Nye systemiske onkologiske behandlinger – kurative / palliative

Peter Meldgaard, overlæge Kræftafdelingen, Aarhus

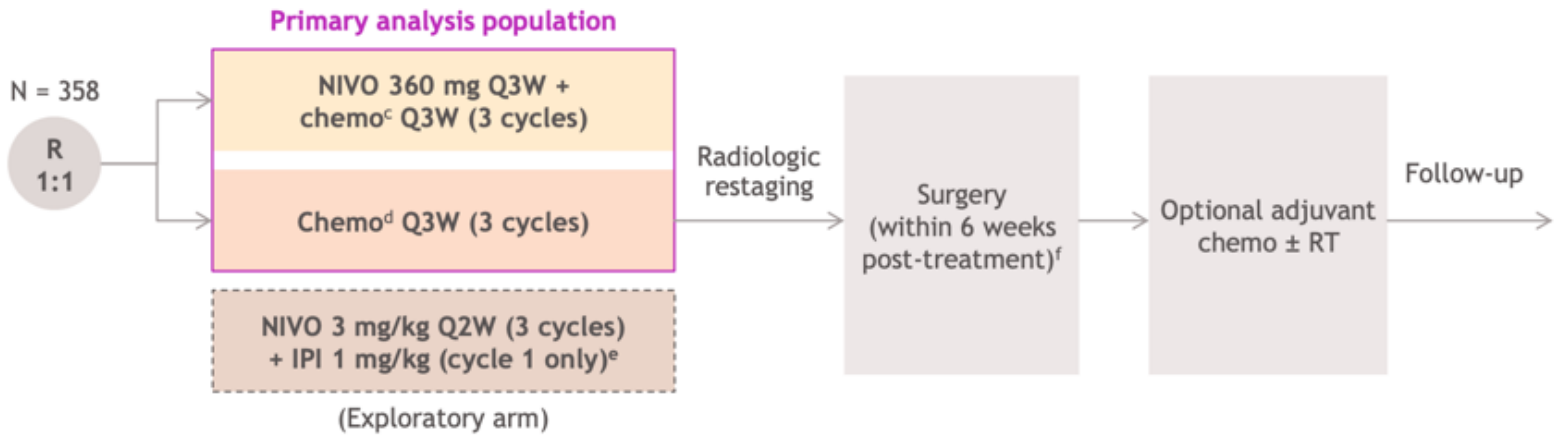
- Præ-operativ behandling
  - Checkmate 816
- Post-operativ behandling
  - ADAURA
- Palliativ behandling
  - IO til mesotheliom

CheckMate 816: Study design

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per 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

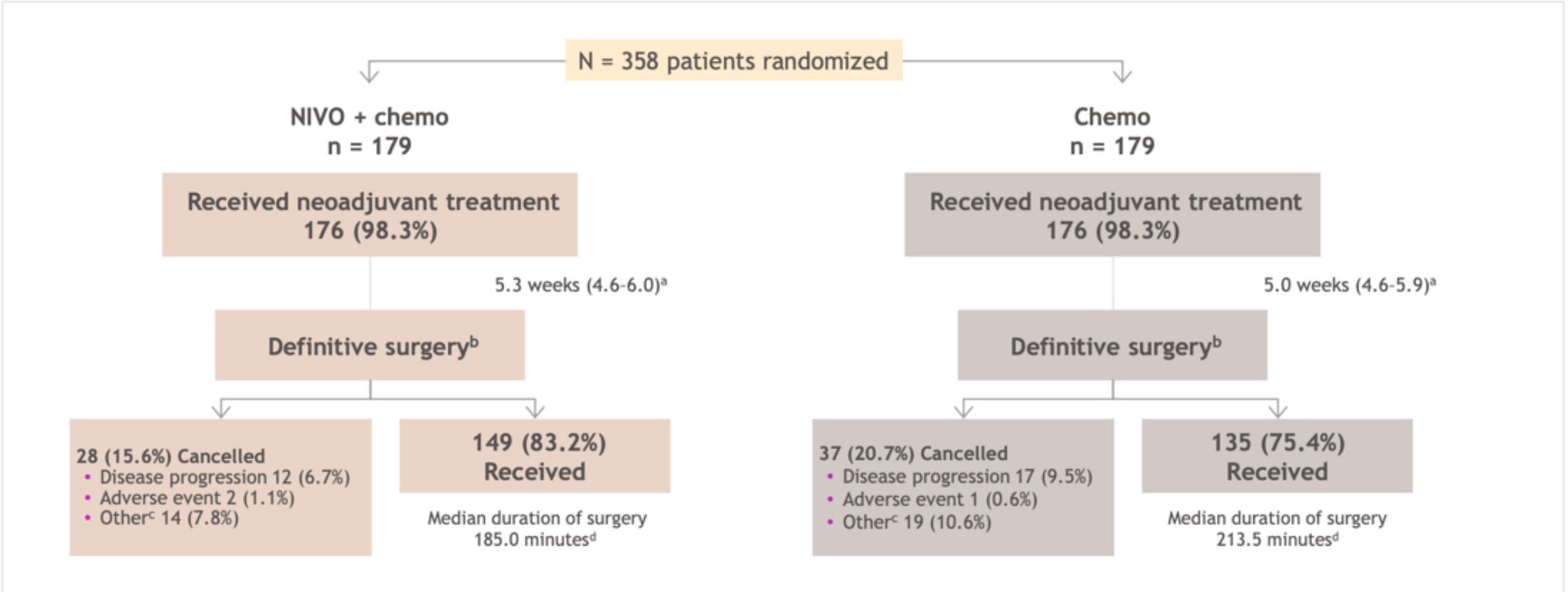
Secondary endpoints
- MPR by BIPR
- OS
- TTDM

Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNAg)
- Feasibility of surgery; peri- and postoperative surgery-related AEs
- Safety

Adapted with permission.

Database locks: September 16, 2020 for pCR, MPR, and radiographic response; October 20, 2021 for EFS, EFS2, and TTDM (minimum/median follow-up, 21 months/29.5 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]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin. [d]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin. [e]Randomized exploratory arm (enrollment closed early). [f]Postoperative assessments with CT with contrast of the chest including the adrenal glands and CT or MRI of other additional suspected/known sites of disease. The first tumor assessment should occur 12 weeks (± 7 days) after definitive surgery per RECIST 1.1 and then should occur every 12 weeks (± 7 days) for 2 years (104 weeks), then every 6 months (24 weeks ± 7 days) for 3 years, and then every year (52 weeks ± 7 days) for 5 years or until disease recurrence or progression confirmed by BICR. [g]Performed using tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring).
AE, adverse event; BICR, blinded independent central review; BIPR, blinded independent pathologic review; chemo, chemotherapy; ctDNA, circulating tumor DNA; EFS, event-free survival; IHC, immunohistochemistry; IPI, ipilimumab; MPR, major pathologic response; NIVO, nivolumab; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed death ligand 1; PS, performance status; R, randomized; RT, radiotherapy; SQ, squamous; TMB, tumor mutational burden; TNM, tumor, node, metastasis; TTDM, time to death or distant metastases.
Forde PM et al. *N Engl J Med.* 2022 Apr 11. doi: 10.1056/NEJMoa2202170. [Online ahead of print].

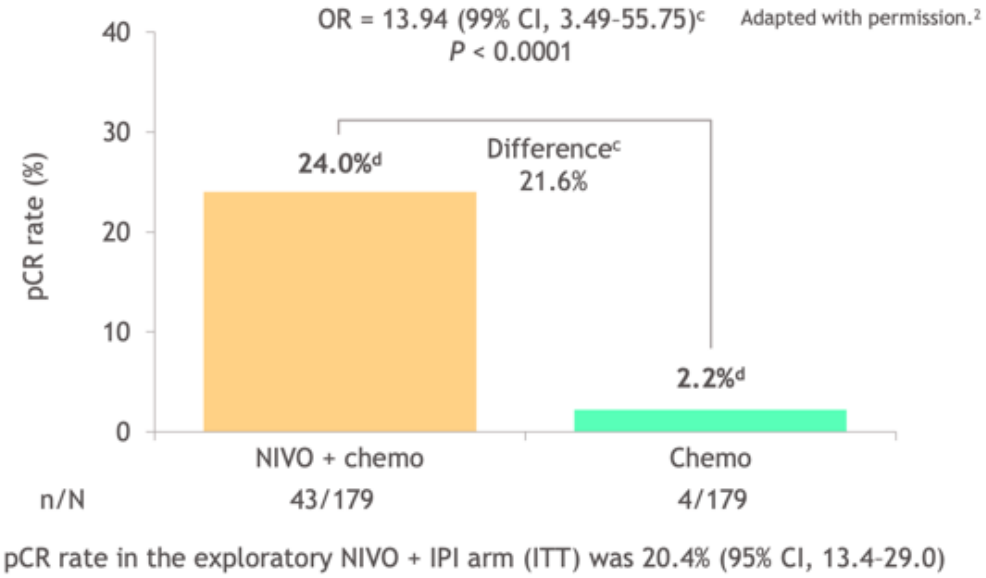
Surgery summary: All randomized patients



[a]Median (IQR) time from last dose to definitive surgery. [b]Definitive surgery was not reported in 2 patients in the NIVO + chemo group and 7 in the chemo group. [c]Other reasons were patient refusal in 9 patients in the NIVO + chemo arm and 8 patients in the chemo arm; consent withdrawal in 3 patients in the chemo arm; COVID-19 in 1 patient in the chemo arm; unfit for surgery due to poor lung function in 2 patients in the NIVO + chemo arm and 4 patients in the chemo arm; and unresectability in 2 patients in each arm. [d]Patients (n) with reported duration of surgery: NIVO + chemo, 122; chemo, 121; IQR for median duration of surgery: NIVO + chemo, 133.0-260.0 minutes; chemo, 150.0-283.0 minutes. | chemo, chemotherapy; IQR, interquartile range; NIVO, nivolumab. | Forde PM et al. N Engl J Med. 2022 Apr 11. doi: 10.1056/NEJMoa2202170. [Online ahead of print].

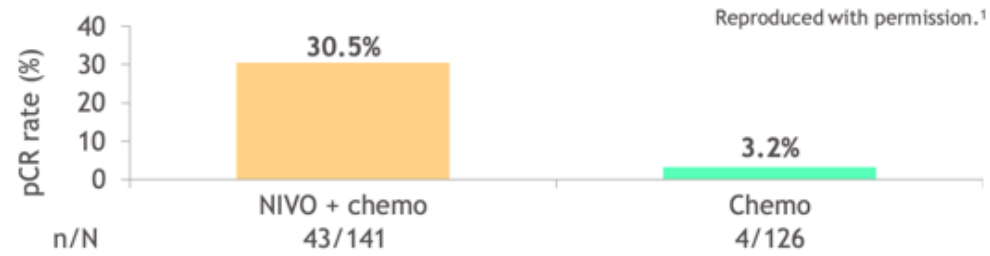
Primary endpoint: pCR[a] rate with neoadjuvant NIVO + chemo vs chemo[1,2]

Primary endpoint: ITT (ypT0N0)[b]

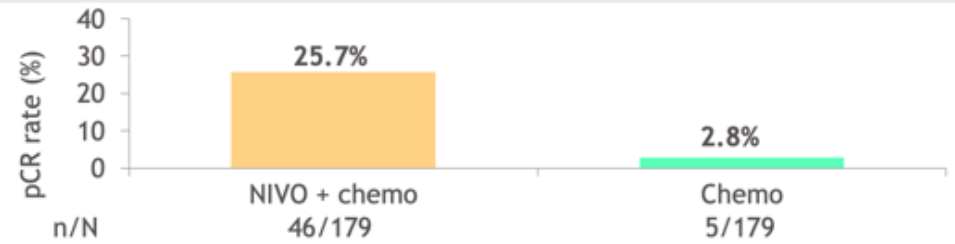


pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4-29.0)

Patients with resection[e] (ypT0N0)



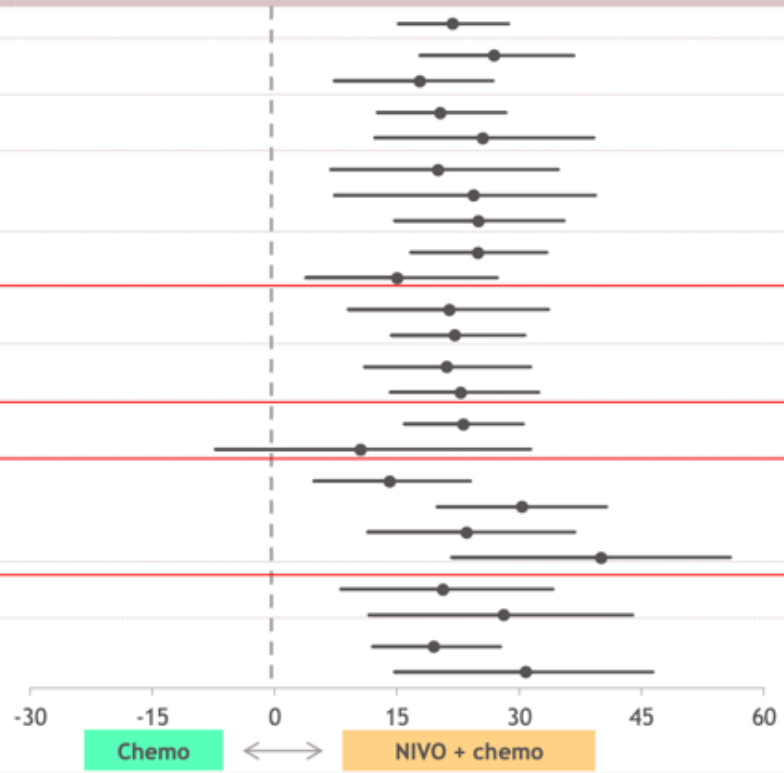
Primary tumor only in ITT (ypT0)



Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.
[a]Per BIPR; pCR: 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes.
[b]ITT principle: patients who did not undergo surgery counted as non-responders for primary analysis. [c]Calculated by stratified Cochran-Mantel-Haenszel method. [d]pCR rates 95% CI: NIVO + chemo, 18.0-31.0; chemo, 0.6-5.6. [e]Patients who underwent definitive surgery with an evaluable pathology sample for BIPR.
BIPR, blinded independent pathologic review; chemo, chemotherapy; IPI, ipilimumab; NIVO, nivolumab; OR, odds ratio; pCR, pathologic complete response; ypT0, no residual viable tumor cells in the primary tumor; ypT0N0, no residual viable tumor cells in primary tumor and lymph node.
1. Forde P et al. Oral presentation at American Association for Cancer Research (AACR) Annual Meeting; April 10-15, 2021; virtual. Abstract CT003. 2. Forde PM et al. *N Engl J Med.* 2022 Apr 11. doi: 10.1056/NEJMoa2202170. [Online ahead of print].

pCR subgroup analysis

	pCR[a] rate, % (95% CI)		Unweighted pCR difference, % (95% CI)	Unweighted pCR difference, % (95% CI)
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	24.0 (18.0-31.0)	2.2 (0.6-5.6)		21.8 (15.2-28.7)
< 65 years (n = 176)	26.9 (18.2-37.1)	0 (0-4.3)		26.9 (17.8-36.7)
≥ 65 years (n = 182)	20.9 (12.9-31.0)	4.2 (1.1-10.3)		17.8 (7.3-26.8)
Male (n = 255)	22.7 (15.7-30.9)	2.4 (0.5-6.7)		20.3 (12.6-28.4)
Female (n = 103)	27.5 (15.9-41.7)	1.9 (< 0.1-10.3)		25.5 (12.3-39.1)
North America (n = 91)	22.0 (10.6-37.6)	2.0 (< 0.1-10.6)		20.0 (6.9-34.8)
Europe (n = 66)	24.4 (12.4-40.3)	0 (0-13.7)		24.4 (7.4-39.3)
Asia (n = 177)	28.2 (19.0-39.0)	3.3 (0.7-9.2)		25.0 (14.7-35.5)
ECOG PS 0 (n = 241)	26.9 (19.1-35.3)	1.7 (0.2-6.0)		24.9 (16.7-33.4)
ECOG PS 1 (n = 117)	18.2 (9.1-30.9)	3.2 (0.4-11.2)		15.0 (3.8-27.3)
Stage IB-II (n = 128)	26.2 (16.0-38.5)	4.8 (1.0-13.3)		21.4 (9.0-33.6)
Stage IIIA (n = 228)	23.0 (15.6-31.9)	0.9 (< 0.1-4.7)		22.1 (14.3-30.7)
Squamous (n = 182)	25.3 (16.6-35.7)	4.2 (1.2-10.4)		21.1 (11.0-31.4)
Non-squamous (n = 176)	22.8 (14.7-32.8)	0 (0-4.3)		22.8 (14.2-32.4)
Current/former smoker (n = 318)	25.6 (19.1-33.1)	2.5 (0.7-6.4)		23.1 (15.9-30.5)
Never smoker (n = 39)	10.5 (1.3-33.1)	0 (0-16.8)		10.5 (-7.3-31.4)
PD-L1 < 1% (n = 155)	16.7 (9.2-26.8)	2.6 (0.3-9.1)		14.1 (4.8-24.0)
PD-L1 ≥ 1% (n = 178)	32.6 (23.0-43.3)	2.2 (0.3-7.9)		30.3 (19.9-40.7)
PD-L1 1-49% (n = 98)	23.5 (12.8-37.5)	0 (0-7.5)		23.5 (11.4-36.8)
PD-L1 ≥ 50% (n = 80)	44.7 (28.6-61.7)	4.8 (0.6-16.2)		40.0 (21.7-55.9)
TMB < 12.3 mut/Mb (n = 102)	22.4 (11.8-36.6)	1.9 (< 0.1-10.1)		20.6 (8.2-34.1)
TMB ≥ 12.3 mut/Mb (n = 76)	30.8 (17.0-47.6)	2.7 (< 0.1-14.2)		28.1 (11.6-43.9)
Cisplatin (n = 258)	21.8 (14.9-30.1)	2.2 (0.5-6.4)		19.5 (12.0-27.7)
Carboplatin (n = 72)	30.8 (17.0-47.6)	0 (0-10.6)		30.8 (14.7-46.4)

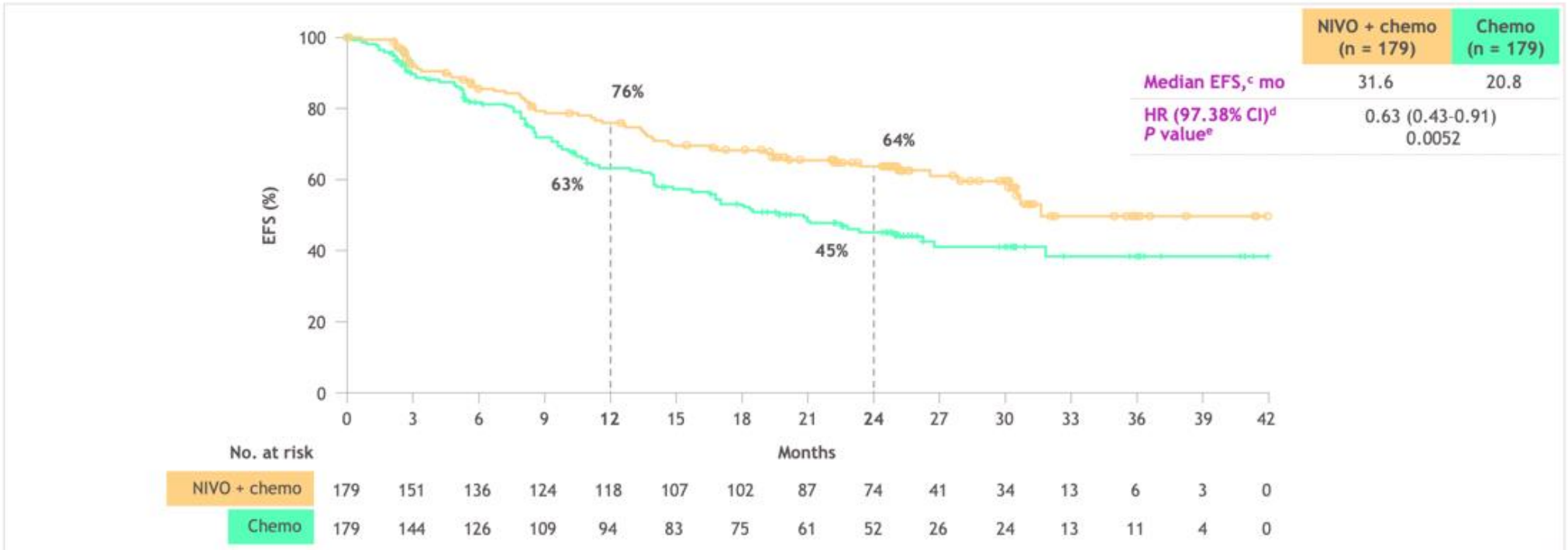


Adapted with permission.

Database lock: September 16, 2020; minimum follow-up: 7.6 mo for NIVO + chemo and chemo arms. [a]Per BIPR in ITT. BIPR, blinded independent pathologic review; chemo, chemotherapy; mut/Mb, mutations per megabase; NIVO, nivolumab; pCR, pathologic complete response; PD-L1, programmed death ligand 1; PS, performance status; TMB, tumor mutational burden.

Forde PM et al. *N Engl J Med*. 2022 Apr 11. doi: 10.1056/NEJMoa2202170. [Online ahead of print].

Primary endpoint: EFS[a,b] with neoadjuvant NIVO + chemo vs chemo



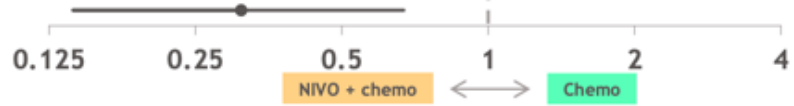
	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS,[c] mo	31.6	20.8
HR (97.38% CI)[d]	0.63 (0.43-0.91)	
P value[e]	0.0052	

Adapted with permission.

Database lock: October 20, 2021; minimum follow-up: 21 months; median follow-up, 29.5 months.
[a]Per BICR. [b]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [c]95% CI = 30.2-NR (NIVO + chemo) and 14.0-26.7 (chemo). [d]95% CI = 0.45-0.87. [e]The significance boundary at this interim analysis was 0.0262.
BICR, blinded independent central review; chemo, chemotherapy; EFS, event-free survival; mo, months; NIVO, nivolumab; NR, not reached.
Forde PM et al. *N Engl J Med*. 2022 Apr 11. doi: 10.1056/NEJMoa2202170. [Online ahead of print].

EFS subgroup analysis

	Median EFS,[a] mo (95% CI)		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	31.6 (30.2-NR)	20.8 (14.0-26.7)		0.63 (0.45-0.87)
< 65 years (n = 176)	NR (31.6-NR)	20.8 (14.0-NR)		0.57 (0.35-0.93)
≥ 65 years (n = 182)	30.2 (23.4-NR)	18.4 (10.6-31.8)		0.70 (0.45-1.08)
Male (n = 255)	30.6 (20.0-NR)	16.9 (13.8-24.9)		0.68 (0.47-0.98)
Female (n = 103)	NR (30.5-NR)	31.8 (13.9-NR)		0.46 (0.22-0.96)
North America (n = 91)	NR (25.1-NR)	NR (12.8-NR)		0.78 (0.38-1.62)
Europe (n = 66)	31.6 (13.4-NR)	21.1 (10.2-NR)		0.80 (0.36-1.77)
Asia (n = 177)	NR (30.2-NR)	16.5 (10.8-22.7)		0.45 (0.29-0.71)
ECOG PS 0 (n = 241)	NR (30.2-NR)	22.7 (16.6-NR)		0.61 (0.41-0.91)
ECOG PS 1 (n = 117)	30.5 (14.6-NR)	14.0 (9.8-26.2)		0.71 (0.41-1.21)
Stage IB-II (n = 127)	NR (27.8-NR)	NR (16.8-NR)		0.87 (0.48-1.56)
Stage IIIA (n = 228)	31.6 (26.6-NR)	15.7 (10.8-22.7)		0.54 (0.37-0.80)
Squamous (n = 182)	30.6 (20.0-NR)	22.7 (11.5-NR)		0.77 (0.49-1.22)
Non-squamous (n = 176)	NR (27.8-NR)	19.6 (13.8-26.2)		0.50 (0.32-0.79)
Current/former smoker (n = 318)	31.6 (30.2-NR)	22.4 (15.7-NR)		0.68 (0.48-0.96)
Never smoker (n = 39)	NR (5.6-NR)	10.4 (7.7-20.8)		0.33 (0.13-0.87)
PD-L1 < 1% (n = 155)	25.1 (14.6-NR)	18.4 (13.9-26.2)		0.85 (0.54-1.32)
PD-L1 ≥ 1% (n = 178)	NR (NR-NR)	21.1 (11.5-NR)		0.41 (0.24-0.70)
PD-L1 1-49% (n = 98)	NR (27.8-NR)	26.7 (11.5-NR)		0.58 (0.30-1.12)
PD-L1 ≥ 50% (n = 80)	NR (NR-NR)	19.6 (8.2-NR)		0.24 (0.10-0.61)
TMB < 12.3 mut/Mb (n = 102)	30.5 (19.4-NR)	26.7 (16.6-NR)		0.86 (0.47-1.57)
TMB ≥ 12.3 mut/Mb (n = 76)	NR (14.8-NR)	22.4 (13.4-NR)		0.69 (0.33-1.46)
Cisplatin (n = 258)	NR (25.1-NR)	20.9 (15.7-NR)		0.71 (0.49-1.03)
Carboplatin (n = 72)	NR (30.5-NR)	10.6 (7.6-26.7)		0.31 (0.14-0.67)

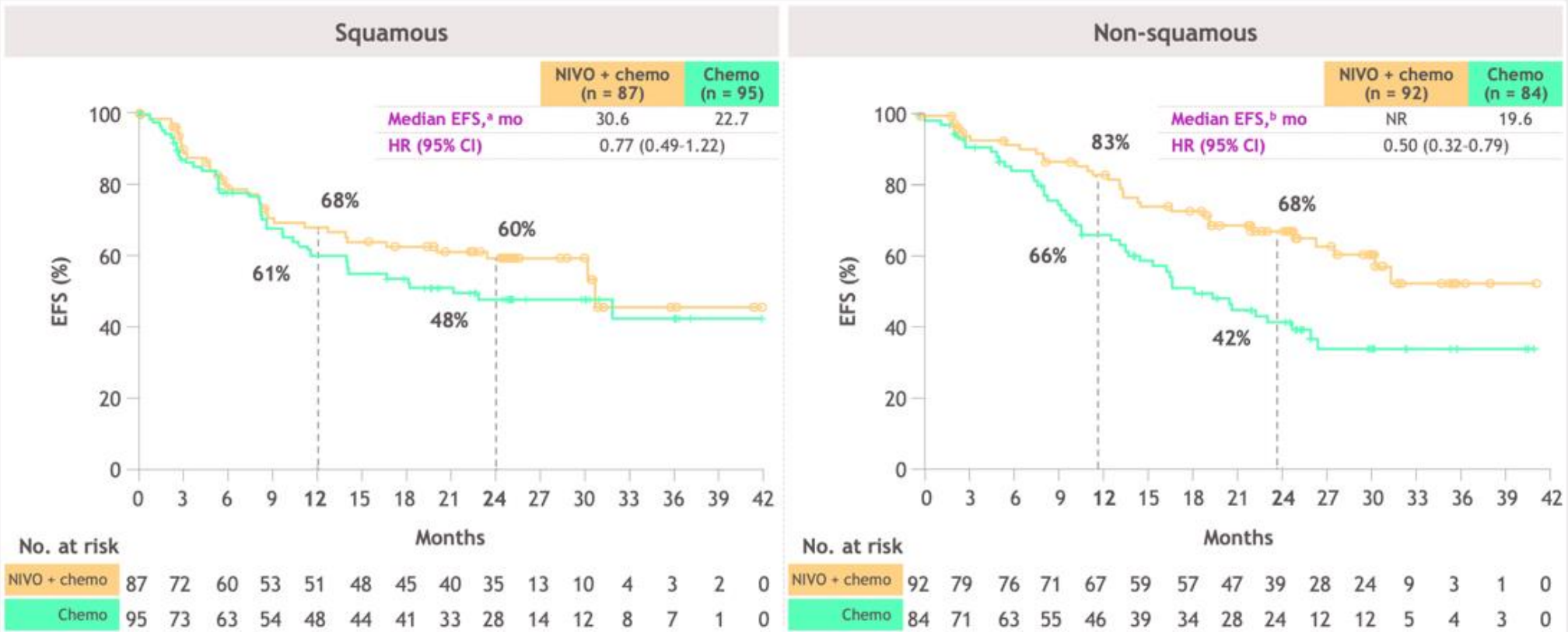


Adapted with permission.

Database lock: October 20, 2021; minimum follow-up: 21 months; median follow-up, 29.5 months. [a]Per BICR. BICR, blinded independent central review; chemo, chemotherapy; EFS, event-free survival; mo, months; mut/Mb, mutations per megabase; NIVO, nivolumab; NR, not reached; PD-L1, programmed death ligand 1; PS, performance status; TMB, tumor mutational burden.

Forde PM et al. *N Engl J Med*. 2022 Apr 11. doi: 10.1056/NEJMoa2202170. [Online ahead of print].

EFS by histology



Database lock: October 20, 2021; minimum follow-up: 21 months; median follow-up, 29.5 months.
[a]95% CI = 20.0-NR (NIVO + chemo) and 11.5-NR (chemo). [b]95% CI = 27.8-NR (NIVO + chemo) and 13.8-26.2 (chemo).
chemo, chemotherapy; EFS, event-free survival; mo, months; NIVO, nivolumab; NR, not reached.
Forde PM et al. *N Engl J Med.* 2022 Apr 11. doi: 10.1056/NEJMoa2202170. [Online ahead of print].

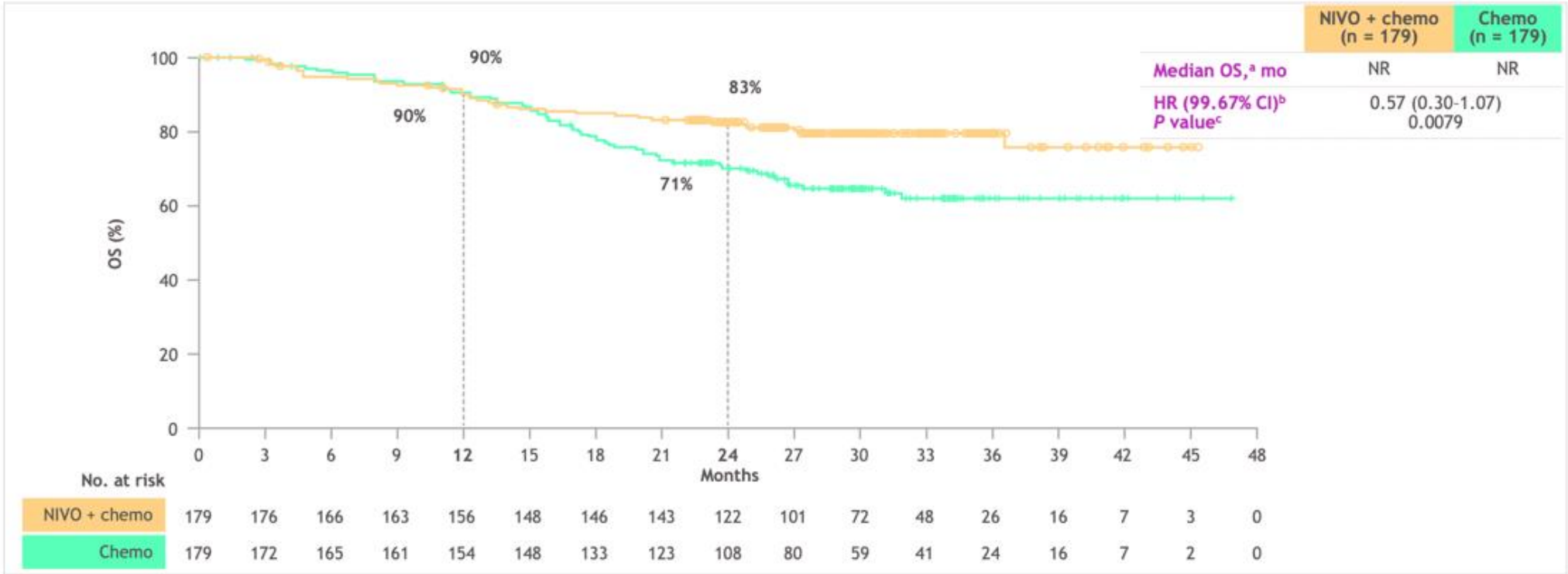
Subsequent therapies

Patients, n (%)	NIVO + chemo (n = 179)	Chemo (n = 179)
Any	38 (21.2)	78 (43.6)
Radiotherapy	20 (11.2)	38 (21.2)
Surgery[a]	3 (1.7)	6 (3.4)
Systemic therapy	31 (17.3)	65 (36.3)
• Chemotherapy	27 (15.1)	40 (22.3)
• Targeted therapy	13 (7.3)	21 (11.7)
• Immunotherapy	10 (5.6)	42 (23.5)
— Pembrolizumab	4 (2.2)	22 (12.3)
— NIVO	2 (1.1)	8 (4.5)
— Atezolizumab	2 (1.1)	8 (4.5)
— Durvalumab	2 (1.1)	6 (3.4)
— Toripalimab	0	1 (0.6)
— Sintilimab	0	1 (0.6)

Adapted with permission

Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if patient never treated), outside of the protocol-specified adjuvant therapy. Patients may have received more than one type of subsequent therapy.
aAny subsequent anticancer (NSCLC) surgery. Most were for palliative reasons or in patients with oligo-metastatic disease; some patients underwent subsequent surgery for the primary tumor.
chemo, chemotherapy; NIVO, nivolumab; NSCLC, non-small cell lung cancer.| Forde PM et al. N Engl J Med. 2022 Apr 11. doi: 10.1056/NEJMoa2202170. [Online ahead of print].

Overall survival: Interim analysis



Adapted with permission.

Database lock: October 20, 2021; minimum follow-up: 21 months; median follow-up, 29.5 months.
[a]95% CI = NR-NR (NIVO + chemo) and NR-NR (chemo). [b]95% CI = 0.38-0.87. [c]Significance boundary for OS (0.0033) was not met at this interim analysis.
chemo, chemotherapy; mo, months; NIVO, nivolumab; NR, not reached; OS, overall survival.
Forde PM et al. *N Engl J Med.* 2022 Apr 11. doi: 10.1056/NEJMoa2202170. [Online ahead of print].

Adverse events summary[1]

Patients (%)	NIVO + chemo (n = 176)		Chemo (n = 176)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
All-cause AEs[a]	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
TRAEs[a]	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Deaths	0		3 (1.7)[b]	
Surgery-related AEs[c,d,e]	62 (41.6)	17 (11.4)	63 (46.7)	20 (14.8)

- NIVO + IPI (n = 111): Any grade and grade 3–4 TRAEs were reported in 65% and 14% of patients, respectively[2]
  - Grade 5 surgery-related AEs occurred in 1 patient (due to septic shock [unrelated to study drug per investigator])

Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms. CTCAE Version 4.0; MedDRA Version: 24.0.

Adapted with permission.

aIncludes events reported between first neoadjuvant dose and 30 days after last dose of neoadjuvant therapy. bTreatment-related deaths in the chemo arm were due to pancytopenia, diarrhea, acute kidney injury (all in 1 patient), enterocolitis, and pneumonia. cDenominator based on patients who underwent definitive surgery (n = 149 in the NIVO + chemo arm, n = 135 in the chemo arm). dIncludes events reported up to 90 days after definitive surgery. eGrade 5 surgery-related AEs (defined as events that led to death within 24 hours of AE onset) were reported in 2 patients in the NIVO + chemo arm and were deemed unrelated to study drug per investigator (1 each due to pulmonary embolism and aortic rupture). AE, adverse event; chemo, chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NIVO, nivolumab; TRAE, treatment-related adverse event.

1. Forde PM et al. N Engl J Med. 2022 Apr 11. doi: 10.1056/NEJMoa2202170. [Online ahead of print]. 2. Forde P et al. Oral presentation at American Association for Cancer Research (AACR) Annual Meeting; April 10-15, 2021; virtual. Abstract CT003.

Summary

- Prognosis of patients with non-metastatic disease remains not satisfying
- While immuno-oncology is well established in the metastatic NSCLC setting, patients with resectable disease had historically few options
- The biological rationale for use of immuno-oncology in the resectable NSCLC setting has resulted in extensive clinical programs across the industry
- In CheckMate 816, the first phase III clinical trial involving immunotherapy in the neoadjuvant setting of NSCLC, nivolumab + chemo demonstrated a statistically significant improvement in pCR and EFS compared with chemo alone
  - Although OS is still immature, an interim analysis already indicates a positive trend
- Immunotherapies such as atezolizumab and pembrolizumab are being introduced as adjuvant therapy options, with more to come
- Multidisciplinary discussion between medical oncologists, surgeons, radiation oncologists, pulmonologists and pathologists will remain key for appropriate patient management

Praksis i DK

- Historisk har vi givet adjuvant behandling – ikke neo-adjuvant
- Hvordan skal vi forholde os til disse data?

- En opgave for DLCG?

- Post-operativ behandling
  - ADAURA

PHASE III ADAURA STUDY DESIGN

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§
- Max. interval between surgery and randomisation:
  - 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)

Randomisation 1:1 (N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- 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, designed for superiority under the assumed DFS HR of 0.70
- **Key secondary endpoints:** DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life
- **Pre-specified exploratory endpoints:** Patterns of recurrence, time to CNS disease recurrence or death (CNS DFS)

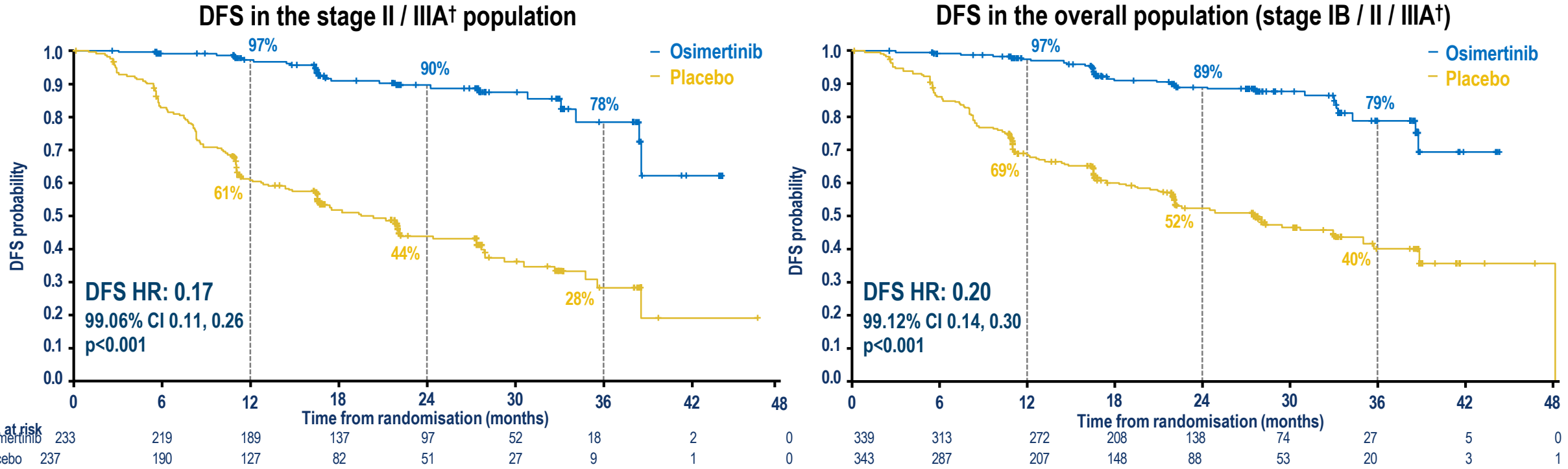
PARIS 2022 ESMO congress

*At the time of recruitment, staging was determined by the AJCC / UICC 7th edition staging manual. †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue. §Patients received a CT scan after resection and within 28 days prior to treatment. ¶Stage IB / II / IIIA.

AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CNS, central nervous system; CT, computerized tomography; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; WHO, World Health Organization

DFS BENEFIT WITH ADJUVANT OSIMERTINIB: ADAURA PRIMARY ANALYSIS

- The ADAURA primary analysis* showed a highly statistically significant and clinically meaningful improvement in DFS with adjuvant osimertinib vs placebo[1,2]



Here we will present an updated analysis of the final DFS data at the protocol-specified maturity of 50%, a pre-specified exploratory analysis of recurrence patterns and updated safety data, after 2 years of further follow up, in which all patients have had the opportunity to receive the full 3 years of adjuvant treatment

PARIS 2022 ESMO congress

Tick marks indicate censored data. *Reported ~2 years earlier than planned following IDMC recommendation. †AJCC / UICC 7th edition staging.

1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38:18_suppl.LBA5.

AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IDMC, Independent Data Monitoring Committee

Data cut-off: January 17, 2020.

BASELINE CHARACTERISTICS (OVERALL POPULATION)

- Demographics and characteristics were generally well balanced between treatment arms
- Proportion of stages was similar when ADAURA patients were re-staged by AJCC / UICC 8th edition staging manual

Characteristics, %	Osimertinib (n=339)	Placebo (n=343)
Sex: male / female	32 / 68	28 / 72
Age: median (range), years	64 (30–86)	62 (31–82)
Smoking history: yes* / no	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
WHO PS: 0 / 1	63 / 37	64 / 36
AJCC / UICC staging at diagnosis (7th edition): IA / IB / II / IIIA / IIIB	0 / 32 / 33 / 35 / 0	0 / 31 / 34 / 35 / 0
AJCC / UICC staging at diagnosis (8th edition)†: IA / IB / II / IIIA / IIIB	1 / 30 / 33 / 32 / 3	<1 / 29 / 35 / 34 / 2
Histology: Adenocarcinoma / other	96 / 4	97 / 3
EGFR mutation at randomisation‡: Ex19del / L858R	55 / 45	55 / 45
Adjuvant chemotherapy: yes / no	60 / 40	60 / 40

PARIS 2022 ESMO congress

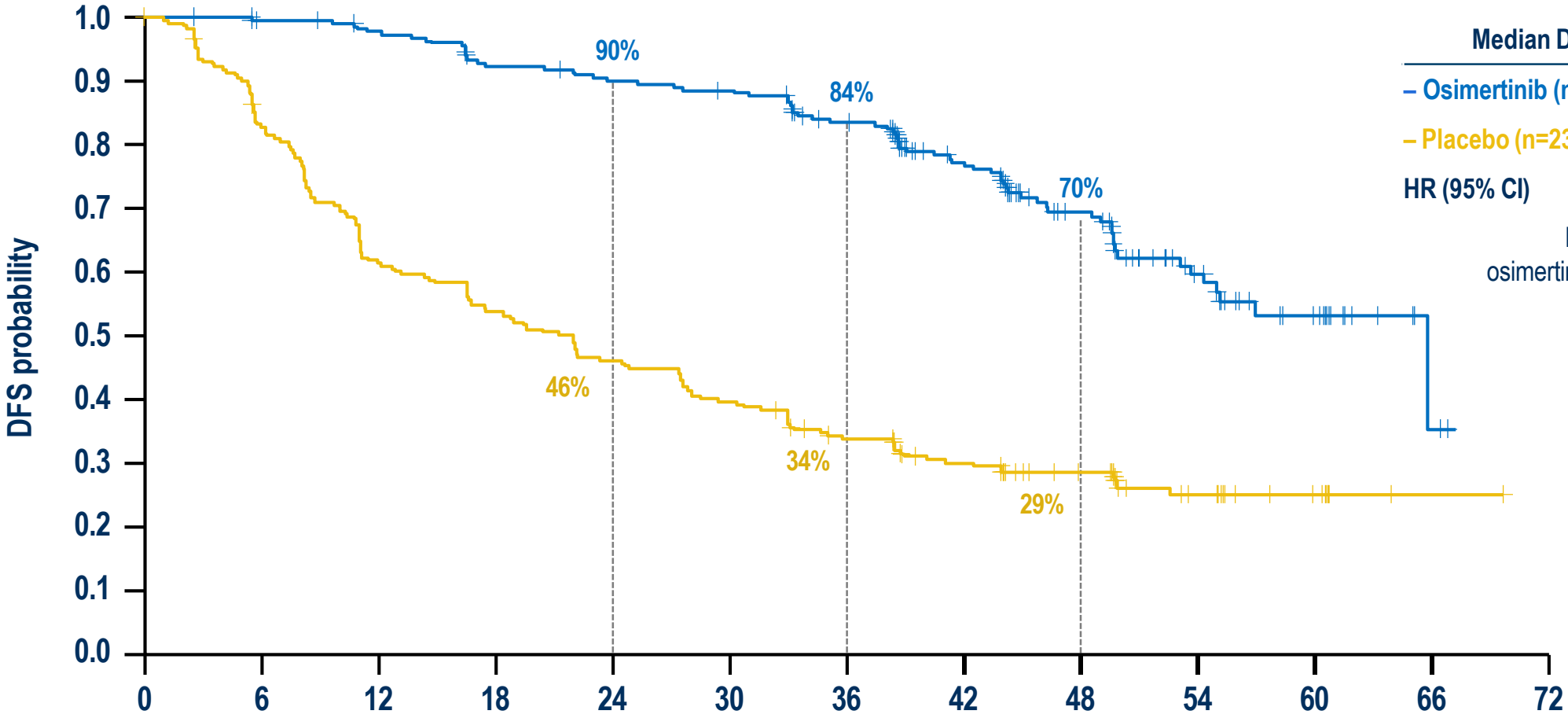
*Formerly: osimertinib n=104 (31%), placebo n=83 (24%); currently: osimertinib n=4 (1%), placebo n=3 (1%). †Disease stage IV: osimertinib n=0, placebo n=1 (<1%); missing: osimertinib n=2 (1%), placebo n=2 (1%). ‡Central test.

1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38:18_suppl.LBA5.

AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; PS, performance status; WHO, World Health Organization

Data cut-off: April 11, 2022.

PRIMARY ENDPOINT: UPDATED DFS IN STAGE II / IIIA DISEASE



Median DFS, months (95% CI)	
– Osimertinib (n=233)	65.8 (54.4, NC)
– Placebo (n=237)	21.9 (16.6, 27.5)
HR (95% CI)	**0.23 (0.18, 0.30)**

Maturity:* 51%
osimertinib 32%, placebo 70%

No. at risk

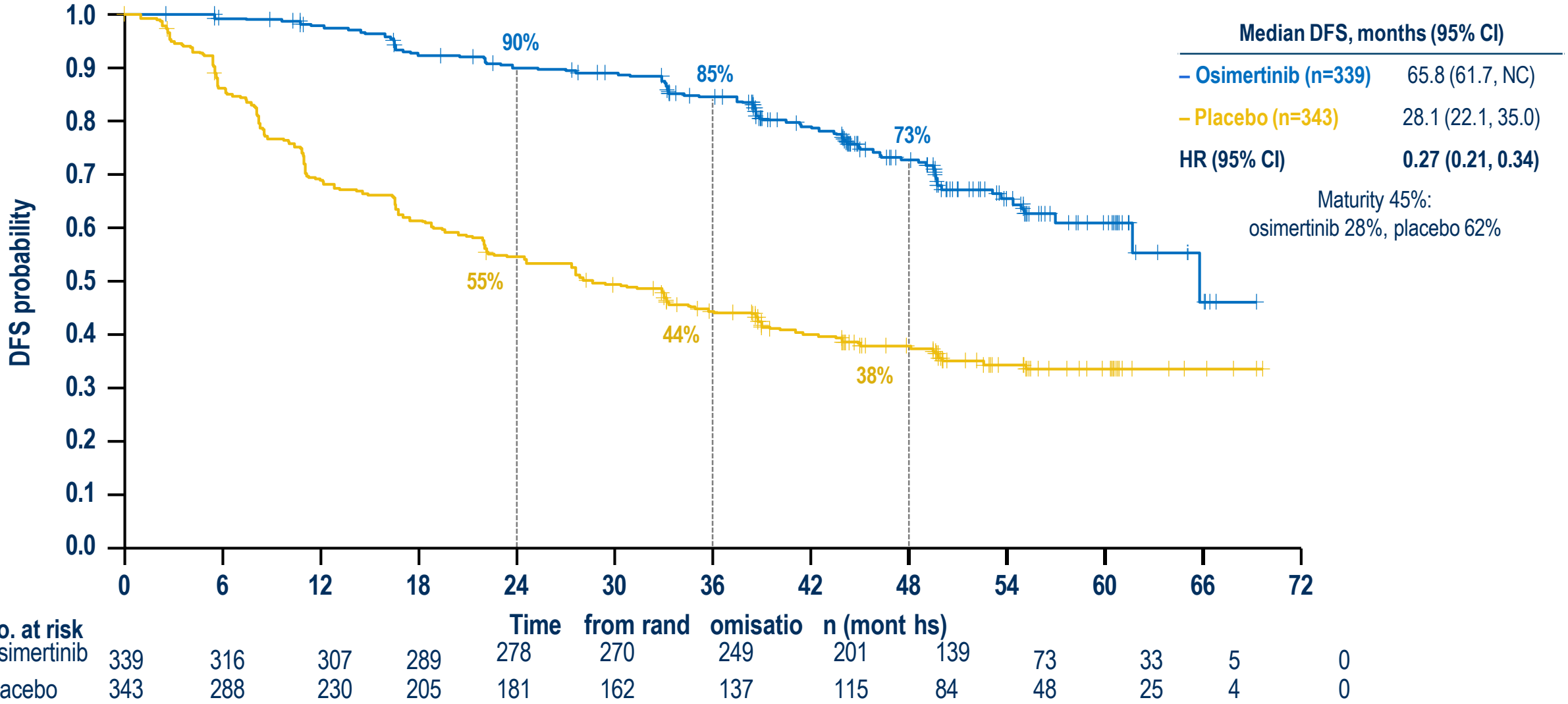
Osimertinib	233	222	216	202	196	192	174	138	90	45	20	2	0
Placebo	237	191	141	124	106	91	74	61	41	23	11	1	0

PARIS 2022 ESMO congress

Median follow-up: osimertinib 44.2 months (range 0 to 67), placebo 19.6 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data. *Planned maturity for DFS analysis: 50%.
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable

Data cut-off: April 11, 2022.

UPDATED DFS IN THE OVERALL POPULATION (STAGE IB / II / IIIA DISEASE)



Median DFS, months (95% CI)	
– Osimertinib (n=339)	65.8 (61.7, NC)
– Placebo (n=343)	28.1 (22.1, 35.0)
HR (95% CI)	**0.27 (0.21, 0.34)**

Maturity 45%:
osimertinib 28%, placebo 62%

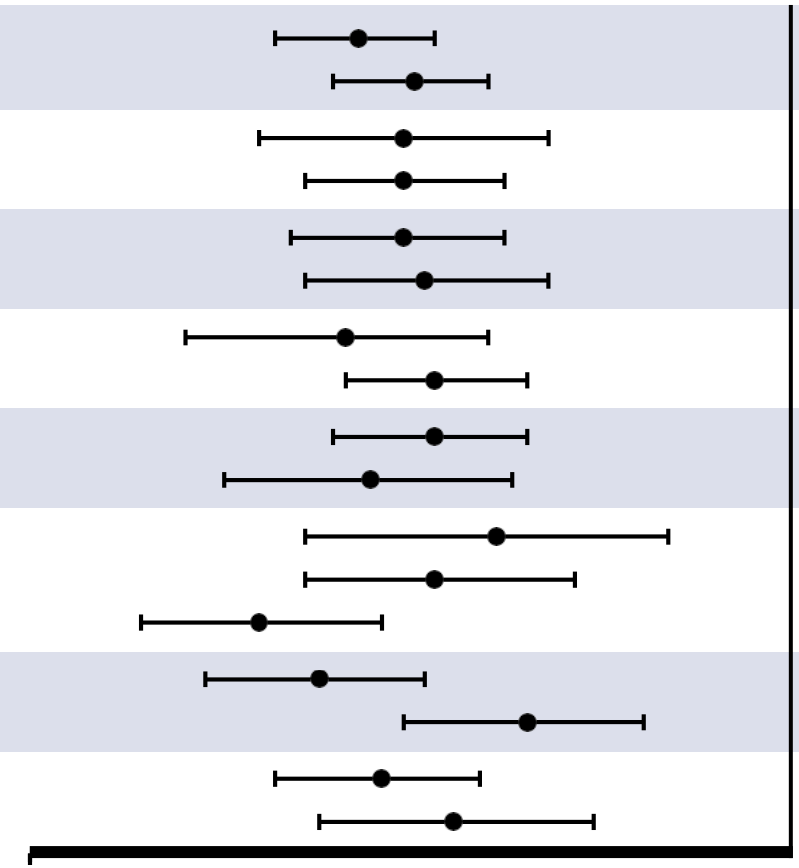
PARIS 2022 ESMO congress

Median follow-up: osimertinib 44.2 months (range 0 to 69), placebo 27.7 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data.
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable
Data cut-off: April 11, 2022.

UPDATED DFS ACROSS SUBGROUPS IN THE OVERALL POPULATION

- A DFS benefit with osimertinib was observed across all predefined subgroups

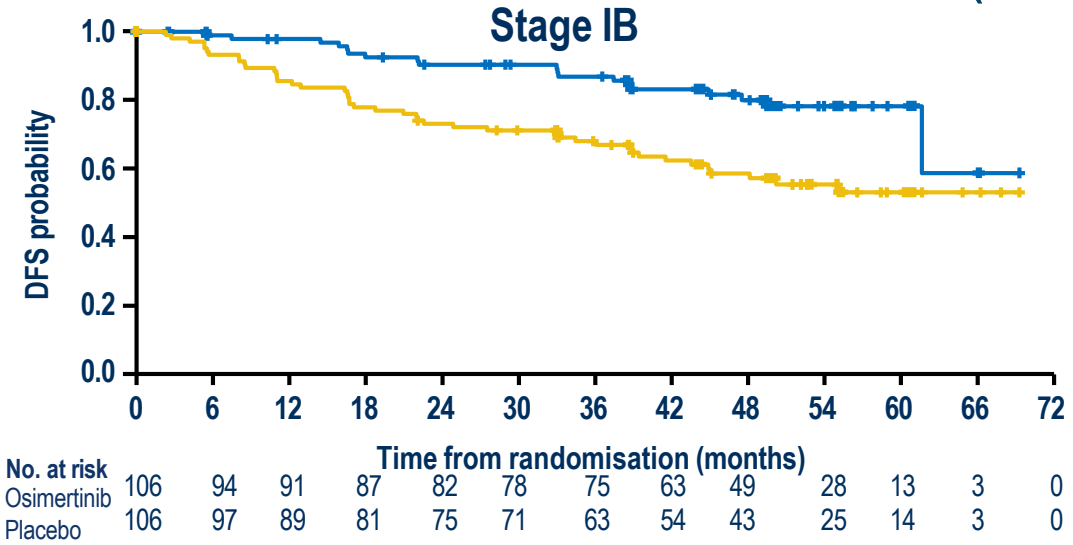
Subgroup		HR	95% CI
Overall (N=682)	Stratified log-rank	0.27	0.21, 0.34
	Unadjusted Cox PH	0.32	0.25, 0.40
Sex	Male (n=204)	0.31	0.20, 0.48
	Female (n=478)	0.31	0.23, 0.42
Age	<65 yr (n=380)	0.31	0.22, 0.42
	≥65 yr (n=302)	0.33	0.23, 0.48
Smoking history	Yes (n=194)	0.26	0.16, 0.40
	No (n=488)	0.34	0.26, 0.45
Race	Asian (n=434)	0.34	0.25, 0.45
	Non-Asian (n=248)	0.28	0.18, 0.43
Stage*	IB (n=212)	0.41	0.23, 0.69
	II (n=236)	0.34	0.23, 0.52
	IIIA (n=234)	0.20	0.14, 0.29
EGFR mutation	Ex19Del (n=378)	0.24	0.17, 0.33
	L858R (n=304)	0.45	0.31, 0.64
Adjuvant chemotherapy	Yes (n=410)	0.29	0.21, 0.39
	No (n=272)	0.36	0.24, 0.55



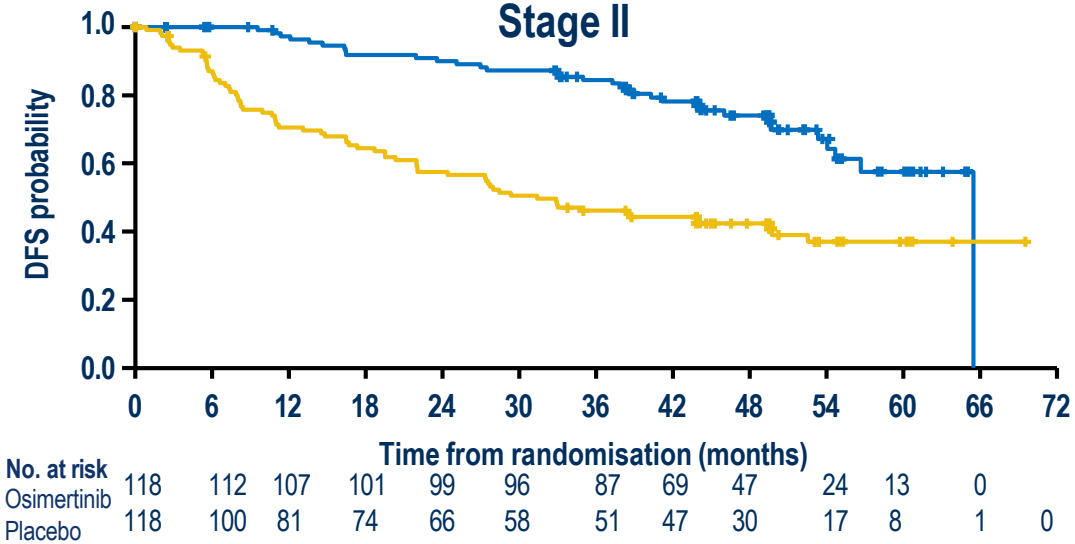
Overall population: stage IB / II / IIIA; DFS by investigator assessment. *AJCC / UICC 7th edition.

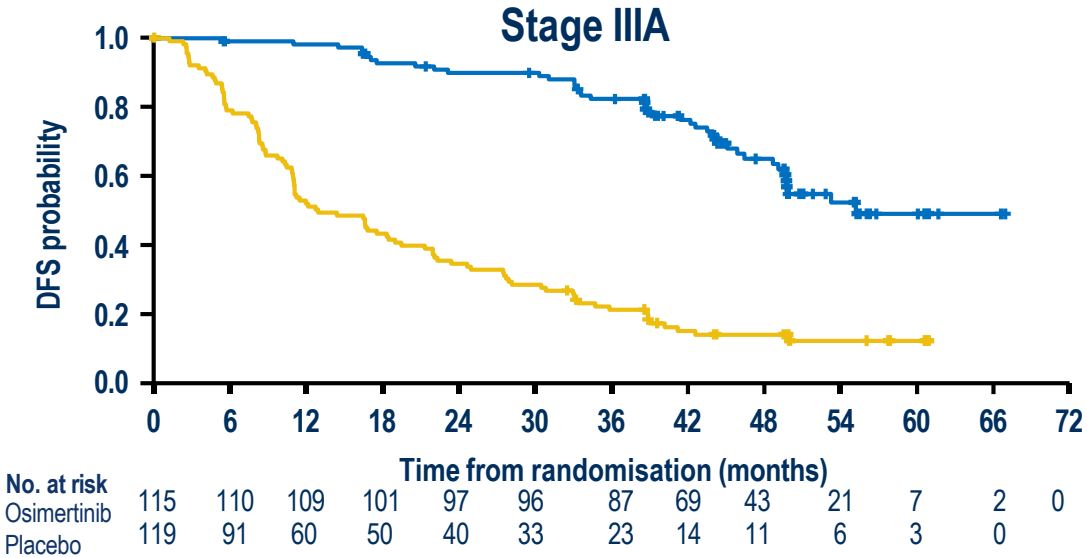
AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; HR, hazard ratio; yr, year.
Data cut-off: April 11, 2022.

UPDATED DFS BY STAGE (AJCC / UICC 7TH EDITION)



	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (70, 87)	74 (64, 82)	65 (54, 74)
– Placebo	59 (48, 68)	42 (33, 51)	14 (8, 22)
Overall HR (95% CI)	**0.41 (0.23, 0.69)**	**0.34 (0.23, 0.52)**	**0.20 (0.14, 0.29)**

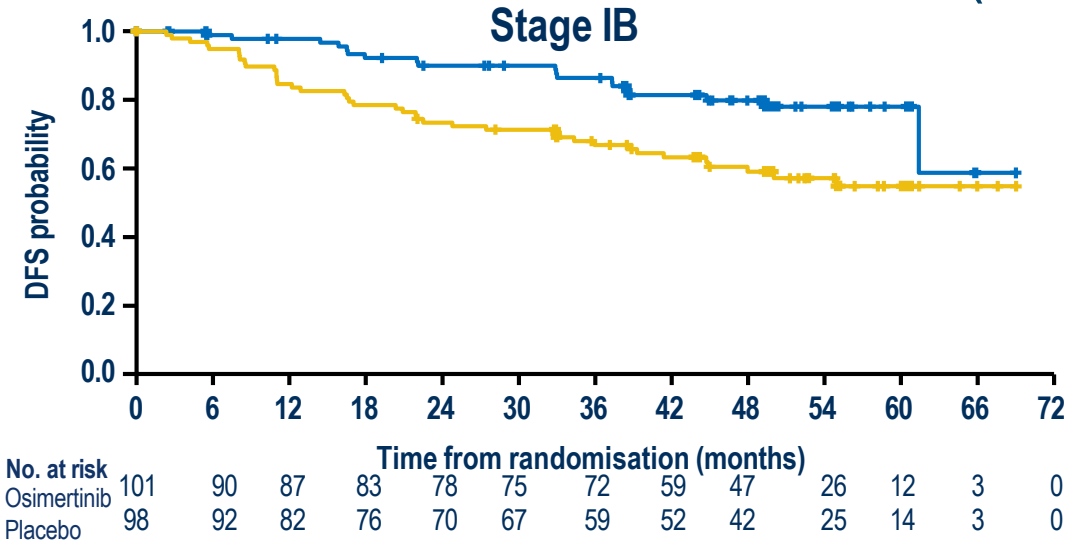




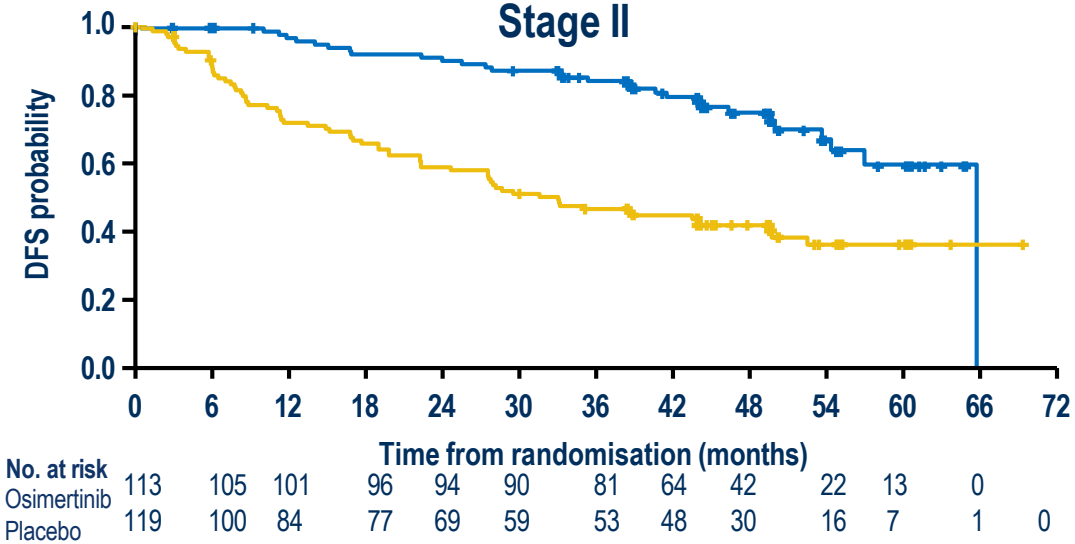
PARIS 2022 ESMO congress

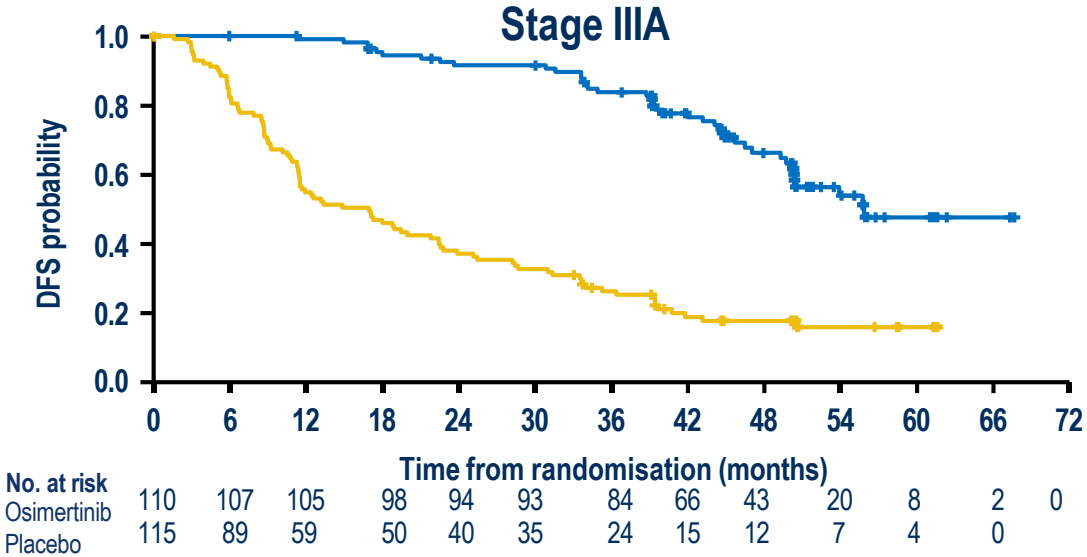
DFS by investigator assessment; Tick marks indicate censored data.
AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio
Data cut-off: April 11, 2022.

UPDATED DFS BY STAGE (AJCC / UICC 8TH EDITION*)



	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (69, 87)	75 (65, 83)	66 (55, 75)
– Placebo	60 (49, 69)	43 (34, 52)	16 (10, 24)
Overall HR (95% CI)	**0.44 (0.25, 0.76)**	**0.33 (0.21, 0.50)**	**0.22 (0.15, 0.31)**



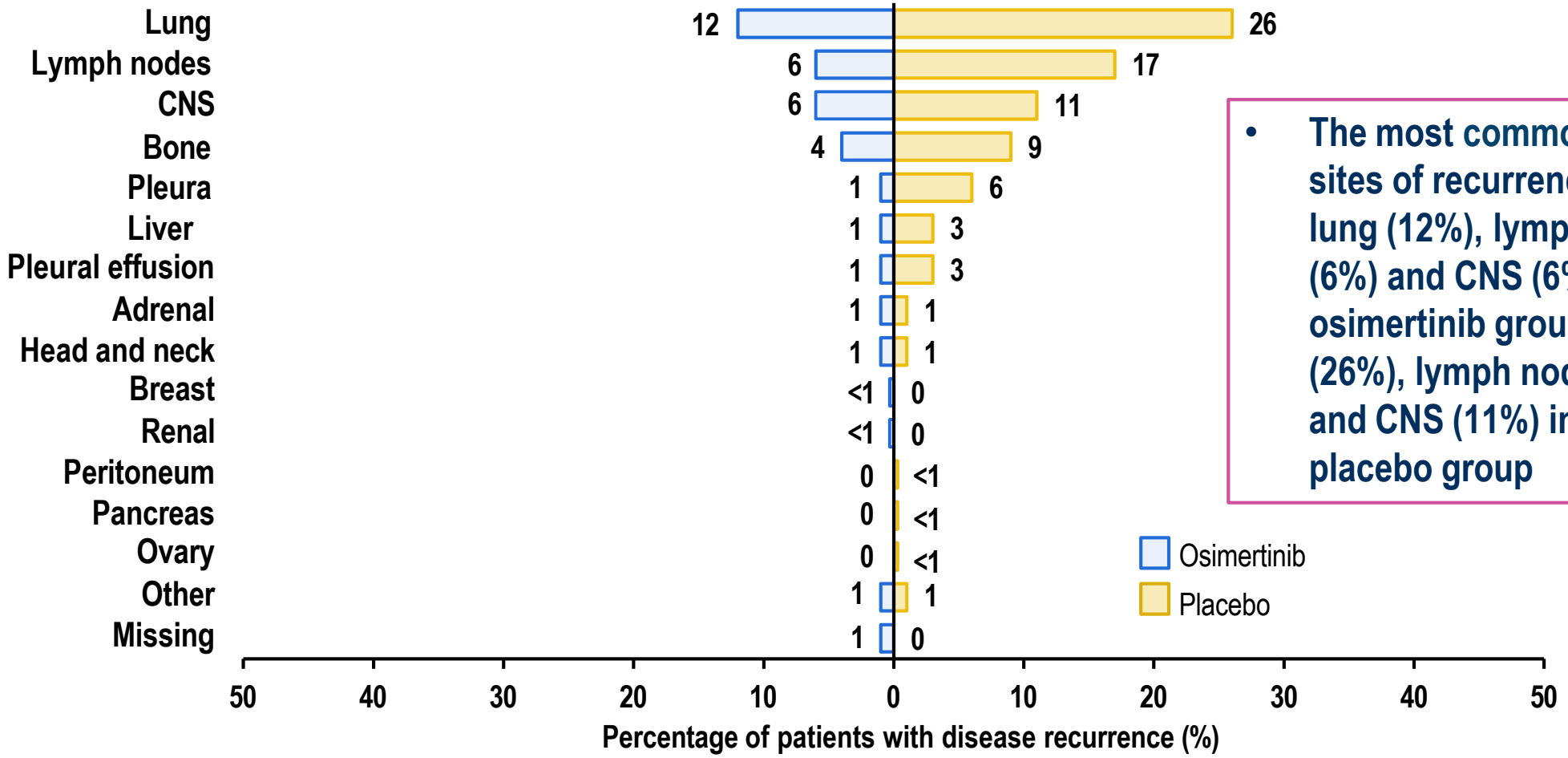


PARIS 2022 ESMO congress

DFS by investigator assessment; Tick marks indicate censored data.
*Re-staging based on data captured in the Pathology at Diagnosis AJCC / UICC 8th edition manual, per investigator assessment requested before the primary analysis.
AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio
Data cut-off: April 11, 2022.

PATTERNS OF DISEASE RECURRENCE (OVERALL POPULATION)

- In the overall population, fewer patients treated with osimertinib had disease recurrence (93/339; 27%) compared with placebo (205/343; 60%)*

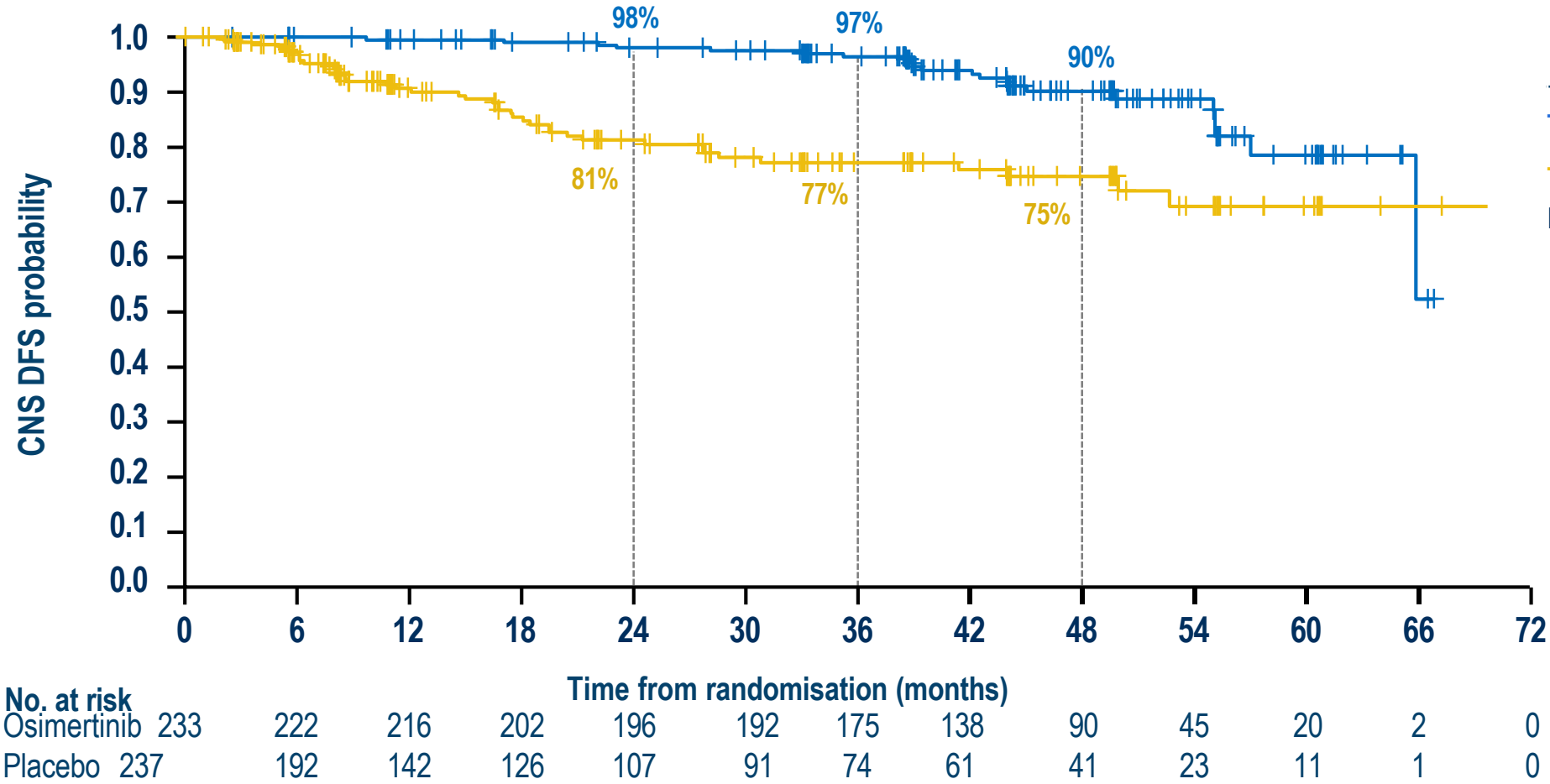


- **The most common first sites of recurrence were lung (12%), lymph nodes (6%) and CNS (6%) in the osimertinib group, and lung (26%), lymph nodes (17%) and CNS (11%) in the placebo group**

*Distant recurrence only: osimertinib 45/339 (13%), placebo 107/343 (31%); local/regional only: osimertinib 42/339 (12%), placebo 78/343 (23%); local/regional and distant: osimertinib 6/339 (2%), placebo 20/343 (6%).
CNS, central nervous system
Data cut-off: April 11, 2022.

UPDATED CNS DFS IN PATIENTS WITH STAGE II / IIIA DISEASE

- Overall, 63 patients (osimertinib n=22, placebo n=41) had CNS DFS events:*
  - 3 (14%) patients were on treatment at the time of CNS recurrence with osimertinib, versus 29 (71%) with placebo



Median CNS DFS, months (95% CI)	
– Osimertinib	NR (65.8, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.24 (0.14, 0.42)**

Maturity 13%:
osimertinib 9%, placebo 17%

PARIS 2022 ESMO congress

Median follow-up: osimertinib 44.2 months, placebo 20.4 months; DFS by investigator assessment; Tick marks indicate censored data.
*Defined as CNS as the first site of disease recurrence, or death without any disease recurrence.
CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; HR, hazard ratio; NC, not calculable; NR, not reached
Data cut-off: April 11, 2022.

CONCLUSIONS

- In this updated DFS analysis of osimertinib vs placebo, patients have been followed for a further 2 years, and all had the opportunity to complete 3 years of planned study treatment
  - Overall, there was a 77% reduction in the risk of disease recurrence or death with adjuvant osimertinib vs placebo (DFS HR 0.23; 95% CI 0.18, 0.30) in the stage II / IIIA population
    - **Median DFS was 65.8 months in the osimertinib arm and 21.9 months in the placebo arm**
  - There was also a 73% reduction in the risk of disease recurrence or death with adjuvant osimertinib vs placebo (DFS HR 0.27; 95% CI 0.21, 0.34) in the overall population (stage IB / II / IIIA)
  - An improvement in DFS was seen regardless of whether patients received prior adjuvant chemotherapy or not
  - DFS benefit across disease stages was consistent following re-staging based on the AJCC / UICC 8th edition manual
  - Osimertinib demonstrated a clinically meaningful improvement in CNS DFS (stage II–IIIA HR: 0.24; 95% CI, 0.14, 0.42)
- The safety profile was consistent with the established safety profile of osimertinib and no new safety concerns were reported with an extended treatment duration; median total duration of exposure to osimertinib was 35.8 months

These updated data reinforce adjuvant osimertinib as the standard of care for patients with EGFRm stage IB–IIIA NSCLC after complete tumour resection, with or without adjuvant chemotherapy

AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; HR, hazard ratio; NSCLC, non-small cell lung cancer. Data cut-off: April 11, 2022.

Adjuvante post-OP trials

ALK

Crizotinib vs. observation (NCT02194738)

Alectinib vs. chemotherapy (NCT03456076)

RET

Selpercatinib vs. Placebo (NCT04819100)

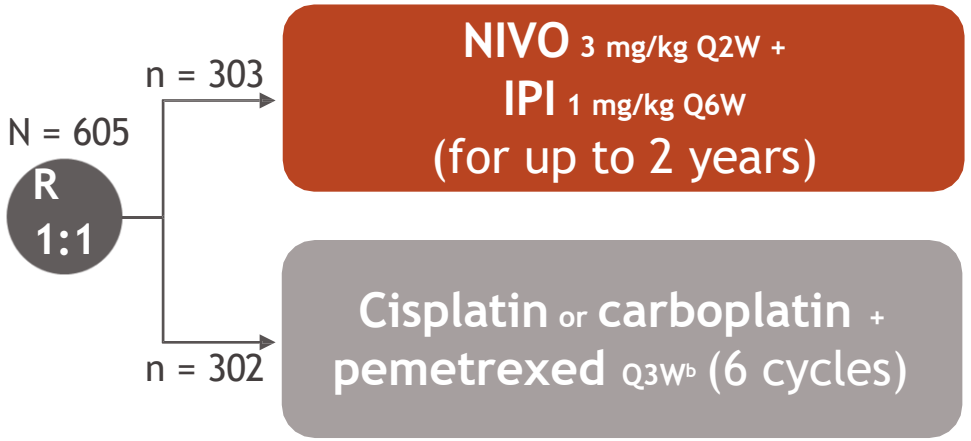
Palliativ behandling

IO til mesotheliom

Study design[a]

Key eligibility criteria
- Unresectable MPM
- No prior systemic therapy
- ECOG PS 0–1

Stratified by
Histology (epithelioid vs non-epithelioid) and sex



Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

Secondary endpoints
- ORR, DCR, and PFS by BICR
- Efficacy by PD-L1[c] expression

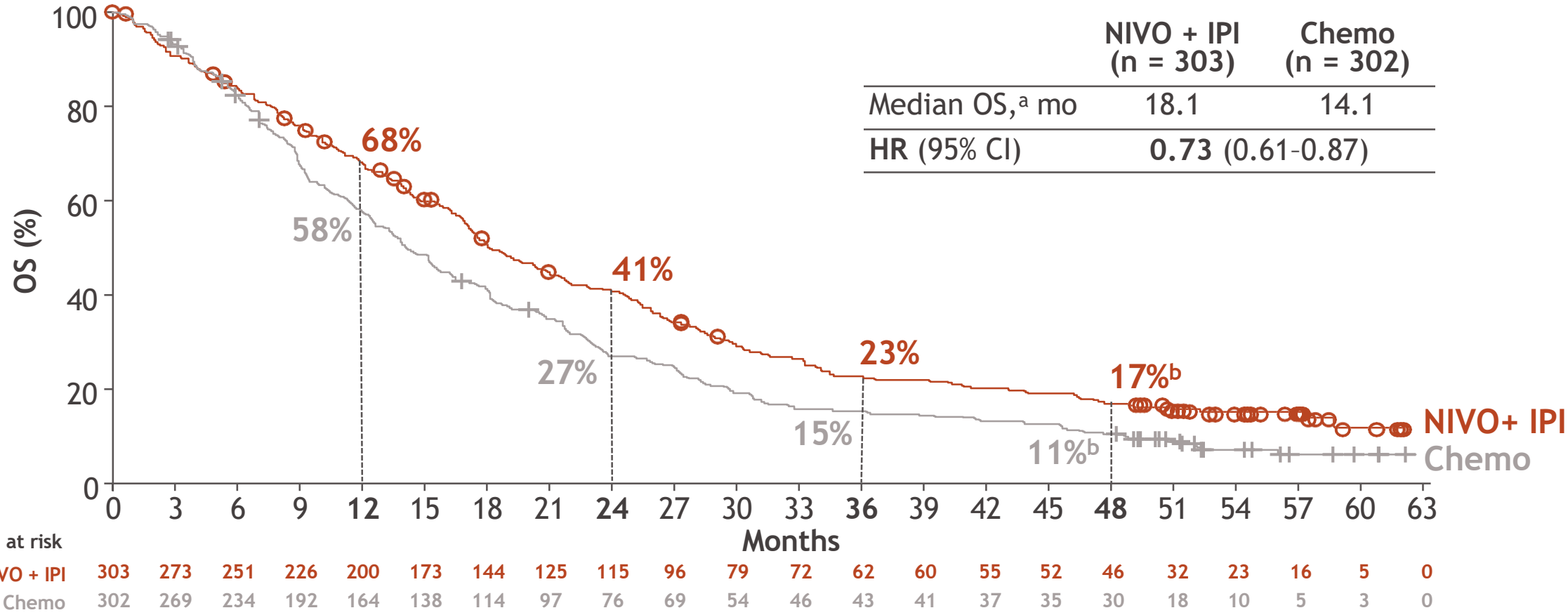
Exploratory endpoints
- Safety and tolerability
- Biomarkers

Database lock: May 6, 2022; minimum / median follow-up for OS: 47.5 months / 55.1 months.

[a]NCT02899299; [b]Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2), Q3W for 6 cycles; [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako).

Baas P, et al. *Lancet* 2021;397:375–386.

4-year update: overall survival in all randomized patients



	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS,[a] mo	18.1	14.1
HR (95% CI)	**0.73** (0.61-0.87)	

- 4-year PFS rates were 9% vs 0% with NIVO + IPI vs chemo[c]
- ORR and DOR were consistent with previous database lock[d]; rate of ongoing responders at 4 years was 16% vs 0%, respectively

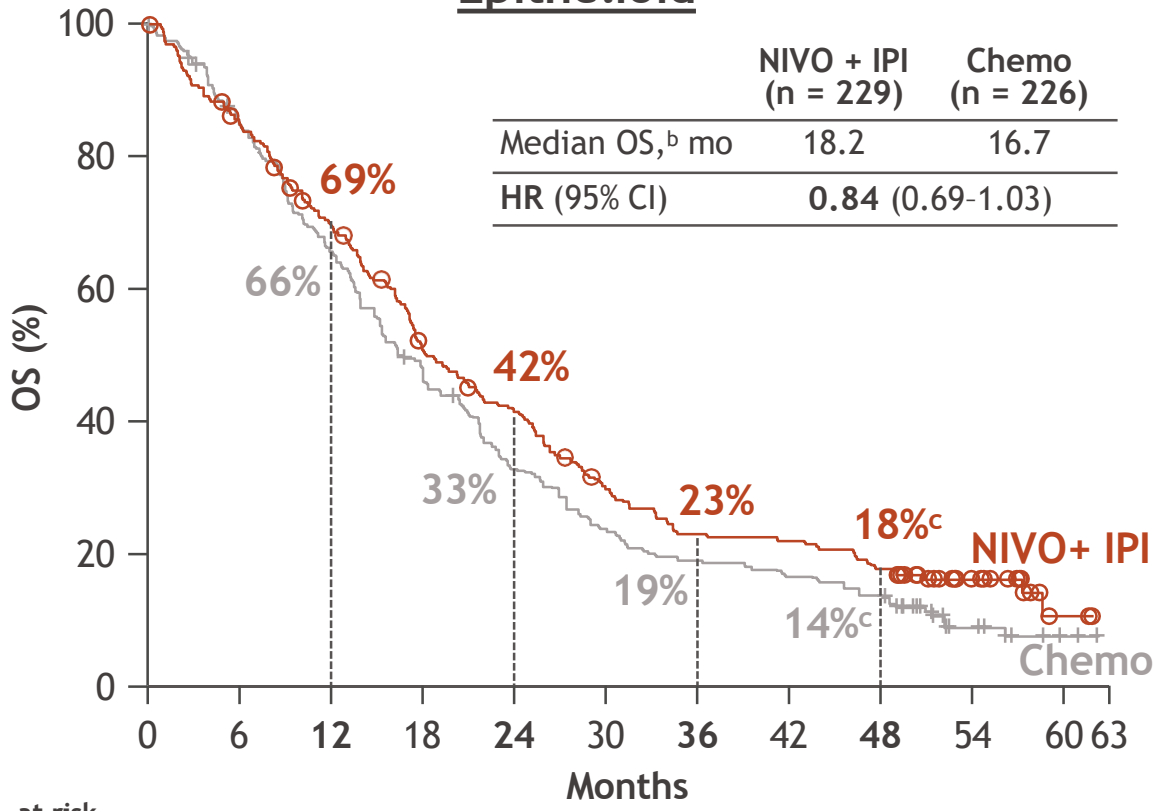
Minimum / median follow-up for OS: 47.5 months / 55.1 months.

Subsequent systemic therapy was received by 46% of patients in the NIVO + IPI arm and 43% in the chemo arm; subsequent immunotherapy was received by 5% and 23%; subsequent chemotherapy was received by 44% and 34%, respectively.

[a]95% CIs were 16.8-21.0 (NIVO + IPI) and 12.4-16.3 (chemo); [b]95% CIs were 12.7-21.5 (NIVO + IPI) and 7.5-14.7 (chemo); [c]Median PFS was 6.8 vs 7.2 months with NIVO + IPI vs chemo (HR, 95% CI: 0.93, 0.77-1.13); [d]ORR was 39.3% vs 44.4%, and median DOR was 11.6 vs 6.8 months.

4-year update: OS by histology[a]

Epithelioid

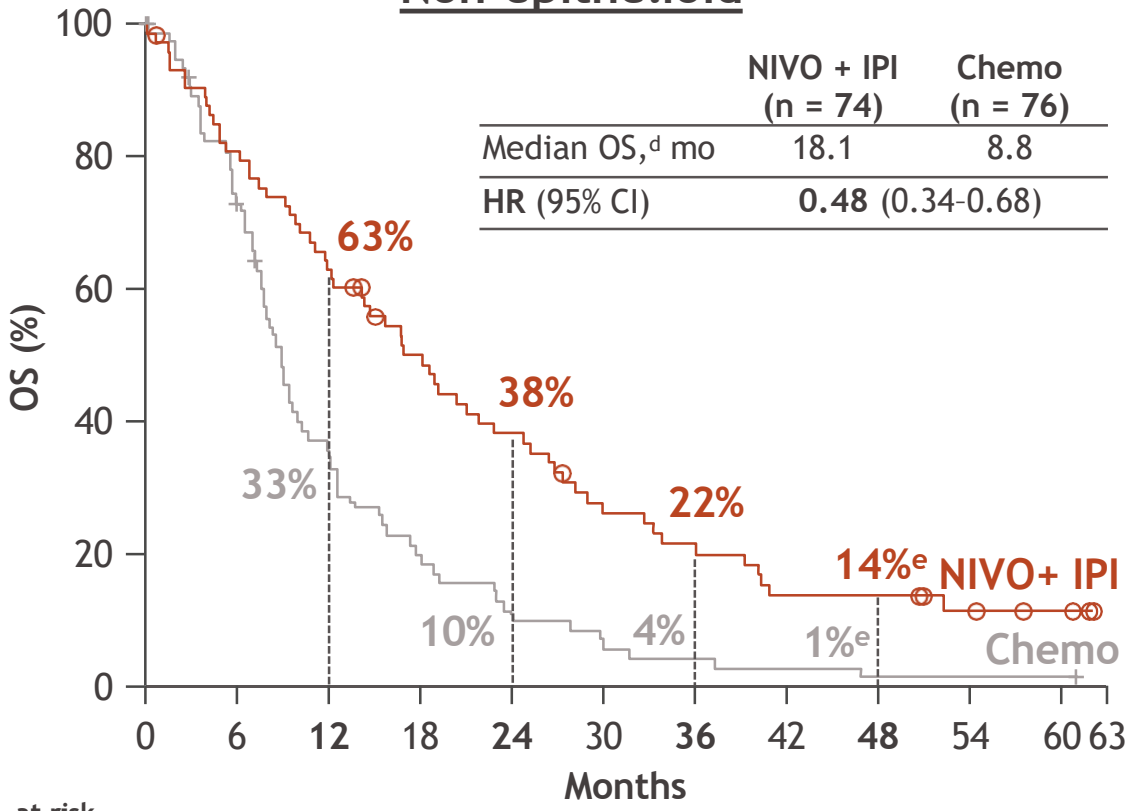


	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS,[b] mo	18.2	16.7
HR (95% CI)	**0.84** (0.69-1.03)	

No. at risk

NIVO + IPI	229	192	154	110	89	62	48	46	37	18	2	0
Chemo	226	182	141	101	69	50	40	35	29	9	2	0

Non-epithelioid



	NIVO + IPI (n = 74)	Chemo (n = 76)
Median OS,[d] mo	18.1	8.8
HR (95% CI)	**0.48** (0.34-0.68)	

No. at risk

NIVO + IPI	74	59	46	34	26	17	14	9	9	5	3	0
Chemo	76	52	23	13	7	4	3	2	1	1	1	0

Minimum / median follow-up for OS: 47.5 months / 55.1 months.

In patients with epithelioid histology, subsequent systemic therapy was received by 48% in the NIVO + IPI arm vs 45% in the chemo arm; subsequent immunotherapy was received by 4% vs 24%; subsequent chemotherapy was received by 46% vs 37%, respectively. In patients with non-epithelioid histology, subsequent systemic therapy was received by 40% in the NIVO + IPI arm vs 37% in the chemo arm; subsequent immunotherapy was received by 7% vs 20%; subsequent chemotherapy was received by 38% vs 26%, respectively.

[a]Histology per CRF; [b]95% CIs were 16.9-21.9 (NIVO + IPI) and 14.9-20.3 (chemo); [c]95% CIs were 13.0-23.2 (NIVO + IPI) and 9.6-18.9 (chemo); [d]95% CIs were 12.2-22.8 (NIVO + IPI) and 7.4-10.2 (chemo); [e]95% CIs were 6.9-23.3 (NIVO + IPI) and 0.1-6.8 (chemo).

Summary

- These results from CheckMate 743 represent the longest reported follow-up with immunotherapy in 1L unresectable MPM; NIVO + IPI continued to provide long-term, durable benefit versus chemo
  - **4-year OS rates:** 17% vs 11%, respectively
  - **4-year PFS rates:** 9% vs 0%, respectively
  - **16% of responders** in the NIVO + IPI arm have ongoing response at 4 years vs none in the chemo arm
- No new safety signals were observed with longer follow-up; rates of grade 3–4 IMAEs were ≤ 5%
- **With a 4-year minimum follow-up, these data from CheckMate 743 continue to confirm NIVO + IPI as a standard of care for unresectable MPM regardless of histology**

Godkendt den 23. marts 2022

Medicinrådets anbefaling vedrørende nivolumab i kombination med ipilimumab til behandling af ikke-resektabel lungehindekræft - version 1.0

Medicinrådet **anbefaler** nivolumab i kombination med ipilimumab som førstelinjebehandling af patienter med lungehindekræft og ikke-epiteloid histologi.

Det er dokumenteret, at behandlingen forlænger patienternes levetid væsentligt, og at en højere andel af patienterne lever mere end tre år sammenlignet med nuværende standardbehandling.

Behandlingen er betydeligt dyrere end platinbaseret kemoterapi. Medicinrådet vurderer dog samlet set, at omkostningerne er rimelige i forhold til effekten.

Medicinrådet **anbefaler ikke** nivolumab i kombination med ipilimumab som førstelinjebehandling af patienter med lungehindekræft og epiteloid histologi, fordi det ikke er dokumenteret, at behandlingen forlænger patienternes levetid.

Behandlingen er samtidig betydeligt dyrere end nuværende standardbehandling.

Medicinrådet har vurderet nivolumab i kombination med ipilimumab som førstelinjebehandling til to grupper af voksne patienter med ikke-resektabelt lungehindekræft (malignt pleuralt mesoteliom) efter vævstype (epiteloid og ikke-epiteloid histologi). Patienterne er alle i performancestatus 0-1. Det er altså patienter i god almentilstand, som tåler kemoterapi og strålebehandling, men hos hvem kræften ikke kan opereres væk/fjernes ved kirurgi.

Take home

Vigtigt med NGS af alle (non-sq) uanset stadie

- Osimertinib til EGFR M+ opererede

Vigtigt med en præcis diagnose af mesotheliomer (epitheliale/sarkomatoide/blanding)

- Afgørende for at kunne tilbyde Ipi/Nivo til ikke-epiteliale

Vigtig med en dansk konsensus vedrørende neo-adjuverende behandling inden OP

- Måske er neo-adjuverende bedre end adjuverende ???