ADJUVANT TARGETED THERAPY IN EGFR MUTATED EARLY STAGE LUNG CANCER

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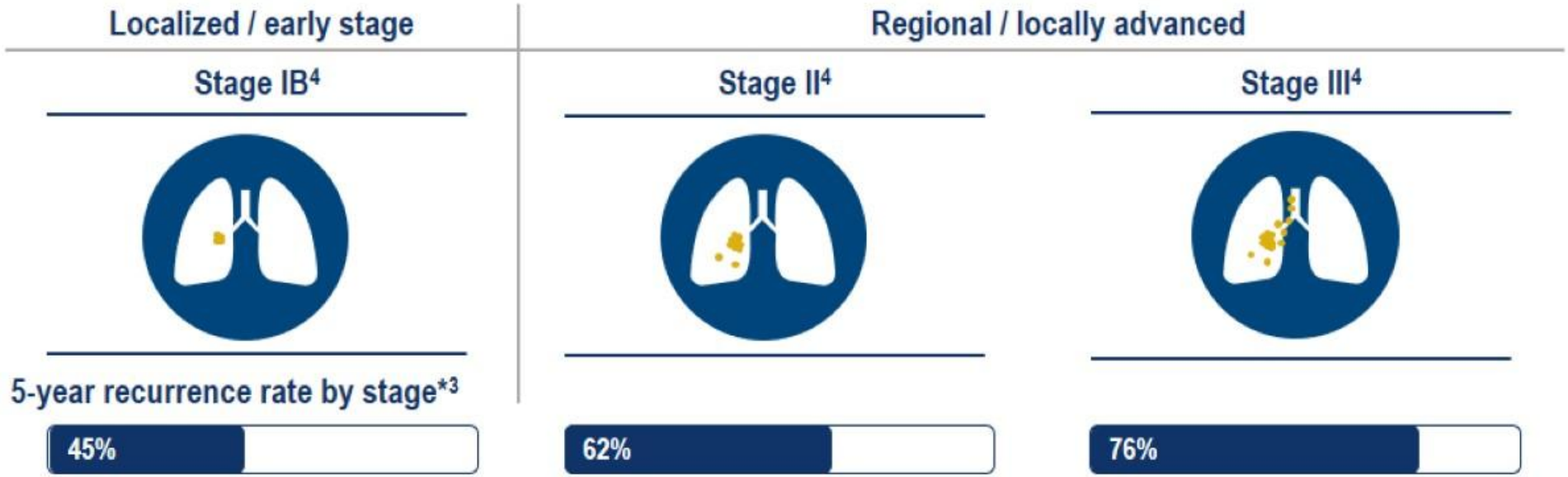
1 in 3 patients with NSCLC present with resectable disease

- Lung cancer is the leading cause of cancer death, accounting for more than 1.7 million deaths annually, and as many deaths as breast, prostate, and colorectal cancers combined[1]
- NSCLC represents 85% of all lung cancer cases,[2] with an estimated 30% of patients presenting with resectable disease at diagnosis[3–5]

Localized / early stage	Regional / locally advanced	
Stage IB[6]	Stage II[6]	Stage IIIA[6]
		

Outcomes in early stage NSCLC need to be improved

- Surgery is the primary treatment for patients with early stage NSCLC[1]
- Adjuvant cisplatin-based chemotherapy is recommended for patients with resected stage II—IIIA NSCLC and select patients with stage IB disease[2]
  - Results from large randomized trials and meta analyses showed a 5-year OS benefit with adjuvant chemotherapy in patients with early stage NSCLC, OS HR 0.89 (95% CI 0.82, 0.96); DFS also favored adjuvant chemotherapy, DFS HR 0.84 (95% CI 0.78, 0.91)[3]
- Overall, disease recurrence or death following surgery and adjuvant chemotherapy remains high across disease stages[3]



Clinical rationale for adjuvant chemotherapy

Surgical stage (6th ed)	5-yr survival%	relapse %	
		local	distant
IA T1N0M0	67	10	15
IB T2N0M0	57	10	30
IIA T1N1M0	55		
IIB T2N1M0 T3N0M0	39 38	12	40
IIIA T3N1M0 T1-3N2M0	25 23	15	60

- distant failure more common than local relapse
- >80% of recurrences occur within 2 years of surgery[1]

1. Scagliotti ASCO 2004

Adjuvant Impact Depends on Stage: NSCLC 5yr OS

Kris, JCO 2017

Blue:
Death (%) with/without chemotherapy

Yellow:
Survival without chemotherapy

Gray:
Survival due to chemotherapy

Red:
Death due to chemotherapy

Presented By David Spigel at TBD

1995 BMJ meta-analysis

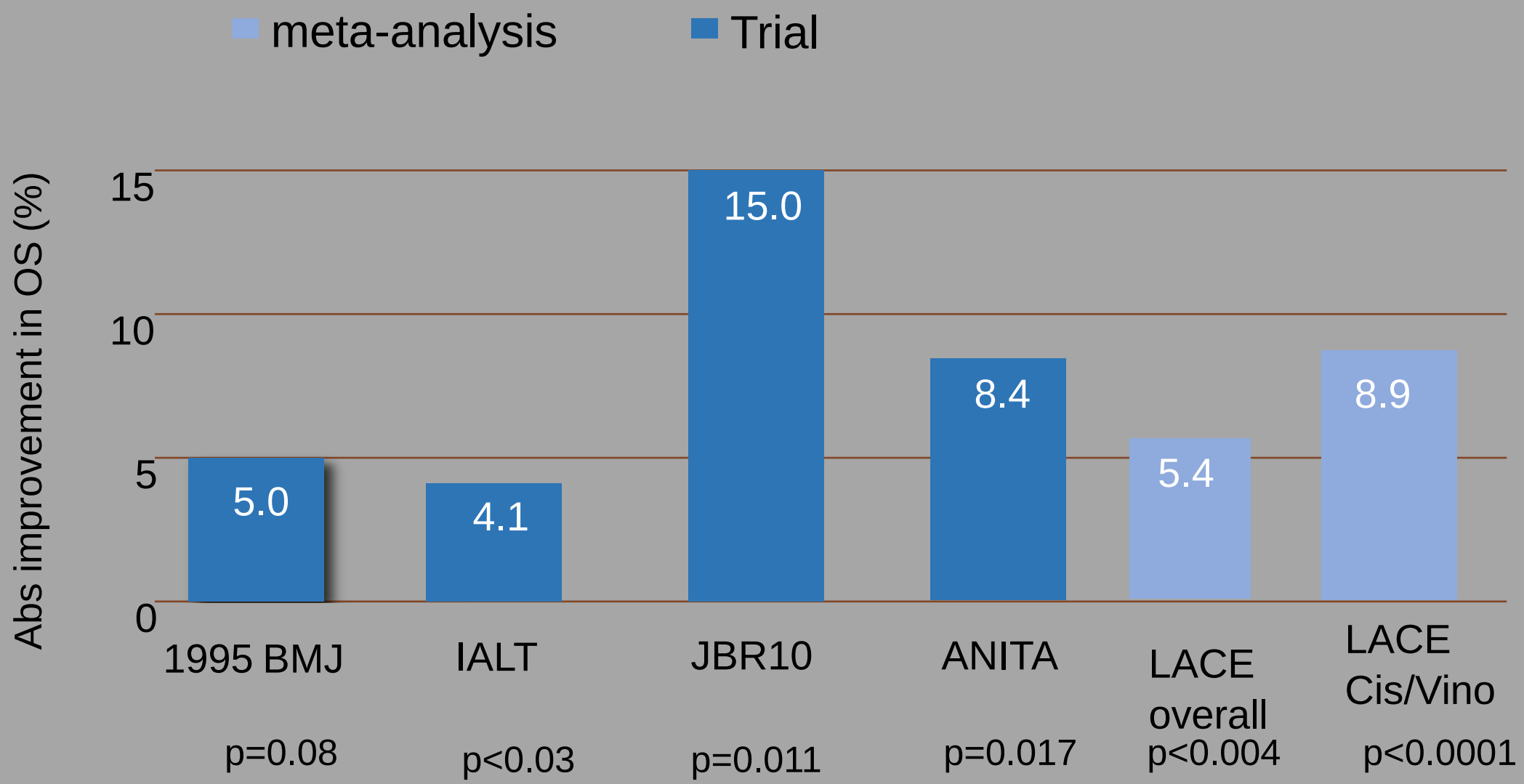
Included 14 trials (4357 patients) of adjuvant chemotherapy

Drug category	Hazard ratio	*p*	5yr survival
Alkylating agents	1.15 (1.04-1.27)	*0.005*	-5%
'Other ' drugs	0.89 (0.72-1.11)	*0.3*	4%
Cisplatin-based	0.87 (0.74-1.02)	*0.08*	5%

- Alkylating agents detrimental (includes mitomycin C & ifosfamide)
- Cisplatin-based therapy reduced the risk of death by 13% (p = 0.08)
- Absolute benefit of 5% at 5yr – did not reach statistical significance

BMJ 1995;311:899-909.

NSCLC – evidence for adj chemo



Based on a limited number of studies, the prevalence of EGFR mutations appears broadly similar across disease stages

Overall estimated prevalence[1]

Asian: 30–40%

Caucasian: 10–20%

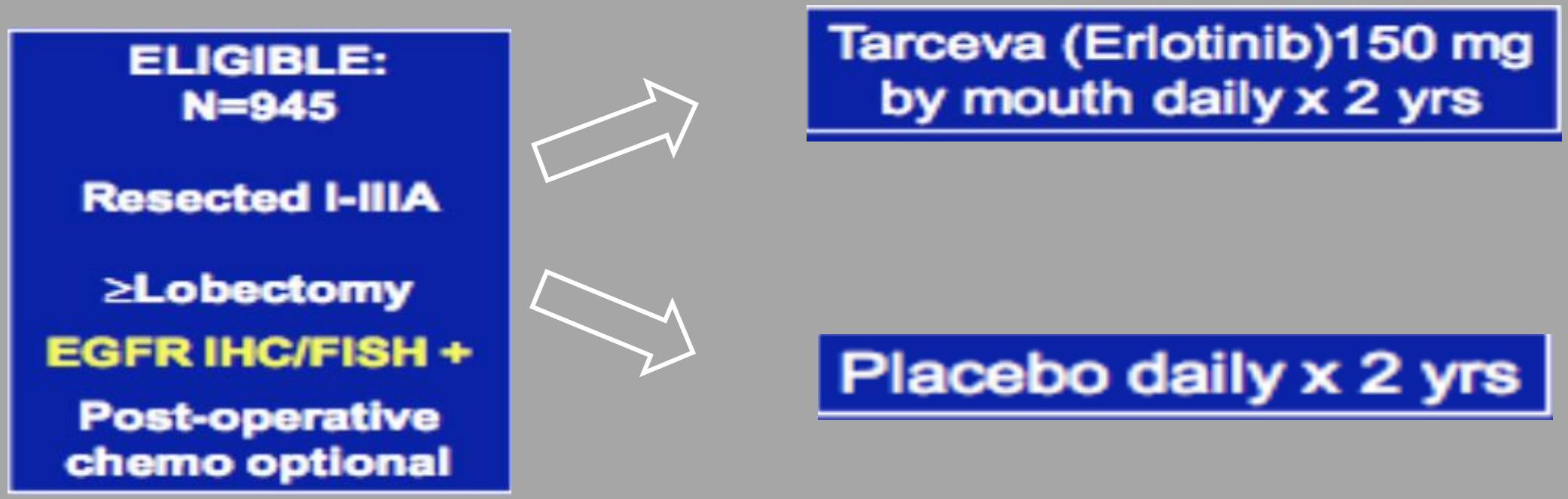
Prevalence estimates for each stage:[a]

Disease stage	Asia	US[b]	Europe
Stage I	34.4–54.8	19.0–40.5	11.5–26.5
Stage II	24.5–47.6	14.9–33.3	4.4–11.1
Stage III	27.8–47.3	17.4–42.9	12.0[c]
Stage IV	33.3–48.9	35.6–40.0	21.7[c]

If EGFR-TKIs were available in the resectable setting, a similar proportion of patients may be able to benefit compared to the advanced setting

1. Li T, et al. *J Clin Oncol* 2013;31:1039–1049

RADIANT



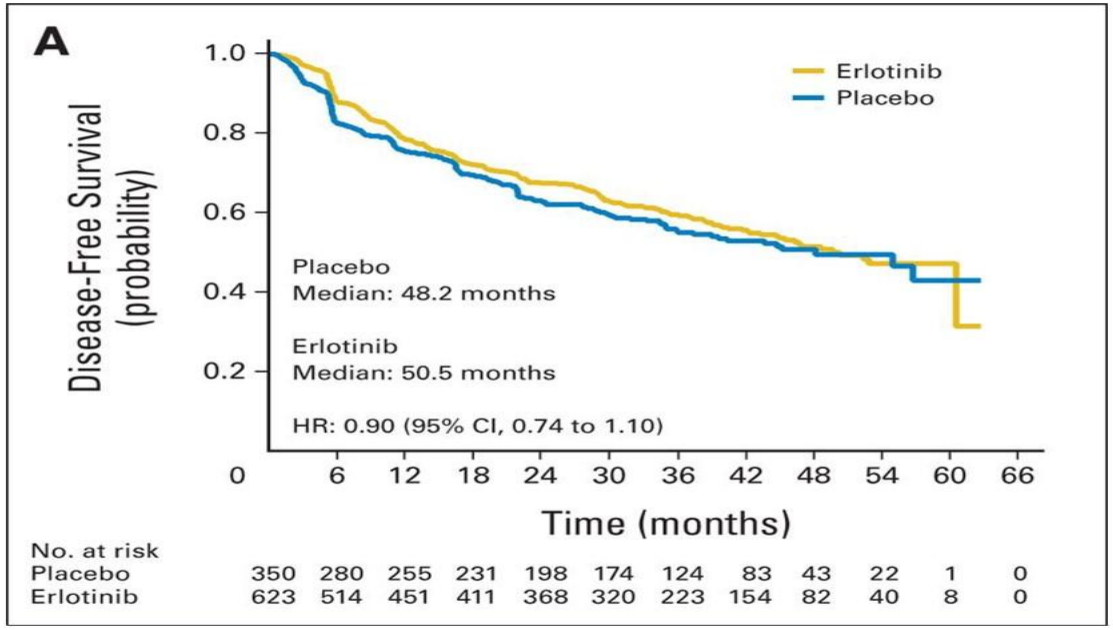
2:1 active drug

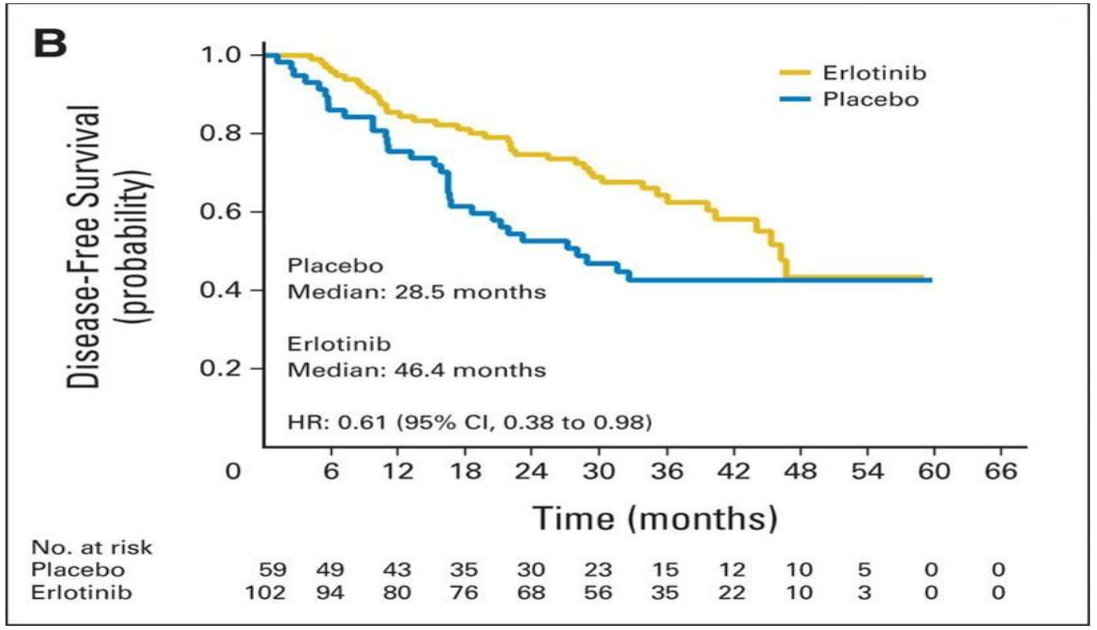
RADIANT

- adjuvant erlotinib (E) therapy in resected NSCLC patients who have overexpression of EGFR protein by immunohistochemistry (IHC) or EGFR gene amplification by fluorescence in situ hybridization (FISH)
- rate of EGFR exon 19 and 21 mutations in this unselected patient population is 12%, 973 patients - approximately 113 patients (about 60 patients per treatment arm) with EGFR mutation.
- Overall adjuvant E did not prolong DFS. EGFR mutation status was not a stratification factor in this trial and was not a prognostic factor

O'Brien ASCO 2015

RADIANT: Adjuvant Erlotinib v Placebo Stage IB-IIIA NSCLC (EGFRwt and EGFRm)





Kelly, JCO 2015

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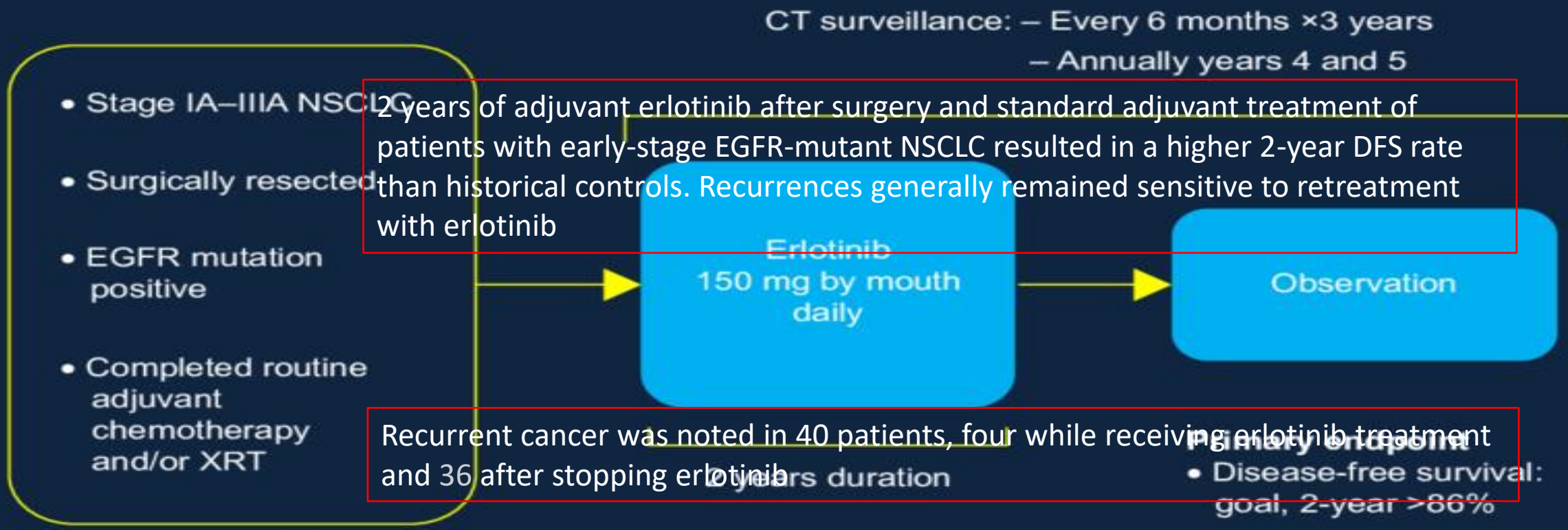
SELECT:[18] study design

- Single-arm Phase II study
- Adjuvant erlotinib following surgery and "standard" therapy



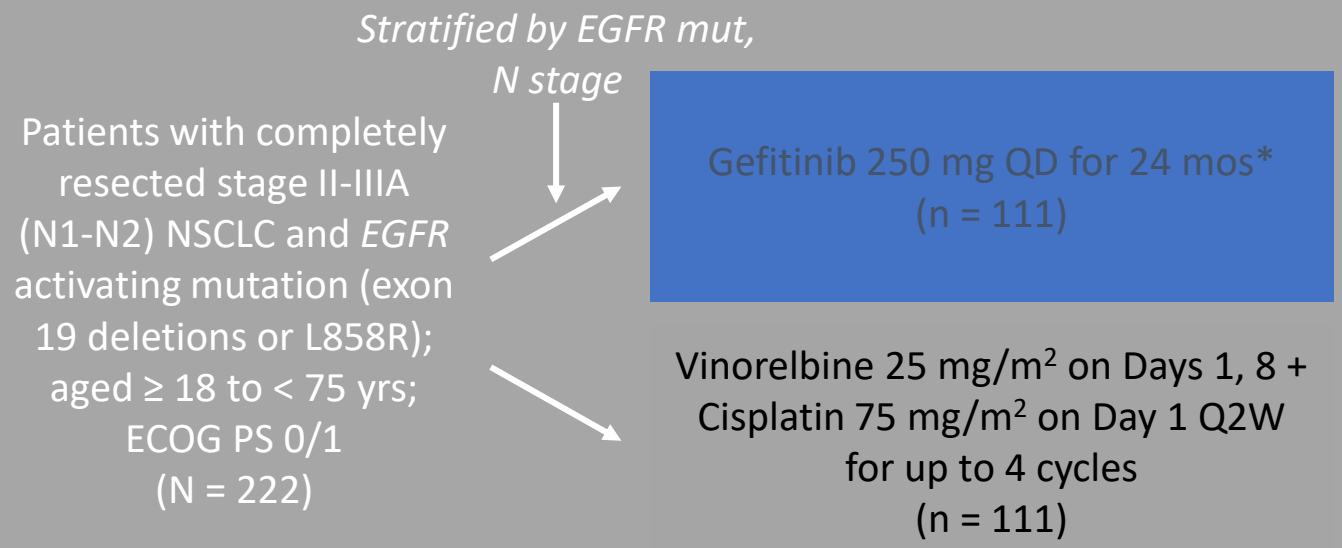
2 years of adjuvant erlotinib after surgery and standard adjuvant treatment of patients with early-stage EGFR-mutant NSCLC resulted in a higher 2-year DFS rate than historical controls. Recurrences generally remained sensitive to retreatment with erlotinib

Recurrent cancer was noted in 40 patients, four while receiving erlotinib treatment and 36 after stopping erlotinib

ADJUVANT-CTONG 1104: Phase III Study of Adjuvant Gefitinib vs Chemotherapy in Chinese Patients With Resected *EGFR*-Mutated NSCLC

ADJUVANT-CTONG 1104: Study Design

- Multicenter, randomized, open-label phase III trial in China
  - Subjects enrolled from September 19, 2011, to April 24, 2014; median follow-up: 80 mos



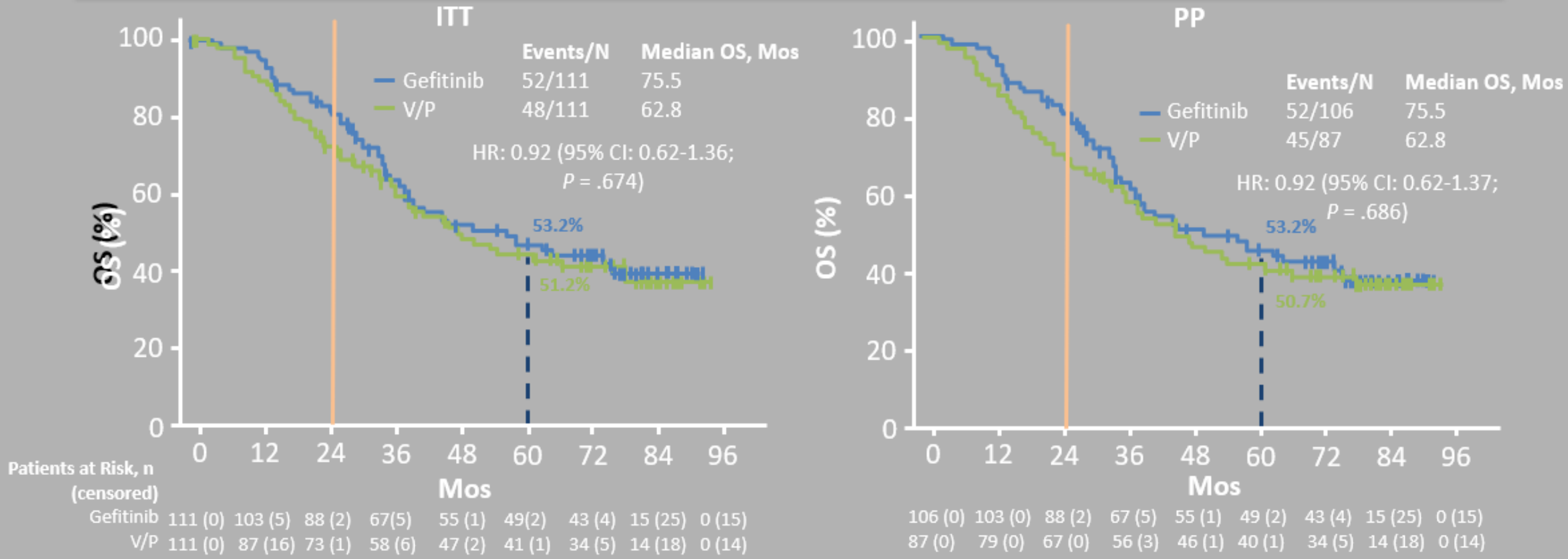
- Primary endpoint: DFS
- Secondary endpoints: OS, 5-yr OS rate, 3-yr/5-yr DFS rate, HRQoL, exploratory biomarker analyses, safety

Efficacy assessed Q12W until Yr 3, then Q6M. *Or until PD or unacceptable toxicity.

- Current analysis assessed OS and 3-yr/5-yr DFS rate in ITT and PP population (as sensitivity analysis)
  - Post hoc analyses evaluated OS with subsequent treatment and response with second-line EGFR TKI

Wu. ASCO 2020. Abstr 9005.

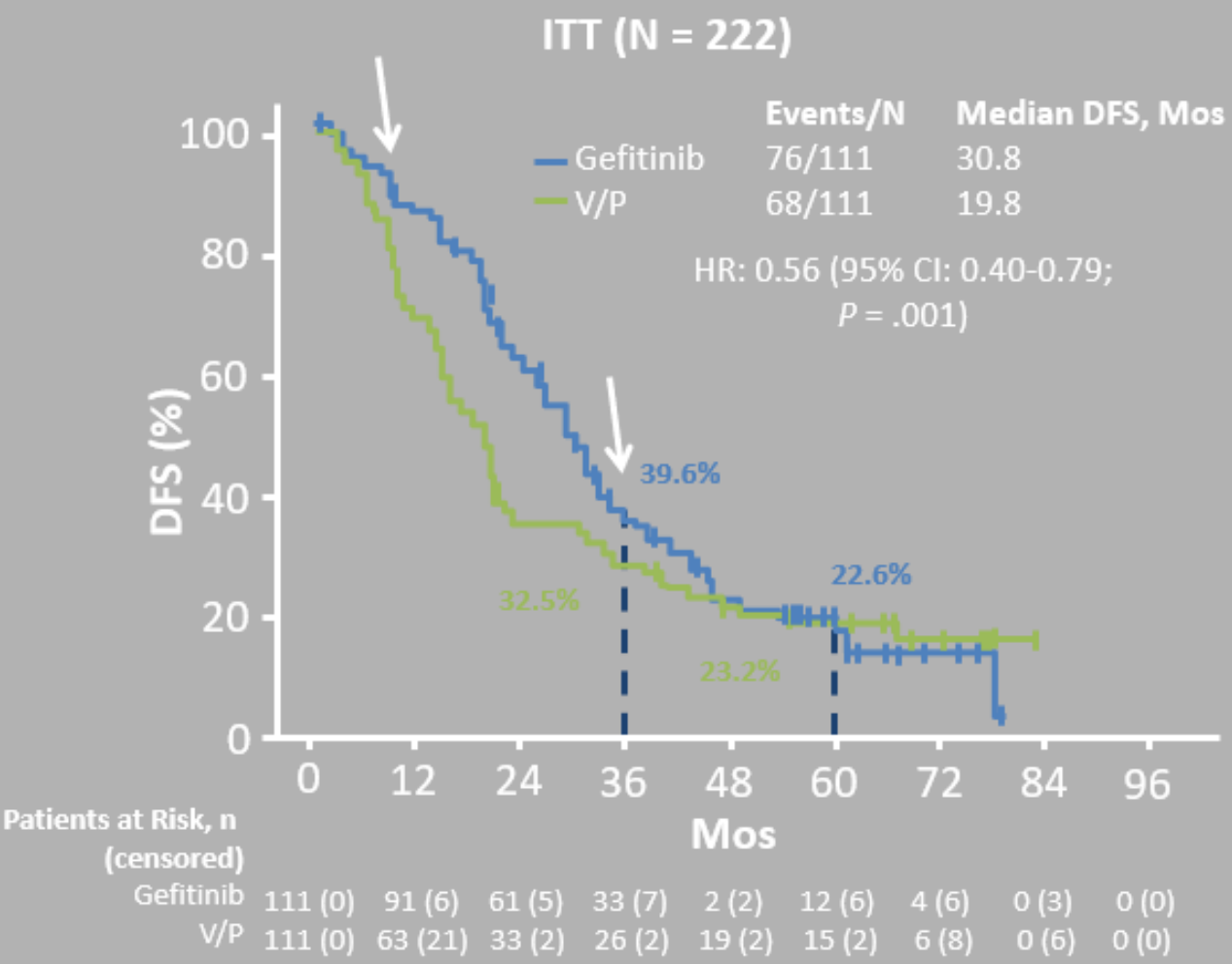
ADJUVANT-CTONG 1104: OS in ITT and PP

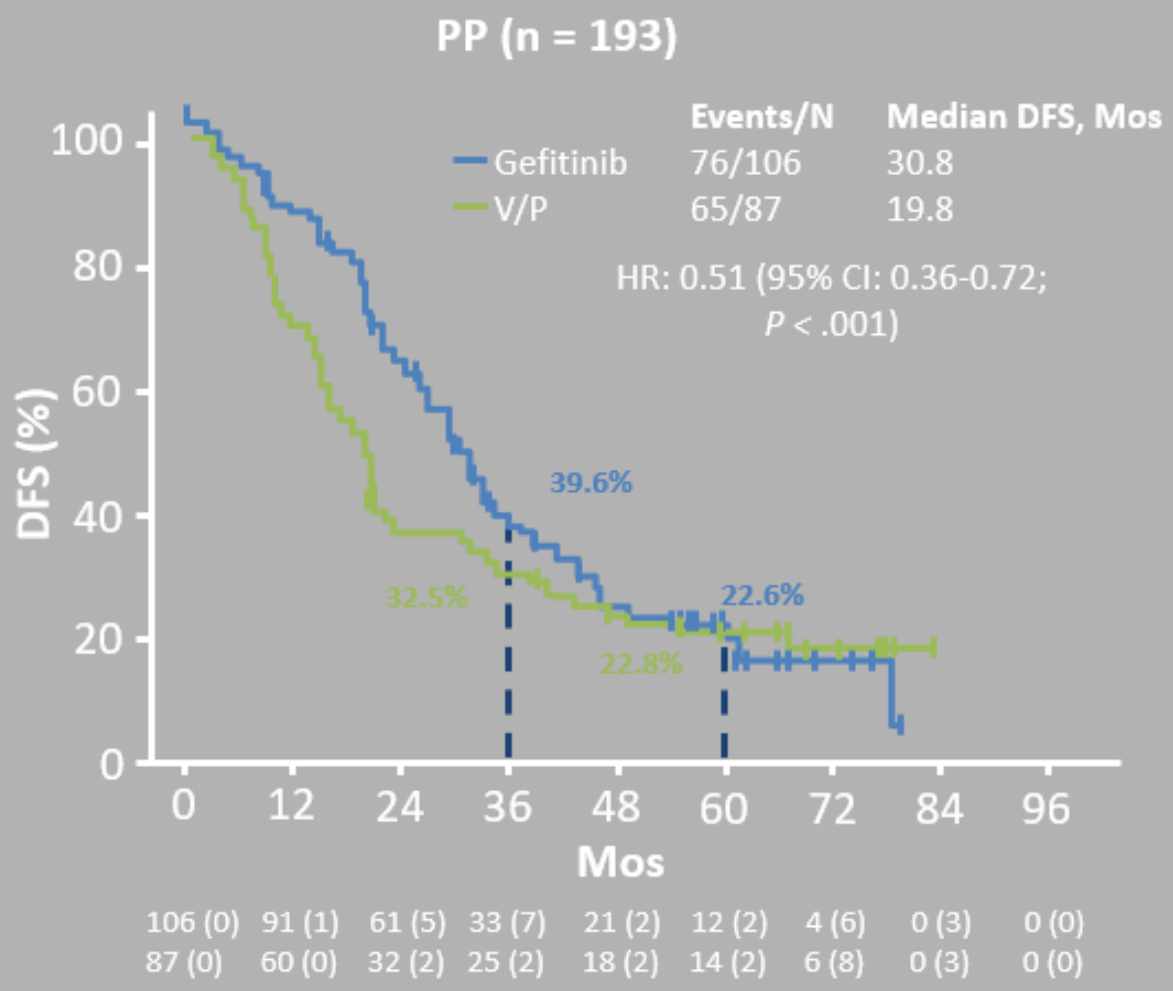


- OS prolonged but not significantly improved with gefitinib vs V/P in ITT and PP, nor in ITT subgroups stratified by age, gender, *EGFR* mutation, LN status (all $P > .05$)

Wu. ASCO 2020. Abstr 9005.

ADJUVANT-CTONG 1104: Updated 3-Yr/5-Yr DFS Rates





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EGFR-TKI in the adjuvant EGFRm NSCLC setting: DFS but not OS benefits have been demonstrated

- Current EGFR-TKI evidence has not translated into approval or a change in clinical practice in the adjuvant setting

SELECT[1]

Stage I–IIIA, EGFRm

Erlotinib after adjuvant chemotherapy ± RT

(n=100)

2-year DFS of 88% versus 76% historical control

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Stage IB–IIIA, EGFR expression / amplification

Erlotinib versus placebo after adjuvant chemotherapy (if received) [n=973]

Clinically meaningful DFS improvement in EGFRm subgroup: 46.4 versus 28.5 months

EVAN[3]

Stage IIIA, EGFRm

Erlotinib versus adjuvant chemotherapy

(n=102)

Significant DFS improvement: 42.4 versus 21.0 months

ADJUVANT / CTONG1104[4]

Stage II–IIIA (N1–N2), EGFRm

Gefitinib versus adjuvant chemotherapy (n=222)

Significant DFS improvement:
28.7 versus 18.0 months
No significant OS improvement : 75.5 vs 62.8 mos (HR: 0.92; 95% CI: 0.62-1.36; *P* = .674)

BR.19[5]

Stage IB–IIIA, EGFR unselected

Gefitinib versus placebo after adjuvant chemotherapy ± RT (if received) [n=503]

No DFS or OS benefit

1. Pennell NA, et al. *J Clin Oncol* 2019;37:97–104; 2. Kelly K, et al. *J Clin Oncol* 2015;33:4007–4014; 3. Yue D, et al. *Lancet Respir Med* 2018;6:863–873;
4. Zhong WZ, et al. *Lancet Oncol* 2018;19:139–148; 5. Goss GD, et al. *J Clin Oncol* 2013;31:3320–3326

Phase III ADAURA: Adjuvant Osimertinib vs Placebo After Complete Resection in Patients With Stage IB-IIIA *EGFR*-Mutated NSCLC

ADAURA Phase III double-blind 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§
Max. 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 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

Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

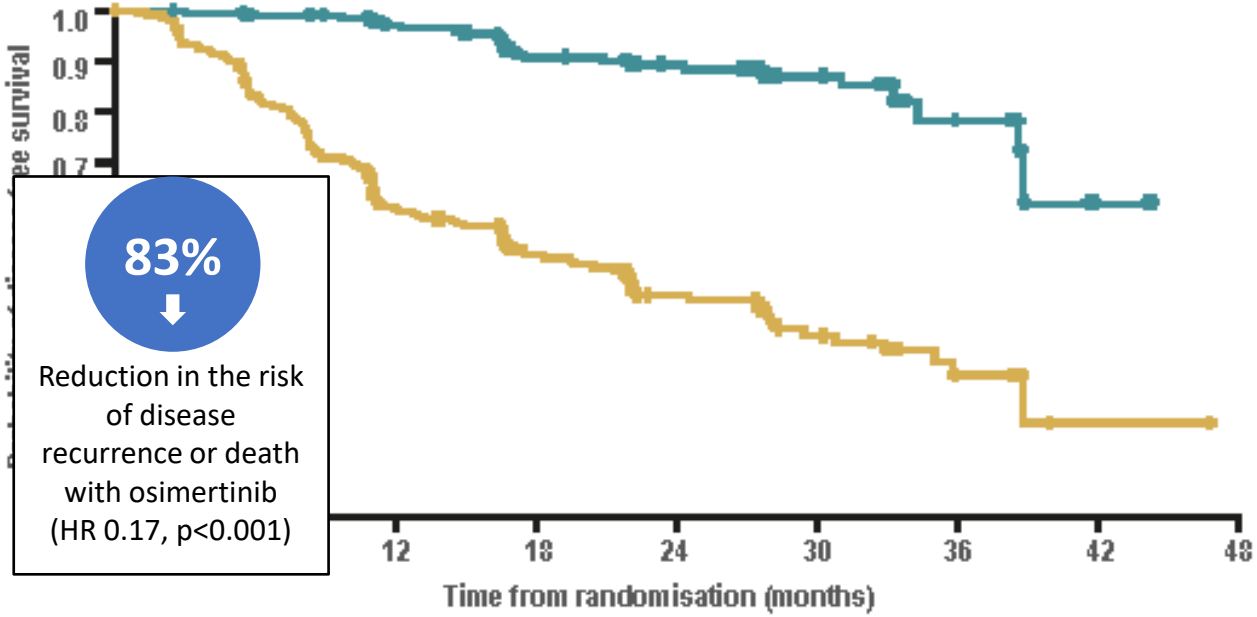
- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue; §Patients received a CT scan after resection and within 28 days prior to treatment; ¶Stage IB / II / IIIA.
CT, computed tomography; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; WHO, World Health Organization.

DFS: Disease Free Survival, OS: Overall Survival

ADAURA: Osimertinib improves DFS versus placebo in resected EGFRm NSCLC

Primary population: Stage II/IIIA



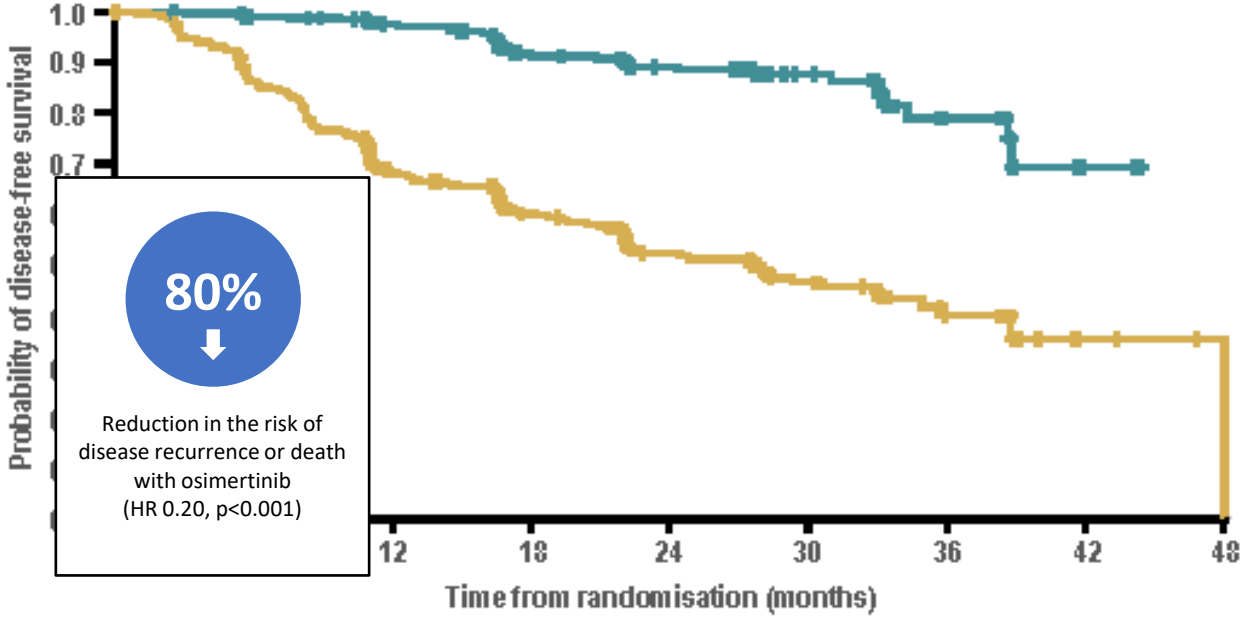
83% ⬇

Reduction in the risk of disease recurrence or death with osimertinib (HR 0.17, p<0.001)

No. at risk									
Osimertinib	233	219	189	137	97	52	18	2	0
Placebo	237	190	127	82	51	27	9	1	0

	Median DFS, months (95% CI)	HR (99.06% CI)
– Osimertinib	NR (38.8, NC)	0.17 (0.11, 0.26) P<0.0001
– Placebo	19.6 (16.6, 24.5)	

Overall population: Stage IB/II/IIIA



80% ⬇

Reduction in the risk of disease recurrence or death with osimertinib (HR 0.20, p<0.001)

No. at risk									
Osimertinib	339	313	272	208	138	74	27	5	0
Placebo	343	287	207	148	88	53	20	3	1

	Median DFS, months (95% CI)	HR (99.12% CI)
– Osimertinib	NR (NC, NC)	0.20 (0.14, 0.30) P<0.0001
– Placebo	27.5 (22.0, 35.0)	

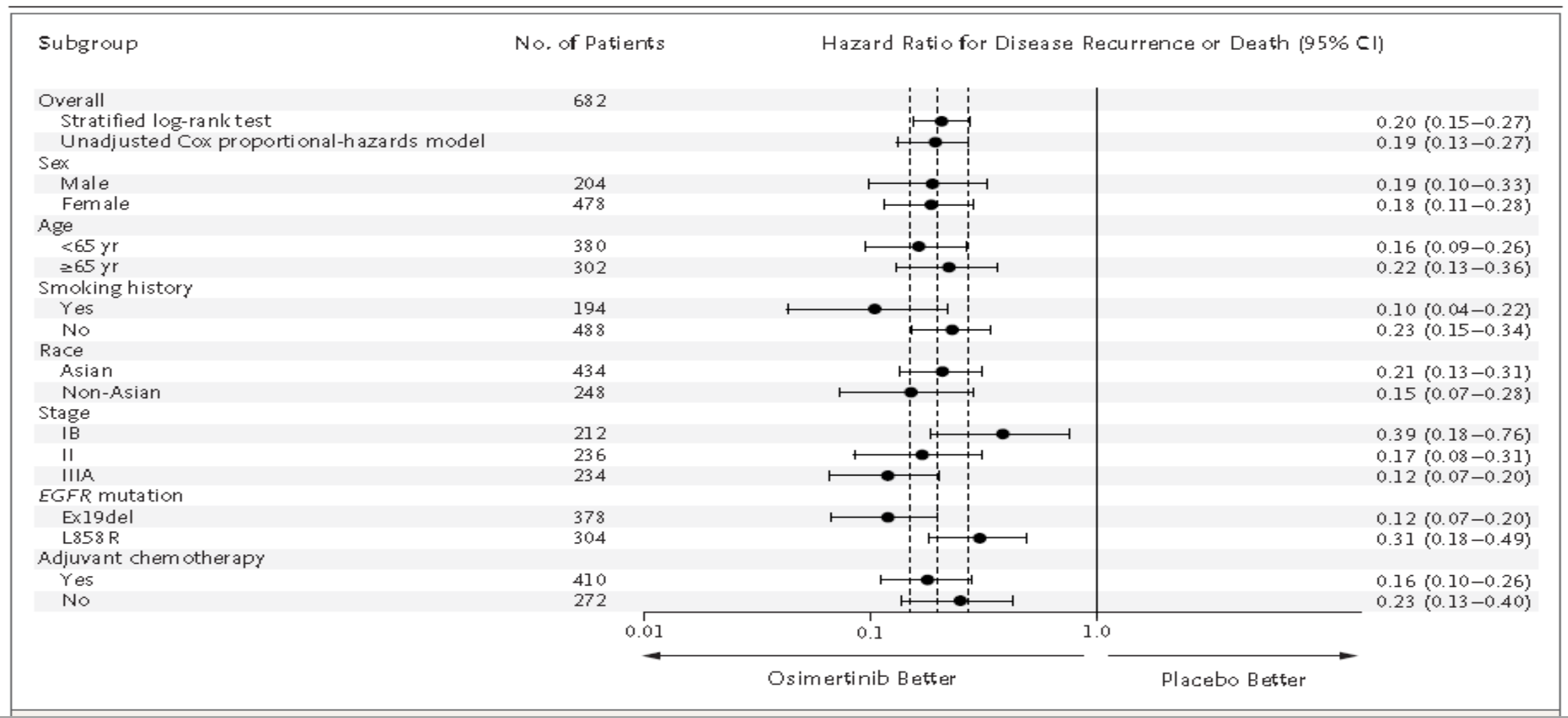
CI, confidence interval; NC, not calculable; HR, hazard ratio; NR, not reached
ADAURA data cut-off: 17 January, 2020

ADAURA: 2-year DFS was consistent for the osimertinib arm across disease stages[19]

	2-Year DFS, % (95% CI)		
Stage	**Osimertinib**	**Placebo**	**HR for DFS (95% CI)**
IB	**88 (78, 94)**	**71 (60, 80)**	0.39 (0.18, 0.76)
II	**91 (82, 95)**	**56 (45, 65)**	0.17 (0.08, 0.31)
IIIA	**88 (79, 94)**	**32 (23, 41)**	0.12 (0.07, 0.20)

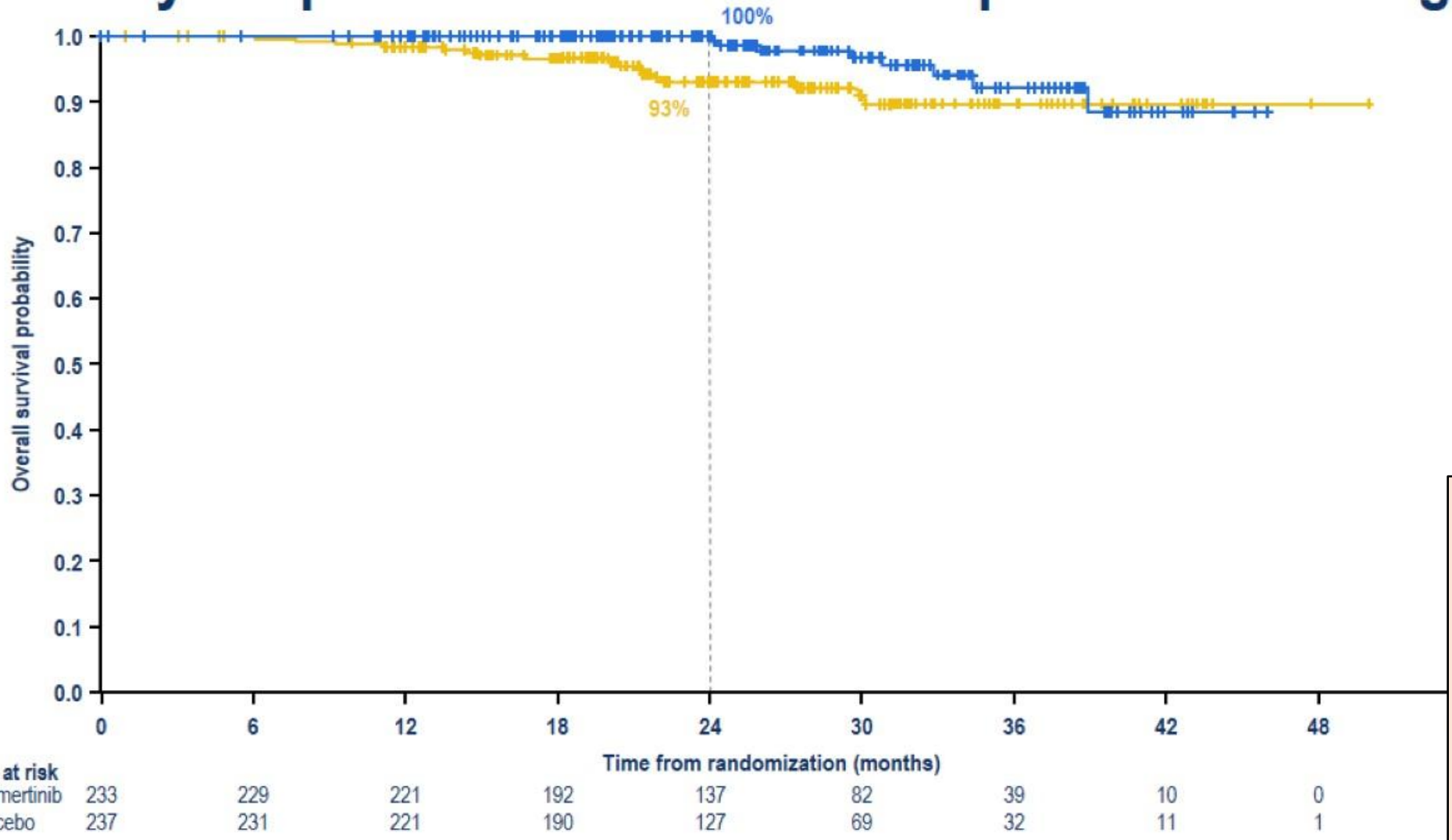
HR <1 implies a lower risk of disease recurrence or death with osimertinib compared with placebo.

Subgroup Analysis of Disease Recurrence or Death, According to Investigator Assessment



1. Wu Y-L et al. Online ahead of print. *NEJM*. 2020.

Early snapshot: overall survival in patients with stage II/IIIA disease

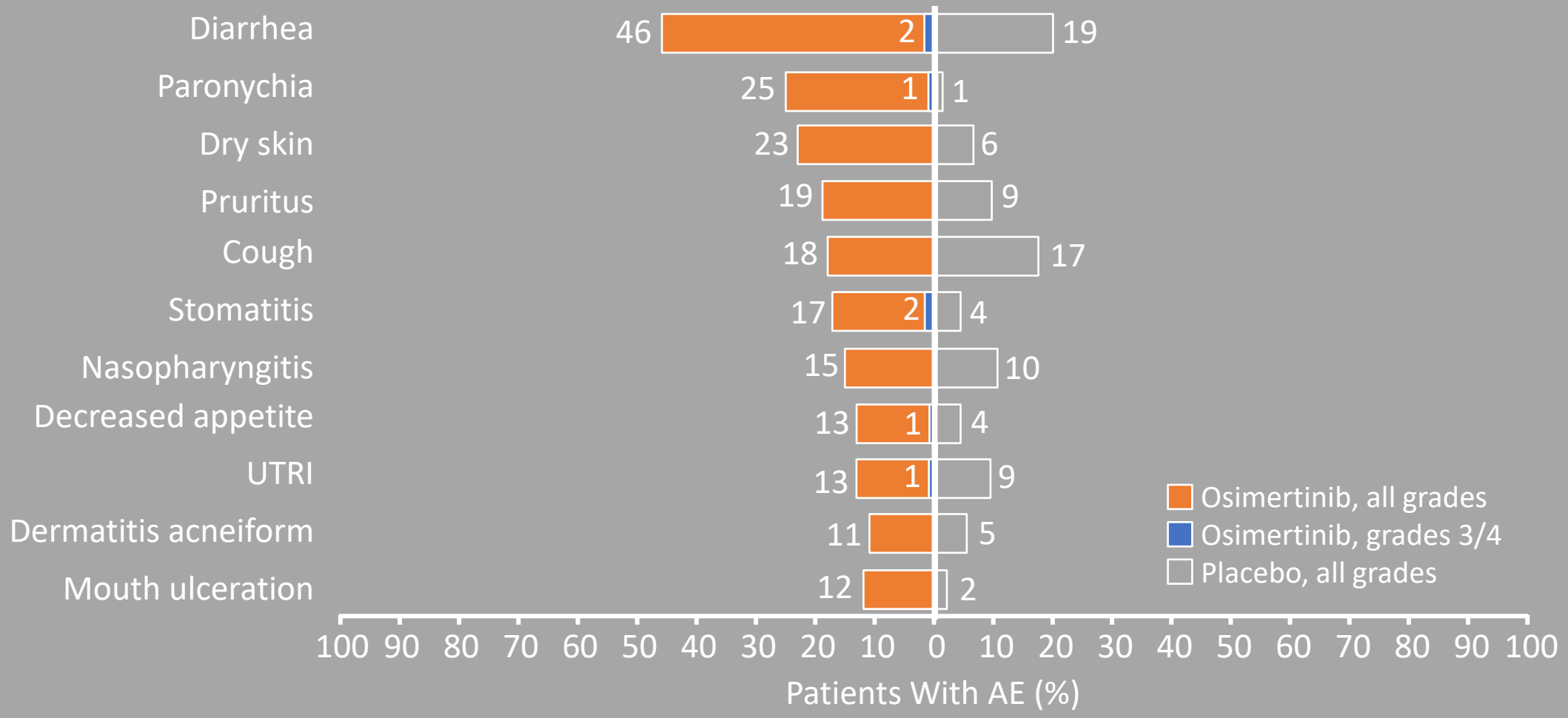


Median OS, months (95% CI)	
– Osimertinib	NR (NC, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.40 (0.18, 0.90)**

Maturity 5%:
osimertinib 3%, placebo 7%

Patients and investigators remain blinded to treatment in order to facilitate assessment of OS at maturity

ADAURA: All-Causality AEs in ≥ 10% of Patients



Herbst. ASCO 2020. Abstr LBA5..

Conclusions

- Adjuvant osimertinib substantially improves DFS in early stage EGFRm NSCLC and should be a new standard of care
- All patients with NSCLC - any stage - should be tested for EGFRm
- Chemotherapy is still a standard part of adjuvant treatment in Stage II and IIIA EGFRm NSCLC

Investigator's perspective

- In unplanned interim analysis, adjuvant osimertinib significantly prolonged DFS vs placebo after complete resection in patients with stage IB/II/IIIA *EGFR*+ NSCLC
  - 83% reduction in risk of recurrence or death with osimertinib in stage II/IIIA disease (primary endpoint; HR: 0.17; $P < .0001$)
  - 79% reduction in the risk of recurrence or death with osimertinib in the overall population (HR: 0.21; $P < .0001$)
  - DFS prolonged with osimertinib across subgroups, including those who received prior adjuvant chemotherapy
- No new safety signals observed with osimertinib
- Investigators concluded that adjuvant osimertinib should be incorporated into standard practice for treating patients with stage IB/II/IIIA *EGFR*-mutated NSCLC following complete resection

Clinician’s perspective

- remarkable benefit in DFS .
- We obviously need to see OS data, but it will take years to mature

Patient’s perspective

- Whats the benefit?

  stage II to IIIA, the original focus group, DFS with a hazard ratio of 0.17;
  including patients with stage IB disease, DFS with a hazard ratio of 0.21.

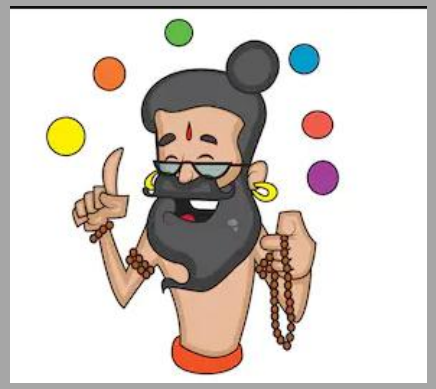
- Will it cure ? Isn't chemotherpy standard treatment?

  Cure: we don’t know yet.
  Chemo remains part of std treatment We may be over-treating by giving osimertinib

- Whats the side effects?

  Well tolerated

- Is it worthy to spend so much?



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Points to ponder

if you stop at 3 years, you might have restarted the clock you delayed.

Does it cure or is it just prolonging the inevitable

Take Home Message

- Definitely there is need for additional adjuvant therapy in early stage resected EGFRm Lung cancer
- Chemotherapy shown benefit but still there is plenty of scope to improve
- EGFR TKI has shown further improvement, specially in terms of DFS, but for OS ?? Benefit pending Osimertinib data maturity
- If feasible Osimertinib is preferable but other TKIs are also option when look into the evidence because accessibility to Osimertinib is very limited in our population.

Thank you