Expanding Treatment Horizons: The Role of Immunotherapy in Stage I Lung Cancer

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Disclosures

I have no disclosures related to this presentation

Resectable NSCLC

- Stage I, II, or III
- In older studies → only 25-30% of NSCLCs are suitable for potentially curative resection
- Still after resection, patients will still be at risk to have recurrence and death.
  - 20-30% of stage I will die in 5 years
  - 60% of stage IIIA will die in 5 years

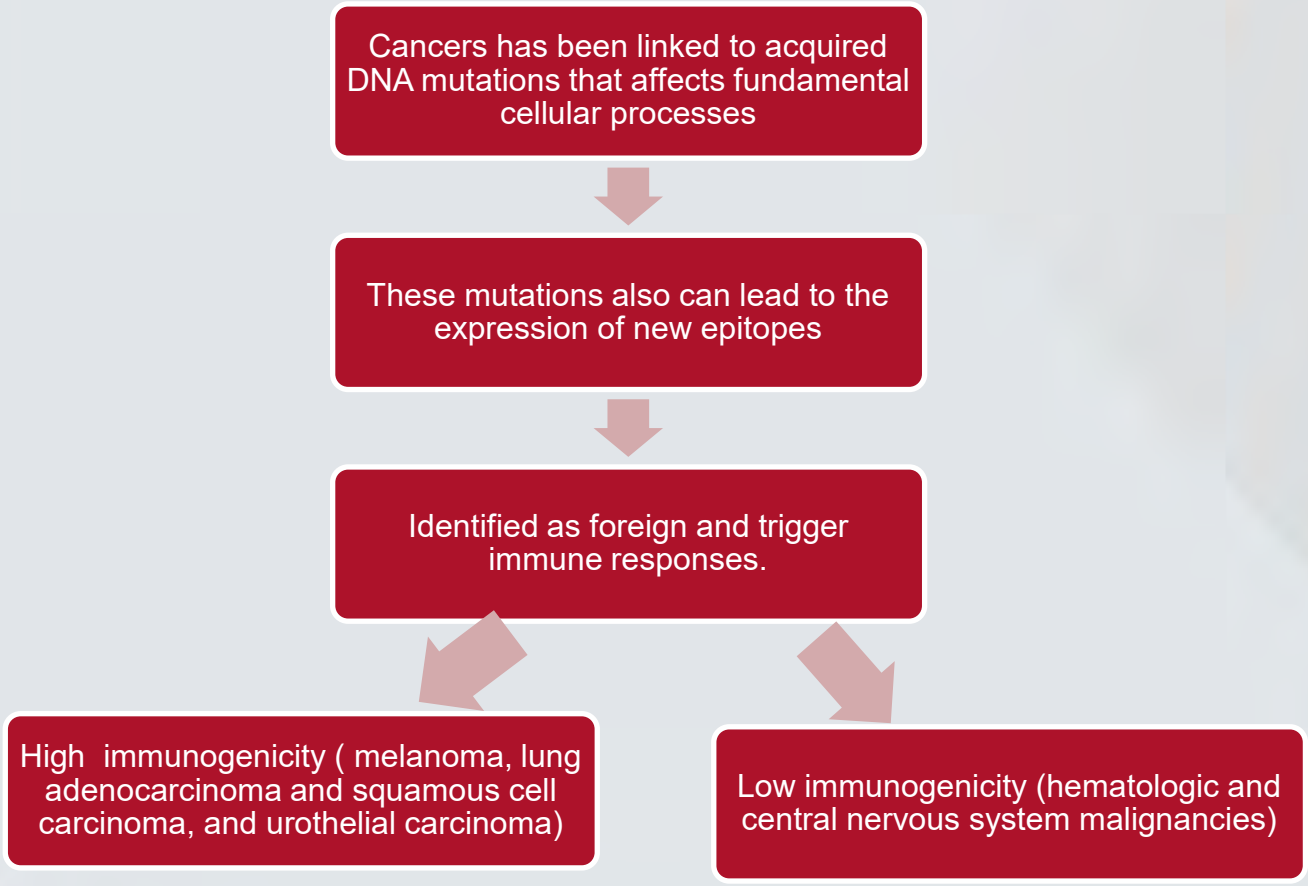
Ann Oncol. 2010;21 Suppl 7:vii196-vii198
J Thorac Oncol. 2015 Jul;10(7):990-1003

Neoadjuvant and Adjuvant Therapies

- Platinum-based chemotherapy
  - SOC for resectable stage II–IIIA disease, can consider in high-risk IB
  - Adjuvant chemo→ The LACE meta-analysis → data from 4584 patients enrolled in five randomized trials → showed a five-year benefit of only 5.4%. The advantage was observed in patients with stage II and III (HR = 0.83; CI, 0.73 to 0.95), but not those with stage I (HR = 0.93; CI, 0.78 to 1.10)
- Recently immunotherapy has been tested in the perioperative setting for stage IB-III

J Natl Compr Canc Netw. 2022;20(8):953-961.

Basics of immunotherapy



DeVita H, et al. Cancer Principles & Practice of Oncology 11th edition. Chapter 17

Tumor infiltrating lymphocytes (TILs)

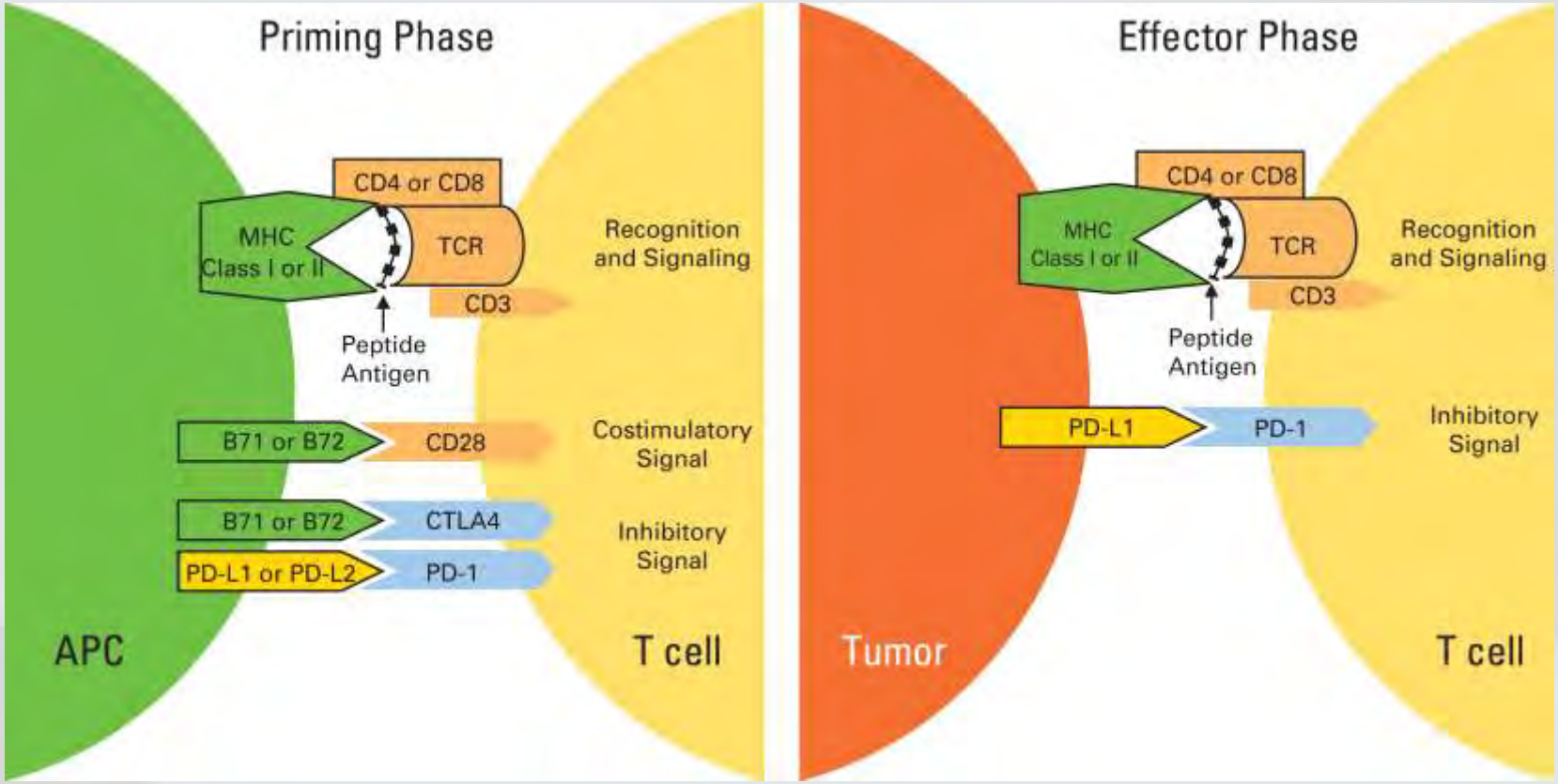


Image from ASCO- SEP 2022- Chapter 4 – Figure 4-2

Immune checkpoint inhibitors (ICIs)

Anti-PD1

- Pembrolizumab
  first approval 2014
- Nivolumab
  First approval 2014
- Cemiplimab
  First approval 2018

Anti-PD-L1

- Atezolizumab
  First approval 2016
- Avelumab
  First approval 2017
- Durvalumab
  First approval 2017

Anti-CTLA4

- Ipilimumab
  - First approval 2011

Neoadjuvant mono-immunotherapy

CheckMate 159

- Design:
  - One of the first pilot studies to evaluate neoadjuvant immunotherapy's safety and feasibility in NSCLC.
  - Phase II trial evaluated 21 patients with stage I–IIIA.
  - Patients received 2 doses of preoperative nivolumab .
- Outcomes:
  - Tumor major pathologic response (MPR): defined as tumor viability <= 10% in the surgical specimen
- Result:
  - MPR→ 45% of patients; 10% had a pathologic complete response
  - Compared to old studies → MPR rate with neoadjuvant chemotherapy has ranged from 16% to 21%.
  - Patients population: 19% had stage I and 81% had stage II or III

N Engl J Med 2018; 378:1976-1986
Lancet Oncol 2014;15:e42–50.

CheckMate 159

Table S3: Pre-treatment clinical stage and post-treatment pathologic stage

Patient number	Pre-treatment clinical stage TNM (stage group)	Pathologic stage at resection TNM (stage group)	Major Pathologic Response (yes/no)	Pathologic downstaging (yes/no)
1	T3N0* (IIB)	T0N1* (IIA)	Yes	Yes
2	T2AN0 (IB)	T2AN0 (IB)	Yes	No
3	T4N1 (IIIA)	T4N1 (IIIA)	No	No
4	T1BN0 (IA)	T1BN0 (IA)	Yes	No
5	T3N0 (IIB)	T2BN0 (IIA)	Yes	Yes
6	T3N1 (IIIA)	T3N1 (IIIA)	No	No
7	T2AN1 (IIA)	T3N1 (IIIA)	No	No
8	T2AN0 (IB)	T2AN0 (IB)	No	No
9	T2AN1 (IIA)	T1AN1 (IIA)	No	No
10	T1AN2 (IIIA)	T1AN0 (IA)	Yes	Yes
11	T1AN0 (IA)	T2AN0 (IB)	No	No
12	T2AN1 (IIA)	T2AN0 (IB)	No	Yes
13	T1AN2 (IIIA)	T2AN2 (IIIA)	No	No
14	T2N2 (IIIA)	T2N2M1a (IV)**	No	No
15	T2BN1 (IIA)	T3N1 (IIIA)	No	No
16	T1BN1 (IIA)	T0N0	Yes	Yes
17	T2AN2 (IIIA)	Unresectable	No	No
18	T2BN1 (IIB)	T1BN0 (IB)	Yes	Yes
19	T3N0 (IIB)	T3N1 (IIIA)	No	No
20	T2bN0 (IIA)	T1AN0 (IA)	Yes	Yes
21	T3N1 (IIIA)	T0N0	Yes	Yes

*Nodal stations 7, 12R and 11R were biopsied pre-treatment via EBUS and were negative. Pre-treatment PET/CT showed uptake in the 8cm primary tumor which was contiguous with the hilum. Post-treatment the N1 nodal station 10R was positive for residual tumor cells, the primary tumor underwent complete pathologic response.

LCMC3 study

- Design:
  - Phase II trial included 181 patients with stage IB-IIIB
  - Patients received 2 doses of neoadjuvant atezolizumab prior to surgery
- Outcome:
  - Primary outcome MPR (MPR; ≤10% viable malignant cells)
- Results:
  - Only 10% were stage IB
  - MPR rate was 20%
  - pCR rate was 7% (8 patients) . Only 1 out of 8 with stage I had pCR

Nat Med. 2022;28(10):2155-2161.
Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 8503

NEOSTAR

- Design:
  - Randomized phase II study, enrolled 44 patients with “operable” NSCLC
  - Neoadjuvant nivolumab or nivolumab + ipilimumab for 3 cycles followed by surgery
- Outcome:
  - Primary endpoint was MPR
- Results:
  - Stage IA was 18% and stage IB was 34%
  - Ipi/nivo: 50% MPR , pCR 38%
  - Nivo: 24% MPR , cPR 10%

Nat Med. 2021;27(3):504-514.

Neoadjuvant immunotherapy

- As monotherapy has some efficacy in inducing tumor response and does not interfere with surgical outcomes.
- However, it is not clear if the pathologic response rates will lead to survival benefit
- Conclusion on stage I is difficult since most trials did not have enough numbers of stage I

Adjuvant Immunotherapy

IMPOWER 010

- Design:
  - phase 3 study , enrolled more than 1000 patients with completely resected stage IB-IIIA
  - Patients were assigned (after receiving adjuvant chemotherapy) to either receiving adjuvant atezolizumab or observation

- Outcomes:
  - DFS
    - Stage II–IIIA population (PD-L1 1% or more)
    - All patients in the stage II–IIIA population
    - Intention-to-treat population (stage IB–IIIA)

Lancet. 2021;398(10308):1344-1357.
Ann Oncol. 2023;S0923-7534(23)00764-0.

	PD-L1 TC ≥1% stage II–IIIA group (SP263)		All stage II–IIIA group		Intention-to-treat group (stage IB–IIIA)	
	Atezolizumab (n=248)	Best supportive care (n=228)	Atezolizumab (n=442)	Best supportive care (n=440)	Atezolizumab (n=507)	Best supportive care (n=498)
Age, years	61 (56-67)	62 (56-68)	62 (56-67)	62 (55-68)	62 (57-67)	62 (56-68)
Age group						
<65 years	156 (63%)	131 (57%)	281 (64%)	263 (60%)	323 (64%)	300 (60%)
≥65 years	92 (37%)	97 (43%)	161 (36%)	177 (40%)	184 (36%)	198 (40%)
Sex						
Male	171 (69%)	147 (64%)	295 (67%)	294 (67%)	337 (66%)	335 (67%)
Female	77 (31%)	81 (36%)	147 (33%)	146 (33%)	170 (34%)	164 (33%)
Race						
White	162 (65%)	166 (73%)	307 (69%)	324 (74%)	362 (71%)	376 (76%)
Asian	78 (31%)	56 (25%)	121 (27%)	106 (24%)	130 (26%)	112 (23%)
Black or African American	2 (<1%)	0	4 (1%)	1 (<1%)	5 (1%)	1 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Multiple	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)
Unknown	5 (2%)	4 (2%)	9 (2%)	7 (2%)	9 (2%)	7 (1%)
ECOG performance status*						
0	140 (56%)	125 (55%)	239 (54%)	252 (57%)	273 (54%)	283 (57%)
1	107 (43%)	102 (45%)	201 (45%)	187 (43%)	232 (46%)	214 (43%)
2	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
Histology						
Squamous	96 (39%)	85 (37%)	150 (34%)	144 (33%)	179 (35%)	167 (34%)
Non-squamous	152 (61%)	143 (63%)	292 (66%)	296 (67%)	328 (65%)	331 (67%)
Tobacco use history						
Never	51 (21%)	41 (18%)	100 (23%)	96 (22%)	114 (23%)	108 (22%)
Previous	163 (66%)	146 (64%)	277 (63%)	270 (61%)	317 (63%)	304 (61%)
Current	34 (14%)	41 (18%)	65 (15%)	74 (17%)	76 (15%)	86 (17%)
Stage						
IB	..	..	..	..	65 (13%)	58 (12%)
IIA	85 (34%)	76 (33%)	147 (33%)	148 (34%)	147 (29%)	148 (30%)
IIB	46 (19%)	37 (16%)	90 (20%)	84 (19%)	90 (18%)	84 (17%)
IIIA	117 (47%)	115 (50%)	205 (46%)	208 (47%)	205 (40%)	208 (42%)
Type of surgery						
Lobectomy	186 (75%)	173 (76%)	335 (76%)	340 (77%)	394 (78%)	391 (79%)
Sleeve lobectomy	3 (1%)	3 (1%)	4 (1%)	4 (<1%)	4 (<1%)	4 (<1%)
Bilobectomy	15 (6%)	9 (4%)	30 (7%)	17 (4%)	31 (6%)	19 (4%)
Pneumonectomy	43 (17%)	42 (18%)	72 (16%)	78 (18%)	77 (15%)	83 (17%)
Other	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
EGFR mutation status†						
Yes	23 (9%)	20 (9%)	49 (11%)	60 (14%)	53 (10%)	64 (13%)
No	123 (50%)	125 (55%)	229 (52%)	234 (53%)	261 (52%)	266 (53%)
Unknown	102 (41%)	83 (36%)	164 (37%)	146 (33%)	193 (38%)	168 (34%)
ALK rearrangement status†						
Yes	12 (5%)	11 (5%)	14 (3%)	17 (4%)	15 (3%)	18 (4%)
No	133 (54%)	121 (53%)	251 (57%)	256 (58%)	280 (55%)	294 (59%)
Unknown	103 (42%)	96 (42%)	177 (40%)	167 (38%)	212 (42%)	186 (37%)
PD-L1 status by SP263‡						
<1%	..	..	181 (41%)	202 (46%)	210 (41%)	234 (47%)
≥1%	248 (100%)	228 (100%)	248 (56%)	228 (52%)	283 (56%)	252 (51%)
PD-L1 status by SP142§						
TC0/1 and IC0/1	77 (31%)	66 (29%)	198 (45%)	198 (45%)	231 (46%)	231 (46%)
TC0/1 and IC2/3	66 (27%)	61 (27%)	127 (29%)	132 (30%)	146 (29%)	145 (29%)
TC2/3 and any IC	105 (42%)	101 (44%)	117 (26%)	110 (25%)	130 (26%)	122 (25%)

Lancet. 2021;398(10308):1344-1357

Results

- There was improvement in DFS and OS for stage II-III patients especially in PD-L1 >50%. Based on this atezolizumab was added to the NCCN guidelines as an adjuvant treatment option for stage II-III with positive PD-L1

- But in ITT population that included stage IB, the change was not significant and data was premature.

Lancet. 2021;398(10308):1344-1357.
Ann Oncol. 2023;S0923-7534(23)00764-0.

KEYNOTE 091

- Design:
  - Phase III , enrolled more than 1000 patients with completely resected stage IB-IIIA NSCLC of any histology or PD-L1 expression level
  - Patients randomized to either pembrolizumab or placebo for up to 18 cycles.

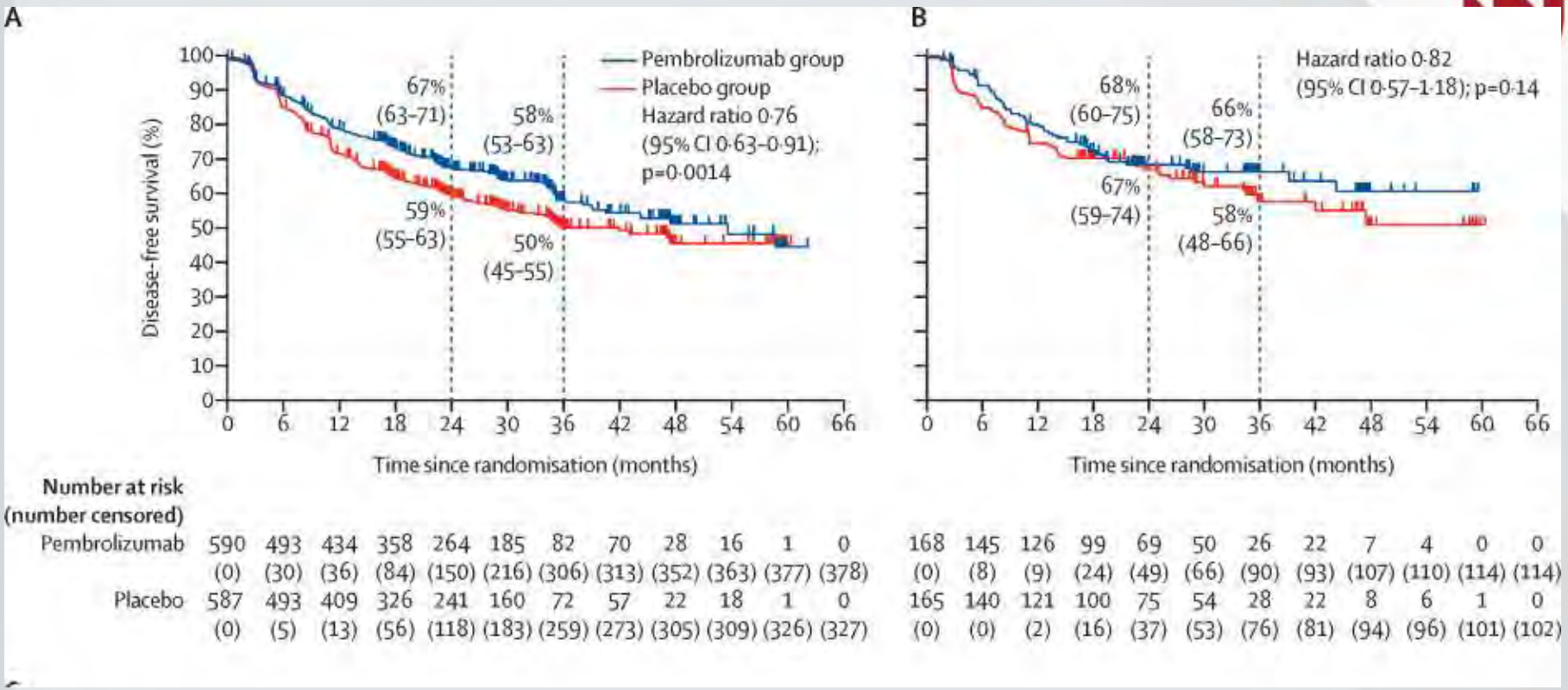
- Outcomes:
  - DFS in the overall population
  - DFS PD-L1 >= 50%

Lancet Oncol. 2022;23(10):1274-1286.

Results

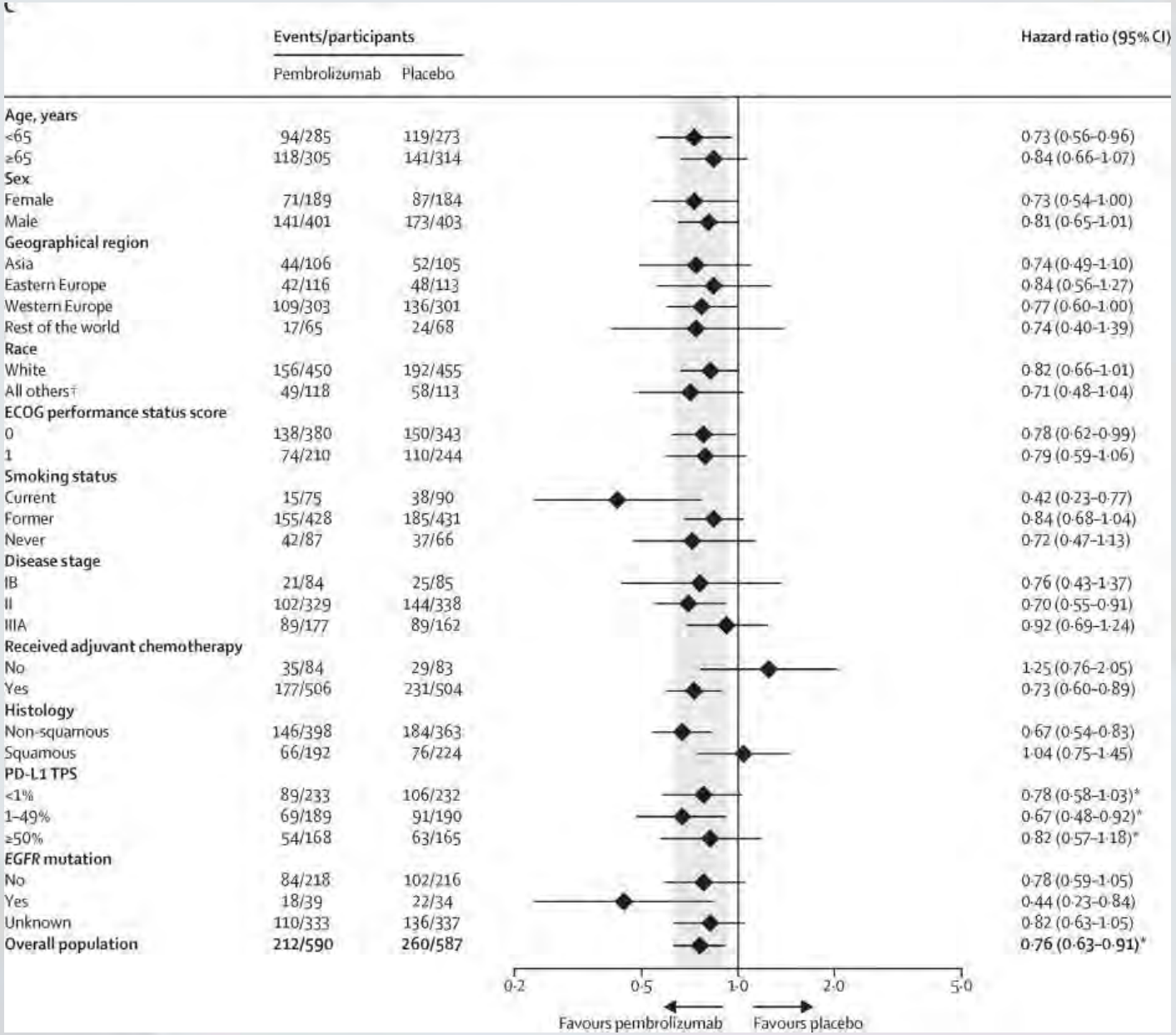
	Overall intention-to-treat population		PD-L1 TPS of ≥50% population	
	Pembrolizumab group (n=590)	Placebo group (n=587)	Pembrolizumab group (n=168)	Placebo group (n=165)
Age, years	65·0 (59·0–70·0)	65·0 (59·0–70·0)	64·5 (60·0–69·5)	65·0 (58·0–71·0)
<65	285 (48%)	273 (47%)	84 (50%)	82 (50%)
≥65	305 (52%)	314 (53%)	84 (50%)	83 (50%)
Sex				
Female	189 (32%)	184 (31%)	47 (28%)	49 (30%)
Male	401 (68%)	403 (69%)	121 (72%)	116 (70%)
Race				
American Indian or Alaskan Native	1 (<1%)	0	1 (1%)	0
Asian	107 (18%)	107 (18%)	29 (17%)	29 (18%)
Black or African American	0	3 (1%)	0	0
Multiple	4 (1%)	1 (<1%)	0	1 (1%)
Other	6 (1%)	2 (<1%)	3 (2%)	1 (1%)
White	450 (76%)	455 (78%)	128 (76%)	127 (77%)
Missing	22 (4%)	19 (3%)	7 (4%)	7 (4%)
Geographical region				
Asia	106 (18%)	105 (18%)	29 (17%)	29 (18%)
Eastern Europe	116 (20%)	113 (19%)	31 (18%)	30 (18%)
Western Europe	303 (51%)	301 (51%)	90 (54%)	89 (54%)
Rest of the world	65 (11%)	68 (12%)	18 (11%)	17 (10%)
ECOG performance status				
0	380 (64%)	343 (58%)	116 (69%)	101 (61%)
1	210 (36%)	244 (42%)	52 (31%)	64 (39%)
Smoking status				
Current	75 (13%)	90 (15%)	24 (14%)	29 (18%)
Former	428 (73%)	431 (73%)	130 (77%)	123 (75%)
Never	87 (15%)	66 (11%)	14 (8%)	13 (8%)
Histology				
Non-squamous	398 (67%)	363 (62%)	103 (61%)	105 (64%)
Squamous	192 (33%)	224 (38%)	65 (39%)	60 (36%)
Disease stage				
IB	84 (14%)	85 (14%)	21 (13%)	22 (13%)
II	329 (56%)	338 (58%)	95 (57%)	93 (56%)
IIIA	177 (30%)	162 (28%)	52 (31%)	50 (30%)
IV	0	2 (<1%)*	0	0
Regional lymph node stage (pN)				
N0	233 (39%)	257 (44%)	47 (28%)	59 (36%)
N1	233 (39%)	223 (38%)	84 (50%)	72 (44%)
N2	124 (21%)	107 (18%)	37 (22%)	34 (21%)
Received adjuvant chemotherapy				
No	84 (14%)	83 (14%)	25 (15%)	24 (15%)
Yes†	506 (86%)	504 (86%)	143 (85%)	141 (85%)
1–2 cycles	35 (6%)	32 (5%)	8 (5%)	8 (5%)
3–4 cycles	471 (80%)	472 (80%)	135 (80%)	133 (81%)
PD-L1 TPS				
<1%	233 (39%)	232 (40%)	0	0
1–49%	189 (32%)	190 (32%)	0	0
≥50%	168 (28%)	165 (28%)	168 (100%)	165 (100%)

(Table 1 continues on next page)



In the overall population→ DFS was 53·6 months (95% CI 39·2 to not reached) in the pembrolizumab group vs 42·0 months (31·3 to not reached) in the placebo group (HR 0·76 [95% CI 0·63–0·91], p=0·0014).

In the PD-L1 TPS of 50% or greater→ DFS was not reached in either the pembrolizumab group (95% CI 44·3 to not reached) or the placebo group (95% CI 35·8 to not reached; HR 0·82 [95% CI 0·57–1·18]; p=0·14).


Events/participants
Pembrolizumab
Placebo
Hazard ratio (95% CI)
Age, years
<65 94/285 119/273 0·73 (0·56–0·96)
≥65 118/305 141/314 0·84 (0·66–1·07)
Sex
Female 71/189 87/184 0·73 (0·54–1·00)
Male 141/401 173/403 0·81 (0·65–1·01)
Geographical region
Asia 44/106 52/105 0·74 (0·49–1·10)
Eastern Europe 42/116 48/113 0·84 (0·56–1·27)
Western Europe 109/303 136/301 0·77 (0·60–1·00)
Rest of the world 17/65 24/68 0·74 (0·40–1·39)
Race
White 156/450 192/455 0·82 (0·66–1·01)
All others† 49/118 58/113 0·71 (0·48–1·04)
ECOG performance status score
0 138/380 150/343 0·78 (0·62–0·99)
1 74/210 110/244 0·79 (0·59–1·06)
Smoking status
Current 15/75 38/90 0·42 (0·23–0·77)
Former 155/428 185/431 0·84 (0·68–1·04)
Never 42/87 37/66 0·72 (0·47–1·13)
Disease stage
IB 21/84 25/85 0·76 (0·43–1·37)
II 102/329 144/338 0·70 (0·55–0·91)
IIIA 89/177 89/162 0·92 (0·69–1·24)
Received adjuvant chemotherapy
No 35/84 29/83 1·25 (0·76–2·05)
Yes 177/506 231/504 0·73 (0·60–0·89)
Histology
Non-squamous 146/398 184/363 0·67 (0·54–0·83)
Squamous 66/192 76/224 1·04 (0·75–1·45)
PD-L1 TPS
<1% 89/233 106/232 0·78 (0·58–1·03)*
1–49% 69/189 91/190 0·67 (0·48–0·92)*
≥50% 54/168 63/165 0·82 (0·57–1·18)*
EGFR mutation
No 84/218 102/216 0·78 (0·59–1·05)
Yes 18/39 22/34 0·44 (0·23–0·84)
Unknown 110/333 136/337 0·82 (0·63–1·05)
Overall population 212/590 260/587 0·76 (0·63–0·91)*
0·2
0·5
1·0
2·0
5·0
Favours pembrolizumab
Favours placebo

Adjuvant immunotherapy

- Data are better compared to neoadjuvant (likely because patients got chemotherapy?).
- Adjuvant immunotherapy is recommended now by the NCCN guidelines in stage II-III.
- Unclear in role in stage I and so far it is not recommended.

PERIOPERATIVE SYSTEMIC THERAPY

Adjuvant Systemic Therapy

- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3,N2]). Principles of Molecular and Biomarker Analysis (NSCL-H).

Preferred (nonsquamous)

- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[2]

Preferred (squamous)

- Cisplatin 75 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[3]
- Cisplatin 75 mg/m² day 1, docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[4]

Other Recommended

- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5]
- Cisplatin 100 mg/m² day 1, vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[6,7]
- Cisplatin 75–80 mg/m² day 1, vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1, etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[6]

Useful in Certain Circumstances

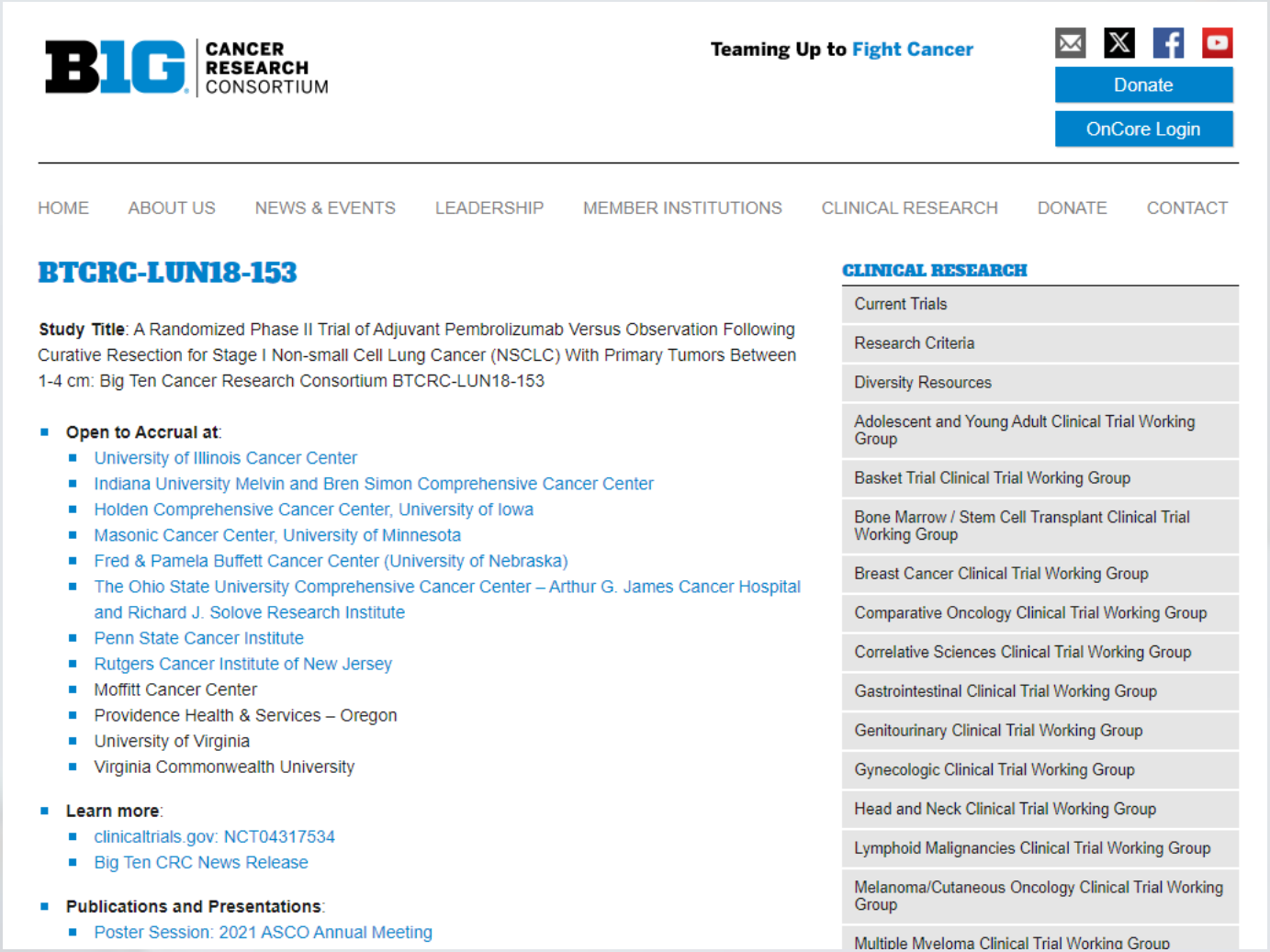
- Chemotherapy Regimens for Patients Not Candidates for Cisplatin-Based Therapy
  - Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[8]
  - Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[9]
  - Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[10] (nonsquamous histology)

All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.

Systemic Therapy Following Previous Adjuvant Systemic Therapy

- Osimertinib 80 mg daily[11]
  - Osimertinib for patients with completely resected stage IB–IIIA or stage IIIB (T3, N2) NSCLC and positive for *EGFR* (exon 19 deletion, exon 21 L858R) mutations who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[12]
  - Atezolizumab for patients with completely resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC with PD-L1 ≥1% and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors.*
- Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks for up to 1 year[13]
  - Pembrolizumab for patients with completely resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors.*

BIG 10 trial



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BTCRC-LUN18-153

Study Title: A Randomized Phase II Trial of Adjuvant Pembrolizumab Versus Observation Following Curative Resection for Stage I Non-small Cell Lung Cancer (NSCLC) With Primary Tumors Between 1-4 cm: Big Ten Cancer Research Consortium BTCRC-LUN18-153

- **Open to Accrual at**:
  - University of Illinois Cancer Center
  - Indiana University Melvin and Bren Simon Comprehensive Cancer Center
  - Holden Comprehensive Cancer Center, University of Iowa
  - Masonic Cancer Center, University of Minnesota
  - Fred & Pamela Buffett Cancer Center (University of Nebraska)
  - The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute
  - Penn State Cancer Institute
  - Rutgers Cancer Institute of New Jersey
  - Moffitt Cancer Center
  - Providence Health & Services – Oregon
  - University of Virginia
  - Virginia Commonwealth University
- **Learn more**:
  - clinicaltrials.gov: NCT04317534
  - Big Ten CRC News Release
- **Publications and Presentations**:
  - Poster Session: 2021 ASCO Annual Meeting

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- Lymphoid Malignancies Clinical Trial Working Group
- Melanoma/Cutaneous Oncology Clinical Trial Working Group
- Multiple Myeloma Clinical Trial Working Group

Perioperative Chemo-Immunotherapy

University of Nebraska Medical Center

CheckMate 816

- Design:
  - Phase III study involved 358 patients with stage IB-IIIA NSCLC without EGFR/ALK mutations
  - Patients received 3 cycles of neoadjuvant nivolumab + platinum-based chemotherapy or chemotherapy alone.

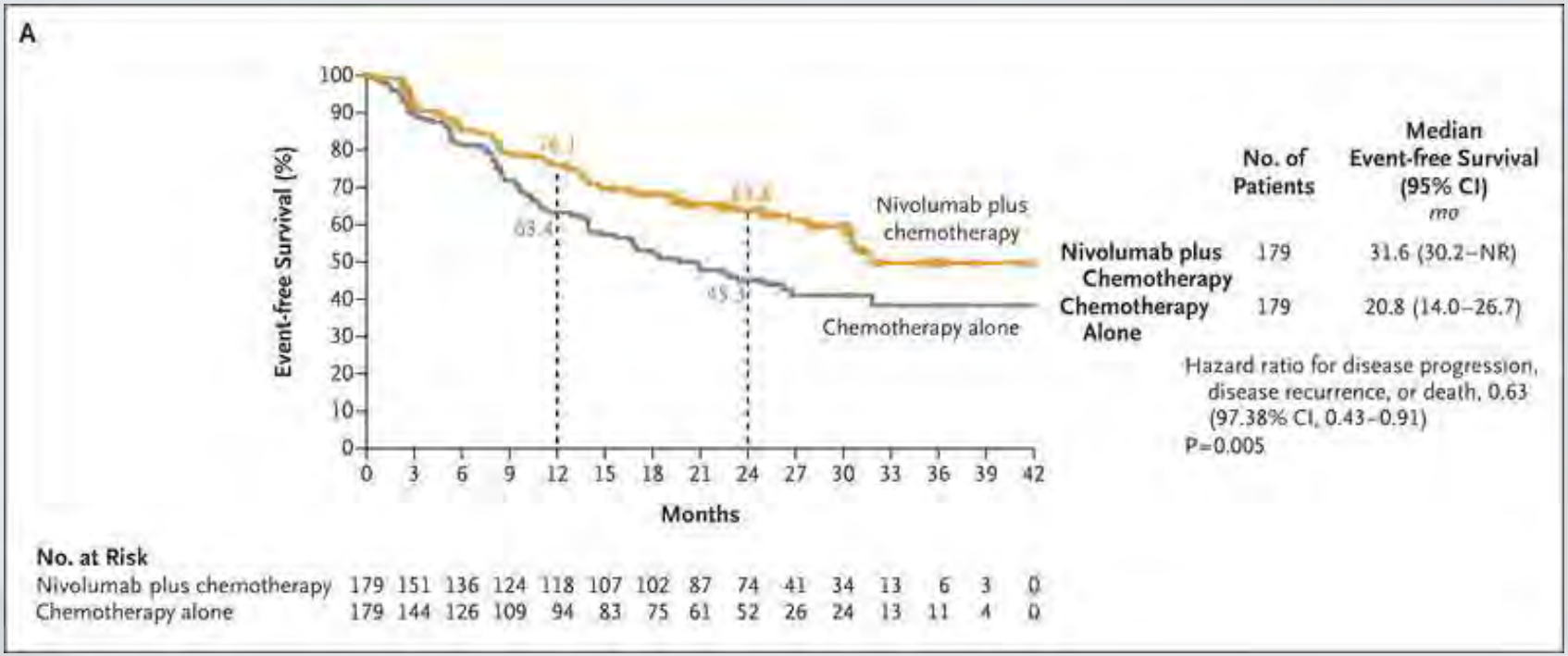
- Outcomes:
  - Event free survival (EFS)
  - Pathological complete response (0% viable tumor in resected lung and lymph nodes)

N Engl J Med 2022; 386:1973-1985

Characteristic	Nivolumab plus Chemotherapy (N=179)	Chemotherapy Alone (N=179)
Age		
Median (range) — yr	64 (41–82)	65 (34–84)
Distribution — no. (%)		
<65 yr	93 (52.0)	83 (46.4)
≥65 yr	86 (48.0)	96 (53.6)
Sex — no. (%)		
Male	128 (71.5)	127 (70.9)
Female	51 (28.5)	52 (29.1)
Geographic region — no. (%)		
North America	41 (22.9)	50 (27.9)
Europe	41 (22.9)	25 (14.0)
Asia	85 (47.5)	92 (51.4)
Rest of the world*	12 (6.7)	12 (6.7)
ECOG performance-status score — no. (%)†		
0	124 (69.3)	117 (65.4)
1	55 (30.7)	62 (34.6)
Disease stage — no. (%)‡		
IB or II	65 (36.3)	62 (34.6)
IIIA	113 (63.1)	115 (64.2)
Histologic type of tumor — no. (%)		
Squamous	87 (48.6)	95 (53.1)
Nonsquamous	92 (51.4)	84 (46.9)
Smoking status — no. (%)§		
Never smoked	19 (10.6)	20 (11.2)
Current or former smoker	160 (89.4)	158 (88.3)
PD-L1 expression level — no. (%)¶		
Could not be evaluated	12 (6.7)	13 (7.3)
<1%	78 (43.6)	77 (43.0)
≥1%	89 (49.7)	89 (49.7)
1–49%	51 (28.5)	47 (26.3)
≥50%	38 (21.2)	42 (23.5)
Tumor mutational burden — no. (%)‖		
Could not be evaluated or was not reported	91 (50.8)	89 (49.7)
<12.3 mutations per megabase	49 (27.4)	53 (29.6)
≥12.3 mutations per megabase	39 (21.8)	37 (20.7)
Type of platinum therapy — no. (%)		
Cisplatin	124 (69.3)	134 (74.9)

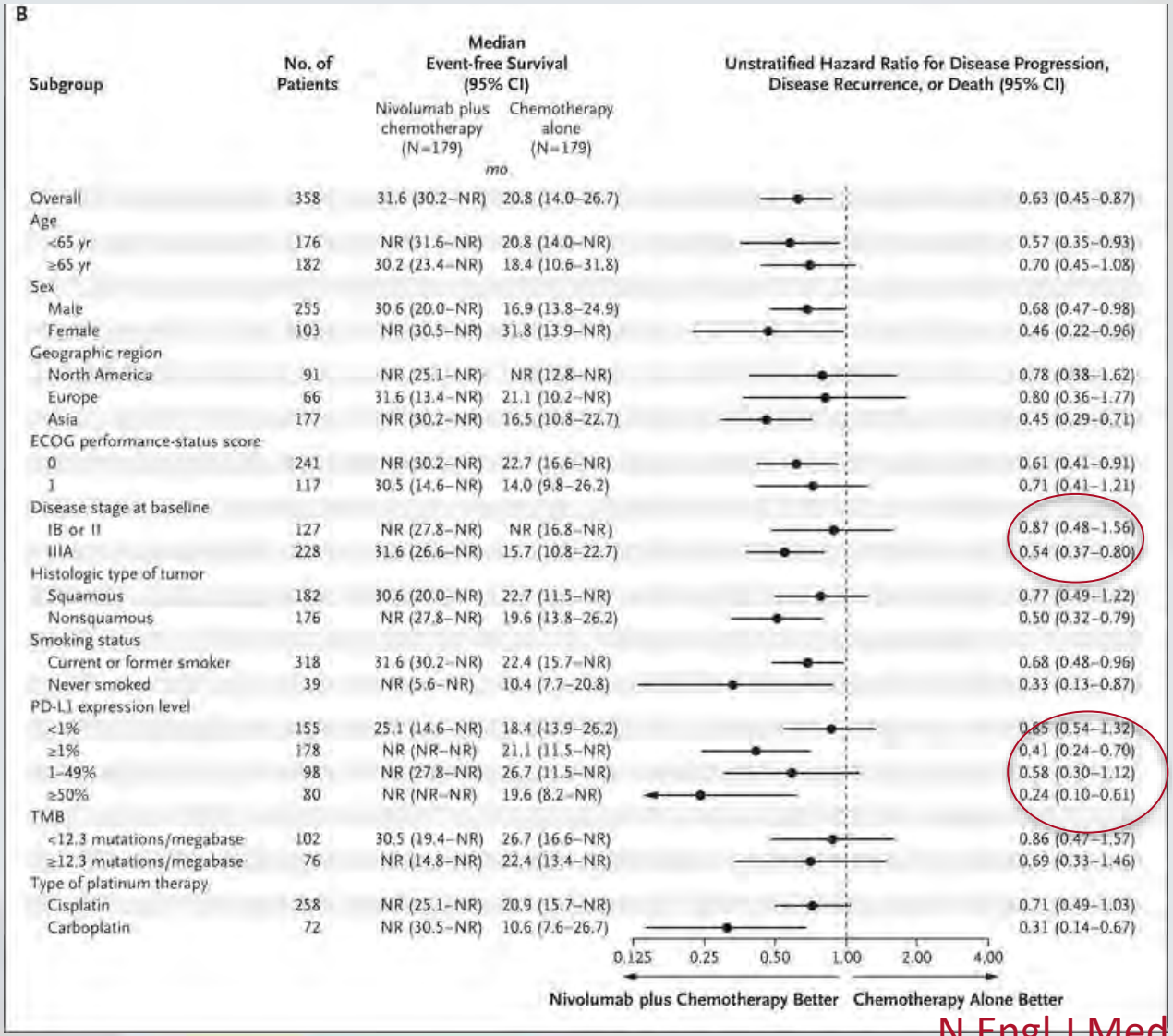
N Engl J Med 2022; 386:1973-1985

EFS



N Engl J Med 2022; 386:1973-1985

EFS



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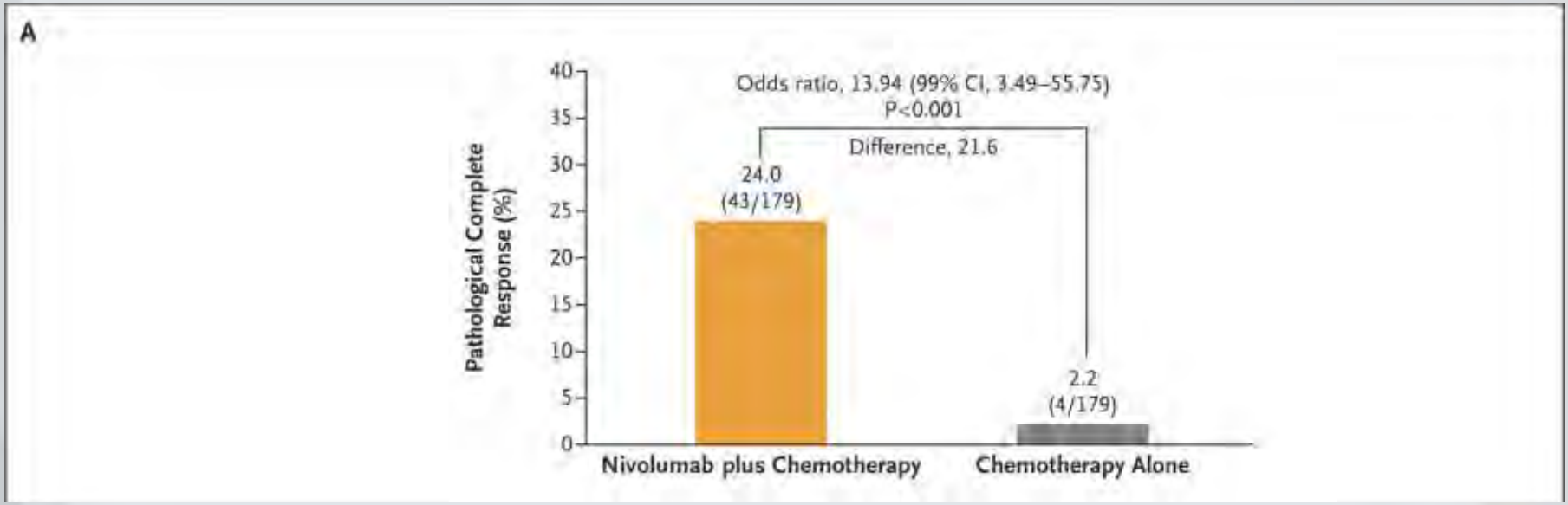
pCR



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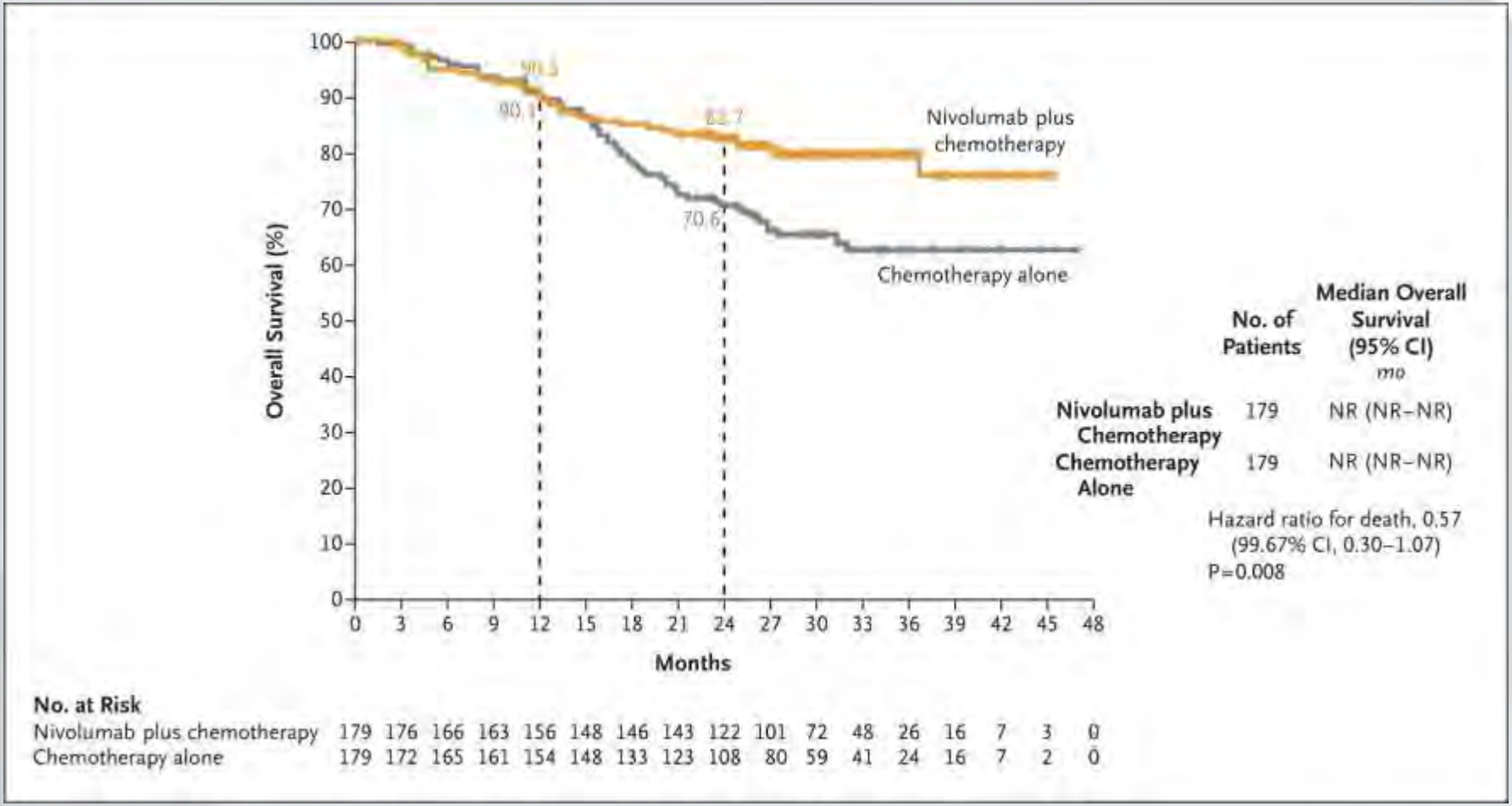
OS

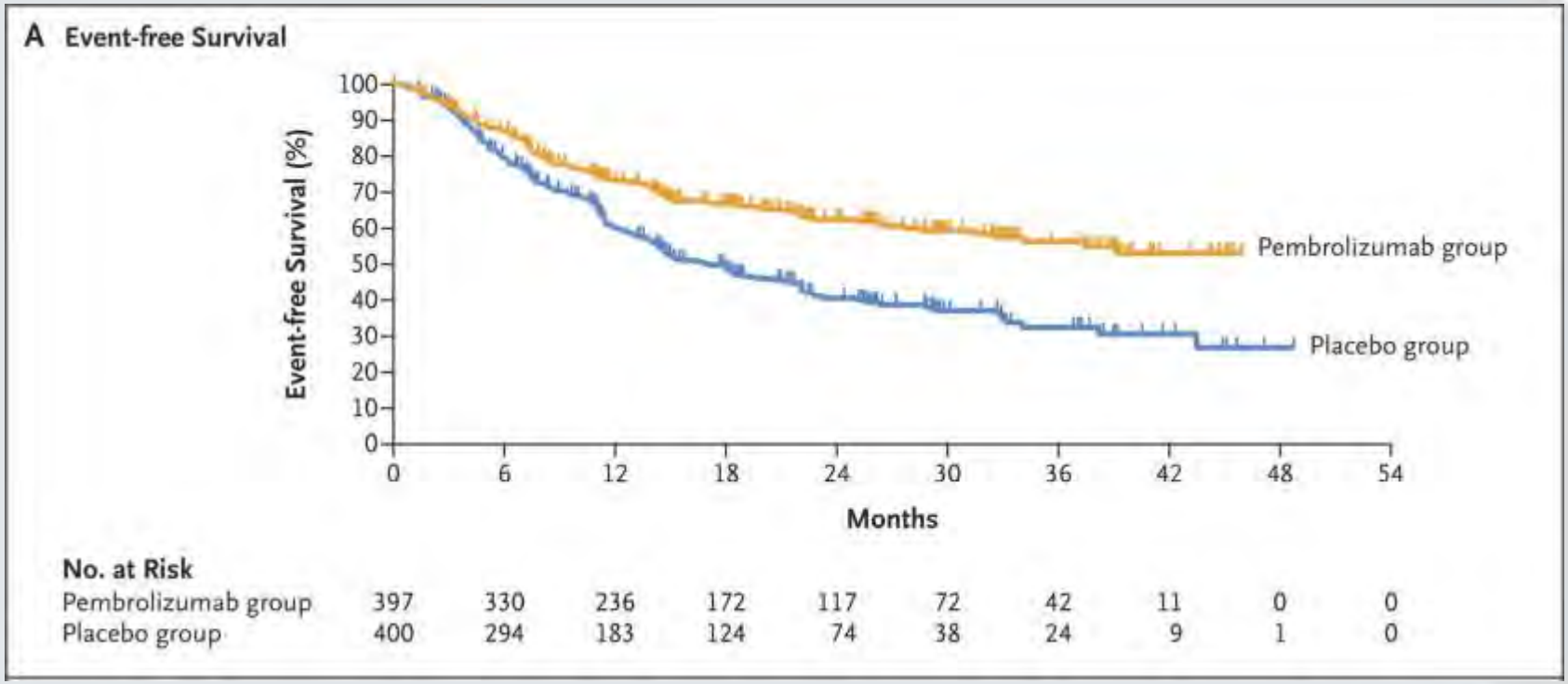


N Engl J Med 2022; 386:1973-1985

KEYNOTE-671

- Design:
  - Phase 3 trial , enrolled stage II-IIIB NSCLC
  - Patients received neoadjuvant pembrolizumab + chemo vs placebo + chemo for 4 cycles→ followed by surgery → either adjuvant pembrolizumab or placebo for up to 13 cycles
- Outcomes:
  - EFS and OS

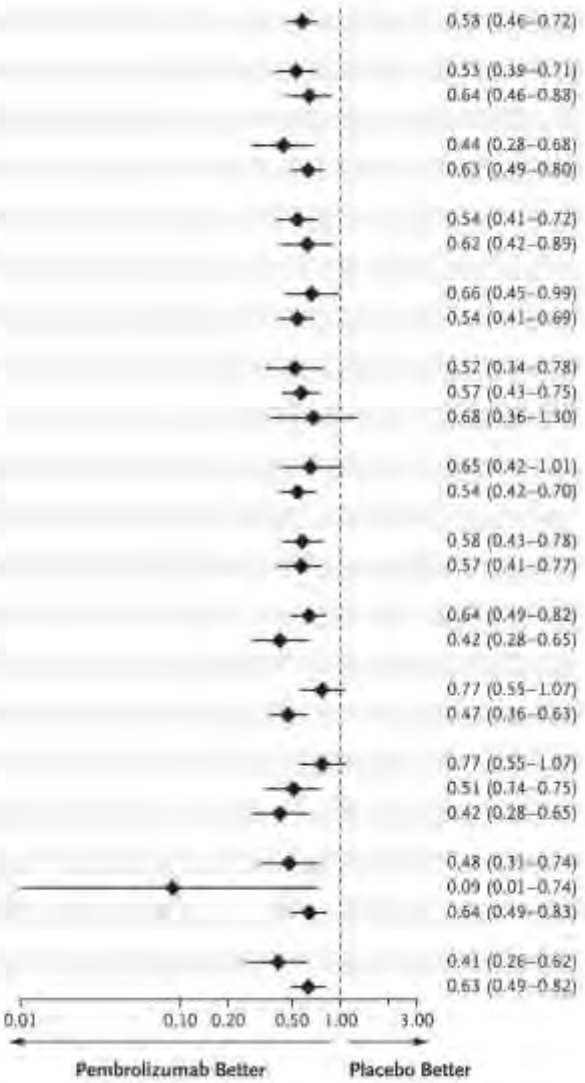
N Engl J Med 2023; 389:491-503

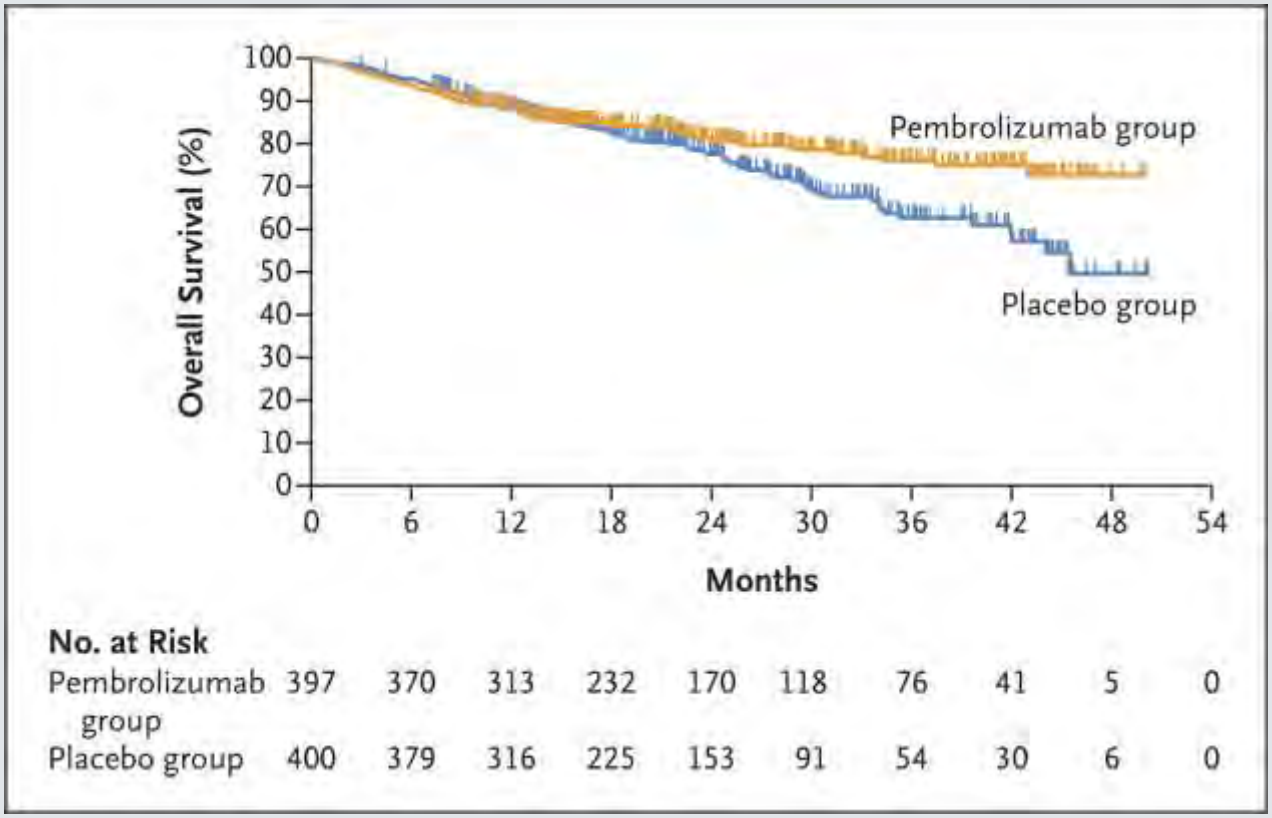


EFS at 2 years : 62.4% vs 40.6% (HR, 0.58; 95% confidence interval [CI], 0.46 to 0.72; P<0.001).

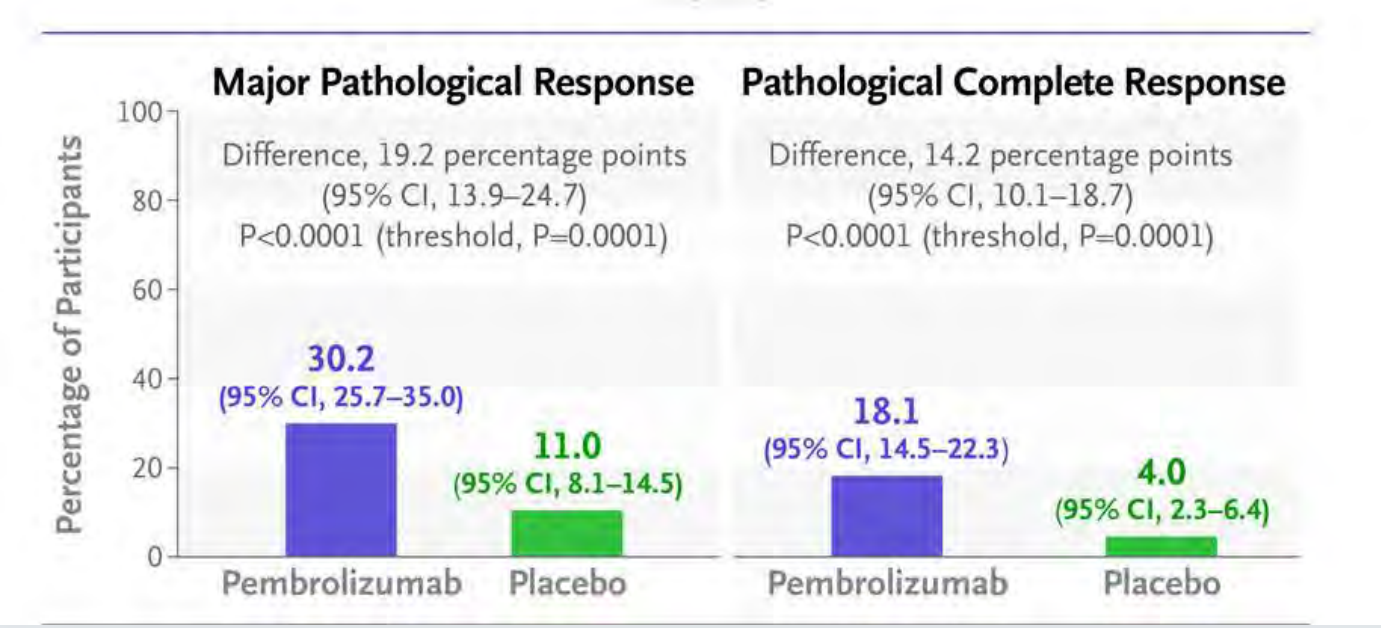
B Subgroup Analysis of Event-free Survival

Subgroup	Pembrolizumab Group	Placebo Group	Hazard Ratio for Event or Death (95% CI)
	no. of events/no. of participants		
All patients	139/397	205/400	0.58 (0.46–0.72)
Age			
<65 yr	74/221	113/214	0.53 (0.39–0.71)
≥65 yr	65/176	92/186	0.64 (0.46–0.88)
Sex			
Female	31/118	55/116	0.44 (0.28–0.68)
Male	108/279	150/284	0.63 (0.49–0.80)
Race			
White	85/250	123/239	0.54 (0.41–0.72)
Other	46/134	70/145	0.62 (0.42–0.89)
Geographic region			
East Asia	43/123	57/121	0.66 (0.45–0.99)
Other	96/274	148/279	0.54 (0.41–0.69)
Smoking status			
Current smoker	37/96	57/103	0.52 (0.34–0.78)
Former smoker	84/247	128/250	0.57 (0.43–0.75)
Never smoked	18/54	20/47	0.68 (0.36–1.30)
Pathological stage			
II	34/118	48/121	0.65 (0.42–1.01)
III	105/279	157/279	0.54 (0.42–0.70)
Histologic features			
Nonsquamous	73/226	107/227	0.58 (0.43–0.78)
Squamous	66/171	98/173	0.57 (0.41–0.77)
PD-L1 TPS (50% cutoff)			
<50%	107/265	142/266	0.64 (0.49–0.82)
≥50%	32/132	63/134	0.42 (0.28–0.65)
PD-L1 TPS (1% cutoff)			
<1%	63/138	80/151	0.77 (0.55–1.07)
≥1%	76/259	125/249	0.47 (0.36–0.63)
PD-L1 TPS			
<1%	63/138	80/151	0.77 (0.55–1.07)
1–49%	44/127	62/115	0.51 (0.34–0.75)
≥50%	32/132	63/134	0.42 (0.28–0.65)
EGFR mutation			
No	31/111	64/127	0.48 (0.31–0.74)
Yes	1/14	10/19	0.09 (0.01–0.74)
Unknown	107/272	131/254	0.64 (0.49–0.83)
ALK translocation			
No	29/104	76/133	0.41 (0.26–0.62)
Unknown	106/281	128/258	0.63 (0.49–0.82)



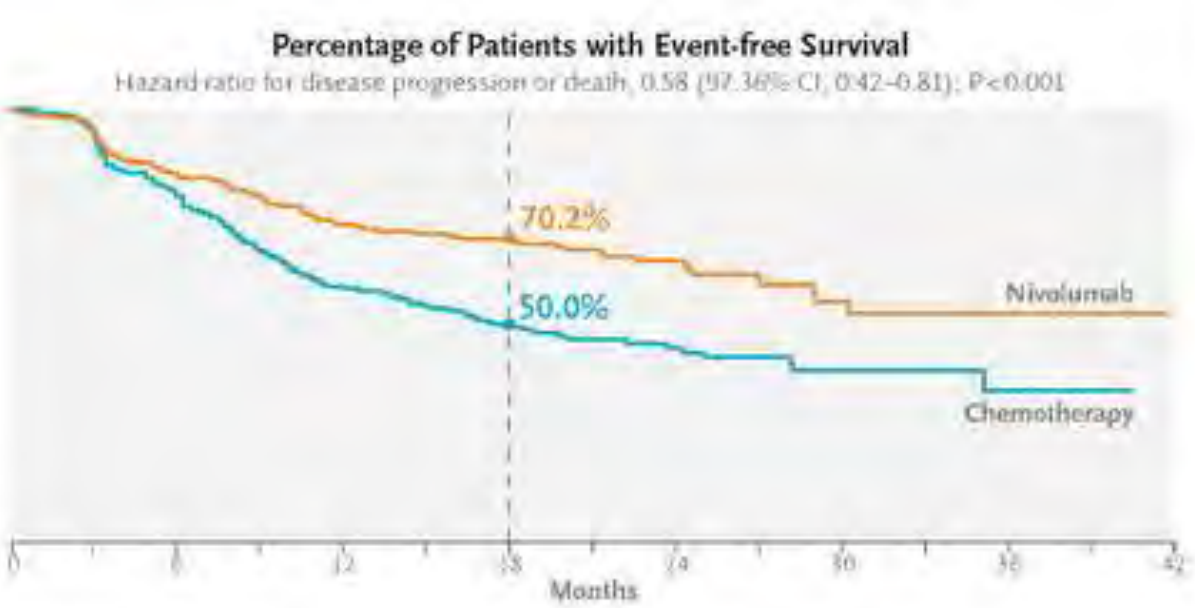


OS at 2 years → 80.9% vs 77.6% (P=0.02, which did not meet the significance criterion).

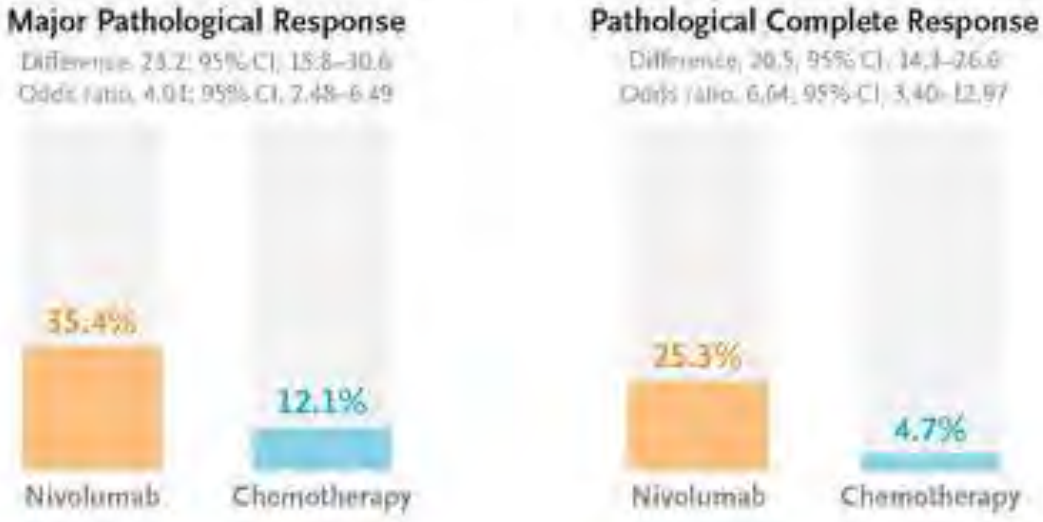

Major Pathological Response
Difference, 19.2 percentage points
(95% CI, 13.9–24.7)
P<0.0001 (threshold, P=0.0001)
Pathological Complete Response
Difference, 14.2 percentage points
(95% CI, 10.1–18.7)
P<0.0001 (threshold, P=0.0001)
Percentage of Participants
100
80
60
40
20
0
30.2
(95% CI, 25.7–35.0)
11.0
(95% CI, 8.1–14.5)
18.1
(95% CI, 14.5–22.3)
4.0
(95% CI, 2.3–6.4)
Pembrolizumab
Placebo
Pembrolizumab
Placebo

CheckMate 77T

- Design:
  - Phase 3 trial , enrolled stage II-IIIB NSCLC
  - Patients received neoadjuvant nivolumab + chemo vs placebo + chemo for 4 cycles→ followed by surgery → either adjuvant nivolumab or placebo for up to one year
- Outcomes:
  - EFS and pathologic response



Pathological complete response and major pathological response (secondary outcomes) also favored nivolumab over chemotherapy.



Perioperative chemotherapy +immunotherapy

- Data is strong for Stage II and III. Improved survival, no interference of surgical outcomes.

- Again, no data to suggest that it should be used in stage I.

PERIOPERATIVE SYSTEMIC THERAPY

- Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors, see below.
- Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors
- Adjuvant Chemotherapy
- Systemic Therapy Following Surgical Resection

Neoadjuvant Systemic Therapy

- All patients should be evaluated for preoperative therapy, with strong consideration for nivolumab or pembrolizumab + chemotherapy for those patients with tumors ≥4 cm or node positive and no contraindications to immune checkpoint inhibitors.[a] Otherwise refer to the Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors.
- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3,N2]). PD-L1 status can be incorporated with other clinical factors to determine patients who may benefit from induction chemotherapy and immunotherapy. Principles of Molecular and Biomarker Analysis (NSCL-H).
- Clinical trials for neoadjuvant nivolumab + chemotherapy excluded patients harboring *EGFR* mutations and *ALK* rearrangements. Thus, exclusion of these biomarkers, at a minimum, is recommended prior to consideration for neoadjuvant nivolumab + chemotherapy.
- After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction systemic therapy as an alternative.

Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors

- Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for 3 cycles[1]
  - Platinum-doublet chemotherapy options include:
    - Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
    - Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)
    - Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)
    - Cisplatin 75 mg/m² day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
  - Chemotherapy regimens for patients who are not candidates for cisplatin-based therapy
    - Carboplatin AUC 5 or AUC 6 day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)
    - Carboplatin AUC 5 or AUC 6 day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)
- Pembrolizumab 200 mg and cisplatin-based doublet therapy every 3 weeks for 4 cycles and then continued as single-agent pembrolizumab as adjuvant treatment after surgery (category 1); Systemic Therapy Following Surgical Resection[2]
  - Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² days 1 and 8 (squamous histology)
  - Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)

Challenges of immunotherapy

1- Learn what biomarkers can predict response to immunotherapy

2-Learn about the current limitations (lack of evidence, cost of therapy, side effects).

3-Duraation of treatment , can it be less than a year?

Summary

- Utilization of chemo-immunotherapy has resulted in better PFS, promising data in OS with acceptable safety profile in stage II and III.

- The utilization of systemic therapy in stage I NSCLC, continues to be limited at this point.

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