TERAPIA ADIUVANTE NELLA MALATTIA ONCOGENE-ADDICTED

CARLO GENOVA

Università degli Studi di Genova

IRCCS Ospedale Policlinico San Martino

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

UNIVERSITÀ DEGLI STUDI
DI GENOVA

DISCLOSURES

Honoraria:

- Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers-Squibb, Eli Lilly, Merck-Sharp-Dohme, Novartis, Roche

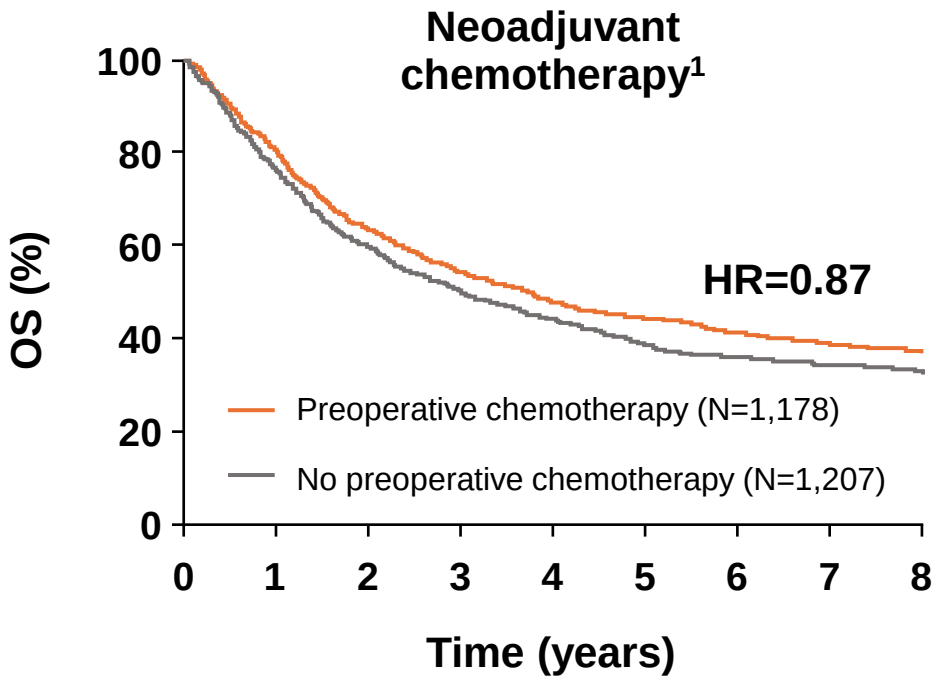
Advisory boards:

- Amgen, AstraZeneca, Bristol-Myers-Squibb, Daiichi-Sankyo, Eli Lilly, Merck-Sharp-Dohme, Novartis, Regeneron, Roche, Takeda

Research grants:

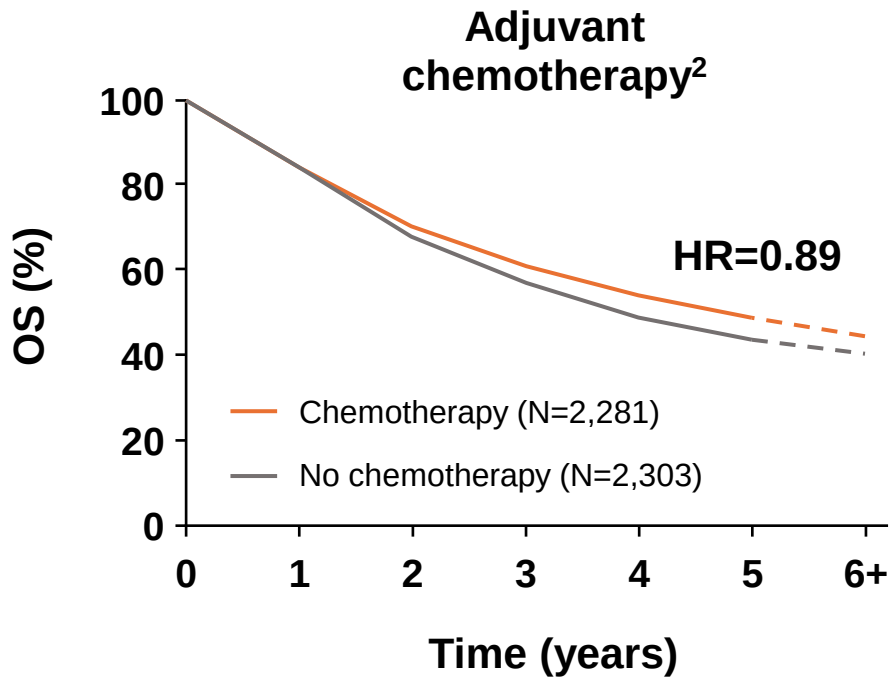
- Bristol-Myers-Squibb; Ministero della Salute; FONICAP-LILT

BENEFIT OF NEOADJUVANT AND ADJUVANT CHEMOTHERAPY



5%

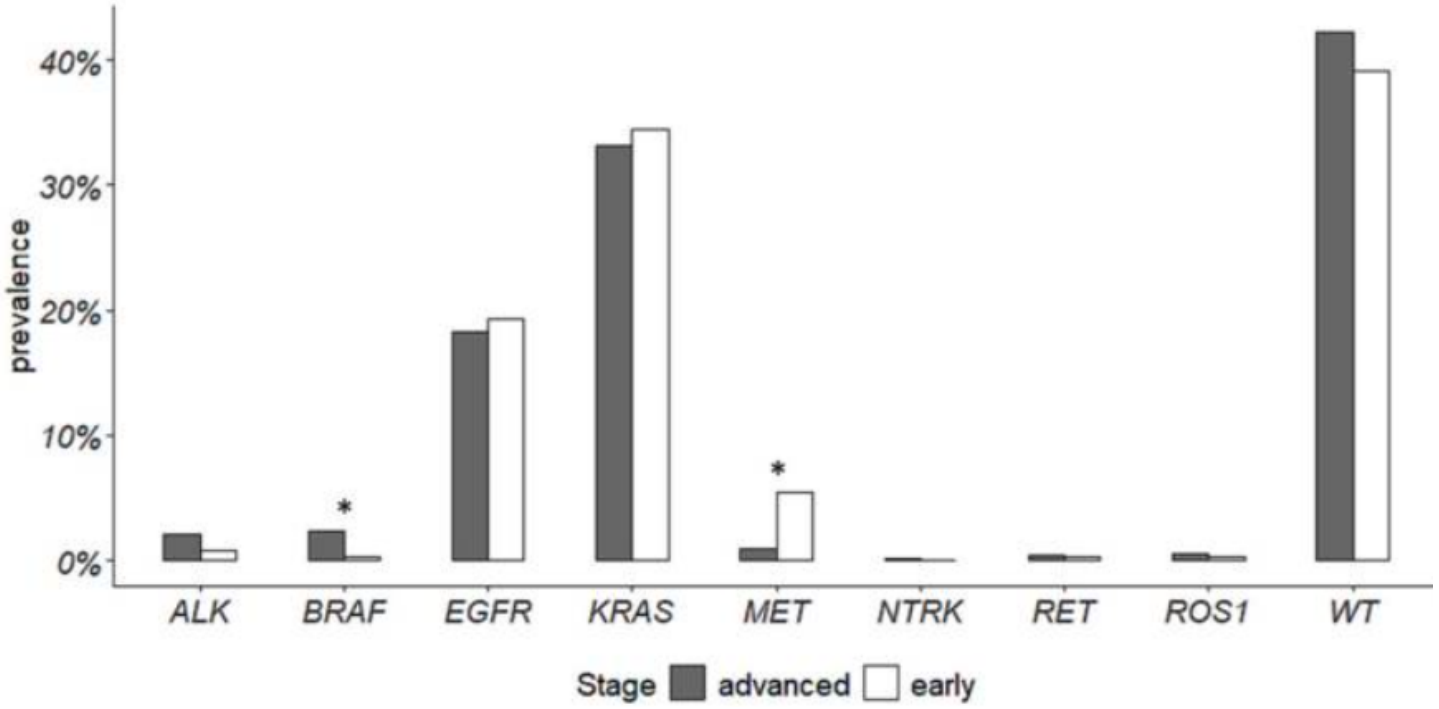
improvement in 5-year OS[1,2]

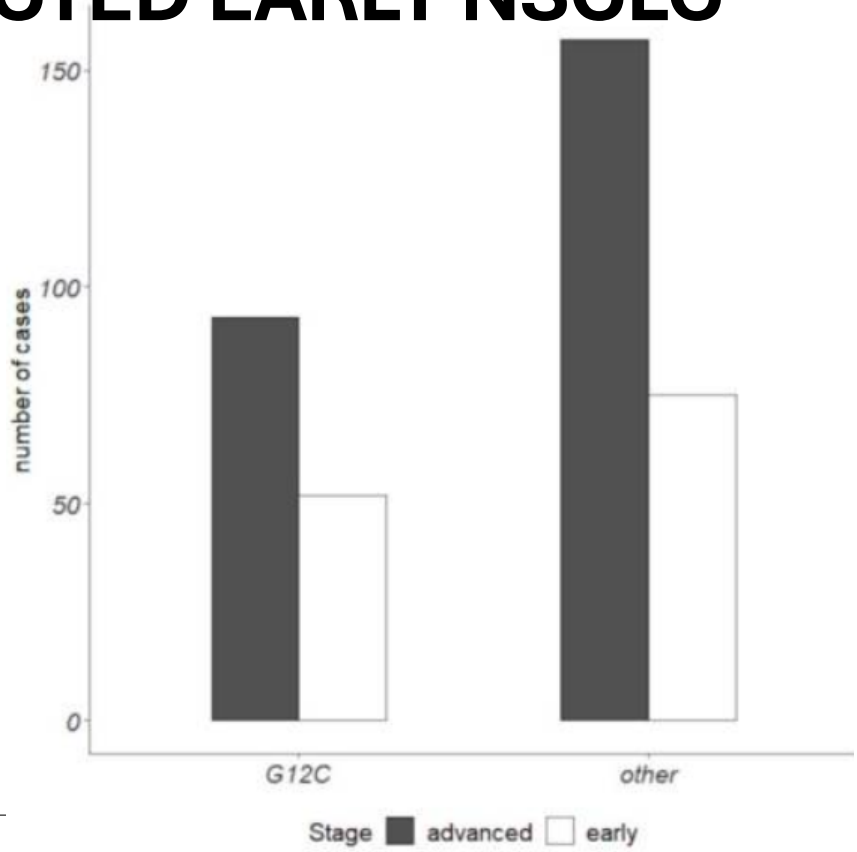


*Data from pooled analyses (analyses use earlier editions of staging guidelines)

1. NSCLC Meta-analysis Collaborative Group. Lancet 2014
2. Pignon, et al. J Clin Oncol 2008
3. Postmus, et al. Ann Oncol 2017

EPIDEMIOLOGY OF ONCOGENE-ADDICTED EARLY NSCLC





Early-Stage NSCLC			
EGFR	**Number of Cases**	**Prevalence among *EGFR* Mutations**	**Prevalence among All Analyzed ES-NSCLC**
Exon 19 in frame deletions	40	56.3%	11.5%
Exon 20 in frame insertions	7	9.9%	2%
p.(L858R)	16	22.5%	4.6%
Uncommon alterations	4	5.6%	1.1%

Mutation type	*Number of cases*
p.(G719A)	2
p.(L861Q)	2

BRUNO R, et Al. Cancers 2024

ADJUVANT TREATMENT FOR EGFR-m NSCLC
Before Osimertinib

Trial	Country	Stage	N	TKI	DFS (mo.) HR; p-value	OS (mo.) HR; p-value	Crossover
RADIANT*	Internat.	IB-IIIIA	161	Erlotinib x 2 y *vs.* Pl	46.4 *vs.* 28.5 0.61 (0.34-0.98)[&]	1.09 (0.54-2.16)	Not Rep.
ADJUVANT	China	II-IIIA	222	Gefitinib x 2y *vs.* CT	30.8 *vs.* 19.6 0.56 (0.40-0.97); 0.001	75.5 *vs.* 62.8 0.92 (0.62-1.36); 0.67	52%
IMPACT	Japan	II-IIIA	234	Gefitinib x 2y *vs.* CT	35.9 *vs.* 25.1 0.92 (0.67-1.28); 0.63	NR *vs.* NR 1.03 (0.65-1.65); 0.89	52%
EVAN	China	III	102	Erlotinib x 2y *vs.* CT	0.38 (0.20-0.70); 0.001	84.2 *vs.* 61.1 0.32 (0.15-0.67)	37%
EVIDENCE	China	II-IIIA	332	Icotinib x 2y *vs.* CT	47.0 *vs.* 22.1 0.36 (0.24-0.55); 0.0001	0.91 (0.42-1.94)	Not Rep.
CORIN	China	IB	128	Icotinib x 1 y *vs.* Pl	NR *vs.* NR 0.23 (0.07–0.81);0.013	P=0.098	83%

The DFS benefit achieved with1st GEGFR TKI in EGFR-mutant early-stage NSCLC, did not translate in OS benefit

Table from Remon – JTO 2023, modified (Kelly – JCO 2015 * Zhong – JCO 2021 * Tada- JCO 2023 * Yue – JCO 2022 * He – Lancet Resp Med 2021 * Ou – eclinicalMed 2023 * Tsuboi – NEJM 2023 *Wang –ASCO 2024)

ADAURA Phase III study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non-squamous NSCLC Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Maximum interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
Stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
Race (Asian vs non-Asian)

Randomization 1:1 (N=682)

Osimertinib 80 mg, once daily

Placebo, once daily

Planned treatment duration: 3 years

Treatment continued until:
- Disease recurrence
- Treatment completion
- Discontinuation criterion met

Follow-up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

Exploratory endpoint: Evaluate the feasibility of ctDNA-based MRD detection to predict disease recurrence during adjuvant osimertinib treatment and post-treatment follow-up

HERBST et Al. ASCO 2023

ADAURA STATISTICAL PLAN

Primary analysis: DFS in the stage II to IIIA population*

Primary endpoint (DFS) reported 2 years early (IDMC recommendation); alpha allocation revised and allocated to unplanned interim analysis. Included interim per-protocol analysis of OS at 5% maturity

↓

Primary analysis: DFS in the overall population (stage IB to IIIA)*

Reported 2 years early (IDMC recommendation)

↓

OS in the stage II to IIIA population†

Final OS analysis when approximately 94 deaths have been observed in the stage II to IIIA population (approximately 20% maturity)

↓

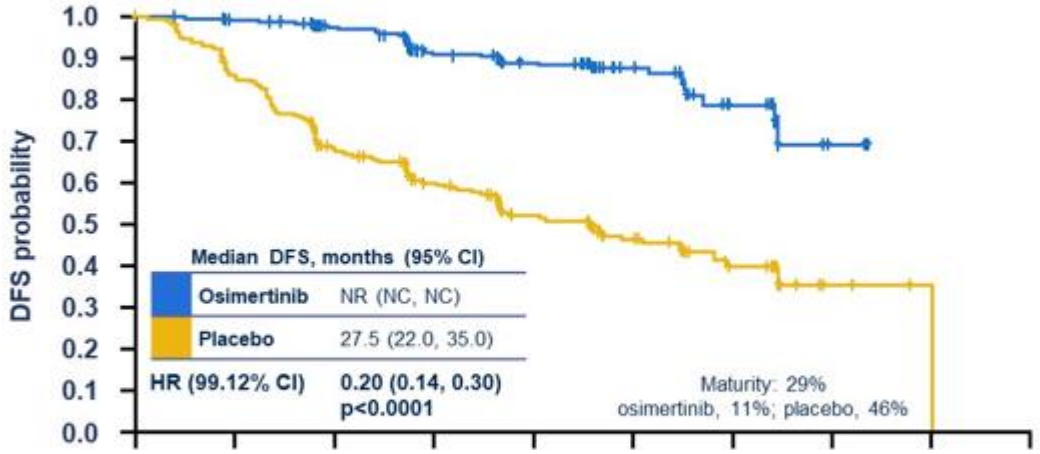
OS in the overall population (stage IB to IIIA)†

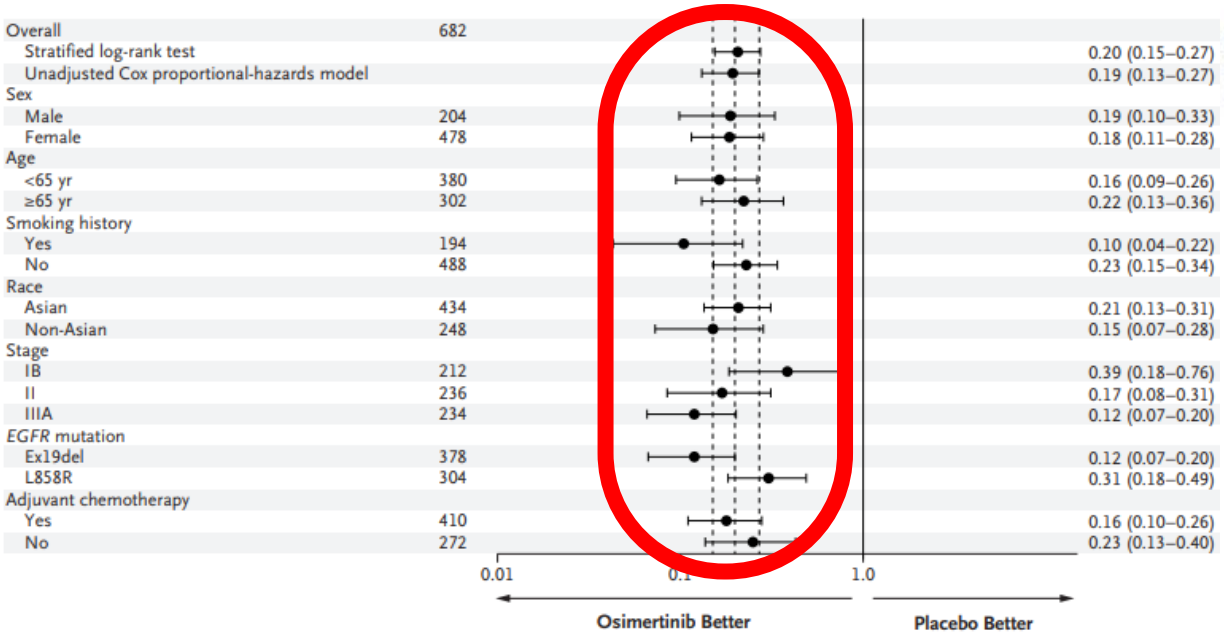
Remaining alpha will be fully exhausted

ADAURA DISEASE-FREE SURVIVAL

ADAURA primary DFS analysis[1,2] (stage IB–IIIA)*

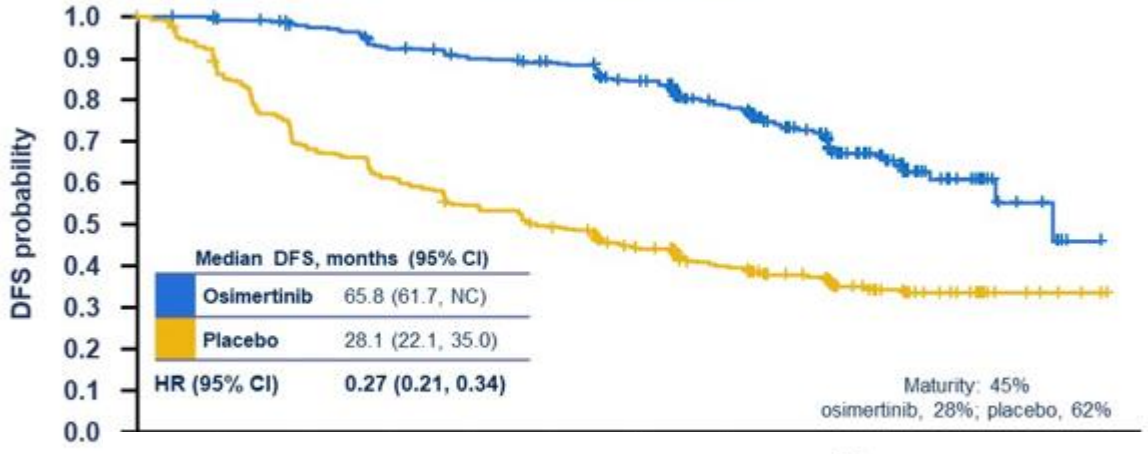
NEJM October 2020





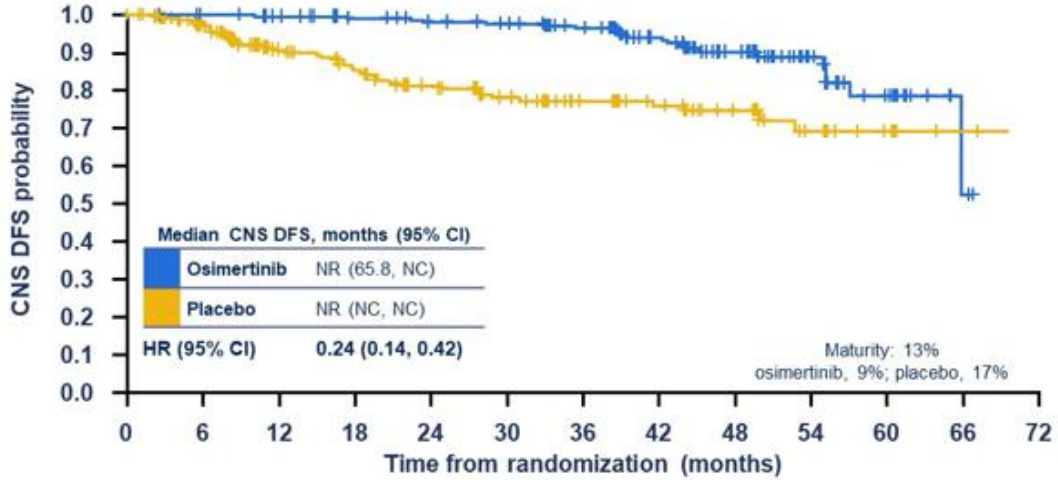
ADAURA updated DFS analysis[3,4] (stage IB–IIIA)†

JCO January 2023



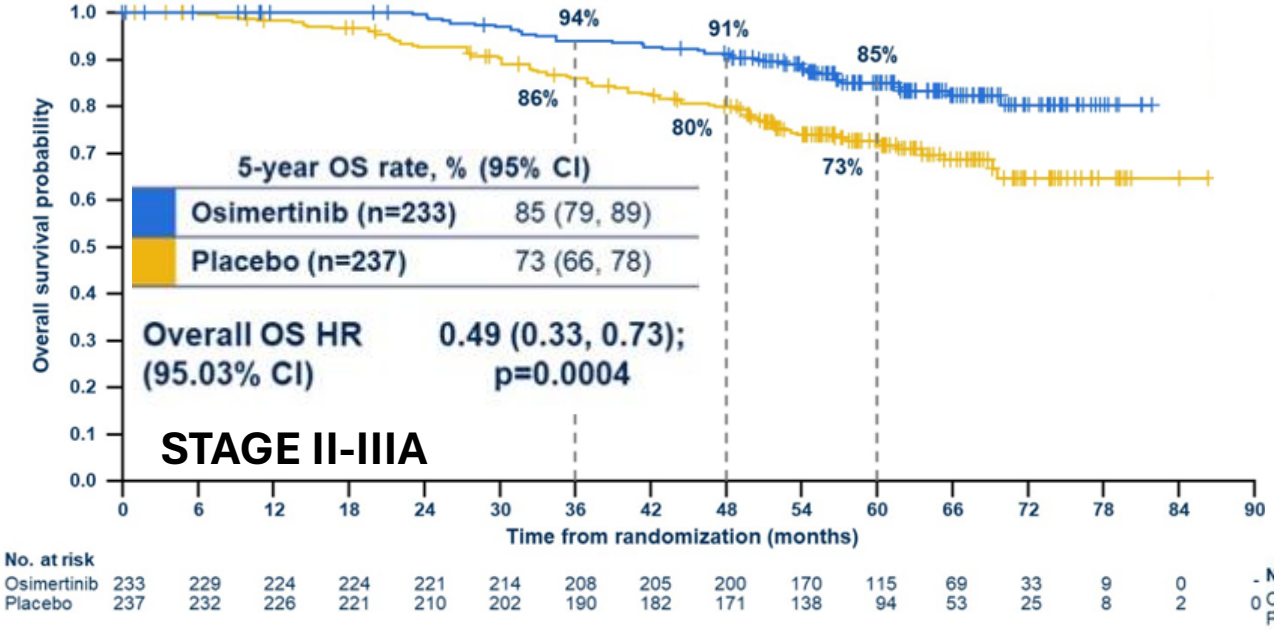
ADAURA updated CNS DFS analysis[5,6] (stage II–IIIA)

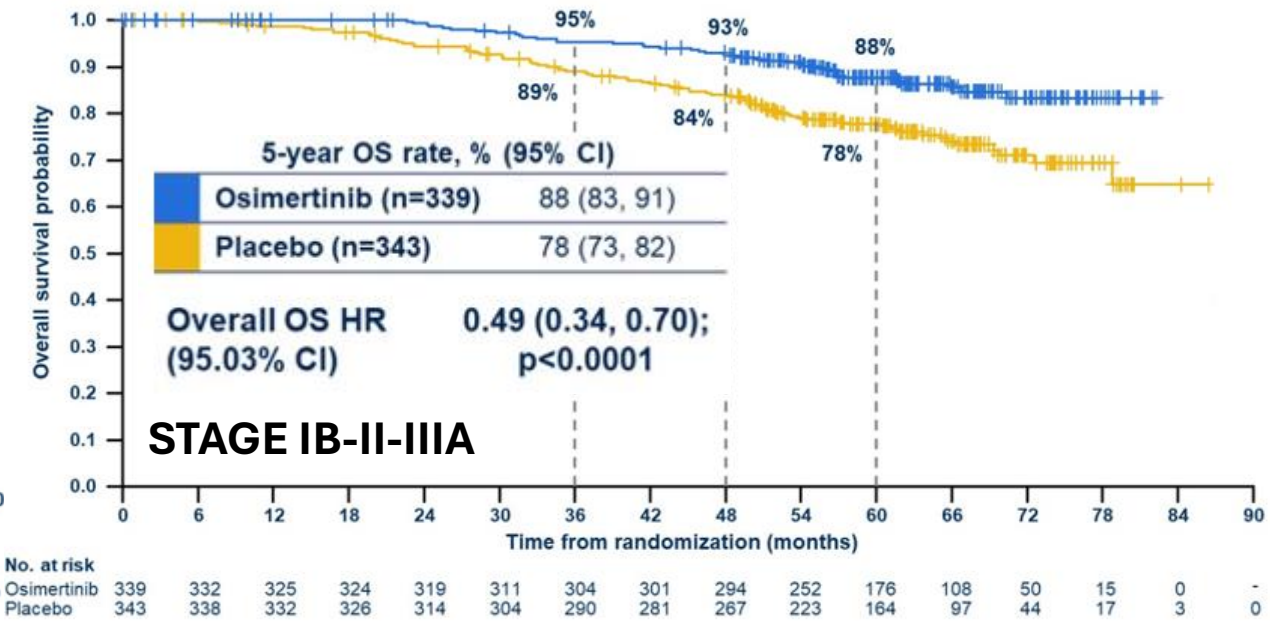
JCO January 2023



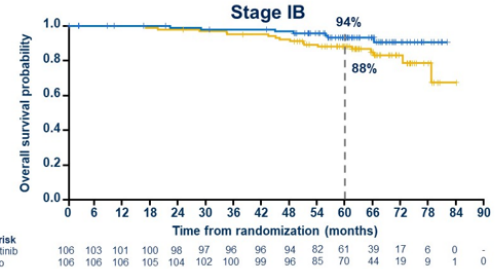
WU NEJM 2020; HERBST et Al. ASCO 2023

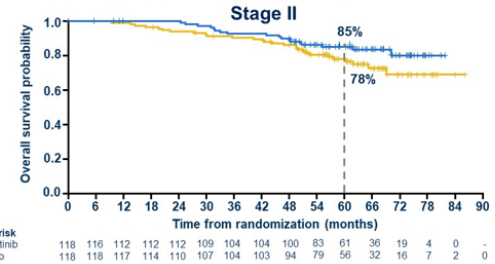
ADAURA OVERALL SURVIVAL

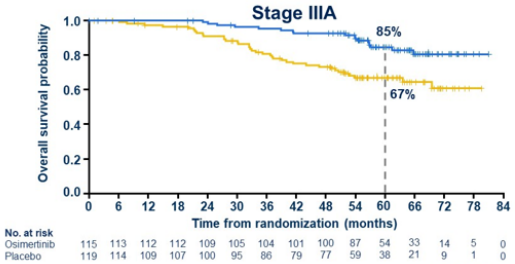




Overall survival by disease stage



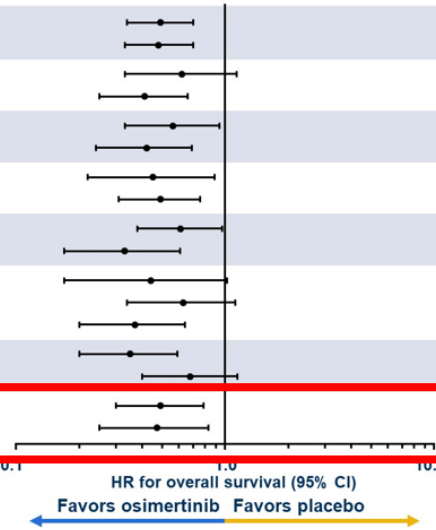




	Stage IB	Stage II	Stage IIIA
5 year OS rate, % (95% CI)			
Osimertinib	94 (86, 97)	85 (77, 91)	85 (76, 91)
Placebo	88 (80, 93)	78 (69, 85)	67 (57, 75)
Overall HR (95% CI)	0.44 (0.17, 1.02)	0.63 (0.34, 1.12)	0.37 (0.20, 0.64)

OS across subgroups: patients with stage IB / II / IIIA disease

Subgroup		No. of events / patients	HR	95% CI
Overall (N=682)	Stratified log-rank	124 / 682	0.49	0.34, 0.70
	Unadjusted Cox PH	124 / 682	0.48	0.33, 0.70
Sex	Male	42 / 204	0.62	0.33, 1.13
	Female	82 / 478	0.41	0.25, 0.66
Age	<65 years	60 / 380	0.56	0.33, 0.94
	≥65 years	64 / 302	0.42	0.24, 0.69
Smoking history	Yes	34 / 194	0.45	0.22, 0.89
	No	90 / 488	0.49	0.31, 0.76
Race	Asian	73 / 434	0.61	0.38, 0.97
	Non-Asian	51 / 248	0.33	0.17, 0.61
Stage*	IB	24 / 212	0.44	0.17, 1.02
	II	46 / 236	0.63	0.34, 1.12
	IIIA	54 / 234	0.37	0.20, 0.64
EGFR mutation	Ex19del	65 / 378	0.35	0.20, 0.59
	L858R	59 / 304	0.68	0.40, 1.14
Adjuvant chemotherapy	Yes	74 / 410	0.49	0.30, 0.79
	No	50 / 272	0.47	0.25, 0.83



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ADAURA SUBSEQUENT TREATMENTS

Subsequent treatments, n (%)	Osimertinib (n=339)	Placebo (n=343)
Patients who received subsequent anti-cancer treatment*	76 (22)	184 (54)
EGFR-TKIs	58 (76)	162 (88)
Osimertinib	31 (41)	79 (43)
Other EGFR-TKIs	28 (37)	114 (62)
Chemotherapy	20 (26)	46 (25)
Radiotherapy	30 (39)	53 (29)
Other anti-cancer treatments	12 (16)	29 (16)

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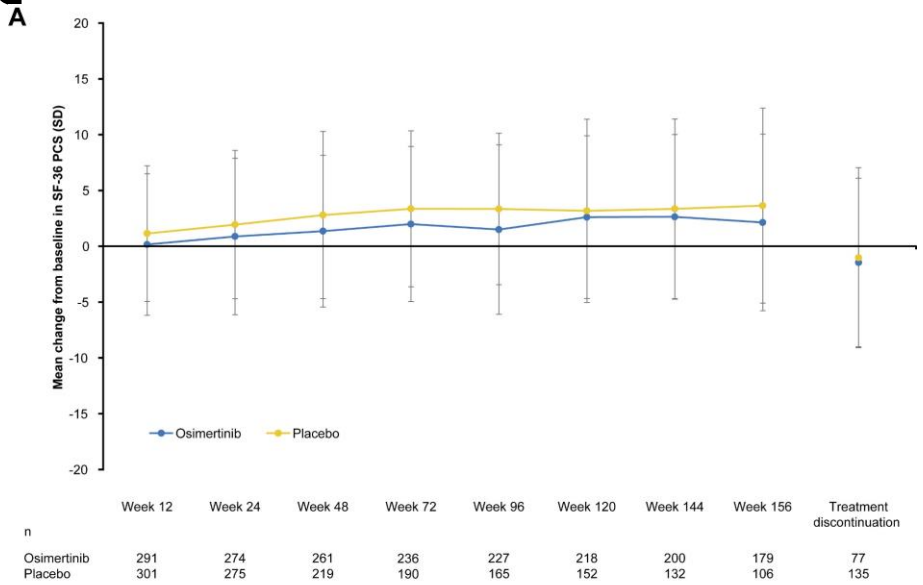
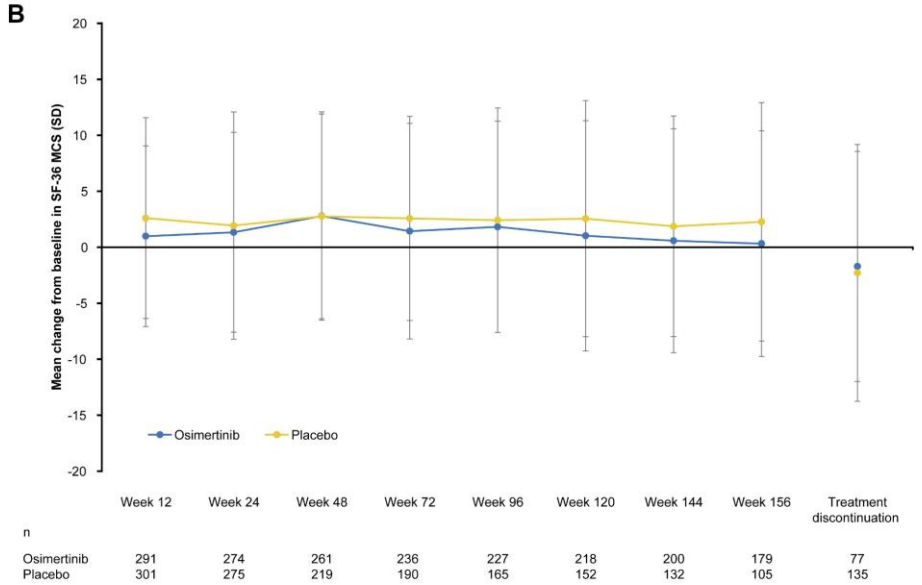
ADAURA SAFETY & QoL

- At the final DFS analysis (data cut-off: April 11, 2022), all patients had completed or discontinued study treatment; the safety profile of adjuvant osimertinib with extended follow-up[1,2] was consistent with the ADAURA primary analysis[3]

AE, any cause*, n (%)	Osimertinib (n=337)	Placebo (n=343)
Any AE	330 (98)	309 (90)
Any AE Grade ≥3	79 (23)	48 (14)
Any AE leading to death	1 (<1)	2 (1)
Any serious AE	68 (20)	47 (14)
Any AE leading to discontinuation	43 (13)	9 (3)
Any AE leading to dose reduction	42 (12)	3 (1)
Any AE leading to dose interruption	91 (27)	43 (13)
AE, possibly causally related*†, n (%)		
Any AE	308 (91)	199 (58)
Any AE Grade ≥3	36 (11)	7 (2)
Any AE leading to death	0	0
Any serious AE	10 (3)	2 (1)

- At the time of the current data cut-off for OS (January 27, 2023), one additional serious AE (COVID-19 pneumonia) had been reported, which occurred >28 days after treatment discontinuation; the investigator determined that this was not treatment related and the patient made a full recovery





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ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R
1:1

N=257

Alectinib 600 mg BID
2 years

Platinum-based chemotherapy†
Q3W; 4 cycles

Recurrence

Recurrence

Further treatments at investigator's choice and survival follow-up

Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

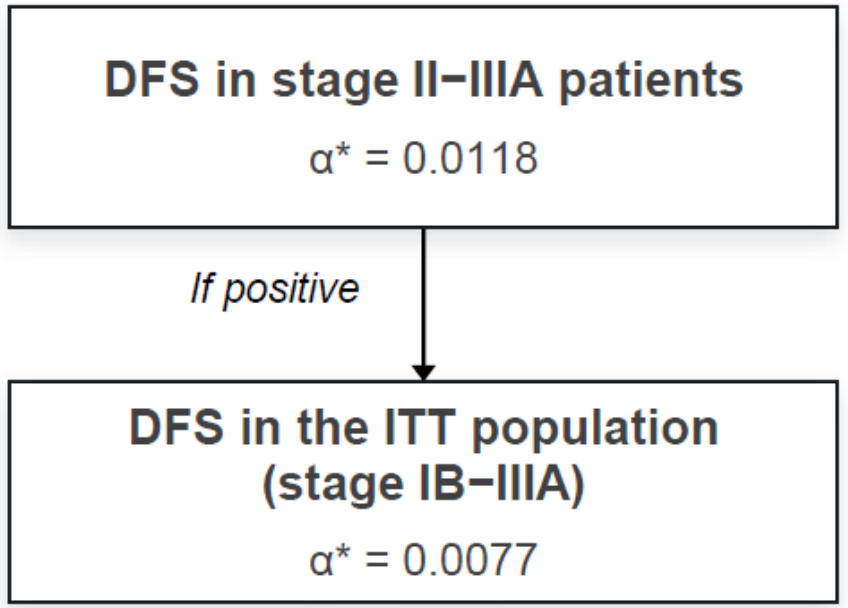
Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

SOLOMON et Al, ESMO 2023

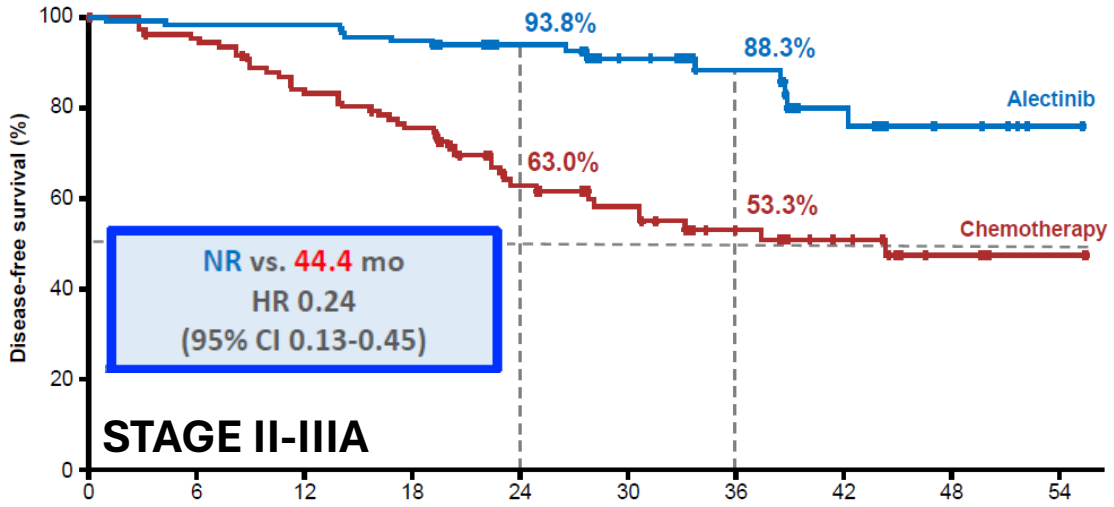
ALINA STATISTICAL PLAN

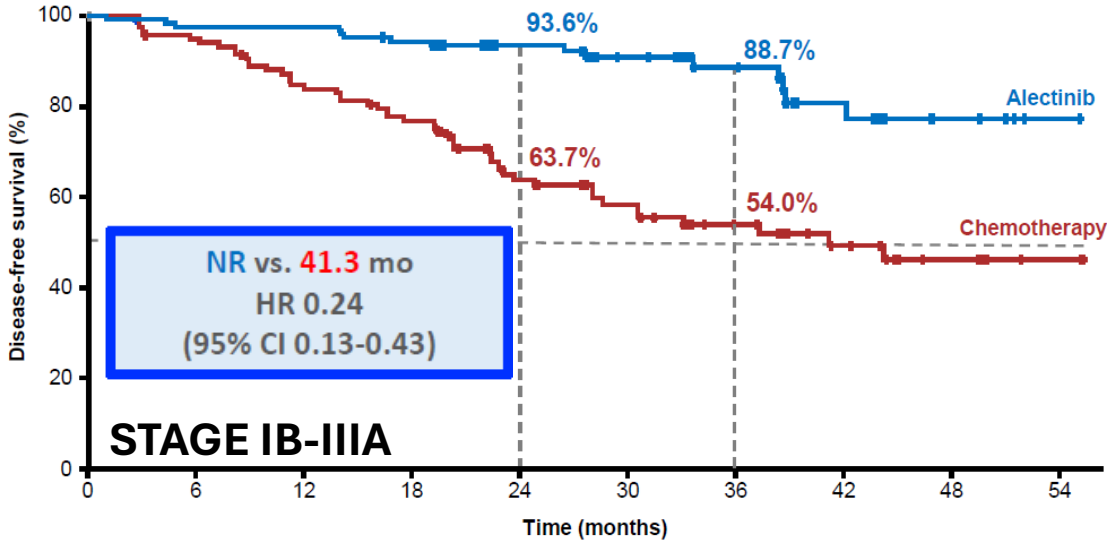
- ALINA was designed to demonstrate superiority of alectinib compared with chemotherapy, with 80% power to detect a DFS HR of:
  - 0.55 in the stage II–IIIA subpopulation
  - 0.58 in the ITT population (stage IB–IIIA)
- One interim analysis was pre-planned after ~67% (59) events in the stage II–IIIA subpopulation

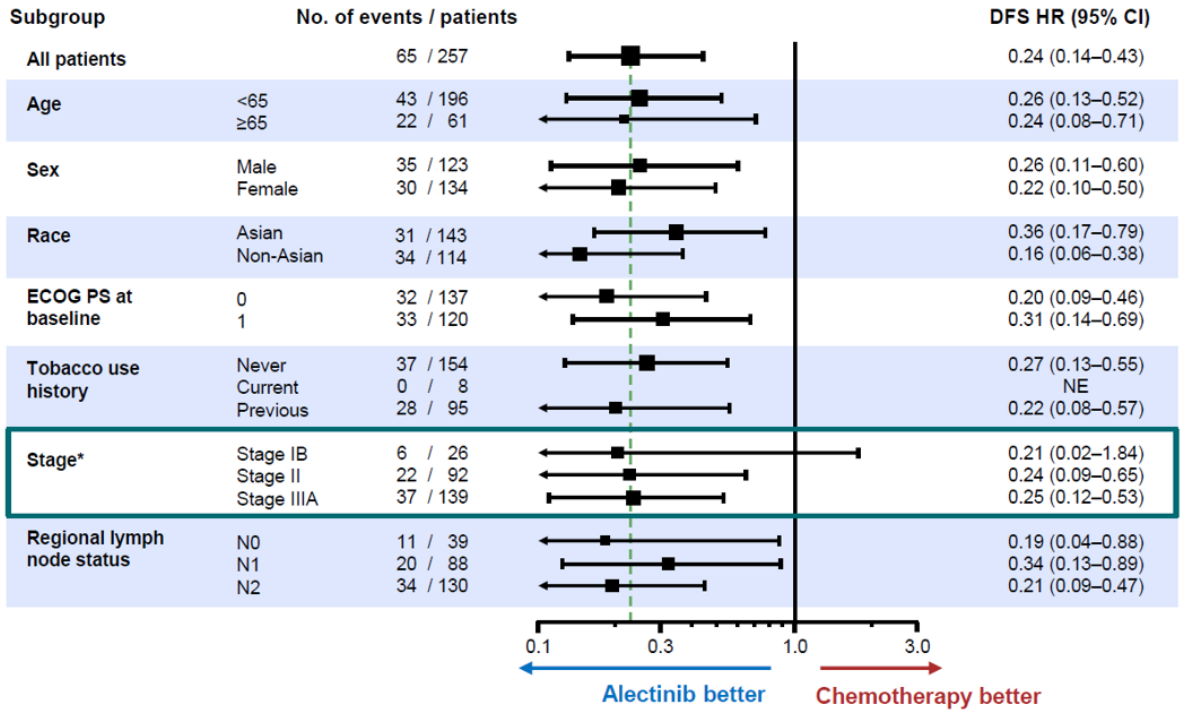
DFS testing hierarchy

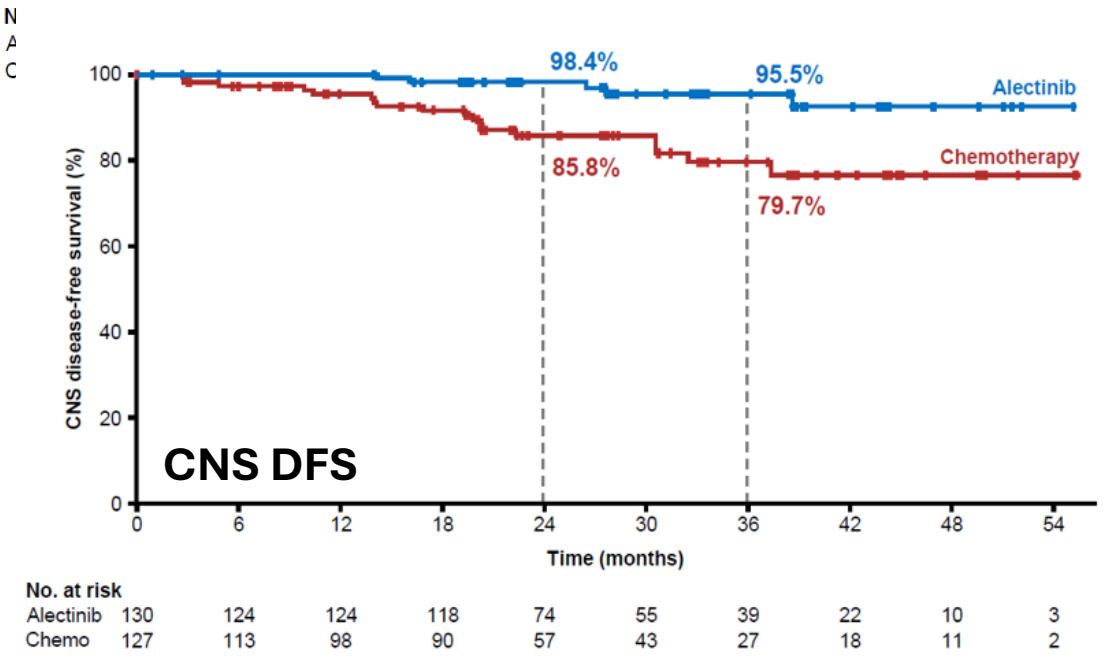


ALINA DISEASE-FREE SURVIVAL









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ALINA SUBSEQUENT TREATMENTS

Number of patients with disease recurrence, n (%)	Alectinib (n=15)	Chemotherapy (n=49)
Patients with any subsequent therapy	13 (87)	43 (88)
Systemic therapy	13 (87)	38 (78)
ALK TKI	7 (47)	37 (76)
Alectinib	4 (27)	29 (59)
Brigatinib	4 (27)	4 (8)
Crizotinib	0	4 (8)
Lorlatinib	0	2 (4)
Ceritinib	0	1 (2)
Chemotherapy	6 (40)	2 (4)
Immunotherapy	1 (7)	1 (2)
Other anti-cancer therapy	1 (7)	1 (2)
Radiotherapy	5 (33)	9 (18)
Surgery	1 (7)	3 (6)

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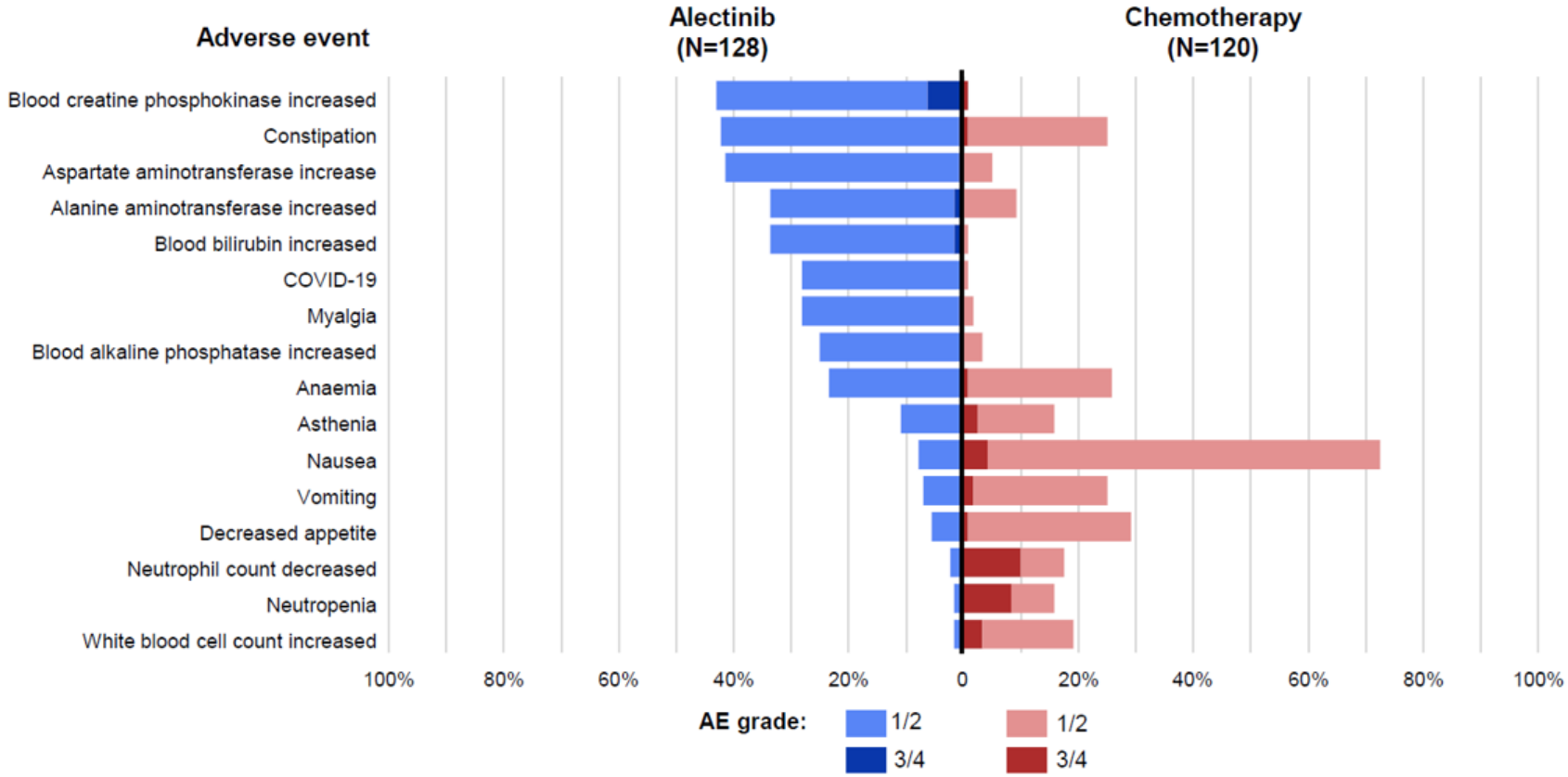
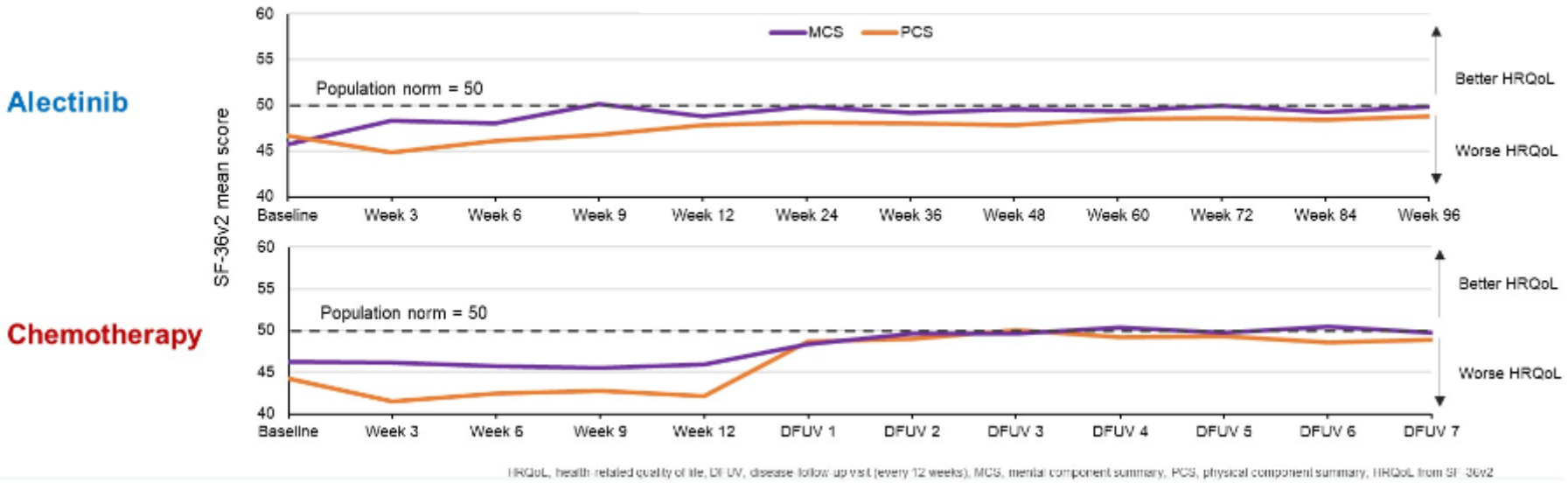
ALINA SAFETY & QoL





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NISHIO et Al, ASCO 2024

OPEN ISSUES

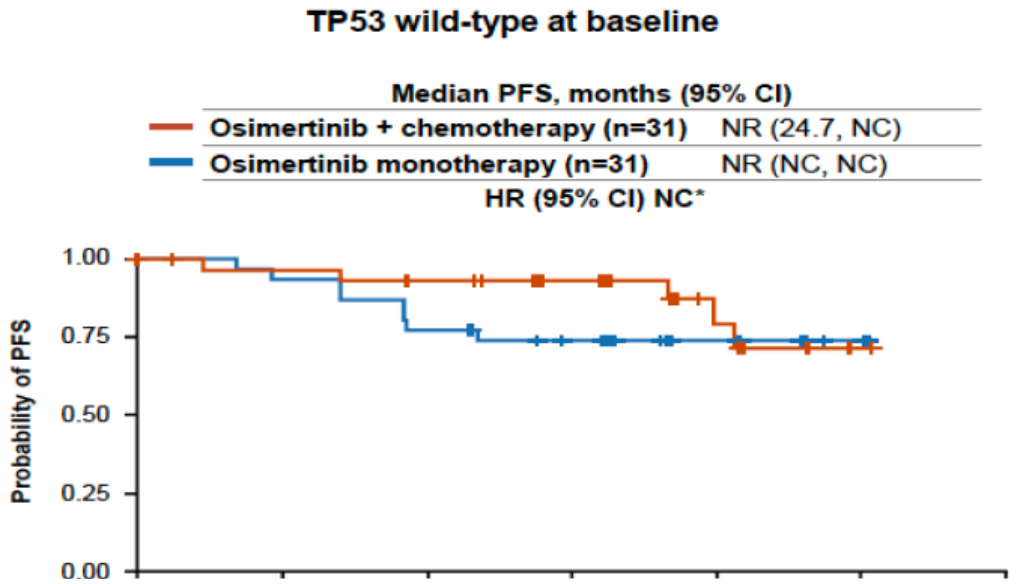
BIOMARKERS FOR CHEMOTHERAPY ?

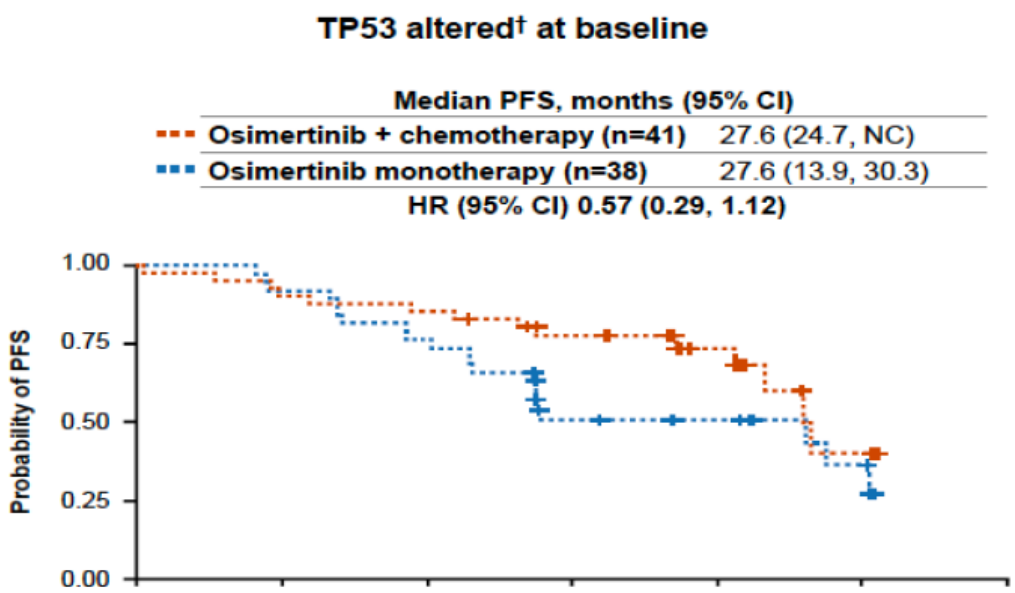
MINIMAL/MOLECULAR RESIDUAL DISEASE (MRD) ?

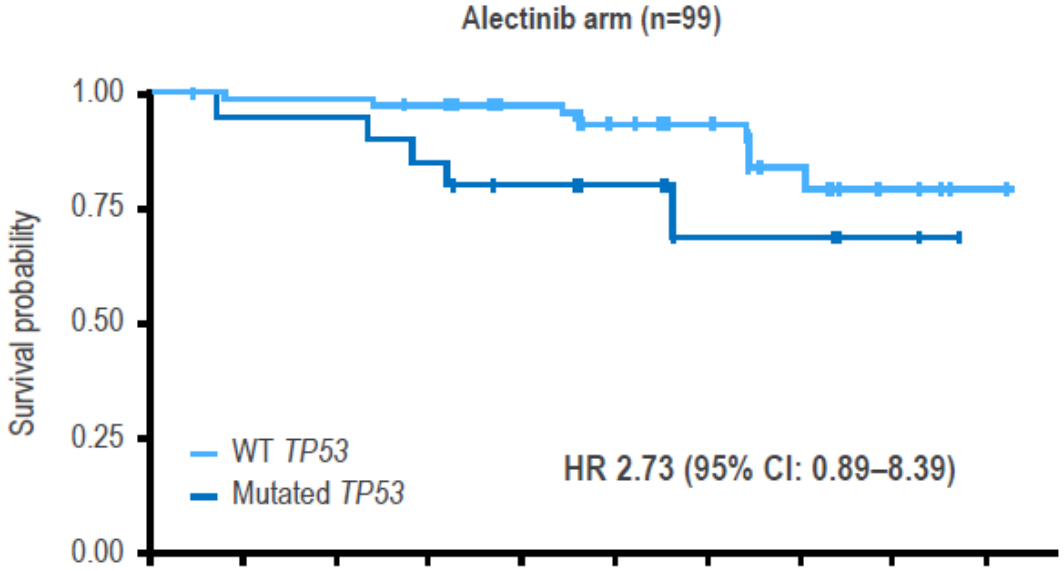
NEOADJUVANT TREATMENT ?

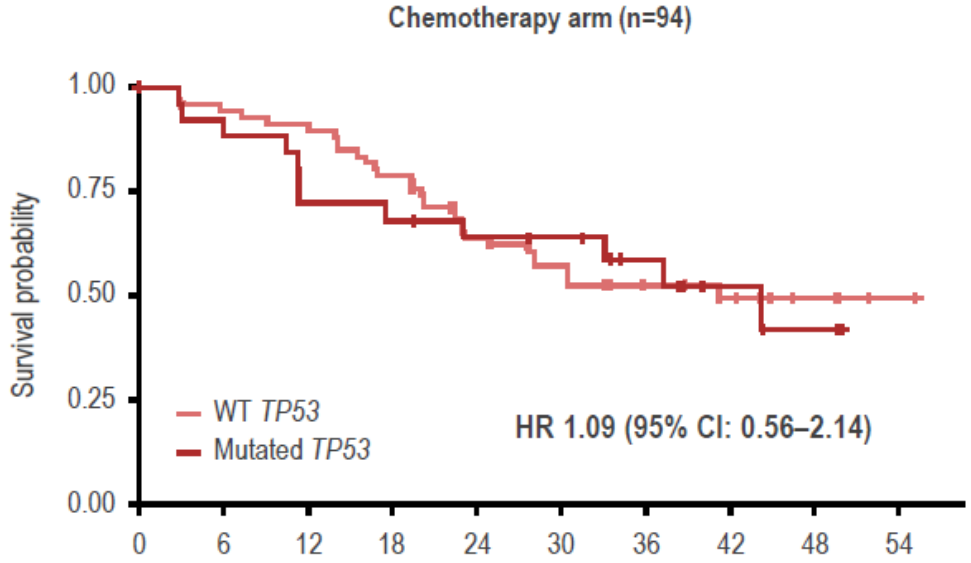
OTHER ONCOGENES ?

BIOMARKERS FOR CHEMOTHERAPY ?









YANG et Al, WCLC 2024

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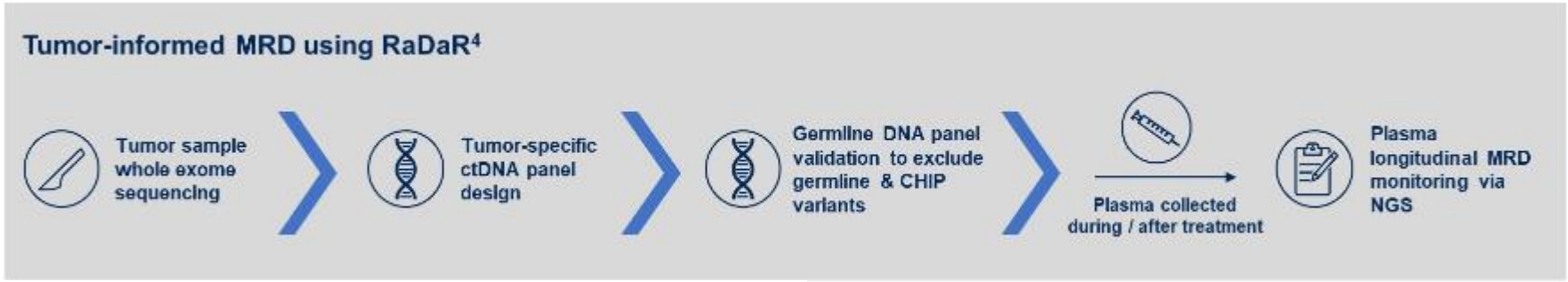
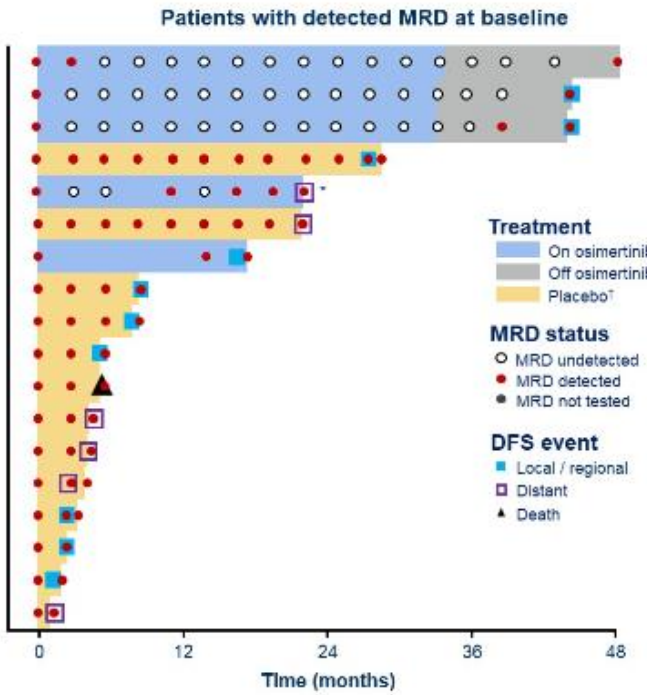
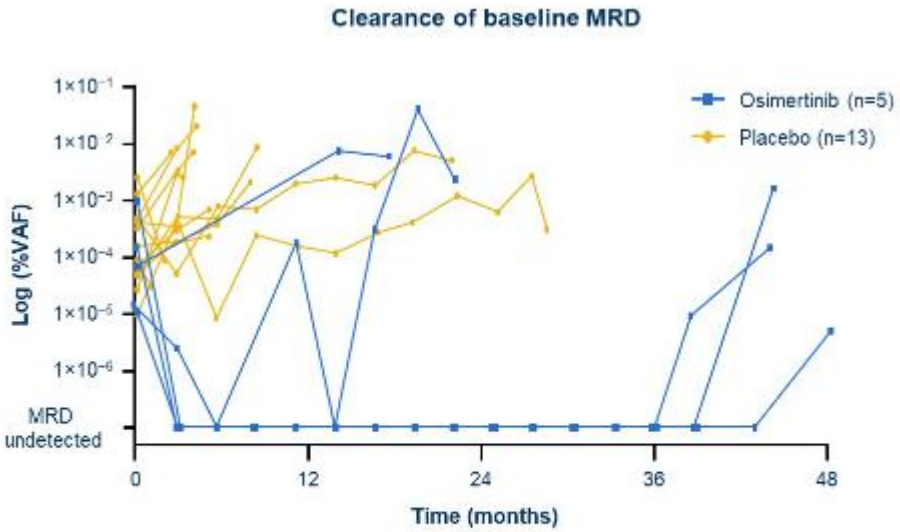
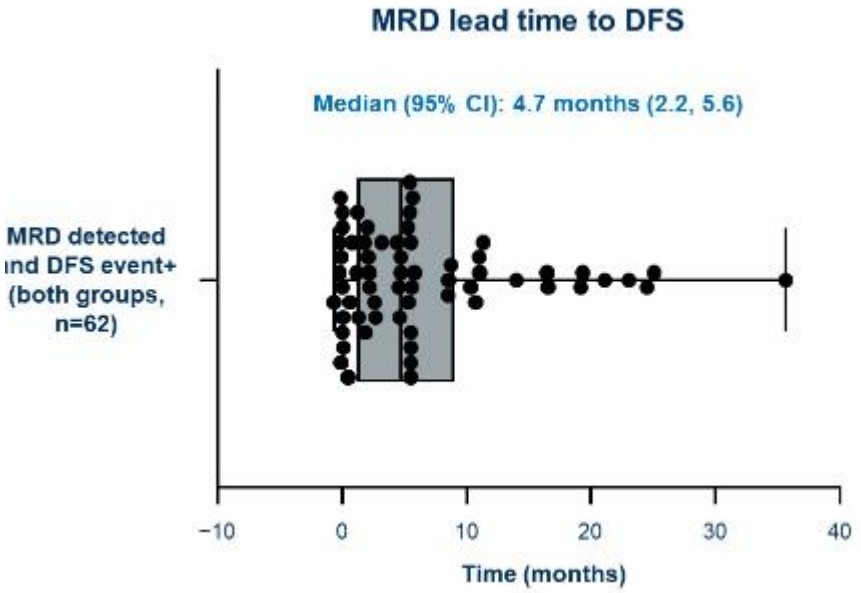
MRD ?

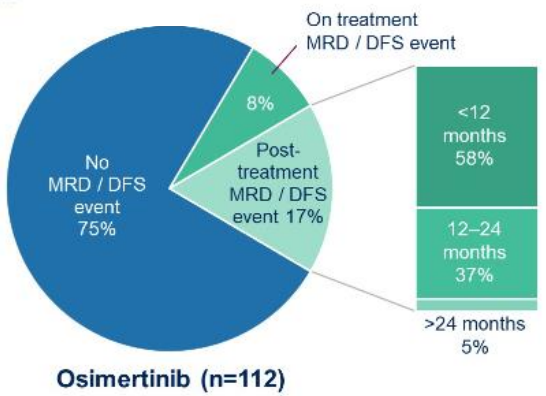


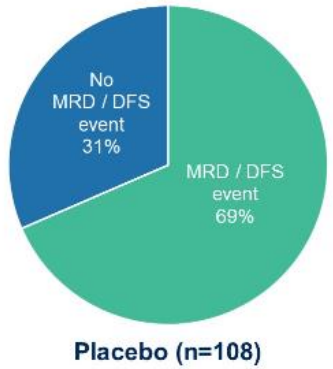




- Of 18 patients with detected MRD at baseline
  - 4 / 5 patients receiving osimertinib cleared MRD
  - 0 / 13 patients receiving placebo cleared MRD







JOHN T, et Al. ASCO 2024

LUMPcure 2 (CTONG 2201)

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Current Trial Report

Adjuvant Therapy-Free Strategy for Stage IB to IIIA Non–Small-Cell Lung Cancer Patients After Radical Resection Based on Longitudinal Undetectable Molecular Residual Disease: Prospective, Multicenter, Single-Arm Study (CTONG 2201)

Jia-Tao Zhang,[1] Song Dong,[1] Wei-Quan Gu,[2] Ning Zhao,[2] Yi Liang,[3] Wen-Fang Tang,[3] Shuo-Yan Liu,[4] Feng Wang,[4] Guang-Suo Wang,[5] Bin Peng,[5] Nan Wu,[6] Shi Yan,[6] Guo-Jun Geng,[7] Ze-Feng Xie,[8] Yan-Long Yang,[9] Jian-Hua Zhang,[10] Tao Zhang,[10] Nuo Yang,[11] Wen-Jie Jiao,[12] Yuan-Yuan Xiong,[13] Miao Cai,[13] Fang Li,[13] Rong-Rong Chen,[13] Hong-Hong Yan,[1] Si-Yang Maggie Liu,[14,15] Xin Yi,[13] Wen-Zhao Zhong,[1] Xue-Ning Yang,[1] Yi-Long Wu[1,15]

Abstract

Background: The utility of circulating tumor DNA to monitor molecular residual disease (MRD) has been clinically confirmed to predict disease recurrence in non-small cell lung cancer (NSCLC) patients after radical resection. Patients with longitudinal undetectable MRD show a favorable prognosis and might not benefit from adjuvant therapy. **Patients and Methods:** The CTONG 2201 trial is a prospective, multicenter, single-arm study (ClinicalTrials.gov identifier, NCT05457049), designed to evaluate the hypothesis that no adjuvant therapy is needed for patients with longitudinal undetectable MRD. Pathologically confirmed stage IB-IIIA NSCLC patients who have undergone radical resection will be screened. Only patients with 2 consecutive rounds of undetectable MRD will be enrolled (first at days 3-10, second at days 30 ± 7 after surgery), and admitted for imaging and MRD monitoring every 3 months without adjuvant therapy. The primary endpoint is the 2-year disease-free survival rate for those with longitudinal undetectable MRD. The recruitment phase began in August 2022 and 180 patients will be enrolled. **Conclusions:** This prospective trial will contribute data to confirm the negative predictive value of MRD on adjuvant therapy for NSCLC patients.**Clinical Trial Registration:** NCT05457049 (CTONG 2201).

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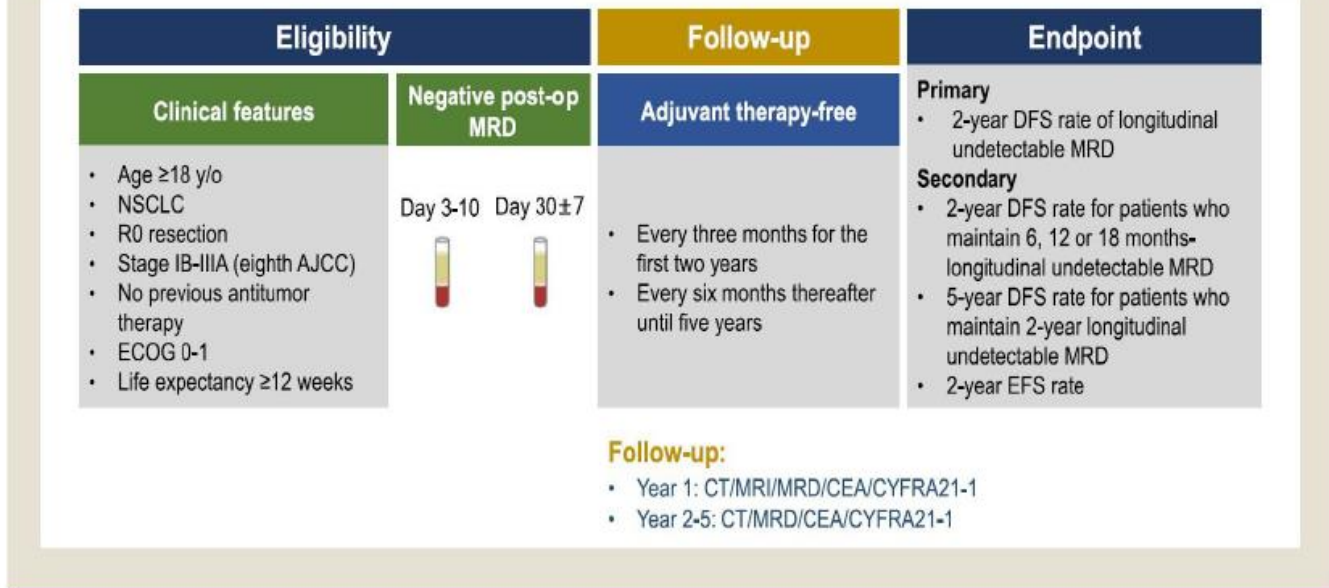
Keywords: Circulating tumor DNA, Adaptive therapy, Minimal residual disease

Figure 1 Study design of CTONG 2201 trial. Abbreviations: AJCC = American Joint Committee on Cancer; y/o = years old; CEA = carcinoembryonic antigen; CYFRA21-1 = cytokeratin 19 fragment; DFS = disease-free survival; EFS = event-free survival; CT = computed tomography; MRD = molecular residual disease; MRI = magnetic resonance imaging; NSCLC = non–small-cell lung cancer.



N=180

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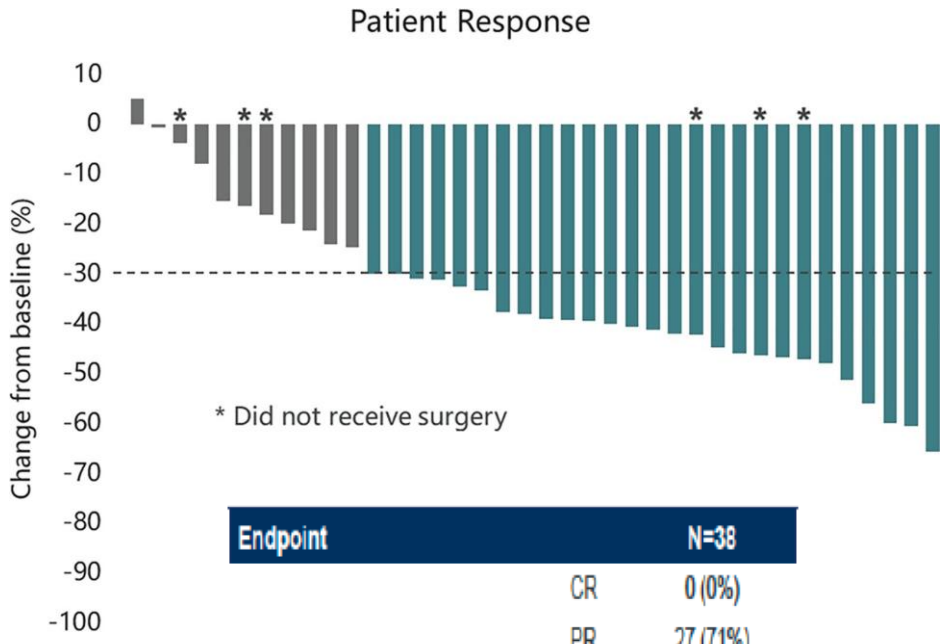
COURTESY OF RITA CHIARI

NEOADJUVANT TREATMENT ?

NEOS (single-arm, phase IIB)



Endpoint		N=38
Tumor Response, n (%)	CR	0 (0%)
	PR	27 (71%)
	SD	11 (29%)
	PD	0 (0%)
ORR		71% (27/38)
DCR		100% (38/38)
R0 resection		94% (30/32)
MPR		11% (3/28)
pCR		4% (1/28)
Pathological response ≥50%		46% (13/28)

ALNEO (single-arm, phase II)

- Resectable locally advanced stage III NSCLC
- Candidate for surgical resection after multidisciplinary discussion
- ALK positive (IHC/FISH/NGS)
- No Previous treatment
- ECOG PS 0-1

Primary Endpoint: MPR by BICR the null hypothesis that the MPR is ≤20%

Secondary Endpoints: pCR by BICR, OR, EFS, DFS, OS, AEs

Pathologic Response	n=18
MPR, n (%)	7 (39)
pCR, n (%)	3 (17)
No MPR, n (%)	6 (33)
Not Assessed, n (%)	5 (28)[a]

Objective Response[b]	n=25
CR, n (%)	1 (4)
PR, n (%)	19 (76)
SD, n (%)	4 (16)
PD, n (%)	1 (4)
ORR, (%)	20 (80)

	n=25
Underwent Surgery, n (%)	21 (84)
R0, n (% of surgery)	18 (86)
Type of surgery, n (%)	
Lobectomy	17 (81)
Pneumonectomy	2 (9.5)
Other Surgery	2 (9.5)
Received adjuvant alectinib, n (% of surgery)	20 (95)[c]
Median interval from surgery, weeks (IQR)	4.5 (2.7–6.0)
Median n of cycles, n (IQR)	6 (1–20)

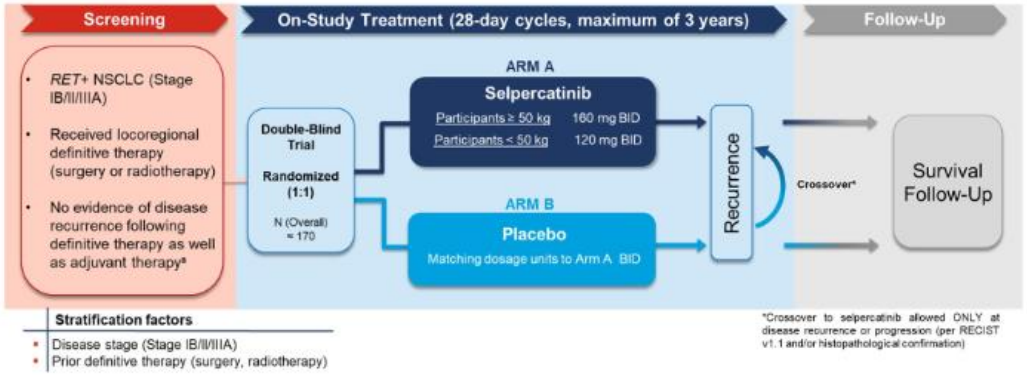
[a]4 patients did not undergo surgery, 1 patient underwent explorative thoracotomy; [b]at pre-surgical evaluation; [c]2 patients received adjuvant alectinib even though surgery was not radical.

Lv C, et Al. Lung Cancer 2023; Leonetti a, et Al. WCLC 2024

OTHER ONCOGENES ?

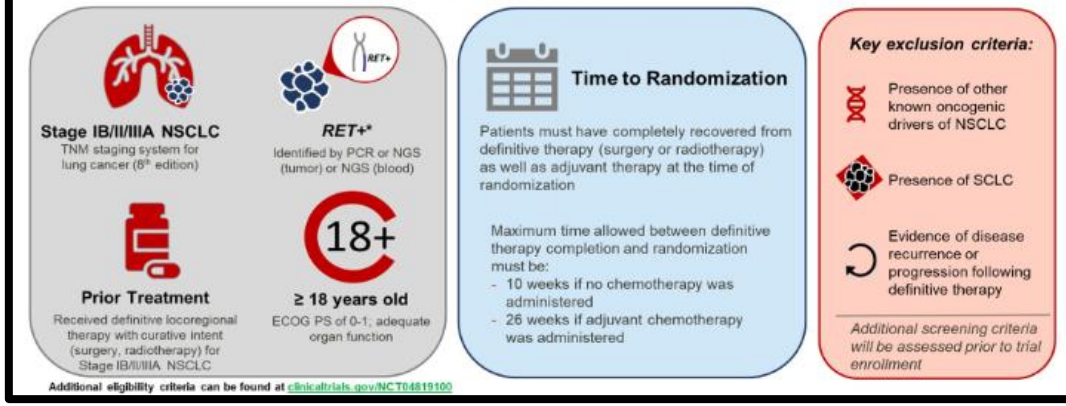
Trial design of LIBRETTO-432 (NCT04819100)

LIBRETTO-432 is a Phase 3, global, multicenter, randomized, double-blind, controlled trial evaluating efficacy and safety of adjuvant selpercatinib versus placebo in patients with *RET*+ Stage IB-IIIA NSCLC following completion of definitive radiotherapy or surgery with curative intent, and other adjuvant therapy if indicated (NCT04819100).



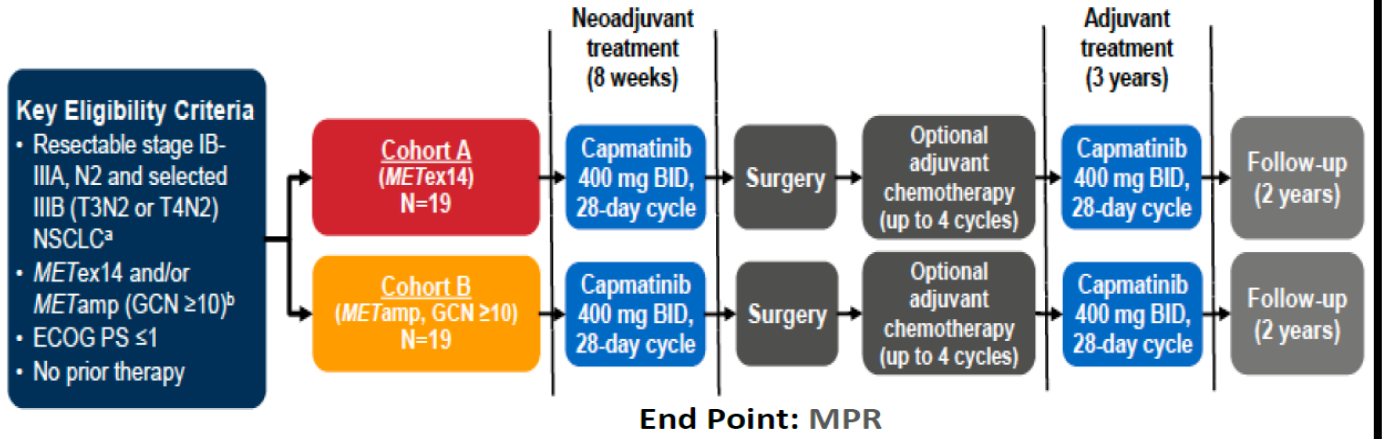
[a]Participants must have undergone the available anti-cancer therapy (including chemotherapy or durvalumab) or not be suitable for it, based on the investigator's discretion

Key Eligibility Criteria



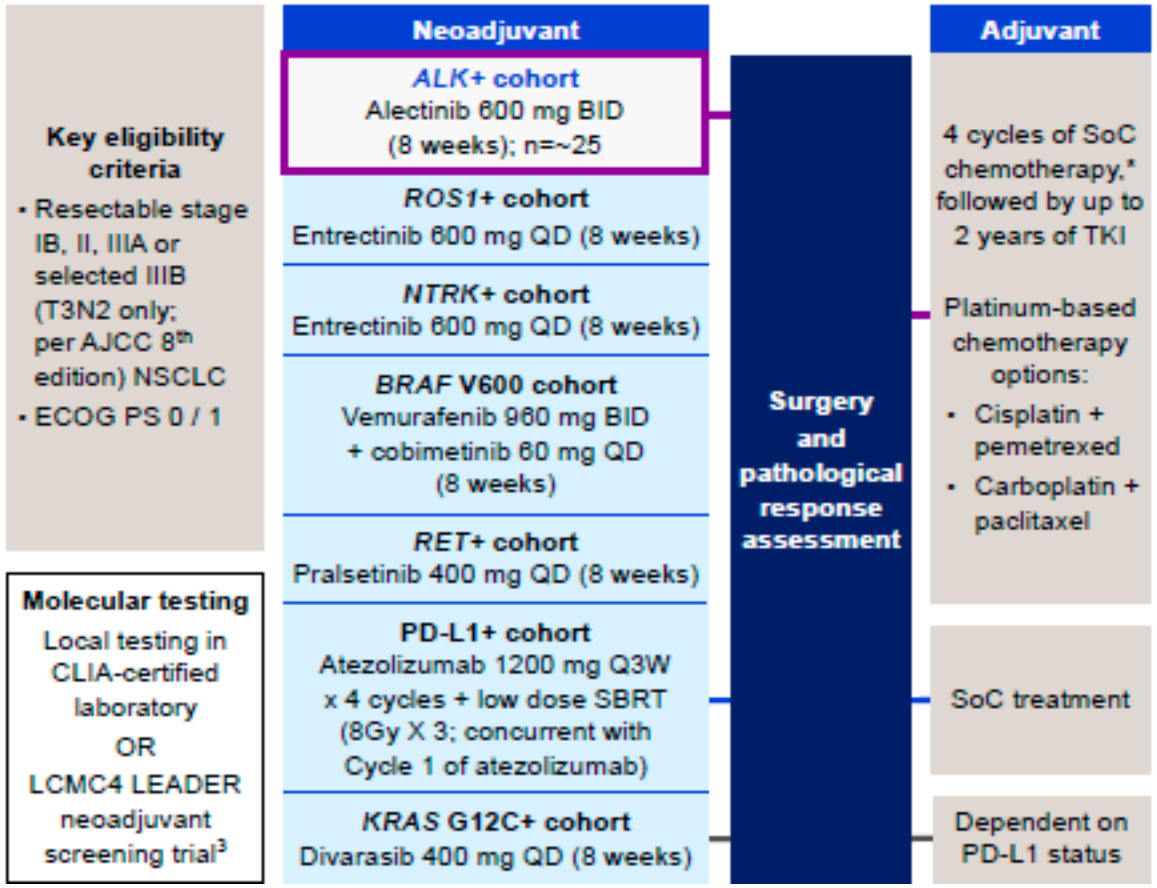
Additional eligibility criteria can be found at clinicaltrials.gov/NCT04819100

GEOMETRY-N (NCT04926831)



End Point: MPR

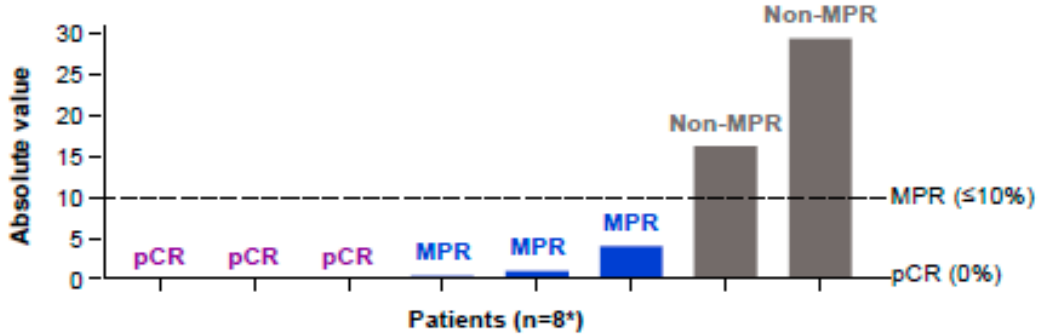
ALK & OTHER ONCOGENES – NAUTIKA1



Pathological response, n (%)*	*ALK*+ cohort (n=9)
Major pathological response†	6 (66.7)
Pathological complete response‡	3 (33.3)
Radiographic response, n (%)	***ALK*+ cohort (n=9)**
Complete response	0
Partial response	4 (44.4)
Stable disease	5 (55.6)
Progressive disease	0

*Assessed locally. †One evaluable patient did not undergo resection and was treated as a non-major pathological response patient. ‡Pathological complete response in the patient with squamous histology.

Figure 2. Weighted percentage viable tumour cells (MPR and pCR)



MPR defined as ≤10% residual viable tumour cells; pCR defined as 0% of viable tumour cells. *In one evaluable patient, resection was not done during surgery, so pathological response was not assessed. MPR, major pathological response; pCR, pathological complete response.

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TAKE HOME MESSAGES

ADJUVANT OSIMERTINIB IMPROVES OVERALL SURVIVAL

ADJUVANT ALECTINIB IMPROVES DISEASE-FREE SURVIVAL

OPEN QUESTIONS

«WHO» and «WHAT» SHOULD WE TEST ?

ROLE OF ADJUVANT CHEMOTHERAPY ?

HOW DO WE MANAGE RECURRENCE ?

THANK YOU!

CARLO.GENOVA@HSANMARTINO.IT

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

UNIVERSITÀ DEGLI STUDI
DI GENOVA