Targeted Therapy in Early Stage Lung Cancer

Kate-Lynn Muir, DO
Hematology Oncology

University of Nebraska Medical Center
Nebraska Medicine

Disclosures:

None.

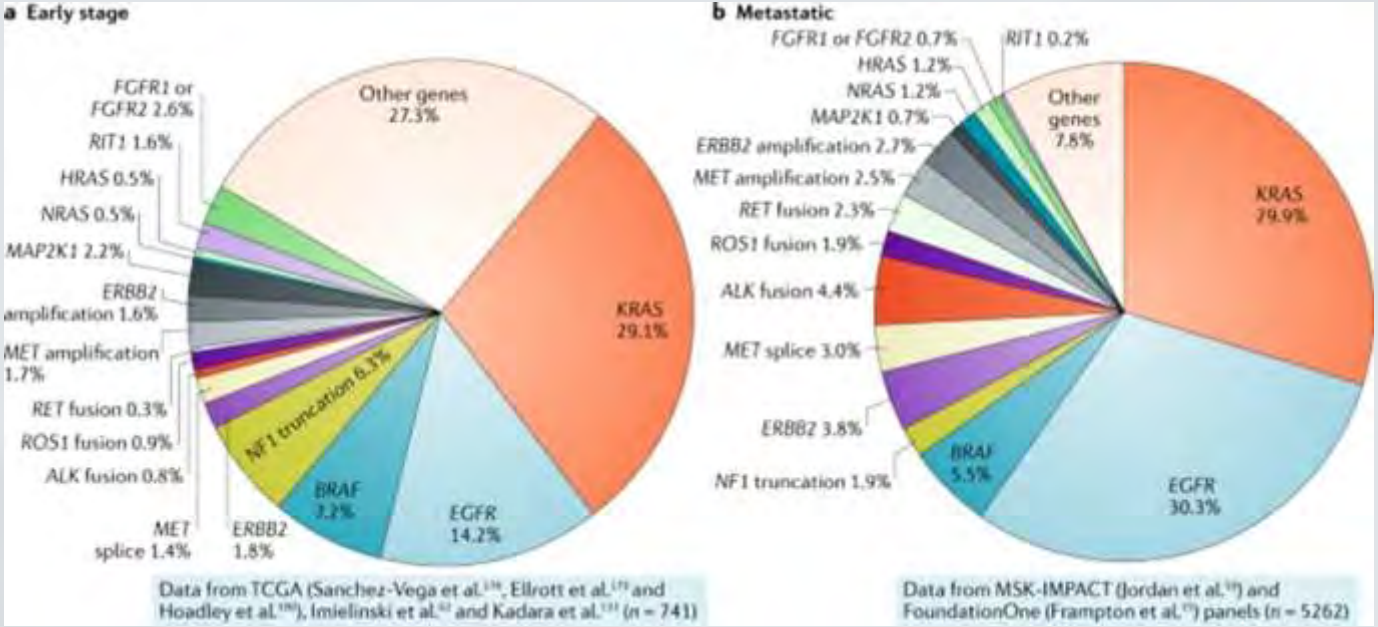
Overview

- Incidence of targetable mutations in lung cancer
- Targetable mutations in adjuvant setting
- Targetable mutations post RT
- Current areas of research
  - Targetable mutations in neoadjuvant setting

Incidence of targetable mutations

- About 30% of NSCLC will have a targetable mutation
  - Most commonly identified is EGFR– exon 19 deletion and L858R less commonly exon 20 insertion and L861Q
  - KRAS– 10-15% of those will be G12C and actionable
  - ALK– 3-4%
  - MET– skipping 3-4%
  - RET – 1-2%
  - BRAF V600 E – 1-2%
  - NTRK – 0.5%

Incidence of targetable mutations in early stage vs metastatic NSCLC



Adjuvant targeted therapy in postoperative setting

ADAURA Trial

The NEW ENGLAND JOURNAL of MEDICINE

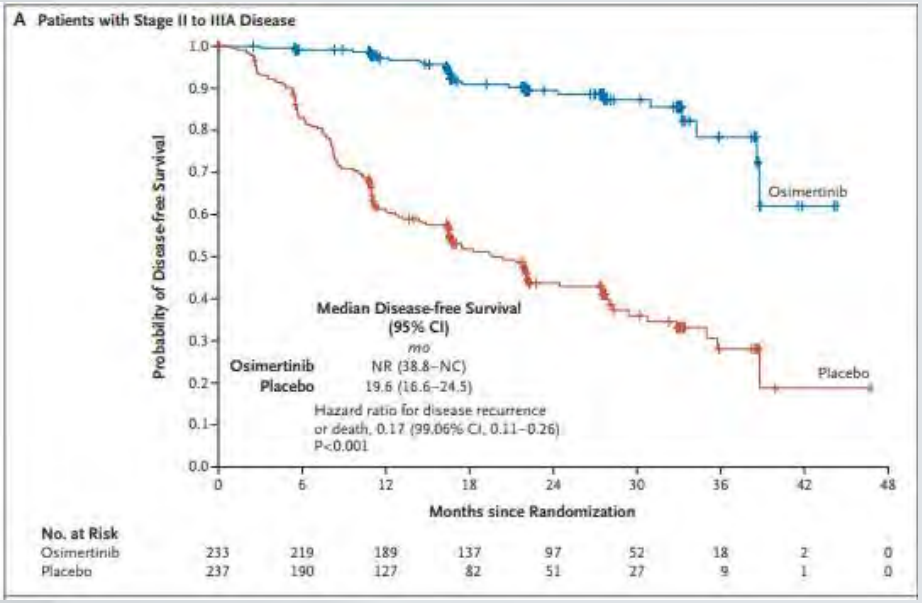
ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

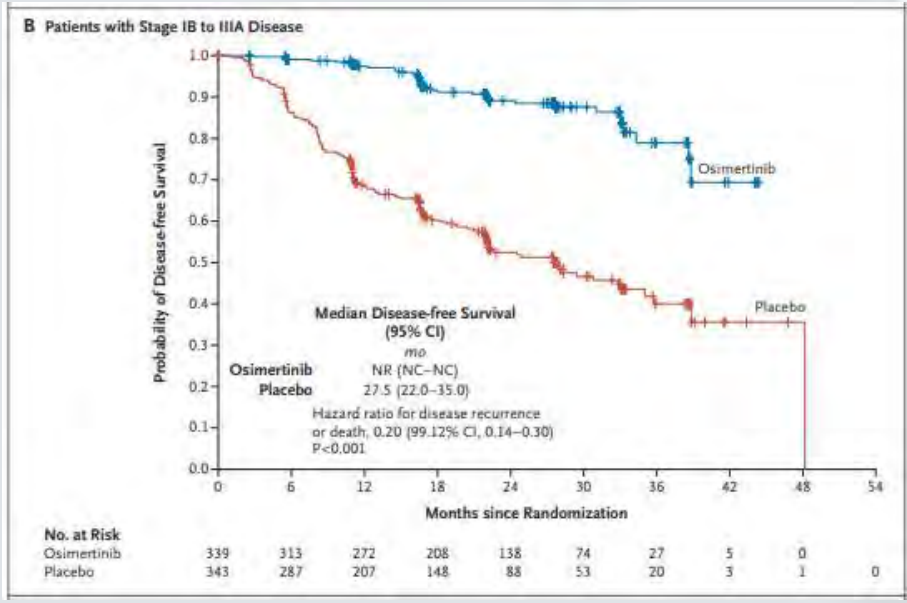
Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D., for the ADAURA Investigators*

ADAURA Trial

- Previous trials looking at EGFR inhibitors in adjuvant setting failed to show statistically significant DFS or OS
- ADAURA included 682 participants with EGFR mutation with stage IB-IIIA NSCLC
- Randomized 1:1 to receive Osimertinib 80 mg daily vs placebo for 3 years after adjuvant chemotherapy if indicated


A Patients with Stage II to IIIA Disease
Probability of Disease-free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Osimertinib
Placebo
Median Disease-free Survival (95% CI)
mo
Osimertinib NR (38.8–NC)
Placebo 19.6 (16.6–24.5)
Hazard ratio for disease recurrence or death, 0.17 (99.06% CI, 0.11–0.26)
P<0.001
0 6 12 18 24 30 36 42 48
Months since Randomization
No. at Risk
Osimertinib 233 219 189 137 97 52 18 2 0
Placebo 237 190 127 82 51 27 9 1 0


B Patients with Stage IB to IIIA Disease
Probability of Disease-free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Osimertinib
Placebo
Median Disease-free Survival (95% CI)
mo
Osimertinib NR (NC–NC)
Placebo 27.5 (22.0–35.0)
Hazard ratio for disease recurrence or death, 0.20 (99.12% CI, 0.14–0.30)
P<0.001
0 6 12 18 24 30 36 42 48 54
Months since Randomization
No. at Risk
Osimertinib 339 313 272 208 138 74 27 5 0
Placebo 343 287 207 148 88 53 20 3 1 0

Results

- Primary end point of disease-free survival stage II-IIIA
  - Stage II to IIIA disease, 90% of those in the osimertinib group and 44% of those in the placebo group were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.17; 99.06% CI, 0.11 to 0.26; P<0.001).
- Secondary end point of disease-free survival in the overall population
  - Stage IB to IIIA disease 89% of those in the osimertinib group and 52% of those in the placebo group were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.20; 99.12% CI, 0.14 to 0.30; P<0.001)
  - 80% reduction in the risk of disease recurrence or death with osimertinib.
- DFS benefit with osimertinib was observed consistently across all predefined subgroups, including all disease stages.

Updated results

- II to IIIA disease, the 5-year overall survival was 85% in the osimertinib group and 73% in the placebo group (overall hazard ratio for death, 0.49; 95.03% confidence interval [CI], 0.33 to 0.73; P<0.001).
- In the overall population (patients with stage IB to IIIA disease), the 5-year overall survival was 88% in the osimertinib group and 78% in the placebo group (overall hazard ratio for death, 0.49; 95.03% CI, 0.34 to 0.70; P<0.001)

Takeaways

- Standard of care in EGFR mutated NSCLC after resection IB-IIIA includes adjuvant chemotherapy if indicated followed by 3 years of Osimertinib
- Question remains if greater than 3 years of Osimertinib would be of benefit

ALINA Trial

The NEW ENGLAND JOURNAL of MEDICINE

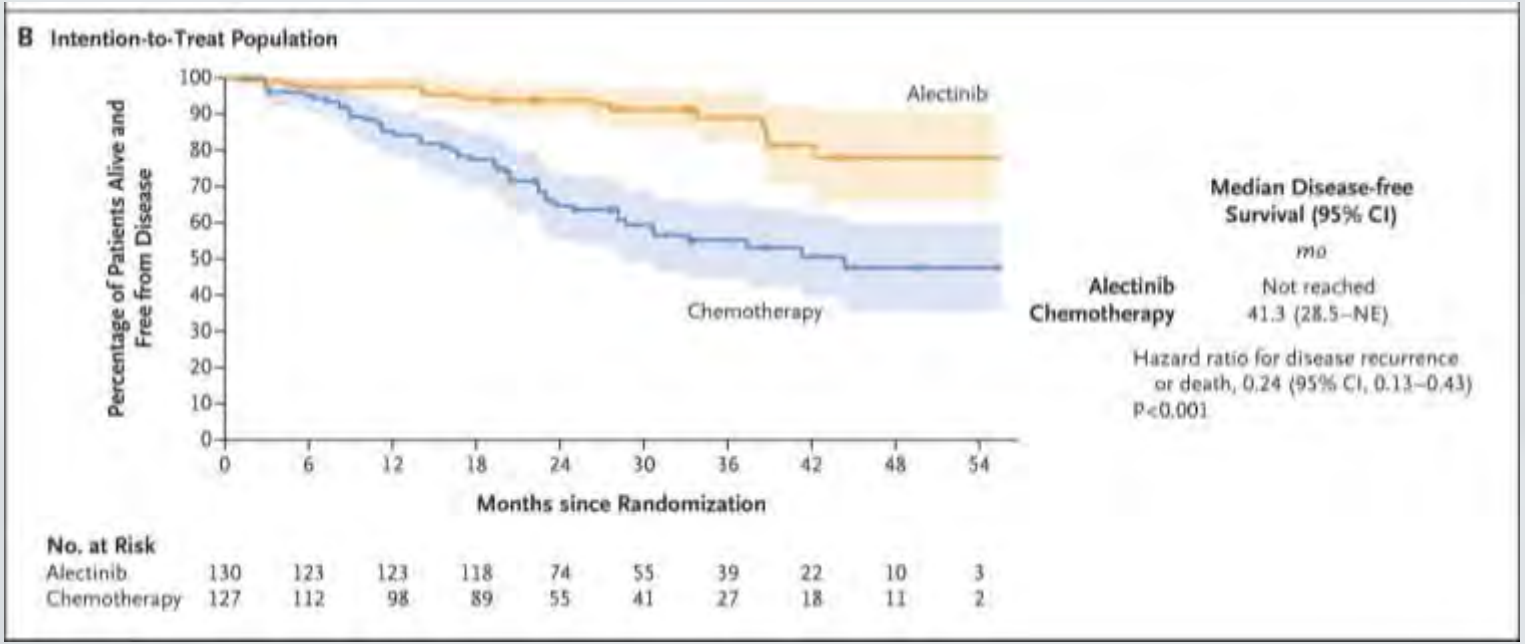
ESTABLISHED IN 1812 APRIL 11, 2024 VOL. 390 NO. 14

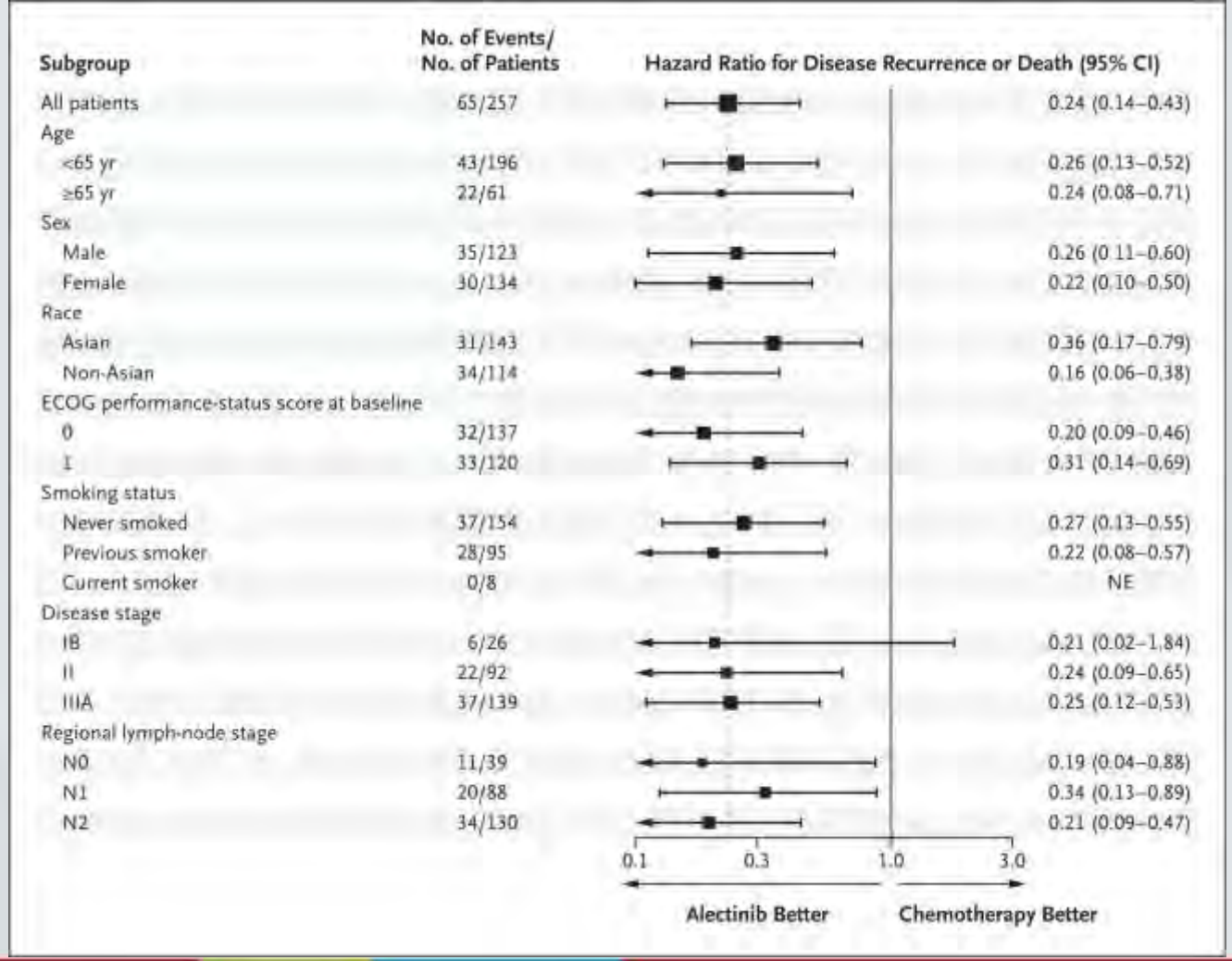
Alectinib in Resected *ALK*-Positive Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Rafal Dziadziuszko, M.D., Ph.D., Jin Seok Ahn, M.D., Ph.D., Fabrice Barlesi, M.D., Ph.D., Makoto Nishio, M.D., Ph.D., Dae Ho Lee, M.D., Ph.D., Jong-Seok Lee, M.D., Ph.D., Wenzhao Zhong, M.D., Ph.D., Hidehito Horinouchi, M.D., Ph.D., Weimin Mao, M.D., Ph.D., Maximilian Hochmair, M.D., Filippo de Marinis, M.D., M. Rita Migliorino, M.D., Igor Bondarenko, M.D., Ph.D., Shun Lu, M.D., Qun Wang, M.D., Tania Ochi Lohmann, Ph.D., Tingting Xu, M.D., Andres Cardona, M.Sc., Thorsten Ruf, M.D., Johannes Noe, Ph.D., and Benjamin J. Solomon, M.B., B.S., Ph.D., for the ALINA Investigators*

ALINA Trial

- Completely resected, *ALK*-positive NSCLC of stage IB (tumors ≥4 cm), II, or IIIA
- Randomly assigned in a 1:1 ratio to receive oral alectinib (600 mg twice daily) for 24 months or intravenous platinum-based chemotherapy in four 21-day cycles


B Intention-to-Treat Population
Percentage of Patients Alive and Free from Disease
100
90
80
70
60
50
40
30
20
10
0
Alectinib
Chemotherapy
0
6
12
18
24
30
36
42
48
54
Months since Randomization
No. at Risk
Alectinib 130 123 123 118 74 55 39 22 10 3
Chemotherapy 127 112 98 89 55 41 27 18 11 2
Median Disease-free Survival (95% CI)
mo
Alectinib Not reached
Chemotherapy 41.3 (28.5–NE)
Hazard ratio for disease recurrence or death, 0.24 (95% CI, 0.13–0.43)
P<0.001


Subgroup
No. of Events/ No. of Patients
Hazard Ratio for Disease Recurrence or Death (95% CI)
All patients 65/257 0.24 (0.14–0.43)
Age
<65 yr 43/196 0.26 (0.13–0.52)
≥65 yr 22/61 0.24 (0.08–0.71)
Sex
Male 35/123 0.26 (0.11–0.60)
Female 30/134 0.22 (0.10–0.50)
Race
Asian 31/143 0.36 (0.17–0.79)
Non-Asian 34/114 0.16 (0.06–0.38)
ECOG performance-status score at baseline
0 32/137 0.20 (0.09–0.46)
1 33/120 0.31 (0.14–0.69)
Smoking status
Never smoked 37/154 0.27 (0.13–0.55)
Previous smoker 28/95 0.22 (0.08–0.57)
Current smoker 0/8 NE
Disease stage
IB 6/26 0.21 (0.02–1.84)
II 22/92 0.24 (0.09–0.65)
IIIA 37/139 0.25 (0.12–0.53)
Regional lymph-node stage
N0 11/39 0.19 (0.04–0.88)
N1 20/88 0.34 (0.13–0.89)
N2 34/130 0.21 (0.09–0.47)
0.1
0.3
1.0
3.0
Alectinib Better
Chemotherapy Better

Results

- Primary end point of DFS
  - Hazard ratio for disease recurrence or death was 0.24 among patients with stage II or IIIA NSCLC and in the intention-to-treat population, which corresponds to a 76% lower risk with adjuvant alectinib than with chemotherapy
- Awaiting maturing OS data

Takeaways

- Category 1 recommendation Alectinib 600 mg twice daily for 24 months for patients with completely resected stage II–IIIA or stage IIIB NSCLC and positive for ALK rearrangements
- Questions remaining:
  - Optimal duration of Alectinib post operatively
  - Would combination or sequential alectinib with chemotherapy provide additional benefit

Targeted therapy post definitive chemoRT

LAURA Trial

The NEW ENGLAND JOURNAL of MEDICINE

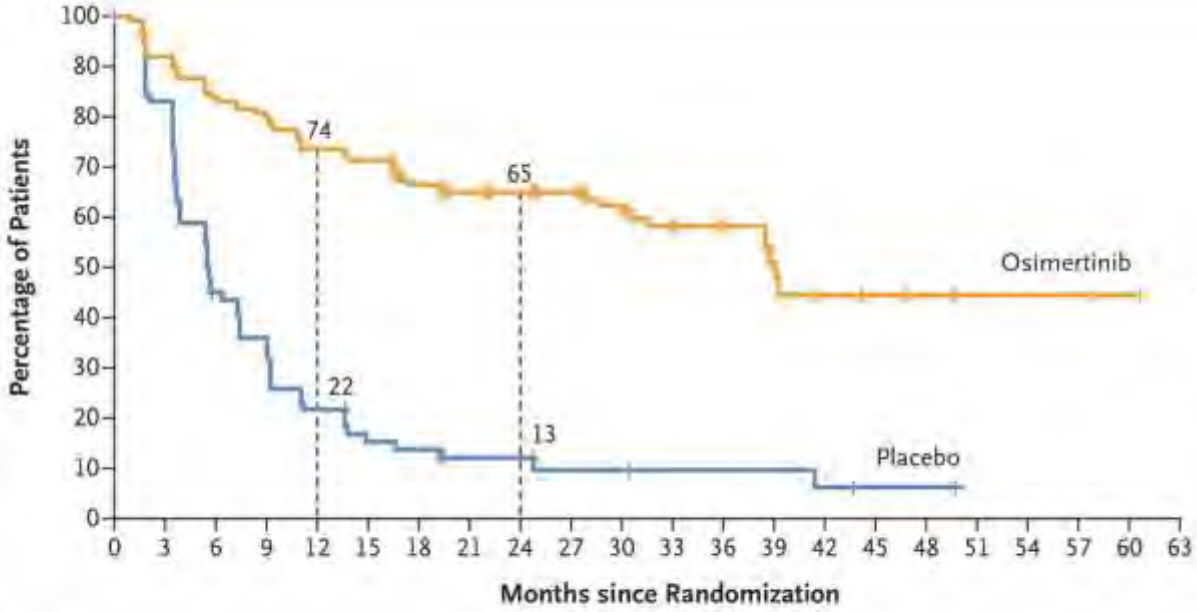
ESTABLISHED IN 1812 AUGUST 15, 2024 VOL. 391 NO. 7

Osimertinib after Chemoradiotherapy in Stage III *EGFR*-Mutated NSCLC

Shun Lu, M.D., Terufumi Kato, M.D., Xiaorong Dong, M.D., Ph.D., Myung-Ju Ahn, M.D., Le-Van Quang, M.D., Nopadol Soparattanapaisarn, M.D., Takako Inoue, M.D., Chih-Liang Wang, M.D., Meijuan Huang, M.D., James Chih-Hsin Yang, M.D., Ph.D., Manuel Cobo, M.D., Mustafa Özgüroğlu, M.D., Ignacio Casarini, M.D., Dang-Van Khiem, M.D., Virote Sriuranpong, M.D., Ph.D., Eduardo Cronemberger, M.D., Toshiaki Takahashi, M.D., Ph.D., Yotsawaj Runglodvatana, M.D., Ming Chen, M.D., Ph.D., Xiangning Huang, Ph.D., Ellie Grainger, M.Sc., Dana Ghiorghiu, M.D., Ph.D., Toon van der Gronde, Pharm.D., Ph.D., and Suresh S. Ramalingam, M.D., for the LAURA Trial Investigators*

LAURA Trial

- Phase 3, double-blind, placebo-controlled trial, randomly assigned patients with unresectable EGFR-mutated stage III NSCLC without progression during or after chemoradiotherapy to receive osimertinib or placebo until disease progression occurred or the regimen was discontinued.
- The primary end point was progression-free survival



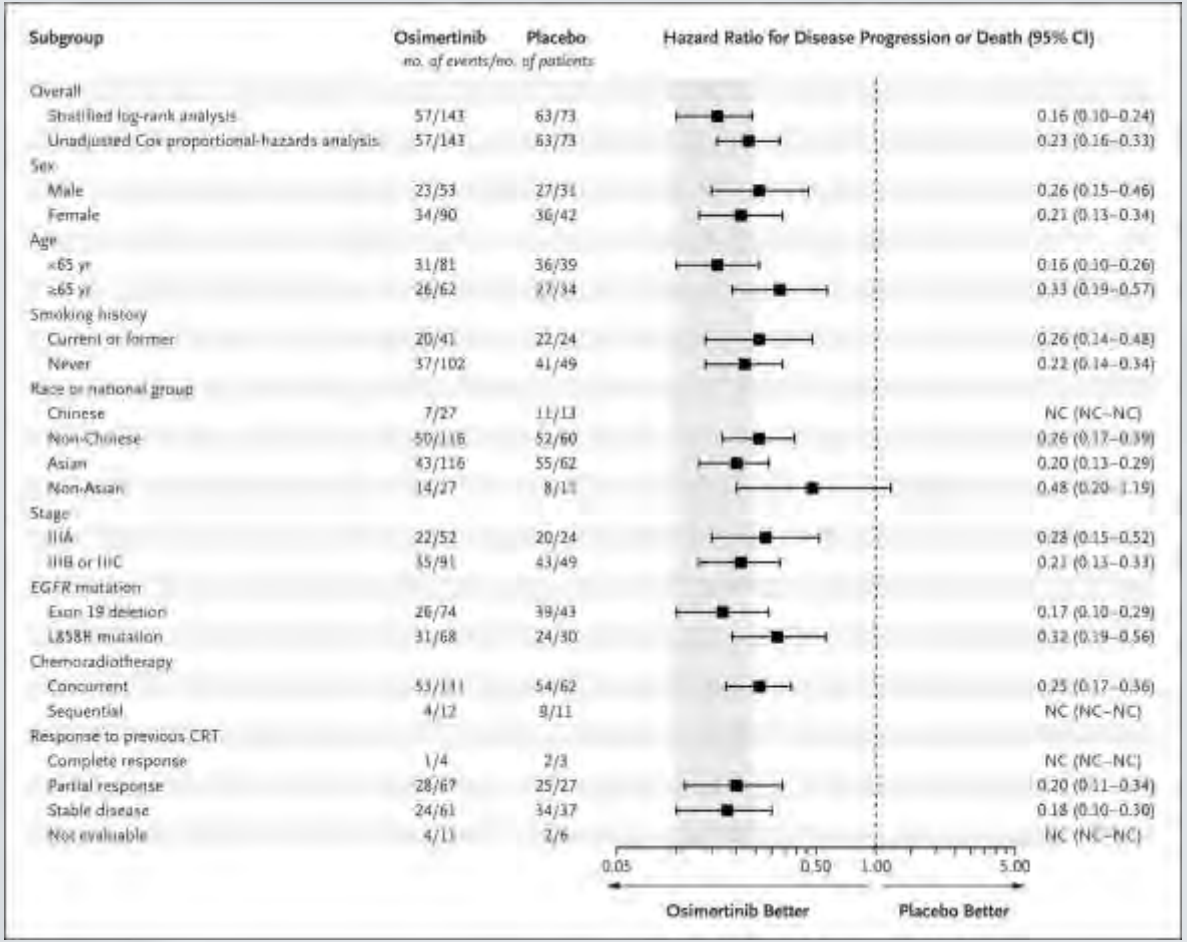
Median Progression-free Survival (95% CI)

	mo
Osimertinib	39.1 (31.5–NC)
Placebo	5.6 (3.7–7.4)

Hazard ratio for disease progression or death, 0.16 (95% CI, 0.10–0.24)
P<0.001

No. at Risk

Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0


Subgroup
Osimertinib
Placebo
no. of events/no. of patients
Hazard Ratio for Disease Progression or Death (95% CI)
Overall
Stratified log-rank analysis 57/143 63/73 0.16 (0.10–0.24)
Unadjusted Cox proportional-hazards analysis 57/143 63/73 0.23 (0.16–0.33)
Sex
Male 23/53 27/31 0.26 (0.15–0.46)
Female 34/90 36/42 0.21 (0.13–0.34)
Age
<65 yr 31/81 36/39 0.16 (0.10–0.26)
≥65 yr 26/62 27/34 0.33 (0.19–0.57)
Smoking history
Current or former 20/41 22/24 0.26 (0.14–0.48)
Never 37/102 41/49 0.22 (0.14–0.34)
Race or national group
Chinese 7/27 11/13 NC (NC–NC)
Non-Chinese 50/116 52/60 0.26 (0.17–0.39)
Asian 43/116 55/62 0.20 (0.13–0.29)
Non-Asian 14/27 8/11 0.48 (0.20–1.19)
Stage
IIIA 22/52 20/24 0.28 (0.15–0.52)
IIIB or IIIC 35/91 43/49 0.21 (0.13–0.33)
EGFR mutation
Exon 19 deletion 26/74 39/43 0.17 (0.10–0.29)
L858R mutation 31/68 24/30 0.32 (0.19–0.56)
Chemoradiotherapy
Concurrent 53/131 54/62 0.25 (0.17–0.36)
Sequential 4/12 9/11 NC (NC–NC)
Response to previous CRT
Complete response 1/4 2/3 NC (NC–NC)
Partial response 28/67 25/27 0.20 (0.11–0.34)
Stable disease 24/61 34/37 0.18 (0.10–0.30)
Not evaluable 4/11 2/6 NC (NC–NC)
0.05
0.50
1.00
5.00
Osimertinib Better
Placebo Better

Results

- Osimertinib resulted in a significant progression-free survival benefit as compared with placebo: the median progression-free survival was 39.1 months with Osimertinib versus 5.6 months with placebo, with a hazard ratio for disease progression or death of 0.16 (95% confidence interval [CI], 0.10 to 0.24; P <0.001)

Takeaways

- Osimertinib should be used post definitive chemoRT in patients with EGFR mutation in exon 19 or L858R
- Questions remaining
  - Does this provide as robust of benefit in stage II EGFR mutated NSCLC?
  - Could amivantamab be of benefit in those with exon 20 insertions?
  - What is optimal duration of Osimertinib?

Studies looking at neoadjuvant targeted therapy

Genomic alteration(s)	Trial number (name)	Phase	Disease stage	Sample size	Targeted therapy	Primary endpoint
ALK	NCT02201992 (ALCHEMIST-ALK, E4512)	3	IB-IIIA	168	Adjuvant crizotinib for 2 years	OS
ALK *ROS1* *NTRK* *BRAF* V600 *RET* *KRAS* G12C	NCT04302025 (NAUTIKA1)[5]	2	II, IIIA, IIIB (T3N2 only)	85	Neoadjuvant matching targeted therapy for 8 weeks, adjuvant targeted therapy for 2 years	MPR
ALK	NCT05015010 (ALNEO)	2	III	33	Neoadjuvant alectinib for 8 weeks, adjuvant alectinib for 2 years	MPR
ALK	NCT05341583	3	II-IIIB	202	Adjuvant ensartinib for 2 years	DFS
ALK	NCT05361564	2	I-IIIA	12	Neoadjuvant brigatinib for 4-10 weeks	Identification of molecular characteristics of drug-tolerant persister cells
RET	NCT04819100 (LIBRETTO-432)[8]	3	IB-IIIA	170	Adjuvant selpercatinib for 3 years	EFS
RET	NCT03157128 LIBRETTO-001 (Cohort 7)	2	IB-IIIA	19	Neoadjuvant selpercatinib for 8 weeks, adjuvant selpercatinib for 3 years	MPR
MET (Cohort A: *MET* exon 14 skipping mutation; Cohort B: High *MET* amplification)	NCT04926831 (GEOMETRY-N)[9]	2	IB-IIIA	42	Neoadjuvant capmatinib for 8 weeks, adjuvant capmatinib for 3 years	MPR
KRAS G12C	NCT05472623 (Neo-Kan)	2	IB-IIIA	42	Neoadjuvant adagrasib for 6 weeks with or without nivolumab	pCR
KRAS G12C	NCT05118854	2	IIA-IIIB	27	Neoadjuvant sotorasib plus platinum pemetrexed	MPR

References

1. Wu YL, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, Lee JS, Zhong W, Horinouchi H, Mao W, Hochmair M, de Marinis F, Migliorino MR, Bondarenko I, Lu S, Wang Q, Ochi Lohmann T, Xu T, Cardona A, Ruf T, Noe J, Solomon BJ; ALINA Investigators. Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2024 Apr 11;390(14):1265-1276. doi: 10.1056/NEJMoa2310532. PMID: 38598794.
2. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, Goldman JW, Laktionov K, Kim SW, Kato T, Vu HV, Lu S, Lee KY, Akewanlop C, Yu CJ, de Marinis F, Bonanno L, Domine M, Shepherd FA, Zeng L, Hodge R, Atasoy A, Rukazenkov Y, Herbst RS; ADAURA Investigators. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Oct 29;383(18):1711-1723. doi: 10.1056/NEJMoa2027071. Epub 2020 Sep 19. PMID: 32955177.
3. Lu S, Kato T, Dong X, Ahn MJ, Quang LV, Soparattanapaisarn N, Inoue T, Wang CL, Huang M, Yang JC, Cobo M, Özgüroğlu M, Casarini I, Khiem DV, Sriuranpong V, Cronemberger E, Takahashi T, Runglodvatana Y, Chen M, Huang X, Grainger E, Ghiorghiu D, van der Gronde T, Ramalingam SS; LAURA Trial Investigators. Osimertinib after Chemoradiotherapy in Stage III *EGFR*-Mutated NSCLC. N Engl J Med. 2024 Aug 15;391(7):585-597. doi: 10.1056/NEJMoa2402614. Epub 2024 Jun 2. PMID: 38828946.
4. Aggarwal, Kim Improving Outcomes for Early-Stage NSCLC Using Targeted Therapy. ASCO Daily News April 3, 2024

HDR © 2017 Dan Schwalm

University of Nebraska Medical Center

Nebraska Medicine