Ανοσοθεραπευτική αντιμετώπιση σε πρώιμο και τοπικά προχωρημμένο ΜΜΚΠ Προκλήσεις και Προοπτικές

Αγγελική Ράπτη

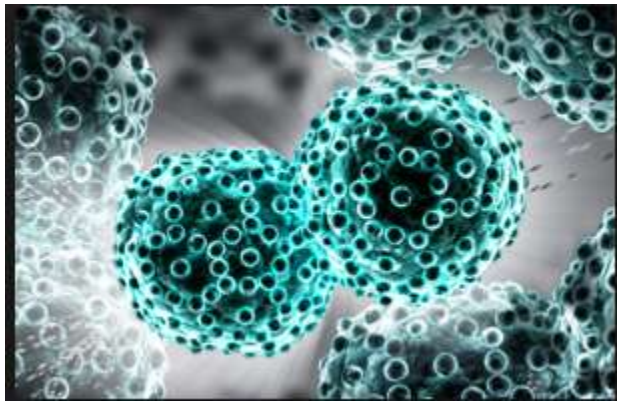
Συντ. Διευθύντρια

2η Πνευμονολογική Κλινική ΝΝΘΑ

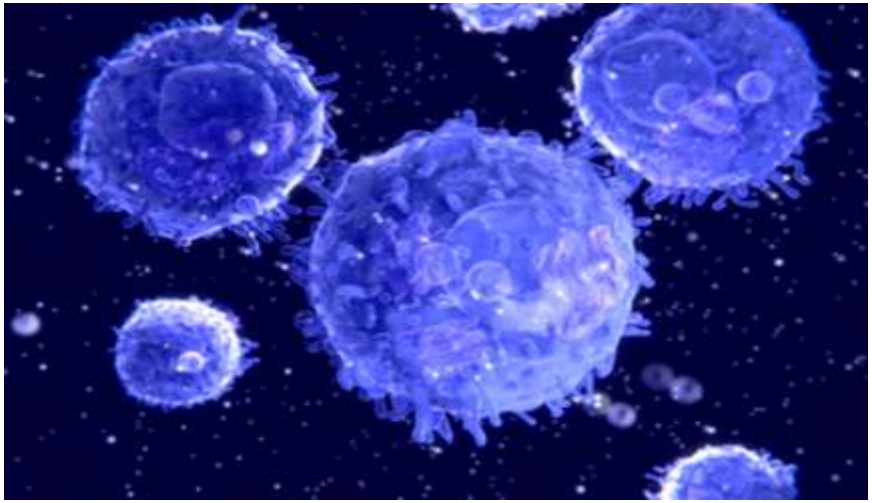
Early stage non-small-cell lung cancer

- Survival for early stage NSCLC remains low
- 5-year survival rates
  - 60% for stage IIA
  - 36% for stage IIIA disease

- 5% improvement in 5-year survival with the addition of chemotherapy to surgery

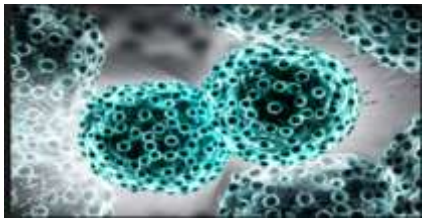


Could an immunotherapy drug be used before surgery to reduce the risk of relapse?



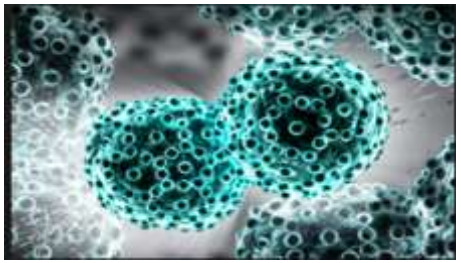
Potential advantages of neoadjuvant treatment

- reduction of tumor size to allow for a potentially less morbid
- ability of patients to tolerate therapy better before surgery compared to afterward
- earlier eradication of nodal and micrometastatic disease



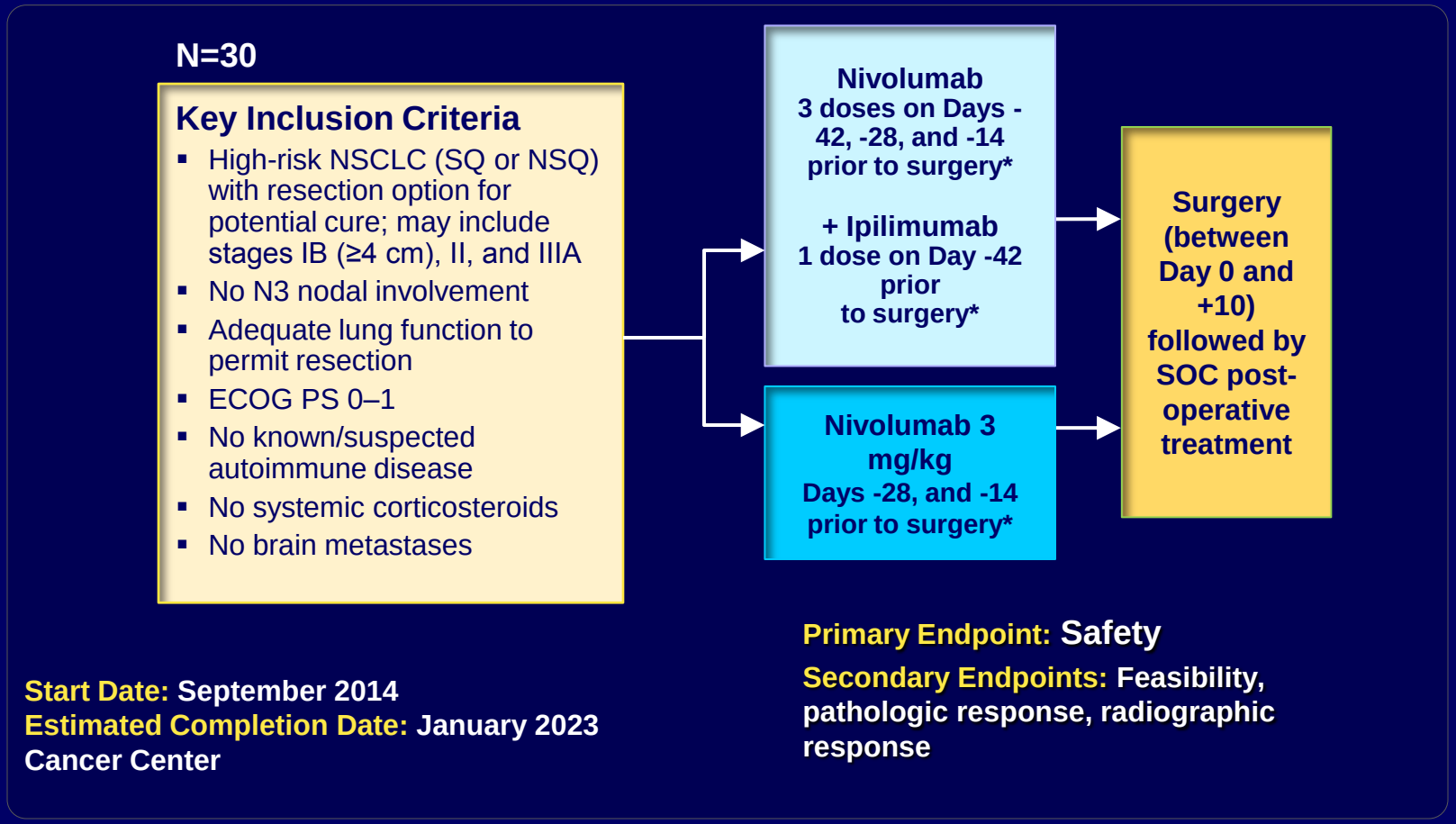
Neoadjuvant immunotherapy

- neoadjuvant (anti–PD-1) treatment of NSCLC uses the primary tumor as an 'auto-vaccine' to induce T-cells against tumor antigens that would then circulate through the body systemically and seek out any distant sites of micrometastases"



NCT02259621: Nivolumab With or Without Ipilimumab .

A phase 2 trial to evaluate nivolumab alone or nivolumab plus ipilimumab as neoadjuvant therapy for early stage, resectable NSCLC

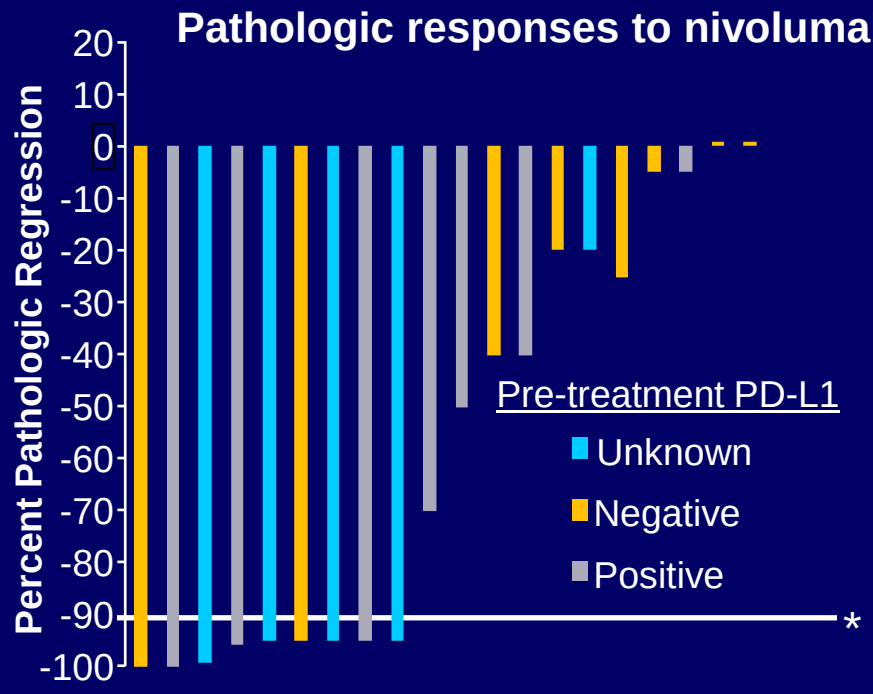


Chaft JE et al. ASCO 2017- AACR 2018

Pathologic Response

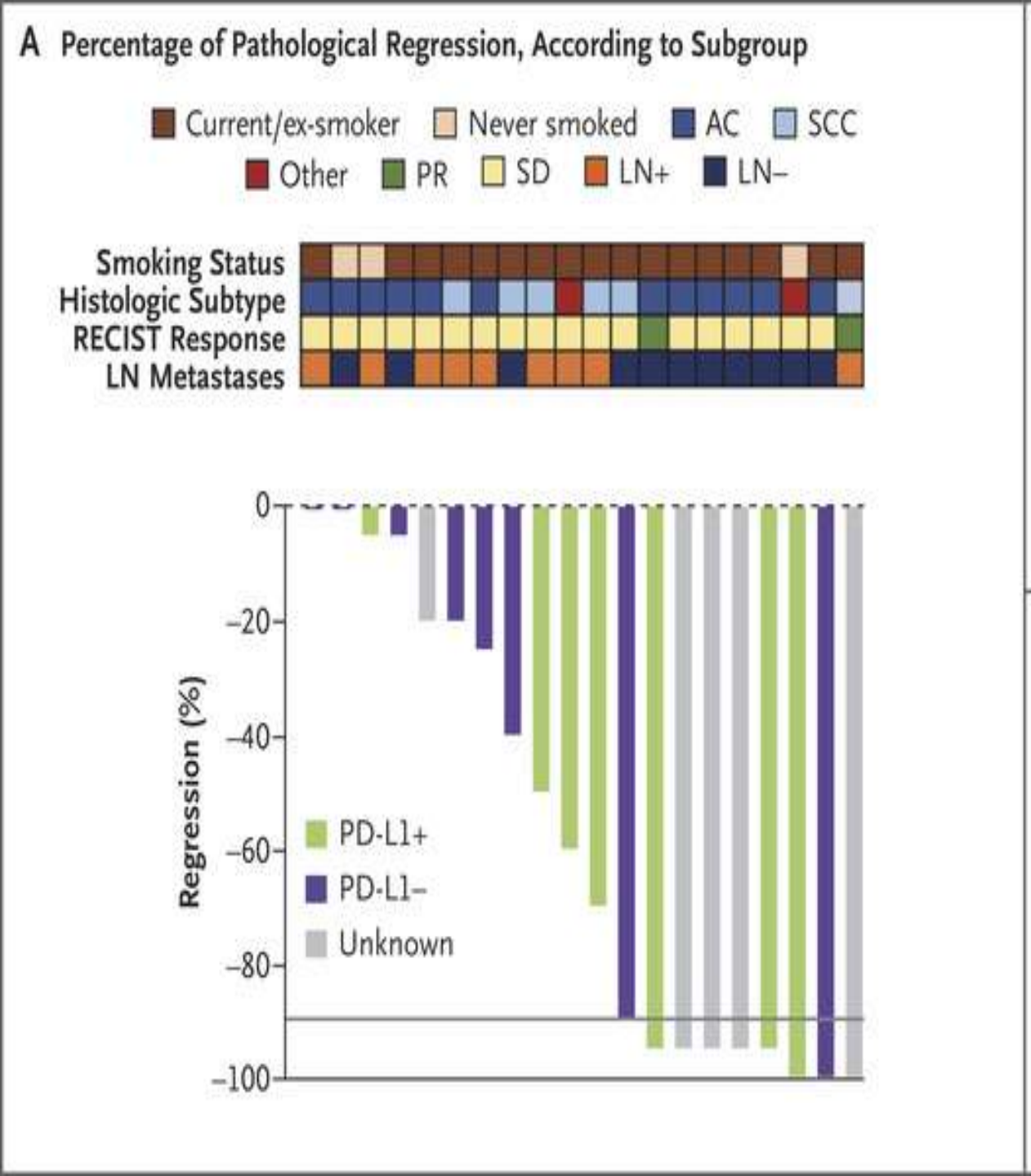
- **MPR* observed in 9/20 cases (45% [95% CI: 24%–63%])**
- **Pre-treatment PD-L1 positivity (≥1% membranous staining [Dako 28-8]) did not correlate with MPR**

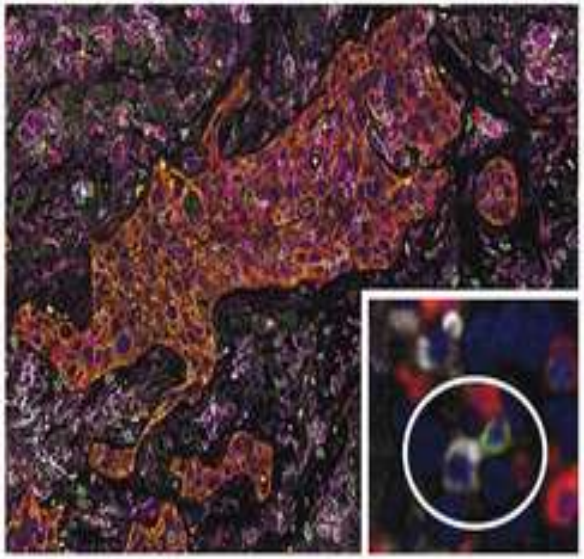
Response (per RECIST v1.1)*	N=21
PR, n (%)	2 (10)
SD , n (%)	18 (85)
PD, n (%)	1 (5)

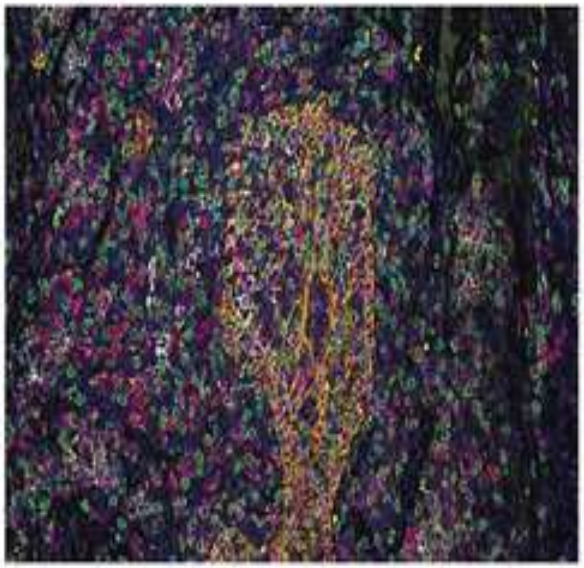


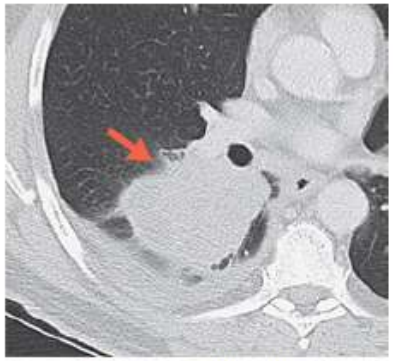
*MPR defined as ≤10% viable tumor cells.

The median degree of pathological regression in the primary tumor was −65% (range, −100 to 0)

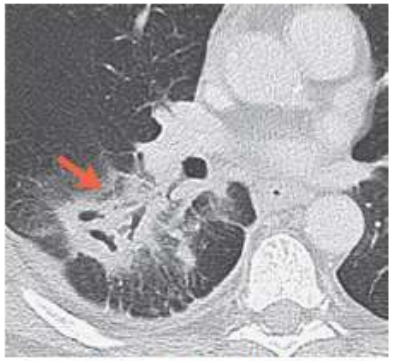

A Percentage of Pathological Regression, According to Subgroup
Current/ex-smoker
Never smoked
AC
SCC
Other
PR
SD
LN+
LN–
Smoking Status
Histologic Subtype
RECIST Response
LN Metastases
Regression (%)
0
–20
–40
–60
–80
–100
PD-L1+
PD-L1–
Unknown


B Biopsy Sample before Nivolumab


C Biopsy Sample after Nivolumab

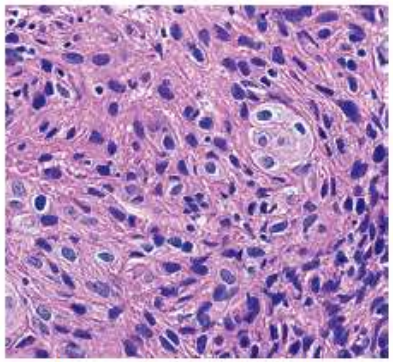


Pretreatment Imaging

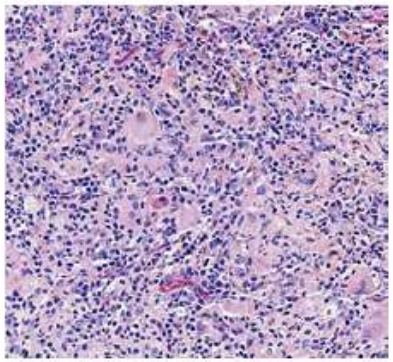


Week 4 (before surgery)

Chest-CT of a 62-year-old male smoker
with stage IIB squamous lung cancer before and after the administration of nivolumab
35% shrinkage with associated tumor cavitation

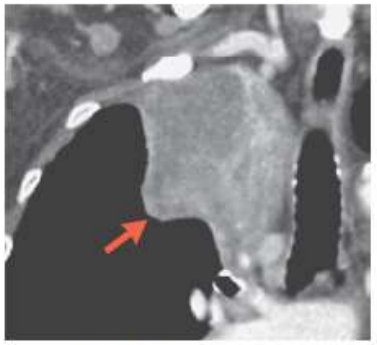


Pretreatment Tumor Biopsy

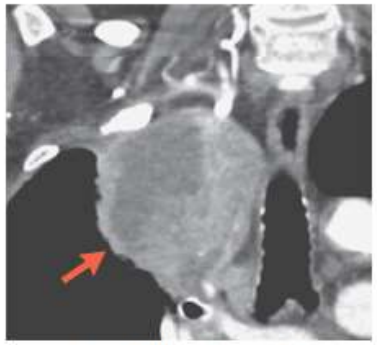


Resection Specimen

100% pathological regression of the primary tumor
but had residual lymph-node metastases
in the resection specimen



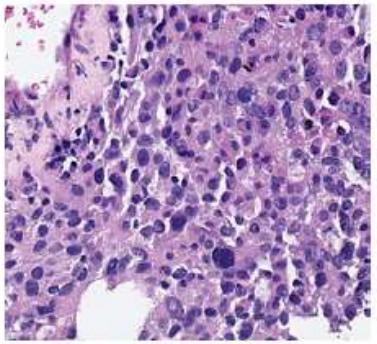
Pretreatment Imaging



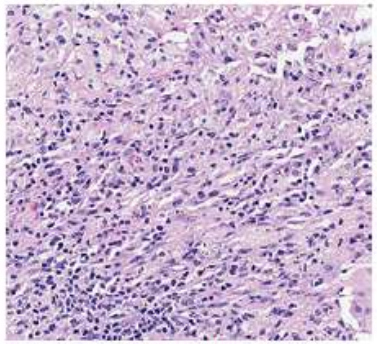
Week 4 (before surgery)

Chest-CT of a 78-year-old female former smoker with stage IIIA lung adeno-ca

in the post-treatment specimen
there was 90% tumor regression.



Pretreatment Tumor Biopsy



Resection Specimen

follow-up

12 months median postoperative follow-up (0.8 to 19.7)

- 16/20 patients (80%) after surgical resection were alive and recurrence-free
- 3 patients had disease progression
- 1patient without recurrence died from a traumatic head injury

At 18 months the recurrence-free survival rate was 73%

Safety Summary

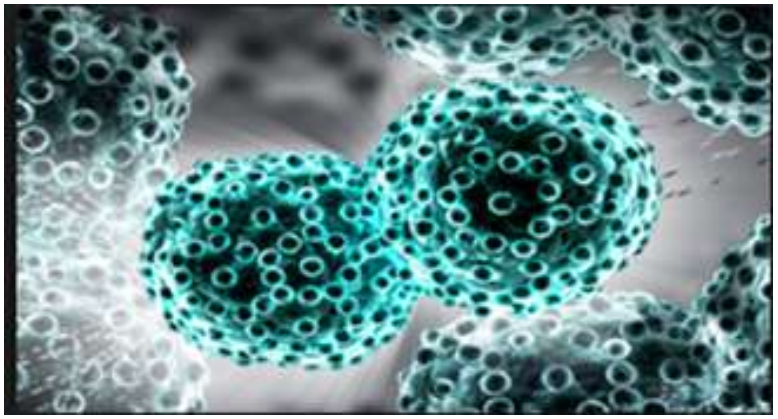
Nivolumab did not delay or interfere with surgery in any patient

Drug-Related AEs in All Treated Patients (N=22)	Any Grade n (%)	Grade 3/4 n (%)
Fever	1* (5)	0
Thyroid dysfunction	1 (5)	0
GI **Anorexia** **Vomiting/diarrhea** **LFT abnormality**	 2 (9) 1 (5) 1(5)	 0 0 0
Pneumonia	0	1* (5)
Infusion reaction	1 (5)	0
CNS (delirium)	1 (5)	0

Chaft JE et al. Poster presented at ASCO 2017. Abstract 8508.

EARLY STAGE NSCLC

Ongoing Trials



Neoadjuvant immunotherapy for NSCLC

Selected trials of neoadjuvant immunotherapy for NSCLC

Trial identifier	Phase	Sponsor	Stage	Intervention	Primary endpoint
NCT02259621	2	Sidney Kimmel Comprehensive Cancer Center	IB –IIIA	Nivolumab with or without ipilimumab	Safety and feasibility
NCT02998528	3	BMS	IB –IIIA	Nivolumab and ipilimumab versus chemotherapy	MPR
NCT03158129	2	M.D. Anderson Cancer Center	I–IIIA	Nivolumab with or without ipilimumab	MPR
NCT02818920	2	Duke University Medical Center	IB –IIIA	Pembrolizumab (neoadjuvant and adjuvant)	Surgical feasibility rate
NCT02927301	2	LCMC-3, Genentech	IB –IIIA	Atezolizumab	MPR
NCT02572843		Swiss Group for Clinical Cancer Research	IIIA (N2)	Durvalumab	Event-free survival (EFS)
NCT03081689	2	Spanish Lung Cancer Group	IIIA (N2)	Nivolumab, carboplatin, paclitaxel	PFS

adjuvant immunotherapy for NSCLC

Selected trials of adjuvant immunotherapy for NSCLC

Trial identifier	Phase	Sponsor	Stage	Intervention	Primary endpoint
NCT02595944	3	National Cancer Institute (NCI)	IB–IIIA	Nivolumab	DFS, OS
NCT02486718	3	Hoffmann-La Roche	IB–IIIA	Atezolizumab	DFS
NCT02273375	3	Canadian Cancers Trials Group	IB-IIIA	Durvalumab	DFS
NCT03130764	2	Columbia University	IB–IIIA	Durvalumab and Tremelimumab	Induced T-cell response rate
NCT02504372	3	EORTC, Merck	IB–IIIA	Pembrolizumab	DFS
NCT03053856	2	Samsung Medical Center	IIIA (N2)	Pembrolizumab	DFS

Prospective multi-arm adjuvant trial -ALCHEMIST – NCT02201992, NCT02193282, NCT02194738

- treatment allocation is based on the genomic features of each tumor

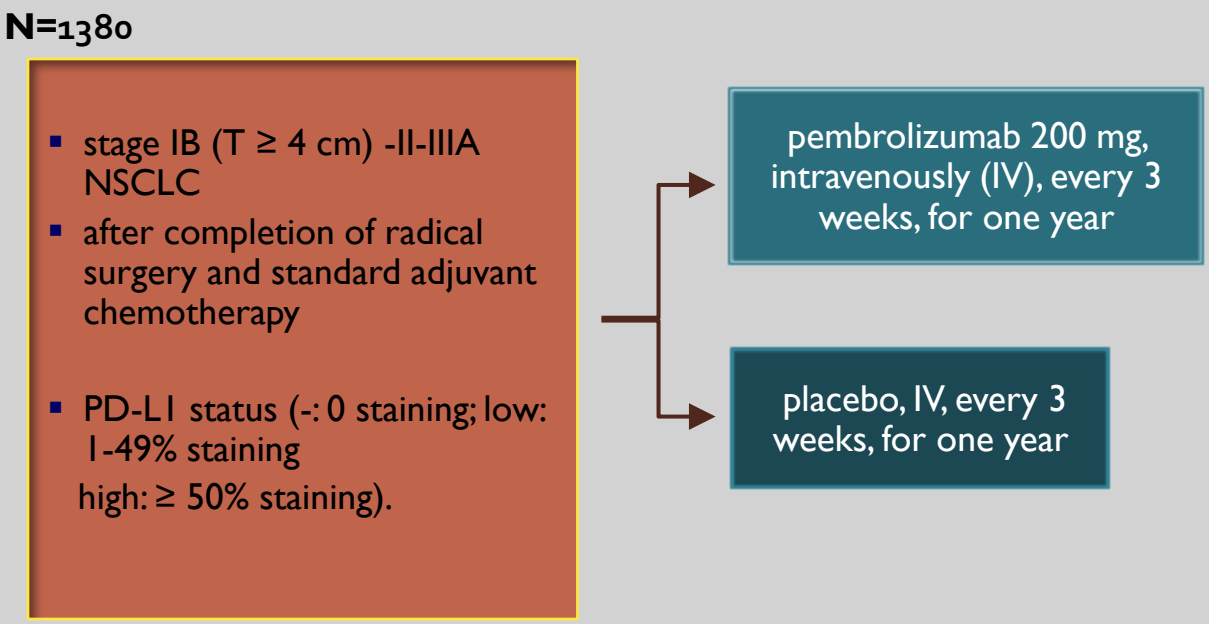
- After completing standard adjuvant treatment, patients are randomized, based on:

  - ALK rearrangements
  - EGFR mutations
  - the absence of both

  to either placebo/crizotinib/erlotinib/ nivolumab

EORTC-ETOP randomized, phase 3 trial with pembrolizumab versus placebo for patients with early stage NSCLC after resection and standard adjuvant chemotherapy

PEARLS (NCT02504372)



Co-Primary Endpoints: **(DFS) in the whole population and DFS in 'high'**

Secondary Endpoints : (OS) Lung Cancer Specific Survival (LCSS)

Estimated Study Completion Date: August 19, 2021

A phase II study of atezolizumab as neoadjuvant and adjuvant therapy in patients (pts) with resectable non-small cell lung cancer (NSCLC).

Dwight Hall Owen, Paul A. Bunn, Bruce E. Johnson, David J. Kwiatkowski, Mark G.

180 patients

Part 1

- Atezolizumab 1200 mg IV / 3 weeks for two doses.
- Surgical resection of tumors following treatment will allow determination of pathologic response rates and potential predictive biomarkers

Part 2

- Atezolizumab adjuvant therapy for up to 12 months in patients who demonstrate clinical benefit in Part 1

Primary endpoint: **major pathologic response rate** (defined as ≤ 10% of viable tumor cells) based on surgical resection.

NCT03081689: Nivolumab Plus Chemotherapy

A phase 2, single-arm, open-label trial to assess the feasibility, safety, and efficacy of neoadjuvant nivolumab plus chemotherapy followed by adjuvant nivolumab in patients with resectable stage IIIA NSCLC

N=46

Key Inclusion Criteria

- Resectable stage IIIA NSCLC
- Performance status of 0 or 1
- No TK domain EGFR mutations
- No ALK alterations
- No active, known, or suspected autoimmune disease
- No systemic treatment with corticosteroids or other immunosuppressive medications within 14 days of randomization
- No history of interstitial lung disease with symptomatic ILD

Nivolumab
360 mg q3w x 3 cycles

+ Chemotherapy
(paclitaxel 200 mg/m^2 + carboplatin AUC 6 q3w) x 3 cycles

Surgery followed by adjuvant nivolumab for 1 year
(240 mg q2w for 4 months followed by 480 mg q4w for 8 months)

Primary Endpoint: PFS

Secondary Endpoints: OS, toxicity profile

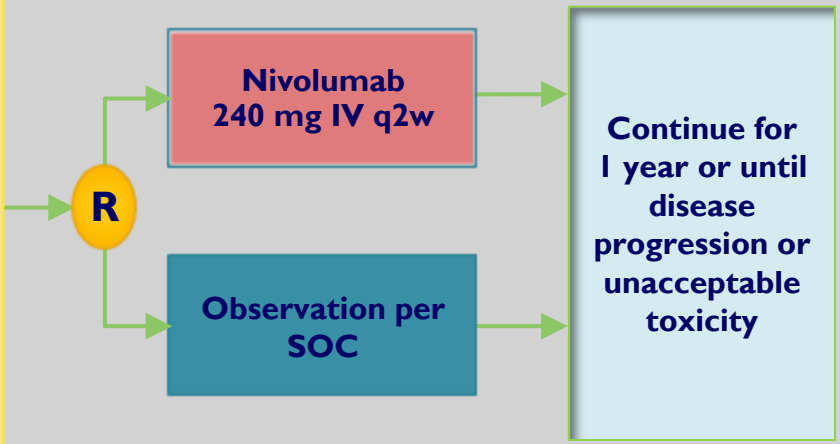
Start Date: April 2017
Estimated Completion Date: June 2022
Status: Recruiting
Sponsor: Spanish Lung Cancer Group

ANVIL (EA5142): Nivolumab

A phase 3 trial to evaluate adjuvant therapy with nivolumab after surgery and chemotherapy for the treatment of patients with Stage IB to IIIA NSCLC

Key Inclusion Criteria

- Stage IB (tumor ≥4 cm), II, or IIIA NSCLC
- Must have undergone complete resection
- Negative surgical margins
- Baseline CT within 30 days of randomization without recurrent disease
- ECOG PS 0–1
- NSQ tumors that are *EGFR* and *ALK* WT
- PD-L1 status tested by central lab
- Must have recovered from surgery and any adjuvant therapy (chemotherapy and/or radiation)

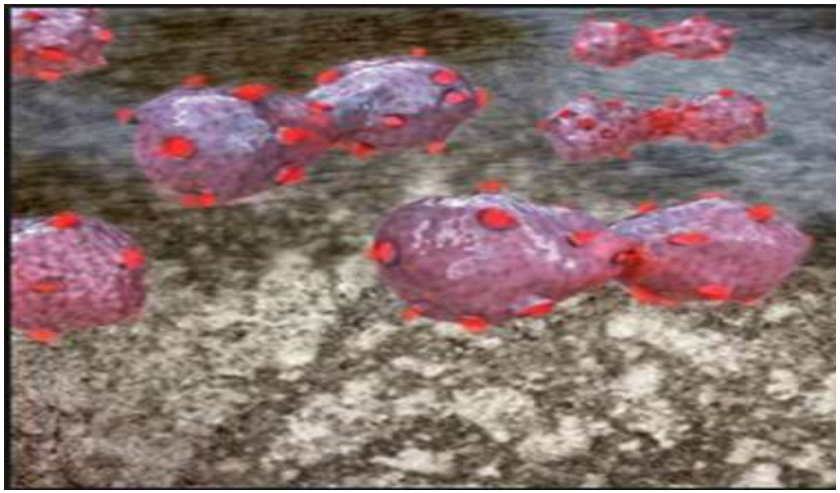


Primary Endpoints: DFS, OS
Secondary Endpoint: Toxicity

Start Date: May 2016
Estimated Primary Completion Date: May 2018
Sponsor: National Cancer Institute

Locally advanced NSCLC

Immunotherapy



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PACIFIC: Study Design

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

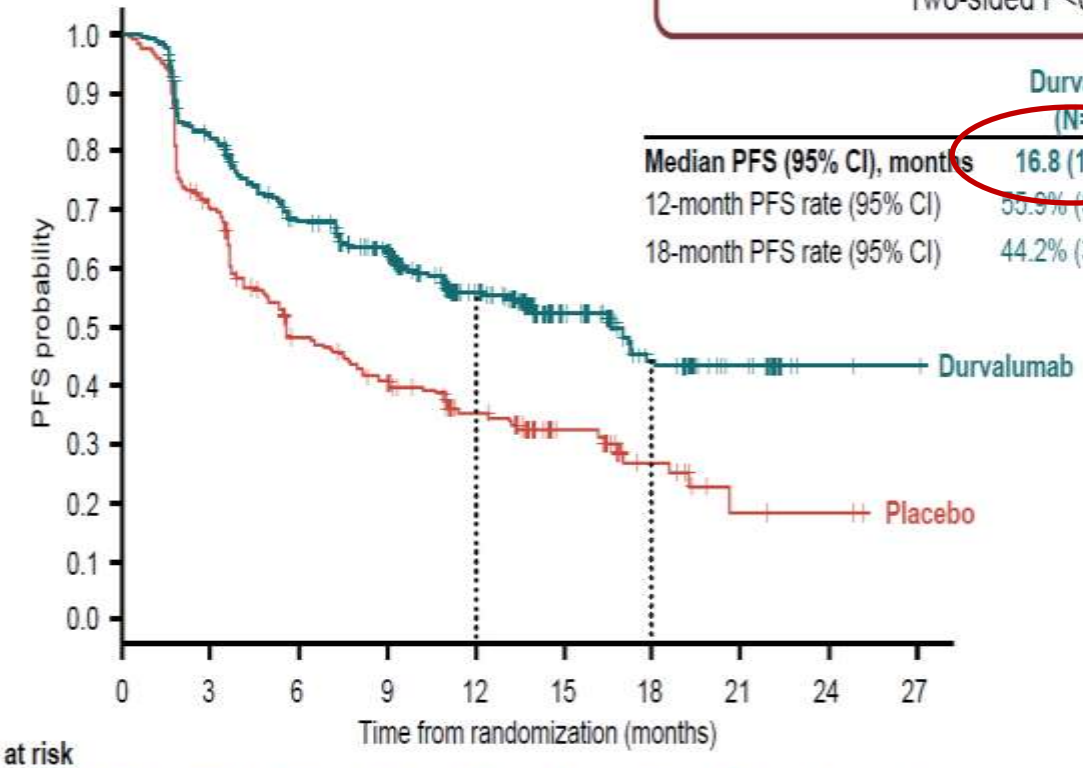
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

*Defined as the time from randomization (which occurred up to 6 weeks post-cCRT) to the first documented event of tumor progression or death in the absence of progression.
ClinicalTrials.gov number: NCT02125461 BICR, blinded independent central review; cCRT, concurrent chemoradiation therapy; DoR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

PFS by BICR (Primary Endpoint; ITT)

Stratified hazard ratio, 0.52 (95% CI, 0.42–0.65)
Two-sided P<0.0001

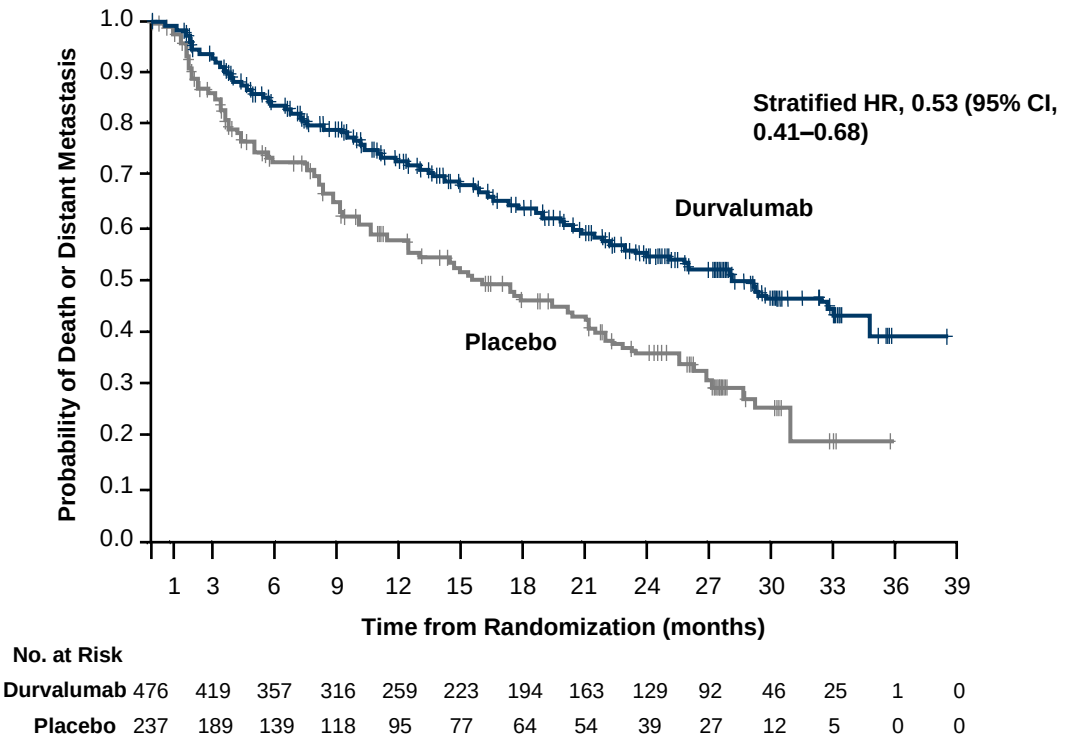
	Durvalumab (N=476)	Placebo (N=237)
Median PFS (95% CI), months	**16.8 (13.0–18.1)**	**5.6 (4.6–7.8)**
12-month PFS rate (95% CI)	55.9% (51.6–60.4)	35.3% (29.0–41.7)
18-month PFS rate (95% CI)	44.2% (37.7–50.5)	27.0% (19.9–34.5)



No. at risk									
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

PACIFIC: Time to Death or Distant Metastasis (TTDM) by BICR (ITT Population)



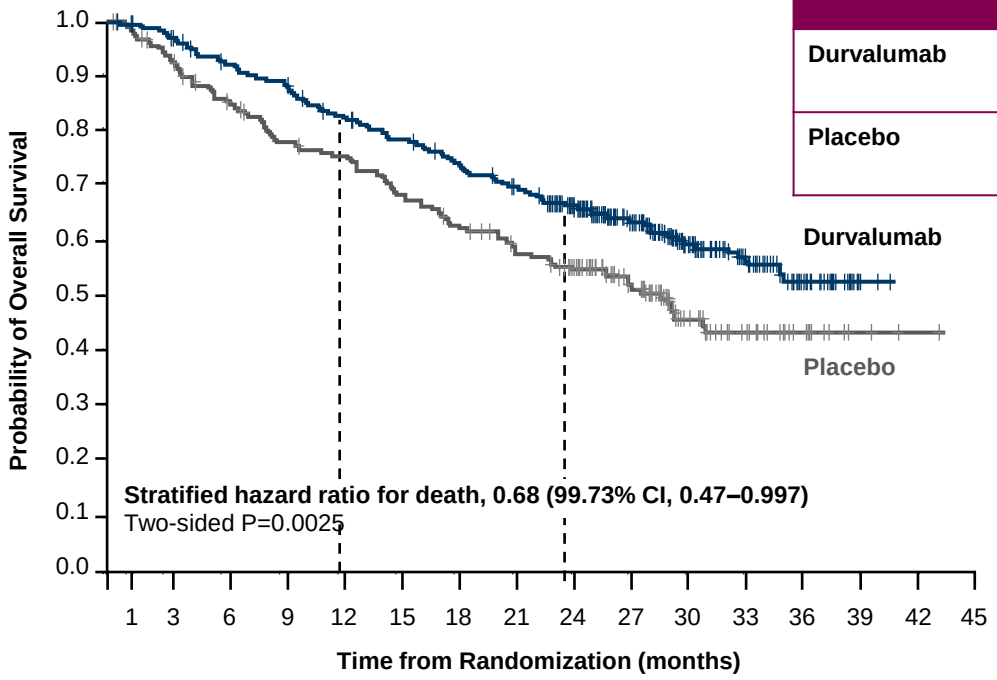
	No. of events / No. of patients	Median TTDM (95% CI) months
Durvalumab	182/476	**28.3** (24.0–34.9)
Placebo	126/237	**16.2** (12.5–21.1)

ITT = intention to treat; HR = hazard ratio; TTDM = time to death or distant metastasis

1.Antonia SJ, et al. Article and supplementary appendix online ahead of print. *N Eng J Med*. 2018.

PACIFIC: Overall Survival – in the ITT Population[a,b]

	No. of events / No. of patients	Median OS (95% CI), months	12-mo OS (95% CI) %	24-mo OS (95% CI) %
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)



No. at Risk																
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

ITT = intent to treat; ; mo = months; NR = not reached; OS = overall survival
[a]Median duration of follow-up for OS was 25.2 months (range 0.2-43.1).
[b]Data cutoff for the first planned OS interim analysis occurred after 299 events (61% of the target 491 events).

1.Antonia SJ, et al. Article and supplementary appendix online ahead of print. *N Eng J Med*. 2018.

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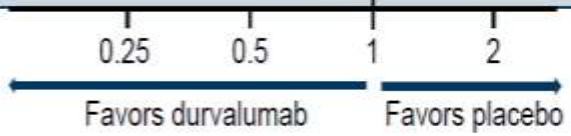
PFS Subgroup Analysis by BICR (ITT)

		Durvalumab No. of patients	Placebo No. of patients	Unstratified HR* (95% CI)
	All patients	476	237	0.55 (0.45–0.68)
Sex	Male	334	166	0.56 (0.44–0.71)
	Female	142	71	0.54 (0.37–0.79)
Age at randomization	<65 years	261	130	0.43 (0.32–0.57)
	≥65 years	215	107	0.74 (0.54–1.01)
Smoking status	Smoker	433	216	0.59 (0.47–0.73)
	Non-smoker	43	21	0.29 (0.15–0.57)
Disease stage	Stage IIIA	252	125	0.53 (0.40–0.71)
	Stage IIIB	212	107	0.59 (0.44–0.80)
Histology	Squamous	224	102	0.68 (0.50–0.92)
	Non-squamous	252	135	0.45 (0.33–0.59)
Best response to cCRT	CR	9	7	–
	PR	232	111	0.55 (0.41–0.75)
	SD	222	114	0.55 (0.41–0.74)
PD-L1 status	≥25%	115	44	0.41 (0.26–0.65)
	<25%	187	105	0.59 (0.43–0.82)
	Unknown	174	88	0.59 (0.42–0.83)
EGFR status	Mutant	29	14	0.76 (0.35–1.64)
	Wild-type	315	165	0.47 (0.36–0.60)
	Unknown	132	58	0.79 (0.52–1.20)



*Hazard ratio and 95% CI not calculated if the subgroup has less than 20 events.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intention-to-treat; EGFR, epidermal growth factor receptor

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Safety Summary*

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	142 (29.9)	61 (26.1)
Grade 5	21 (4.4)	13 (5.6)
Leading to discontinuation	73 (15.4)	23 (9.8)
Any-grade treatment-related AEs, n (%)	322 (67.8)	125 (53.4)
SAEs, n (%)	136 (28.6)	53 (22.6)
Any-grade immune-mediated AEs, n (%)	115 (24.2)	19 (8.1)
Grade 3/4	16 (3.4)	6 (2.6)

*Two patients randomized to placebo received at least one dose of durvalumab and were considered part of the durvalumab arm for safety reporting.
Safety analysis set. AE, adverse event; SAE, serious adverse event

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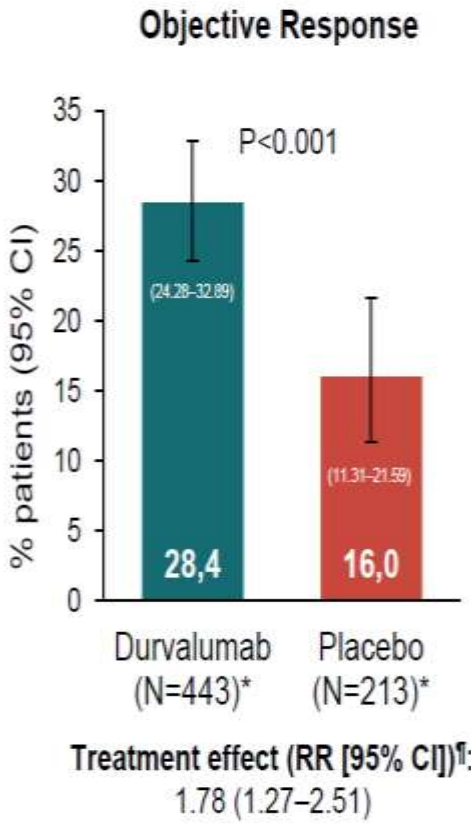
Most Frequent AEs*

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event, n (%)	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/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
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)

Safety analysis set (all-causality). *Occurring in >11% of patients in either treatment arm. Two patients randomized to placebo received at least one dose of durvalumab and were considered part of the durvalumab arm for safety reporting. †Pneumonitis/radiation pneumonitis was assessed by investigators with subsequent review and adjudication by the study sponsor. In addition, pneumonitis, as reported in the table, is a grouped term, which includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis. AE, adverse event

MADRID 2017 ESMO congress

Antitumor Activity by BICR (ITT)



Treatment effect (RR [95% CI])¶:
1.78 (1.27–2.51)

	Durvalumab (N=443)*	Placebo (N=213)*	Treatment effect (HR [95% CI])¶
Best overall response, n (%)†			
Complete response	6 (1.4)	1 (0.5)	
Partial response	120 (27.1)	33 (15.5)	
Stable disease	233 (52.6)	119 (55.9)	
Progressive disease	73 (16.5)	59 (27.7)	
Non-evaluable	10 (2.3)	1 (0.5)	
Duration of response, months			
Median (95% CI)	NR	13.8 (6.0–NR)	0.43 (0.22–0.84)
Ongoing response at data cutoff, %‡			
At 12 months	72.8	56.1	
At 18 months	72.8	46.8	

*Patients with measurable disease at baseline, as determined by either of the two independent reviewers; †One patient could not be grouped into any of the best overall response categories due to inconsistency in the baseline assessment for measurable disease between the two independent central reviewers. ‡Percentages calculated by Kaplan-Meier method; ¶Placebo was the reference group when RR and HR were calculated; therefore, an RR value greater than 1 is in favor of durvalumab and an HR value less than 1 is in favor of durvalumab
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reached; RR, relative risk

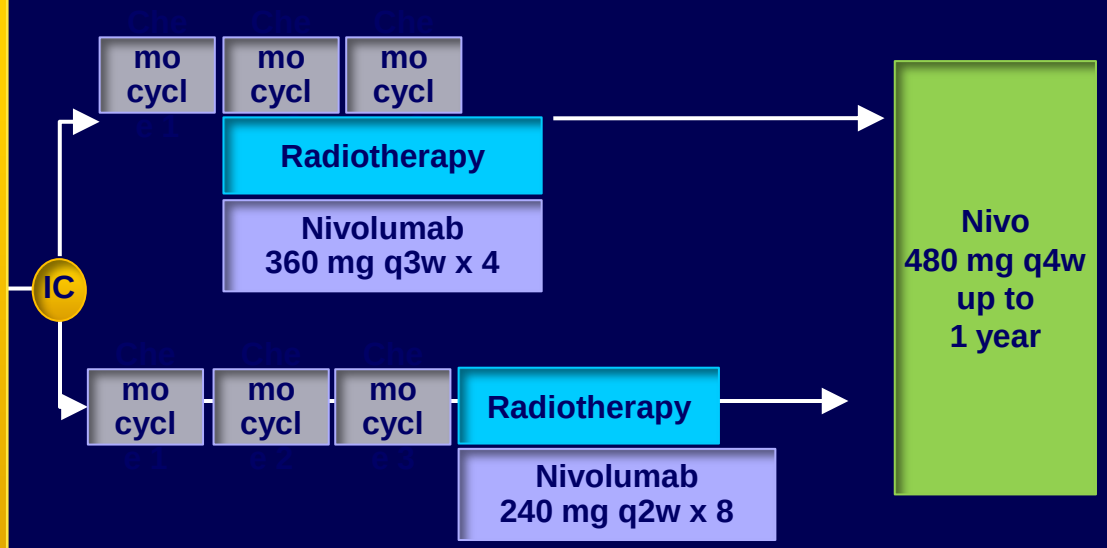
NICOLAS: Nivolumab Plus Chemotherapy and Radiotherapy

A phase 2 trial to evaluate the addition of nivolumab to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC*

N=43

Key Inclusion Criteria

- Stage IIIA or IIIB NSCLC
- Nodal status N2 or N3 proven by biopsy, except for overt cT4 disease
- Previous delivery of ≤1 triweekly cycle of Pt-based chemotherapy
- ECOG PS 0–1
- AEs from previous therapies resolved to Grade <2
- No metastatic disease
- No previous radiotherapy to chest
- No prior **chemotherapy, radiotherapy** or targeted therapy for NSCLC†



Primary Endpoints: Rate of Grade ≥3 pneumonitis, observed up to 6 months post radiotherapy

Secondary Endpoint: PFS, ORR per RECIST v1.1, TTF, OS, AEs

Start Date: August 2015
Estimated Completion Date: August 2019
Sponsor: European Thoracic Oncology Platform

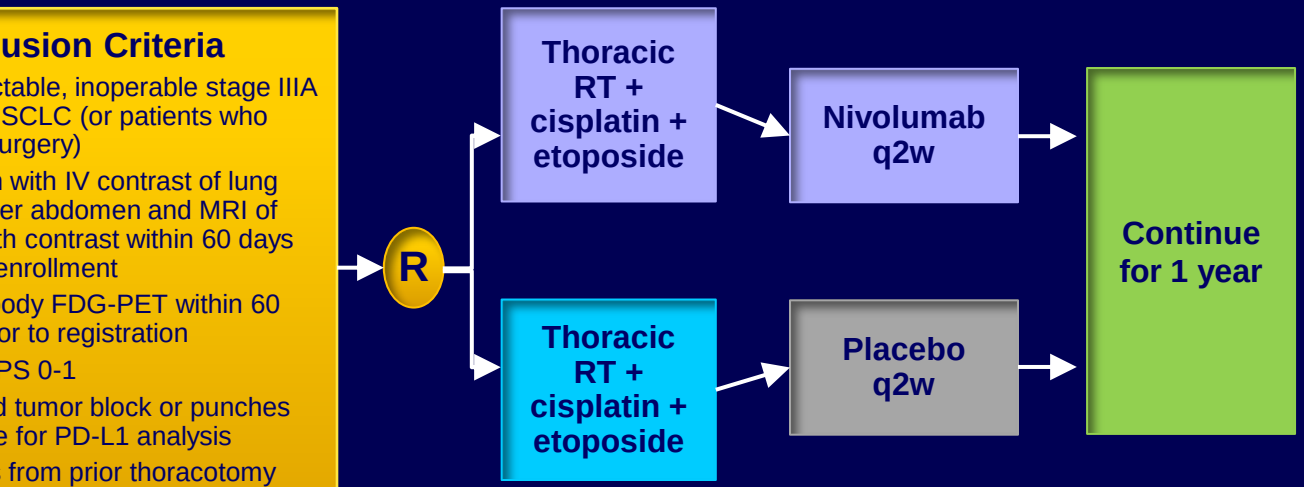
RTOG 3505: Chemotherapy Followed by Nivolumab in inoperable stage IIIA or IIIB NSCLC

A phase 3, double-blind trial of cisplatin and etoposide plus thoracic radiation therapy, followed by nivolumab or placebo for locally advanced NSCLC

N=660

Key Inclusion Criteria

- Unresectable, inoperable stage IIIA or IIIB NSCLC (or patients who refuse surgery)
- CT scan with IV contrast of lung and upper abdomen and MRI of brain with contrast within 60 days prior to enrollment
- Whole body FDG-PET within 60 days prior to registration
- Zubrod PS 0-1
- Archived tumor block or punches available for PD-L1 analysis
- 3 weeks from prior thoracotomy
- FEV_1 >1.2 liters and DLCO ≥50% predicted



Primary Endpoints: OS, PFS

Start Date: October 2016
Estimated Completion Date: October 2024