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Advances in Neoadjuvant Lung Cancer Therapy

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ACS Cancer Programs

American College of Surgeons

Disclosures

Honorariums

- Novocure
- Amgen

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- Biontech
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- Systimmune, Inc.
- Zymeworks Inc.

Definitions

Adjuvant	Surgery → Chemotherapy/IO
Neoadjuvant	Chemotherapy/IO → Surgery
Perioperative	Chemotherapy/IO → Surgery → IO

Adjuvant Chemotherapy

- 1995 Non-Small Cell Lung Cancer Collaborative Group: meta-analysis of 52 studies conducted between the 1960s and 1991. 5% overall survival benefit at five years, hazard ratio 0.87 (p=0.08)
- 2008 LACE Collaborative Group meta-analysis of 5 studies, 4584 patients with resected non-small lung cancer treated with platinum after surgery versus no additional therapy.

  5.4% decreased risk of death at five years compared to no chemotherapy, hazard ratio 0.89, confidence interval 0.82-0.96, p=0.005.

  Significant benefit was seen only in stage II and stage IIIA disease

Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ*. 1995;311(7010):899-909.
Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552-3559. doi:10.1200/JCO.2007.13.9030

Adjuvant Chemotherapy: Stage 1B Survival

CALGB 9633 randomized 344 patients with resected stage IB non-small cell cancer to four cycles chemotherapy or observation

Pts with tumors >=4 cm: HR 0.69 for OS , 95% confidence 0.48-0.99, p=0.043.

Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol*. 2008;26(31

Neoadjuvant vs Adjuvant Chemotherapy in NSCLC

Stage IIIA (N2) patients treated in single arm studies with neoadjuvant chemotherapy had resection rates of 56-88 %, pCR of 4.6-20%, and 3 year OS 26-52%

Meta-analysis in 2014 of 10 neoadjuvant trials and 22 adjuvant trials

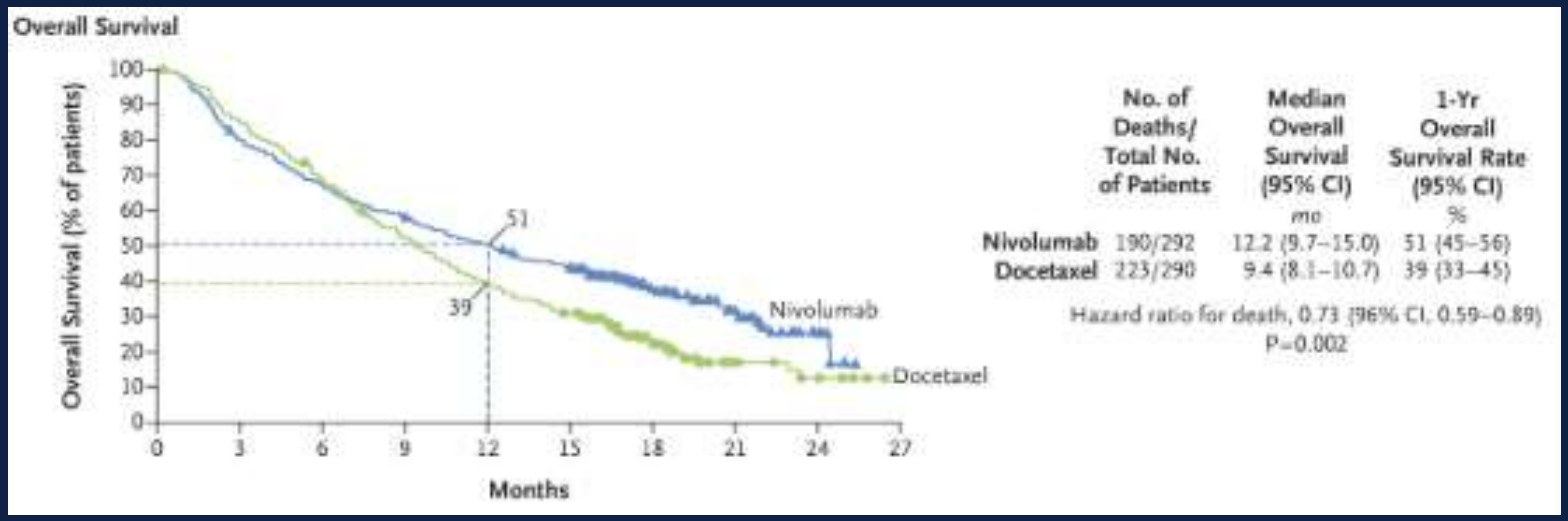
OS HR pre-op RX 0.80, post-op 0.81

Both Neoadjuvant and adjuvant chemotherapy 4-5% OS benefit at 5 years

McElnay P, Lim E. Adjuvant or neoadjuvant chemotherapy for NSCLC. J Thorac Dis. 2014;6 Suppl 2(Suppl 2):S224-S227. doi:10.3978/j.issn.2072-1439.2014.04.26

Immunotherapy in NSCLC Metastatic

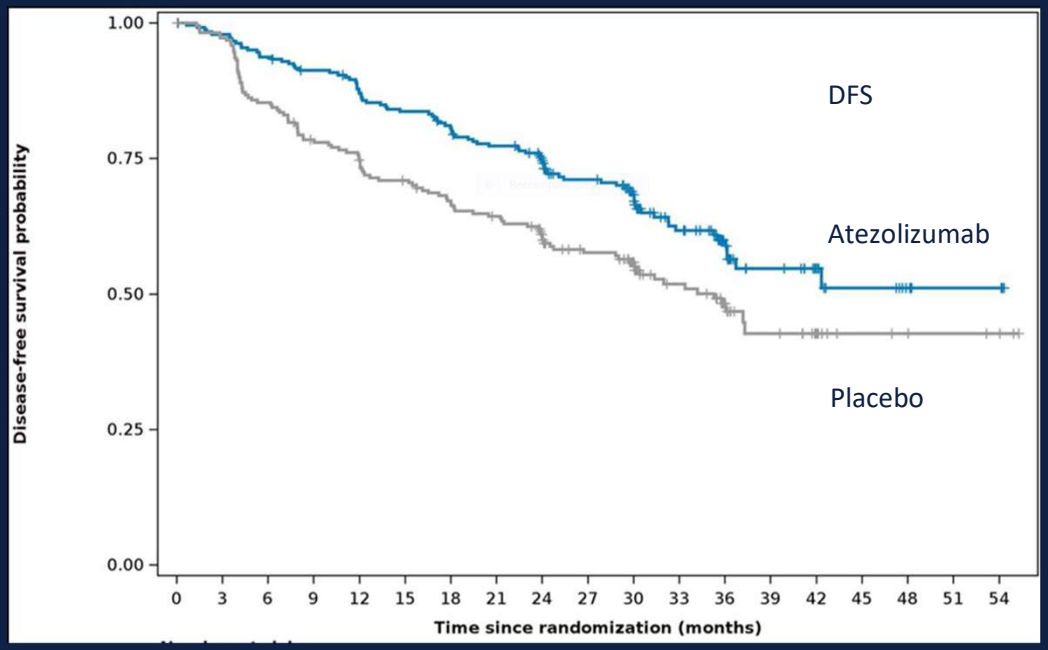
Nivolumab versus Docetaxel in Advanced Nonsquamous NSCLC



Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(17):1627-1639 doi:10.1056/NEJMoa1507643

Immunotherapy in Adjuvant NSCLC

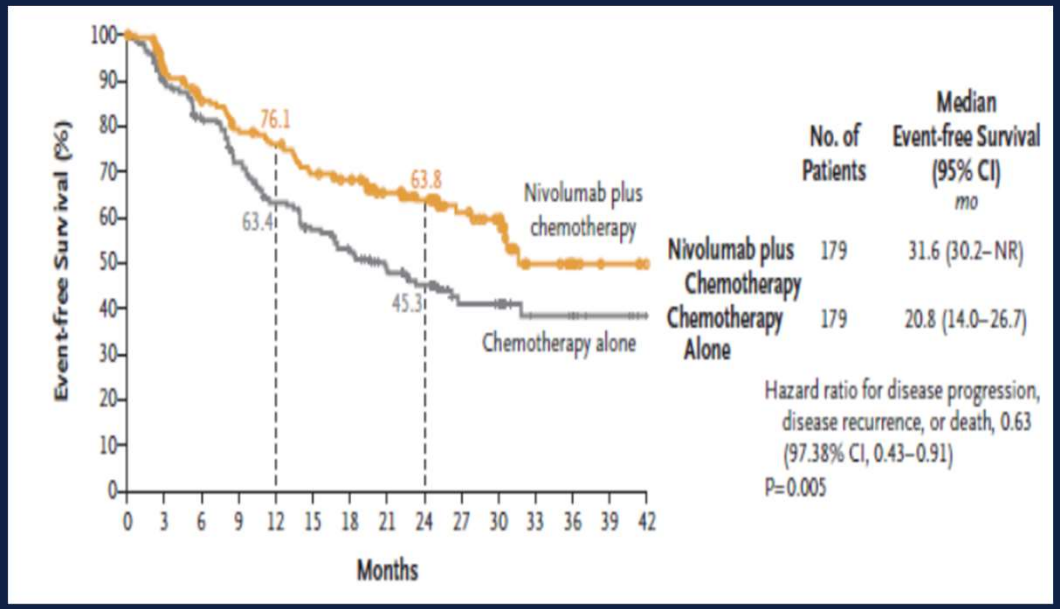
IMPOWER 010 study showed DFS benefit of adjuvant atezolizumab after Cis-Platinum based adjuvant chemotherapy, OS trend



Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial [published correction appears in Lancet. 2021 Nov 6;398(10312):1686. doi: 10.1016/S0140-6736(21)02135-8.]. *Lancet*. 2021;398(10308):1344-1357. doi:10.1016/S0140-6736(21)02098-5

Neoadjuvant chemo+/- Nivolumab: CheckMate 816

- 358 Pts randomized
- Chemo + Nivo EFS 30.2 months
  Chemo alone EFS 20.8 months
- HR 0.63 P=0.005
- 2 year EFS 63.8% vs 45.3%



Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med*. 2022;386(21):1973-1985. doi:10.1056/NEJMoa2202170

Neoadjuvant Chemo +/- Perioperative Nivolumab or Placebo: CheckMate 77T

NSCLC stage IB (4cm) to IIIA (N2) 461 Pts Randomized:

Neoadjuvant Nivolumab plus chemo → Surgery → adjuvant Nivolumab

Neoajuvant placebo plus chemo → Surgery → adjuvant placebo

	Chemo + Perioperative Placebo	Chemo + Perioperative Nivolumab	
pCR (%)	4.7	25.3	
18 Month EFS (%)	50	70.2	HR 0.58, p<0.001

Cascone T, Awad MM, Spicer JD, et al. Perioperative Nivolumab in Resectable Lung Cancer. N Engl J Med. 2024;390(19):1756-1769. doi:10.1056/NEJMoa2311926

Pembrolizumab added to Neoadjuvant Chemotherapy: KEYNOTE-671

797 patients stage II, IIIA, or IIIB (N2) randomized:

Chemotherapy + Pembrolizumab → Surgery → Pembrolizumab

Chemotherapy + Placebo → Surgery → Pembrolizumab

	Neoadjuant chemo+ placebo	Neoadjuvant chemo + Pembrolizumab	
pCR	4.0%	18.1%	P<0.0001
2 yr EFS	40.6%	62.4%	HR 0.58, p<0.001
2 yr OS	77.6%	80.9%	

Wakelee H, Liberman M, Kato T, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. *N Engl J Med*. 2023;389(6):491-503. doi:10.1056/NEJMoa2302983

AEGEAN Perioperative Durvalumab for Resectable NSCLC

- 802 pts with resectable NSCLC stage II to IIB (N2) randomized
- Neoadjuvant chemo + Durvalumab q 3 weeks x 4
- Neoadjuvant chemo + Placebo q 3 weeks x 4
- Post-op patients continued on Durvalumab or Placebo q 4 weeks x 12

	Neoadjuvant chemo + Perioperative Placebo	Neoadjuvant chemo + Perioperative Durvalumab	
pCR (%)	4.3	17.2	P<0.001
12 month EFS (%)	64.5	73.4	95% CI 58.8-69.6, 67.9-78.1

Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. *N Engl J Med*. 2023;389(18):1672-1684. doi:10.1056/NEJMoa2304875

Meta-Analysis of 8 Randomized Trials of Neoadjuvant Immunotherapy with Chemotherapy

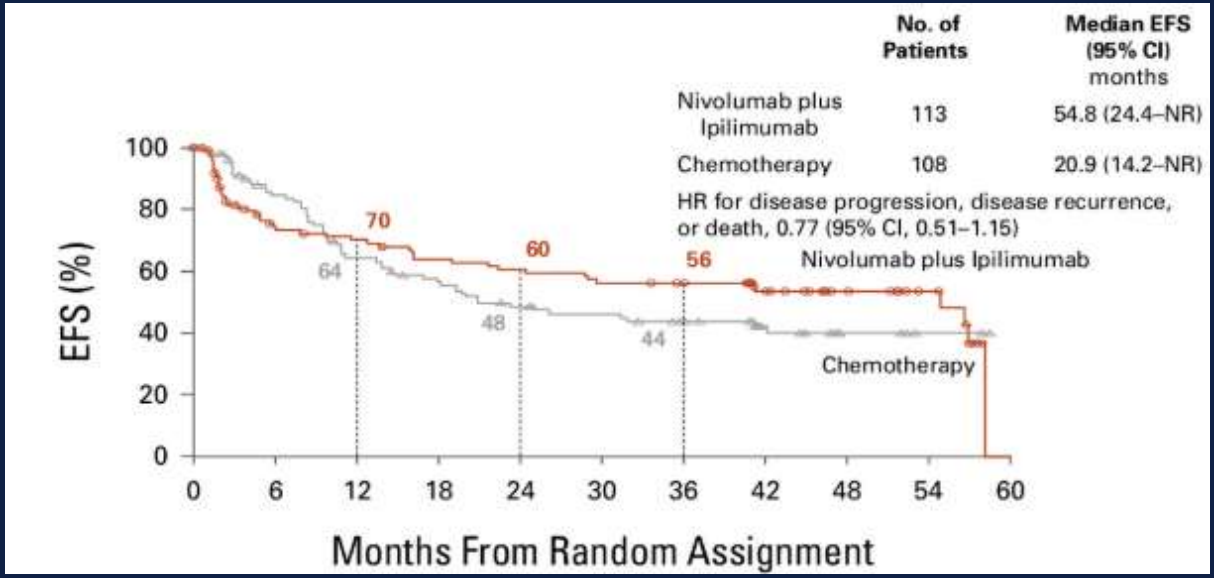
Source (phase)	Treatment (No. of cycles)		Primary end point	Patients, No.		2-y EFS (95% CI)		*P* value	pCR rate (95% CI)		*P* value	Surgery, exp vs control, %
	Control	Exp		Control	Exp	Control	Exp		Control	Exp		
Forde et al,[13] 2022; CheckMate 816 (3)	PBC (3), surgery	Nivolumab, 360 mg, plus PBC (3), surgery	EFS and pCR	179	179	45.3 (NR)	63.8 (NR)	<.001	2.2 (0.6-5.6)	24.0 (18.0-31.0)	<.001	83.2 vs 75.4
Heymach et al,[21] 2023; AEGEAN (3)	Placebo plus PBC (4), surgery, and placebo (12)	Durvalumab, 1500 mg, plus PBC (4), surgery, and durvalumab (12)	EFS by BICR; pCR	374	366	52.4 (45.4-59.0)	63.3 (56.1-69.6)	<.001	4.3 (2.5-6.9)	17.2 (13.5-21.5)	<.001	77.6 vs 76.7
Lei et al,[22] 2023; TD-FOREKNOW (2)	Platinum based chemotherapy with nab-paclitaxel (3), surgery	Camrelizumab, 200 mg, every 3 wk for 3 cycles plus PBC plus nab-paclitaxel (3), surgery	pCR	45	43	67.6 (48.0-81.2)	76.9 (56.3-88.7)	NA	8.9 (2.5-21.2)	32.6 (19.1-48. 5)	<.001	93.0 vs 93.3
Zhang et al,[15] 2021; Neotorch (3)	Placebo plus PBC (3), surgery, placebo plus PBC (1), and then placebo (13)	Toripalimab, 240 mg, every 3 wk plus PBC (3), surgery, toripalimab, 240 mg, every 3 wk plus PBC (1), and toripalimab, 240 mg (13)	EFS in stage III by investigators; mPR evaluated by BIPR in stage III	202	202	38.7 (NR)	64.7 (NR)	<.001	1 (0.1-3.5)	28.2 (22.1-35.0)	<.001	82.2 vs 73.3
Provencio et al,[23] 2023; NADIM II (2)	PBC (3), surgery, and observation	Nivolumab, 360 mg, plus PBC (3), surgery, and nivolumab, 480 mg (6)	pCR	29	57	40.9 (26.2-63.6)	67.2 (55.8-81.0)	NA	7 (1-23)	37 (24-51)	.02	93.0 vs 69.0
Wakelee et al,[14] 2023; KEYNOTE-671 (3)	Placebo plus PBC (4), surgery, and placebo (13)	Pembrolizumab, 200 mg, plus PBC (4), surgery, and pembrolizumab, 200 mg (13)	EFS and OS	400	397	40.6 (34.8-46.3)	62.4 (56.8-67.5)	<.001	4 (2.3-6.4)	18.1 (14.5-22.3)	<.001	82.1 vs 79.4
Cascone et al,[16] 2023; CheckMate 77T (3)	Placebo plus PBC (4), surgery, and placebo (12)	Nivolumab, 360 mg, plus PBC (4), surgery, and nivolumab, 480 mg (12)	EFS by BICR	232	229	50.0 (NR)	70.0 (NR)	<.001	4.7 (2.4-8.3)	25.3 (19.8-31.5)	NR	78.0 vs 77.0
Yue et al,[24] 2023; RATIONALE-315 (3)	Placebo plus PBC (4), surgery, and placebo (8)	Tislelizumab, 200 mg, plus PBC (3), surgery, and tislelizumab, 400 mg (8)	mPR by BIPR and EFS by BICR	227	226	NR	NR	NA	5.7 (NR)	40.7 (NR)	<.001	84.1 vs 76.2

Banna GL, Hassan MA, Signori A, et al. Neoadjuvant Chemo-Immunotherapy for Early-Stage Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. *JAMA Netw Open*. 2024;7(4):e246837. Published 2024 Apr 1. doi:10.1001/jamanetworkopen.2024.6837

Neoadjuvant Nivolumab + Ipilimumab vs Chemotherapy NSCLC CheckMate 816, 3rd Arm

221 pts stage IB-IIIA randomized to:

- Day 1, 15, 29 Nivloumab with Day 1 Ipilimumab → Surgery
- Chemotherapy q 3 weeks x 3 → Surgery



Awad MM, Forde PM, Girard N, et al. Neoadjuvant Nivolumab Plus Ipilimumab Versus Chemotherapy in Resectable Lung Cancer. *J Clin Oncol*. Published online January 8, 2025. doi:10.1200/JCO-24-02239

Is Adjuvant Immunotherapy needed after Neoadjuvant chemoimmunotherapy?

- Forde et al performed a propensity score-weighting analysis
- CheckMate 77T 139 pts:
  - Chemoimmunotherapy → Surgery → Adjuvant immunotherapy
- CheckMate 816 147 pts:
  - Chemoimmunotherapy → Surgey → No further therapy

	CheckMate 77T Neoadjuvant chemotherapy and Immunotherapy + adjuvant Immunotherapy	CheckMate 816 Neoadjuvant chemotherapy and Immunotherapy	
EFS	Benefit for adding adjuvant IO		HR 0.61

Forde, P.M. et al. Perioperative vs Neoadjuvant Nivolumab for Resectable NSCLC: Patient-Level Data Analysis of CheckMate 77T vs CheckMate 816Journal of Thoracic Oncology, Volume 19, Issue 10, S2

Is Adjuvant Immunotherapy needed after Neoadjuvant chemoimmunotherapy?

Not a clear consensus at this time

Considerations

- EGFR and ALK mutated pts: no
- Risk of Recurrence, initial stage and Path findings
- pCR pts
- PD-L1 positive pts

Takeaways

- Neoadjuvant and adjuvant chemotherapy both improve 5 yr OS in resected stage 1B (>=4 cm) through IIIB NSCLCA Pts by 5.4%
- Adding Immunotherapy to adjuvant chemotherapy improves survival further
- Adding Immunotherapy to Neoadjuvant chemotherapy significantly improves the pCR rate and long term outcomes
- Combining 2 Immunotherapy drugs in the Neoadjuvant setting has a high pCR rate
- The role of adjuvant immunotherapy in patients who received Neoadjuvant chemotherapy and immunotherapy is promising

Thank You