Redefining the Management of Early Stage and LA NSLCLC Patients

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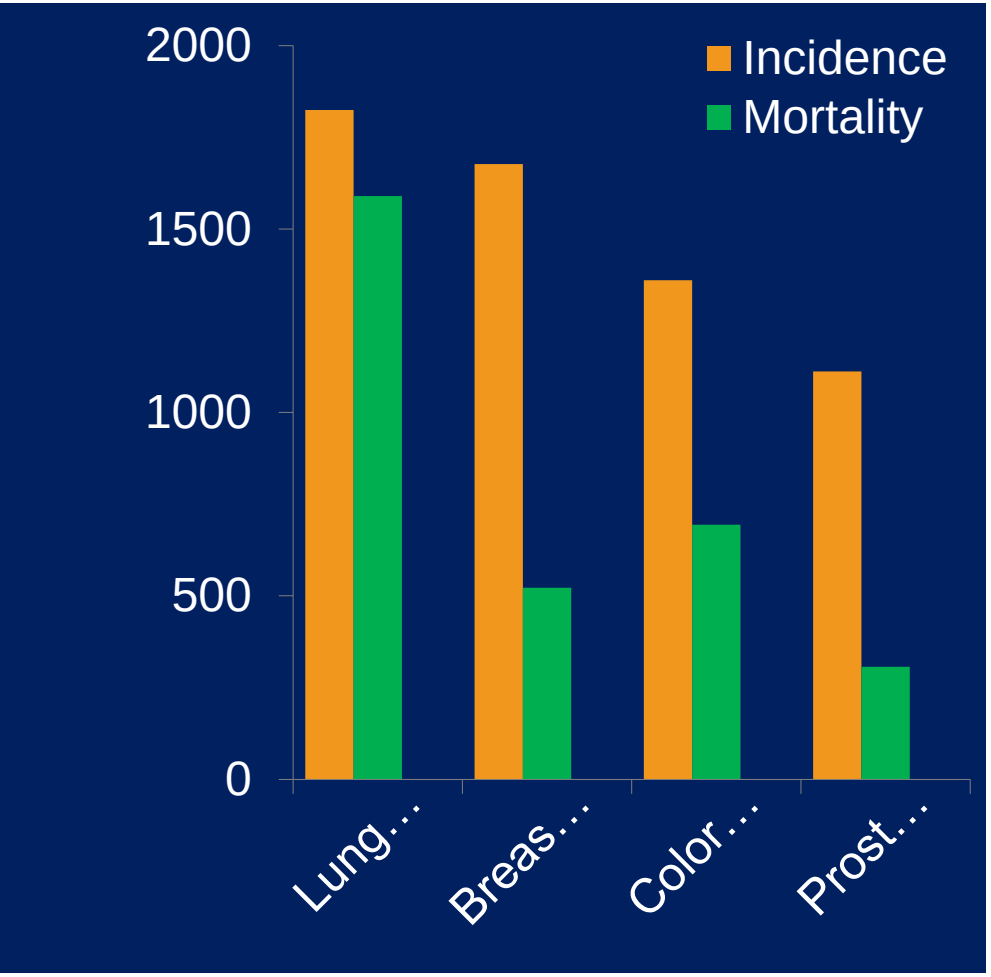
Disease Burden

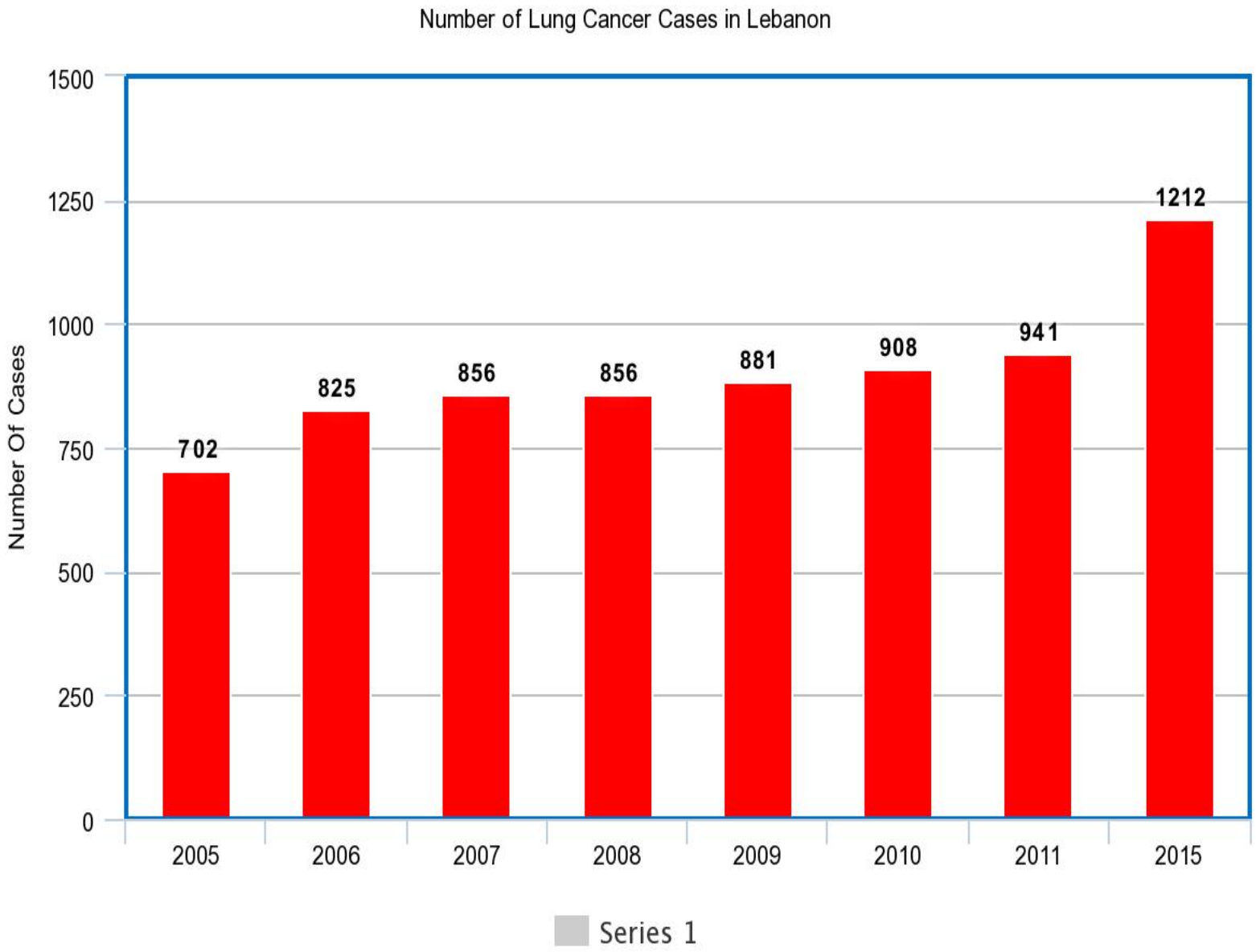


1.82 million[1]
estimated new cases worldwide

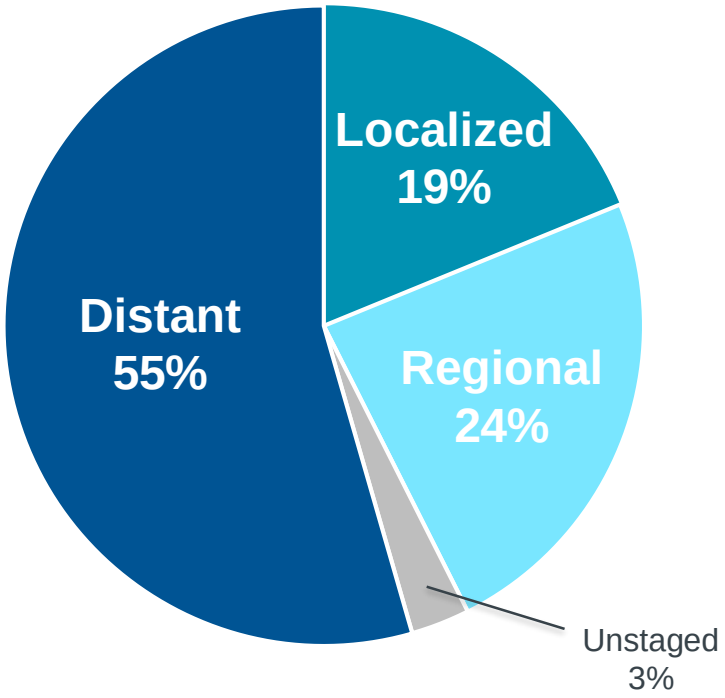
1.59 million[1]
(1 in 5) estimated deaths worldwide

More people die from lung cancer than breast, colorectal and prostate cancers combined[1]

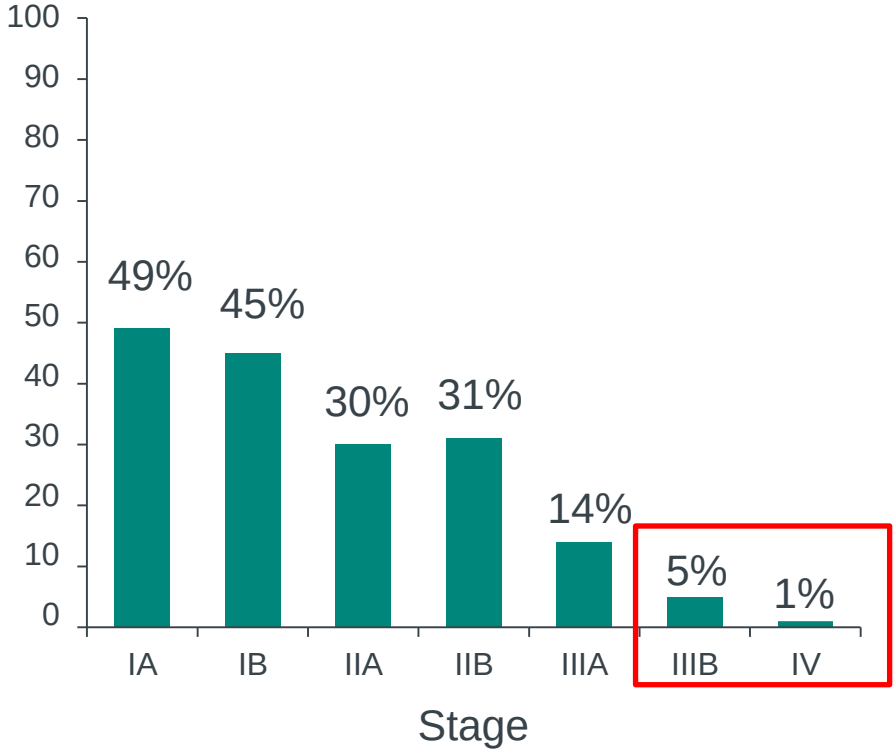
Within Europe, ~1,000 people die from lung cancer every day[1,2]


Number of Lung Cancer Cases in Lebanon
Number Of Cases
1500
1250
1000
750
500
250
0
702
825
856
856
881
908
941
1212
2005
2006
2007
2008
2009
2010
2011
2015
Series 1
meta-chart.com

NSCLC Stage Distribution in the United States[1,a]



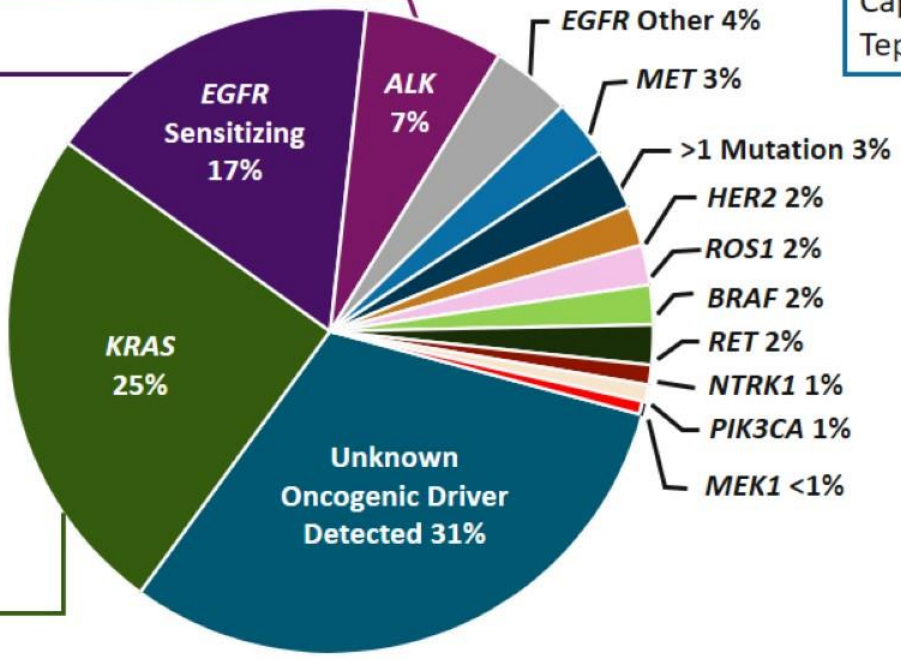
5-Year Observed Survival Rate in the United States[2,b]



[a]Based on United States Surveillance, Epidemiology, and End Results (SEER) data from 2005–2011.
[b]Based on survival rates published in 2007. The data were calculated from the National Cancer Institute's SEER database, based on people who were diagnosed with NSCLC between 1998–2000.
NSCLC = non–small cell lung cancer.

1. Howlader N et al. *SEER Cancer Statistics Review, 1975-2012*. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER website, April 2015
2. American Cancer Society. Lung Cancer (Non-Small Cell). http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-survival-rates. Accessed October 27, 2015.

In 2021 ~ 50% of Patients With Nonsquamous NSCLC Have an Alteration Targetable by an FDA-Approved Agent



***ALK*:**
Crizotinib
Alectinib
Ceritinib
Lorlatinib
Brigatinib

***EGFR* Sensitizing:**
Gefitinib
Erlotinib
Afatinib
Osimertinib
Dacomitinib

***KRAS* G12C:**
Sotorasib

***MET*ex14:**
Capmatinib
Tepotinib

***ROS1*:**
Crizotinib
Entrectinib

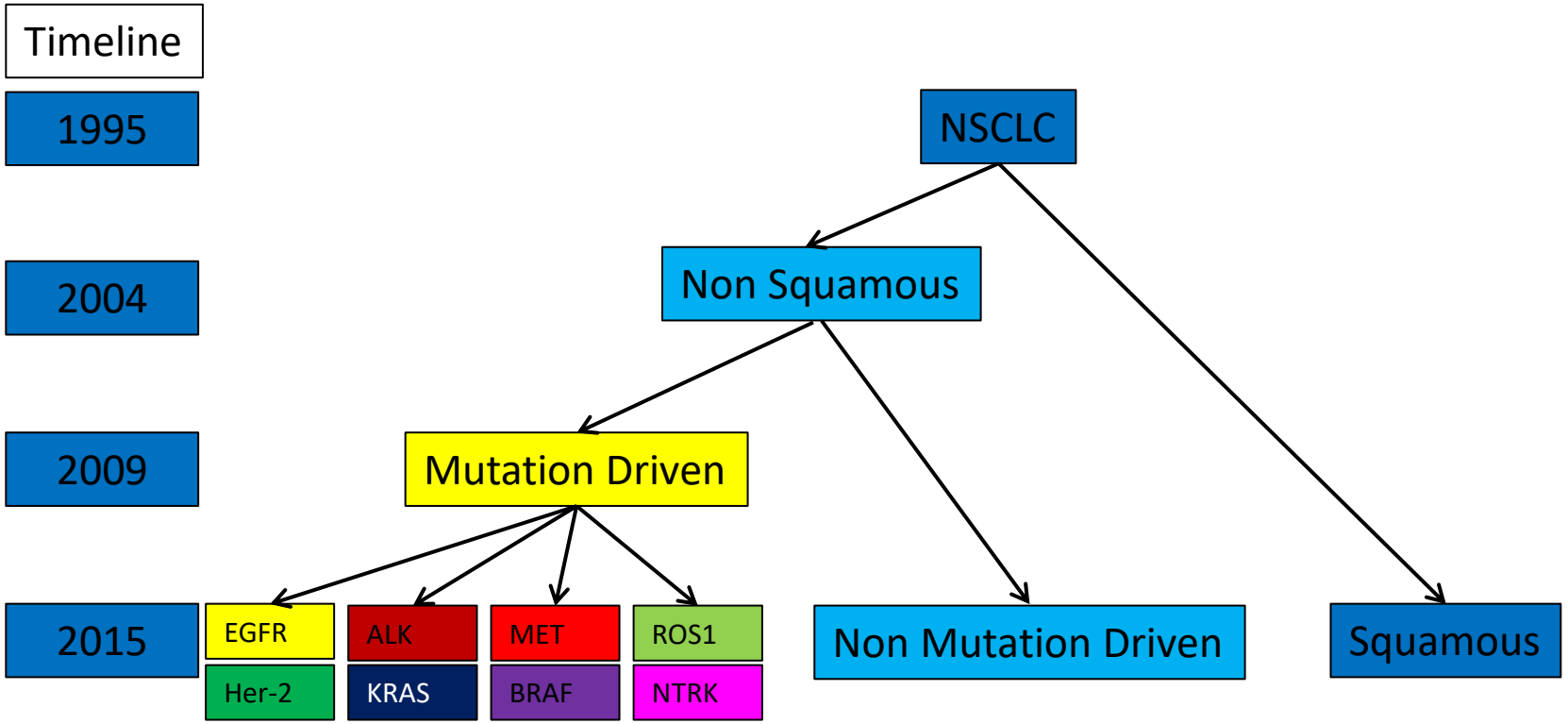
***BRAF* V600E:**
Dabrafenib*

***RET* fusion:**
Selpercatinib
Pralsetinib

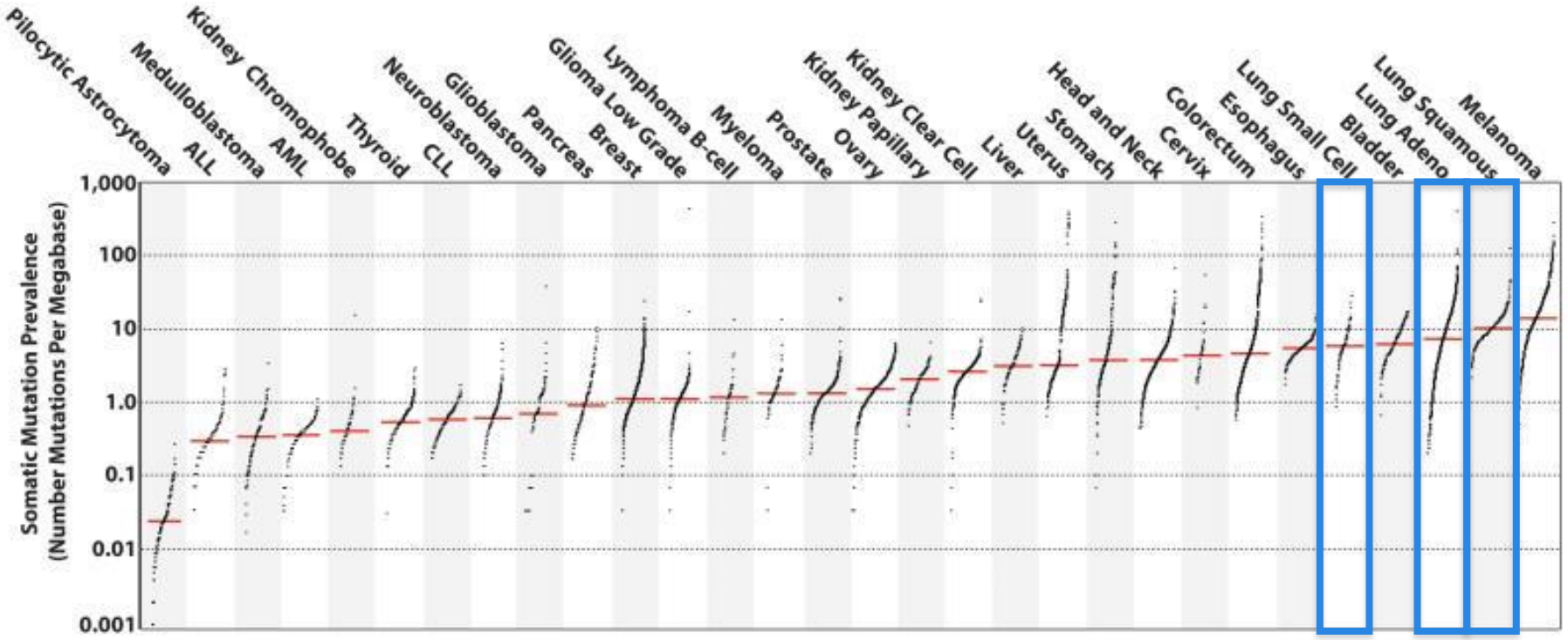
***NTRK* fusion:**
Entrectinib
Larotrectinib

*Approved in combination with trametinib (MEK inhibitor) for *BRAF* V600E mutation.

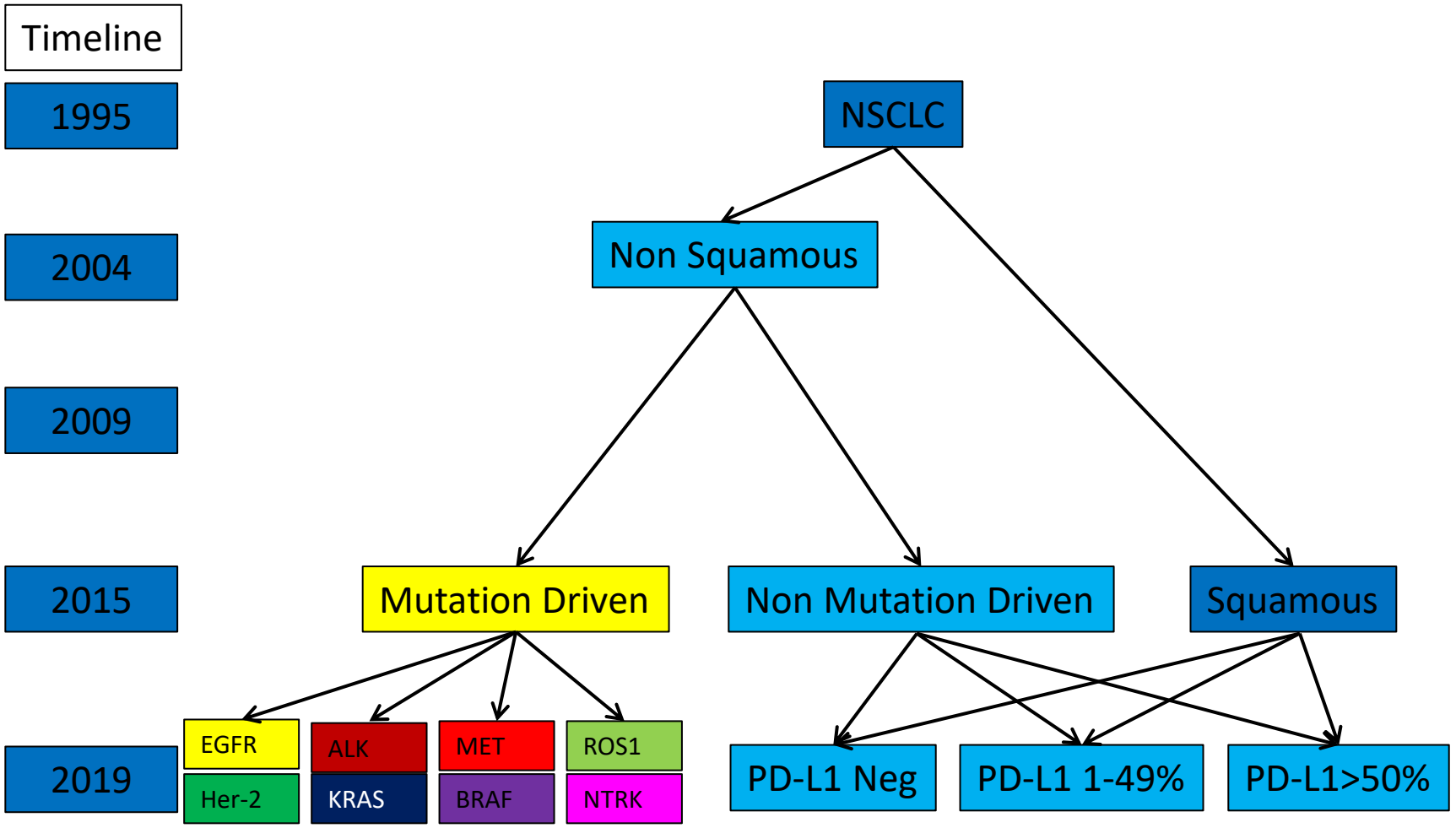
Modified from: Li T, et al. *J Clin Oncol*. 2013;31:1039-49. Tsao AS, et al. *J Thorac Oncol*. 2016;11:613-638.


Timeline
1995
2004
2009
2015
NSCLC
Non Squamous
Mutation Driven
EGFR
ALK
MET
ROS1
Her-2
KRAS
BRAF
NTRK
Non Mutation Driven
Squamous

Lung cancers have a high mutation burden



Alexandrov et al., *Nature* 2013


Timeline
1995
2004
2009
2015
2019
NSCLC
Non Squamous
Mutation Driven
Non Mutation Driven
Squamous
EGFR
ALK
MET
ROS1
Her-2
KRAS
BRAF
NTRK
PD-L1 Neg
PD-L1 1-49%
PD-L1>50%

What about earlier stage disease?

Stage III NSCLC is a heterogeneous disease[1]

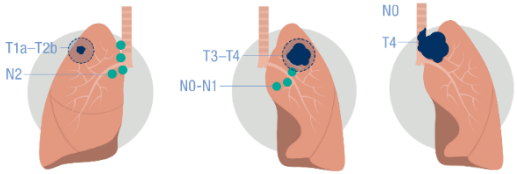
Approximately one-third of patients with NSCLC present with Stage III disease, and the majority have unresectable tumours[2,3]

THE *IASLC STAGING MANUAL IN THORACIC ONCOLOGY, VERSION 8* SUBDIVIDES STAGE III NSCLC INTO IIIA, IIIB, AND IIIC PRESENTATIONS[4]

STAGE IIIA

Example tumour size and location for Stage IIIA

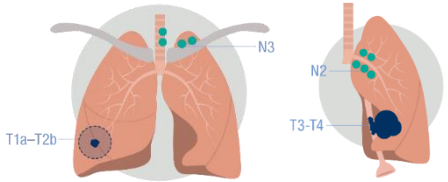
No distant metastases



STAGE IIIB

Example tumour size and location for Stage IIIB

No distant metastases

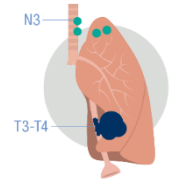


STAGE IIIC

Example tumour size and location for Stage IIIC

No distant metastases

Stage IIIC was previously part of IIIB



International guidelines strongly recommend evaluation of each Stage III NSCLC case by a multidisciplinary team (MDT)[5,6]

TUMOURS (T) LYMPH NODE METASTASES (N)

IASLC=International Association for the Study of Lung Cancer; NSCLC=non-small cell lung cancer.

References: 1. Eberhardt WE et al. *Ann Oncol.* 2015;26(8):1573-1588. **2.** Aupérin A et al. *J Clin Oncol.* 2010;28(13):2181-2190. **3.** Johnson DH. *Chest.* 2000;117(4)(suppl 1):123S-126S. **4.** Detterbeck FC et al. *Chest.* 2017;151(1):193-203. **5.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). https://www.nccn.org/guidelines/recently-published-guidelines. Accessed November 2021. **6.** Postmus PE et al. *Ann Oncol.* 2017;28(suppl 4):iv1-iv21.

In Stage III NSCLC, cure is the treatment goal[1]

CURRENT PRACTICE IN UNRESECTABLE STAGE III NSCLC[1,2]

- **Up to 89% of unresected patients will eventually progress to metastatic NSCLC[3,4]**
- **The 5-year survival rate for patients with unresectable Stage III NSCLC is about 15%[4,5]**

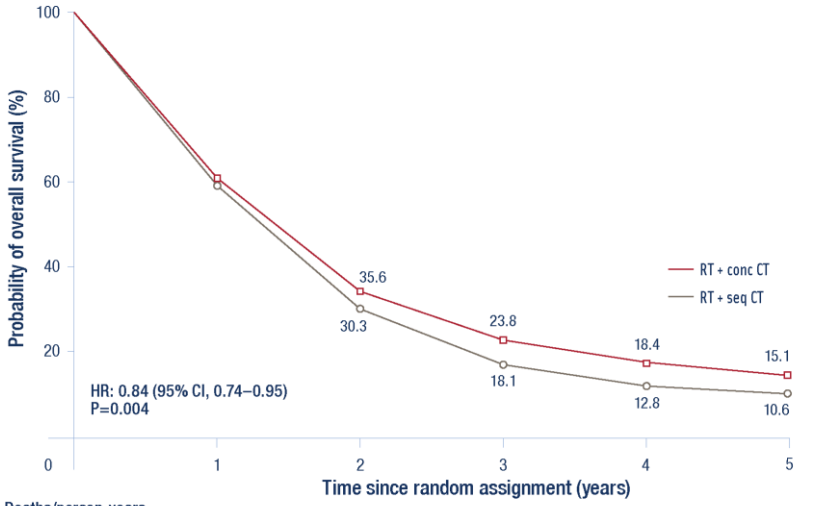
*ESMO NSCLC Clinical Practice Guidelines 2017 recommend: Patients with NSCLC who are treated with radical intent should be followed for treatment-related complications, detection of treatable relapse, or occurrence of second primary lung cancer. Surveillance every 6 months for 2 years with a visit including history, physical examination, and—preferably contrast-enhanced—volume chest CT scan at least at 12 and 24 months is recommended, and thereafter an annual visit including history, physical examination, and chest CT scan in order to detect second primary tumours. For individual patients, follow-up with 6-monthly CT scans for 3 years is recommended for patients who are suitable for salvage treatment (eg, surgery, local ablative therapy). The frequency of the follow-up visits can be tailored to the individual patient for those not suitable for salvage treatment.[6]

CT=computed tomography; ESMO= European Society for Medical Oncology; NSCLC=non-small cell lung cancer.

References: 1. Eberhardt WE et al. *Ann Oncol.* 2015;26(8):1573-1588. **2.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines https://www.nccn.org/guidelines/recently-published-guidelines. Accessed November 2021. **3.** Albain KS et al. *Lancet.* 2009;374(9687):379-386. **4.** Gandara DR et al. *Clin Lung Cancer.* 2006;8(2):116-121. **5.** Aupérin A et al. *J Clin Oncol.* 2010;28(13):2181-2190. 6.Postmus PE et al. *Ann Oncol.* 2017;28(suppl 4):iv1-iv21

Concurrent versus Sequential Therapy

OVERALL SURVIVAL OF STAGE III NSCLC FOLLOWING CONCURRENT CRT[2]



Deaths/person-years by period	0y–1y	1y–2y	2y–3y	3y–4y	>4y
RT + conc CT (n=603)	240/498	147/276	67/171	30/116	37/186
RT + seq CT (n=602)	253/491	171/242	70/129	30/83	23/126

Adapted from Aupérin A et al. J Clin Oncol 2010;28(13):2181-2190.

Concurrent CRT gives superior outcomes over sequential CRT in unresectable stage III NSCLC[2-5]

Of patients with stage III NSCLC who receive concurrent CRT, 15.1% achieve 5-year OS[2]

Concurrent CRT OS benefit over sequential:[2]

- 5.7% absolute benefit at 3 years
- 4.5% absolute benefit at 5 years

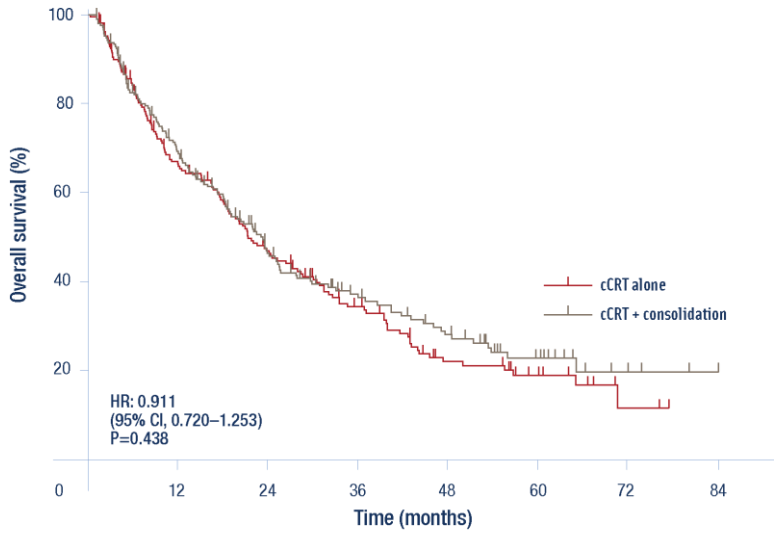
EVIDENCE AROUND CONSOLIDATION CT

CI=confidence interval; Conc CT=concurrent chemotherapy; CRT=chemoradiotherapy; CT=chemotherapy; ESMO= European Society for Medical Oncology; HR=hazard ratio; NSCLC=non-small cell lung cancer; OS=overall survival; RT=radiation therapy; seq CT=sequential chemotherapy.

References: 1. Eberhardt WE et al. *Ann Oncol.* 2015;26(8):1573-1588. **2.** Aupérin A et al. *J Clin Oncol.* 2010;28(13):2181-2190. **3.** Uitterhoeve AL et al *Radiat Oncol* 2007;2:27. **4.** Curran WJ et al. *J Natl Cancer Inst.* 2011;103(9):1452-1460 **5.** Spigel DR and Greco FA *Semin Surg Oncol* 2003;21(2):98-110.

Role of Consolidation Chemotherapy

OVERALL SURVIVAL[1]



	Patients	Events	mOS (95% CI)
cCRT alone	211	145	20.63 (17.58–26.28)
cCRT + consolidation	209	134	21.78 (17.71–24.74)

Adapted from Ahn JS et al. *J Clin Oncol* 2015;33(24):2660-2666.

In a multinational phase III trial, the addition of consolidation treatment to concurrent CRT provided no significant benefit in OS for unresectable stage III NSCLC patients[1]

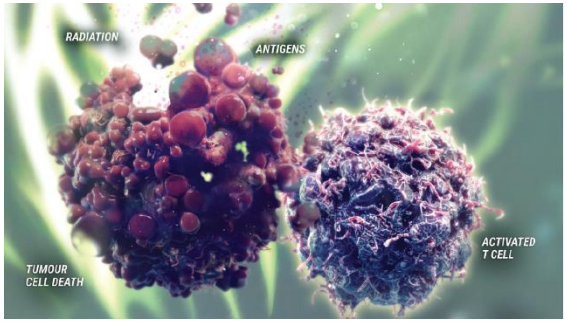
CI=confidence interval; cCRT= concurrent chemoradiotherapy; HR=hazard ratio; NSCLC=non-small cell lung cancer; OS=overall survival.

Reference: 1. Ahn JS et al. *J Clin Oncol* 2015;33(24):2660-2666.

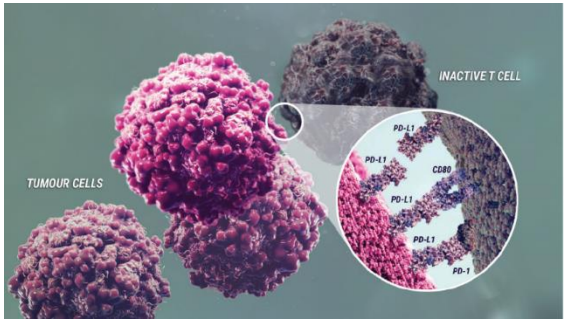
Role of the immune system following radiation therapy

The PD-L1 pathway plays a key role in tumour progression[1-5]

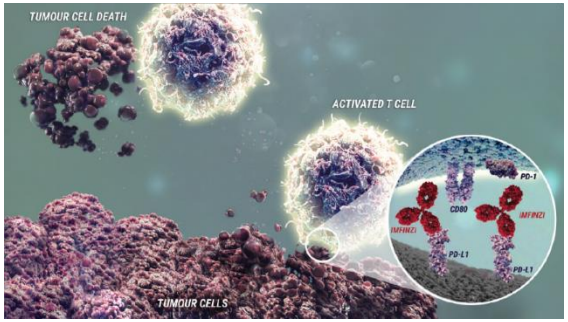
Increased PD-L1 expression following radiation has been observed in pre-clinical models[1-5]



Radiation induces tumour cell death, releasing a diverse array of tumour antigens[3-5]



As a result, PD-L1 is upregulated, inhibiting the increased T cell activity and promoting tumour regrowth[1,2]



IMFINZI blocks PD-L1 and reinvigorates T cells, enhancing the immune response[6]

Radiation primes the immune system; IMFINZI enables the immune response[1-6]

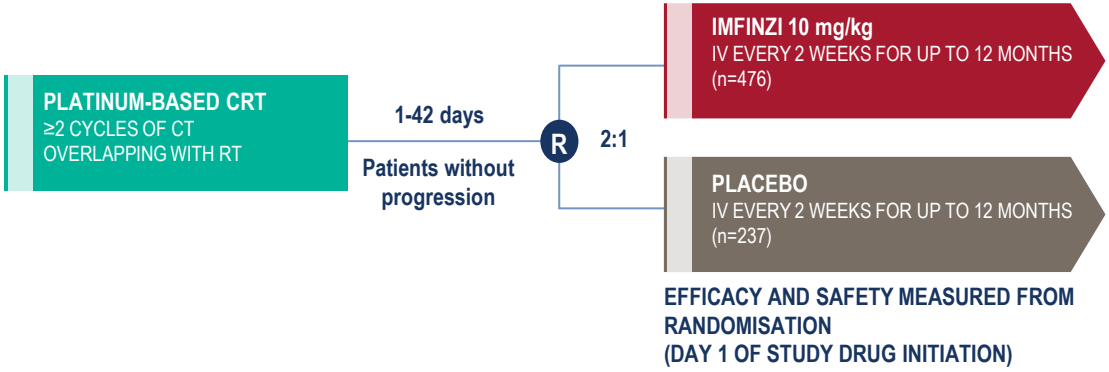
CD80=cluster of differentiation 80; PD-1=programmed cell death-1; PD-L1:=programmed cell death ligand-1

References: 1. Dovedi SJ et al. *Cancer Res.* 2014;74(19):5458-5468. **2.** Deng L et al. *J Clin Invest.* 2014;124(2):687-695. **3.** Lugade AA et al. *J Immunol.* 2005;174(12):7516-7523. **4.** Reits EA et al. *J Exp Med.* 2006;203(5):1259-1271. **5.** Chakraborty M et al. *Cancer Res.* 2004;64(12):4328-4337. **6.** Stewart R et al. *Cancer Immunol Res.* 2015;3(9):1052-1062.

PACIFIC Trial

A randomised, double-blind, placebo-controlled, international study[1]

PATIENTS WITH UNRESECTABLE, LOCALLY ADVANCED (STAGE III*) NSCLC[1,2]



CO-PRIMARY ENDPOINTS[1]:

- Overall survival (OS)
- Progression-free survival (PFS)†

SECONDARY ENDPOINTS INCLUDE[1,3]:

- OS at 24 months
- PFS at 12 and 18 months
- Health-related quality of life (HRQoL)
- Safety and tolerability

- CT included cisplatin or carboplatin (or both) plus one of the following: etoposide, vinorelbine, paclitaxel, vinblastine, docetaxel, or pemetrexed[4]
- 92% of patients had received a total dose of 54-66 Gy of radiation[3]
- Selected patient characteristics at study start: median age 64 years; 70% male; 53% Stage IIIA; 46% squamous[3]
- Patients were enrolled regardless of PD-L1 expression or EGFR/ALK status[1]

*According to the *Staging Manual in Thoracic Oncology, version 7*, of the International Association for the Study of Lung Cancer; the study included patients who are now classified as Stage IIIC.[2,5]
†PFS was based on blinded independent central review (BICR) using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[1]

ALK= anaplastic lymphoma kinase; CT= chemoradiation; EGFR= epidermal growth factor receptor; IV= intravenous; NSCLC= non small cell lung cancer; RT= radiation therapy

References: 1. Antonia SJ et al. *N Engl J Med*. 2018;379(24):2342-2350. **2.** International Association for the Study of Lung Cancer. https://cancerstaging.org/references-tools/quickreferences/Documents/LungMedium.pdf. Accessed August 27, 2018. **3.** IMFINZI. Prescribing Information. **4.** Antonia SJ et al. *N Engl J Med*. 2017;377(20):1919-1929. **5.** Detterbeck FC et al. *Chest*. 2017;151(1):193-203.

Patient Demographics

BASELINE DEMOGRAPHICS	IMFINZI (n=476)	PLACEBO (n=237)
Sex		
Male	70.2%	70.0%
Female	29.8%	30.0%
Age at randomisation		
Median (range)	64 (31-84)	64 (23-90)
Smoking status		
Current smoker	16.6%	16.0%
Former smoker	74.4%	75.1%
Never smoked	9.0%	8.9%

DISEASE CHARACTERISTICS	IMFINZI (n=476)	PLACEBO (n=237)
NSCLC disease stage		
IIIA	52.9%	52.7%
IIIB*	44.5%	45.1%
Other	2.5%	2.1%
Tumour histology		
Squamous	47.1%	43.0%
Non-squamous	52.9%	57.0%
PD-L1 expression status†		
≥25%	24.2%	18.6%
<25%	39.3%	44.3%
Unknown	36.6%	37.1%
WHO performance status		
0	49.2%	48.1%
1	50.4%	51.5%
Not reported	0.4%	0.4%

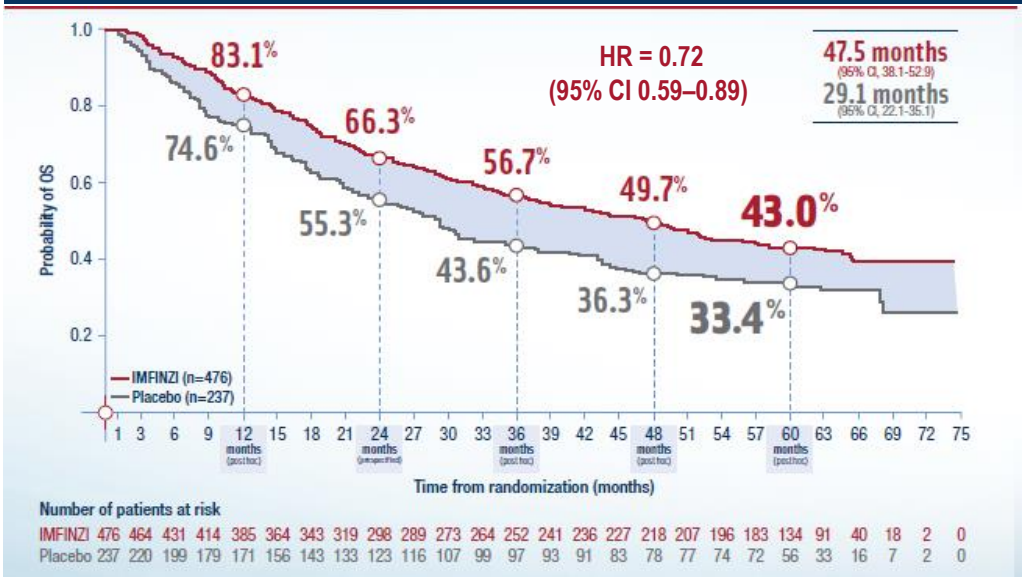
*Includes Stage IIIC as defined in the *Staging Manual in Thoracic Oncology, version 8*, of the International Association for the Study of Lung Cancer.[2]
†PD-L1 status was retrospectively analysed using the Ventana SP263 PD-L1 assay in 451 patients with available samples, taken prior to concurrent platinum-based CRT.[1]

CRT= chemoradiotherapy; NSCLC= non small cell lung cancer; PD-L1= programmed cell death ligand-1; WHO= World Health Organisation

References: 1. Antonia SJ et al. *N Engl J Med.* 2018;379(24):2342-2350 (including supplementary appendix). **2.** Detterbeck FC et al. *Chest.* 2017;151(1):193-203.

5-year Overall Survival Data

5-YEAR OS IN ITT POPULATION[1]*



IN THE ITT POPULATION

- Updated 5-year OS (34.2 months median follow-up): median OS was 47.5 months with IMFINZI vs 29.1 months with placebo[1†]
- Primary OS analysis (25.2 months median follow-up): Median OS was not reached with IMFINZI vs 28.7 months with placebo[2‡]

28% reduction in the risk of death with Durvalumab vs placebo
(HR: 0.72; 95% CI: 0.59–0.89)[1]

*Patients were retrospectively tested for PD-L1 expression on tumour cell using the Ventana PD-L1 (SP263) IHC assay, where available. 63% of patients provided a tissue sample of sufficient quality and quantity to determine PD-L1 expression and 37% were unknown[2]

†Updated post-hoc OS analysis at ~5 years after randomisation. Analysis was not intended to show statistical significance[1]

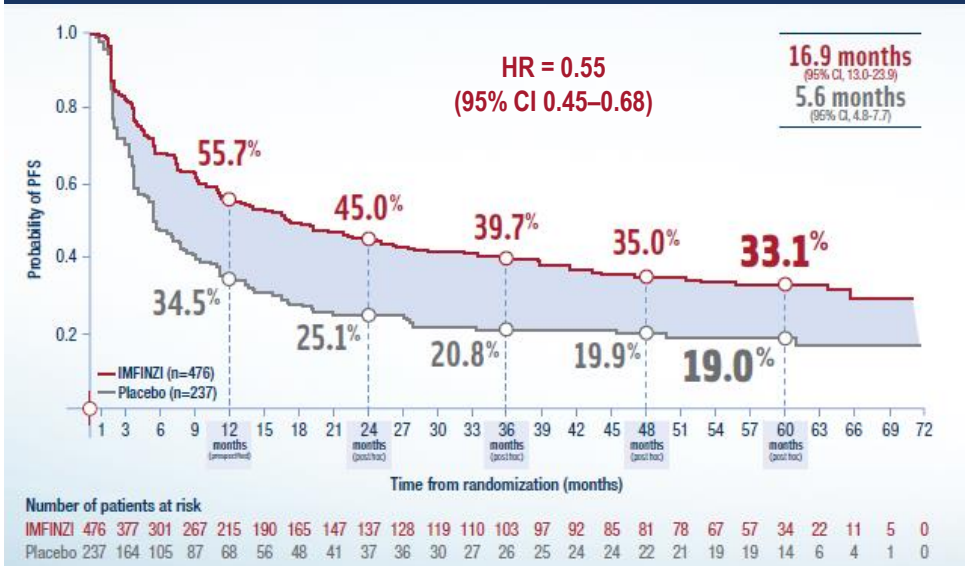
‡The primary 2-year OS analysis was conducted after 299 deaths for 42% maturity (61% of targeted events).[2]

CRT= chemoradiotherapy; CI= confidence interval; HR= hazard ratio; IHC= immunohistochemistry; ITT= intent-to treat; mOS= median overall survival; OS= overall survival; PD-L1= programmed death ligand-1.

References: 1. Spigel D. et al. Presented at ASCO 2021. Abstract 8511; 2. Antonia S et al. *N Engl J Med*. 2018;379:2342–2350 (including supplementary appendix).

5-year Progression-Free Survival Data

5-YEAR PROGRESSION-FREE SURVIVAL (ITT POPULATION)[1]



5-YEAR UPDATED PFS ANALYSIS[1*]

Median PFS: 16.9 months with IMFINZI vs 5.6 months with placebo

- 5 years PFS rate was 33% with IMFINZI vs 19% with placebo

Improvement in 18-month PFS rate[2]

14.5-month median follow-up after randomization

- Median PFS: 16.8 months with IMFINZI vs 5.6 months with placebo
- 48% reduction in the risk of progression or death vs placebo (HR=0.52; P<0.0001)
- 1-year PFS rate was 56% with IMFINZI vs 35% with placebo[†]

45% reduction in the risk of death or disease progression with Durvalumab vs placebo (HR: 0.55; 95% CI: 0.45–0.68)[1]

*Measured based on RECIST v1.1 criteria by BICR. The primary PFS analysis was conducted after 371 events (81% of targeted 458 events) with a median follow-up of 14.5 months. The post hoc 5-year PFS analysis was conducted at ~5 years after last patient was randomized and was not powered to show statistical significance.[1,2]

[†] 95% CI was 51% to 60% with IMFINZI vs 29% to 42% with placebo[2]

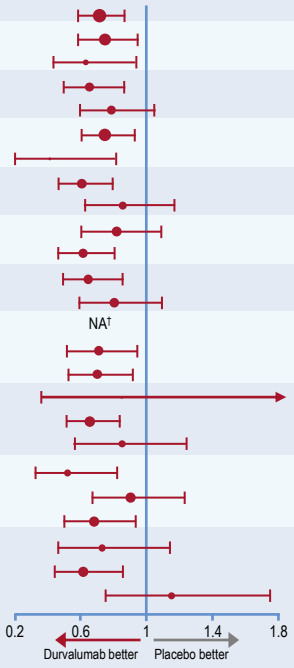
CI= confidence interval; CRT= chemoradiotherapy; BICR= blinded independent central review; HR= hazard ratio; ITT= intent-to treat; PFS= progression free survival; RECIST= response evaluation criteria in solid tumors

References: 1 . Spigel D. et al. Presented at ASCO 2021. Abstract 8511. **2.** Antonia SJ et al. *N Engl J Med.* 2017;377(20):1919-1929.

OS Subgroup Analysis

OS IN PRESPECIFIED SUBGROUPS (ITT)*

OS		No. of events / No. of patients (%)
All patients		419/713 (58.8)
Sex	Male	304/500 (60.8)
	Female	115/213 (54.0)
Age at randomisation	<65 years	209/391 (53.5)
	≥65 years	210/322 (65.2)
Smoking status	Smoker	384/649 (59.2)
	Non-smoker	35/64 (54.7)
NSCLC disease stage	Stage IIIA	277/377 (60.2)
	Stage IIIB	182/319 (57.1)
Tumour histologic type	Squamous	205/326 (62.9)
	All other	214/387 (55.3)
Prior definitive CT	Cisplatin	215/395 (54.4)
	Carboplatin	190/301 (63.1)
Best response to prior treatment	Complete response	9/16 (56.3)
	Partial response	186/349 (53.3)
	Stable disease	216/338 (63.9)
***EGFR* mutation status**	Positive	25/43 (58.1)
	Negative	275/482 (57.1)
	Unknown	119/188 (63.3)
PD-L1 status (pre-specified)	≥25%	78/159 (49.1)
	<25%	175/292 (59.9)
	Unknown	166/262 (63.4)
PD-L1 status (post-hoc)	1–24%	81/144 (56.3)
	≥1%	159/303 (52.5)
	<1%	94/148 (63.5)



- 5-year updated OS results for subgroups were consistent with the results reported at the time of the primary analyses[1]

Data cut off: 11 January 2021. *Treatment effect estimated using an unstratified Cox proportional hazards model (with treatment as the only covariate). Updated analysis not designed to show statistical significance; †HR and 95% CI not calculated if the subgroup had <20 events.
CI= confidence interval; CT= chemotherapy; EGFR epidermal growth factor receptor; ITT= intent to treat; NA= not applicable; NSCLC= non-small cell lung cancer; OS= overall survival; PD-L1= programmed death ligand-1.
References: 1. Spigel DR et al. Abstract #8511. Presented at ASCO 2021.

Treatment Initiation

Patients who initiated IMFINZI within 14 days following CRT had a 57% reduction in the risk of death vs placebo (HR=0.43; 95% CI, 0.28-0.66)[1]

PRESPECIFIED ANALYSIS OF OS BASED ON TIME TO IMFINZI INITIATION (ITT POPULATION)[1]

Subgroup		Patients		Unstratified HR for Death (95% CI)
		IMFINZI	Placebo	
LAST RAD TO RANDOMISATION	<14 days	120	62	0.43 (0.28-0.66)
	≥14 days	356	175	0.79 (0.61–1.02)

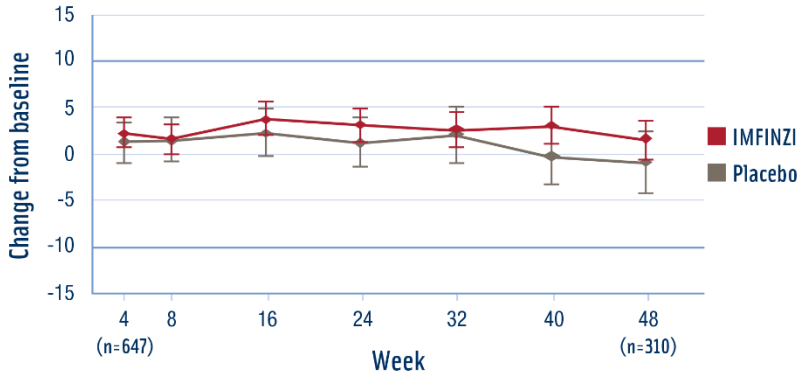
Engage with the multidisciplinary team (MDT) to initiate
The PACIFIC Regimen: CRT rapidly followed by Durvalumab[2]

CI= confidence interval; CRT= chemoradiotherapy; HR= hazard ratio; ITT= intent-to treat.

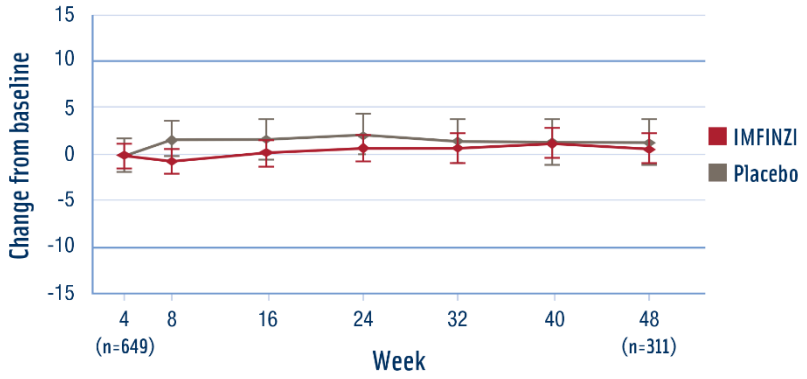
Reference: 1. Gray JE et al. Poster presented at the American Society of Clinical Oncology (ASCO) Annual meeting; May 31–June 4 2019: Chicago, IL, USA. Poster 8526.. **2.** IMFINZI. Prescribing Information.

Comparable QoL

GLOBAL HEALTH STATUS/QoL (ITT POPULATION)[1]



PHYSICAL FUNCTIONING (ITT POPULATION)[1]



No clinically meaningful difference from baseline (average over 12 months) in patient-reported key lung cancer symptom scores with IMFINZI vs placebo.[2]

No significant change from baseline in overall HRQoL at week 48 in patients receiving Durvalumab vs placebo[2]

Patient-reported key lung cancer symptoms, physical function, and global health status/QoL were evaluated using the EORTC QLQ-C30 v3 questionnaire and its lung cancer module, QLQ-LC13. Changes from baseline for key symptoms (EORTC QLQ-LC13: cough, dyspnoea, chest pain; EORTC QLQ-C30: fatigue and appetite loss, physical functioning, and global health status) were analysed using a mixed model for repeated measures (MMRM). Deterioration or improvement was defined as a change in score from baseline ≥±10. Compliance with completing the EORTC QLQ was high and similar between the IMFINZI and placebo groups up to week 48 (>80%).[2]

EORTC= European Organisation for the Research and Treatment of Cancer; HRQoL= health related quality of life; ITT= intent to treat; QOL= quality of life; QLQ-LC13= Quality of Life Questionnaire-Lung Cancer 13; QLQ-C30= Quality of Life Questionnaire-Cancer 30

References: 1. Hui R et al. Data presented at: IASLC 18th World Conference on Lung Cancer; October 15-18, 2017; Yokohama, Japan. **2.** Hui R et al. *J Thorac Oncol.* 2017;12(11)(suppl 2):S1601-S2433.

Side Effect Profile

ADVERSE REACTIONS REPORTED IN ≥10% OF PATIENTS (VERY COMMON)[1]	IMFINZI (n=475)		Placebo (n=234)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Cough	35.2%	0.4%	25.2%	0.4%
Fatigue	24.0%	0.2%	20.5%	1.3%
Dyspnoea	22.3%	1.5%	23.9%	2.6%
Radiation pneumonitis	20.2%	1.5%	15.8%	0.4%
Diarrhoea	18.5%	0.6%	19.7%	1.3%
Pyrexia	15.2%	0.2%	9.4%	0.0%
Nausea	14.3%	0.0%	13.2%	0.0%
Decreased appetite	14.3%	0.2%	12.8%	0.9%
Pneumonia	13.3%	4.4%	7.7%	3.8%
Pneumonitis	12.6%	1.9%	7.7%	1.7%
Arthralgia	12.4%	0.0%	11.1%	0.0%
Upper respiratory tract infection	12.4%	0.2%	10.3%	0.0%
Pruritus	12.4%	0.0%	5.1%	0.0%
Rash	12.2%	0.2%	7.7%	0.0%
Constipation	11.8%	0.2%	8.5%	0.0%
Hypothyroidism	11.6%	0.2%	1.7%	0.0%
Headache	10.9%	0.2%	9.0%	0.9%
Asthenia	10.7%	0.6%	13.2%	0.4%
Back pain	10.5%	0.2%	11.5%	0.4%
Musculoskeletal pain	8.2%	0.6%	10.3%	0.4%
Anaemia	7.6%	2.9%	11.1%	3.4%

EORTC= European Organisation for the Research and Treatment of Cancer; QLQ-LC13= Quality of Life Questionnaire-Lung Cancer 13

Grade 3 or 5 pneumonitis or radiation pneumonitis occurred in 3.4% & 1.1% of patients on IMFINZI and 3.0% & 1.7% on placebo.[2]

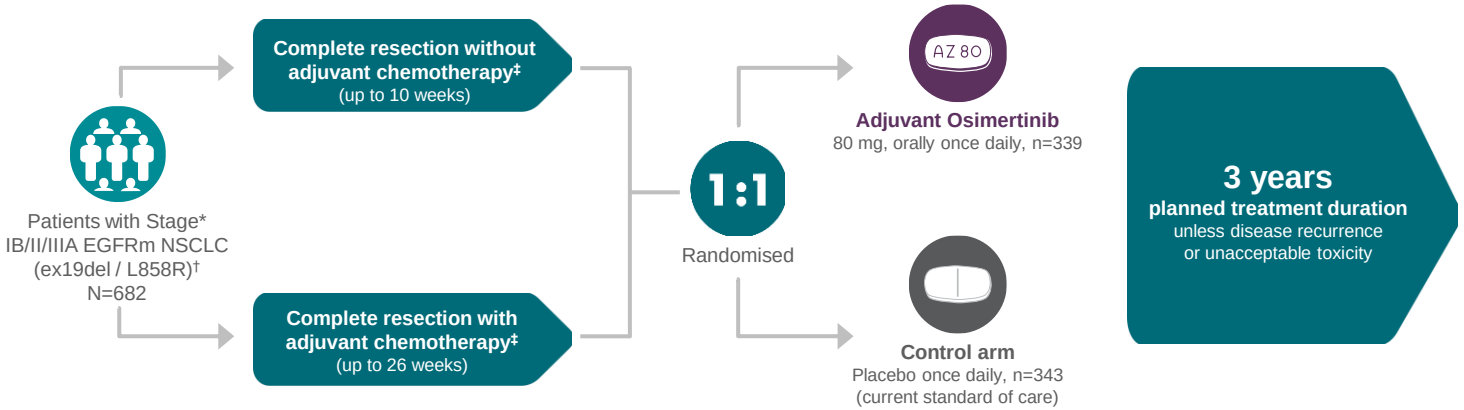
Grade 5 adverse reactions of any cause occurred in 4.4% of patients on IMFINZI vs 6.4% on placebo.[1]

Treatment with IMFINZI resulted in no clinically meaningful difference in patient-reported key lung cancer symptom scores (as measured by the EORTC QLQ-LC13) compared with placebo as assessed by a difference of ≥10 points.[2]

Reference: 1. Antonia SJ et al. *N Engl J Med.* 2018;379(24):2342-2350. Supplementary appendix **2.** Imfinzi. Summary of Product characteristics.

What about EGFR-mutated early-stage disease?

ADAURA Trial



*AJCC 7th edition.
†Centrally confirmed in tissue.
‡Per physician discretion. Prior, post, or planned radiotherapy was not allowed. Neoadjuvant chemotherapy was not allowed.

Primary endpoint: Disease-free survival (DFS) in patients with Stage II to IIIA NSCLC
Secondary endpoints: DFS in overall population, DFS at 2, 3, and 5 years, overall survival, safety, health-related quality of life[1,2]

- The ADAURA study was powered to show a hazard ratio (HR) of 0.7 in favor of the Osimertinib arm[1]

Although interim results were independently unblinded due to overwhelming efficacy, patients and investigators remain blinded to treatment[1]

CI= confidence interval; DFS= disease free survival; EGFR= epidermal growth factor receptor; EGFRm= EGFR mutation-positive; HR= hazard ratio; NSCLC= non-small cell lung cancer

1. Wu Y-L, Tsuboi M, He J, et al; ADAURA Investigators. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2027071. **2.** AstraZeneca. AZD9291 Versus Placebo in Patients With Stage IB-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy. (ADAURA). Available at: https://www.clinicaltrials.gov/ct2/show/NCT02511106. NLM identifier: NCT02511106. Accessed November, 2021.

Patient characteristics

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

Characteristic, %	Osimertinib (n=339)	Control arm (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	32/34/35	32/34/34
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

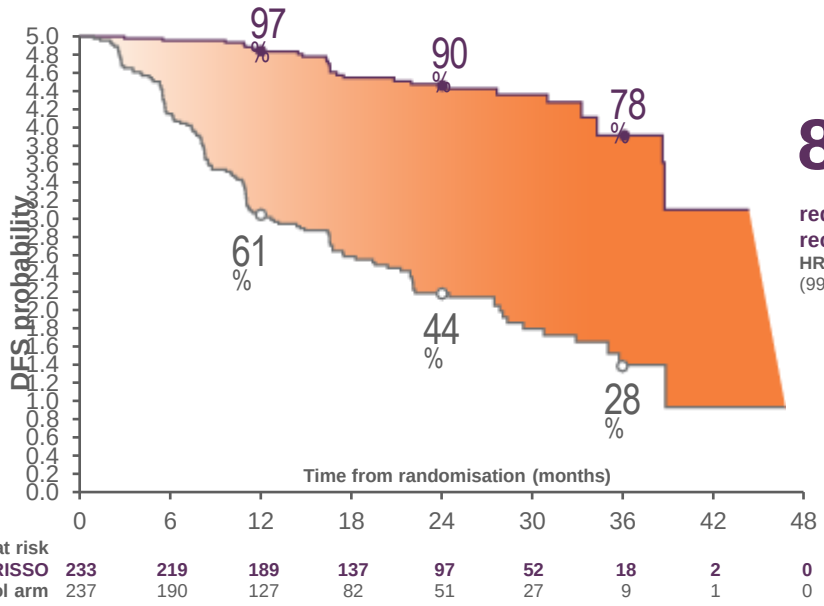
*Former: Osimertinib n=104, control arm n=83; current: Osimertinib n=4, control arm n=3.

†Includes bronchial gland carcinoma (NOS); Osimertinib n=1, control arm n=2; malignant adenosquamous carcinoma; Osimertinib n=4, control arm n=5; other: Osimertinib n=11, control arm n=7.

‡Central test.

1. Wu Y-L, Tsuboi M, He J, et al; ADAURA Investigators. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2027071.

Disease-Free Survival in Stage II/IIIA



83%

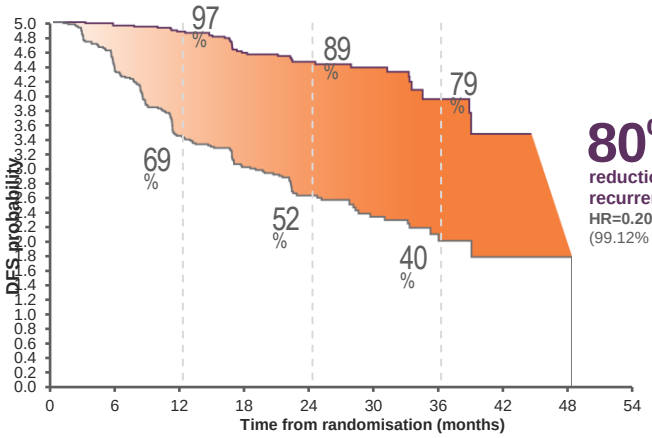
reduction in risk of recurrence or death
HR=0.17
(99.06% CI: 0.11, 0.26; *P*<0.001)

Median DFS: Not reached in the Osimertinib arm (95% CI: 38.8, NC) vs 19.6 months in the placebo arm (95% CI: 16.6, 24.5). Data maturity was 33% at time of analysis.

CI= confidence interval; DFS= disease free survival; HR= hazard ratio; NC= not countable; NSCLC= non-small cell lung cancer

1. Wu Y-L, Tsuboi M, He J, et al; ADAURA Investigators. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2027071. **2.** TAGRISSO® (osimertinib). Summary of Product Characteristics.

Disease-Free Survival in Stage I-IIIA



80%
reduction in risk of recurrence or death
HR=0.20
(99.12% CI: 0.14, 0.30; *P*<0.001)

Median DFS: Not reached in the TAGRISSO arm (95% CI: NC, NC) vs 27.5 months in the control arm (95% CI: 22.0, 35.0). Data maturity was 29% at time of analysis.

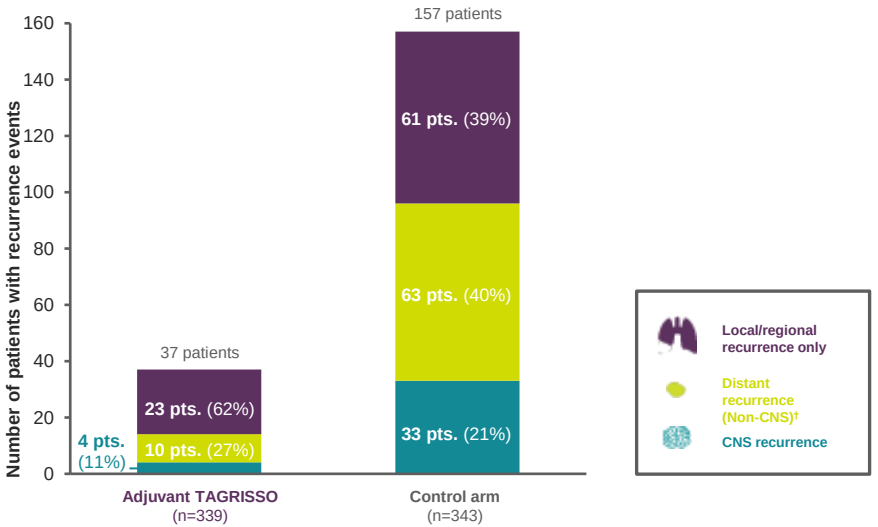
Patients alive and disease-free at 24 months[1]

Stage IB	Stage II	Stage IIIA
88% vs 71%	**91%** vs 56%	**88%** vs 32%
HR=0.39	HR=0.17	HR=0.12

CI= confidence interval; DFS= disease free survival; EGFR= epidermal growth factor receptor; EGFRm= EGFR mutation-positive; HR= hazard ratio; NC= not countable; NSCLC= non-small cell lung cancer

1. Wu Y-L, Tsuboi M, He J, et al;. ADAURA Investigators. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2027071.
2. TAGRISSO® (osimertinib). Summary of Product Characteristics.

Pattern of Recurrence



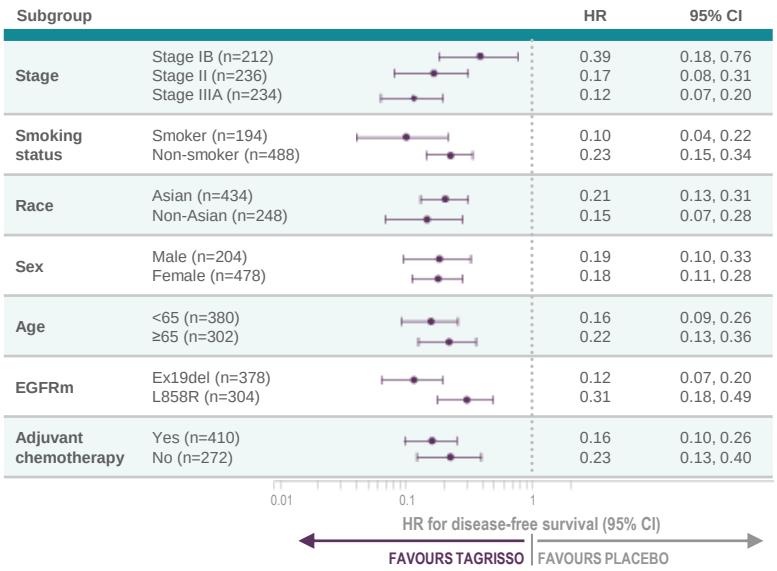
*Significance in this context refers to clinical significance as opposed to statistical significance. The analysis was exploratory and post-hoc.
†Includes patients with both distant and local/regional recurrences.

Adjuvant Osimertinib achieved an 82% reduction in the risk of recurrence to the CNS (HR=0.18 [95% CI: 0.10, 0.33])

CI= confidence interval; CNS= central nervous system; HR= hazard ratio; NSCLC= non-small cell lung cancer

1. Wu Y-L, Tsuboi M, He J, et al; ADAURA Investigators. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2027071.

Subgourp Analysis



Adjuvant TAGRISSO demonstrated consistent DFS benefit regardless of stage, race, smoking history, or use of prior adjuvant chemotherapy

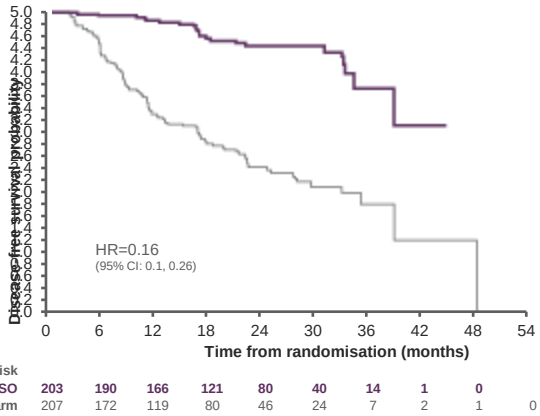
CI= confidence interval; DFS= disease free survival; EGFR= epidermal growth factor receptor; EGFRm= EGFR mutation-positive; HR= hazard ratio; NSCLC= non-small cell lung cancer

1. Wu Y-L, Tsuboi M, He J, et al; ADAURA Investigators. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2027071.

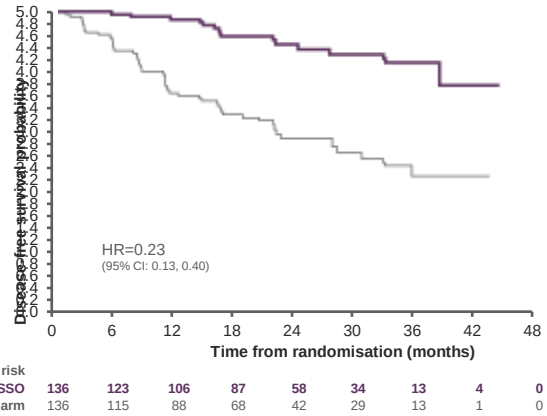
DFS according to Chemotherapy Administration

DFS in patients with/without adjuvant chemotherapy (overall population)

With adjuvant chemotherapy[2]



Without adjuvant chemotherapy[2]



- Delivery of adjuvant chemotherapy after resection was allowed, but not mandatory[1]
- Adjuvant chemotherapy decisions were made by the physician and the patient and occurred prior to study enrolment[1]

CI= confidence interval; DFS= disease free survival; HR= hazard ratio; NSCLC= non-small cell lung cancer

1. Wu Y-L, Tsuboi M, He J, et al; ADAURA Investigators. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2027071. **2**. Wu Y-L, Tsuboi M, He J, et al; ADAURA Investigators. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2027071 (Supplementary appendix)

Safety Profile

	TAGRISSO (n=337)		Control arm (n=343)
Adverse reactions reported (all causality, ≥10% of patients)	Overall frequency (all grades)	Grade ≥3	Overall frequency (all grades)
Diarrhea	46%	2%	20%
Paronychia	25%	1%	1%
Dry skin	23%	<1%	6%
Pruritus	19%	0%	9%
Cough	18%	0%	17%
Stomatitis	18%	2%	4%
Nasopharyngitis	14%	0%	10%
URTI	13%	1%	10%
Decreased appetite	13%	1%	4%
Mouth ulceration	12%	0%	2%
Dermatitis acneiform	11%	0%	5%

URTI=upper respiratory tract infection.
Overall, the proportion of patients who had a CTCAE ≥ Grade 3 AE was low in both treatment arms (TAGRISSO: 20.2%; placebo: 13.4%), indicating that the majority of AEs reported in the study were mild or moderate

- At time of safety analysis, zero deaths had been reported as an AE outcome in the Osimertinib arm compared with one death in the control arm
- In the ADAURA, FLAURA and AURA studies, diarrhoea was reported in 47% of patients of which 38% were Grade 1 events, 7.9% Grade 2 and 1.4% were Grade 3; no Grade 4 or 5 events were reported[2]
- Overall, HRQoL was maintained in the adjuvant Osimertinib arm with no clinically meaningful differences vs placebo, despite prolonged treatment[3]
  - These results were consistent regardless of prior adjuvant chemotherapy

HRQol= health related quality of life

1. Wu Y-L, Tsuboi M, He J, et al; ADAURA Investigators. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2027071.
2. TAGRISSO® (osimertinib). Summary of Product Characteristics.
3. Majem M, Goldman JW, John T, et al. Patient-reported outcomes from ADAURA: osimertinib as adjuvant therapy in patients with resected EGFR mutated (EGFRm) NSCLC [presentation]. Presented at: World Conference on Lung Cancer (WCLC); January 28-31, 2021. Abstract number OA06.03

By demonstrating overwhelming efficacy, adjuvant TAGRISSO has potential to revolutionise the treatment of resected NSCLC[1]

TAGRISSO has transformed the treatment of patients with resected EGFRm NSCLC by delivering unprecedented disease-free survival across Stages IB to IIIA

Adjuvant TAGRISSO delivered unparalleled disease-free survival

- **83% reduced risk of recurrence or death** vs control arm in patients with Stage II to IIIA resected EGFRm NSCLC (HR=0.17 [99.06% CI: 0.11, 0.26]; *P*<0.001)
- **80% reduced risk of recurrence or death** vs control arm in all patients with resected EGFRm NSCLC (Stage IB/II/IIIA) (HR=0.20 [99.12% CI: 0.14, 0.30]; *P*<0.001)

Adjuvant TAGRISSO significantly protected against the risk of distant disease recurrences, preserving the potential for localised intervention*

- In the adjuvant TAGRISSO arm there were 14 distant recurrence events (including CNS recurrences) compared with 96 in the control arm

In the ADAURA study, adjuvant TAGRISSO significantly protected against the risk of CNS progression*

- 82% reduced risk of CNS progression vs control arm (HR=0.18 [95% CI: 0.10, 0.33])

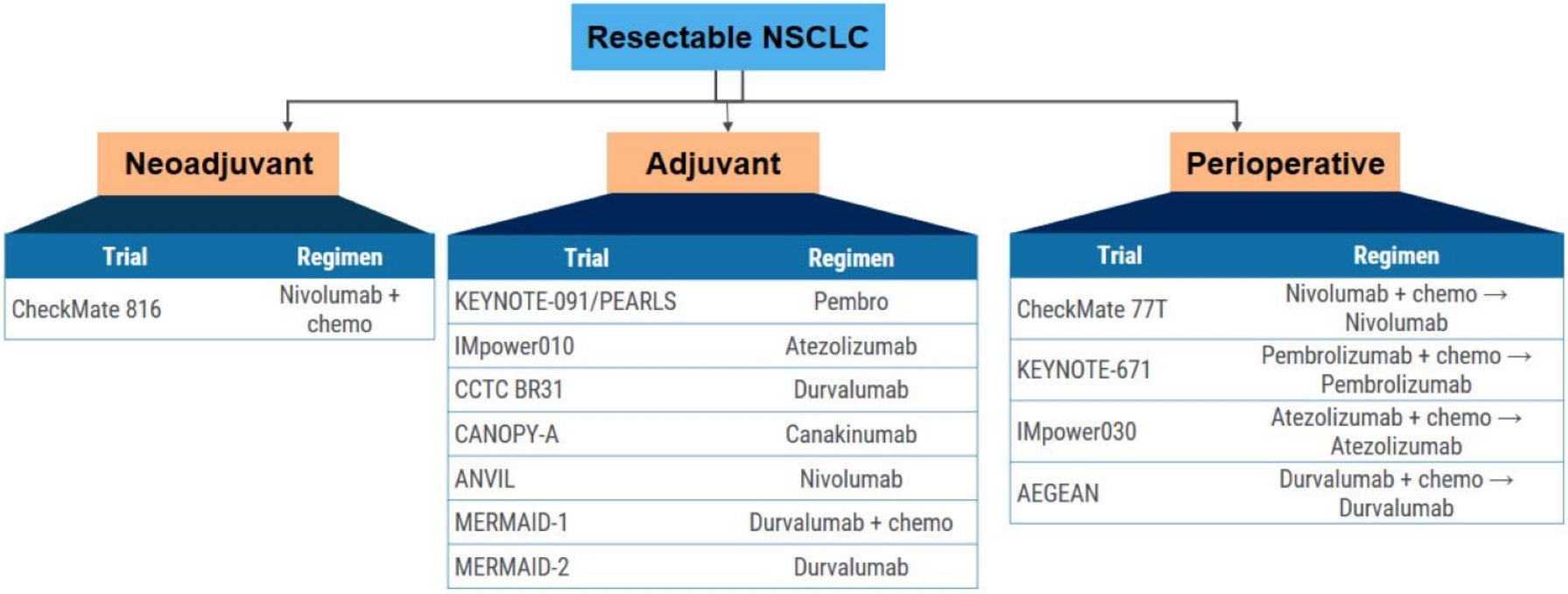
*Significance in this context refers to clinical significance as opposed to statistical significance. The analysis was exploratory and post-hoc
.

CI= confidence interval; CNS= central nervous system; DFS= disease free survival; EGFR= epidermal growth factor receptor; EGFRm= EGFR mutation-positive; HR= hazard ratio; NSCLC= non-small cell lung cancer

1. Wu Y-L, Tsuboi M, He J, et al; ADAURA Investigators. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2027071.

THANK YOU

The Neo-Adjuvant and Perioperative Treatment Landscape Will Expand as IO-Based Therapies are Further Explored in NSCLC



Trial	Regimen
CheckMate 816	Nivolumab + chemo

Trial	Regimen
KEYNOTE-091/PEARLS	Pembro
IMpower010	Atezolizumab
CCTC BR31	Durvalumab
CANOPY-A	Canakinumab
ANVIL	Nivolumab
MERMAID-1	Durvalumab + chemo
MERMAID-2	Durvalumab

Trial	Regimen
CheckMate 77T	Nivolumab + chemo → Nivolumab
KEYNOTE-671	Pembrolizumab + chemo → Pembrolizumab
IMpower030	Atezolizumab + chemo → Atezolizumab
AEGEAN	Durvalumab + chemo → Durvalumab

Cascone, T. Presented at: ASCO 2022.

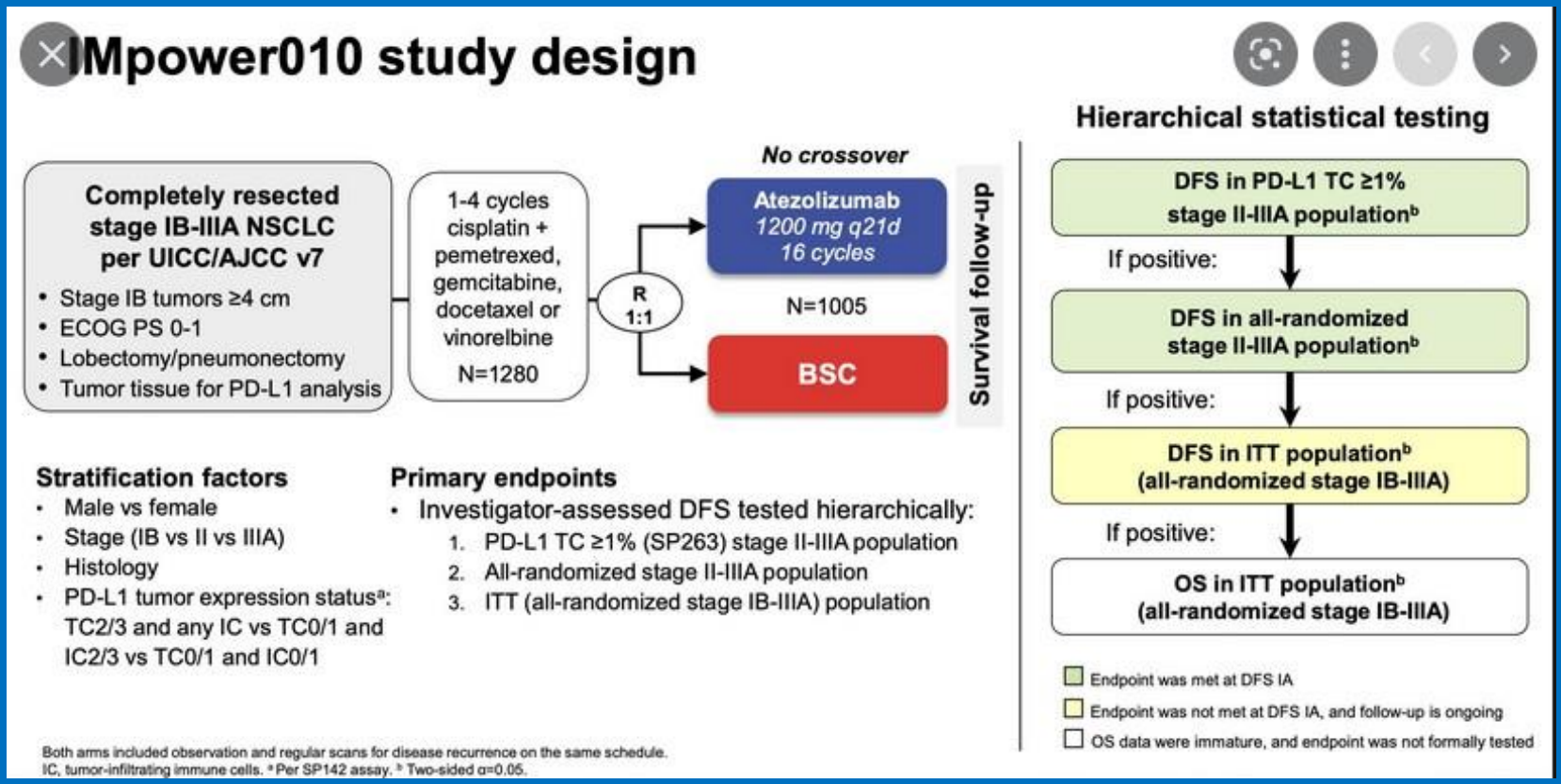
Role of Adjuvant Chemotherapy for "High Risk" stage I disease

Tsutani et al, ASCO 2019, abst 8500; Pathak et al, ASCO 2019, abst 8519

- Some data suggests benefits if visceral pleural invasion, LVI, high grade tumor, increased tumor size
- Larger data set refutes this
- NOT standard to offer adjuvant chemo for any stage IA patients and only SELECT stage IB patients

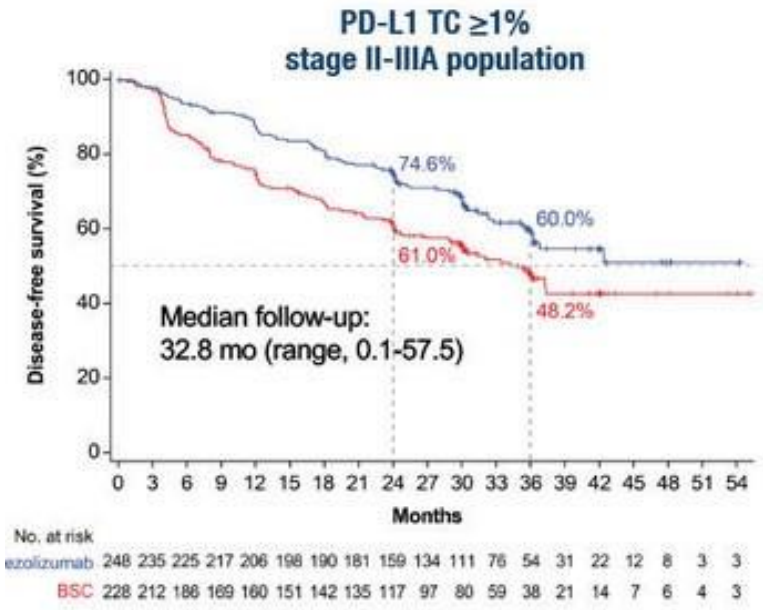
The Era of Adjuvant Immunotherapy is Here!

Immunotherapy in Stage I-III NSCLC



Felip et al, Lancet Oncology 2021:398:1344-1357

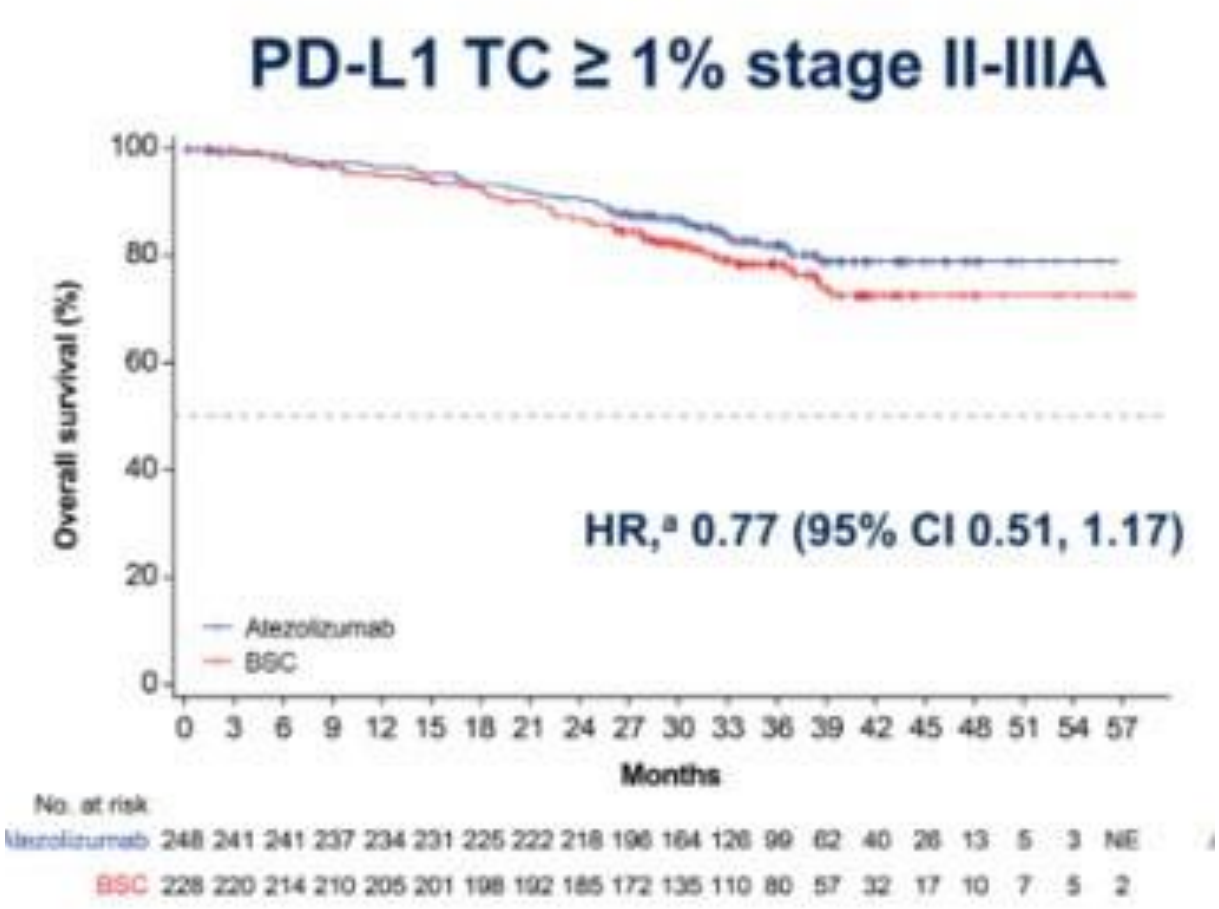
DFS in the PD-L1 TC ≥1%[a] stage II-IIIA, all-randomised stage II-IIIA and ITT populations (primary endpoint)[1]



	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]	

TAGRISSO® osimertinib

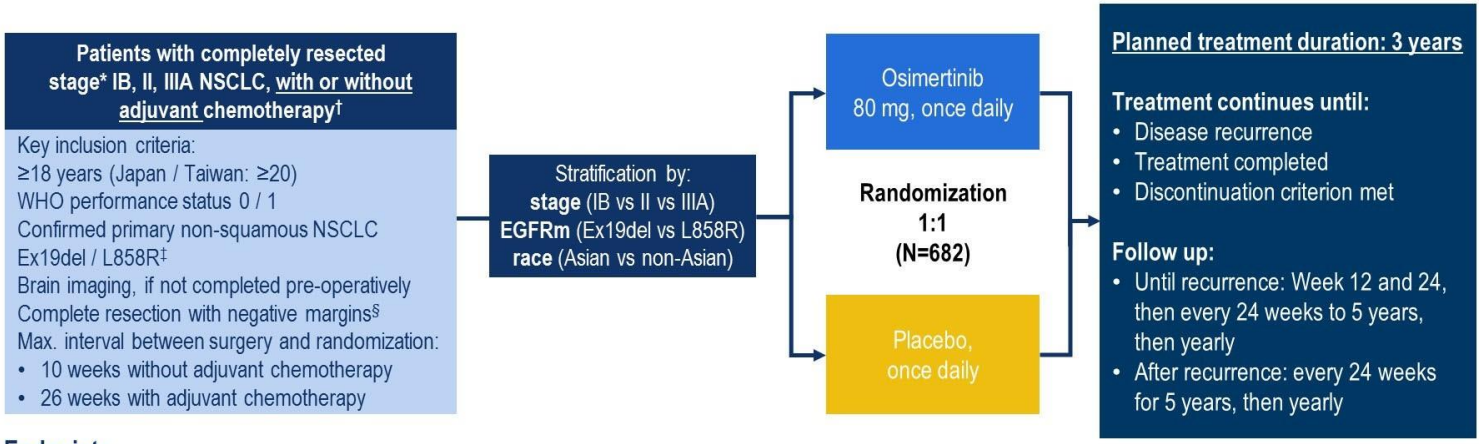
1st Planned Interim Analysis of OS



TAGRISSO® osimertinib

The Era of Adjuvant Targeted Therapy is ALSO Here!

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

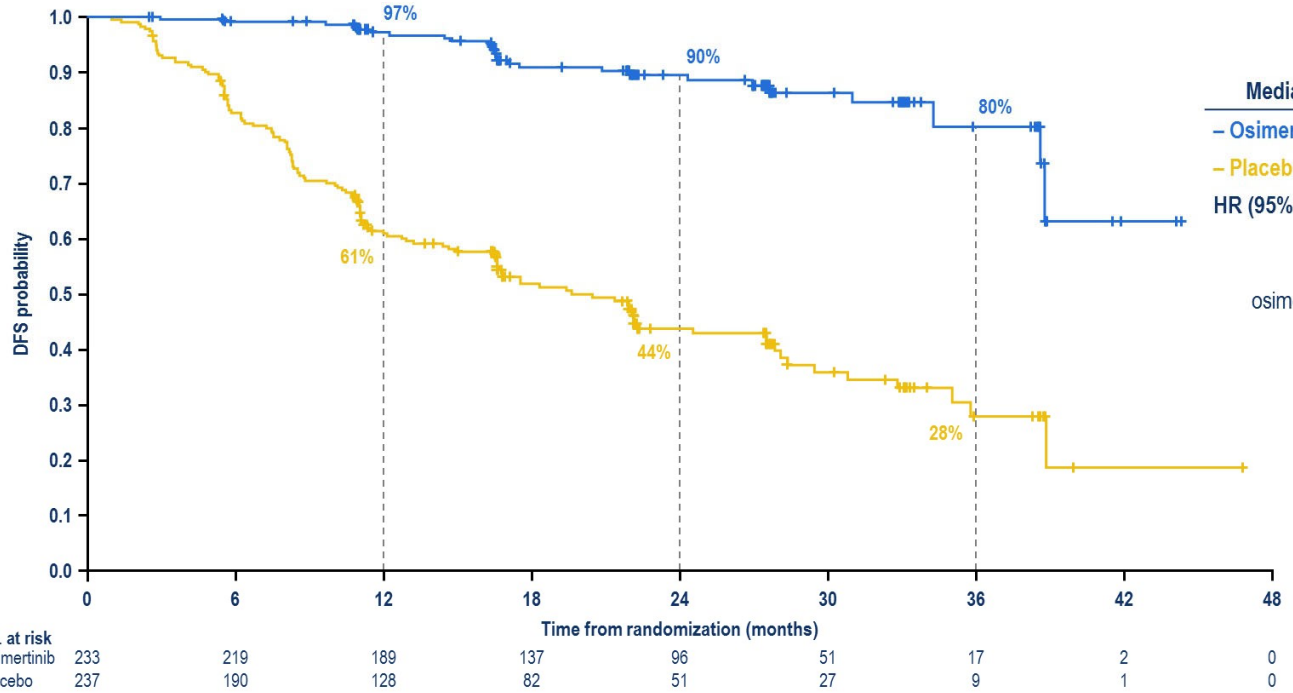
- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

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.

Wu et al, N Engl J Med 2020; 383:1711-172

TAGRISSO® osimertinib

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

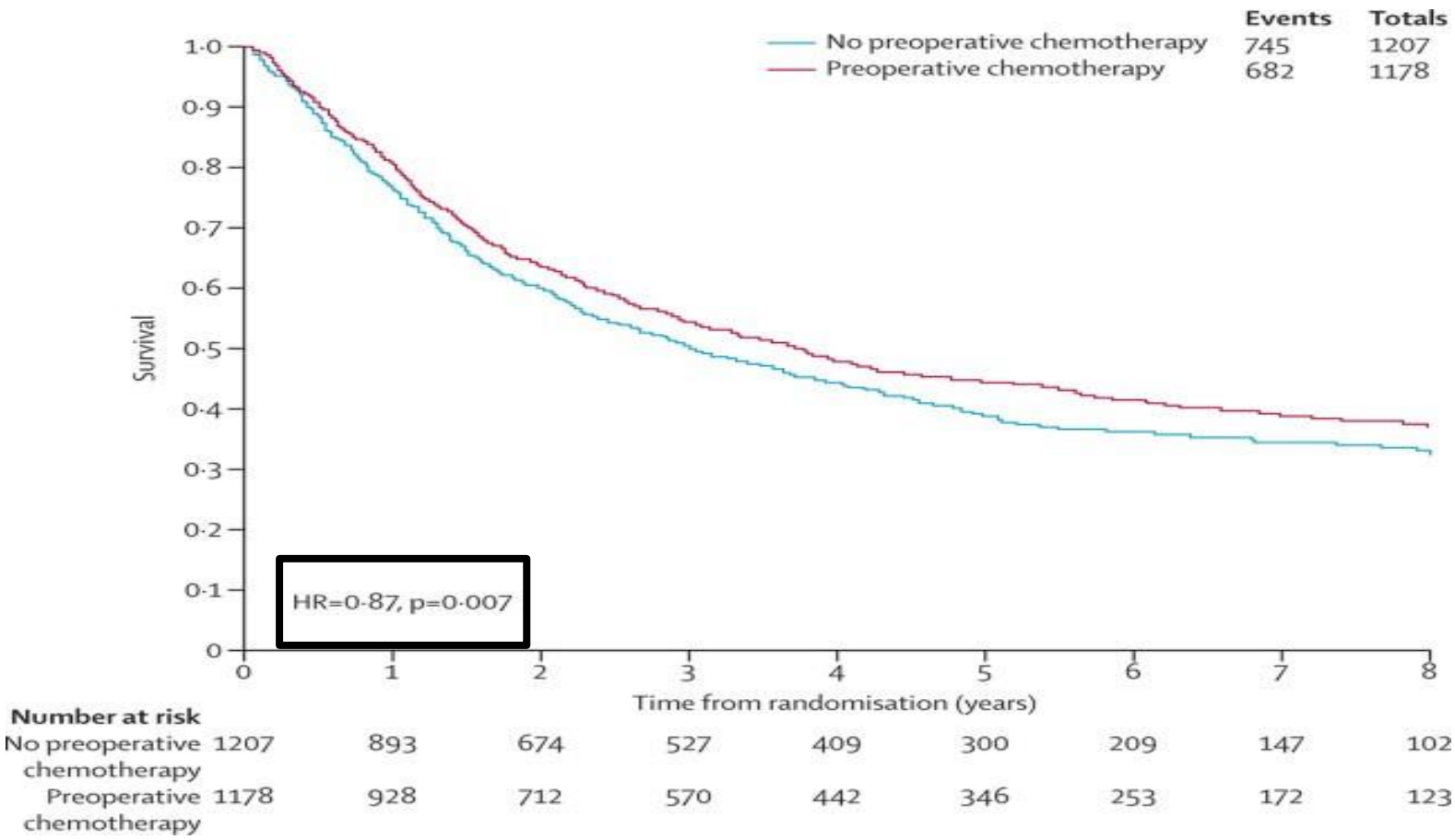
Maturity 33%:
osimertinib 11%, placebo 55%

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.

TAGRISSO® osimertinib

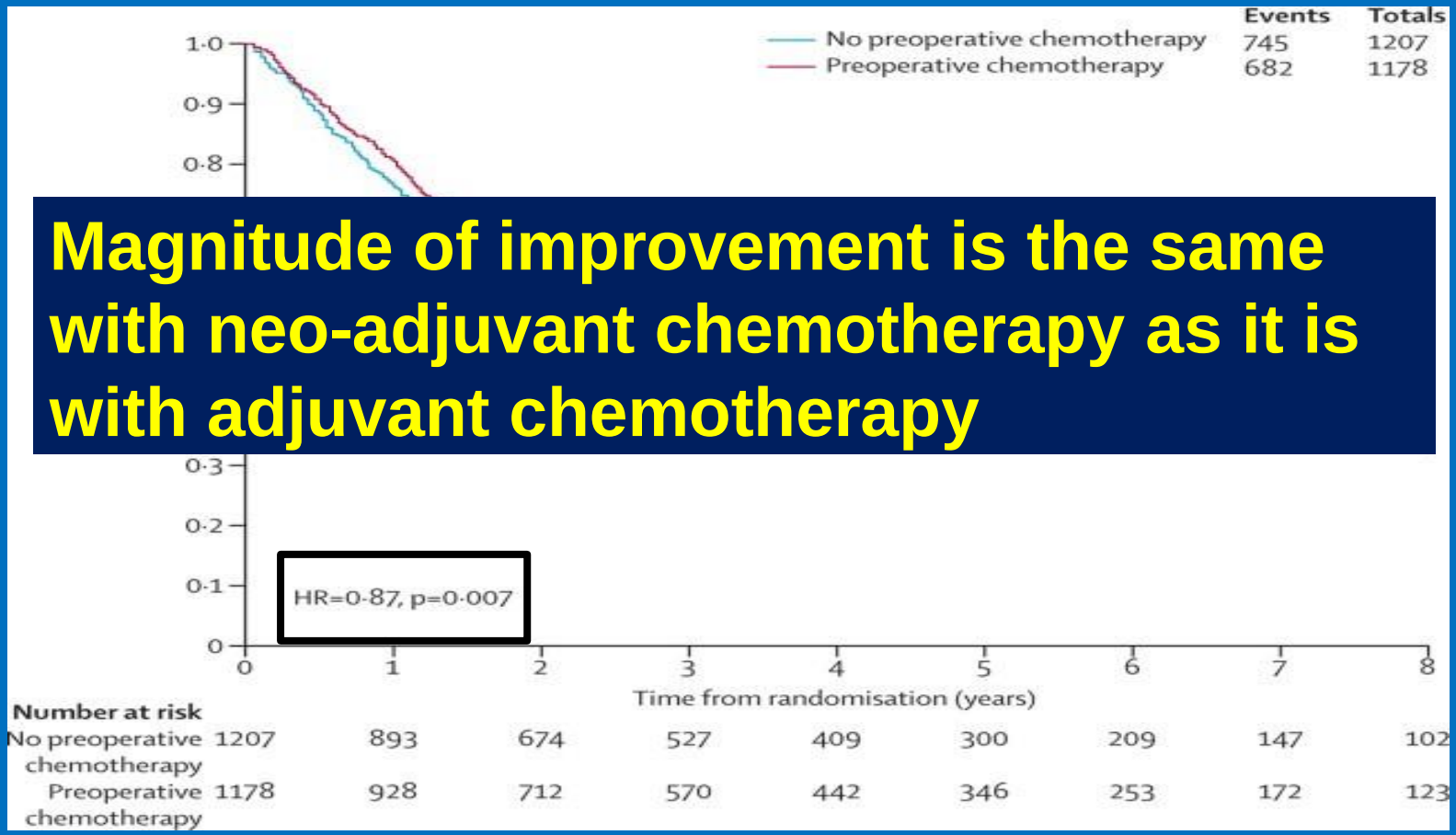
What about neo-adjuvant chemotherapy?

Neo-adjuvant studies: a systematic review and meta-analysis of individual participant data



Neo-adjuvant studies: a systematic review and meta-analysis of individual participant data

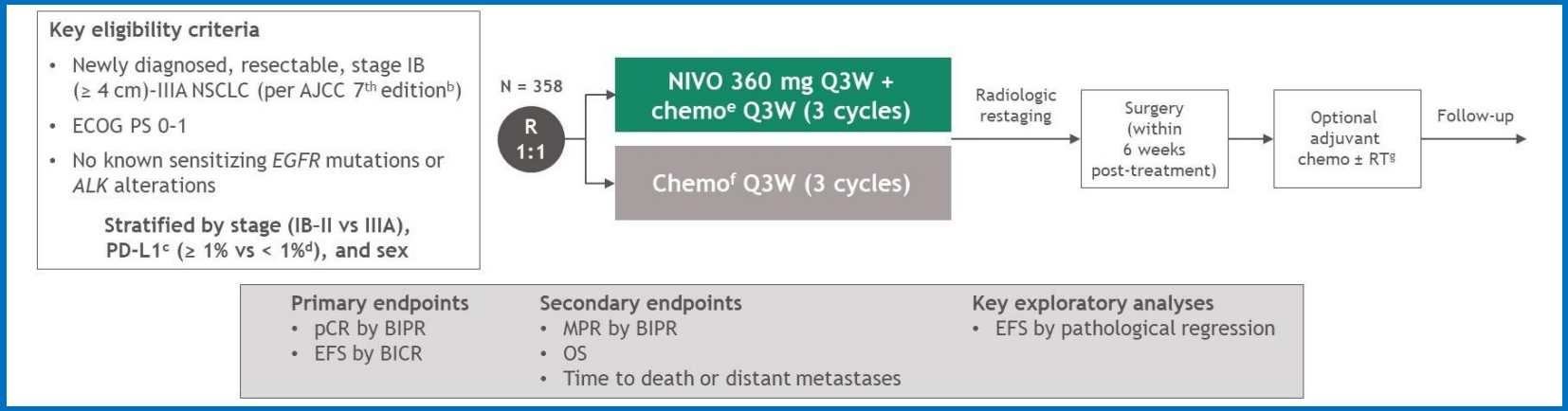
NSCLC meta-analysis collaborative group. Lancet 2014;383:1561-71



Magnitude of improvement is the same with neo-adjuvant chemotherapy as it is with adjuvant chemotherapy

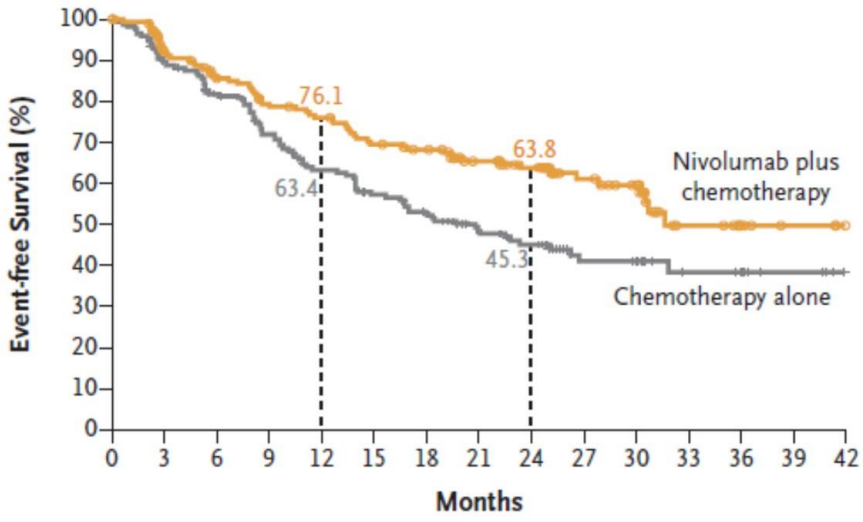
Neo-Adjuvant Chemo-Immunotherapy

CheckMate 816 Phase III Study Design



Forde et al, NEJM 2022

Neoadjuvant Chemo-immunotherapy improves EFS



	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

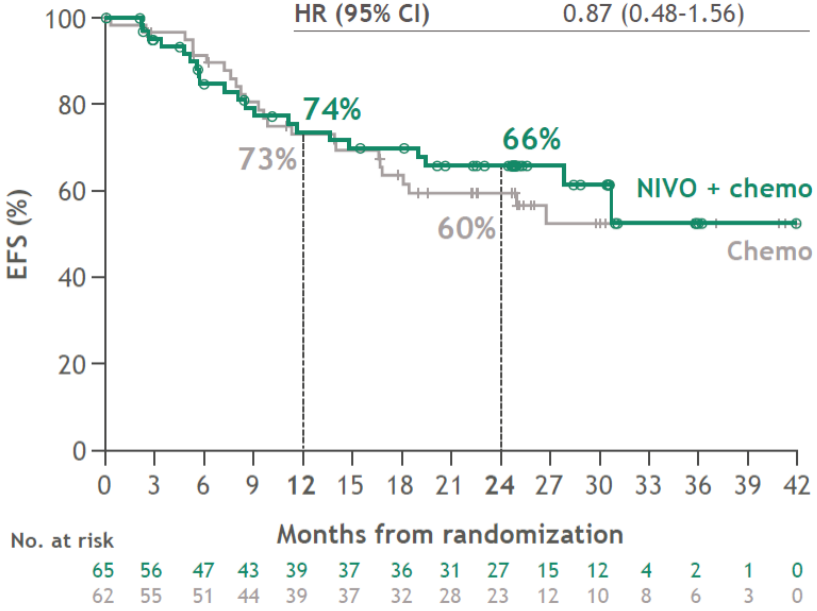
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

TAGRISSO® osimertinib

EFS by baseline stage of disease

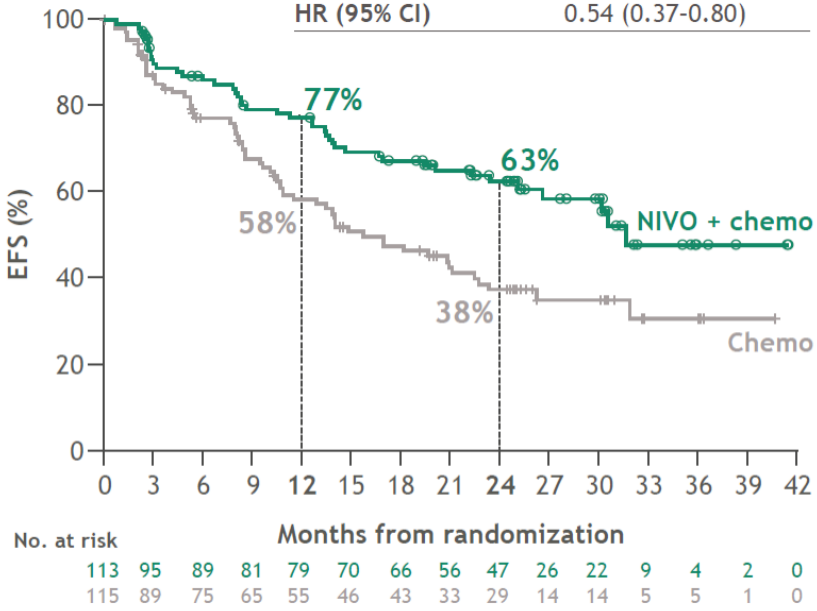
Stage IB-II

	NIVO + chemo (n = 65)	Chemo (n = 62)
Median EFS,[a] mo	NR	NR
HR (95% CI)	0.87 (0.48-1.56)	



Stage IIIA

	NIVO + chemo (n = 113)	Chemo (n = 115)
Median EFS,[b] mo	31.6	15.7
HR (95% CI)	0.54 (0.37-0.80)	



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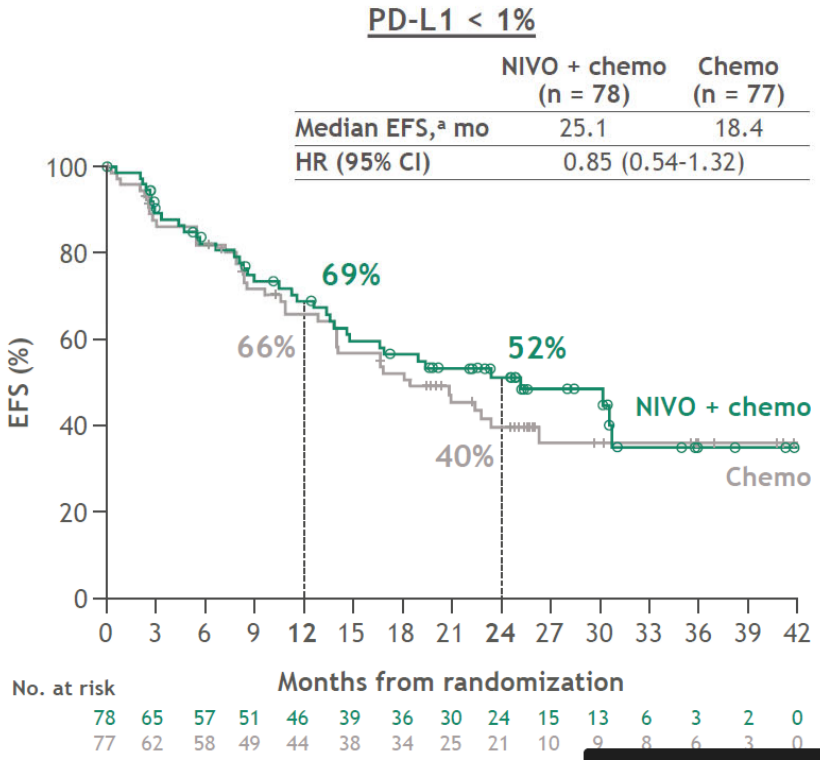
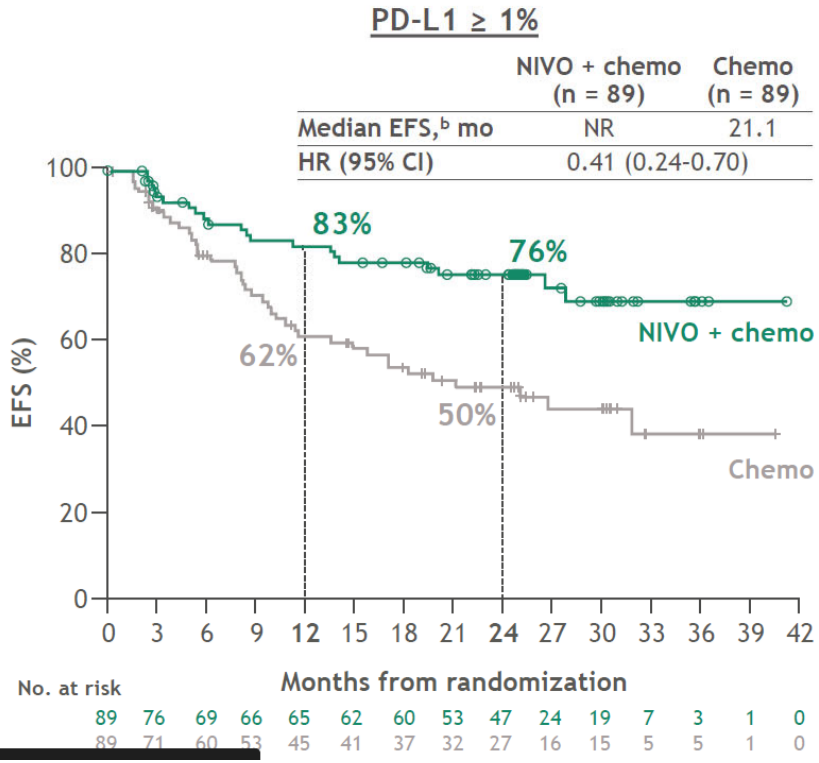
EFS by tumor PD-L1 expression < 1% or ≥ 1%





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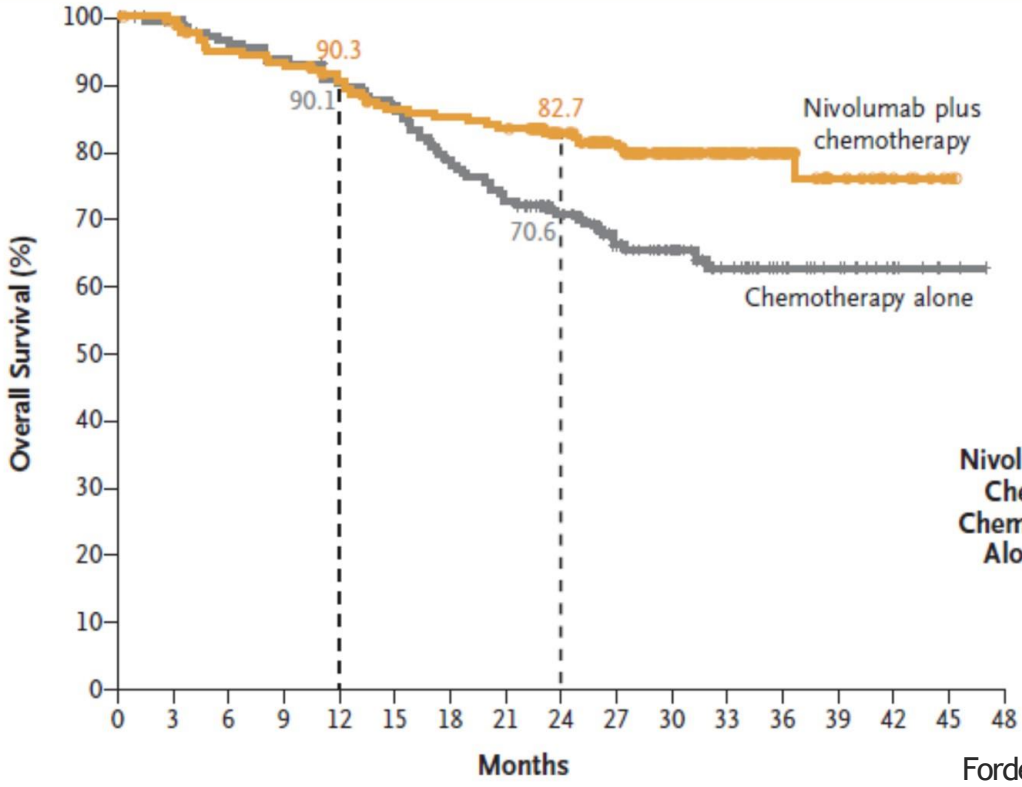
Neoadjuvant Chemo-immunotherapy improves OS



	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57
(99.67% CI, 0.30–1.07)
P=0.008

Forde, et al. NEJM 2022

Now we have randomized phase III data in the modern era of adjuvant chemotherapy

Lung ART: Trial Design

Possibility pre-op CT

Completely resected NSCLC with proven **N2** involvement

Possibility Post-op CT

RANDOM

No mediastinal PORT (Post-Operative RadioTherapy)

Conformal Mediastinal PORT 54 Gy/27 to 30 fr

Primary endpoint
DFS

Secondary endpoints
Local control
OS
2nd cancer
Late Toxicity

Stratification factors : Center, Administration of CT (no CT vs Post-op CT vs pre-op CT alone), Histology (SCC vs other), Extent of mediastinal lymph node involvement (0 vs 1 vs 2+), Histology (SCC vs others), use of pre-treatment PET-scan (yes/no)

Statistical considerations: 700 pts necessary to show a 10% DFS difference at 3 years (from 30% in the control arm to 40%) Power of 80%, Type one error of 5%, 2-sided log-rank test

Pechoux CL et al, Ann Oncol. 2020;31(suppl_4):S1142-S1215

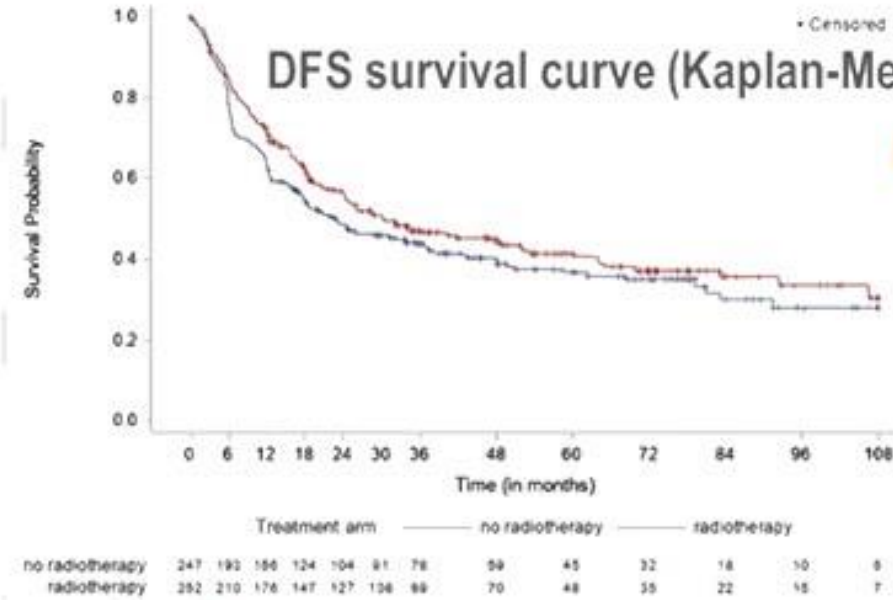
VIRTUAL 2020 ESMO congress

Disease-Free Survival 2/3 (Primary Endpoint; ITT

DFS components (First Event)

	Control	PORT
All DFS events*	152	144
Mediastinal relapse	70 (46.1 %)	36 (25.0%)
Brain metastasis	27 (17.8%)	34 (23.6%)
Other metastasis	71 (46.7%)	71 (49.3%)
Death	8 (5.3%)	21 (14.6%)

* Patients can have more than one event at the same time
Causes of death:
Control arm: 2 2nd Primary,1 vascular,4 unknown, 1 non cancer related
PORT arm: 11 cardio-pulmonary;2 PORT toxicity;4 2nd Primary;1 progression,3 unknown.

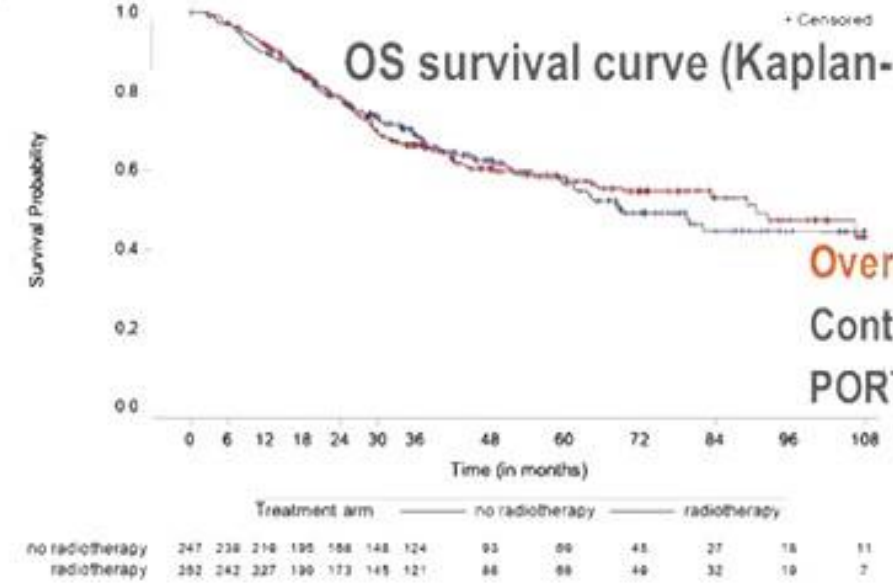


Main analysis (Adj Cox Model)

HR = 0.85

95% CI = [0.67;1.07]

p value = 0.16



Overall Survival rates at 3 years

Control arm: 68.5% (95% CI = [61;75])

PORT arm: 66.5% (95% CI = [59;73])

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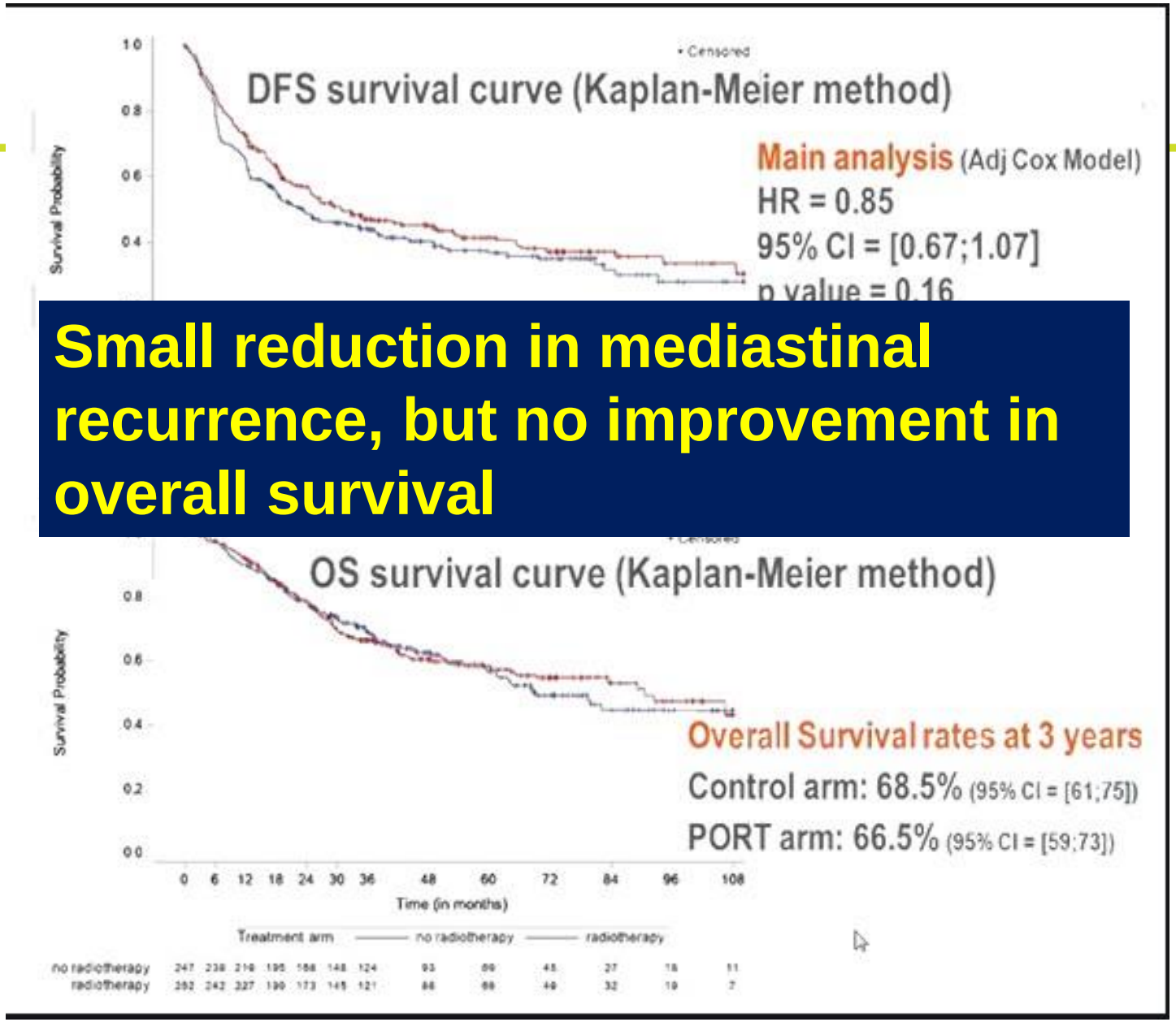

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Summary

- Neo-adjuvant chemo + Nivo is a standard for patients with stage III (stage I,II?) without EGFR/ALK alterations
- Adjuvant chemo followed by Atezo for 1 year is standard for patients with stage II or III with PD-L1 $\geq$ 1% and no EGFR/ALK alterations
- Adjuvant Osimertinib is standard for patients with stage II or III (stage I?) following adjuvant chemo X 4 in patients with EGFR exon 19 del or exon 21 L858R mutations
- Limited role for PORT (positive margins)

How do we best manage IIIA disease in a medically operable patient with resectable disease?

This study calls into question the role for XRT when undergoing surgery

Summary: Stage IIIA resectableNSCLC

- Most patients should be managed with CRT followed by Durvalumab
- Neo-adjuvant chemo + Nivo is a good option for some patients
- Surgery followed by adjuvant chemo X 4 followed by Atezo for 1 year is an option if patient is PD-L1 $\geq$ 1%
- Select patients should be considered for CRT followed by surgery
- Who NOT to do surgery on?
  - Significant weight loss or PS $\geq$ 2
  - Borderline cardio-respiratory status
  - Multi-level N2 disease?
  - Pneumonectomy?

Non-surgical strategies for stage III NSCLC

- Sequential chemoradiation or concurrent chemoradiation are each superior to radiation alone
  - CALGB 8433, RTOG 8808
  - Cochrane data base
- Concurrent chemoradiation is superior to sequential chemoradiation
  - Furuse et al, RTOG 9410, Pierre et al
  - Auperin et al (Meta-analysis)
  - Cochrane data base

Take Home Points

- No single best regimen
- EP/XRT and Carbo/Taxol/XRT are both reasonable
- Cis/PEM/XRT is not superior to EP/XRT but is reasonable to consider in patients with non-squamous NSCLC