NSCLC. Adjuvant/Locally Advanced

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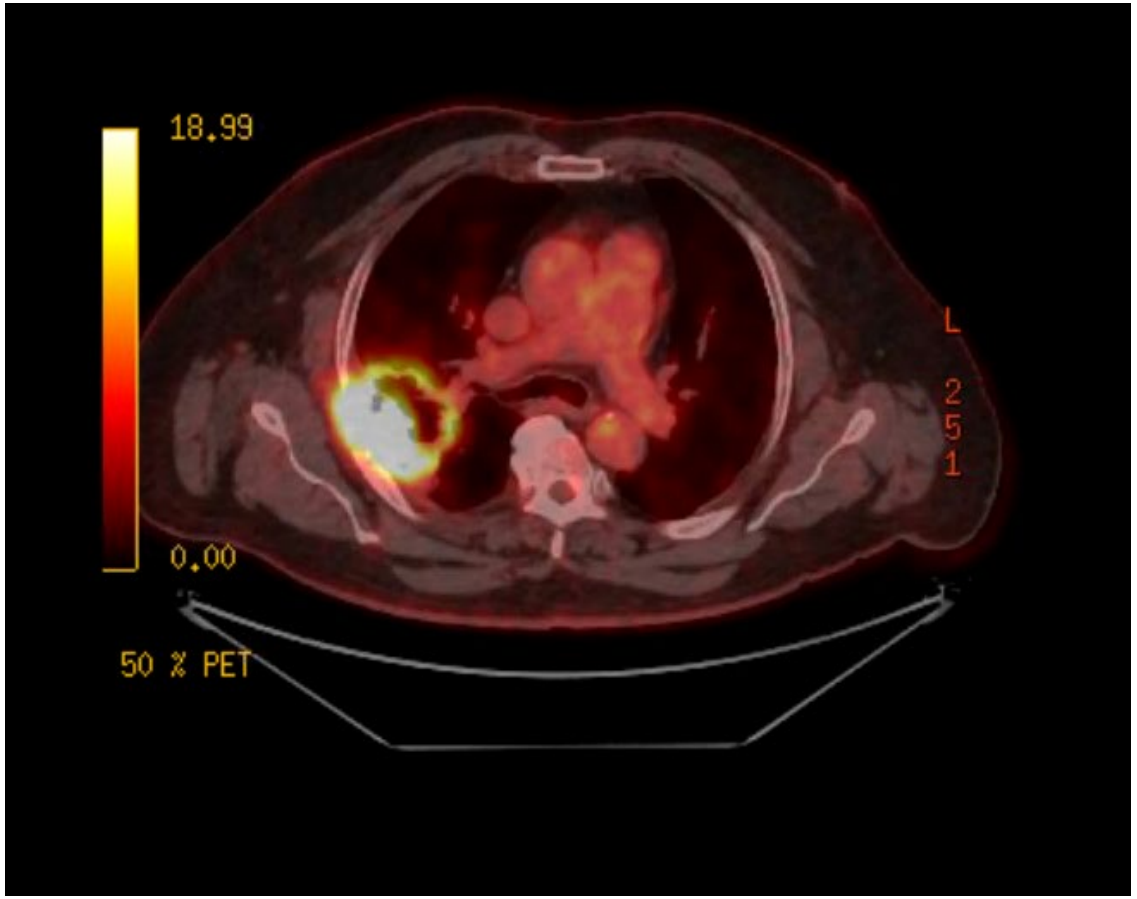
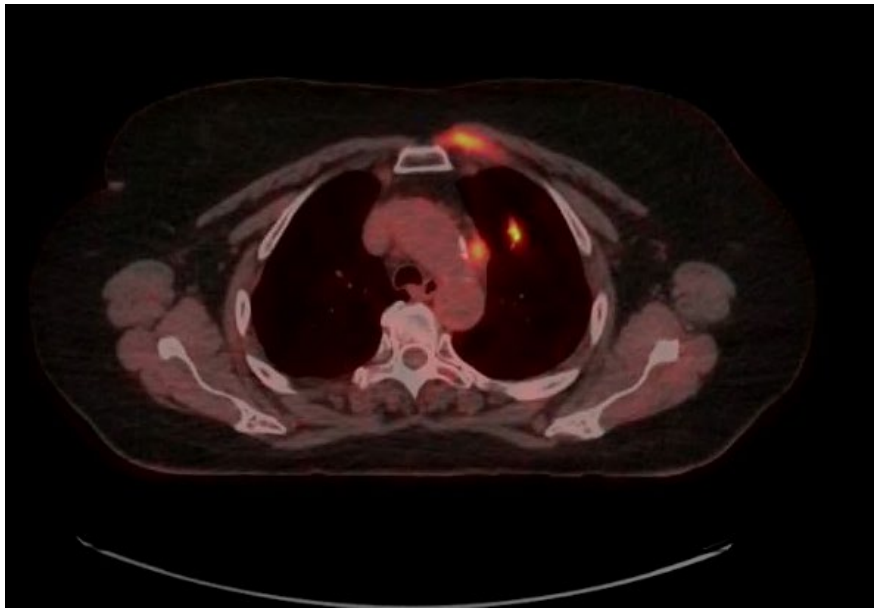
Stage I to stage IIIA

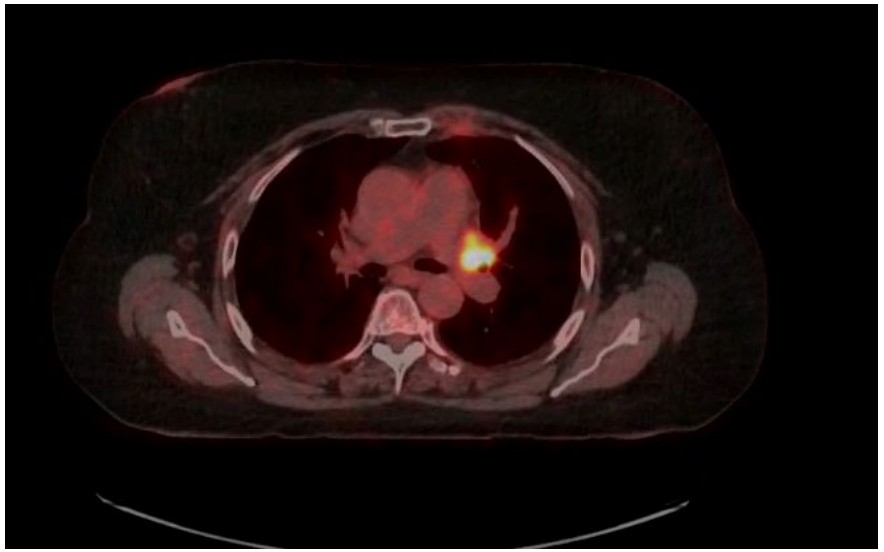
- Treatment goal for patients with stage I to III is curative. Although prognosis is still dismal for a variety of reasons.
- Between 40-50% of patients with stage IB, 55-70% of patients with stage II and and the great majority of patients with stage IIIA will have recurrent disease if surgery is the only modality of treatment.
- The role of adjuvant chemotherapy was been widely studied and although the benefits are small they have been consistent.

Heterogenous group



T4, NO, MO Stage IIIA





T1A, N2, MO Stage IIIA

Clinical evidence for adjuvant treatment.

- Lung Adjuvant Cisplatin Evaluation (LACE) group performed a pooled analysis of individual patient data from the largest cisplatin-based adjuvant trials performed since 1995, including 5 trials, with a total of 4,584 patients.
- Established a reduction in mortality of 5.4% at 5 years in patients who received chemotherapy compared with those who did not (hazard ratio [HR] = 0.89; 95% CI, 0.82–0.96; *P* = .005).
- No benefit in stage IA. But present in stage IB (0.93; 95% CI, 0.78 to 1.10) stage II (HR= 0.83; 95% CI, 0.73 to 0.95) and stage III (HR= 0.83; 95% CI, 0.72 to 0.94)

Pignon, JCO, 2008

Clinical evidence

- A Cochrane meta-analysis in 2015 confirmed the benefits of adjuvant chemotherapy after evaluating 26 trials and 8,447 patients and showing an increase in overall survival by 4% at 5 years with the addition of adjuvant chemotherapy.
- Currently the recommendation is for a platinum doublet.
- Vinorelbine is the most widely studied partner but pemetrexed is preferred for non-squamous and gemcitabine or docetaxel for squamous.
- Cisplatin is preferred. Use of carboplatin is controversial and should only be reserved for patients in special circumstances.
- Treatment should start within 4-8 weeks after surgery

Cochrane Database Syst Rev. 2015

Stage IB

- Controversial.
- 344 patients with confirmed T2N0 NSCLC were randomly assigned to carboplatin and paclitaxel vs BSC.
- Survival was not significantly different (hazard ratio [HR], 0.83; CI, 0.64 to 1.08; P = .12).
- Subgroup analysis showed only benefit in patients with large tumors (>more then 4 cm) (HR, 0.69; CI, 0.48 to 0.99; P = .043).

Strauss, JCO, 2008.

PORT

- If margins are negative there is no role for patients with stage II disease .
- Controversial area in patients with stage IIIA. Mostly retrospective studies had been positive.
- ESMO 2020. LungART, Phase 3 study that randomized 501 patients with stage IIIA with N2 disease that had previously received surgery +/- chemotherapy. At a median follow-up of 4.8 years DFS was no diferent (3 year 47.1 vs 43.8% HR =0.85 (95% CI = [0.67;1.07]; p =0.16). OS (3-year OS of 66.5% vs 68.5%) was not statistically significant

Neoadjuvant treatment

- Benefits include prognostication, potential for downstaging.
- However is difficult to establish in which patients this should be the standard.
- Best subset of patients such as those with single station stage IIIA disease, superior sulcus tumors or those with chest wall invasion in the setting of N1 nodal involvement.
- Key, as in the management of all patients with early stage disease, is the use of a multidisciplinary team.

Immunotherapy

- Several clinical trials are establishing the role of immunotherapy both in the neoadjuvant and adjuvant studies.
- Several early phase studies have shown an increase in the rate of complete responses when neoadjuvant immunotherapy is used.
- Nivo or Nivo/Ipi. NCT01822496
- Pembrolizumab. NCT03425643
- Durvalumab. NCT03800134.
- Atezolizumab. NCT03456063, Impower 010 (improvement in DFS in patients with stage II-IIIA, HR 0.79 (95%CI 0.64-0.96, p=0.0205)

Special populations

- EGFR

ADAURA Phase III double-blind 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 randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization 1:1 (N=682)

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

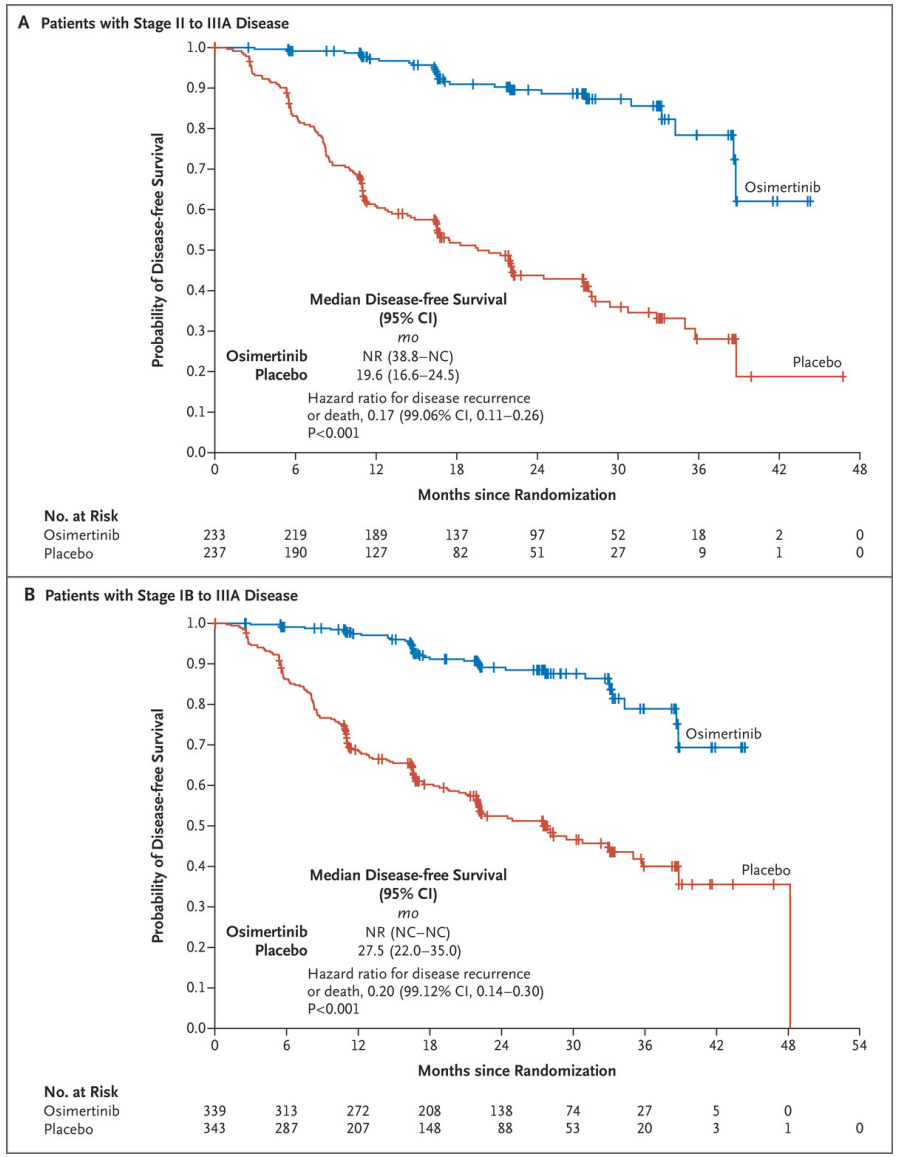
Planned treatment duration: 3 years

Treatment 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**: 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**



Y Wu et al. N Engl J Med 2020;383:1711-1723.

So, now what?

- Now approved by the FDA.
- How will OS be affected, how many patients will cross-over?
- Osimertinib is well tolerated and has an impressive DFS advantage.
- What is the role of chemotherapy?
- Cost for 3 years of therapy is exorbitant.
- This evidence should not be extrapolated to other cancers that have mutations drivers.

Conclusion regarding adjuvant therapy.

- Benefit is small but exists.
- Proper staging is essential.
- Patients should be managed by a multidisciplinary team.
- Cisplatin doublet is the preferred regimen for patients that are candidates.
- Immunotherapy and targeted therapy are likely to play a role in the near future.

Locally advanced disease

- For patients with inoperable stage II disease, multistation stage IIIA or stage IIIB disease the standard of care is concurrent chemotherapy and radiation.
- Several clinical trials have established that concurrent therapy offers a survival advantage over sequential treatment. At the price of increase adverse events.
- Meta-analysis of 6 RCT HR 0.84, 95% CI 0.74-0.95, with an absolute benefit of 5.7 percent OS at three years and 4.5 percent at five years.
- Important for patients who have poor PS.

Auperin JCO, 2010

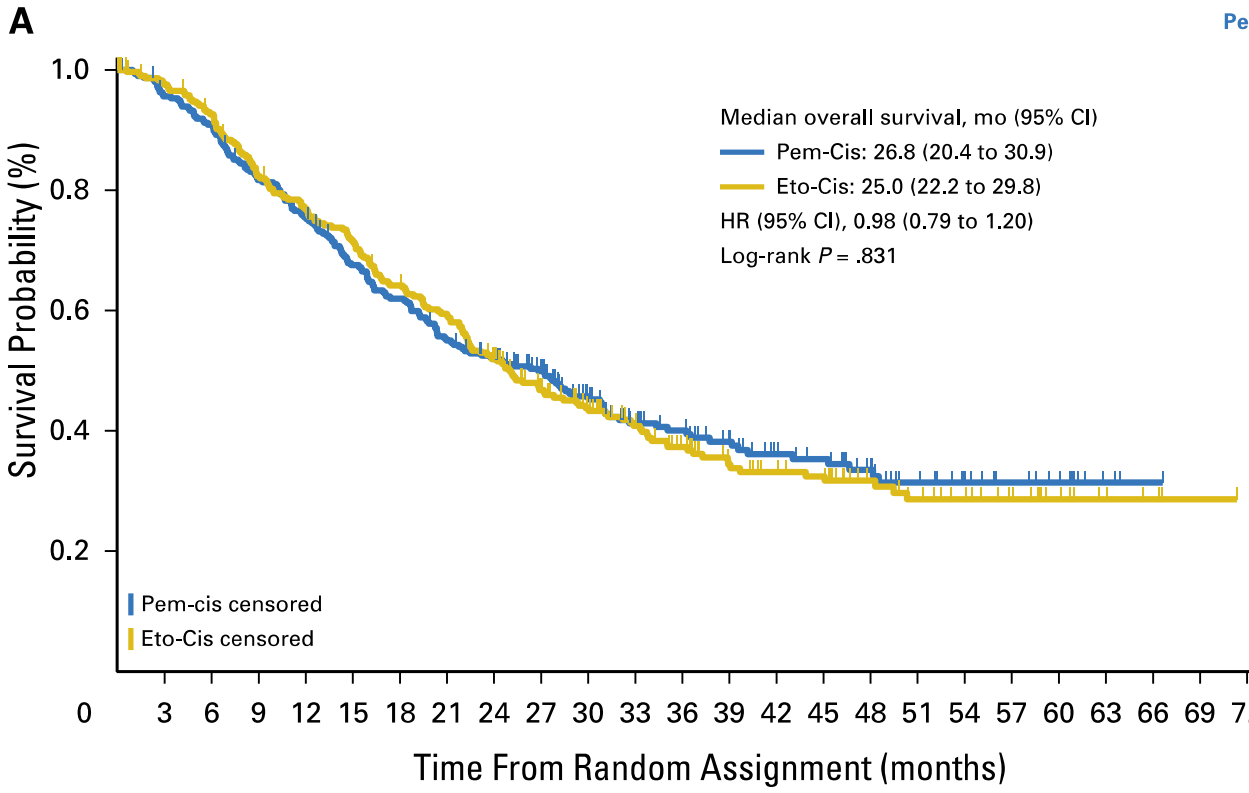
Role of higher dose of radiation

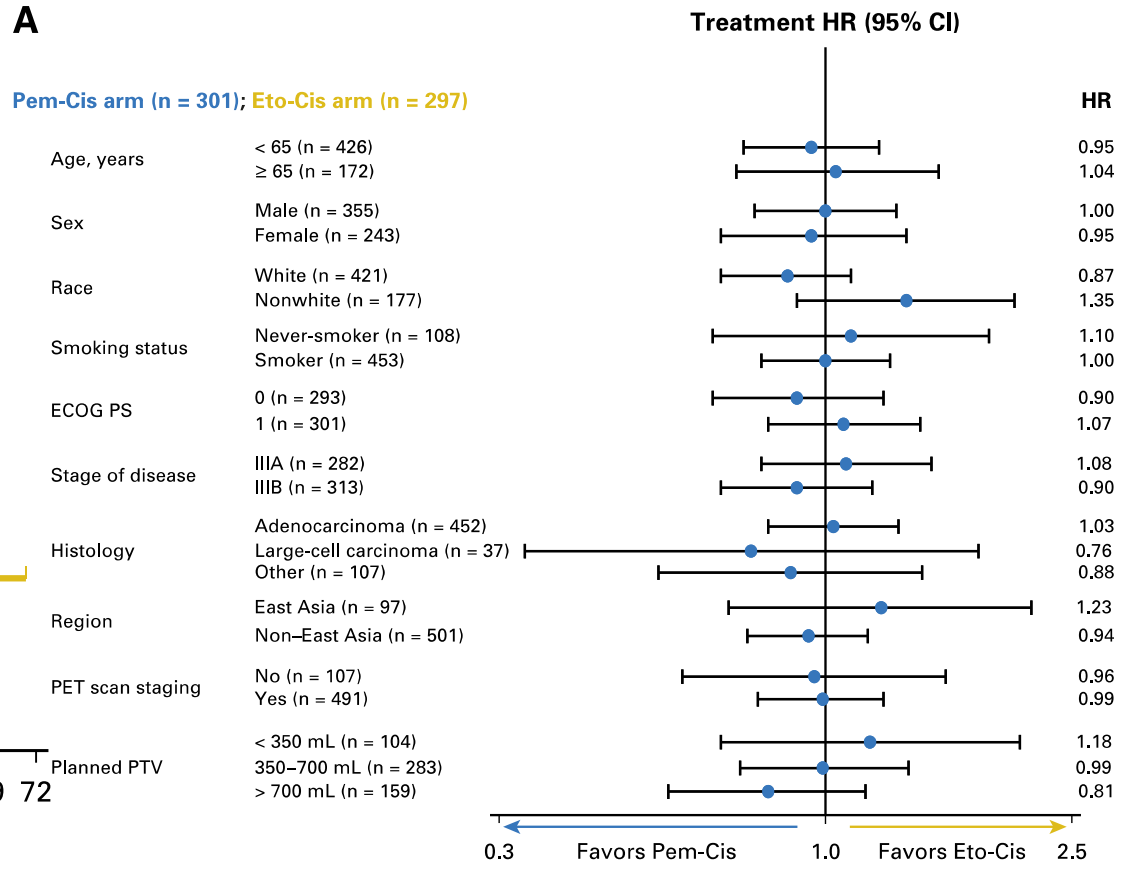
- Increased dose of radiation is not beneficial. RTOG 0617 randomized patients to either standard-dose (60 Gy/30 daily fractions) or high-dose RT (74 Gy/37 daily fractions).
- High-dose (74 Gy) RT was associated with a shorter survival and an increased risk of death compared with conventional-dose (60 Gy) RT (median, 20 versus 29 months; HR 1.38, 95% CI 1.09-1.76).

Chemotherapy

- Platinum-doublet is the standard.
- Long debate as to what chemotherapy is the best partner along side with radiation.
- Before the era of immunotherapy:
- Cisplatin-etoposide likely equal to carboplatin and paclitaxel.
- More adverse events in the former and need for additional consolidation in the latter.
- Few randomized studies have actually been conducted.
- PROCLAIM. Compared EP vs cisplatin-pemetrexed in 598 patients

PROCLAIM





Senana, JCO, 2016

Adverse events

- Patients in the pemetrexed arm received consolidation pemetrexed alone.

Senana, JCO, 2016

CTCAE Term	Overall Study			
	Arm A (n = 283)		Arm B (n = 272)	
	Any Gr*	Gr 3–4	Any Gr*	Gr 3–4
≥ 1 CTCAE	281 (99.3)	181 (64.0)	269 (98.9)	**209 (76.8)**
Laboratory				
Neutrophils/granulocytes (ANC/AGC)	121 (42.8)	69 (24.4)	**149 (54.8)**	**121 (44.5)**
Hemoglobin	114 (40.3)	25 (8.8)	124 (45.6)	37 (13.6)
Leukocytes (total WBC)	104 (36.7)	64 (22.6)	111 (40.8)	82 (30.1)
Lymphopenia	61 (21.6)	51 (18.0)	52 (19.1)	40 (14.7)
Platelets	55 (19.4)	19 (6.7)	**85 (31.3)**	29 (10.7)
Potassium, serum low	18 (6.4)	8 (2.8)	29 (10.7)	9 (3.3)
Nonlaboratory				
Nausea	**170 (60.1)**	10 (3.5)	137 (50.4)	11 (4.0)
Fatigue	154 (54.4)	17 (6.0)	146 (53.7)	13 (4.8)
Dysphagia	143 (50.5)	23 (8.1)	115 (42.3)	18 (6.6)
Esophagitis	136 (48.1)	44 (15.5)	138 (50.7)	56 (20.6)
Vomiting	110 (38.9)	11 (3.9)	90 (33.1)	17 (6.3)
Anorexia	91 (32.2)	11 (3.9)	79 (29.0)	10 (3.7)
Rash: dermatitis associated with radiation‡	77 (27.2)	0 (0.0)	64 (23.5)	4 (1.5)
Constipation	71 (25.1)	1 (0.4)	72 (26.5)	4 (1.5)
Mucositis/stomatitis‡	**62 (21.9)**	3 (1.1)	40 (14.7)	5 (1.8)
Pneumonitis	**48 (17.0)**	5 (1.8)	29 (10.7)	7 (2.6)
GI pain‡	**46 (16.3)**	5 (1.8)	23 (8.5)	2 (0.7)
Weight loss	46 (16.3)	3 (1.1)	45 (16.5)	1 (0.4)
Cough	46 (16.3)	1 (0.4)	33 (12.1)	1 (0.4)
Infection‡	42 (14.8)	8 (2.8)	33 (12.1)	7 (2.6)
Dyspnea	**42 (14.8)**	6 (2.1)	23 (8.5)	4 (1.5)
Diarrhea	38 (13.4)	3 (1.1)	40 (14.7)	5 (1.8)
Heartburn/dyspepsia	38 (13.4)	4 (1.4)	30 (11.0)	1 (0.4)
Neuropathy, sensory	37 (13.1)	0 (0.0)	**56 (20.6)**	0 (0.0)
Pulmonary/upper respiratory pain‡	35 (12.4)	6 (2.1)	34 (12.5)	5 (1.8)
Pain other than pulmonary or GI‡	33 (11.7)	1 (0.4)	**53 (19.5)**	4 (1.5)
Rash‡	33 (11.7)	0 (0.0)	27 (9.9)	1 (0.4)
Renal event‡	**30 (10.6)**	5 (1.8)	16 (5.9)	4 (1.5)
Fever (in the absence of neutropenia)	29 (10.2)	0 (0.0)	24 (8.8)	1 (0.4)
Dizziness	29 (10.2)	2 (0.7)	21 (7.7)	1 (0.4)
Dysgeusia	29 (10.2)	0 (0.0)	21 (7.7)	0 (0.0)
Alopecia	23 (8.1)	0 (0.0)	**98 (36.0)**	1 (0.4)
Febrile neutropenia	16 (5.7)	15 (5.3)	28 (10.3)	26 (9.6)

Role of immunotherapy

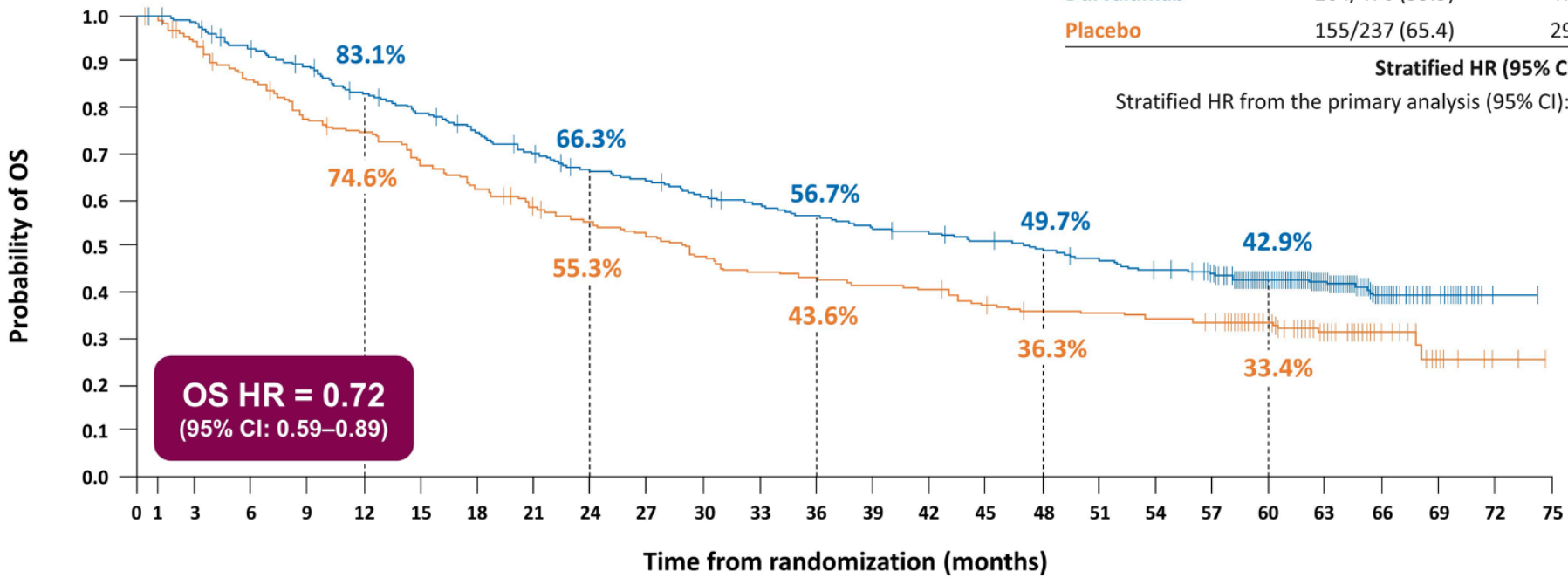
- PACIFIC study was the most important game changer.
- 713 patients were randomized 2:1 to receive durvalumab after the concurrent phase of radiation.
- Chemotherapy partners was dealer’s choice but no consolidation treatment was allowed.

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

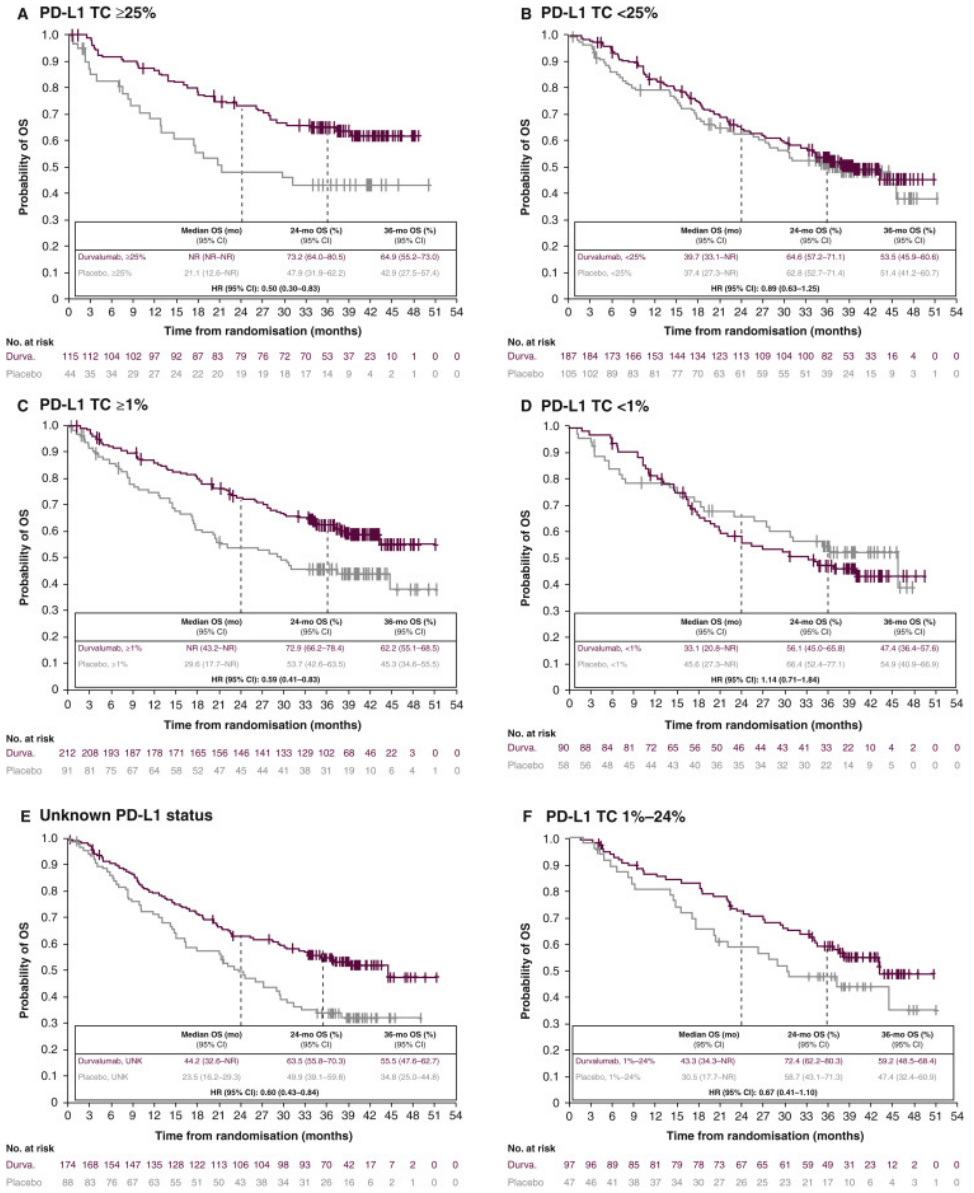
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

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]

PDL1 status.

- OS favored durvalumab, versus placebo, across all PD-L1 subgroups but one, patients with TC <1% (HR, 1.36; 95% CI, 0.79–2.34).
- However this is not a proper endpoint and was done post-hoc.



Paz-Ares. Ann Oncol. 2020

Adverse Events of Any Cause.

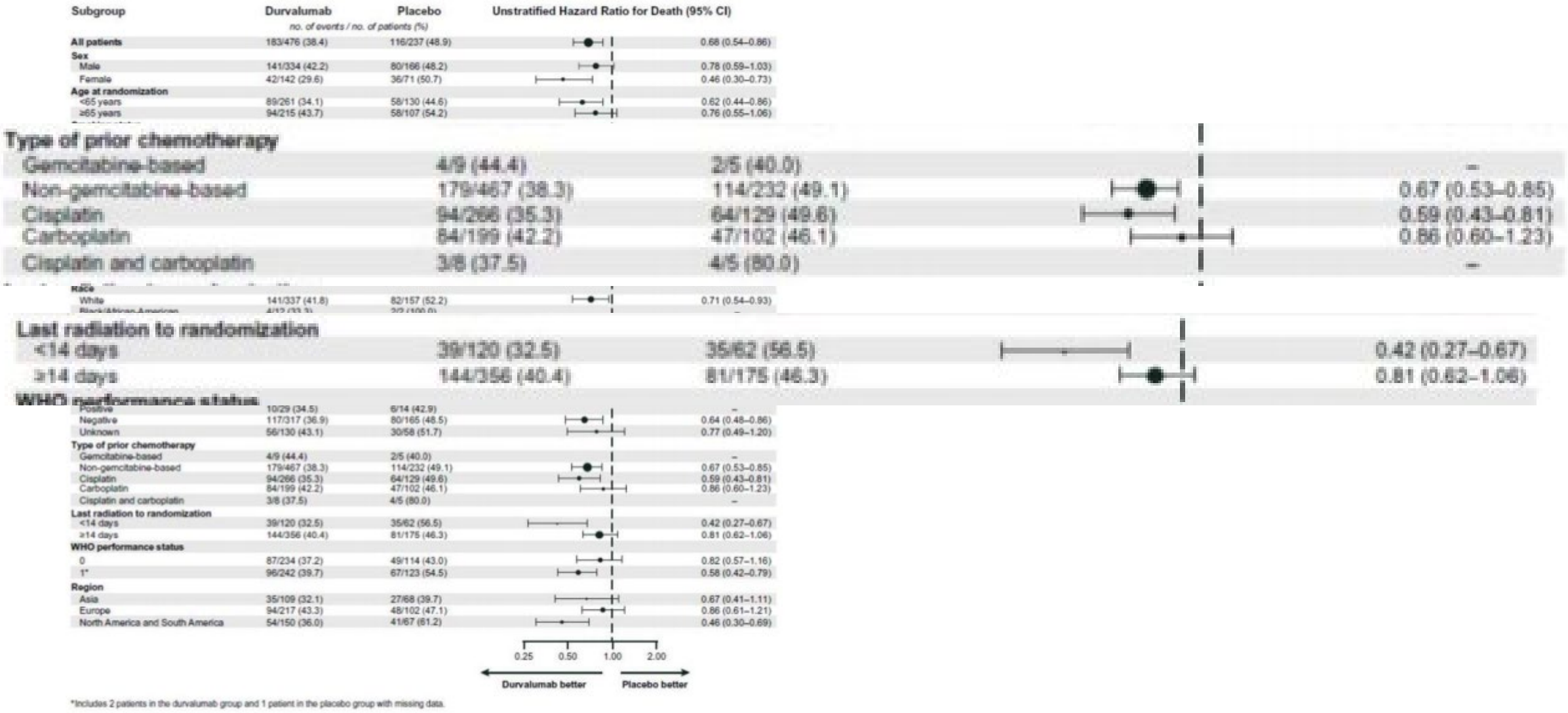
Table 3. Adverse Events of Any Cause.

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

Event†	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade‡	Grade 3 or 4	Any Grade‡	Grade 3 or 4
	number of patients with an event (percent)			
Any event	115 (24.2)	16 (3.4)	19 (8.1)	6 (2.6)
Pneumonitis	51 (10.7)	8 (1.7)	16 (6.8)	6 (2.6)
Hypothyroidism	44 (9.3)	1 (0.2)	3 (1.3)	0
Hyperthyroidism	13 (2.7)	0	0	0
Rash	5 (1.1)	2 (0.4)	1 (0.4)	0
Dermatitis	5 (1.1)	0	0	0

Antonia SJ et al. N Engl J Med 2017;377:1919-1929.

Subgroup analysis.



*Includes 2 patients in the durvalumab group and 1 patient in the placebo group with missing data.

Special populations.

EGFR mutation				
Positive	10/29 (34.5)	6/14 (42.9)		–
Negative	117/317 (36.9)	80/165 (48.5)		0.64 (0.48–0.86)
Unknown	56/130 (43.1)	30/58 (51.7)		0.77 (0.49–1.20)

- Patients with driver mutations.
- Really controversial area.
- Do this patients benefit from immunotherapy?
- Does prior immunotherapy put patients at risk for pneumonitis if a TKI is subsequently needed?
- Is there any role for using targeted therapy in this setting?

New trials are being done.

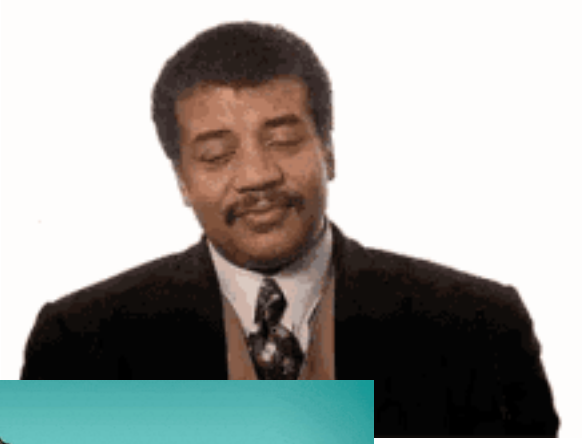
- NCT01822496. An NRG trial was designed that used crizotinib and erlotinib before chemoradiaiton.
- NCT03521154. LAURA study. Osimertinib after chemoradiation.
- Patients with less common drivers. ROS1, BRAF, MET. Data free zone.

Post treatment surveillance.

- No consensus as to what is ideal.
- Could be tailored to what is received as the risk of recurrence.
- Our groups typical schedule is q3 months visit with labs and PE and imaging done q 6 months during the first 2 years.

KEYNOTE-042

- Randomized study **locally advanced** or metastatic NSCLC with PD-L1 expression greater than or equal to 1% patients were randomized to either pembrolizumab or chemotherapy.
- Subgroup analyses showed a trend toward benefit in patients presenting with locally advanced NSCLC in particular (HR 0.74; 95% CI, 0.49–1.13), although the absolute number of patients in this subgroup was small (n = 160).
- FDA approved pembrolizumab for patients with stage III NSCLC with PD-L1 expression greater than or equal to 1% who are not candidates for surgery or chemoradiation.



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