2024 Updates in Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

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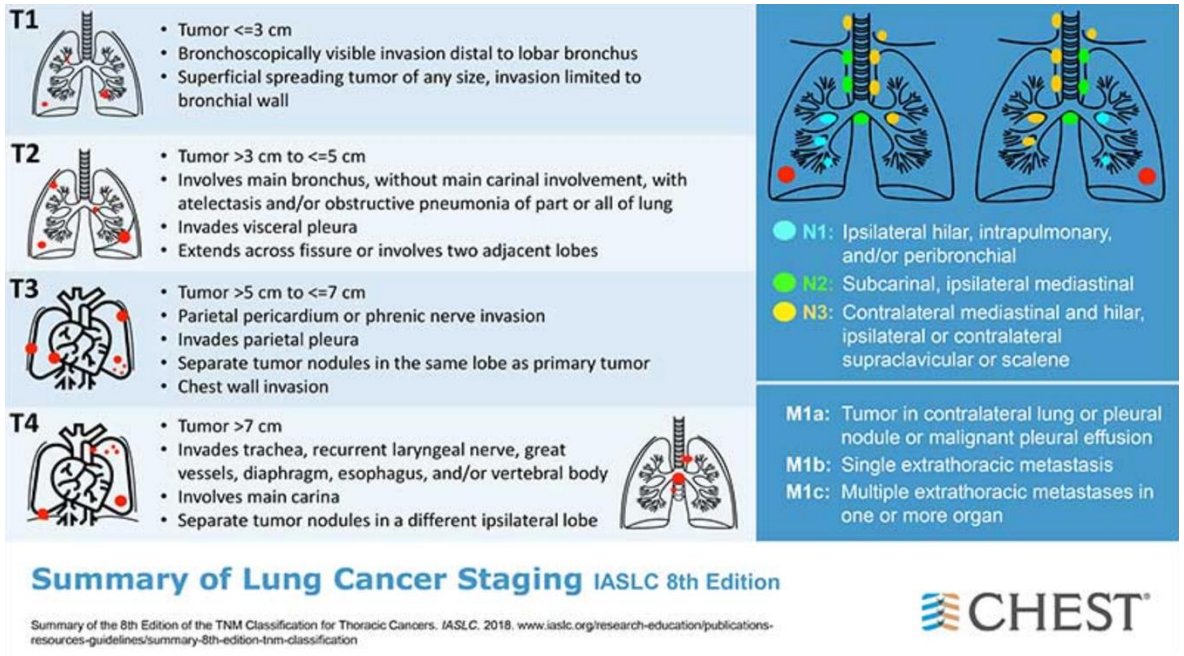
Outline

- Background: Early Stage NSCLC
- Update #1: Neoadjuvant/perioperative incorporation of PD-1 therapy
- Update #2: Adjuvant incorporation of TKIs for EGFR and ALK mutated NSCLC

Background: Early Stage NSCLC

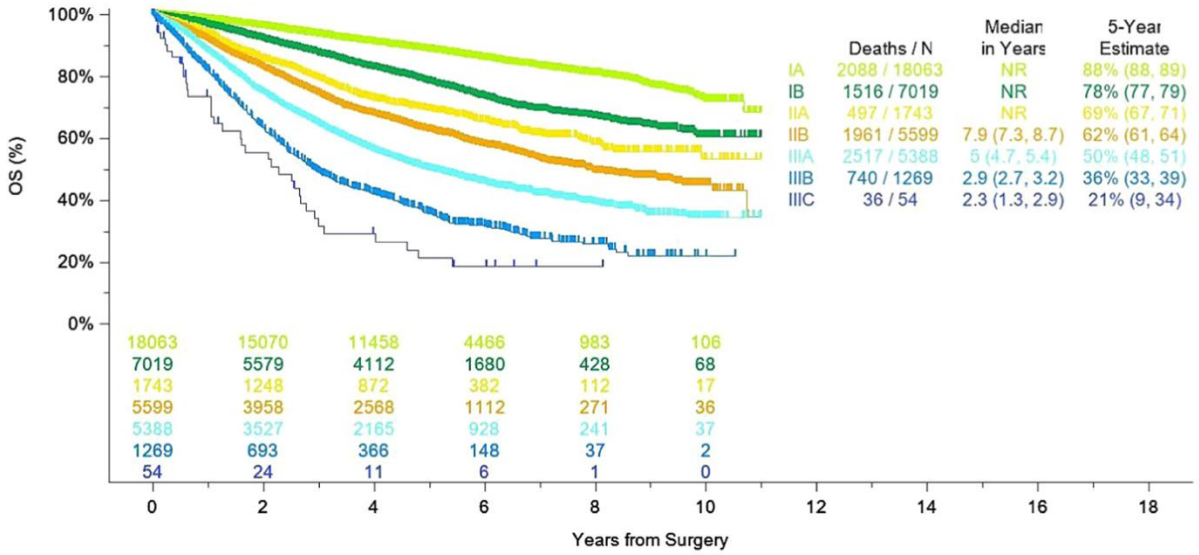


- <u>Stage I and II</u>: approx 30%
  - Disease limited to one lung, not involving mediastinum
- <u>Stage III</u>: approx 30%
  - Involvement of mediastinum, or tumor >7cm with positive hilar nodes

Morgensztern et al. JTO, 2010.

Lung cancer is highly lethal

Survival by Pathologic Stage, Applying the 8th edition Classification to the 9th edition Database



Presentation	Occurrence	5 year OS
Local	Stage I-IIA	69-88%
Regional (lymph nodes)	Stage IIB	62%
	Stage IIIA	50%
	Stage IIIB	36%
	Stage IIIC	21%

Even though we manage these patients with curative intent multimodality therapy, the majority of patients with nodal involvement will relapse and die within 5 years

Rami-Porta et al. IASLC Lung Cancer Staging Project, JTO, July 2024.

Pacific Trial: Durvalumab after Chemoradiation for Unresectable Stage III

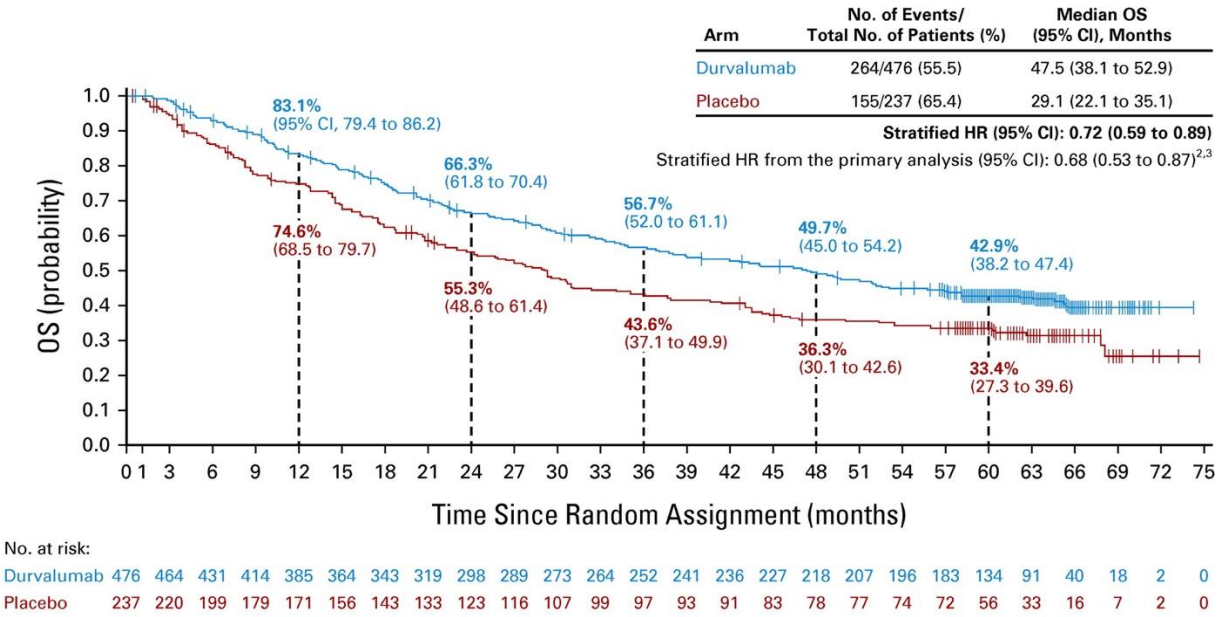
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2017 VOL. 377 NO. 20

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

- Stage III NSCLC patients (N=713) treated with chemorads without disease progression, randomized 2:1 to durvalumab vs placebo x 1 year.
- 5-year update: OS 42.9% (durva) vs. 33.4%
- Post hoc analysis: PD-L1<1% did not benefit



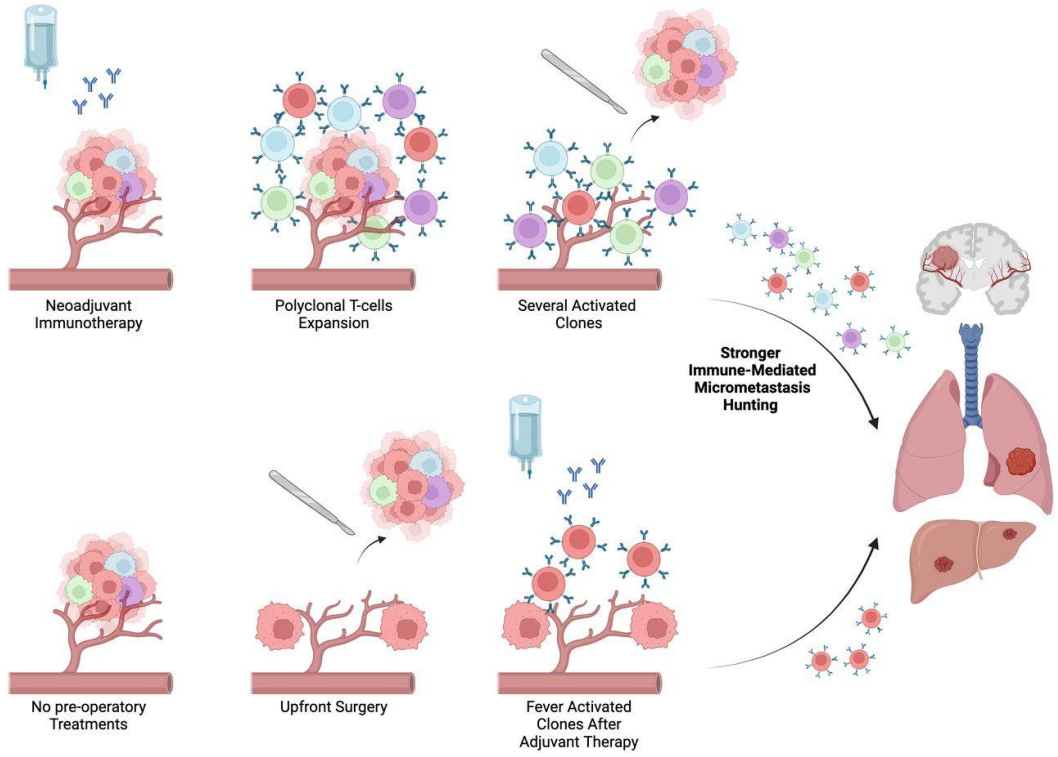
Antonia et al, NEJM, 2017.

Paz-Ares, Ann Oncol, 2020.

Spigel, JCO, 2022.

Rationale for Immune Checkpoint Inhibitors (ICI) in Neoadjuvant Therapy

- ICI may mediate better immune response if given:
  - while original tumor is still present (greater neoantigen load)
  - before primary lymphatic system is disrupted (better T cell priming)
  - before surgery-induced immune suppression/disturbance
- Knowing the pathologic response could guide adjuvant therapy



Jervaso, JITC, 2024.

Xu, Cancer Immunol Immunother, 2015.

Update #1: 4 trials incorporating ICI into neoadjuvant/perioperative treatment

CheckMate-816 (April 2022)

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

KEYNOTE-671 (Aug 2023)

Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer

H. Wakelee, M. Liberman, T. Kato, M. Tsuboi, S.-H. Lee, S. Gao, K.-N. Chen, C. Dooms, M. Majem, E. Eigendorff, G.L. Martinengo, O. Bylicki, D. Rodríguez-Abreu, J.E. Chaft, S. Novello, J. Yang, S.M. Keller, A. Samkari, and J.D. Spicer, for the KEYNOTE-671 Investigators*

AEGEAN (Oct 2023)

Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer

J.V. Heymach, D. Harpole, T. Mitsudomi, J.M. Taube, G. Galffy, M. Hochmair, T. Winder, R. Zukov, G. Garbaos, S. Gao, H. Kuroda, G. Ostoros, T.V. Tran, J. You, K.-Y. Lee, L. Antonuzzo, Z. Papai-Szekely, H. Akamatsu, B. Biswas, A. Spira, J. Crawford, H.T. Le, M. Aperghis, G.J. Doherty, H. Mann, T.M. Fouad, and M. Reck, for the AEGEAN Investigators*

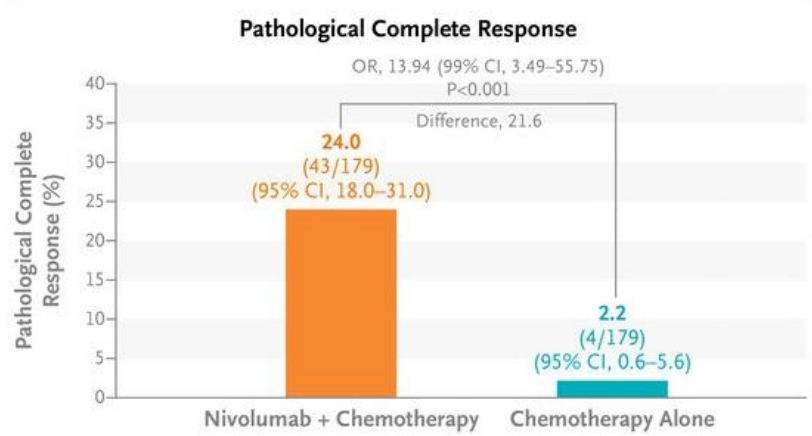
CheckMate-77T (May 2024)

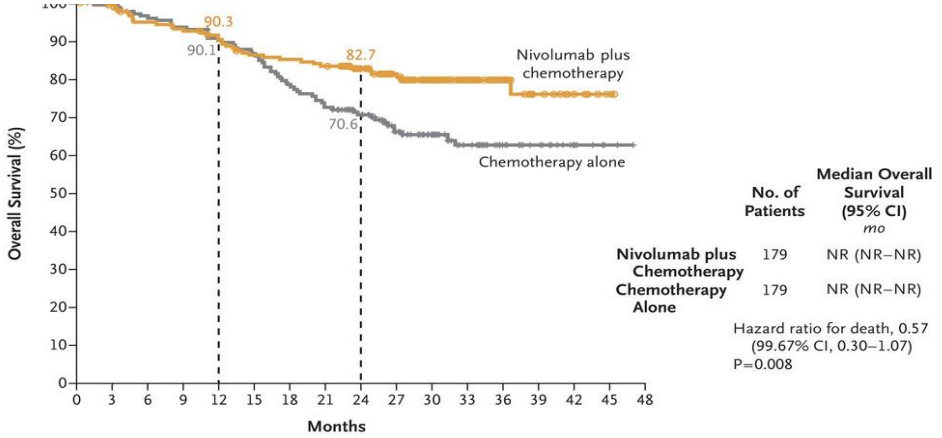
Perioperative Nivolumab in Resectable Lung Cancer

T. Cascone, M.M. Awad, J.D. Spicer, J. He, S. Lu, B. Sepesi, F. Tanaka, J.M. Taube, R. Cornelissen, L. Havel,* N. Karaseva, J. Kuzdzal, L.B. Petruzelka, L. Wu, J.-L. Pujol, H. Ito, T.-E. Ciuleanu, L. de Oliveira Muniz Koch, A. Janssens, A. Alexandru, S. Bohnet, F.V. Moiseyenko, Y. Gao, Y. Watanabe, C. Coronado Erdmann, P. Sathyanarayana, S. Meadows-Shropshire, S.I. Blum, and M. Provencio Pulla, for the CheckMate 77T Investigators†

Checkmate 816

- International, phase 3, randomized, open-label study of stage IB (>4cm) to IIIA resectable NSCLC (N=505) to 3 cycles of nivolumab plus platinum-based chemotherapy vs. platinum-based chemotherapy alone.





- 24-month OS: 82.7 v. 70.6 but not statistically significant

Forde PM, NEJM, 2022.

Checkmate 816

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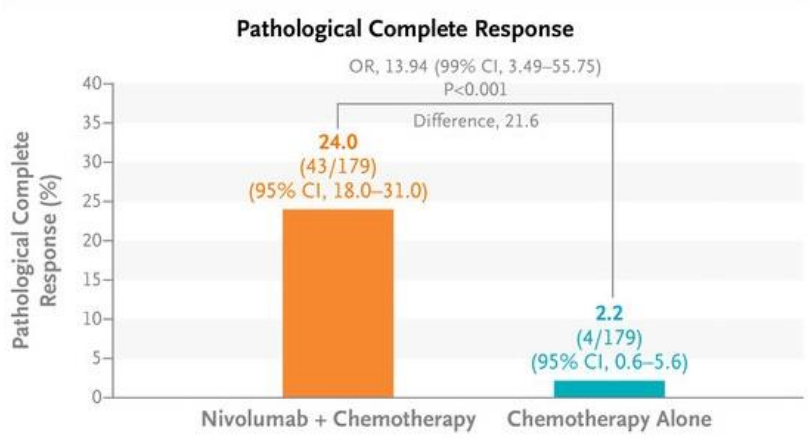
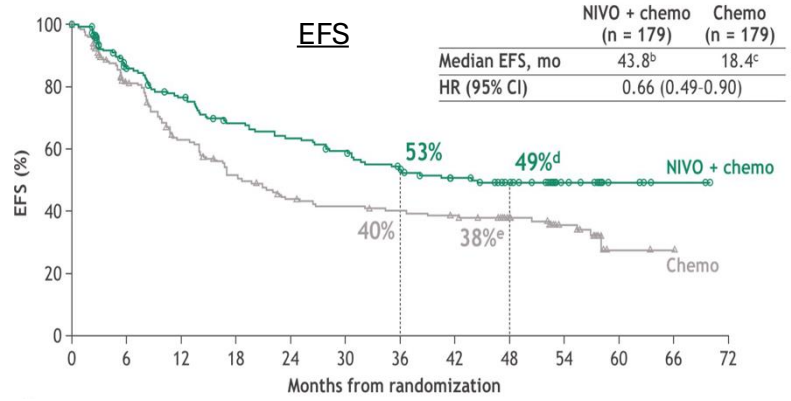
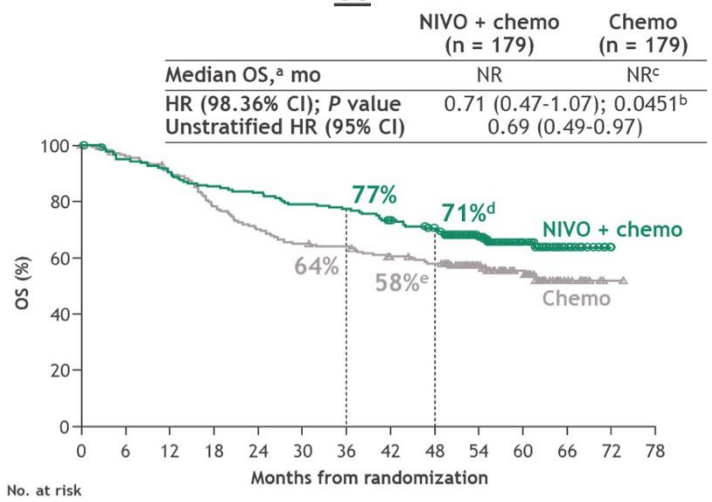


- 4-year update (ASCO 2024):





- Median EFS 43.8m v. 18.4 m (HR 0.66)
- Favorable 4-yr OS trend: 71% v. 58%
- Nivo+chemo arm: pts with pCR (vs. no pCR) had 4-yr OS 95% v. 63%

Spicer, ASCO oral pres (abstract LBA8010), 2024.

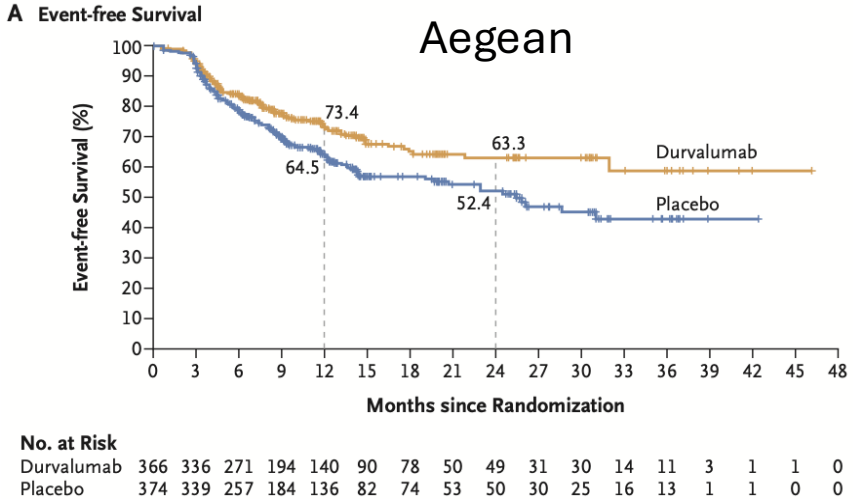
Forde PM, NEJM, 2022.

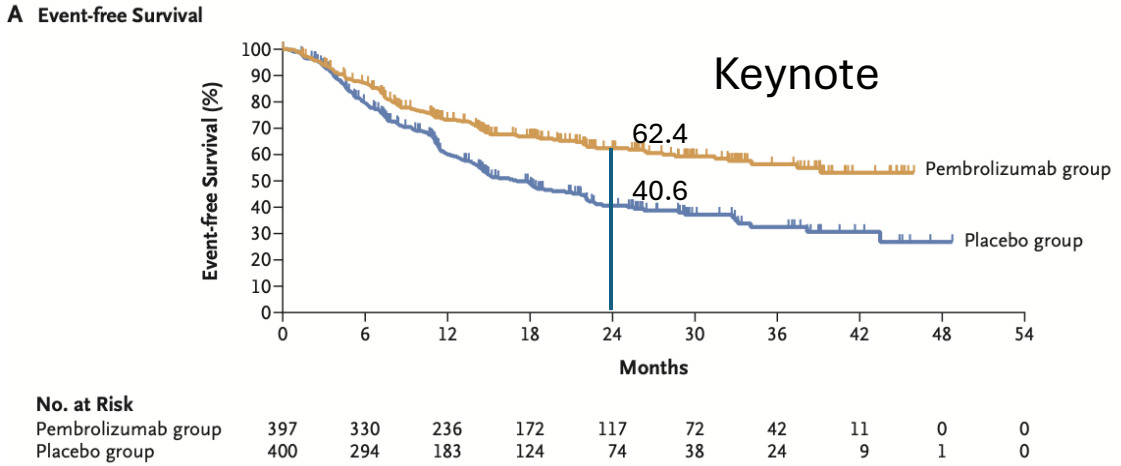
Comparative Data from 4 Neoadjuvant Studies

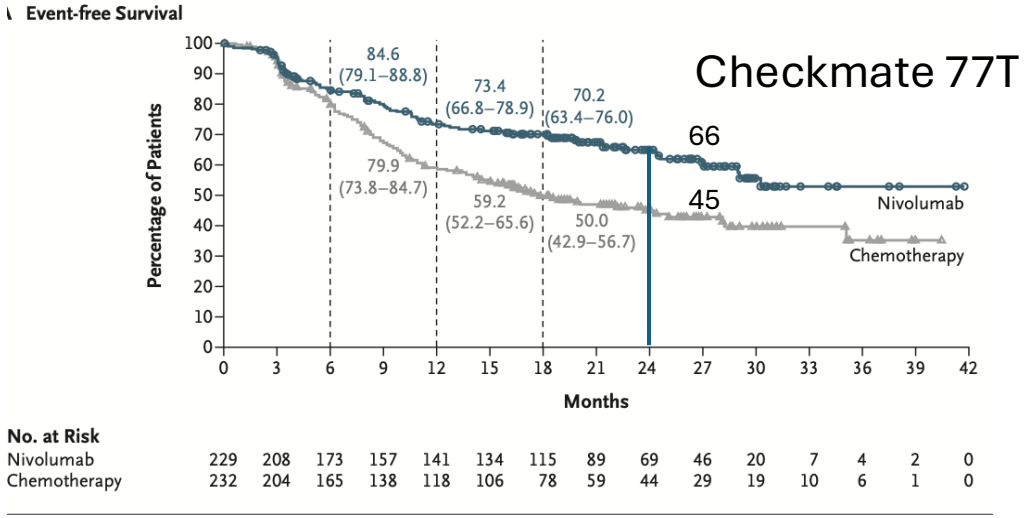
Study	Checkpoint 77T	Keynote 671	Checkmate 816	Aegean
Primary Endpoint	EFS	Dual EFS and OS	Dual EFS and pCR	Dual EFS and pCR
Underwent surgery	77.7 vs 76.7%	82.1 vs 73.2%	83.2 vs 75,4%	77.6 vs 76.7%
Received adjuvant treatment	62 vs 65.5%	73.2 vs 66.9%	11.9 vs 22.2%	65.8 vs 63.4%
Pathological Complete Response	25.3 vs 4.7%	18.1 vs 4%	24 vs 2.2%	17.2 vs 4.3%
Major Pathological Response	35.4 vs 12.1%	30.2 vs 11%	36.9%	33.3 vs 12.3%
EFS at 2 years	66 vs 45%	62.4 vs 40.6%	63. vs 45.3%	63.3 vs 52.4%
Median EFS	NR vs 18.4 m	NR vs 17m	31.6 vs 20.8 m	NR vs 25.9
HR for EFS	0.58; 97.36%CI, 0.42 to 0.81; P<0.001	0.58; 95% CI, 0.46 to 0.72; P<0.001	0.63; 97.38% CI, 0.43 to 0.91; P=0.005	0.68 (95% CI 0.53 to 0.88; p=0.004)
Overall Survival	Not reached	NR vs 45.5m	Not reported	Not reported

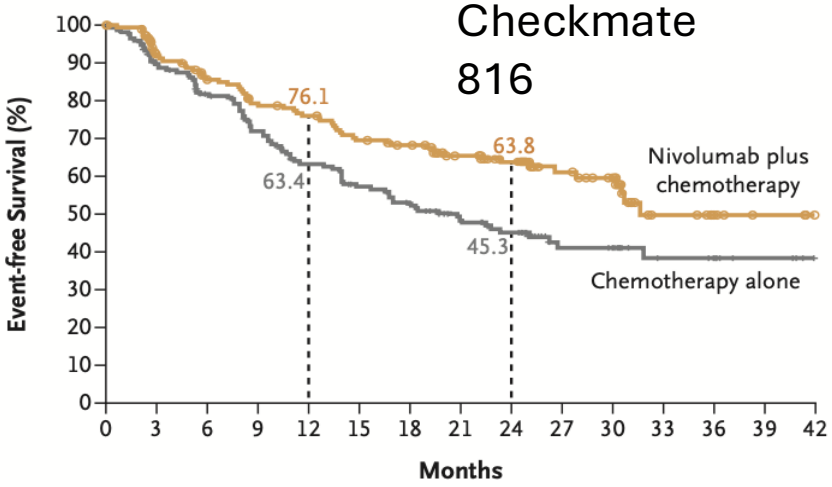
Table from Rafael Santana Davila

No obvious differences in outcomes, so far









Slide from Rafael Santana Davila

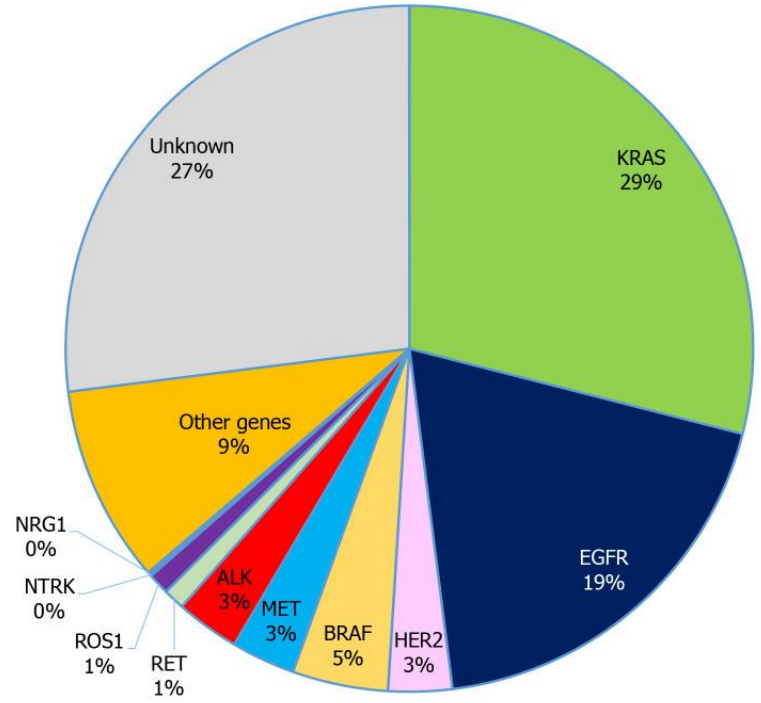
Update #1: Conclusions

- FDA approvals: (resectable NSCLC, >4cm or node positive, without EGFR/ALK)
  - Neoadjuvant only: neoadjuvant nivo+platinum chemo x 3 cycles
  - Perioperative: neoadjuvant pembro + chemo x 4 cycles, then pembro x 1 year
  - Perioperative: neoadjuvant durva + chemo x 4 cycles, then durva x 1 year

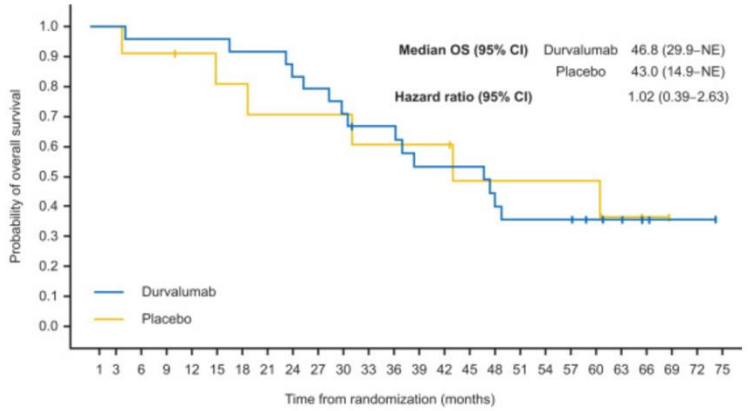
- Neoadjuvant v. perioperative ICI for resectable NSCLC?
  - No obvious difference in outcomes, so far
  - For now, we favor neoadjuvant chemo-IO for 3 cycles only (without adjuvant PD-1): less therapy/fewer visits, lower cost
    - But this includes discussion with patient

- How should we use pathologic response?
  - Uncertain: pCR could identify patients who don't need more therapy (eg. PRADO trial in melanoma) or identify patients who stand to benefit the most from highly effective therapy
  - Patients without major pathologic response: continue IO?

Update #2: Adjuvant TKIs for EGFR/ALK



LungCancerAlliance.org
Chevallier et al. World J Clin Oncol. 2021



- Post hoc subset analysis of PACIFIC: EGFR/ALK patients do not appear to benefit from durva
- PD-1 therapy prior to osimertinib increases risk for pneumonitis

Oshima et al, Jama Oncol, 2016.
Naidoo et al, JTO, 2023.

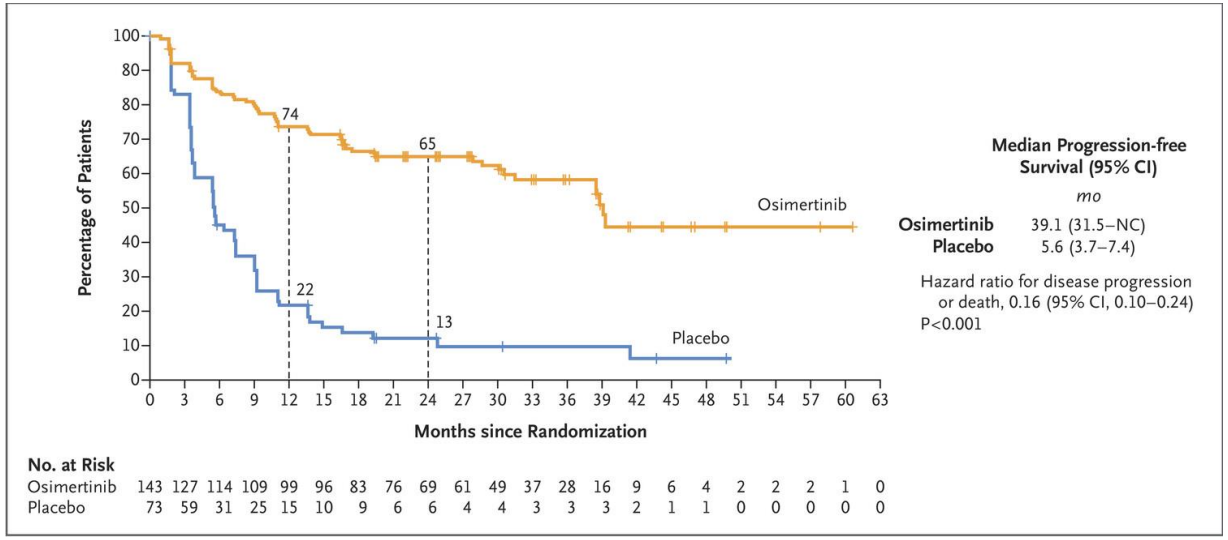
ASCO Plenary 2024: Osimertinib after Chemorads in Stage III EGFR-mutated NSCLC (LAURA)

- Ph 3, double-blind, placebo-controlled, 2:1 randomized, international trial (N=216) of locally advanced, unresectable stage III, EGFR mut NSCLC pts after chemorads
- Improvement in PFS 39.1 v 5.6m
- OS not fully mature but interim analysis

favored osi (cross over allowed)

- New brain mets: 8% (osi) v. 29% (placebo)
- Osi offered indefinitely until disease

progression

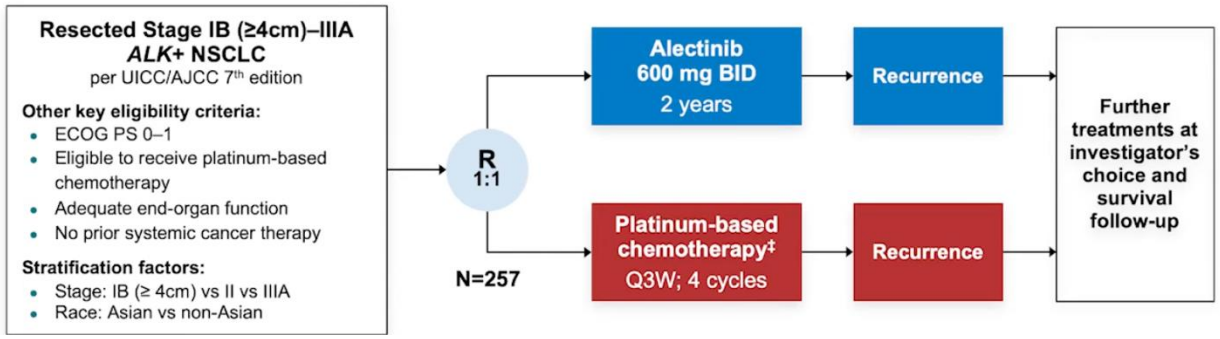


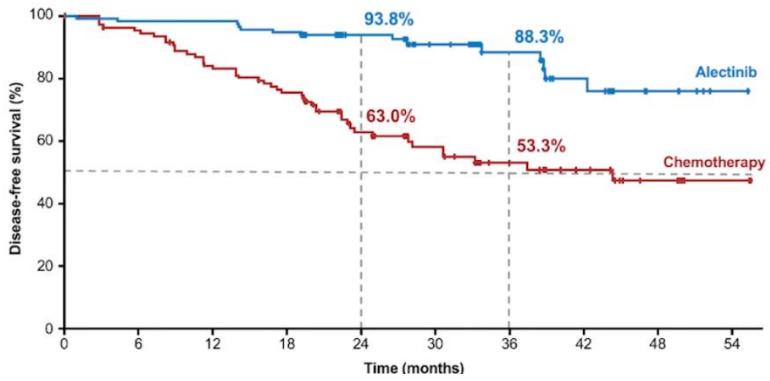
Lu, NEJM, 2024.

LAURA: Considerations

- Practice-changing study, but……
- **OS benefit is not yet known**
- Osimertinib seems to postpone disease recurrence, but does it cure anyone?
- Potential advantages for adjuvant use: preventing CNS progression which can have permanent impact on QOL, likely OS benefit (minimizing tumor burden for as long as possible may delay outgrowth of diverse, more oncogenic clones)
- Disadvantages for indefinite, adjuvant use: cost, side effects (diarrhea, rash), some patients are cured after chemorads and do not need indefinite treatment, QOL impact of losing a meaningful treatment option for stage IV period
- Future: We will need de-escalation studies to figure out who can stop osi

ALK+ NSCLC: Adjuvant alectinib (ALINA)





	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p‡<0.0001	

- Ph 3, open-label, randomized, international, (N=257), stage IB (>4cm)-IIIA, resected:
  - Alectinib x 2 years v. platinum chemo x 4 cycles 3-yr DFS 88% (alectinib) v. 53% (chemo). HR 0.24
- 3-yr DFS 88% (alectinib) v. 53% (chemo). HR 0.24
- HR for CNS recurrence/death: 0.22
- OS data is immature
- May 2024: FDA approved alectinib for adjuvant use in resected, ALK+ NSCLC, stage IB (>4cm), II or IIIA.

Wu, NEJM, 2024.

ALINA: Considerations

- Same concerns as LAURA: OS benefit is not yet known
- Omission of adjuvant chemotherapy:
  - Adjuvant chemo cures 5.4% patients (LACE meta-analysis)
  - Are TKIs curing any patients, or just prolonging disease recurrence?
  - Should alectinib be given after adjuvant chemo?
- ALK+ NSCLC has higher rates of CNS metastases (50%)
  - CNS protection may have bigger impact on QOL
- Duration of alectinib?
- Do we need to consider lorlatinib in adjuvant setting?

Pignon, JCO, 2008.

Summary of 2024 Updates in Early Stage NSCLC

- Neoadjuvant/perioperative PD-1 therapy for resectable NSCLC:
  - Everyone should get PD-1 along with neoadjuvant chemo: meaningful benefit from PD-1 exposure prior to surgery
  - Whether to follow surgery with a year of additional PD-1 therapy: Our clinic does not. No obvious advantage, so far—need longer follow up. Consider patient preference. Could consider pathologic response, but no data yet.

- New era of adjuvant TKI for EGFR/ALK+ NSCLC:
  - Unresectable, stage III EGFR+ NSCLC: Chemorads, followed by adjuvant osimertinib x indefinitely
  - Resected ALK+ NSCLC: Adjuvant alectinib x 2 years
  - Hopefully OS benefit will pan out

Questions?

- Thanks to Rafael Santana-Davila and Keith Eaton, THN colleagues, and patients, for sharing material and wisdom.