Advances in management for resectable Non Small Cell Lung Cancer

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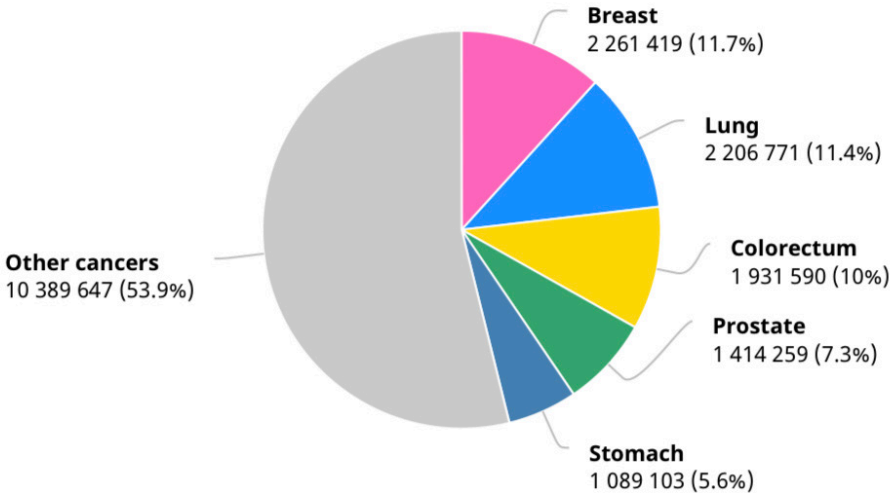
World

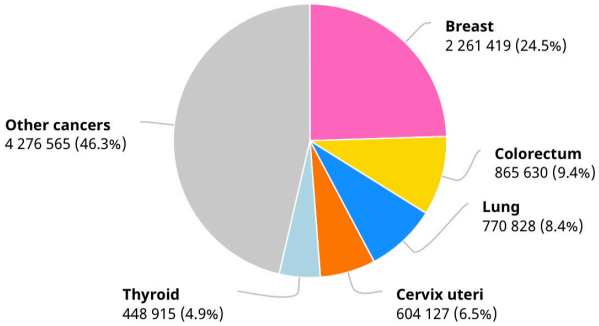
Source: Globocan 2020

Number of new cases in 2020, both sexes, all ages



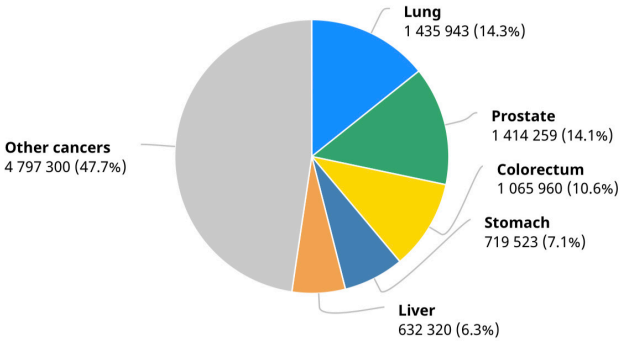
Total: 19 292 789

Number of new cases in 2020, females, all ages



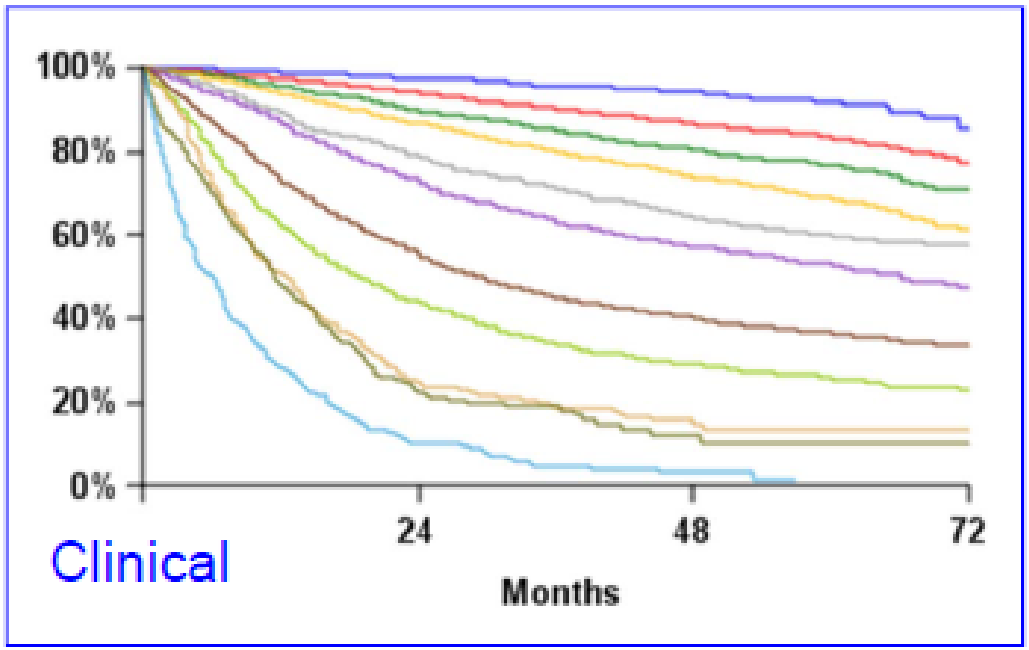
Total: 9 227 484

Number of new cases in 2020, males, all ages



Total: 10 065 305

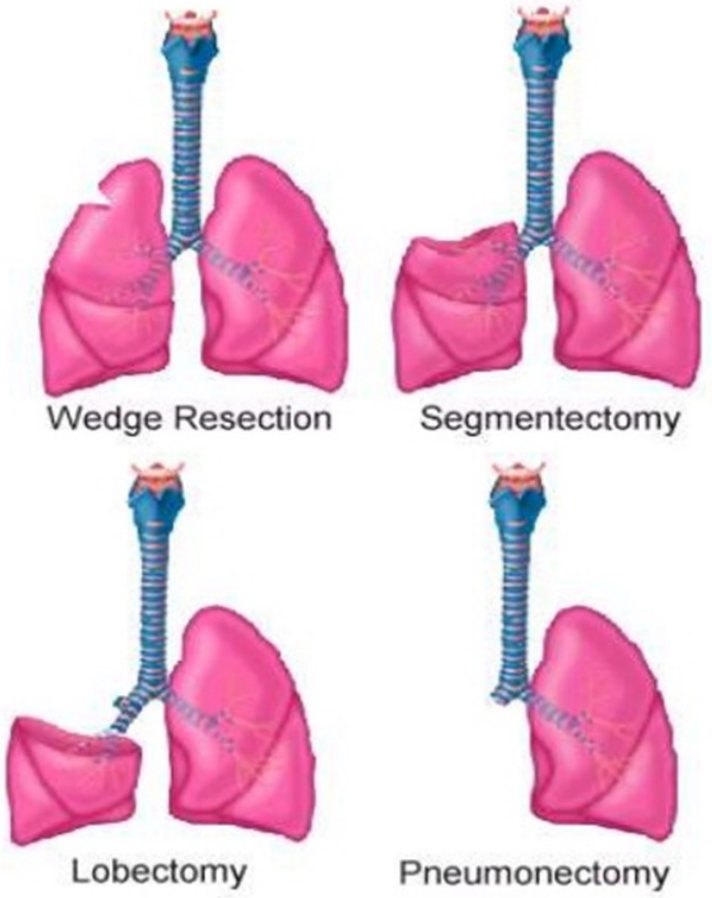
Overall Survival by Stage NSCLC



	Events/N	MST	24 months	60 months
IA1	68/781	NR	97%	92%
IA2	505/3105	NR	94%	83%
IA3	546/2417	NR	90%	77%
IB	560/1928	NR	87%	68%
IIA	215/585	NR	79%	60%
IIB	605/1453	66.0	72%	53%
IIIA	2052/3200	29.3	55%	36%
IIIB	1551/2140	19.0	44%	26%
IIIC	831/986	12.6	24%	13%
IVA	336/484	11.5	23%	10%
IVB	328/398	6.0	10%	0%

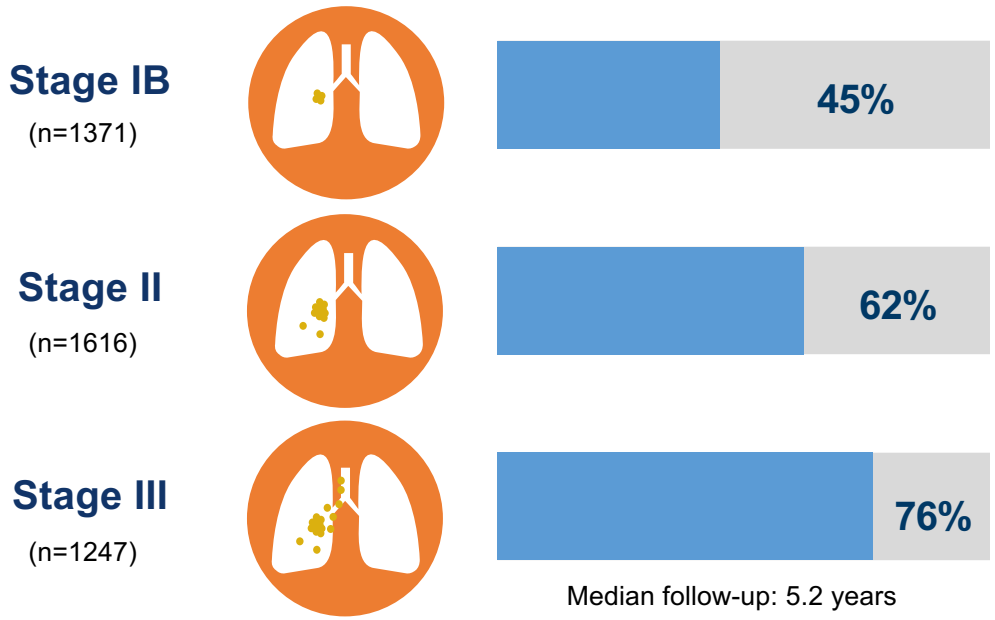
Goldstraw P et al. J Thorac Oncol 2016; 11: 39-51.

Surgical therapy for Resectable NSCLC



Disease Recurrence or Death following Surgery Remains High Across disease Stages in NSCLC

5-Year Rate of Recurrence or Death in Resectable NSCLC From a Global Meta-Analysis[3,a,b]



Even when treated with adjuvant chemotherapy, the majority of resectable stage IB-III patients will have a recurrence or will have died within 5 years[3]

- Until 2020, adjuvant cisplatin-based chemotherapy was the only recommended adjuvant therapy following complete resection of stage II to IIIA NSCLC; which, at 5 years following complete resection, the absolute survival benefit of chemotherapy versus no chemotherapy treatment was only 5%[5]

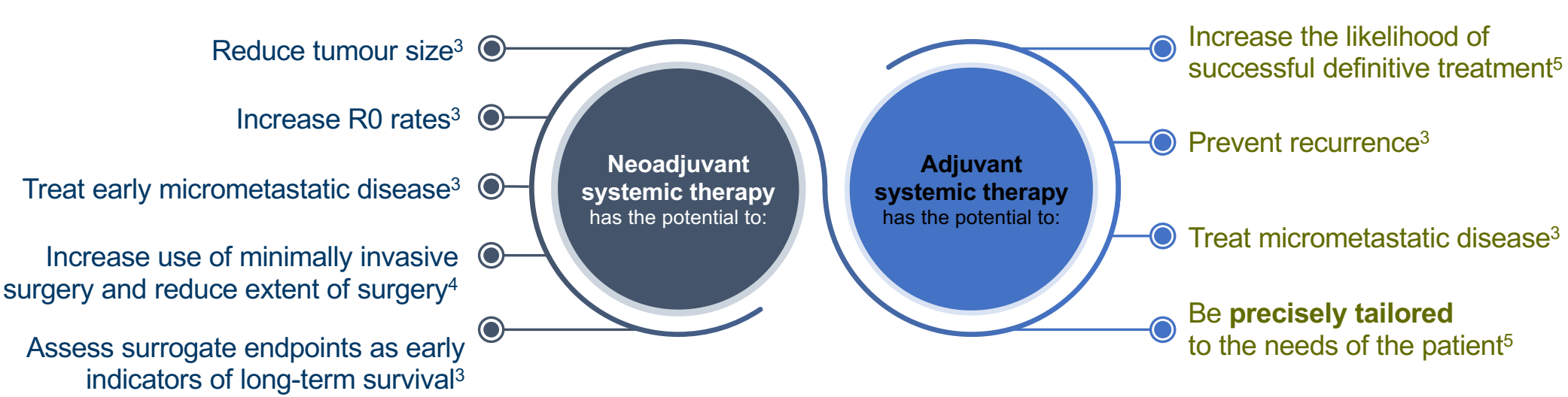
In a clinical study, nearly 40% of patients treated with adjuvant chemotherapy recurred with metastatic NSCLC[4,c]

[a]Pooled analysis of 5 randomized trials with 4584 patients; Trials compared postoperative cisplatin-based chemotherapy vs no chemotherapy or cisplatin-based chemotherapy plus postoperative radiotherapy (administered sequentially) vs postoperative radiotherapy alone in patients with completely resected NSCLC.[3] [b]Recurrence of disease at any site and death from any cause. [c]The study included a total of 1867 patients with stage I-III disease with 932 randomly assigned to the chemotherapy group and 935 to the control group. Of the total population, 40% had Stage III disease and 572 patients had planned radiotherapy.[4,5]

References and abbreviations in the notes sections

Recurrence with traditional (neo)adjuvant CTX is an unmet need in resectable NSCLC

Neoadjuvant or adjuvant CTX have shown **modest clinical survival benefits** (DFS and OS) in early-stage NSCLC[1,2]



DFS, disease-free survival; OS, overall survival; R0, margin-negative resection

1. Nagasaka M, Gadgeel SM. *Expert Rev Anticancer Ther.* 2018;18:63-70; 2. NSCLC Meta-analysis Collaborative Group. *Lancet.* 2014;383:1561-1571; 3. Shukla N, Hanna N. *Lung Cancer (Auckl).* 2021;12:51-60;
4. Forde PM, et al. *N Engl J Med.* 2022;386:1973-1985; 5. West HJ, Jin JO. *JAMA Oncol.* 2015;1:698

Medical advances have contributed to improved outcomes for resectable NSCLC[1,2]

The treatment landscape for resectable NSCLC is rapidly evolving due to the number of trials including neoadjuvant and / or adjuvant treatments[3]

Adjuvant IO[3-6]
- IMpower010
- KEYNOTE-091
- BR.31
- ANVIL

Adjuvant targeted therapy[7]
- ADAURA
- ALINA

Neoadjuvant CTX + IO[8]
- CheckMate 816

Neoadjuvant IO + CTX and adjuvant IO[9-13]
- AEGEAN
- KEYNOTE-671
- IMpower030
- CheckMate 77T
- Neotorch

CTX, chemotherapy

1. Yang S-M, et al. *J Formos Med Assoc* 2017;116:917–923; 2. Li C, et al. *Cancer Biol Med* 2022;19:591–608; 3. Felip E, et al. *Lancet* 2021;398:1344–1357; 4. O'Brien M, et al. *Lancet Oncol* 2022;23:1274–1286; 5. ClinicalTrials.gov. BR.31. https://clinicaltrials.gov/ct2/show/NCT02273375. Accessed March 2023; 6. ClinicalTrials.gov. ANVIL. https://www.clinicaltrials.gov/ct2/show/NCT02595944. Accessed March 2023; 7. Wu Y-L, et al. *N Engl J Med* 2020;383:1711–1723; 8. Forde PM, et al. *N Engl J Med* 2022;386:1973–1985; 9. Heymach JV, et al. *Clin Lung Cancer* 2022;23:e247–e251; 10. Tsuboi M, et al. *Ann Oncol* 2020;31(Suppl 4):S801–S802;
11. Peters S, et al. *Ann Oncol* 2019;30(Suppl 2):ii30; 12. Cascone T, et al. *J Clin Oncol* 2019;38(Suppl):TPS9076; 13. ClinicalTrials.gov. Neotorch. https://clinicaltrials.gov/ct2/show/NCT04158440. Accessed March 2023

Data includes ongoing clinical trials and is being updated.
Nivolumab, Toripalimab is not approved in Vietnam. Durvalumab, pembrolizumab is not approved in Vietnam for perioperative treatment in resectable NSCLC patients. Atezolizumab is not approved in Vietnam for neoadjuvant treatment in resectable NSCLC patients. Alectinib is not approved in Vietnam for adjuvant treatment in resected NSCLC patients.

ADAURA – Adjuvant EGFR TKI

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§
- Maximum 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 continued until:
- Disease recurrence
- Treatment completion
- 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 endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

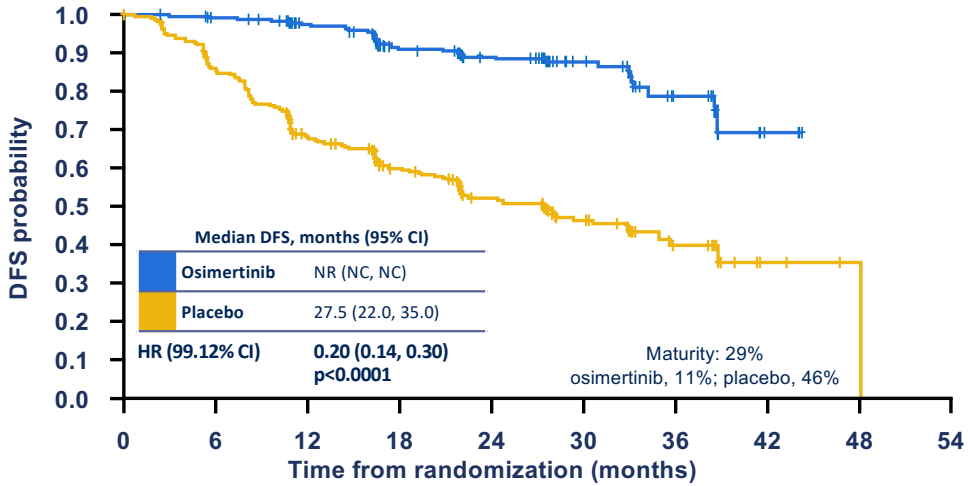
1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38(Suppl 18): abstract / oral LBA5
*At the time of recruitment, staging was determined by the AJCC / UICC Staging Manual 7th edition. Patients with stage IB disease were not eligible in Japan. †Pre-operative, post-operative, or planned radiotherapy was not allowed.
‡Centrally confirmed in tissue. §Patients received a CT scan after resection and within 28 days prior to treatment.
AJCC, American Joint Committee on Cancer; CT, computerized tomography; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival; UICC, Union for International Cancer Control; WHO, World Health Organization

Adjuvant osimertinib has significantly improved DFS

- Adjuvant osimertinib demonstrated highly statistically significant[1,2] and clinically meaningful improvement in DFS in completely resected EGFRm NSCLC vs placebo in both the primary (stage II−IIIA) and overall (IB−IIIA) populations, along with a tolerable safety profile[1–4]

ADAURA primary DFS analysis[1,2] (stage IB−IIIA)*

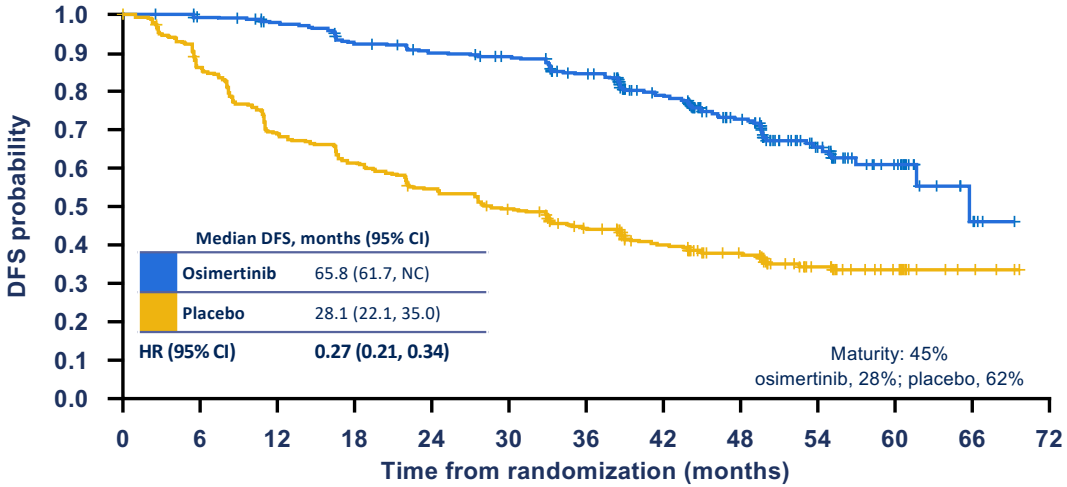
NEJM October 2020



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

ADAURA updated DFS analysis[3,4] (stage IB−IIIA)†

JCO January 2023



No. at risk														
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

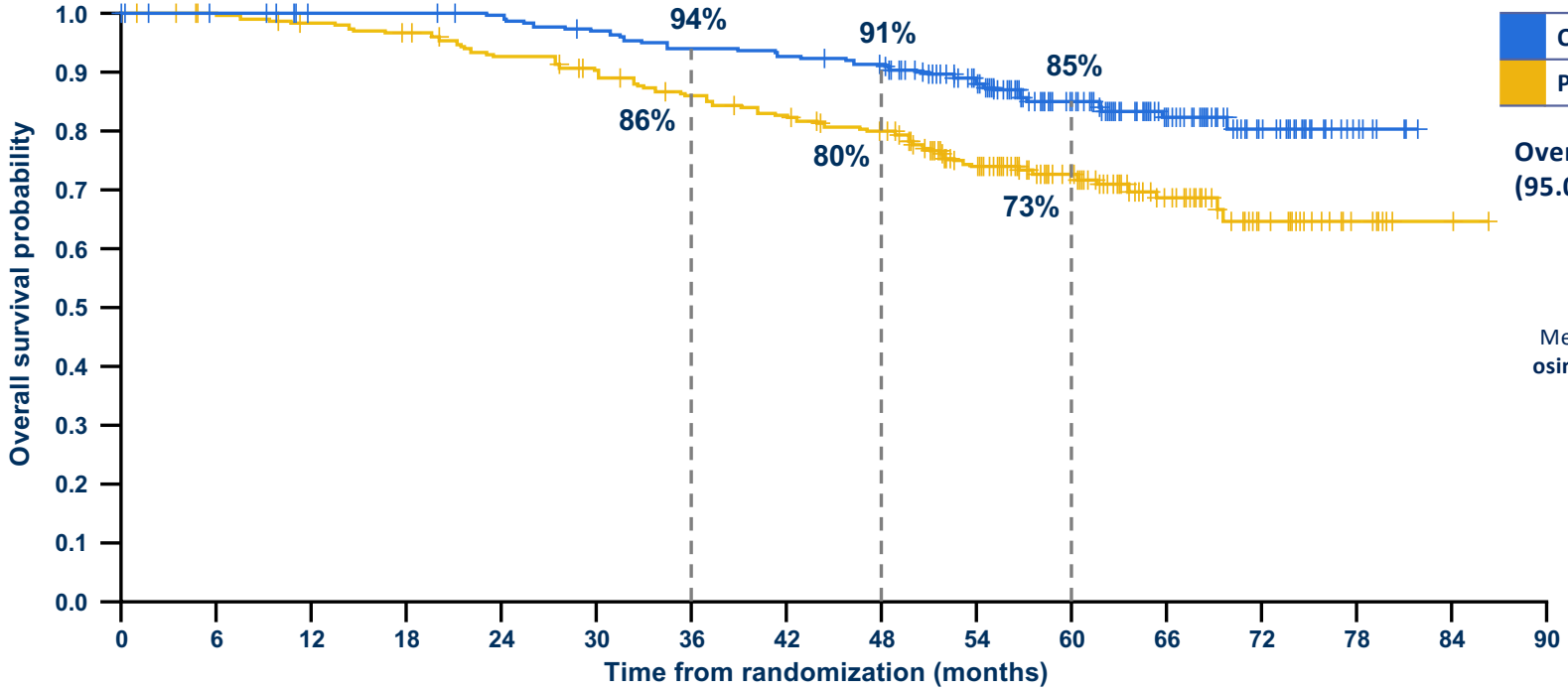
*Data cut-off: January 17, 2020. †Data cut-off: April 11, 2022.

1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38(Suppl 18): abstract / oral LBA5; 3. Herbst et al. J Clin Oncol 2023;41:1830–1840; 4. Tsuboi et al. Ann Oncol 2022;33(Suppl 7): abstract / oral LBA47.

CI, confidence interval; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; HR, hazard ratio; NC, not calculable; NR, not reached; NSCLC, non-small cell lung cancer

ADAURA-Overall survival: patients with stage II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the primary population of stage II−IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)

Overall OS HR (95.03% CI) **0.49 (0.33, 0.73); p=0.0004**

Maturity: 21%
osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
osimertinib 61.7 months, placebo 60.4 months

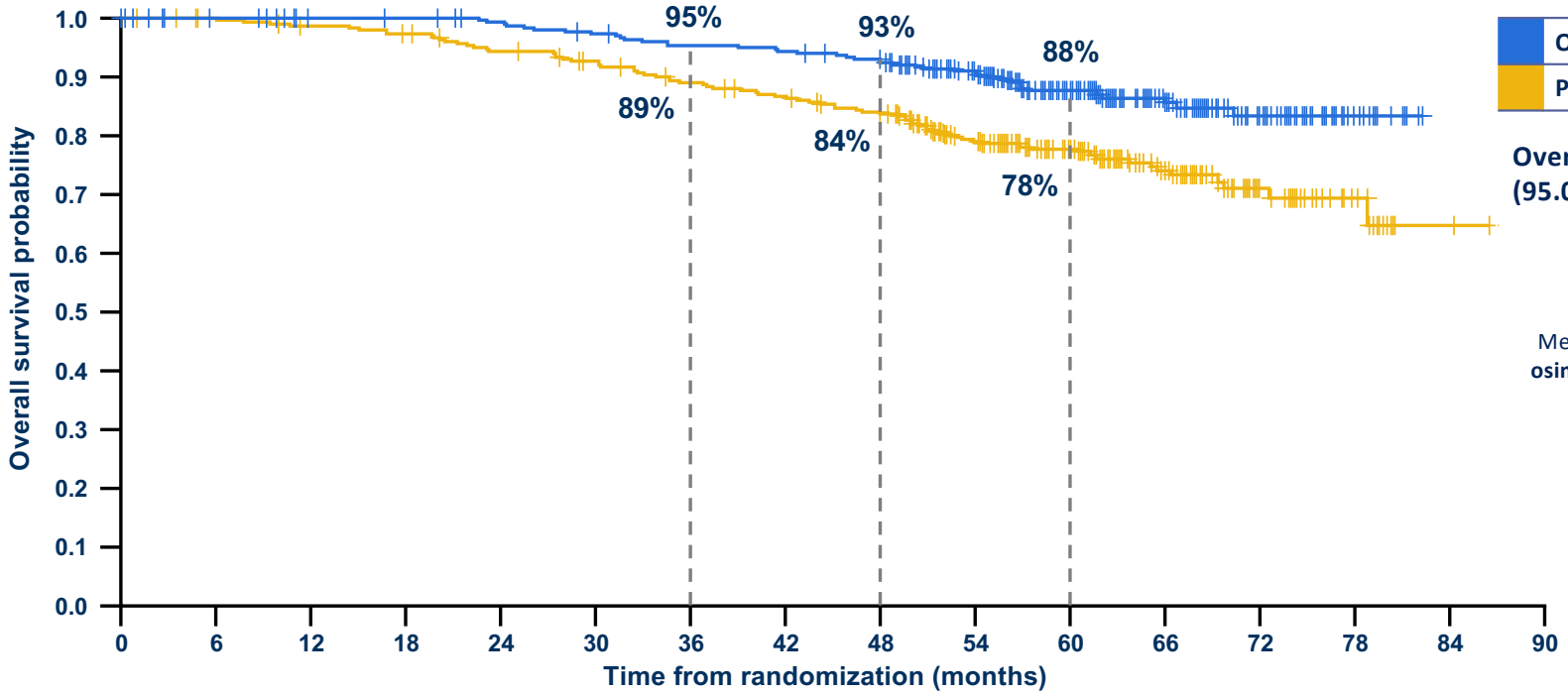
No. at risk

Osimertinib	233	229	224	224	221	214	208	205	200	170	115	69	33	9	0	-
Placebo	237	232	226	221	210	202	190	182	171	138	94	53	25	8	2	0

Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 59.9 months, placebo 56.2 months.
Herbst R, et al. Abstract £LBA3. Presented at ASCO Congress, June 2023, Chicago.
CI, confidence interval; HR, hazard ratio; OS, overall survival

ADAURA-Overall survival: patients with stage IB/II/IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the overall population of stage IB–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI) **0.49 (0.34, 0.70); p<0.0001**

Maturity: 18%
osimertinib 12%, placebo 24%

Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

No. at risk

Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	-
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.

Herbst R, et al. Abstract £LBA3. Presented at ASCO Congress, June 2023, Chicago.

CI, confidence interval; HR, hazard ratio; OS, overall survival

ALINA – Adjuvant ALK TKI*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R 1:1

N=257

Alectinib 600 mg BID 2 years → **Recurrence**

Platinum-based chemotherapy† Q3W; 4 cycles → **Recurrence**

Further treatments at investigator's choice and survival follow-up

Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

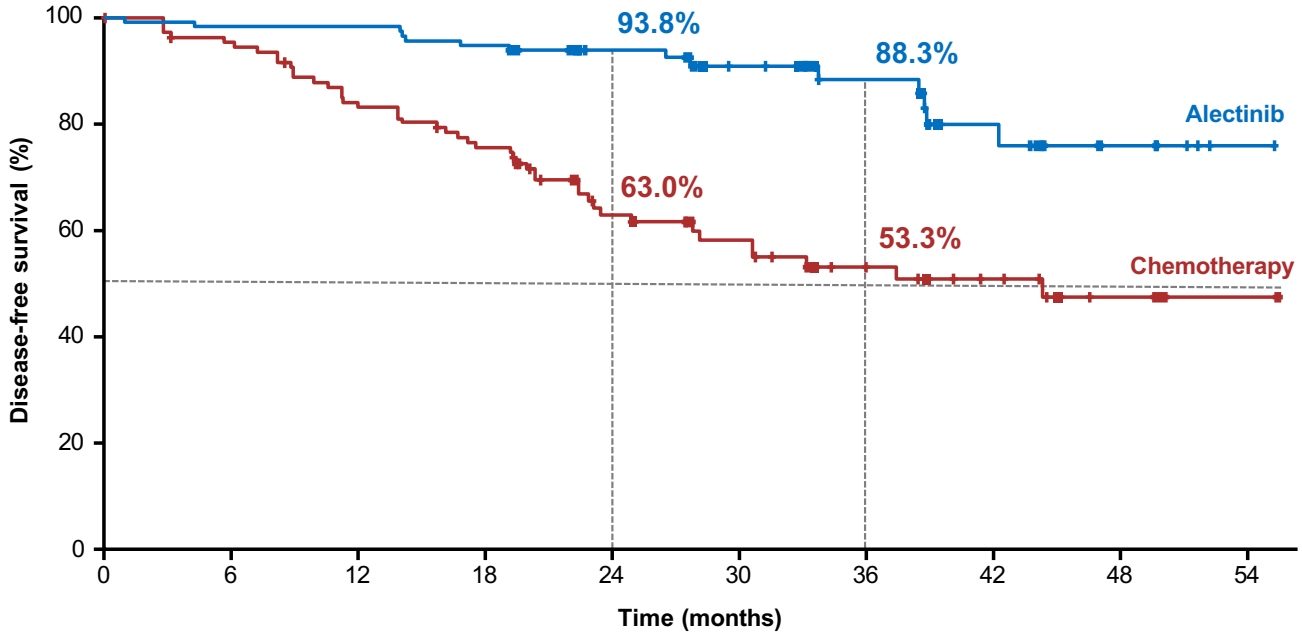
Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

Alectinib is not approved in Vietnam for adjuvant treatment in resected NSCLC patients.

Ben Solomon, presented at ESMO Congress 2023, LBA2

DFS: stage II–IIIA*



No. at risk

Alectinib	116	111	111	107	67	49	35	21	10	3
Chemo	115	102	88	79	48	35	23	17	10	2

	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	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months

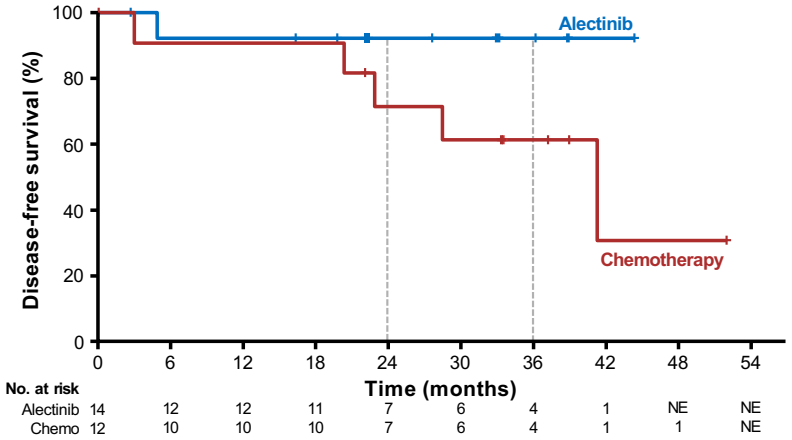
*Per UICC/AJCC 7th edition; †Stratified log rank; DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

Ben Solomon, presented at ESMO Congress 2023, LBA2

Alectinib is not approved in Vietnam for adjuvant treatment in resected NSCLC patients.

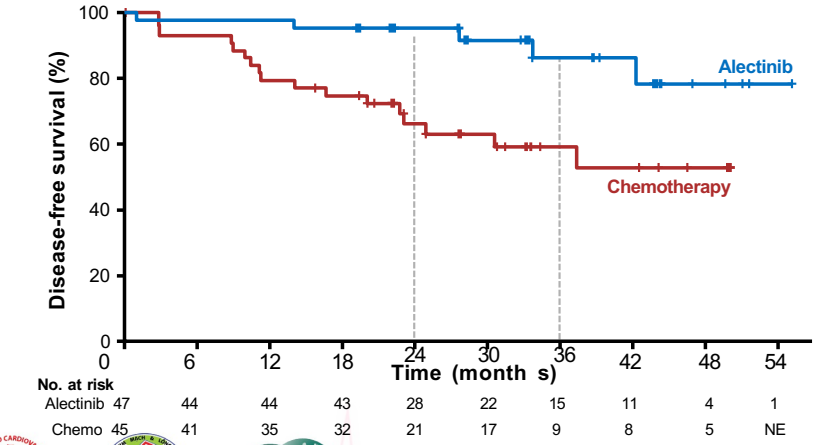
DFS by stage*

Stage IB

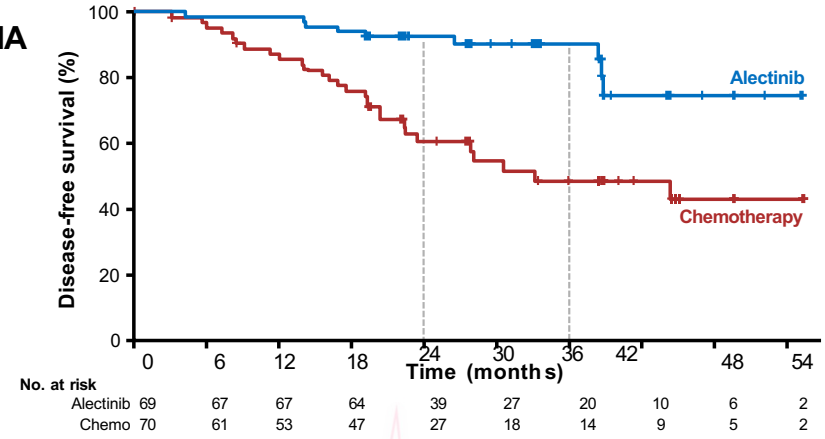


2-year DFS rate, % (95% CI)	Stage IB (n=26)	Stage II (n=92)	Stage IIIA (n=139)
Alectinib	92.3 (77.8, 100.0)	95.6 (89.5, 100.0)	92.7 (86.4, 98.9)
Chemotherapy	71.6 (44.2, 99.0)	66.3 (51.7, 81.0)	60.7 (47.9, 73.5)
HR† (95% CI)	0.21 (0.02, 1.84)	0.24 (0.09, 0.65)	0.25 (0.12, 0.53)

Stage II



Stage IIIA



Data cut-off: 26 June 2023

*Per UICC/AJCC 7th edition; †Unstratified analysis

Alectinib is not approved in Vietnam for adjuvant treatment in resected NSCLC patients.

Ben Solomon, presented at ESMO Congress 2023, LBA2

Adjuvant IO therapy for resectable NSCLC

Positive readout

BR.31[1]	**Resected Stage IB** (≥4 cm) **to IIIA** (AJCC, 7th edition) **With or without adjuvant platinum-based CT**	R, N=1415	**Durvalumab** by IV for 12 months **Placebo** by IV for 12 months	**1EP: DFS in PD-L1 TC ≥25% and *EGFR*-/*ALK*- patients** **2EP: DFS, OS, safety and tolerability, QOL**
✓ **KEYNOTE-091**[2,3] **Recommended regimen in the NCCN guidelines**	**Resected Stage IB** (≥4 cm) **to IIIA** (AJCC, 7th edition) **With or without adjuvant platinum-based CT**	R, N=1177	**Pembrolizumab** Q3W × up to 18 cycles **Placebo** Q3W × up to 18 cycles	**1EP: DFS** **2EP: OS, LCSS**
ANVIL[4]	**Resected Stage IB** (≥4 cm) **to IIIA** (AJCC, 7th edition) **With adjuvant platinum-based CT**	R, N=903	**Nivolumab** Q4W × up to 13 cycles **Observation**	**1EP: DFS, DFS PD-L1 >50%, OS** **2EP: AEs**
✓ **IMpower010**[5,6] **Recommended regimen in the NCCN guidelines**	**Resected Stage IB** (≥4 cm) **to IIIA** (AJCC, 7th edition) **With adjuvant platinum-based CT**	R, N=1280	**Atezolizumab** Q3W × 16 cycles **Observation**	**1EP: DFS** **2EP: OS (ITT population), DFS at 3 and 5 years, DFS (PD-L1 subpopulation), AEs, ATAs, PK**

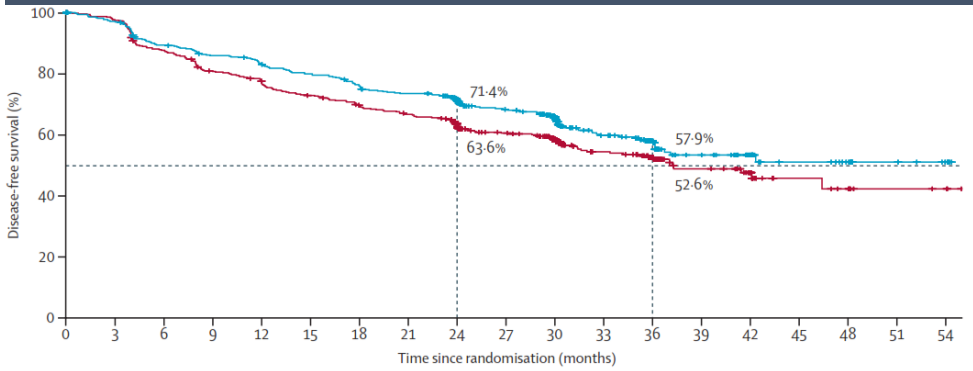
•AE, adverse event; *ALK*, anaplastic lymphoma kinase; AJCC, American Joint Committee on Cancer; ATA, anti-therapeutic antibodies; CT, chemotherapy; DFS, disease-free survival; *EGFR*, epidermal growth factor receptor; EP, end point; IO, immuno-oncology; ITT, intent-to-treat; IV, intravenous; LCSS, Lung Cancer Symptom Scale; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PK, pharmacokinetics; QOL, quality of life; Q3W, every 3 weeks; R, randomisation;
TC, tumour cells

1. NCT02273375. Updated 29 March 2023. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02273375 (Accessed 2 May 2023); 2. NCT02504372.Updated 30 March 2023. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02504372 (Accessed 2 May 2023); 3. O'Brien M, et al. Lancet Oncol 2022;23:1274–1286; 4 NCT02595944. Updated 26 April 2023. Available from: https://clinicaltrials.gov/ct2/show/NCT02595944 (Accessed 2 May 2023); 5. Felip E, et al. Lancet 2021;398:1344–1357; 6. NCT02486718. Updated 2 May 2023. Available from: https://clinicaltrials.gov/ct2/show/NCT02486718 (Accessed 2 May 2023); 6. Felip E, et al. Lancet 2021;398:1344–1357

Note: trial comparisons are for discussion purposes only. As head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and / or make any conclusions as the study design, demographics and other criteria may be different. Nivolumab is not approved in Vietnam. Durvalumab, pembrolizumab is not approved in Vietnam for perioperative treatment in resectable NSCLC patients.

Adjuvant IO - Overall DFS results (Stage IB–IIIA disease)

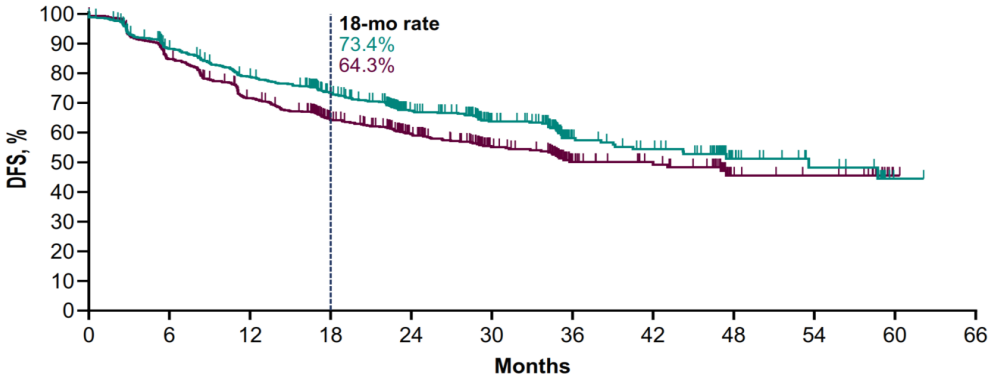
IMpower010[1]



ITT	Atezolizumab	BSC
Median DFS, months (95% CI)	**NE** (36.1, NE)	**37.2** (31.6, NE)
HR (95% CI)	**0.81** (0.67, 0.99)	
P-value	**0.040**	

Stage II-IIIA	Atezolizumab	BSC
Median DFS, months (95% CI)	**42.3** (36.0, NE)	**35.3** (30.4, 46.4)
HR (95% CI)	**0.79** (0.64, 0.96)	
P-value	**0.020**	

KEYNOTE-091[2]



ITT	Pembrolizumab	Placebo
Median DFS, months (95% CI)	**53.6** (39.2, NR)	**42.0** (31.3, NR)
HR (95% CI)	**0.76** (0.63, 0.91)	
P-value	**0.0014**	

Note: trial comparisons are for discussion purposes only. Head-to-head comparisons are not advised, owing to differences in study design, patient population, etc.

SC, best supportive care; CI, confidence interval; DFS, disease-free survival;; HR, hazard ratio; mo, month; NE, not estimable; NR, not reached;

1. Felip E, et al. Lancet 2021;398:1344–1357; 2. Paz-Ares L, et al. Oral presentation at ESMO Virtual Plenary 2022 (Abstract VP3-2022)

Pembrolizumab is not approved in Vietnam for perioperative treatment in resectable NSCLC patients.

Adjuvant treatment has improved long-term outcomes for resectable NSCLC

NCCN-recommended adjuvant treatment following complete resection (R0)[1]

Pathological stage	Recommended adjuvant treatment[1] Test for PD-L1 status, EGFRm, and ALK rearrangement (stages IB–IIIA, IIIB [T3,N2])
Stage IA (N0, no lymph nodes)	Observation
Stage IB (N0, no lymph nodes)	Observation CTX for high-risk patients followed by osimertinib[a]
Stage IIA (N0, no lymph nodes)	Observation CTX for high-risk patients followed by atezolizumab[b,c] or pembrolizumab[d,e] or osimertinib[a]
Stage IIB (N0 / N1 lymph nodes)	CTX followed by atezolizumab[b,c] or pembrolizumab[d,e] or osimertinib[a]
Stage IIIA / IIIB (N1 / N2 lymph nodes)	CTX followed by atezolizumab[b,c] or pembrolizumab[d,e] or osimertinib[a] or sequential CTX and consider radiotherapy

Adjuvant platinum-based combination CTX is associated with ~5% improvement in survival vs observation[2,3]

IMpower010: Atezolizumab improved disease-free survival vs best supportive care after adjuvant CTX in resected Stage II–IIIA NSCLC, especially in patients with PD-L1 >1%[4]

KEYNOTE-091: Pembrolizumab significantly improved disease-free survival vs placebo in completely resected, PD-L1-unselected, Stage IB–IIIA NSCLC[5]

ADAURA: Osimertinib significantly improved disease-free survival vs placebo in patients with resected Stage IB–IIIA, EGFR mutation-positive NSCLC[6]

In addition to these improvements with adjuvant treatment, systemic therapy in the neoadjuvant setting may allow earlier treatment of subclinical micrometastatic disease, further improving long-term outcomes[7]

- [a]Osimertinib for patients with EGFR exon 19 deletion or exon 21 L858R who received previous adjuvant CTX or are ineligible to receive platinum-based CTX; [b]For patients with PD-L1 ≥1% and negative for EGFR exon 19 deletion or exon 21 L858R mutations or ALK rearrangements who received previous adjuvant CTX; [c]Atezolizumab has a different label in the EU: adjuvant treatment after platinum-based CTX in NSCLC with PD-L1 expression ≥50% without EGFR-mutant and ALK+ NSCLC; [d]For patients whose tumours are negative for EGFR exon 19 deletion or exon 21 L858R mutations or ALK rearrangements who received previous adjuvant CTX. The benefit for patients with PD-L1 <1% is unclear; [e]Pembrolizumab is FDA-approved for adjuvant treatment after platinum-based CTX for Stage IB (T2a ≥4 cm), II or IIIA NSCLC; but is not yet EMA approved

1. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed March 2023; 2. IALT Collaborative Group. *N Engl J Med* 2004;350:351–360;
3. Pignon JP, et al. *J Clin Oncol* 2008;26:3552–3559; 4. Felip E, et al. *Lancet* 2021;398:1344–1357; 5. O'Brien M, et al. *Lancet Oncol* 2022;23:1274–1286; 6. Wu Y-L, et al. *N Engl J Med* 2020;383:1711–1723; 7. Bilusic M. *Expert Rev Anticancer Ther* 2022;22:561–573.

17

Pembrolizumab is not approved in Vietnam for perioperative treatment in resectable NSCLC patients.

Neoadjuvant ± adjuvant IO therapy for resectable NSCLC

✓ Positive readout

Trial	Population	Randomisation	Neoadjuvant arms		Adjuvant arms	Endpoints
✓ CheckMate 816[3,4] Recommended regimen in the NCCN guidelines	Stage IB (≥4 cm) to IIIA (T3N2) (AJCC, 7th edition) *EGFR*wt/*ALK*wt	R Open label N=358	Nivolumab + CT Q3W × up to 3 cycles; platinum-based CT alone	SURGERY		1EP: pCR, EFS 2EP: MPR, OS
✓ AEGEAN[1,2]	Stage IIA to IIIB (T3–4N2) (AJCC, 8th edition) *EGFR*wt/*ALK*wt	R N=802	Durvalumab + CT Q3W × 4 cycles; platinum-based Placebo + CT	SURGERY	Durvalumab Q4W × 12 cycles Placebo	1EP: pCR, EFS 2EP: MPR, DFS, OS
✓ KEYNOTE-671[5,6]	Stage II to IIIB (T3–4N2) (AJCC, 8th edition) *EGFR*/*ALK* status not tested	R N=786	Pembrolizumab + CT Q3W × up to 4 cycles; cisplatin-based Placebo + CT	SURGERY	Pembrolizumab Q3W × 13 cycles Placebo	1EP: EFS, OS 2EP: pCR, MPR
IMpower030[7,8]	Stage II to IIIB (T3N2) (AJCC, 8th edition) *EGFR*wt/*ALK*wt	R N=453	Atezolizumab + CT Q3W × 4 cycles; platinum-based Placebo + CT	SURGERY	Atezolizumab Q3W × 16 cycles Best supportive care	1EP: EFS 2EP: pCR, MPR, OS
✓ CheckMate 77T[9-11]	Stage II to IIIB (T3N2) (AJCC, 8th edition) *EGFR*wt/*ALK*wt	R N=452	Nivolumab + CT Q3W × 4 cycles; platinum-based Placebo + CT	SURGERY	Nivolumab Best supportive care	1EP: EFS 2EP: pCR, MPR, OS

- AJCC, American Joint Committee on Cancer; *ALK*, anaplastic lymphoma kinase; CT, chemotherapy; DFS, disease-free survival; EFS, event-free survival; *EGFR*, epidermal growth factor receptor; EP, end point; HLR, high-level readout; IO, immuno-oncology; MPR, major pathological response; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathological complete response;
  Q#W, every #weeks; R, randomisation; wt, wild-type

1. NCT03800134. Updated 18 April 2023. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03800134 (Accessed 2 May 2023); 2. Heymach JV, et al. Clin Lung Cancer 2022;23:e247–e251; 3. NCT02998528. Updated 25 April 2023. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02998528 (Accessed 2 May 2023); 4. Forde PM, et al. N Engl J Med 2022;386:1973–1985; 5. [illegible] Updated 7 April 2023. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03456063 (Accessed 2 May 2023); 8. Peters S, et al. Ann Oncol 2019;30:ii30; 9. NCT04025879. Updated 31 January 2023. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04025879 (Accessed 2 May 2023); 10. Cascone T, et al. J Clin Oncol 2019;3[illegible]; 11. Gray J, et al. Poster presentation at [illegible] 2021; Spring Session (Abstract BR [illegible])

Data includes ongoing clinical trials and is being updated. Note: trial comparisons are for discussion purposes only. As head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and / or make any conclusions as the study design, demographics and other criteria may be different.

Nivolumab is not approved in Vietnam. Durvalumab, pembrolizumab is not approved in Vietnam for perioperative treatment in resectable NSCLC patients. Atezolizumab is not approved in Vietnam for neoadjuvant treatment in resectable NSCLC patients.

ATCSA2023
Ho Chi Minh city, Vietnam

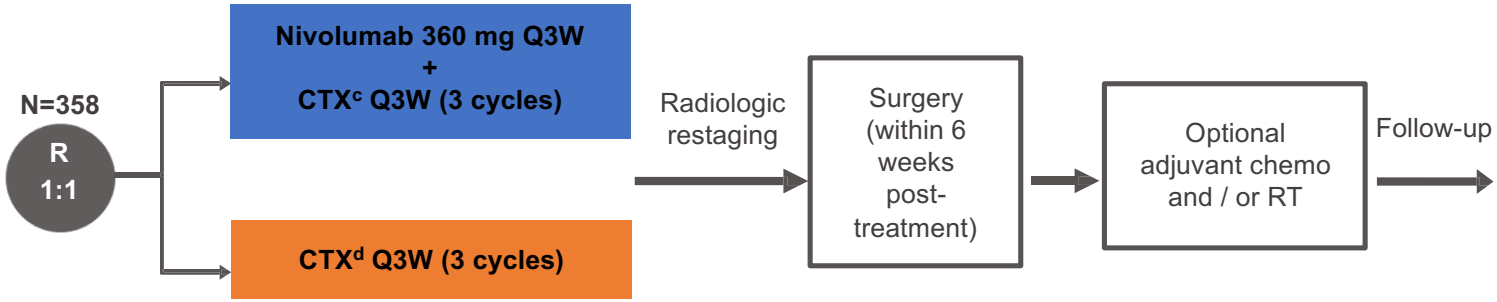
CheckMate 816 – Neoadjuvant IO + CTX

- CheckMate 816 (NCT02998528) is a randomised, open-label Phase 3 study investigating **neoadjuvant nivolumab + CTX vs CTX alone** in patients with resectable NSCLC
- Based on primary analysis data, nivolumab + CTX was approved in the neoadjuvant setting for adult patients with NSCLC (tumours ≥4 cm and / or node positive) in the US; EMA label expected soon

Key eligibility criteria

- Newly diagnosed, resectable, Stage IB (≥4 cm)–IIIA NSCLC (per AJCC TNM 7th edition)
- ECOG PS 0–1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by stage (IB–II vs IIIA), PD-L1[a] (≥1% vs <1%[b]), and sex



Primary endpoints:

- pCR by BIPR
- EFS by BICR

Secondary endpoints:

- MPR by BIPR
- OS
- TTDM

Exploratory analyses:

- EFS by surgical outcomes
- pCR and EFS by 4-gene inflammatory signature score

In this update, 3-year efficacy and safety results from CheckMate 816 were reported, as well as exploratory biomarker analyses

Database lock date: 14 October 2022. Minimum / median follow-up: 32.9 / 41.4 months

[a]Determined by the PD-L1 IHC 28 8 pharmDx assay (Dako); [b]Included patients with PD-L1 expression status not evaluable and indeterminate; [c]Non-squamous: pemetrexed + cisplatin or paclitaxel + carboplatin; squamous: gemcitabine + cisplatin or paclitaxel + carboplatin; [d]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pemetrexed + cisplatin (non-squamous only), or paclitaxel + carboplatin

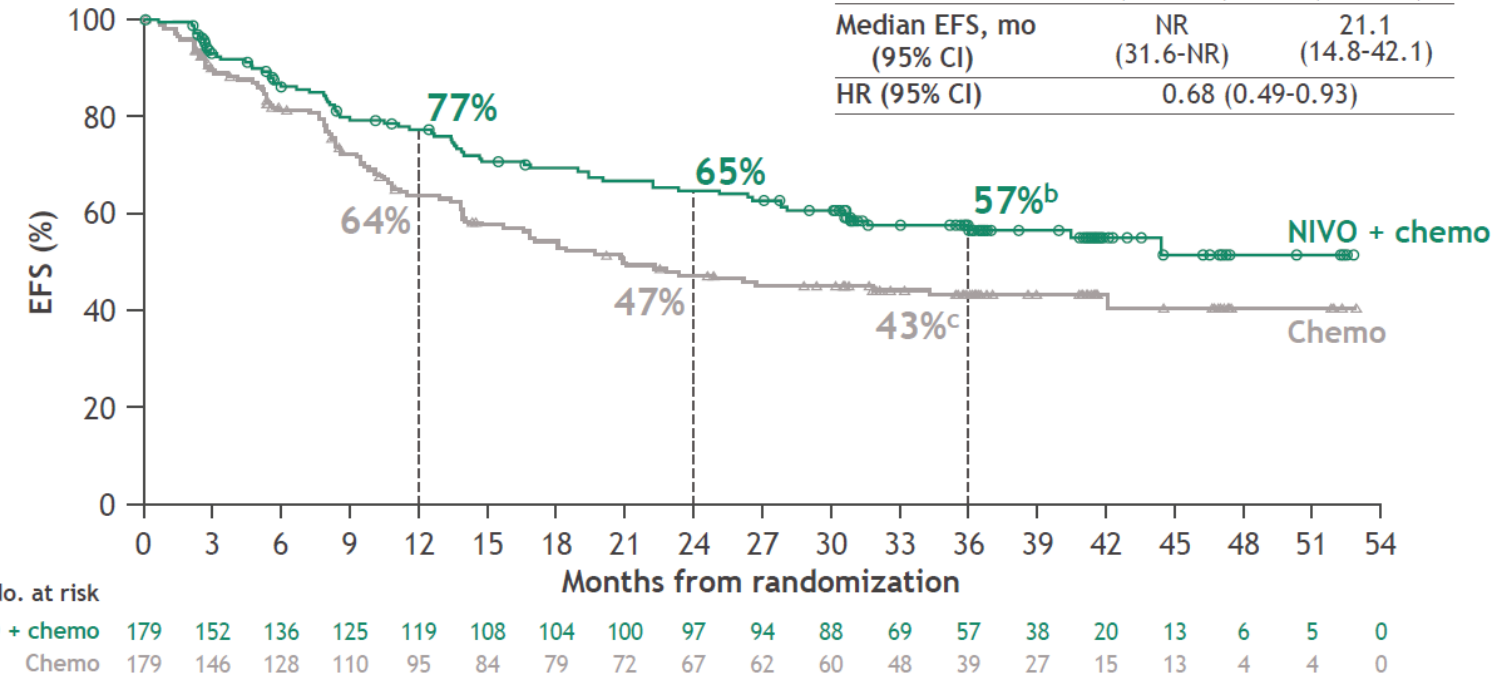
BIPR, blinded independent pathologic review; TTDM, time to distant metastasis or death

Girard N, et al. Oral presentation at: ELCC 2023; 29 March–1 April 2023; Copenhagen, Denmark. Abstract 84O

Nivolumab is not approved in Vietnam.

CHECKMATE 816: 3-year EFS Update

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo (95% CI)	NR (31.6-NR)	21.1 (14.8-42.1)
HR (95% CI)	0.68 (0.49-0.93)	



Minimum/median follow-up: 32.9/41.4 months.

[a]Exploratory analysis. Time from randomization to any disease progression precluding surgery, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause per BICR. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b,c]95% CIs for 3-year EFS rates: [b]48-64; [c]35-51.

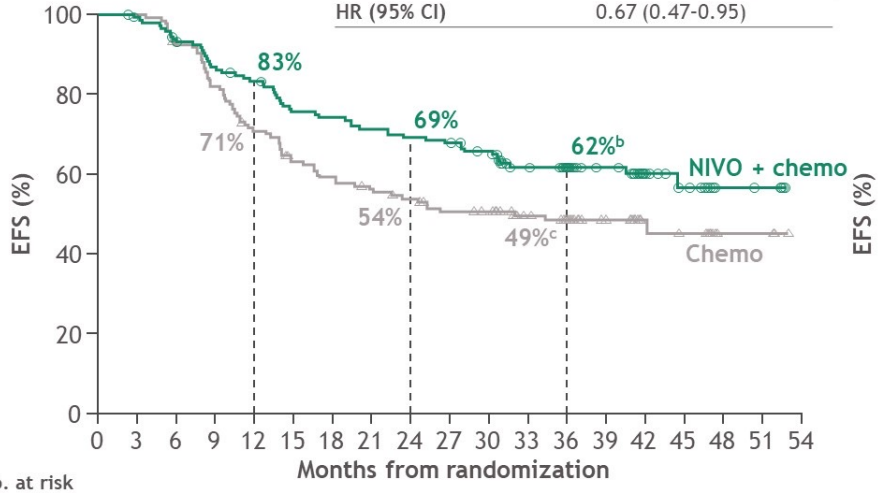
Girard N, et al. Oral presentation at: ELCC 2023; 29, March–1 April 2023; Copenhagen, Denmark. Abstract 84O

Nivolumab is not approved in Vietnam.

CHECKMATE816: 3-year EFS Update
EFS[a] by definitive surgery status

With definitive surgery

	NIVO + chemo (n = 149)	Chemo (n = 135)
Median EFS, mo (95% CI)	NR (44.4-NR)	31.8 (18.0-NR)
HR (95% CI)	0.67 (0.47-0.95)	

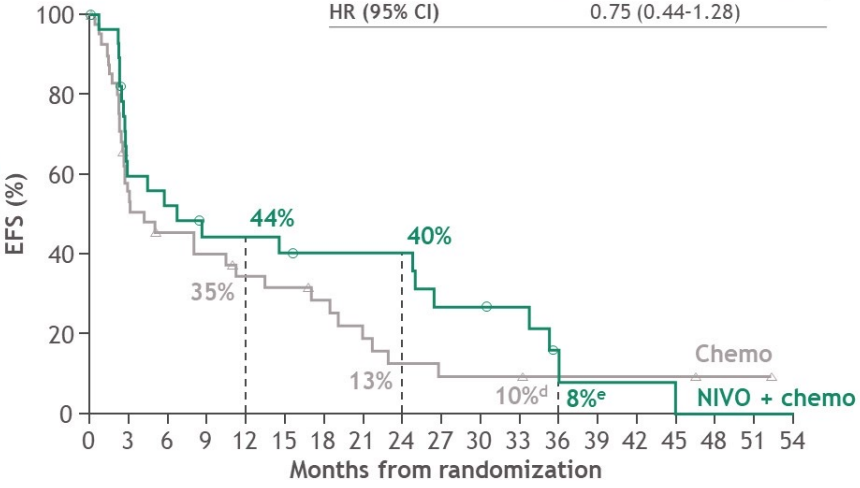


No. at risk

NIVO + chemo	149	146	134	125	119	107	105	101	98	96	90	71	60	40	22	15	7	6	0
Chemo	135	135	125	110	94	82	77	72	68	62	60	48	39	26	14	12	3	3	0

Without definitive surgery

	NIVO + chemo (n = 30)	Chemo (n = 44)
Median EFS, mo (95% CI)	6.7 (2.7-24.9)	4.1 (2.5-11.2)
HR (95% CI)	0.75 (0.44-1.28)	



	30	16	14	11	11	10	9	9	9	6	6	5	1	1	1	0	0	0	0
	44	21	17	15	12	11	9	6	4	3	3	3	2	2	2	2	1	1	0

Minimum/median follow-up, 32.9/41.4 months.

[a]Secondary definition: time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, or death due to any cause; patients receiving subsequent therapy were not censored. [b-e]95% CI: [b]53-69; [c]40-57; [d]2-22; [e]1-28.

Jonathan Spicer, etal. Poster 8521 at: ASCO 2023;

Nivolumab is not approved in Vietnam.

AEGEAN: Neoadjuvant IO + CTX, then adjuvant IO

Study population

- Treatment-naïve
- ECOG PS 0 or 1
- Resectable NSCLC[a] (stage IIA–IIIB[N2]; AJCC 8th edition)
- Lobectomy, sleeve resection, or bilobectomy as planned surgery[a]
- Confirmed PD-L1 status[b]
- No documented *EGFR/ALK* aberrations[a]

N=802 randomized

R 1:1

Randomization stratified by:
- Disease stage (II vs III)
- PD-L1 expression (≥1% vs <1%)

Durvalumab 1500 mg IV + platinum-based CT[c] Q3W for 4 cycles → **Surgery[d]** → **Durvalumab 1500 mg IV** Q4W for 12 cycles

Placebo IV + platinum-based CT[c] Q3W for 4 cycles → **Surgery[d]** → **Placebo IV** Q4W for 12 cycles

Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented EGFR/ALK aberrations[e]

Primary:
- pCR by central lab (per IASLC 2020)
- EFS using BICR (per RECIST v1.1)

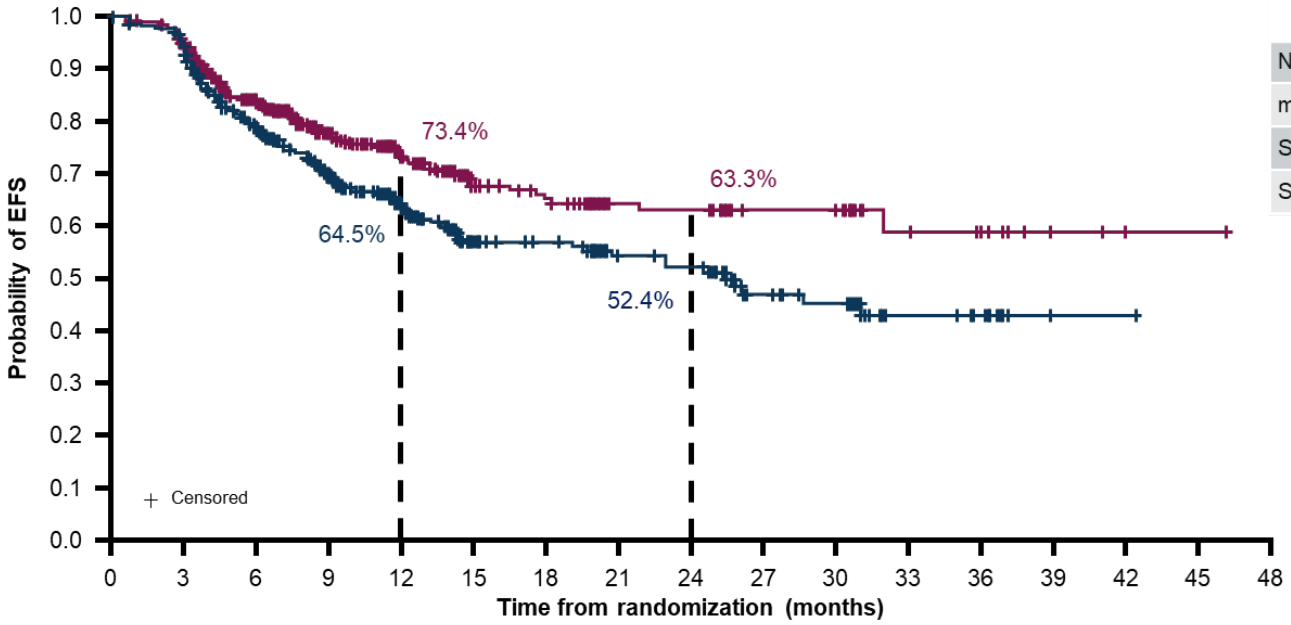
Key secondary:
- MPR by central lab (per IASLC 2020)
- DFS using BICR (per RECIST v1.1)
- OS

[a] The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented *EGFR/ALK* aberrations; [b]Ventana SP263 immunohistochemistry assay; [c]Choice of CT regimen determined by histology and at the investigator's discretion. For non-squamous: cisplatin + pemetrexed or carboplatin + pemetrexed. For squamous: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment); [d]PORT was permitted where indicated per local guidance; [e]All efficacy analyses reported in this presentation were performed on the mITT population, which includes all randomized patients who did not have documented *EGFR/ALK* aberrations.

AJCC = American Joint Committee on Cancer; ALK =anaplastic lymphoma kinase; BICR = blinded independent central review; CT = chemotherapy; DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; EGFR= epidermal growth factor receptor; IASLC = International Association for the Study of Lung Cancer; IV = intravenous; mITT = modified intent-to-treat; MPR = major pathologic response; NSCLC = non-small cell lung cancer; OS = overall survival; pCR, = pathologic complete response; PD-L1 = programmed cell death ligand-1; PORT = post-operative radiotherapy; PS = performance status; Q*W = every * weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1. Heymach JV et al. Presented at AACR; April 14-19, 2023; Orlando, FL.

Durvalumab is not approved in Vietnam for perioperative treatment in resectable NSCLC patients.

EFS by RECIST v1.1 (BICR) (mITT) (First Planned Interim Analysis of EFS)



	D arm	P arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank P-value	0.003902	

Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

No. at risk:

D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

DCO = November 10, 2022.

EFS is defined as time from randomization to the earliest of: (A) PD that precludes surgery; (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; (C) local/distant recurrence using BICR per RECIST v1.1; or (D) death from any cause.

[a]HR <1 favors the durvalumab arm versus the placebo arm. Median and landmark estimates calculated using the Kaplan–Meier method; HR calculated using a stratified Cox proportional hazards model; and *P*-value calculated using a stratified log rank test. Stratification factors: disease stage (II vs III) and PD-L1 expression status (<1% vs ≥1%). Significance boundary = 0.009899 (based on total 5% alpha), calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary.

D = durvalumab; DCO = data cut-off; BICR = blinded independent central review; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; mITT = modified intent-to-treat; NR = not reached; PBO = placebo; PD = progressive disease; PD-L1 = programmed cell death ligand-1; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

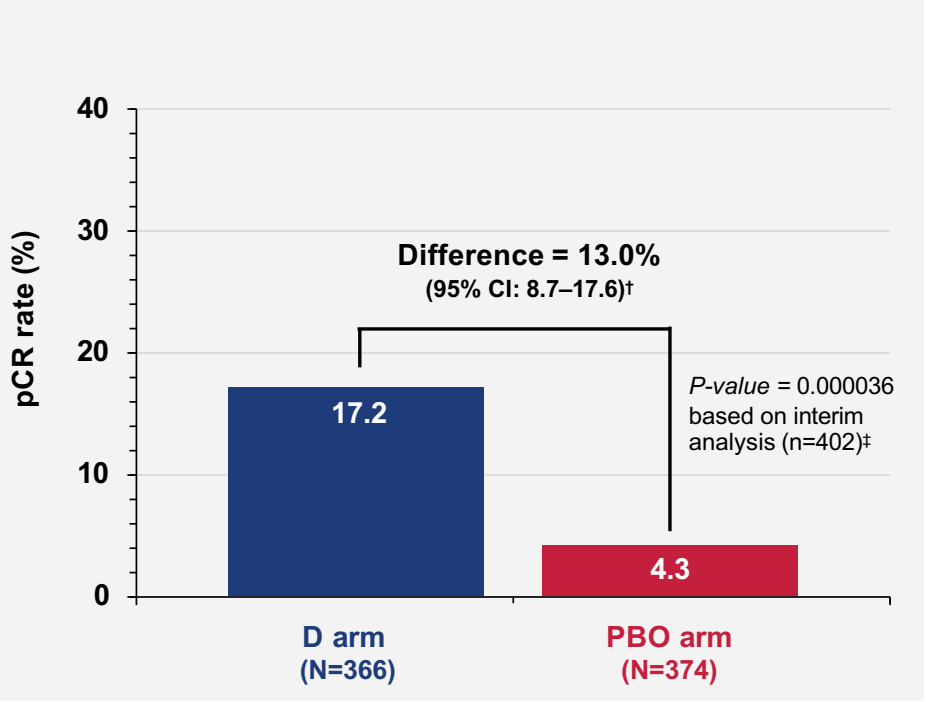
Heymach JV et al. Presented at AACR; April 14-19, 2023; Orlando, FL.

Durvalumab is not approved in Vietnam for perioperative treatment in resectable NSCLC patients.

Pathologic response per IASLC 2020 methodology* (mITT)

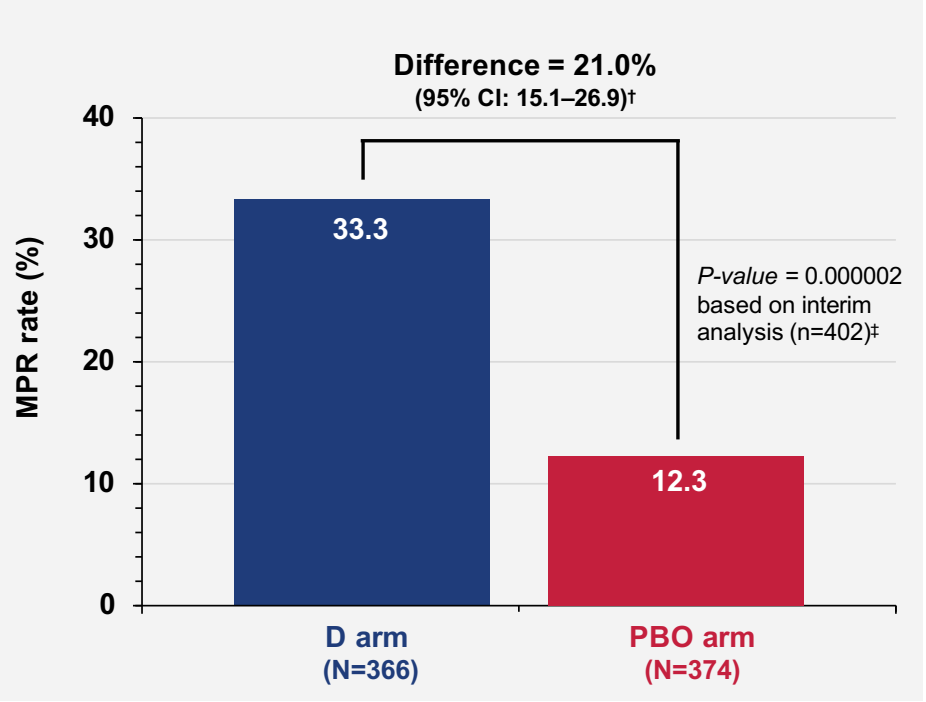
Final analysis

pCR (central lab)



pCR = a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes

MPR (central lab)

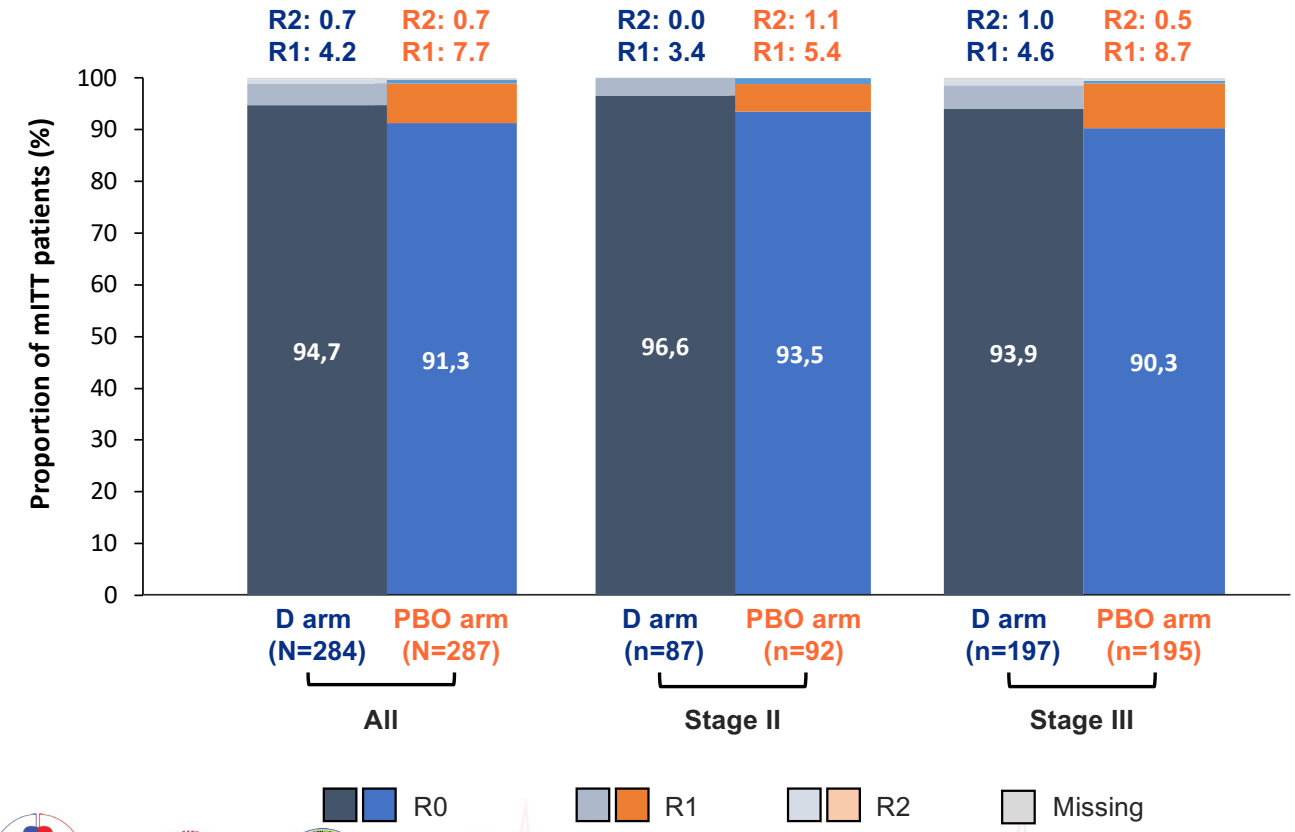


MPR = less than or equal to 10% viable tumor cells in lung primary tumor after complete evaluation of the resected lung cancer specimen

*Using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumor bed (Travis WD, et al. *J Thorac Oncol* 2020;15:709-40). pCR = a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes. MPR = less than or equal to 10% viable tumor cells in lung primary tumor after complete evaluation of the resected lung cancer specimen. To be eligible for pathologic assessment, patients needed to have received three cycles of neoadjuvant study Tx per protocol. Patients who were not evaluable were classified as non-responders. †CIs calculated by stratified Miettinen and Nurminen method. ‡No formal statistical testing was performed at the pCR final analysis (DCO: Nov 10, 2022; n=740 [data shown]). Statistical significance was achieved at the interim pCR analysis (DCO: Jan 14, 2022; n=402; *P*-value for pCR/MPR calculated using a stratified Cochran-Mantel-Haenszel test with a significance boundary = 0.000082 calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary).

Durvalumab is not approved in Vietnam for perioperative treatment in resectable NSCLC patients.

Resection status by disease stage (completed surgery; mITT)



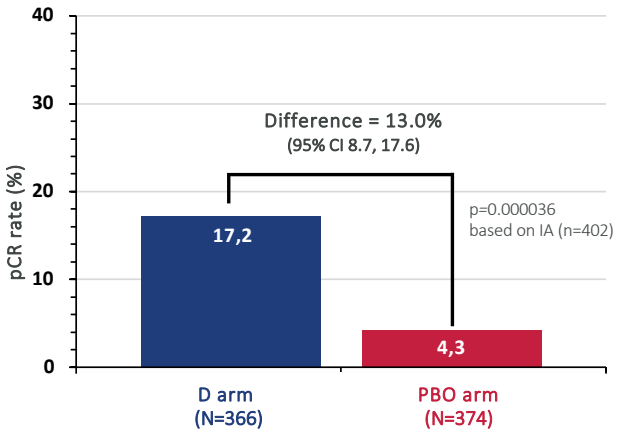
Regardless of disease stage, ***the addition of perioperative durvalumab to neoadjuvant CT did not adversely impact the feasibility, type, approach, or timing of surgery*** in patients with resectable NSCLC and resulted in numerically higher R0 resection rates.

Tetsuya Mitsudomi, et al. Surgical Outcomes with Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab in Resectable NSCLC (ALCHEMIST). Presented at WCLC 2023, OA 12.05

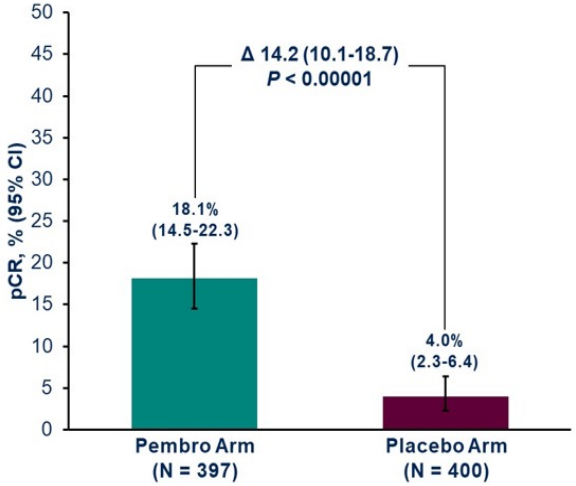
Durvalumab is not approved in Vietnam for perioperative treatment in resectable NSCLC patients.

Perioperative trials pCR – pathological complete response

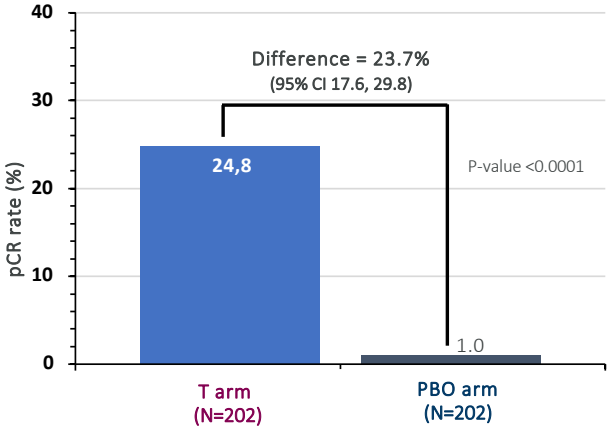
AEGEAN[1]*



KEYNOTE-671[2]*



Neotorch[3]



Data includes ongoing clinical trials and is being updated.
Toripalimab is not approved in Vietnam. Durvalumab, pembrolizumab is not approved in Vietnam for perioperative treatment in resectable NSCLC patients.

Note: trial comparisons are for discussion purposes only. As head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and / or make any conclusions as the study design, demographics and other criteria may be different

*Using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumour bed (Travis WD, et al. *J Thorac Oncol.* 2020;15:709-740). pCR defined as the absence of residual invasive cancer in resected primary tumour and lymph nodes (ypT0 / Tis ypN0)

1. Heymach J, et al. Oral presentation at AACR 2023 (Abstract CT005); 2. Wakelee H, et al. *J Clin Oncol.* 2023;41(Suppl 17):Abstract LBA100; 3. Lu S, et al. *J Clin Oncol.* 2023;41(Suppl 17):Abstract 8501

Role of MDT in resectable NSCLC[1,2]

Multidisciplinary teams make key decisions on treatment strategy

Patients with resectable tumours may have multiple treatment options, including surgery, radiotherapy and systemic therapies

Key functions of the multidisciplinary team:

- Identify which patients are eligible for resection, especially those with stage III disease
- Make decisions on key treatment strategies, including choice of neoadjuvant and adjuvant treatments
- Choose neoadjuvant and adjuvant treatment strategies, considering each patient on a case-by-case basis

Different institutions and countries will have different approaches to the roles and functions of the multidisciplinary team

MDT, multidisciplinary team

1. Postmus PE, et al. Ann Oncol 2017;28(Suppl 4):iv1–iv21; 2. NCCN. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. Version 3.2020. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed April 2020

MDT improved treatment outcomes for patients[1]

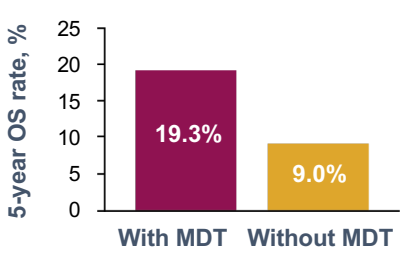
5-year OS is 19.3% in NSCLC patients treated after MDT discussions vs.

9.0% in patients without MDT (p<0.001)[2]

2X

5-YEAR OS RATES

WITH MDT[2]



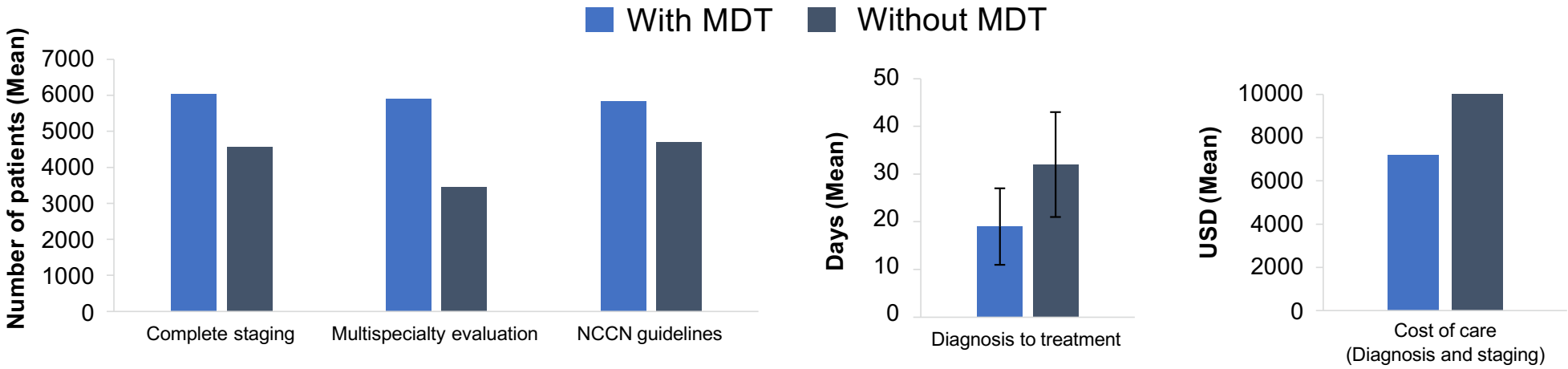
Multidisciplinary team (MDT) with Medical Oncologist, Radiation Oncologist, Radiologist, Surgeon, Pulmonologist and other specialties helps define the most appropriate treatment strategy for patients[3]

1. Denton E, et al. J Multidiscip Healthc. 2016;9:137-144. 2. Bilfinger TV, et al. Clin Lung Cancer. 2018;19(4):346-351. 3. Eberhardt WE, et al. Ann Oncol. 2015;26(8):1573-1588.

Multidisciplinary Team Help Improve Quality of Care and May Reduce Healthcare Costs in Patients With NSCLC

15,731 patients with NSCLC were identified at 49 hospitals in the Premier database[a] and followed for 6 years

Comparison of Patients With and Without MDT (*P*<0.0001)



MDT increased number of patients receiving complete staging, multispecialty evaluation, and adherence to nationally accepted care guidelines

MDT decreased time from diagnosis to treatment as well as facility costs for diagnosis and staging

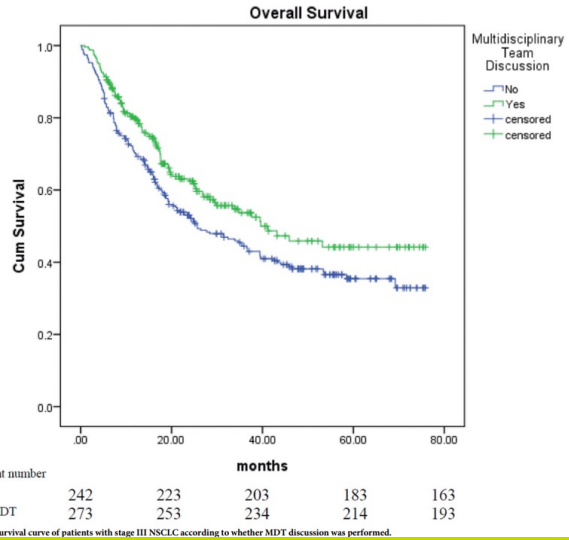
[a]The Premiere database (Premier Inc., Charlotte,NC). NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer. Freeman RK, et al. Ann Thorac Surg. 2015;100:1834-1838.

RESEARCH ARTICLE

Multidisciplinary team discussion results in survival benefit for patients with stage III non-small-cell lung cancer

Hsiu-Ying Hung[1☯], Yen-Han Tseng[2,3☯], Heng-Sheng Chao[2,3], Chao-Hua Chiu[2,3], Wen-Hu Hsu[3,4], Han-Shui Hsu[3,4], Yu-Chung Wu[3,4], Teh-Ying Chou[3,5], Chun-Ku Chen[3,6], Keng-Li Lan[3,7], Yi-Wei Chen[3,7], Yuan-Hung Wu[3,7], Yuh-Min Chen[2,3,8]*

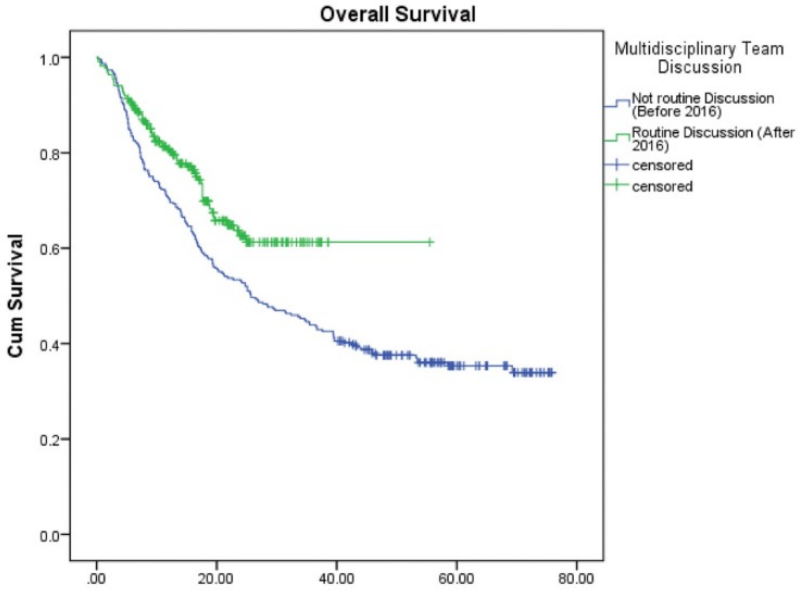
OS benefit of MDT



Patient number					
MDT	242	223	203	183	163
No MDT	273	253	234	214	193

Fig 1. Survival curve of patients with stage III NSCLC according to whether MDT discussion was performed.

Median OS of patients treated with MDT is 41,2 months, vs. 25,7 months of patients treated without MDT (p = 0.018)



Patient number					
Routine Discussion	219	200	180	160	140
Not Routine Discussion	296	165	120	40	0

Fig 2. Survival curve of patients with stage III NSCLC treated before and after February 2016.

Hung H-Y, Tseng Y-H, Chao H-S, Chiu CH, Hsu W-H, Hsu H-S, et al. (2020) Multidisciplinary team discussion results in survival benefit for patients with stage III nonsmall-cell lung cancer. PLoS ONE 15(10): e0236503.
https://doi.org/10.1371/journal. pone.0236503

Conclusions

- Perioperative systemic therapies are rapidly evolved, including adjuvant, neoadjuvant and perioperative treatments.
- Adjuvant NSCLC clinical trials with EGFR-TKI (ADAURA), ALK-TKI (ALINA), IO (IMpower010, KN091) showed improved PFS benefit (and OS with ADAURA).[1-4]
- Neoadjuvant NSCLC clinical trials (CM816) or perioperative trials (AEGEAN, KN671) recently have showed evidences supporting neoadjuvant treatment.[5-7]
- With continuous updates in resectable NSCLC, multidisciplinary team (MDT) plays the important role in decisions of optimized diagnosis and treatment for patients.