CURRENT ROLE OF ADJUVANT TARGETED THERAPY IN NSCLC

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March 31, 2023

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The Blueprint: EGFR (del 19 and L858R)- ADAURA

Phase 3, Randomized, Double-blind, Placebo-controlled

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§
- Max. interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

STRATFICATION BY:

Stage (IB vs II vs IIIA)

EGFRm (Ex19del vs L858R)

race (Asian vs non-Asian)

R
1:1
N=682

OSIMERTINIB
80 mg, once daily

PLACEBO
once daily

Primary Endpoint

DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70

Secondary Endpoint

DFS in the overall population

DFS at 2, 3, 4, and 5 years,

OS, safety, health-related quality of life

Planned treatment duration: 3 years

TREATMENT CONTINUES UNTIL:

- Disease recurrence
- Treatment completed
- 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

Following IDMC recommendation, study unblinded early due to efficacy - study had completed enrollment and all patients were followed at least 1 year.

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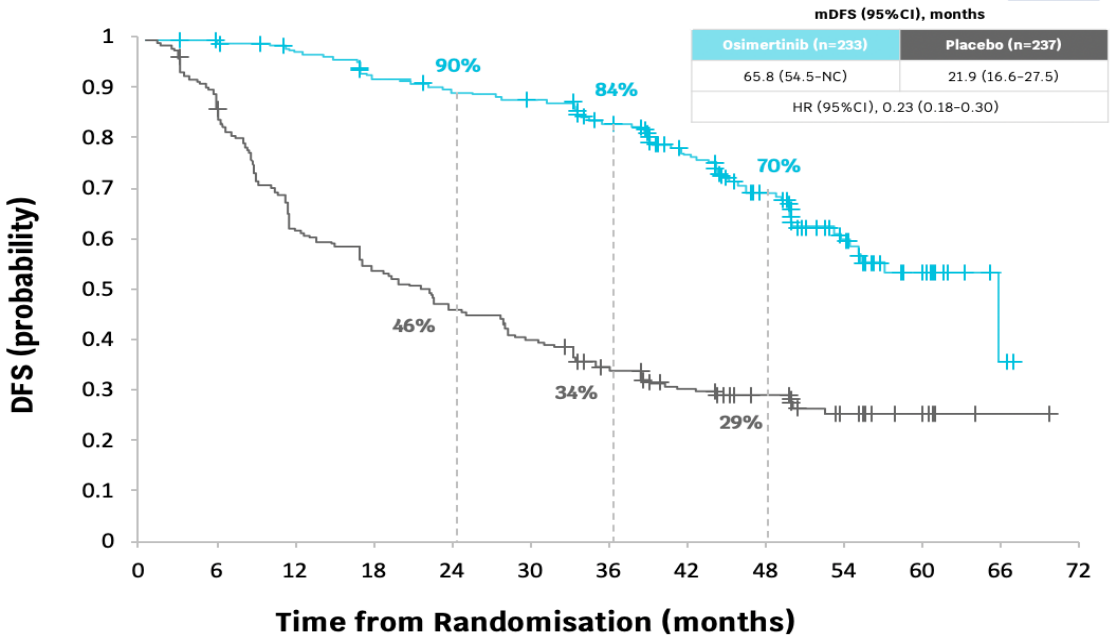
The Blueprint: EGFR (del 19 and L858R)

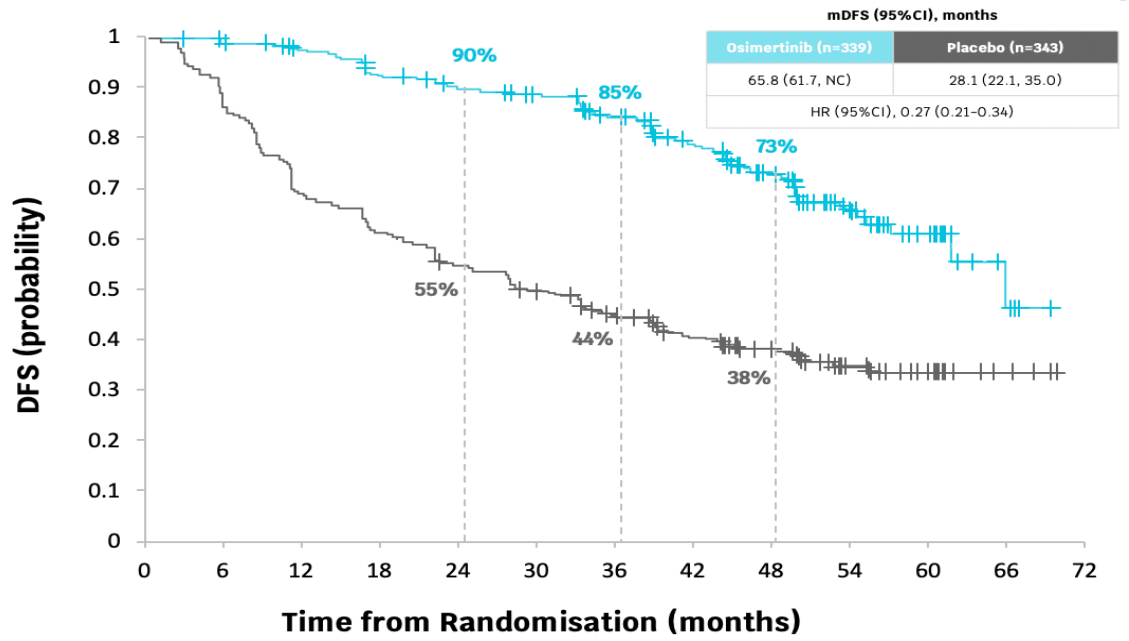
DFS in patients with stage II/IIIA disease and overall population: Stage IB/II/IIIA

II/IIIA Disease



No. at risk													
Osimertinib	233	222	216	202	196	192	174	138	90	45	20	2	0
Placebo	237	191	141	124	106	91	74	61	41	23	11	1	0

Overall Population: IB/II/IIIA Disease



No. at risk													
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

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The Blueprint: EGFR (del 19 and L858R)

DFS benefit observed in all predefined subgroups

Subgroup		HR	95% CI
Overall (N = 682)	Stratified log-rank	0.27	0.21, 0.34
	Unadjusted Cox PH	0.32	0.25, 0.40
Sex	Male (n = 204)	0.31	0.20, 0.48
	Female (n = 478)	0.31	0.23, 0.42
Age	<65 yr (n = 380)	0.31	0.22, 0.42
	≥65 yr (n = 302)	0.33	0.23, 0.48
Smoking history	Yes (n = 194)	0.26	0.16, 0.40
	No (n = 488)	0.34	0.26, 0.45
Race	Asian (n = 434)	0.34	0.25, 0.45
	Non-Asian (n = 248)	0.28	0.18, 0.43
Stage*	IB (n = 212)	0.41	0.23, 0.69
	II (n = 236)	0.34	0.23, 0.52
	IIIA (n = 234)	0.20	0.14, 0.29
EGFR mutation	Ex19Del (n = 378)	0.24	0.17, 0.33
	L858R (n = 304)	0.45	0.31, 0.64
Adjuvant chemotherapy	Yes (n = 410)	0.29	0.21, 0.39
	No (n = 272)	0.36	0.24, 0.55

Tsuboi, M. ESMO, Sept 2022

Some of the Criticism Surrounding ADAURA

1) **Staging evaluations could have been more robust**
   - PET, MRI Brain, Mediastinal Staging Evaluation were allowed but not mandated in study
   - Did the trial design to mirror, “real world” practices bias in favor of understaging
2) **Is DFS a fair and appropriate endpoint in the use of adjuvant therapies?**
   - Can circulating tumoral DNA and/or plasma evaluation help better stratify these outcomes in our future studies
3) **How will use of EGFR blockade influence use of Adjuvant Chemotherapy?**
4) **COST??? TIMING???**

EGFR Future Direction

1) **Duration:** Open label, single arm-phase II, multinational, multicenter study evaluating efficacy and safety of 5 years of Osimertinib in EGFRm NSCLC (stage II-IIB) following complete resection with or without adjuvant chemo

    - opened Feb 5, 2023

    -180 planned patients

2) **Before surgery:** NeoAdaura – phase III, randomized, 3 arm multinational, multicenter study of neoadjuvant Osimertinib as monotherapy or in combination with chemotherapy vs SOC chemotherapy in EGFRm resectable NSCLC

    - opened in Dec 2020

    - 328 planned patients

    - three arms (SOC chemo + placebo and SOC chemo + Osimertinib and Monotherapy)

ALK Fusions

1) **Alchemist (E4512): Crizotinib vs Observation** (difficulty with recruiting last few patients- started in 2014) – 168 patients
2) **Alina:** Alectinib vs chemotherapy as adjuvant therapy in patients with Stage IB-IIIA resected disease (about to complete) – 257 patients
3) **Nautika1:** Phase II, neoadjuvant and adjuvant study of multiple therapies in biomarker-selected patients with resectable Stage Ib-III NSCLC

- Opened Nov 6, 2020

- Alk Cohort: 8 weeks of neoadjuvant alectinib before surgical resection. All patients who have PR or no radiographic progression will be eligible to 4 cycles of chemotherapy and up to 2 years of alectinib

-Ros1 Cohort: 8 weeks of entrecinib neoadjuvant treatment before surgical resection. All patients who have PR or no radiographic progression will be eligible to 4 cycles of chemotherapy and up to 2 years of entrecinib

-NTRK Cohort: 8 weeks of entrecinib neoadjuvant treatment before surgical resection. All patients who have PR or no radiographic progression will be eligible to 4 cycles of chemotherapy and up to 2 years of entrecinib

- BRAF Cohort: 8 weeks of venumarafenib BID and cobimetinib neoadjuvant treatment before surgical resection. All patients who have PR or no radiographic progression will be eligible to 4 cycles of chemotherapy and up to 2 years of venumrafenib and cobimetinib

- Ret Cohort: 8 weeks of neoadjuvant pralsetinib before surgical resection. All patients who have PR or no radiographic progression will be eligible to 4 cycles of chemotherapy and up to 2 years of pralsetinib

MET (skipping mutation as well as met amplification)

1) Geometry- N: Phase II of neoadjuvant and adjuvant capmatinib in NSCLC

- opened August 2022
- 38 patients
- two cohorts (Cohort A – NSCLC with Met exon 14 skipping and Cohort B – NSCLC with high met amp)
- 8 weeks of capmatinib BID in neoadjuvant setting prior to resection followed by 3 years of adjuvant capmatinib in adjuvant setting

RET

1) **Libretto 432**- phase III study of adjuvant selpercatinib vs placebo in stage IB-IIIA ret-fusion NSCLC
    - opened Dec 2021
    - 170 participants
    - 3 years of therapy and can receive SOC Chemotherapy
2) **Nautika1**- Ret arm with pralsetinib

Take Homes

1) **Is the Standard of care now Next Generation Sequencing for All Patients with Stage Ib-III NSCLC- Tissue not plasma (they are all resected)**
   - These trials are partially neoadjuvant so please consider NGS on initial biopsy
2) **There are clinical trials available for the many of the targets seen in NSCLC**
3) **Our blueprint (EGFR) has demonstrated the clinical importance of finding these targets and please consider referring these patients to clinical trials**
4) **This was not a complete list and developing trials are always underway. Please contact your thoracic oncology friends to see availability of trials for participation for your patients with actionable targets**