The Role of immunotherapy and targeted therapy in early-stage NSCLC

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Disclosure of Conflicts of Interest

- Speaker Bureau: Lilly, AstraZeneca, BMS, Blueprint, Genentech, Regeneron
- Permission to use slides obtained from ASCO/Authors

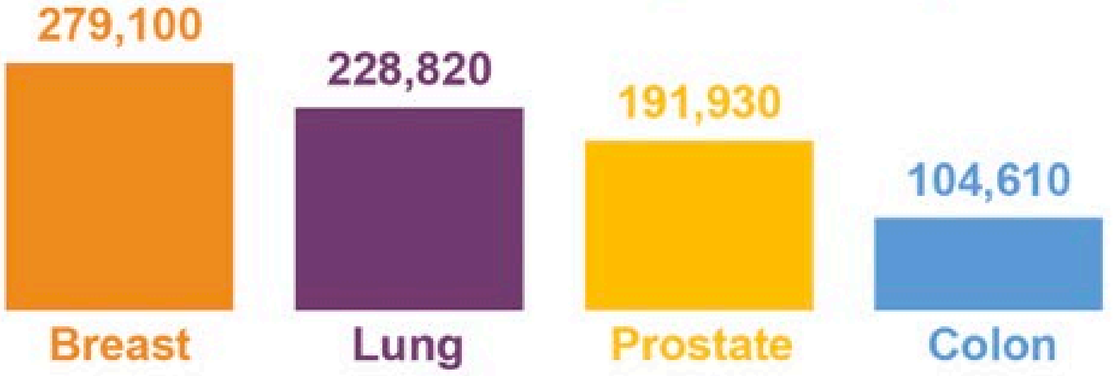
New Cases

will be diagnosed with lung cancer in 2020 in the US[1]

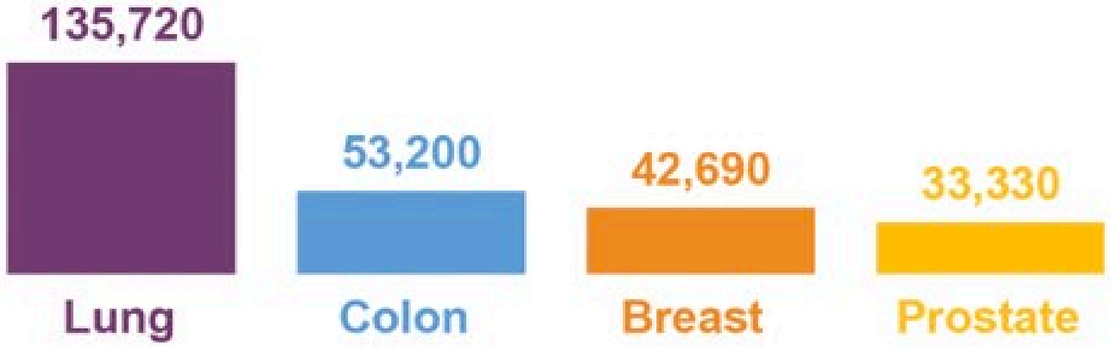
Deaths

will be from lung cancer in 2020 in the US[1]

Estimated Cases by Tumor Type[2]



Estimated Deaths by Tumor Type[2]



Lung Cancer Screening

The NLST studied the risks and benefits of screening with LDCT in >53,000 patients at high risk of lung cancer[1a]

20%↓
vs Chest X-ray

The mortality rate from lung cancer for patients with high risk factors using LDCT was reduced by **20%**[1]

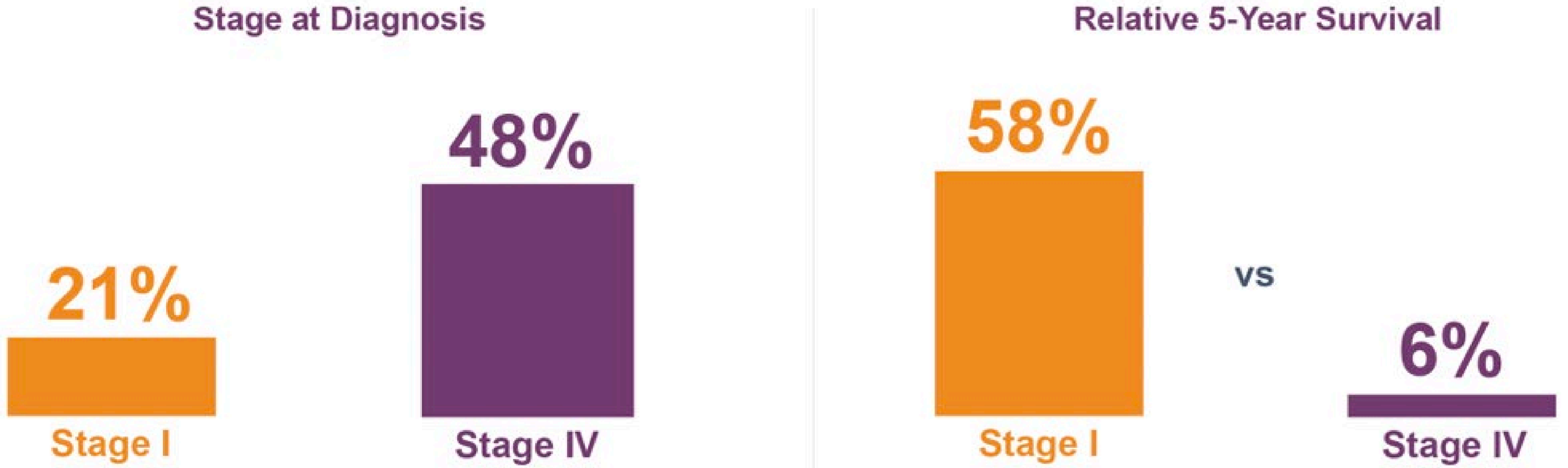
70%

of people found to have cancer in the LDCT arm of the NLST were diagnosed at an early stage[1]

/320

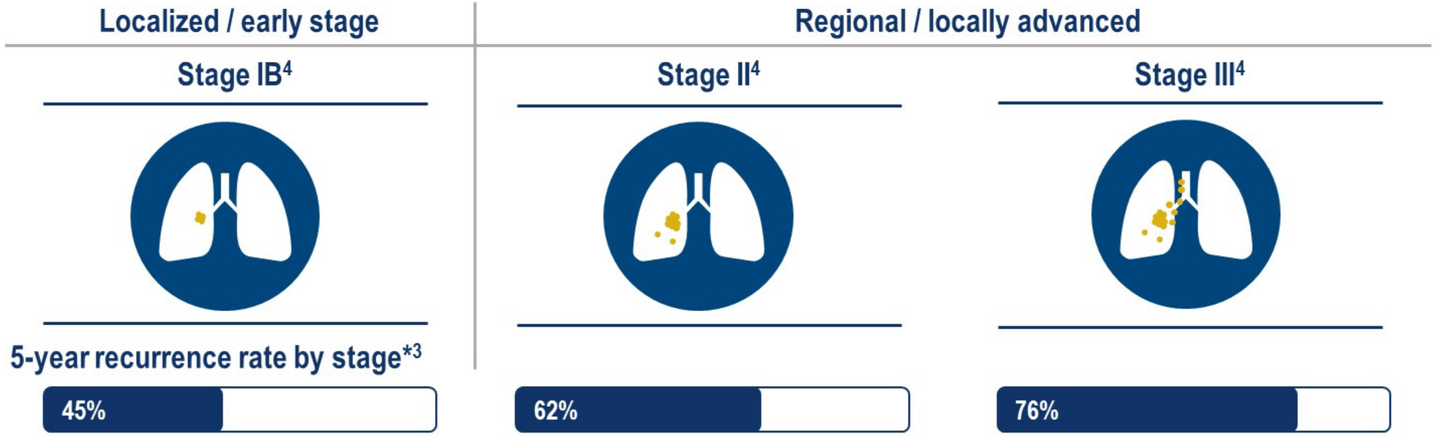
320 LDCT screenings to prevent **1 death** from lung cancer[1]

Lung Cancer Survival



Outcomes in early stage NSCLC need to be improved

- Surgery is the primary treatment for patients with early stage NSCLC[1]
- Adjuvant cisplatin-based chemotherapy is recommended for patients with resected stage II–IIIA NSCLC and select patients with stage IB disease[2]
  - Results from large randomized trials and meta analyses showed a 5-year OS benefit with adjuvant chemotherapy in patients with early stage NSCLC, OS HR 0.89 (95% CI 0.82, 0.96); DFS also favored adjuvant chemotherapy, DFS HR 0.84 (95% CI 0.78, 0.91)[3]
- Overall, disease recurrence or death following surgery and adjuvant chemotherapy remains high across disease stages[3]



1. Chansky et al. J Thorac Oncol 2017;12:1109–1121; 2. Kris et al. J Clin Oncol 2017;35:2960–2974; 3. Pignon et al. J Clin Oncol 2008;26:3552–3559; 4. AJCC Cancer Staging Manual. 7th edn. Springer, 2010.
*Median follow up: 5.2 years, data based on AJCC Staging Manual 6th edition.
AJCC, American Joint Committee on Cancer; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

Presented By Roy Herbst at TBD

Neoadjuvant Immunotherapy in NSCLC

Why consider neoadjuvant therapy in localized NSCLC?

Advantages

- Addresses micrometastatic disease early
- Potential for increased compliance with systemic therapy
- Pathologic response may be early surrogate endpoint for survival
- Facilitates translational studies

Disadvantages

- Delays surgery
- Risk of progression prior to surgery
- Potential for increased surgical complications
- Potential for overtreatment

Neoadjuvant Therapy potential advantages

- Preoperative systemic therapy for patients with resectable NSCLC offers the advantage of reducing tumor size
- increasing the rate of R0 resections
- Abrogating progressive disease by earlier treatment of micro-metastases
- Major pathologic response (MPR) after neoadjuvant treatment
- May provide a surrogate for long-term survival
- Benefit has been demonstrated with neoadjuvant chemotherapy

Neoadjuvant Immunotherapy potential advantages

Neoadjuvant ICI has a more favorable safety profile than platinum-based chemotherapy

Changes in the tumor microenvironment that allow for immune tolerance and escape occur in early-stage disease *

A recent retrospective analysis (711 pts) demonstrated that patients with resected tumors harboring higher levels of CD8+ cytotoxic T cells, CD20+ B cells, and CD 56/57 NK cells had improved disease-free survival (DFS) and OS #

Patients whose tumors harbored increased FoxP3+ T regulatory cells had worse OS #

* Lavin YT, Kobayashi S, Leader A, et al. Cell. 2017;169:750765. doi:10.1016/j.cell.2017.04.01415

Tuminello S, Veluswamy R, Lieberman-Cribbin W, et al. Oncotarget. 2019;10:7142–7155. doi:10.18632/oncotarget.27392

First pilot study Nivolumab

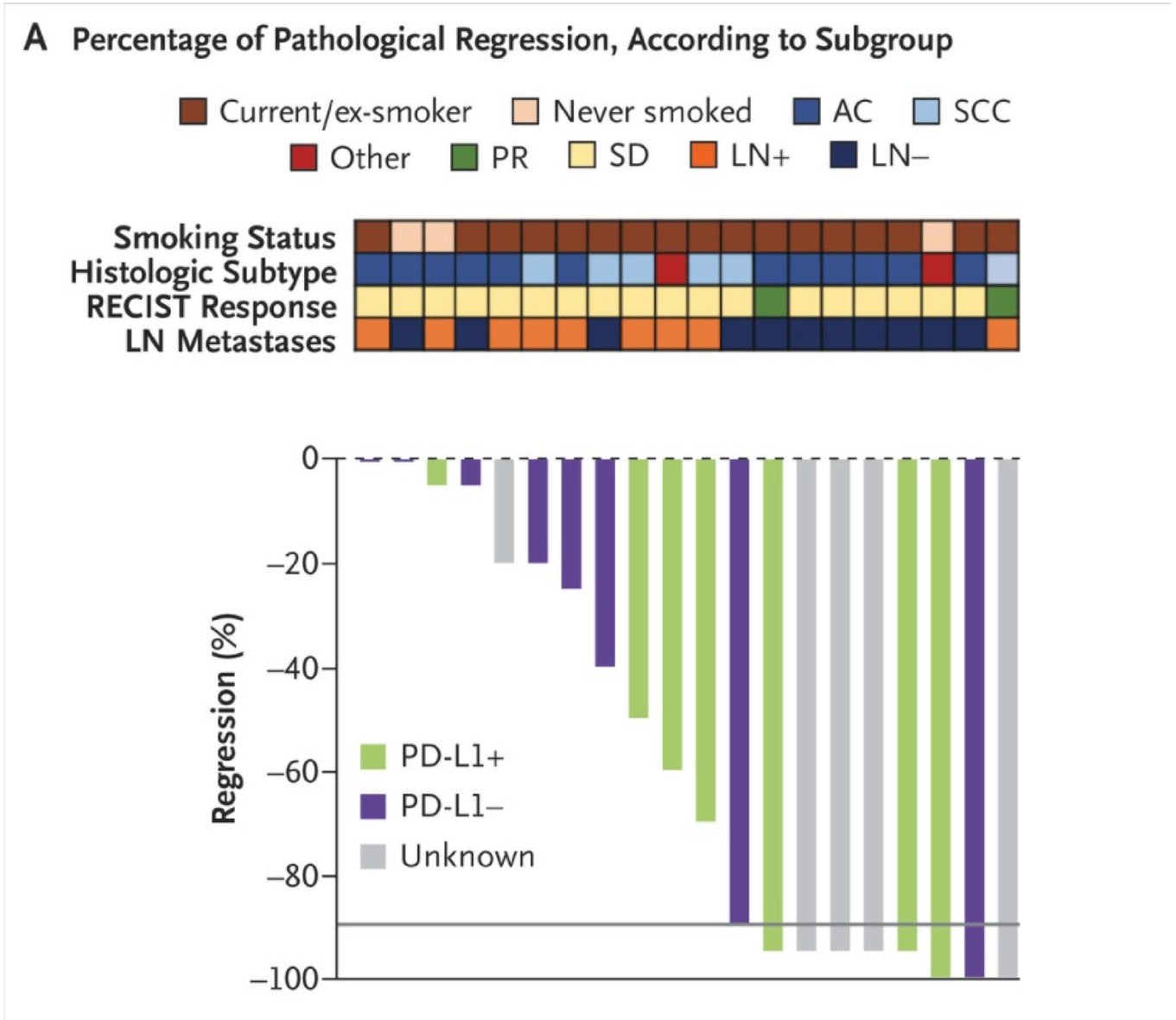
Early evidence of responses to neo-adjuvant ICI

- Eligible patients were 18 years of age or older and had stage I, II, or IIIA NSCLC that was deemed to be surgically resectable
- Key exclusion criteria were immunodeficiency, ongoing systemic immunosuppressive therapy, active autoimmune or infectious disease, and clinically significant concurrent cancer
- The primary end points were safety and feasibility
- The patients (21) received two doses of intravenous nivolumab (at a dose of 3 mg per kilogram of body weight) every 2 weeks
- Surgery was planned 4 weeks after the first dose (20 pts)

• Forde PM, Chaft JE, Smith KN, et al. N Engl J Med. 2018;378:1976 – 1986. doi:10.1056/NEJMoa1716078

Early evidence of responses to neo-adjuvant ICI

- Clinical responses: PR 10%, SD 86%, PD 5%
- Pathological downstaging: 40%
- Major Pathologic Response: 45%
- Median degree of pathological regression in the primary tumor was −65%
- No correlation with PDL-1 expression



• Forde PM, Chaft JE, Smith KN, et al. N Engl J Med. 2018;378:1976 – 1986. doi:10.1056/NEJMoa1716078

Neoadjuvant ICI: Pembrolizumab

- Patients with stage I–II NSCLC (AJCC version 7) enrolled
- Ten patients received 2 doses of pembrolizumab followed by surgery in 1 week
- MPR 40%
- No correlation between PDL-1 score and MPR

Bar J, Urban D, Ofek E, et al:
JCO 2019;37:8534

Neoadjuvant ICI: Atezolizumab

Kwiatowski DJ, Rusch VW, Chaft JE. JCO 2019;37:8503

- Patients with stage I–IIIB NSCLC (AJCC version 7) enrolled
- Total 84 patients **received 2 doses of** Atezolizumab followed **by surgery**
- MPR 19%
- Tumor regression by > 50% seen in 49% of patients
- No correlation between PDL-1 score and MPR

Trials of neoadjuvant ICI in resectable NSCLC

Trial NCT Number	Trial Name	Phase	Stage	Treatment	Primary Endpoint	MPR (No. of Patients)	PCR (No. of Patients)
NCT02259621		Phase 2	IB-IIIA	Nivolumab	Safety/ Feasibility	9/20 (45%)	3/20 (15%)
NCT02927301	LCMC3	Phase 2	IB-IIIB	Atezolizumab	MPR	15/77 (19.5%)	4/77 (5%)
ChiCTR-OIC -17013726		Phase 1B	IB-IIIA	Sintilimab	Adverse events	15/37 (40.5%)	6/37 (16.2%)
NCT03158129	NEOSTAR	Phase 2	IA-IIIA	Nivolumab or nivolumab + ipilimumab	MPR	10/34 (29%)	6/34 (15%)
NCT02938624	MK3475-223	Phase 1	I–II	Pembrolizumab	Safety/MPR	4/10 (40%)	Not reported
NCT02818920	TOP 1501	Phase 2	IB-IIIA	Pembrolizumab	Surgical feasibility rate	Ongoing	Ongoing
NCT02572843	SAKK 16/14	Phase 2	IIIA	Durvalumab	EFS	Ongoing	Ongoing

Shukla N, Hanna N. Lung cancer targets and therapy 2021:12 51–60

Is there a correlation between MPR and outcome

- End point in these early trials is MPR or PCR
- Is this a surrogate for OS, PFS and long-term outcome?

- Prospective trial of 55 resectable patients IIIA/IIIB
- Chemo/rad 94.5%
- Chemo alone 5.5%
- Peri-operative mortality 3.6%

- Five-year survival:
- MPR 53.5% Non-MPR 18%

- PFS:
- MPR 49.4 Non-MPR 18.5%

Thorac Cardiovasc Surg 2020; 68(07): 639-645
DOI: 10.1055/s-0039-1679884

Is there a correlation between MPR and outcome

- End point in these early trials is MPR or PCR
- Is this a surrogate for OS, PFS and long-term outcome?

- Retrospective rial of 759 patients with PCR (pT0N0)

- Stage I 5.8%
- Stage II 26.4%
- Stage III 68.9%

- Survival associated with:
- Young age
- Female
- LN's removed
- No RT
- No pneumonectomy

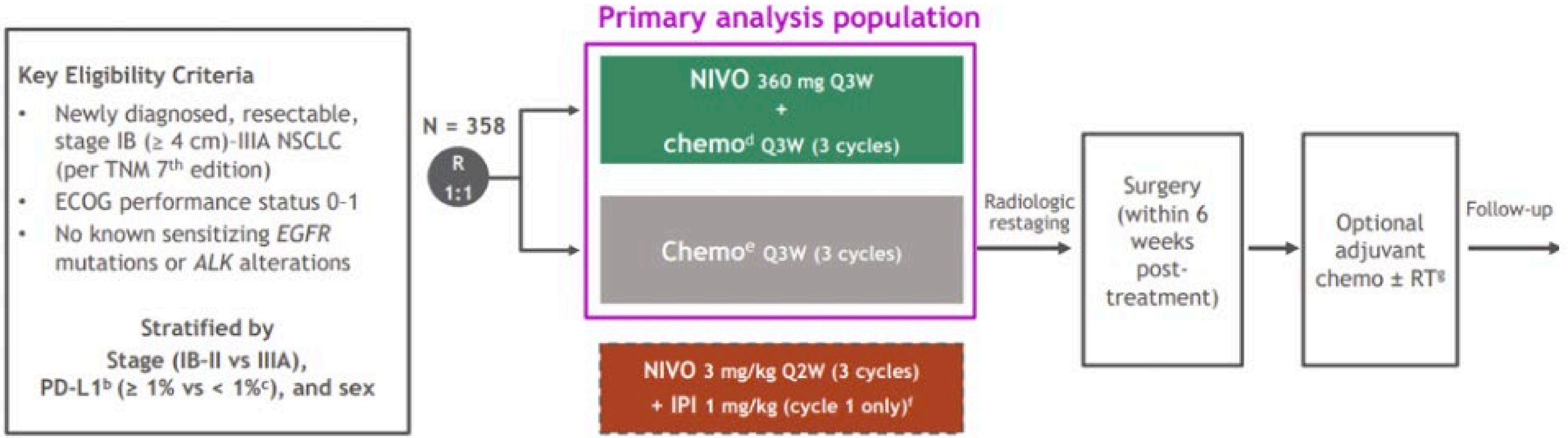
- No difference in 5-yr survival among stages

Sassorossi C, et al. Clin Lung Cancer. 2021. PMID: 32718773

Select trials of neoadjuvant chemoimmunotherapy in NSCLC

Trial NCT Number	Trial Name	Phase	Stage	Treatment	Primary Endpoint	MPR (No. of Patients)	PCR (No. of Patients)
NCT03081689	NADIM	Phase 2	IIIA	Nivolumab + carboplatin/paclitaxel	PFS	34/41 (83%)	26/41 (63%)
NCT02716038		Phase 2	IB-IIIA	Atezolizumab + cabroplatin/Nab-paclitaxel	MPR	7/11 (63.6%)	3/11 (37.3%)
NCT02572843	SAKK 6/14	Phase 2	IIIA	Durvalumab + cisplatin/docetaxel	EFS	33/55 (60.0%)	10/55 (18.2%)
NCT02998528	Checkmate 816	Phase 3	IB-IIIA	Nivolumab + ipilimumab or nivolumab + chemotherapy	EFS/PCR	Not reported	24%
NCT04304248	NeoTPD01	Phase 2	IIIA-IIIB	Toripalimab + carboplatin/pemetrexed or Nab-paclitaxel	MPR	20/30 (66.7%)	15/30 (50%)
NCT03838159	NADIM II	Phase 2	IIIA-IIIB	Nivolumab + carboplatin/paclitaxel	PCR	Ongoing	Ongoing
NCT03871153	HCRN LUN17-321	Phase 2	III	Durvalumab + carboplatin/paclitaxel + radiation	PCR	Ongoing	Ongoing
NCT03456063	IMpower030	Phase 3	II–IIIB	Atezolizumab + platinum chemotherapy	MPR and EFS	Ongoing	Ongoing
NCT04061590		Phase 2	I–IIIA	Pembrolizumab + cisplatin/pemetrexed	% of patients with TIICs	Ongoing	Ongoing

Checkmate 816



Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

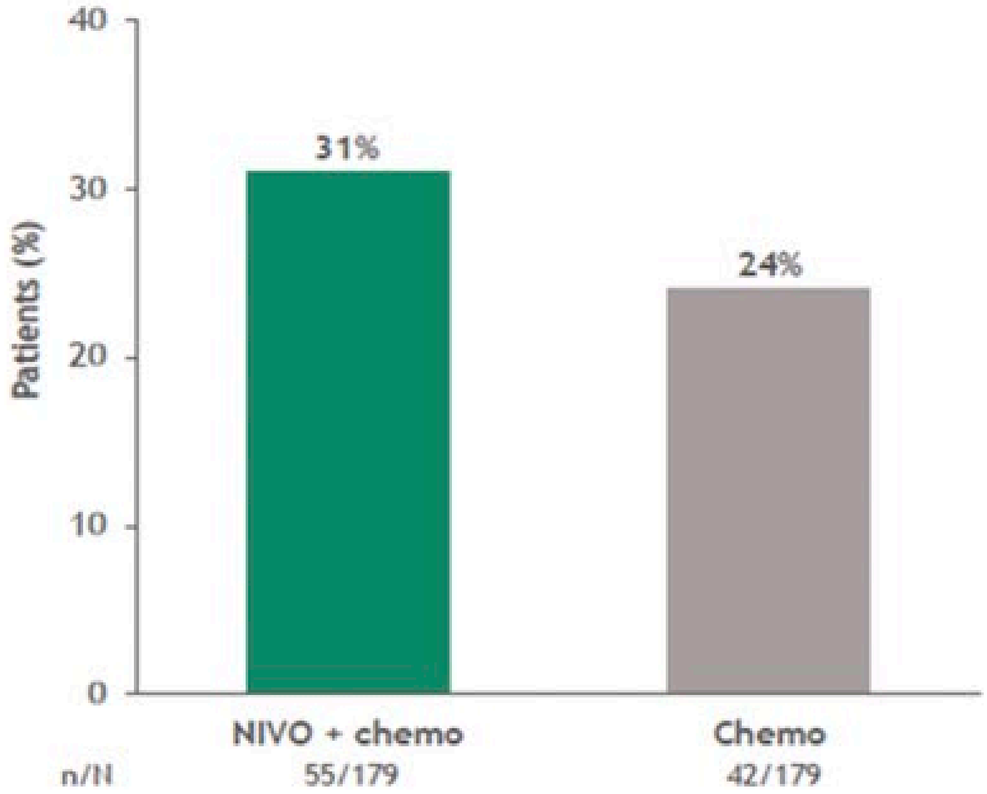
Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

Response rate clinical and radiographic

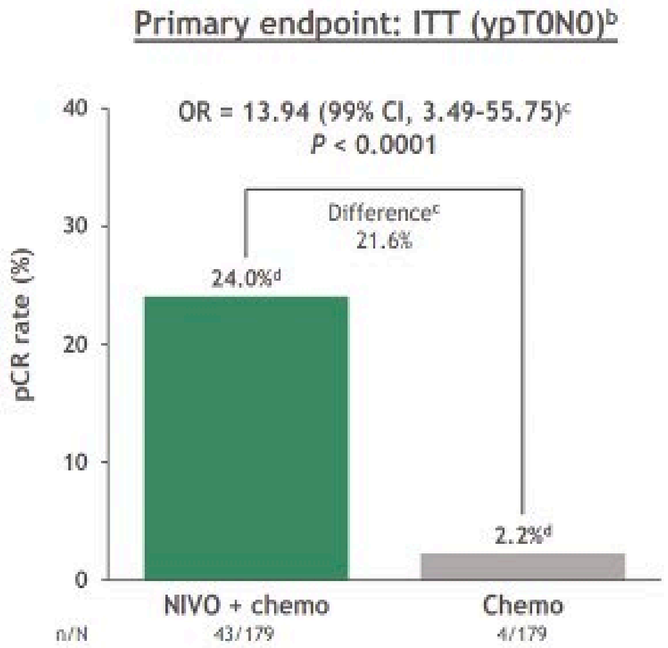
Objective response rate

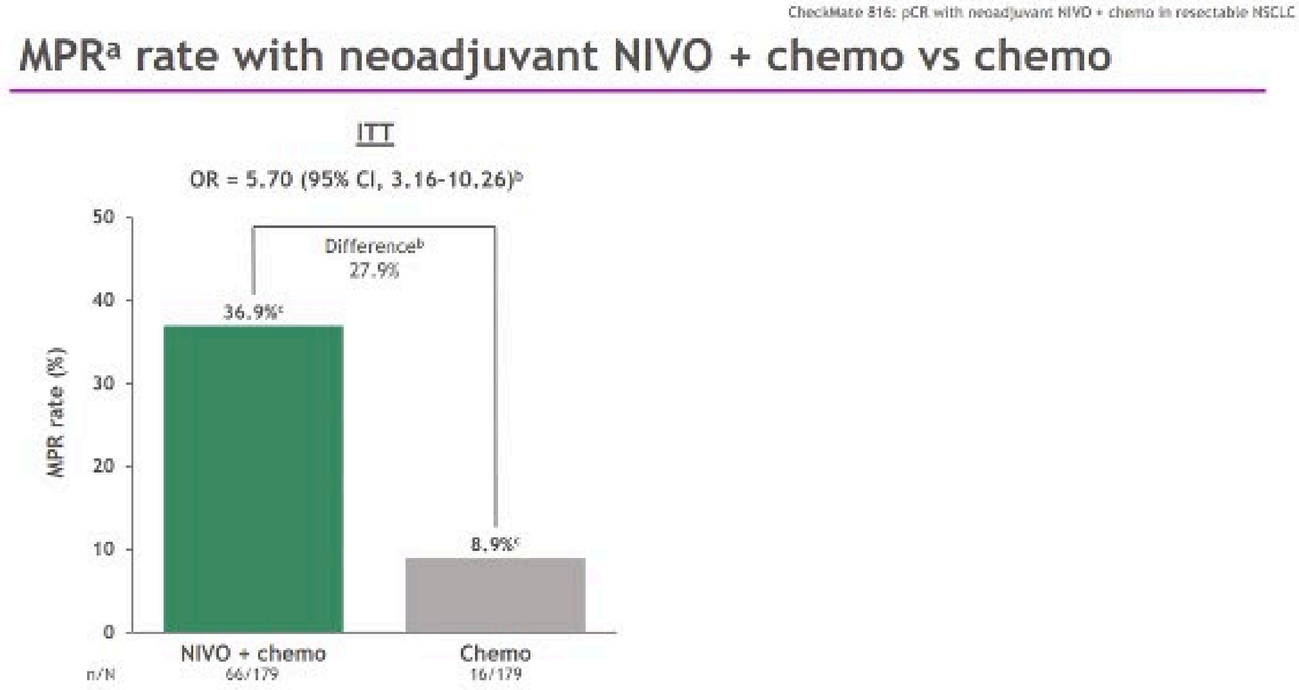
Patients, n (%)	NIVO + chemo (n = 179)	Chemo (n = 179)
ORR[a]	96 (54)[b]	67 (37)[b]
Best overall response		
Complete response	1 (1)	3 (2)
Partial response	95 (53)	64 (36)
Stable disease	70 (39)	88 (49)
Progressive disease	8 (4)	11 (6)
Not evaluable	1 (1)	1 (1)
Not reported	4 (2)	12 (7)

Patients with radiographic down-staging[c]



Primary endpoint: pCR rates





Conclusion

- CheckMate 816 showed a statistically significant improvement in the primary endpoint of pCR (OR = 13.94 [99% CI, 3.49-55.75]; *P* < 0.0001), and benefit was consistent across disease stages, histologies, TMB, and PD-L1 expression levels
  - MPR and ORR were also improved
  - The study continues to mature for the EFS primary endpoint
- The addition of neoadjuvant NIVO to chemo maintained a tolerable safety profile and did not impede the feasibility of surgery
- In an exploratory subset analysis, ctDNA clearance was more frequent with NIVO + chemo vs chemo and appeared to be associated with pCR
- CheckMate 816 is the first phase 3 study to show the benefit of neoadjuvant immunotherapy + chemo combination for resectable NSCLC, and NIVO in combination with chemo could represent a potential new neoadjuvant option for these patients

Impower 030:

Phase III study evaluating neoadjuvant treatment of resectable stage II-IIIB non-small cell lung cancer (NSCLC) with atezolizumab (atezo) + chemotherapy

- Resectable stage II, IIIA, or select IIIB (T3N2) NSCLC (per AJCC/UICC, 8th)
- Randomized to receive 4 cycles of neoadjuvant atezo + chemo (1200 mg Q3W, Arm A) or placebo + chemo (Arm B)
- Combined with investigator choice platinum doublet
- Patients in Arm A will receive adjuvant atezo treatment for 16 cycles or until disease recurrence or unacceptable toxicity
- Patients in Arm B will receive best supportive care

Can IO be combined with radiation

- IO combined with radiation in Head and Neck cancer showed the following

1. Radiation stimulates the immune response locally and increases immune-mediated tumor kill besides direct cytotoxic effect

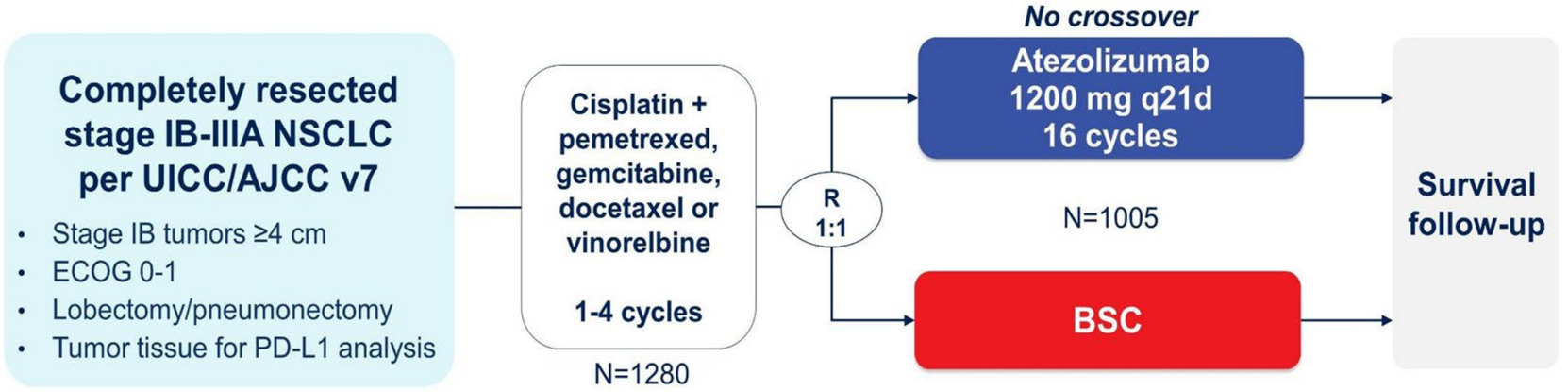
2. Radiation also destroys immune cells and may reduce the effectiveness of immune stimulation

3. Current models highly suggest that hypo-fractionated radiation may strike a good balance between both mechanisms and may be best suited for combination with IO based on animal models

4. Challenge with modification of radiation fractions in lung cancer

ADJUVANT IMMUNOTHERAPY IN NSCLC

IMpower010: study design



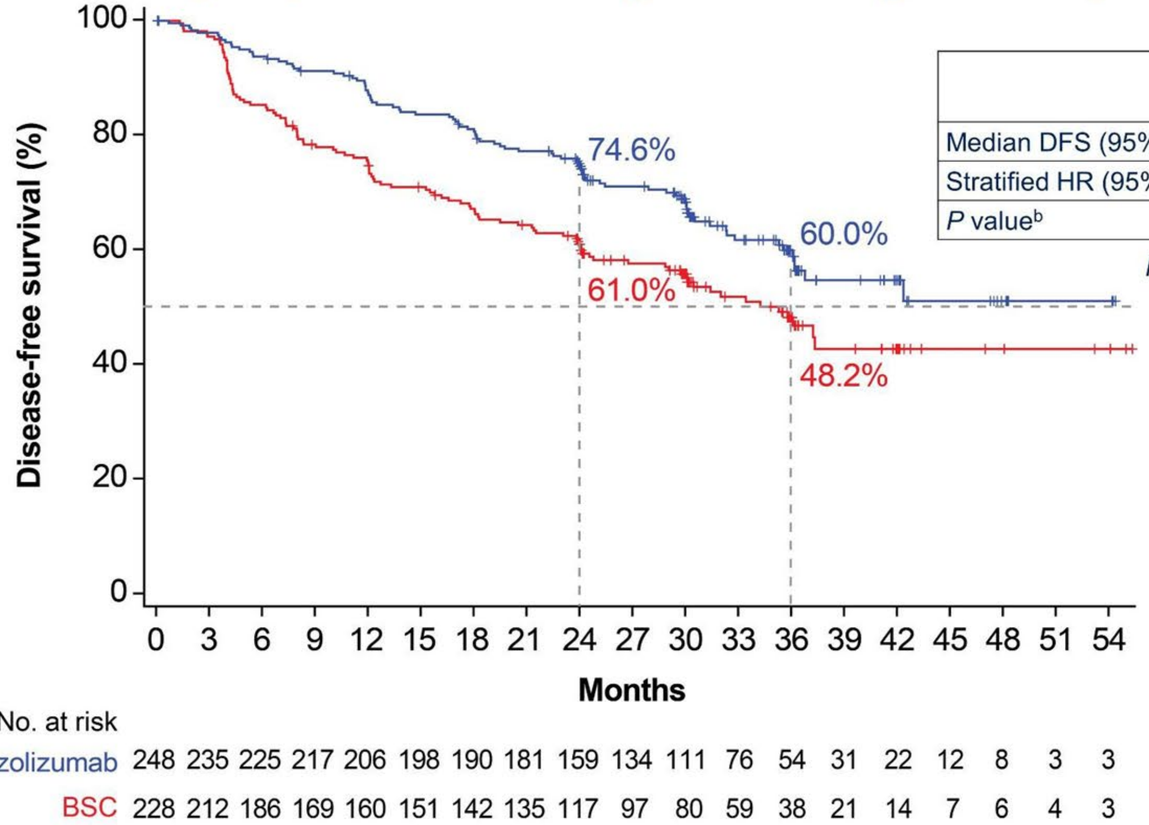
Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA population (primary endpoint)

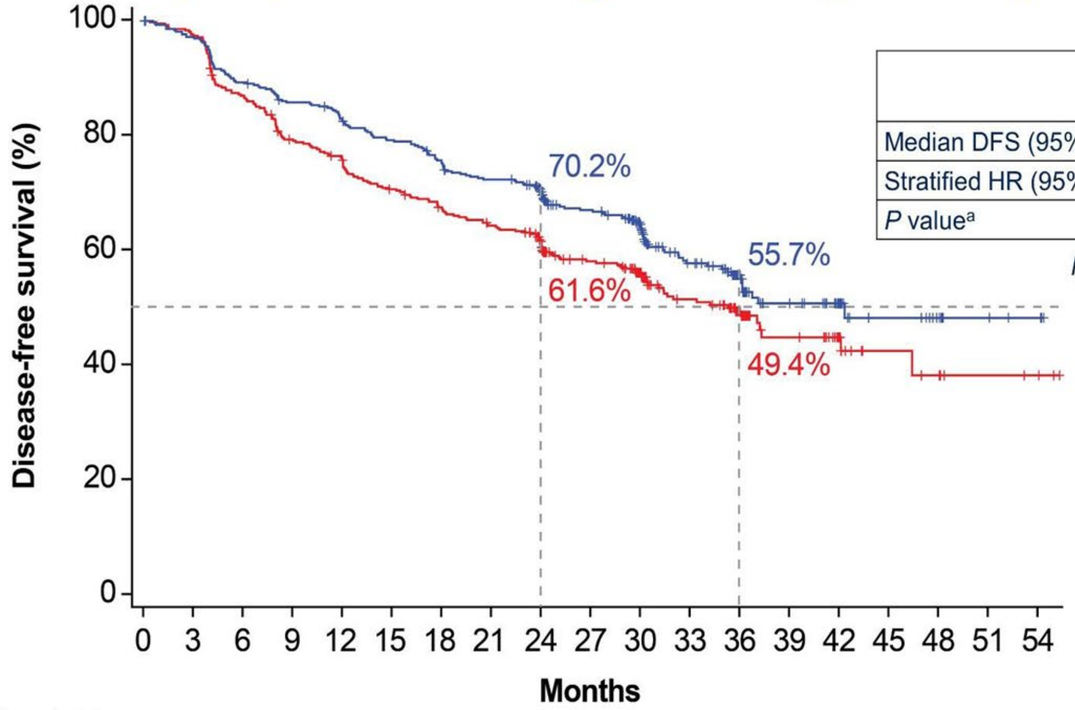


	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

Median follow-up: 32.8 mo (range, 0.1-57.5)

Clinical cutoff: January 21, 2021. CI, confidence interval; HR, hazard ratio; NE, not evaluable. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.

IMpower010: DFS in the all-randomized stage II-IIIA population (primary endpoint)



	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

Median follow-up: 32.2 mo (range, 0-57.5)

No. at risk																			
Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] Crossed the significance boundary for DFS.

IMpower010: conclusions

- IMpower010 is the first Phase III study of cancer immunotherapy to demonstrate DFS improvement in the adjuvant NSCLC setting after platinum-based chemotherapy
  - Adjuvant atezolizumab following complete resection and adjuvant chemotherapy showed statistically significant DFS benefit in the PD-L1 TC ≥1% stage II-IIIA (HR, 0.66; 95% CI: 0.50, 0.88) and all-randomized stage II-IIIA (HR, 0.79; 95% CI: 0.64, 0.96) populations, with enriched clinical benefit in patients whose tumors express PD-L1
- IMpower010 will continue for DFS and OS analyses in the ITT population
  - DFS in the ITT population, including patients with stage IB disease, did not cross the significance boundary at this interim DFS analysis
  - At this pre-planned interim DFS analysis, OS data were immature and not formally tested
- The safety profile of atezolizumab was consistent with prior experience of atezolizumab monotherapy across indications and lines of therapy
- Atezolizumab may be considered a practice-changing adjuvant treatment option for patients with PD-L1 TC ≥1% stage II-IIIA NSCLC

Adoptive T-cell therapy and other activated cellular therapy in the adjuvant setting

- Data on adoptive T-cell therapy in metastatic NSCLC has established the feasibility and early benefit in early phase II trials.
- Limited Phase II trials looking at this treatment in the adjuvant setting is currently also being investigated
- Immunotherapy has ranged from:
  - Adoptive transfer of activated T cells for specific antigens (MAGE A3, NYE-ESO) using pheresed T cells- Results have been mixed [1]
  - Adoptive transfer of autologous activated killer T-cells and dendritic cells isolated from resected lymph nodes- early data positive, small sample size [2]

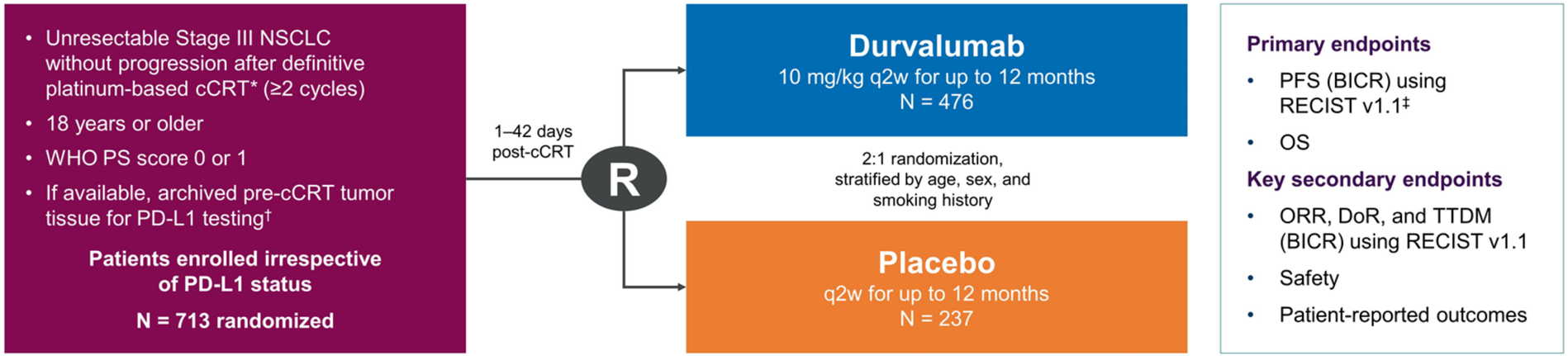
- This approach continues to be investigated

1- Johan F Vansteenkiste et al. Lancet Oncol. 2016 Jun;17(6):822-835. doi: 10.1016/S1470-2045(16)00099-1. Epub 2016 Apr 27.

2- Kimura et al. Cancer Immunol Immunother. 2015 Jan;64(1):51-9.

IMMUNOTHERAPY IN LOCALLY ADVANCED NSCLC

PACIFIC: Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Trial



- **Updated analyses of OS and PFS, assessed ~5 years after the last patient was randomized (data cutoff: 11 January 2021; exploratory, post-hoc analysis)**
  - **Treatment effects were estimated using stratified log-rank tests in the ITT population**
  - **Medians and yearly landmark rates were estimated using the Kaplan–Meier method**

BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; ITT, intent-to-treat; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

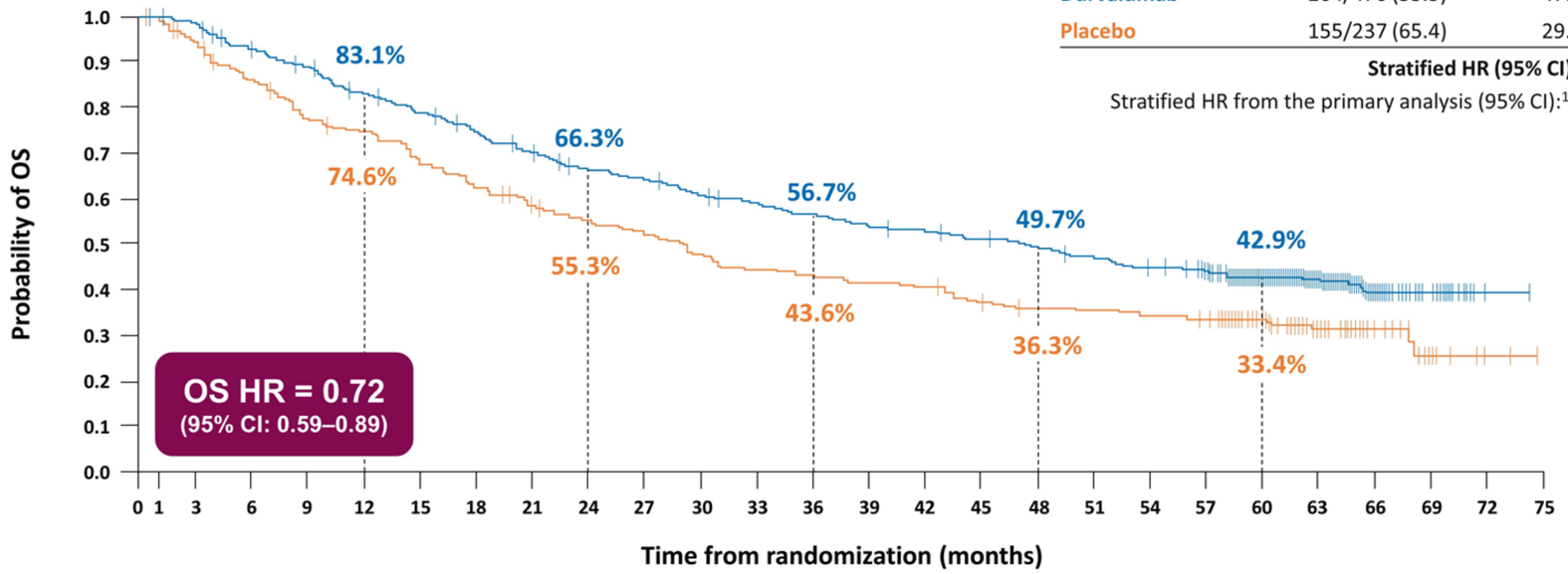
NCT02125461. *Radiation dosage typically 60–66 units of gray in 30–33 fractions. †Using the Ventana SP263 immunohistochemistry assay. ‡Defined as the time from randomization to the date of objective disease progression or death by any cause in the absence of progression

Updated OS (ITT)

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	264/476 (55.5)	47.5 (38.1–52.9)
Placebo	155/237 (65.4)	29.1 (22.1–35.1)

Stratified HR (95% CI): 0.72 (0.59–0.89)

Stratified HR from the primary analysis (95% CI):[1,2] 0.68 (0.53–0.87)



No. at risk

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).

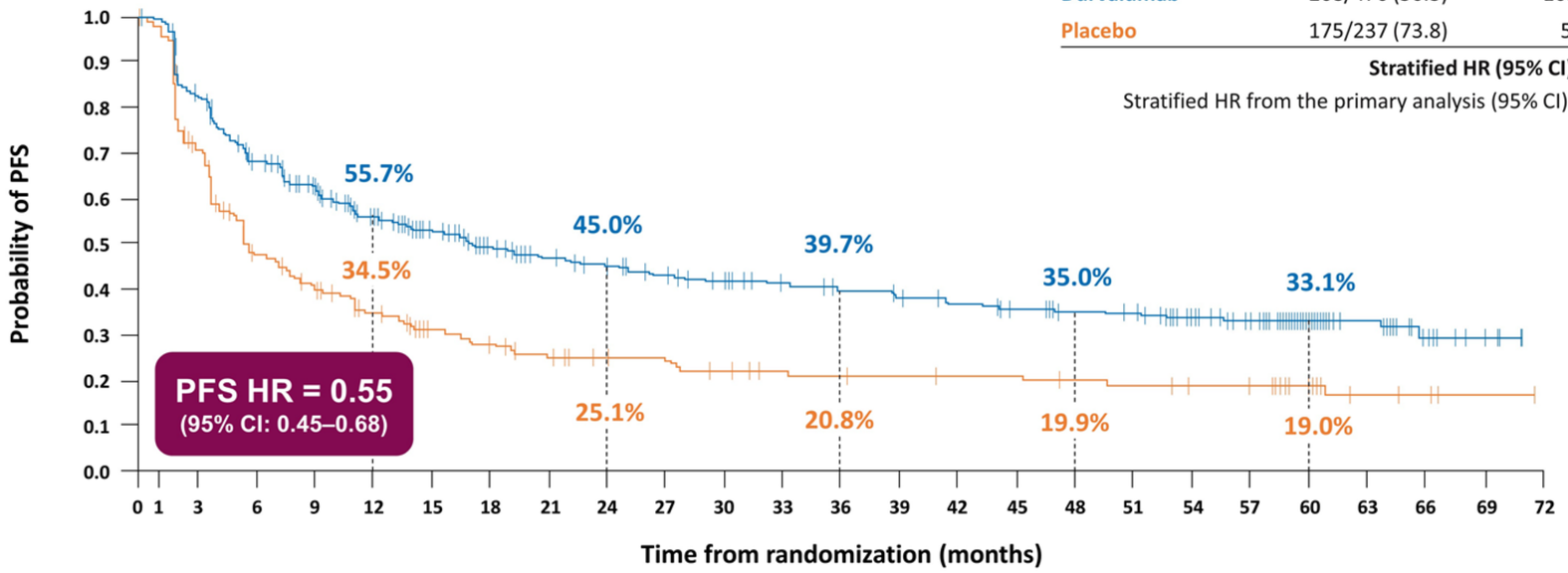
1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

Updated PFS (ITT; BICR)

	No. of events/ total no. of patients (%)	Median PFS (95% CI), months
Durvalumab	268/476 (56.3)	16.9 (13.0–23.9)
Placebo	175/237 (73.8)	5.6 (4.8–7.7)

Stratified HR (95% CI): 0.55 (0.45–0.68)

Stratified HR from the primary analysis (95% CI):[1] 0.52 (0.42–0.65)



No. at risk

Durvalumab	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival

Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).

1. Antonia SJ, et al. New Engl J Med 2017;377:1919–29

Targeted therapy in early stage disease

Neoadjuvant EGFR TKI: Early signals

- A phase II single-arm study assessing the impact of 28 days of neoadjuvant gefitinib in stage I NSCLC
- RR 50%
- More fibrosis
- Lower cell proliferation
- Residual tumor cells concentrated in fibrous stroma with TILs.

J Clin Oncol. 2009 Dec 20; 27(36):6229-36.

Neoadjuvant EGFR TKI: Early signals

- Other trials showed:

- Improved RR
- Downstaging
- Trend towards improved survival

- However studies were small, unable to draw robust conclusions

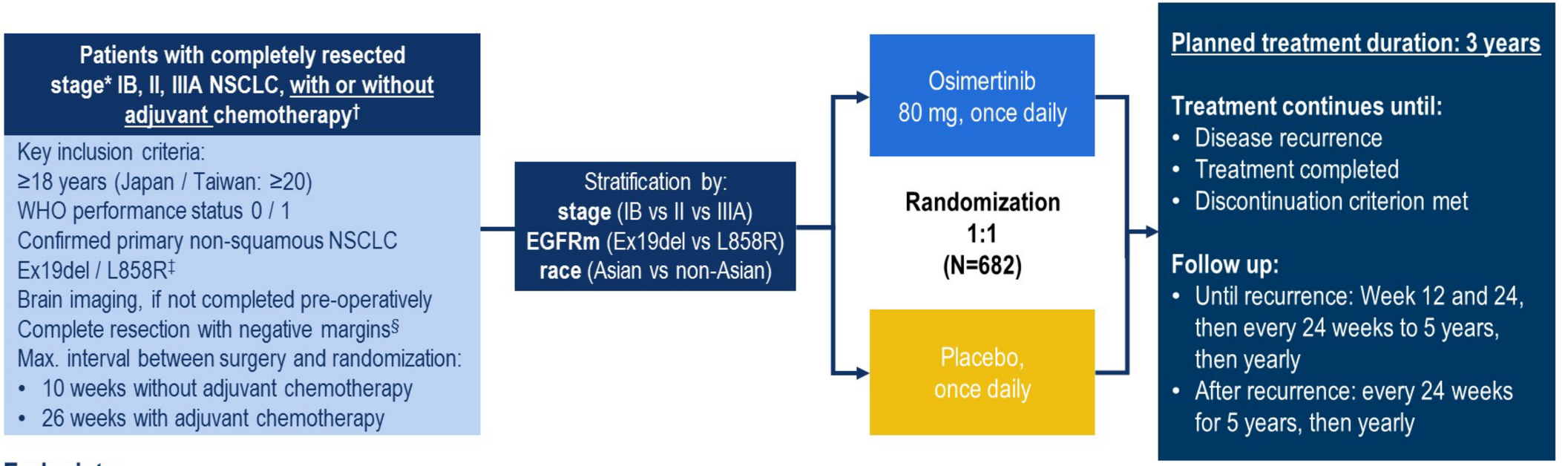
J Hematol Oncol. 2015 May 17; 8():54
Oncologist. 2019 Feb; 24(2):157-e64.
J Int Med Res. 2020 Apr; 48(4):300060519887275

- Neoadjuvant EGFR TKI trials

EMERGING	II	Neoadjuvant + adjuvant	IIIA EGFR-mutated NSCLCs	erlotinib for 6 weeks then 1 year post-op vs. cisplatin-gemcitabine	ORR	NCT01407822
NCT03203590	III	neoadjuvant	II-IIIA EGFR-mutated NSCLC	gefinitib for 8 weeks vs. carboplatin-vinorelbine	2 year DFS	NCT03203590
NeoADAURA	III	neoadjuvant	II-IIIA EGFR-mutated NSCLC	osimertinib +/− platinum-pemetrexed vs. platinum-pemetrexed	MPR	NCT04351555
NCT04302025	II	Neoadjuvant +/− adjuvant	IB-IIIB NSCLC with altered ALK, ROS1, NTRK or BRAF	8 weeks neoadjuvant +/− adjuvant with alectinib, entrectinib or vemurafenib+cobimetinib	MPR	NCT04302025
NCT03088930	II	neoadjuvant	IA-IIIA NSCLC with altered MET, ROS1 or ALK	crizotinib for 6 weeks	ORR	NCT03088930

Targeted therapy in the adjuvant setting

ADAURA Phase III double-blind study design



Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †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. CT, computed tomography; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; WHO, World Health Organization.

Presented By Roy Herbst at TBD

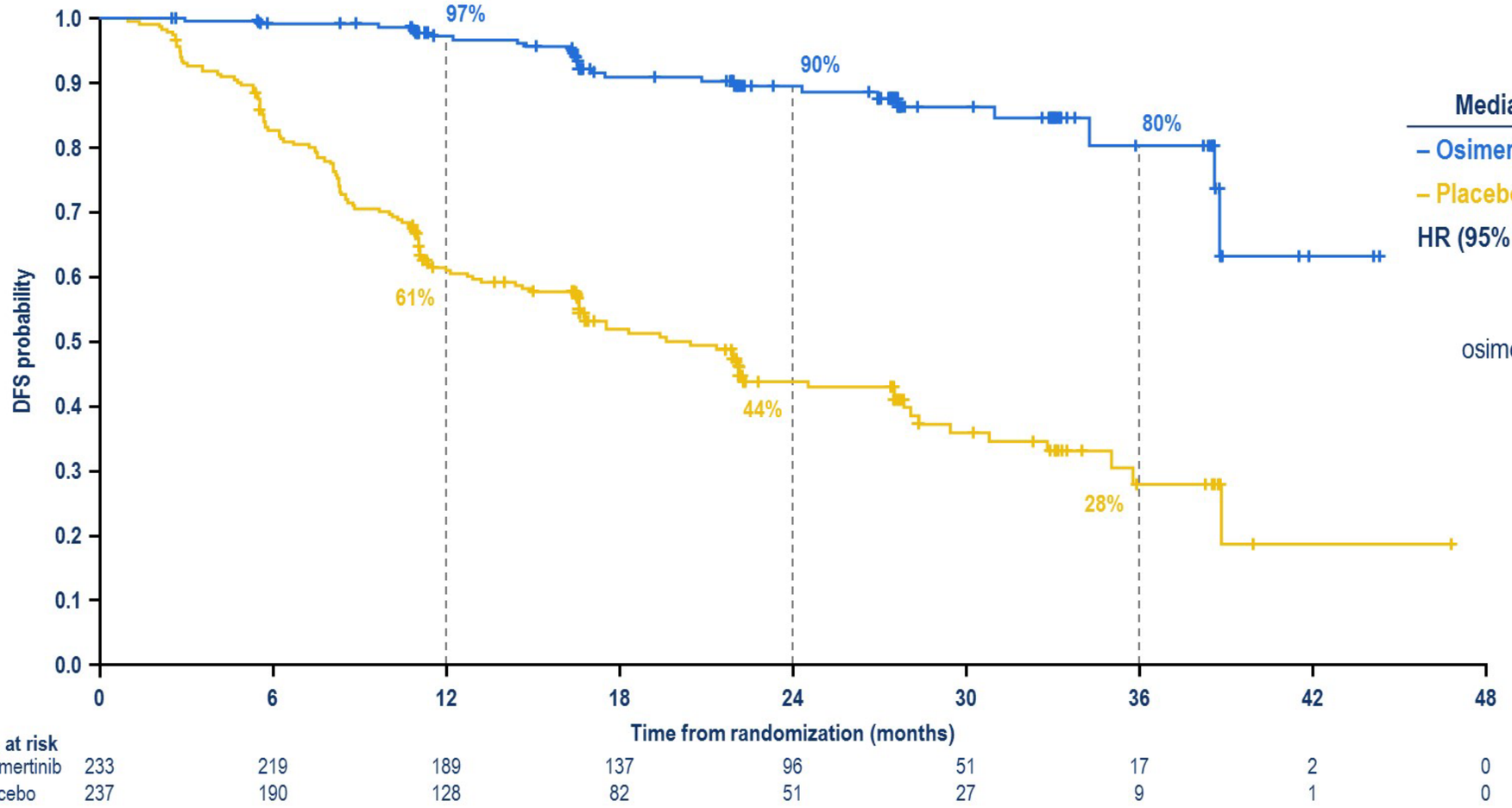
Baseline characteristics in the overall population (stage IB/II/IIIA)

Characteristic, %	Osimertinib (n=339)	Placebo (n=343)
Sex: male / female	32 / 68	28 / 72
Age, median (range), years	64 (30–86)	62 (31–82)
Smoking status: smoker* / non-smoker	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
WHO performance status: 0 / 1	64 / 36	64 / 36
AJCC staging at diagnosis (7th edition): IB / II / IIIA	31 / 35 / 34	31 / 34 / 35
Histology: adenocarcinoma / other†	95 / 5	96 / 4
EGFR mutation at randomization‡: Ex19del / L858R	55 / 45	56 / 44
Adjuvant chemotherapy: yes / no	55 / 45	56 / 44

ADAURA data cut-off: January 17, 2020. *Former: osimertinib n=104, placebo n=83; current: osimertinib n=4, placebo n=3; never: osimertinib n=231, placebo n=257; †Includes bronchial gland carcinoma (NOS): osimertinib n=1, placebo n=2; malignant adenosquamous carcinoma: osimertinib n=4; placebo n=5; other: osimertinib n=11; placebo n=7; ‡Central test.

Presented By Roy Herbst at TBD

Primary endpoint: DFS in patients with stage II/IIIA disease



Median DFS, months (95% CI)	
– Osimertinib	NR (38.8, NC)
– Placebo	20.4 (16.6, 24.5)
HR (95% CI)	**0.17 (0.12, 0.23); p<0.0001**

Maturity 33%:
osimertinib 11%, placebo 55%

No. at risk									
Osimertinib	233	219	189	137	96	51	17	2	0
Placebo	237	190	128	82	51	27	9	1	0

ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 22.1, placebo: 15.0 months;
DFS by investigator assessment; Tick marks indicate censored data.
NC, not calculable; NR, not reached.

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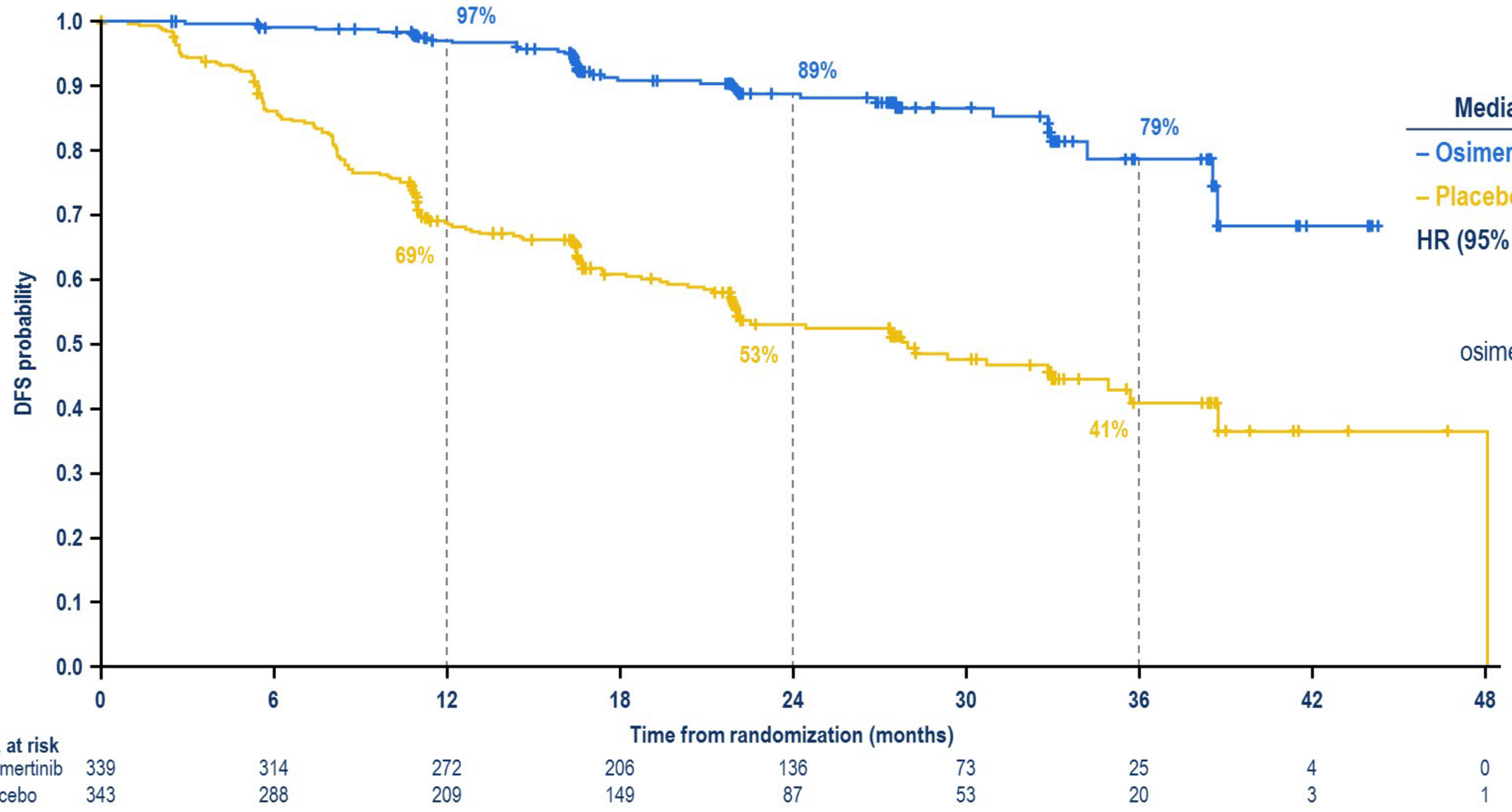
Secondary endpoint: DFS in the overall population (stage IB/II/IIIA)



Median DFS, months (95% CI)	
– Osimertinib	NR (NC, NC)
– Placebo	28.1 (22.1, 35.8)
HR (95% CI)	**0.21 (0.16, 0.28); p<0.0001**

Maturity 29%:
osimertinib 12%, placebo 46%

ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 22.1, placebo: 16.6 months;
DFS by investigator assessment; Tick marks indicate censored data.

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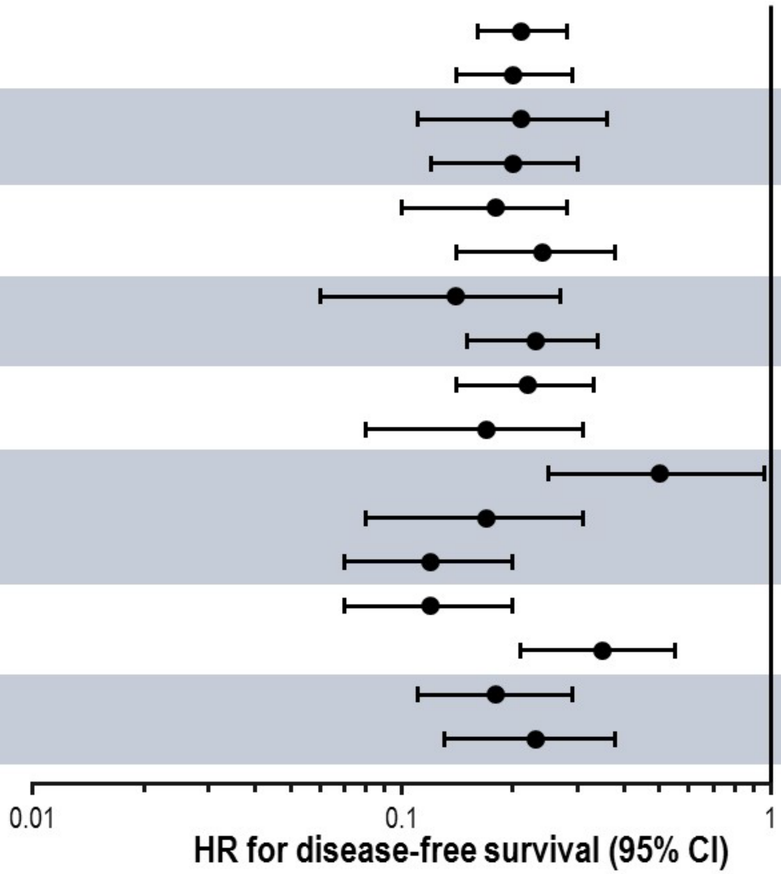
DFS across subgroups in the overall population

Subgroup		HR	95% CI
Overall (N=682)	Stratified log-rank	0.21	0.16, 0.28
	Unadjusted Cox PH	0.20	0.14, 0.29
Sex	Male (n=204)	0.21	0.11, 0.36
	Female (n=478)	0.20	0.12, 0.30
Age	<65 (n=380)	0.18	0.10, 0.28
	≥65 (n=302)	0.24	0.14, 0.38
Smoking status	Smoker (n=194)	0.14	0.06, 0.27
	Non-smoker (n=488)	0.23	0.15, 0.34
Race	Asian (n=434)	0.22	0.14, 0.33
	Non-Asian (n=248)	0.17	0.08, 0.31
Stage	Stage IB (n=212)	0.50	0.25, 0.96
	Stage II (n=236)	0.17	0.08, 0.31
	Stage IIIA (n=234)	0.12	0.07, 0.20
EGFRm	Ex19del (n=378)	0.12	0.07, 0.20
	L858R (n=304)	0.35	0.21, 0.55
Adjuvant chemotherapy	Yes (n=378)	0.18	0.11, 0.29
	No (n=304)	0.23	0.13, 0.38



ADAURA data cut-off: January 17, 2020. Overall population: stage IB / II / IIIA. DFS by investigator assessment.

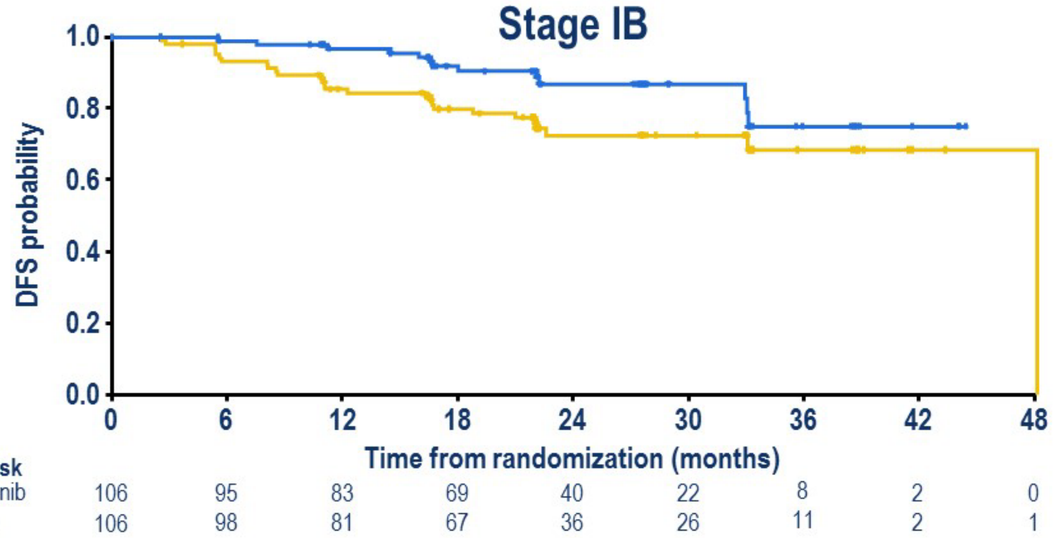
DFS by stage

	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	**0.50 (0.25, 0.96)**	**0.17 (0.08, 0.31)**	**0.12 (0.07, 0.20)**

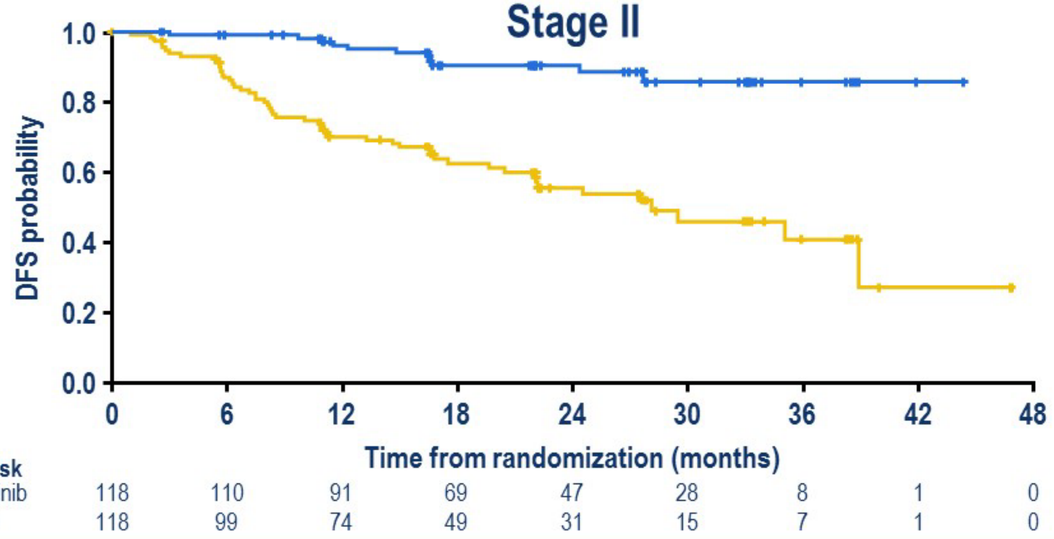
- In the osimertinib arm, 2 year DFS rates were consistent across stages IB, II, and IIIA disease
- Maturity (overall population: stage IB / II / IIIA) 29%: osimertinib events 12%, placebo events 46%

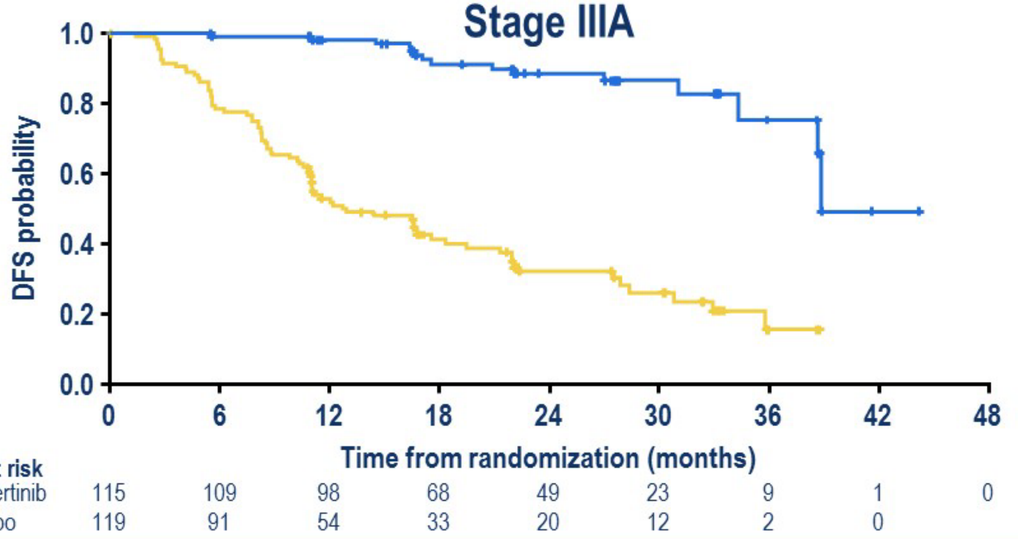
ADAURA data cut-off: January 17, 2020.

DFS by stage



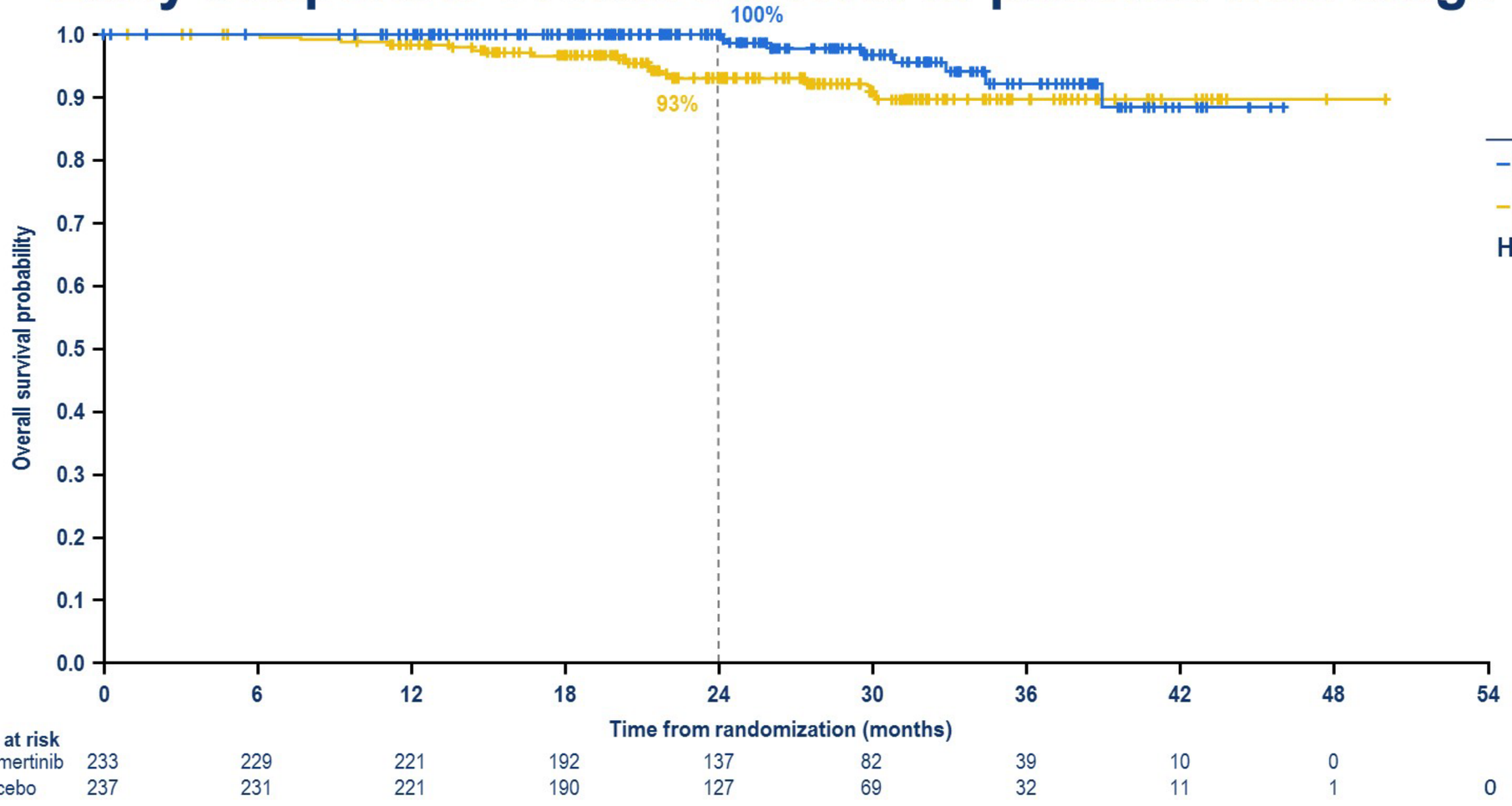
	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	0.50 (0.25, 0.96)	0.17 (0.08, 0.31)	0.12 (0.07, 0.20)





ADAURA data cut-off: January 17, 2020.
Tick marks indicate censored data.

Early snapshot: overall survival in patients with stage II/IIIA disease



Median OS, months (95% CI)	
– Osimertinib	NR (NC, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.40 (0.18, 0.90)**

Maturity 5%:
osimertinib 3%, placebo 7%

ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 26.1, placebo 24.7 months.
Tick marks indicate censored data.

Safety summary

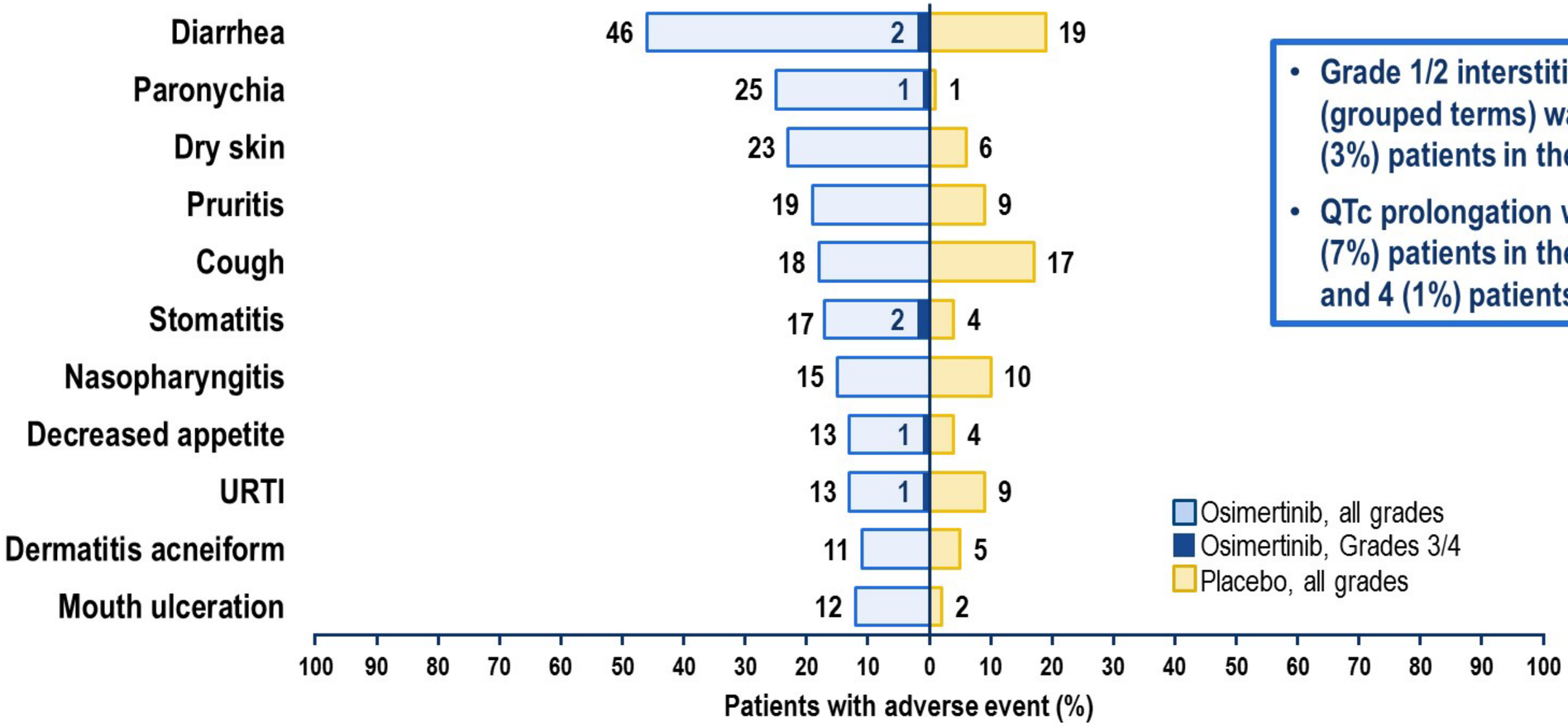
AE, any cause*, n (%)	Osimertinib (n=336)	Placebo (n=343)
Any AE	327 (97)	306 (89)
Any AE Grade ≥3	68 (20)	48 (14)
Any AE leading to death	0	1 (<1)
Any serious AE	54 (16)	44 (13)
Any AE leading to discontinuation	38 (11)	15 (4)
Any AE leading to dose reduction	25 (7)	2 (1)
AE, possibly causally related†, n (%)		
Any AE	303 (90)	190 (55)
Any AE Grade ≥3	32 (10)	9 (3)
Any AE leading to death	0	0
Any serious AE	9 (3)	2 (1)

ADAURA data cut-off: January 17, 2020.

*Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category counted once in each of those categories; †As assessed by the investigator, includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy. AE, adverse event.

All causality adverse events (≥10% of patients)

Median duration of exposure: osimertinib: 22.3 months (range 0 to 43), placebo: 18.4 months (range 0 to 48)



- Grade 1/2 interstitial lung disease (grouped terms) was reported in 10 (3%) patients in the osimertinib arm*
- QTc prolongation was reported in 22 (7%) patients in the osimertinib arm and 4 (1%) patients in the placebo arm†

ADAURA data cut-off: January 17, 2020.
One patient in the placebo arm reported a Grade 5 pulmonary embolism.
*Grade 1, n=6; Grade 2, n=4; †osimertinib: Grade 1, n=14; Grade 2, n=5; Grade 3, n=3; placebo: Grade 1, n=3; Grade 3, n=1.
URTI, upper respiratory tract infection.

Conclusions

- Adjuvant osimertinib is the first targeted agent in a global trial to show a statistically significant and clinically meaningful improvement in DFS in patients with stage IB / II / IIIA EGFRm NSCLC
  - Overall, there was a 79% reduction in the risk of disease recurrence or death with osimertinib (DFS HR 0.21 [95% CI 0.16, 0.28]; p<0.0001)
  - Osimertinib vs placebo DFS rates at 2 years were 89% vs 53%, respectively
- A consistent improvement in DFS was seen regardless of whether patients received prior adjuvant chemotherapy
- The safety profile was consistent with the established safety profile of osimertinib, with mild EGFR-TKI class effects reported; median duration of exposure to osimertinib was 22 months

Adjuvant osimertinib will provide a highly effective, practice changing treatment for patients with stage IB / II / IIIA EGFRm NSCLC after complete tumor resection

ADAURA data cut-off: January 17, 2020.

Summary

- Immunotherapy continues to be an important modality in the treatment of NSCLC
- Neoadjuvant approach seems to be the most promising in early-stage resectable disease
- Adjuvant IO has become the standard of care
- Targeted therapy remains standard of care in the adjuvant setting
- Neoadjuvant approaches remain experimental