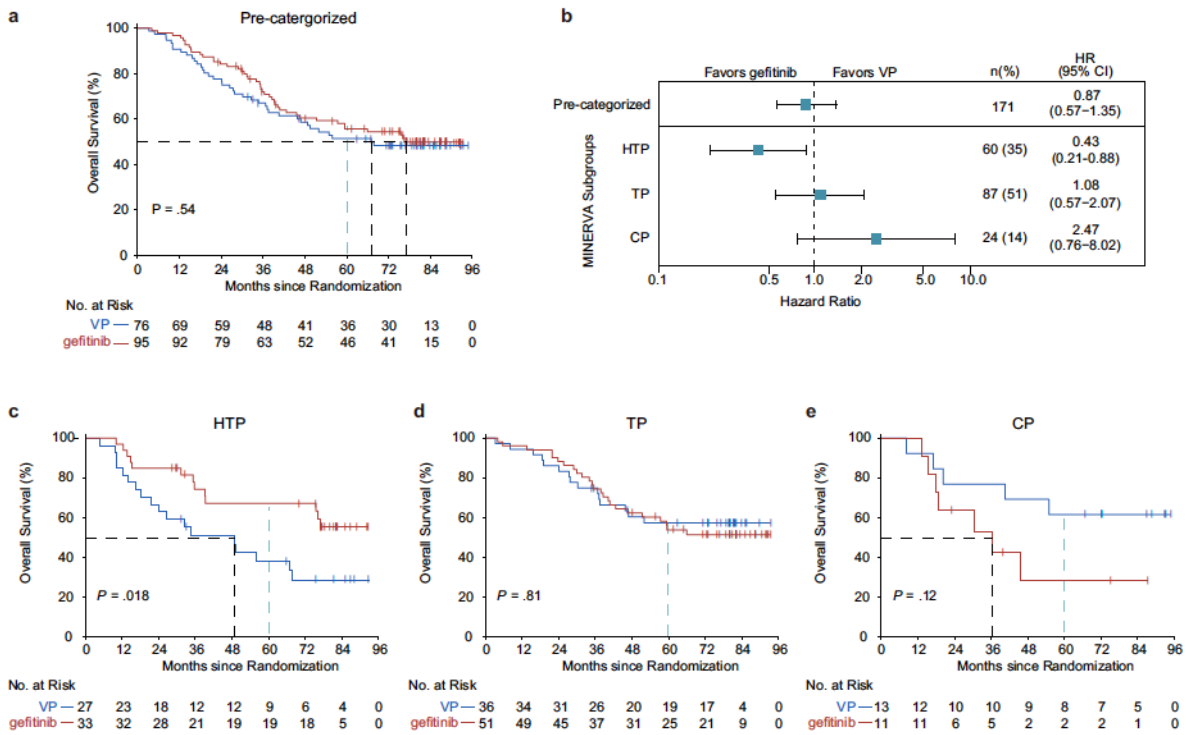
Wu YL et al. *J Thorac Oncol*. 2022;17(3):423-433; Wu YL et al. *N Engl J Med.* 2023;383(18):1711-1723. Tsuboi et al NEJM 2023 (s4)

Multiplegene INdex to Evaluate the Relative benefit of Various Adjuvant therapies (MINERVA) score

ADJUVANT trial . 171 patients with genomic profiling







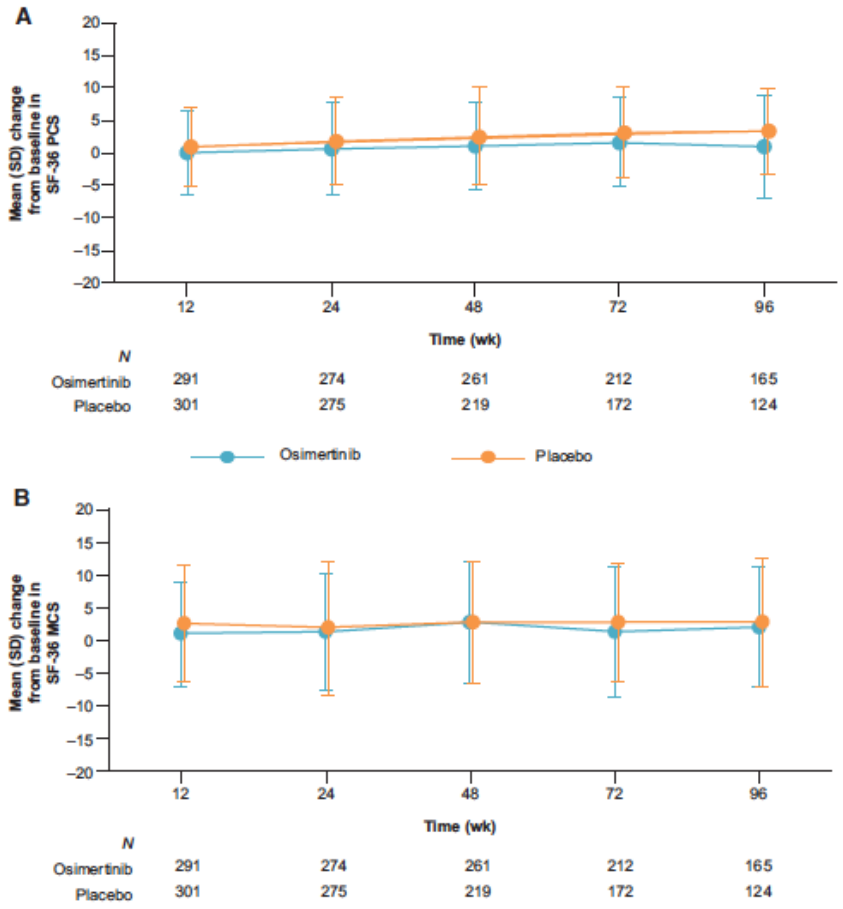
Si-Yang Liu et al Nature Communications 2021

Next questions to answer

- What is an optimal duration of adjuvant targeted therapy
- Is chemotherapy necessary for all patients
- How do we manage long term toxicity of adjuvant targeted therapy
- Is there a benefit in neoadjuvant approach
- What about other rare mutations
- Very early stages (IA1, IA2, IA3, IB)
- MRD

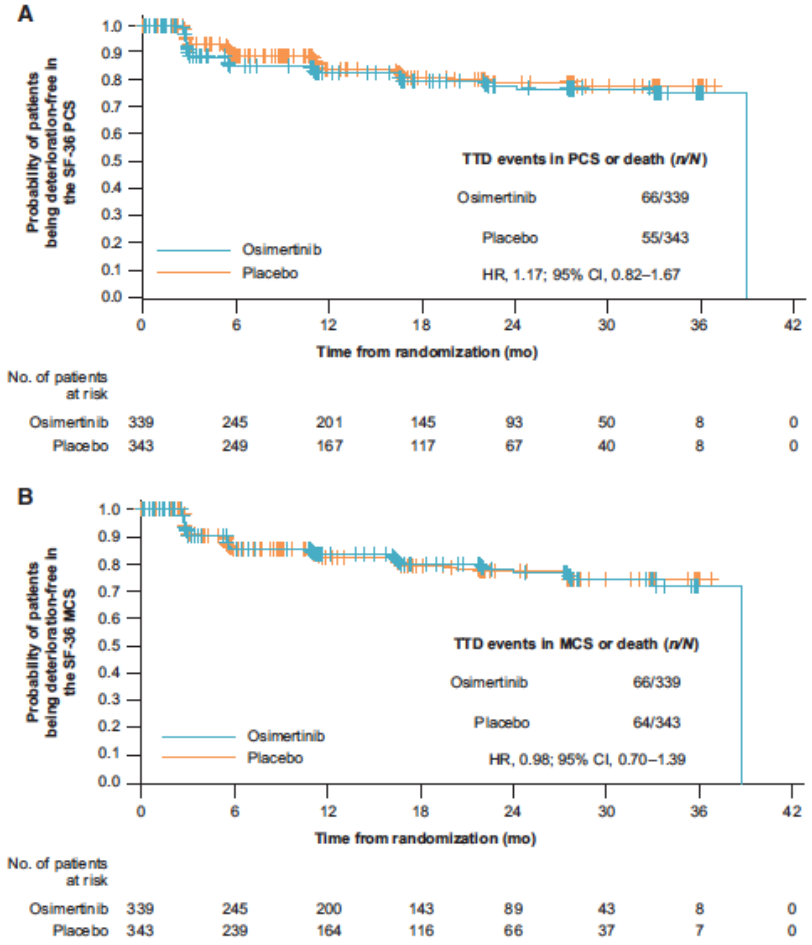
HRQ0L SF 36. No meaningful differences

PCS and MCS T scores



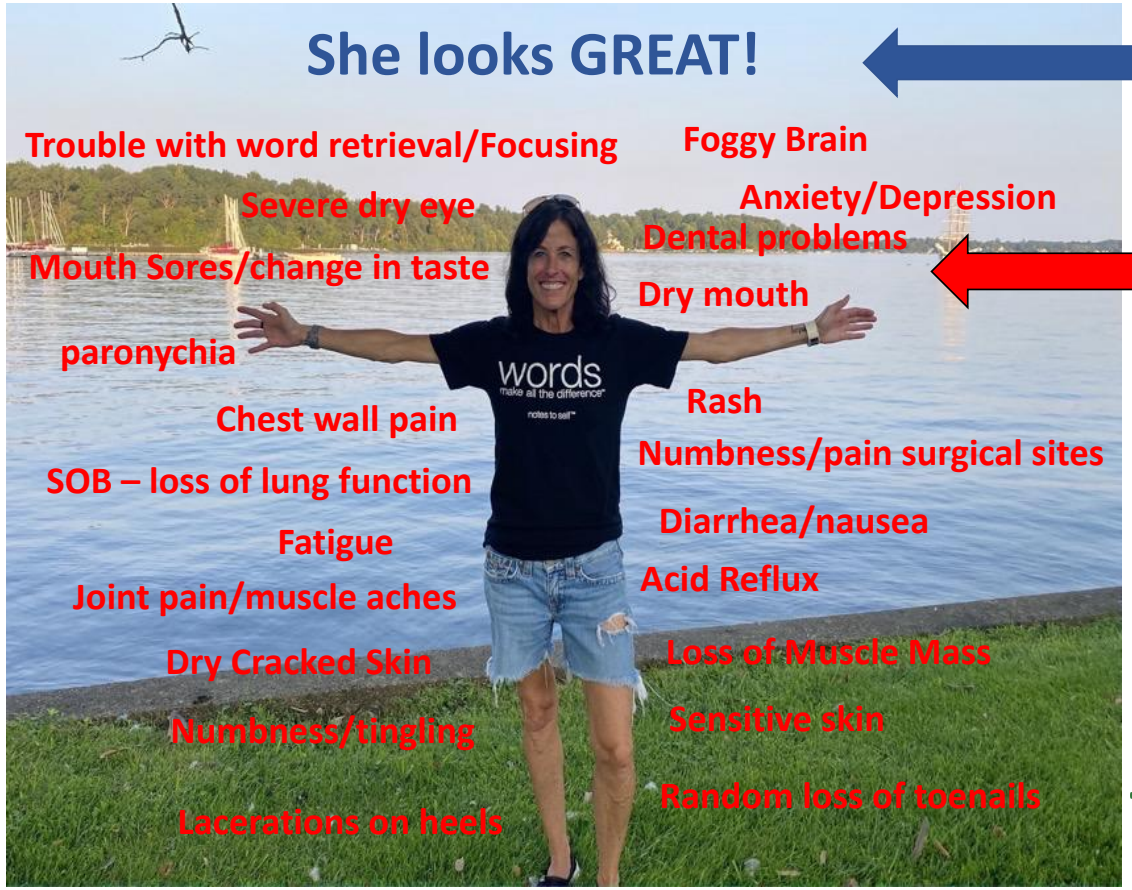
PCS physical component score
MCS mental component score

Time to deterioration of PCS and MCS scores



Margarita Majem1 et al Clinical Cancer Research 2022

Do we know how to measure toxicity on the patient level?



How my care team and others perceive I feel

How I actually feel

The term *manageable* to clinicians and researchers **does not equal** tolerable for patients on indefinite, multiple lines of therapy!

Tolerable is Relative!

Jill Feldman, Lung Cancer Patient and Advocate @jillfeldman4

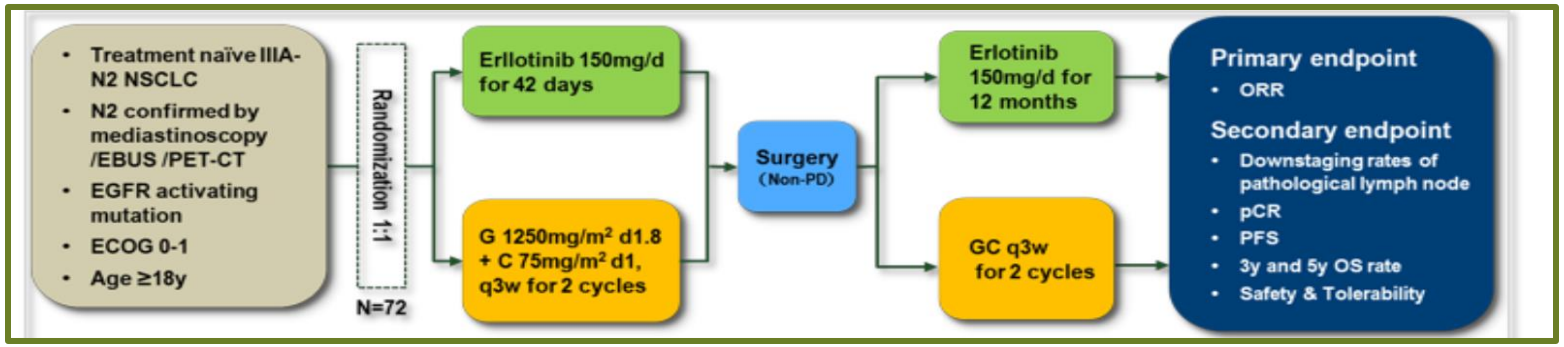
While HRQoL was not impaired in a measurable way. This does not mean that our patients do not have side effects

Next questions to answer

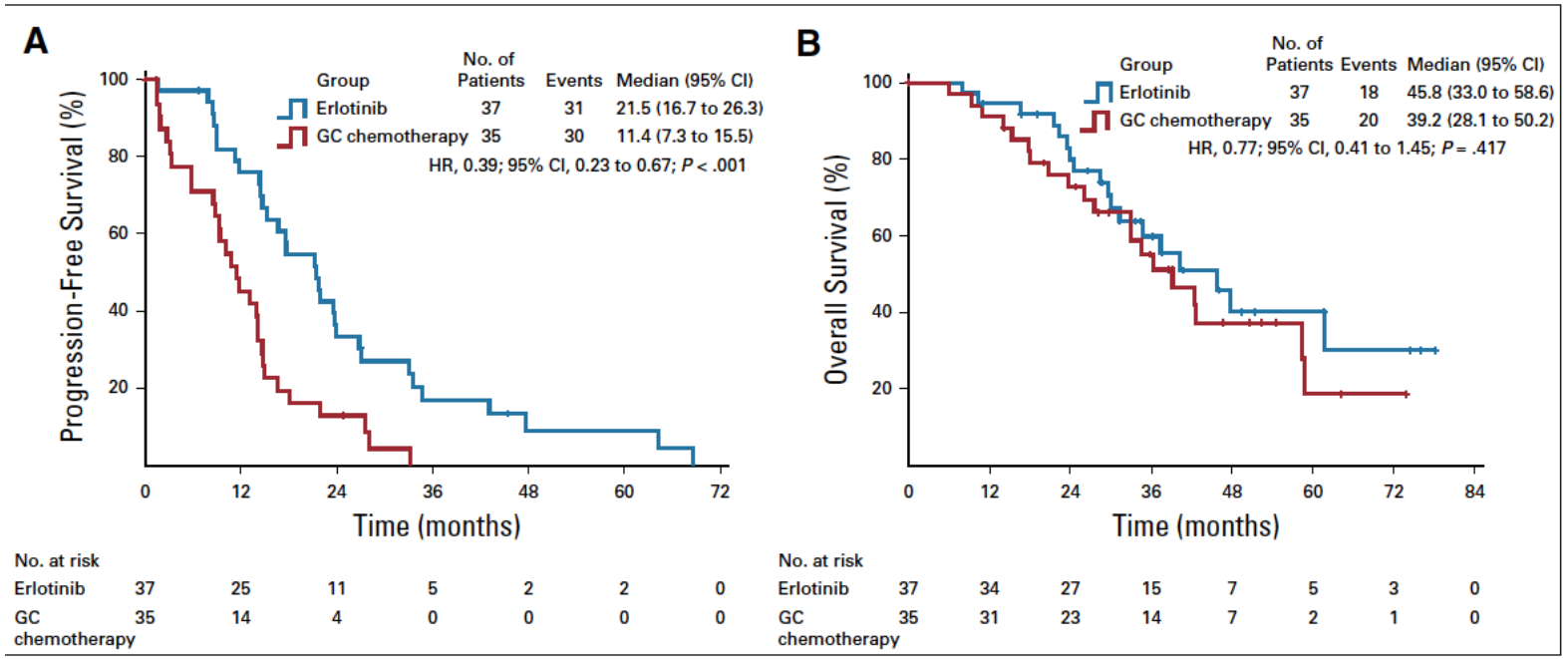
- What is an optimal duration of adjuvant targeted therapy
- Is chemotherapy necessary for all patients
- How do we manage long term toxicity of adjuvant targeted therapy
- Is there a benefit in neoadjuvant approach
- What about other rare mutations
- Very early stages (IA1, IA2, IA3, IB)
- MRD

Neoadjuvant trials EGFR

EMERGING –CTONG 1103



N=72
ORR 54.1% vs 34.3% (OR, 2.26; 95% CI, 0.87 to 5.84; P = .092)
pCR 0%
MPR 9.7% vs 0%



Zhong et al JCO 2018

Neoadjuvant Osimertinib trials

NeOs

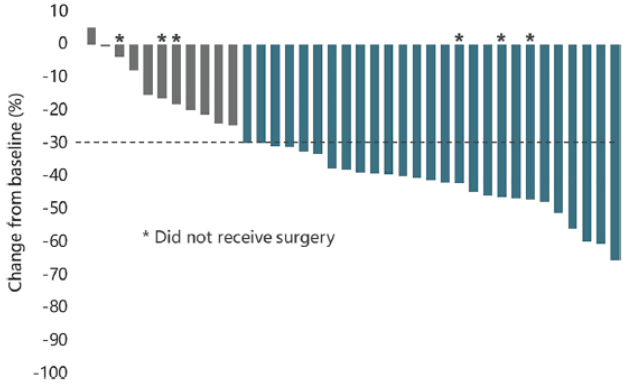
N=40 IIA-IIIB

Osimertinib x 6 weeks

ORR 71.1 %

R0 resection 93.8 %

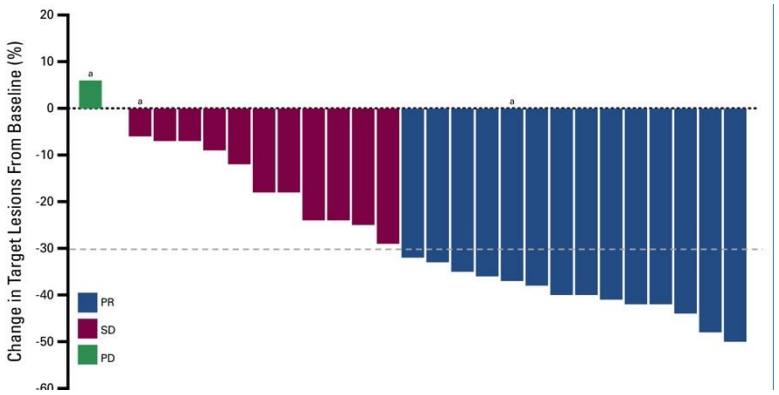
MPR 10.7% pCR3.6%



LV et al Lung Cancer 2023

Blakely et al

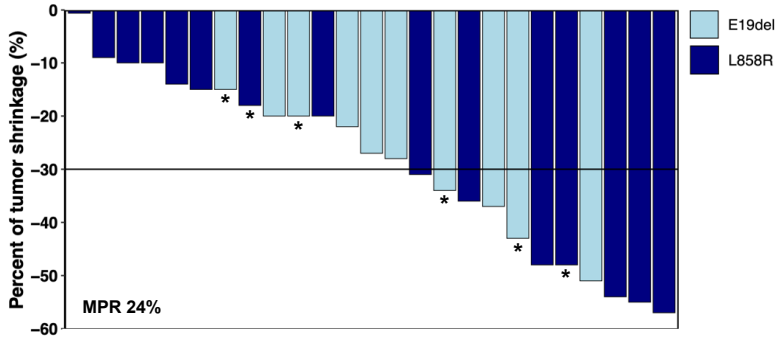
- N=27
- Osimertinib 4-8 weeks
- ORR 51%
- R0 resection 96%
- MPR 16.7%, pCR 0



Blakely et al JCO 2024

NORA

- N=25 I-IIIA
- Osimertinib 8 weeks
- ORR 44%
- R0 resection 100%
- MPR 24%, pCR 0



Lee et al JTO 2023

ALK TKI

- Phase II SAKULA trial
- neoadjuvant ceritinib for 12 weeks for *ALK*-positive stage II-III NSCLC
- Only enrolled 7 patients (stage IIIA) and was closed due to slow accrual
- One patient withdrew from the study (dose limiting toxicity)
- 100% ORR and 6 patients underwent surgical resection of which 57% MPR and 28% pCR

Zenke JTO 2019

- Phase II
- neoadjuvant crizotinib (28-120 days)
- 11 patients
- ORR 91%
- R0 91%
- 2 patients with pCR (18%)

Zhang et al JTO 2018

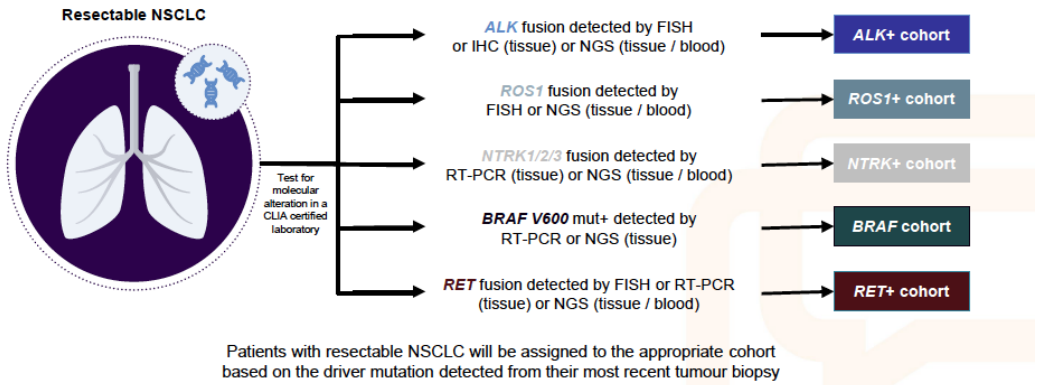
Ongoing neoadjuvant trials

Study	Phase	Stage	Regimen	N	Primary end point
NEOADAURA NCT04351555	III	II-IIIB	Osi vs Osi+chemo vs chemo->investigators choice osimertinib	351	MPR
ANSWER NCT04455594	II	IIIA N2	Almonertinib vs erlotinib +chemotherapy	168	ORR
NEOIPOWER NCT05104788	II	II-IIIB	Icotinib + chemotherapy -> surgery	27	MPR
NCT04201756	II	III	Afatinib 16 w-> surgery-> afatinib X 1y	47	ORR
NCT03749213	II	IIIA N2	Icotinib 8w-> surgery-> icotinib 2Y	36	ORR
NeolazBAL NCT05469022	II	EGFF mt on BAL	Lazertinib x 9 weeks ->surgery-> laz 3 year		

Ongoing neoadjuvant trials

Study	Phase	Stage	Regimen	N	Primary end point
NCT05118854	II	IIA-IIIB	Sotorasib + plat doublet	27	MPR
NeoCAN NCT05472623	II	IB-IIIA	Adagrasib Adagrasib + plat doublet	21 21	pCR
Geometry N NCT04926831	II	IB-IIIA	Capmatinib x 8 weeks _> surgery -> capmatinib x 3 years	9 stage 1 42 stage 2	MPR
NAUTIKA1			Multiple drivers		

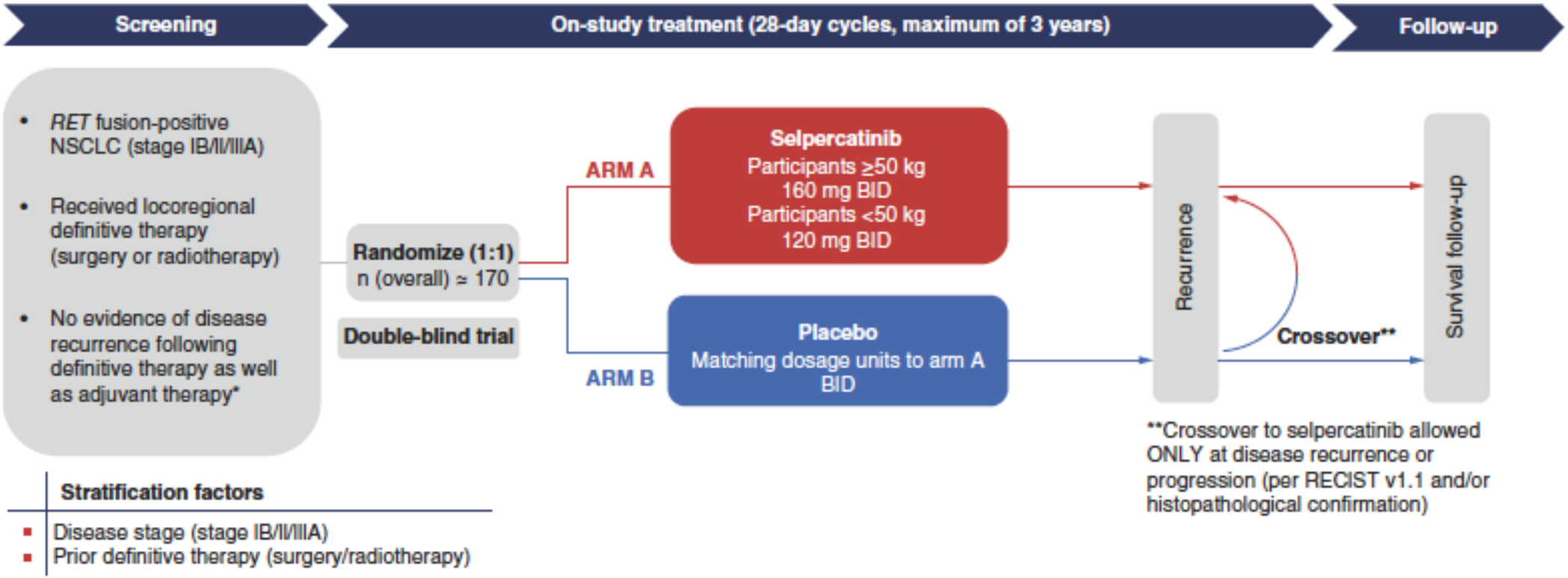
NAUTIKA-1 (NCT04302025)



Next questions to answer

- What is an optimal duration of adjuvant targeted therapy
- Is chemotherapy necessary for all patients
- How do we manage long term toxicity of adjuvant targeted therapy
- Is there a benefit in neoadjuvant approach
- What about other rare mutations
- Very early stages (IA1, IA2, IA3, IB)
- MRD

Libretto 432 NCT04819100

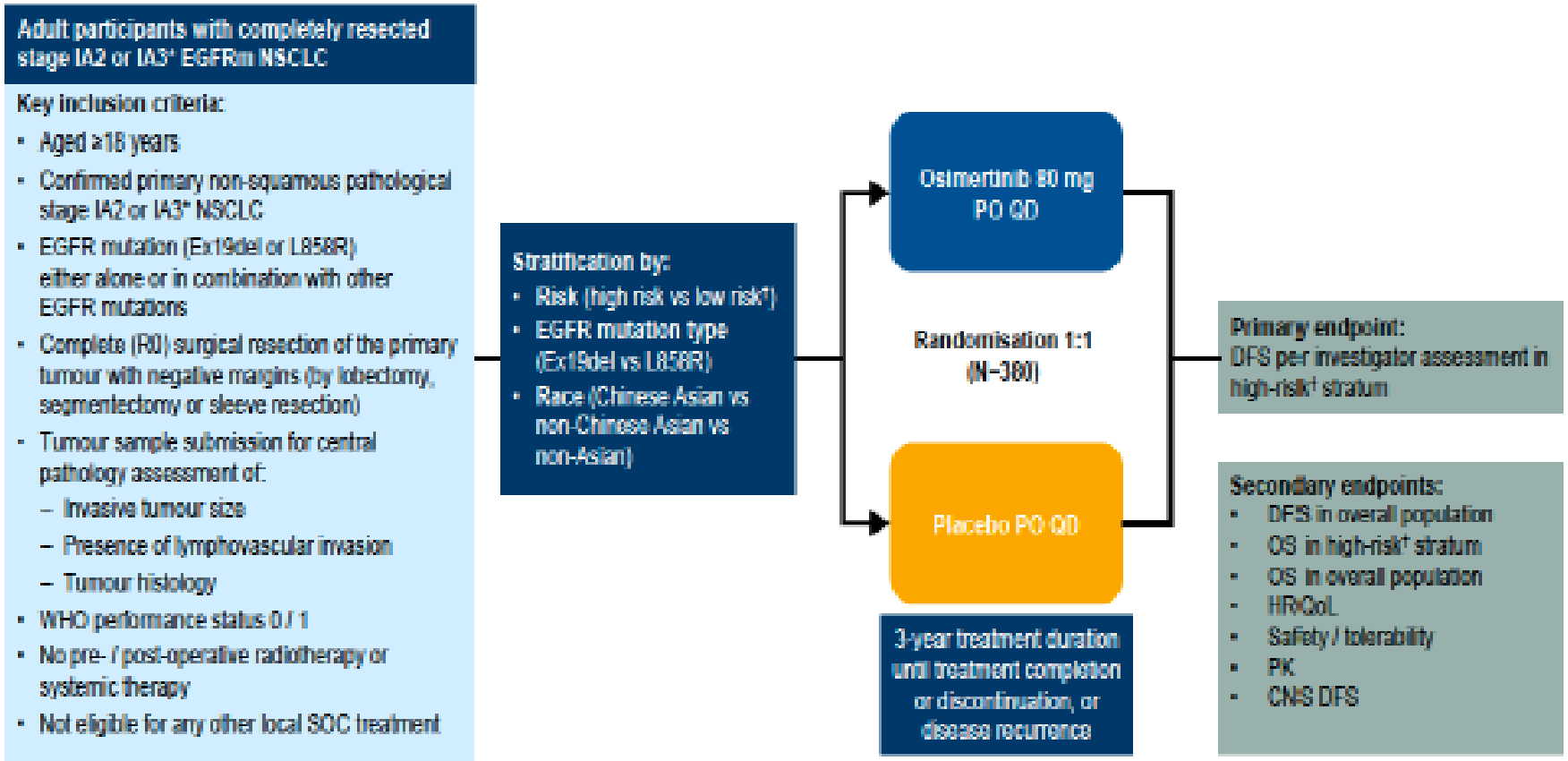


Next questions to answer

- What is an optimal duration of adjuvant targeted therapy
- Is chemotherapy necessary for all patients
- How do we manage long term toxicity of adjuvant targeted therapy
- Is there a benefit in neoadjuvant approach
- What about other rare mutations
- Very early stages (IA1, IA2, IA3, IB)
- MRD

Figure 1. ADAURA2 study design

- ADAURA2 (NCT05120349) is a Phase III, global, randomised, double-blind, placebo-controlled study of adjuvant osimertinib in stage IA2–IA3 EGFRm (Ex19del or L858R) NSCLC following complete tumour resection



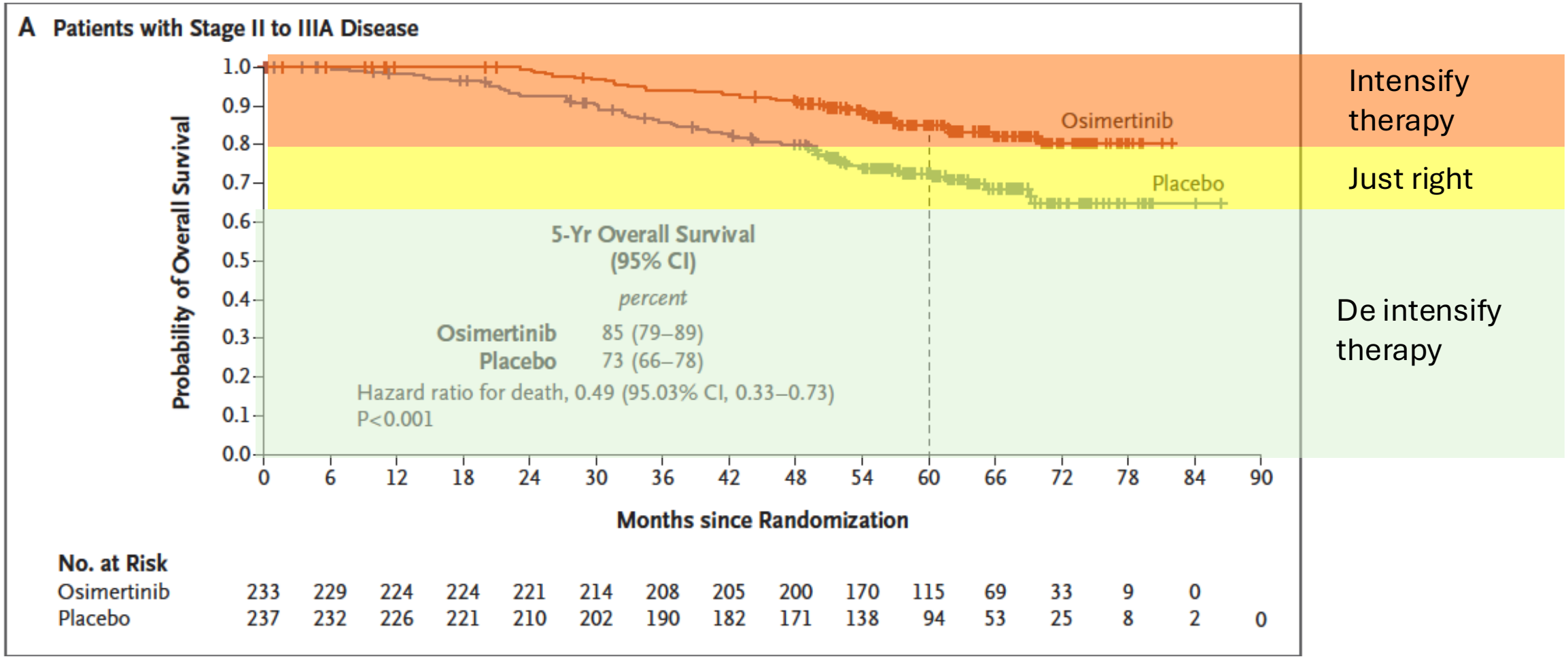
*Based on the eighth edition UICC / AJCC TNM staging system. †High risk defined as presence of ≥1 of the following factors: largest diameter of invasive component of primary tumour >2 cm, lymphovascular invasion and / or high-grade histology (≥20% micropapillary, solid or complex gland adenocarcinoma). Low risk defined as absence of any high-risk factors.

AJCC, American Joint Committee on Cancer; CNS, central nervous system; DFS, disease-free survival; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HRQoL, health-related quality of life; NSCLC, non-small cell lung cancer; OS, overall survival; PK, pharmacokinetics; PO, orally; QD, once daily; SOC, standard of care; TNM, tumour, nodes and metastases; UICC, Union for International Cancer Control; WHO, World Health Organization.

Next questions to answer

- What is an optimal duration of adjuvant targeted therapy
- Is chemotherapy necessary for all patients
- How do we manage long term toxicity of adjuvant targeted therapy
- Is there a benefit in neoadjuvant approach
- What about other rare mutations
- Very early stages (IA1, IA2, IA3, IB)
- MRD

Can we individualize treatment decisions



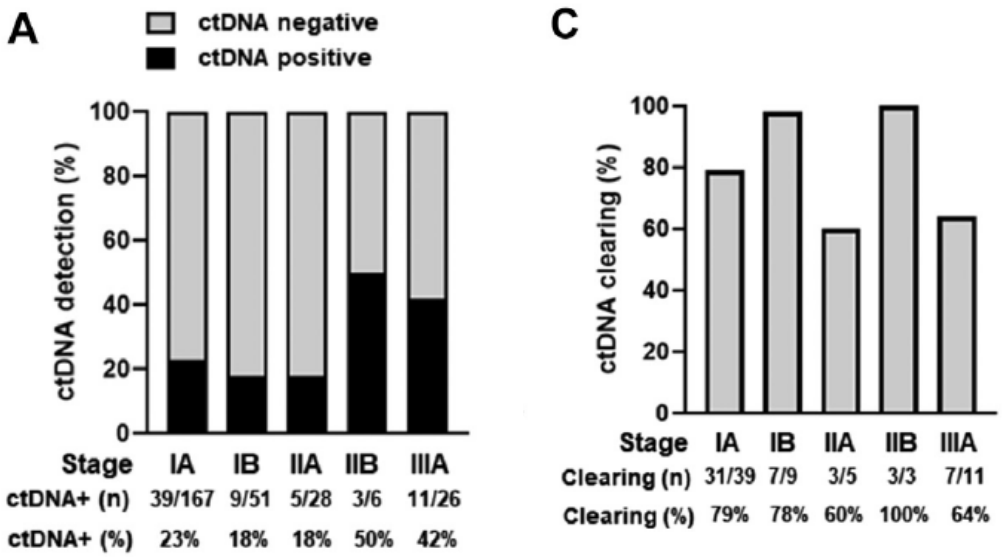
Tsuboi et al NEJM 2023

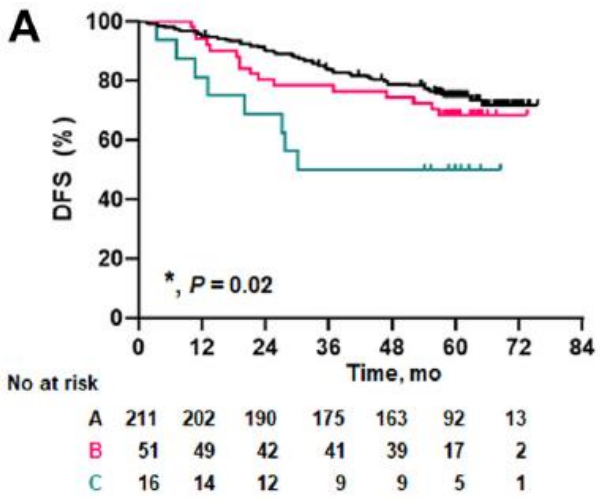
Baseline ctDNA-positive or MRD-positive status is associated with poor DFS in curative resected stages I to IIIA EGFR-M.

- Prospective cohort, 278 completely resected stage IA to IIII EGFR-mutant NSCLC (60% stage IA), longitudinal ctDNA status by ddPCR
- Pre-surgery ctDNA detected in 67 (24.1%) patients
  - ✓ 76% (51 of 67) exhibited ctDNA clearance 4 wks after surgery
- Higher 3-year DFS in patients who were ctDNA negative at baseline:
  - ✓ ctDNA negative at baseline (N=211), 3-yr DFS 83.3%
  - ✓ ctDNA positive and MRD negative after surgery (N=51), 3-yr DFS 78%
  - ✓ ctDNA positive and MRD positive after surgery (N=16), 3-yr DFS 50%

Baseline ctDNA

Post surgical clearance



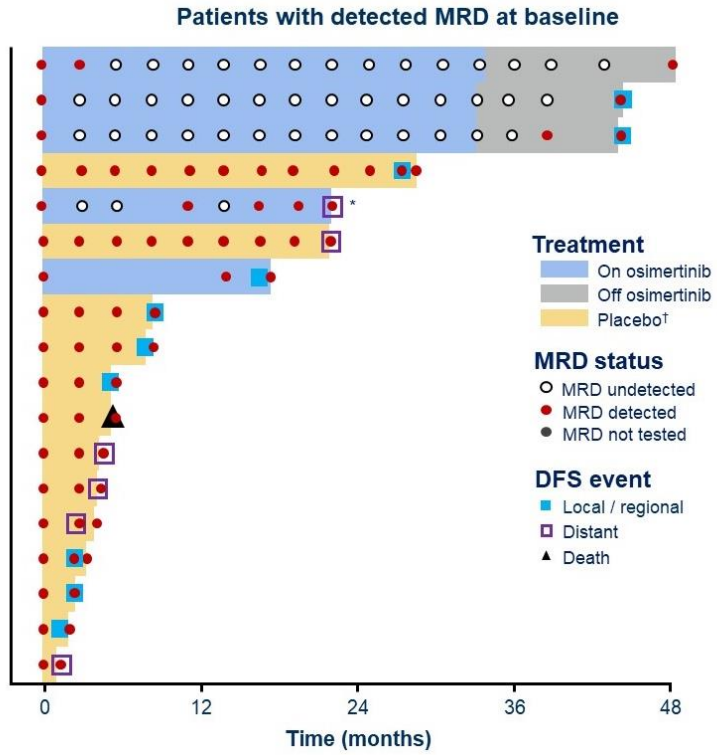


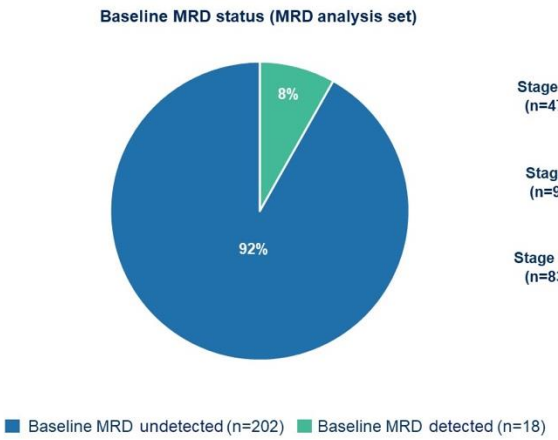
A ctDNA neg
B ctDNA pos,MRD neg
C ctDNA pos, MRD pos

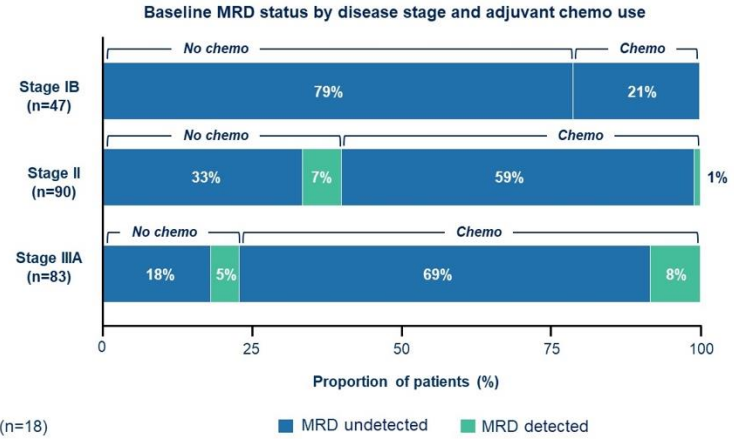
Jung et al JTO 2023

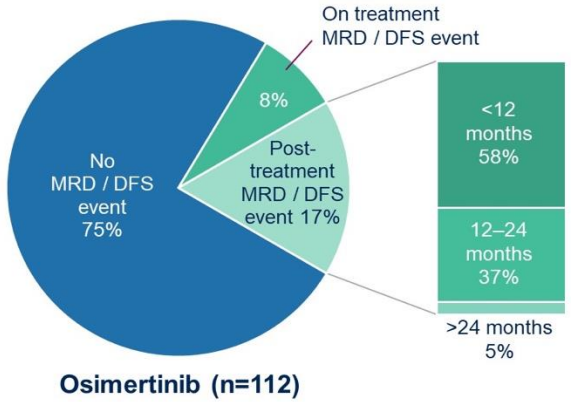
Tumor Informed MRD in ADAURA

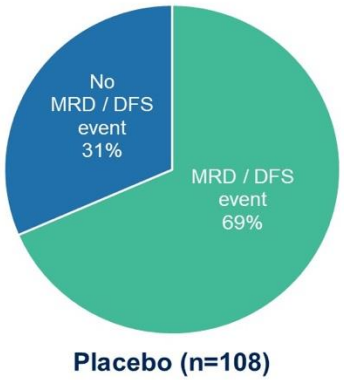
- MRD technology RaDaR
- 220 (112 Osimertinib, 108 Placebo) had MRD assay built
- Majority of patients had undetected MRD at baseline
- MRD detection at baseline was associated with worse outcome
- 18 patients with detected MRD at baseline
  - 4/5 cleared in Osimertinib group
  - 0/13 cleared in Placebo group
- Most MRD/DFS events in Osimertinib arm happened after Osimertinib discontinuation





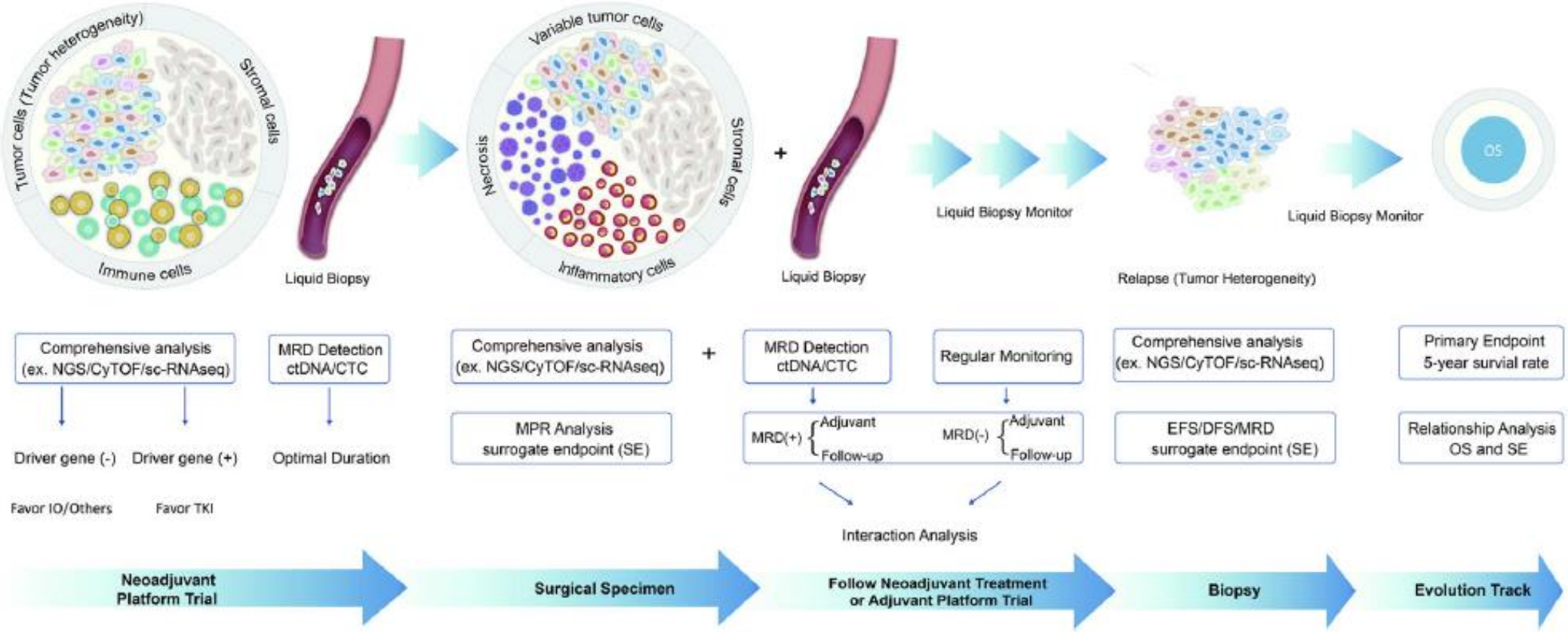






John et al ASCO 2024

Perioperative Clinical Trial design

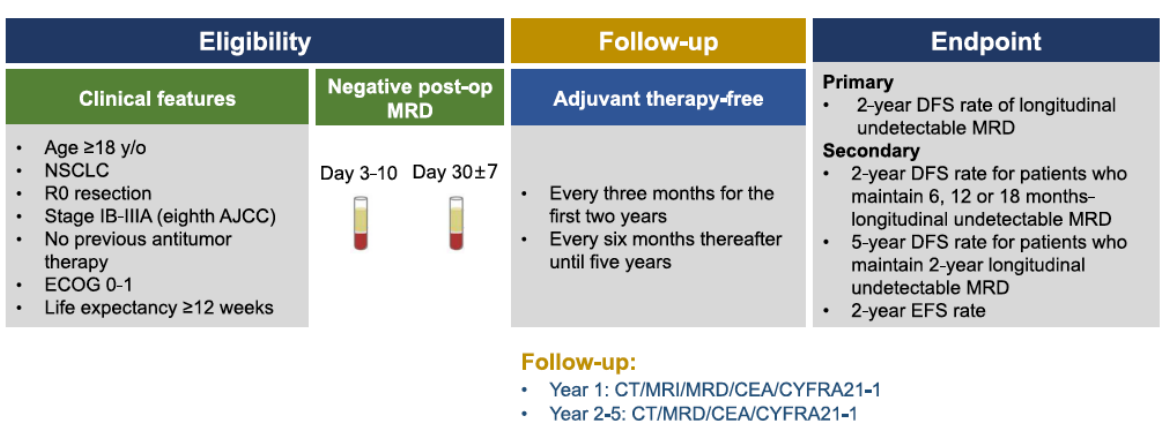


Liu SY, Wu YL et al. Curr Treat Options in Oncol 2022

Adjuvant trials based on MRD

CTONG2201/NCT05457049:
Adjuvant Therapy Omission for Resected NSCLC Patients With Longitudinal Undetectable MRD

Patients with stage IB-IIIA s/p curative resection
2 negative MRD (day 3-10, Day 30+/-7)
No adjuvant therapy
Tumor informed MRD_Navigator, Beijing GenePlus Technology Co., Ltd



Zhang et al Clinical Lung cancer 2023

FATE/CTONG 2105 (NCT05536505):
Adjuvant Treatment based on MRD for EGFR Mutant NSCLC

Patients with stage IB-IIIA s/p curative resection
2 negative MRD (day 3-10, Day 30+/-7)
MRD + icotinib stop and go
MRD – observation till MRD + then Osimertinib stop and go

MRD, challenges to be addressed

- Best technology for MRD detection
- Development of robust MRD technologies is vital with the aim of minimizing the false-negative rates

Multidisciplinary approach.

Image generated by DALL-E

MultiD collaborations are important

The adjuvant therapy discussion begins with the surgeon

“But I thought you got it all!”

Summary

- Testing for oncogenic drivers is important for all disease stages
  - FDA approval for adjuvant therapy for EGFR and ALK
  - Opportunity to enroll into clinical trials.
- Chemotherapy is still important and has a small but well proven benefit
- In EGFR mt adjuvant Osimertinib prolongs OS
- Many questions still need to be answered
  - Duration of therapy
  - Very early stage
  - Role of intensification or deintensification of therapy
  - Role of neoadjuvant TKI
- Other less frequent alterations will present a challenge with trial recruitment

Questions