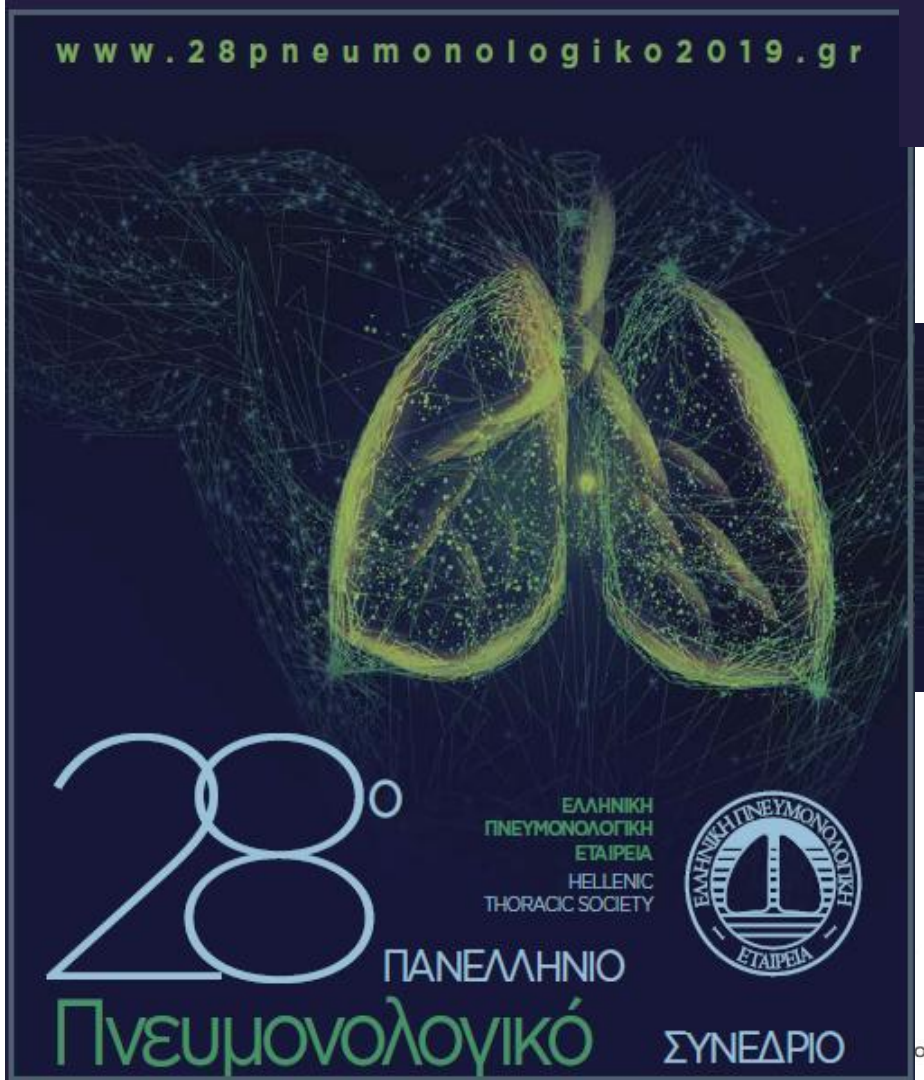


28ο ΠΑΝΕΛΛΗΝΙΟ Πνευμονολογικό ΣΥΝΕΔΡΙΟ

Μη Μικροκυτταρικός καρκίνος σταδίου ΙΙΙ: Συνδυασμένη θεραπευτική προσέγγιση

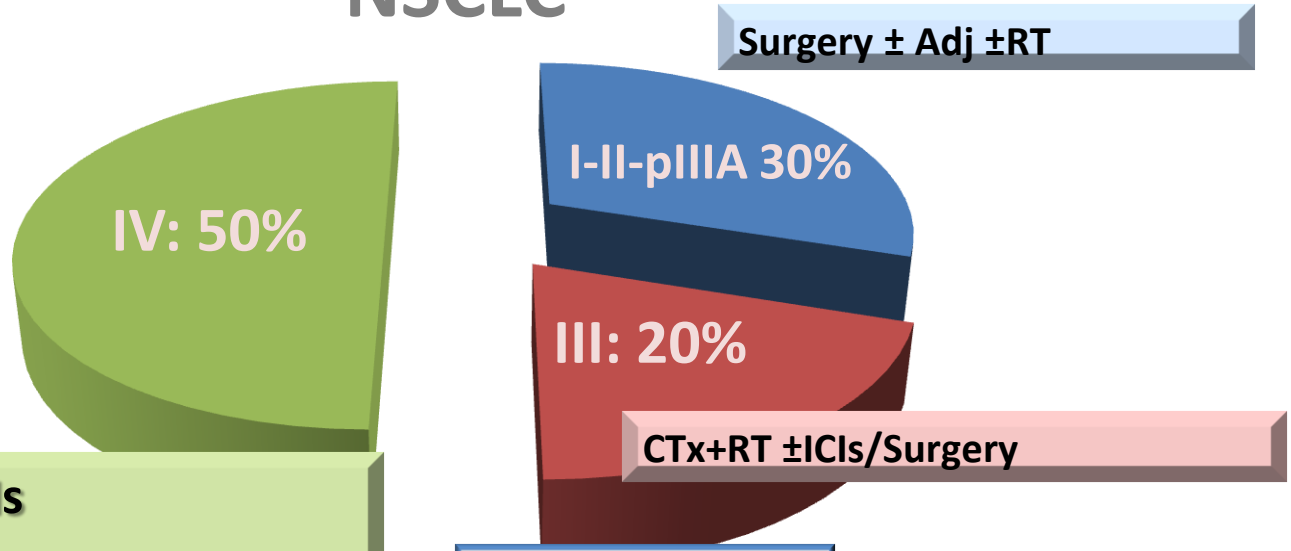
Ο ρόλος της Ανοσοθεραπείας στην αντιμετώπιση του σταδίου ΙΙΙ

Ανδριανή Χαρπίδου *MD, Ph.D, FCCP*
Πνευμονολόγος
3η Πανεπιστημιακή Παθολογική Κλινική ΕΚΠΑ, Νοσοκομείο ΝΝΘΑ «Σωτηρία»

Disclosures

Honorarium for lectures and satellite symposium: BMS, Pfizer, Astra Zeneca, MSD, Roche
Consultation: Boerhinger Ingerlheim, Astra Zeneca

NSCLC



CTx/Targeted /ICIs
± Palliation Tx RT or Bronchoscopy

Clinical Staging
CTs/MRIs
Bronchoscopy-
EBUS/EUS-TBNA
PET
Cervical Mediastinoscopy
VATS

Stage III NSCLC

Stage groupings

	N0	N1	N2	N3	M1a any N	M1b any N	M1c any N
T1a	IA1	IIB	IIIA	IIIB	IVA	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVA	IVB

Goldstraw P et al. J Thorac Oncol 2016; 11: 39-51.

Stage III NSCLC

Controversies in multidisciplinary approach

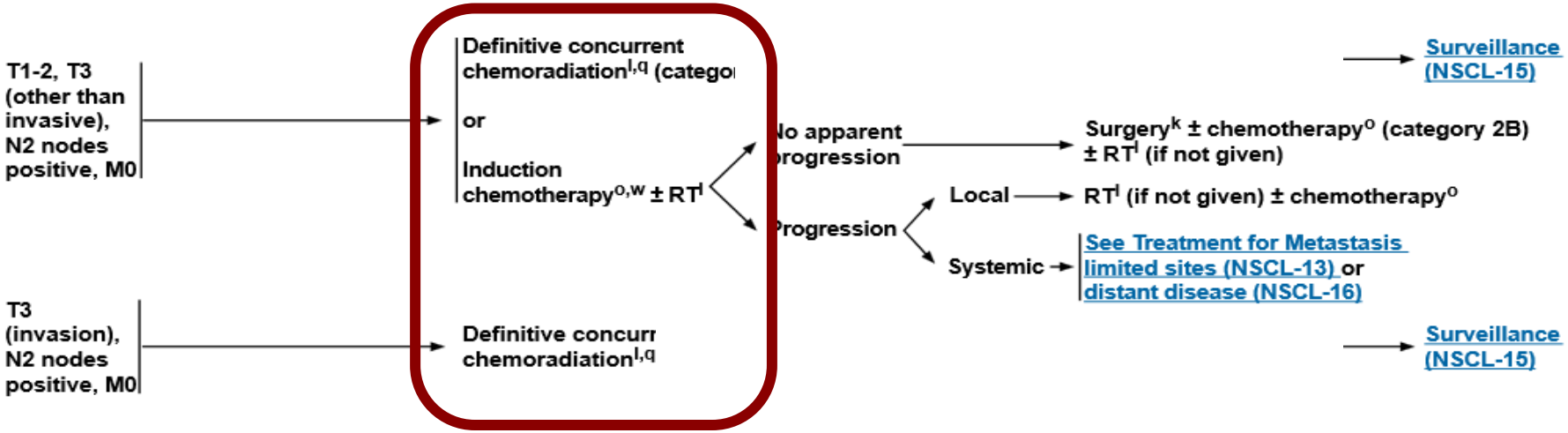
- Which stage III patients are ***resectable vs unresectable***

- ***Treatment:*** neoadjuvant chemotherapy vs CRT vs adjuvant chemotherapy
  - SEER database shows better outcomes with postoperative radiation

Stage III NSCLC

- Stage III NSCLC unresectable - The role of ICIs
- Can we improve the PACIFIC in locally advanced NSCLC?
- What about moving immunotherapy into earlier stages of disease?
- How we can identify patients who will benefit most from immunotherapy?

NCCN Guidelines®: Treatment Algorithm for Confirmed Stage IIIA,B NSCLC



[k]See Principles of Surgical Therapy (NSCL-B).
[l]See Principles of Radiation Therapy (NSCL-C).
[n]After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.
[o]See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

Stage III NSCLC unresectable

Meta-analysis of Concurrent CRT vs Sequential CT + RT in Locally Advanced NSCLC: OS

Stage III NSCLC unresectable

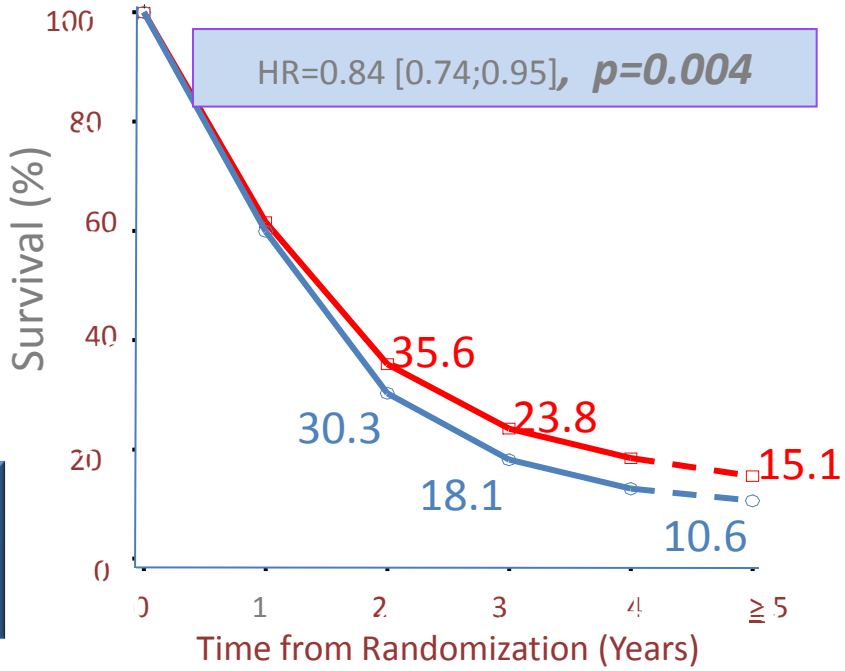
Meta-analysis of Concurrent CRT vs Sequential CT + RT in Locally Advanced NSCLC: OS

- Outcomes with sequential CRT[2]:
  - ***Median OS: 17.4 months***
  - 5-year survival rate: 10.6%

- Outcomes with concurrent CRT[2]:
  - ***Median OS: 18.6 months***
  - 5-year survival rate: 15.1%

- ↓ risk of locoregional progression *(HR: 0.77; P = .01)*
- No difference in rates of distant progression between strategies

Acute esophageal toxicity *(grade 3/4)* ***increased*** *from 4% to 18% (RR: 4.9; 95% CI: 3.1-7.8; P < .001)*
No *difference in acute* ***pulmonary toxicity***



CRT=chemoradiation therapy; NSCLC=non-small cell lung cancer;OS=overall survival.

Aupérin A, et al. J Clin Oncol. 2010;28:2181-2190

Stage III NSCLC unresectable

Unmet Needs in Stage III Unresectable NSCLC- Application strategies for CTx-RT

Concurrent Chemoradiotherapy

slight improvement in median OS Only 15% 5y survival rate

Potentially curable

a) Increase doses - *Of Radiotherapy*

Study	Treatment Arms	Patient	Outcomes		Conclusion
			PFS	OS	
RTOG 0617 (2014)	• Randomly assigned to receive ○ CRT (60 Gy) ○ CRT (74 Gy)	Untreated patients stage III (N = 544)	Median PFS: • **CRT (60 Gy)**: 11.8 months • **CRT (74 Gy)**: 9.8 months	Median OS: • **CRT (60 Gy)**: **28.7 months** • **CRT (74 Gy)**: **20.3 months**	**No improvement of OS with higher doses**

1. *Bradley JD, et al. Lancet Oncol. 2015;16:187-199.*

Stage III NSCLC unresectable

Unmet Needs in Stage III Unresectable NSCLC- Application strategies for CTx-RT

Concurrent Chemoradiotherapy

slight improvement in median OS, only 15% in 5y survival rate

Potentially curable

a) Increase doses - *Of Chemotherapy*

Induction Chemotherapy → Concurrent Chemoradiotherapy

Study	Treatment Arms	Patient	Outcomes		Conclusion
			PFS	OS	
CALGB 39801 (2007)	• **Arm A**: CRT with carboplatin AUC 2 & paclitaxel 50 mg/m² • **Arm B**: Two cycles of carboplatin AUC 6 and paclitaxel 200 mg/m² and concurrent CRT	Stage III unresectable (N = 366)	Median FFS: • **Arm A**: 7 months • **Arm B**: 8 months	Median OS: • **Arm A:** 12 months • **Arm B:** 14 months	**Induction therapy prior to concurrent CRT increased toxicity and *did not prolong significantly survival versus CRT alone***

Concurrent Chemoradiotherapy → *Consolidation Chemotherapy*

Study	Treatment Arms	Patient	Outcomes		Conclusion
			PFS	OS	
HOG/USO	• Cisplatin 50 mg/m² and etoposide 50 mg/m² followed by radiation therapy • Patients without disease progression were randomly assigned to receive docetaxel 75 mg/m² versus observation	Stage III unresectable (N = 203)	No significant difference in PFS between the two arms (*P* = 0.960)	Median OS: • **Observation**: 23.2 months • **Docetaxel**: 21.2 months (***P* = 0.883)**	**Consolidation docetaxel increased toxicity and *did not* improve survival versus CRT alone**
KCSG-LU05-04	• **Observation arm**: Concurrent CRT (CCRT) alone • **Consolidation arm**: CCRT plus docetaxel and cisplatin	Inoperable stage IIIA or IIIB (N = 459)	Median PFS: • **Consolidation arm:** 8.1 months • **Observation arm:** 9.1 months(*P* = 0.36)	Median OS: • **Consolidation arm:** 21.8 months • **Observation arm:** 20.6 months (***P* = 0.44)**	**Consolidation docetaxel plus cisplatin *did not* improve survival when added to CRT**

1. *Lilenbaum R, et al. J Thorac Oncol. 2015;10:143-147.*
2. *Ahn JS, et al. J Clin Oncol. 2015;33:2660-2666*

Stage III NSCLC unresectable

Unmet Needs in Stage III Unresectable NSCLC- Application strategies for CTx-RT

Potentially curable

Concurrent Chemoradiotherapy

slight improvement in median OS *Only 15% in 5y survival rate*

b) Add Targeted Agents

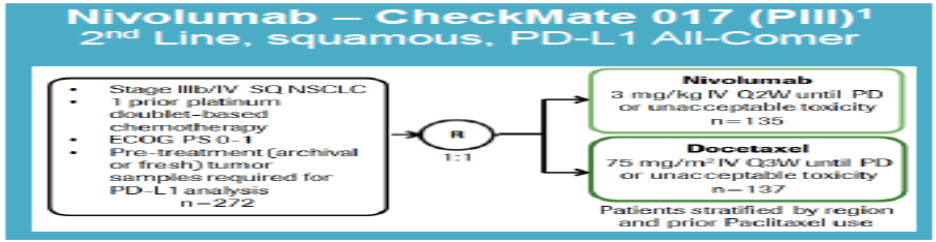
Study	Treatment Arms	Patient n	Outcomes		Conclusion
			PFS	OS	
RTOG 0617	• Randomly assigned to receive ○ CRT (60 Gy) ○ CRT (74 Gy) ○ CRT (60 Gy) plus cetuximab ○ CRT (74 Gy) plus cetuximab	Untreated patients stage III (N = 544)	Median PFS: • **CRT (60 Gy)**: 11.8 months • **CRT (74 Gy)**: 9.8 months • **With cetuximab**: 10.8 months • **Without cetuximab**: 10.7 months	Median OS: • **CRT (60 Gy)**: 28.7 months • **CRT (74 Gy)**: 20.3 months • **With cetuximab**: 25 months • **Without cetuximab**: 24 months	**The addition of cetuximab to concurrent CRT did not improve survival versus concurrent CRT alone**
CALGB 30605	• Carboplatin, nab-paclitaxel 100 mg/m^2 followed by erlotinib 150 mg with CRT	Stage IIIA or IIIB unresectable (N = 75)	Median PFS: • 11 months	Median OS: • 17 months	**The addition of erlotinib to RT provided no significant survival benefit over RT alone after induction CT**
SWOG S0023	• **Initial Cohort**: Cisplatin 50 mg/m^2, etoposide 50 mg/m^2, concurrent thoracic radiation followed by docetaxel 75 mg/m^2 • Gefitinib 250 mg versus placebo	Untreated patients stage III (N = 672)	Median PFS: • **Gefitinib**: 8.3 months • **Placebo**: 11.7 months	Median OS: • **Gefitinib**: 23 months • **Placebo**: 35 months	**The addition of gefitinib consolidation in an unselected patient population decreased survival versus control arm**

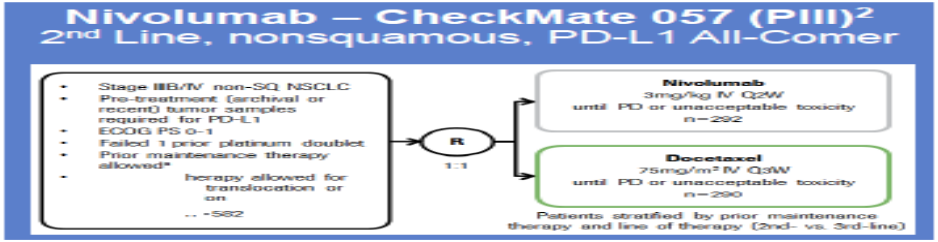
1. *Bradley JD, et al. Lancet Oncol. 2015;16:187-199.* 2.*Lilenbaum R, et al. J Thorac Oncol. 2015;10:143-147.* 3.*Kelly K, et al. J Clin Oncol. 2008;26:2450-2456.*

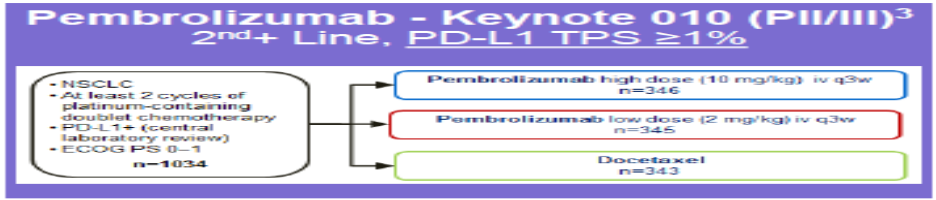
Personalized therapy in metastatic NSCLC

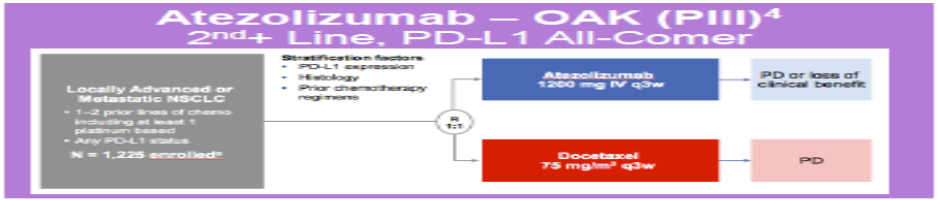
Chemotherapy^*	Targeted TKI Therapy	Checkpoint Inhibitors
Histologic subtyping for chemotherapy	Genomics-driven TKIs: ▪ EGFR ▪ ALK ▪ ROS1 ▪ BRAF V600E	Anti–PD-1 Anti–PD-L1
From 1980s-today	From 2009 - today	From 2015 -today

PD-1 mAbs from May 2017









tional Institutes of Health. www.clinicaltrials.gov/show/NCT01642004. Accessed December 9, 2016. 2. National Institutes of Health. .clinicaltrials.gov/show/NCT01673867. Accessed December 9, 2016. 3. National Institutes of Health. .clinicaltrials.gov/show/NCT01905657. Accessed December 9, 2016. 4. Barlesi F, et al. *Ann Oncol.* 2016;27(Suppl 6): Abstract LBA44.

Stage III NSCLC unresectable - The role of ICIs

Justification of the use Combination Strategies

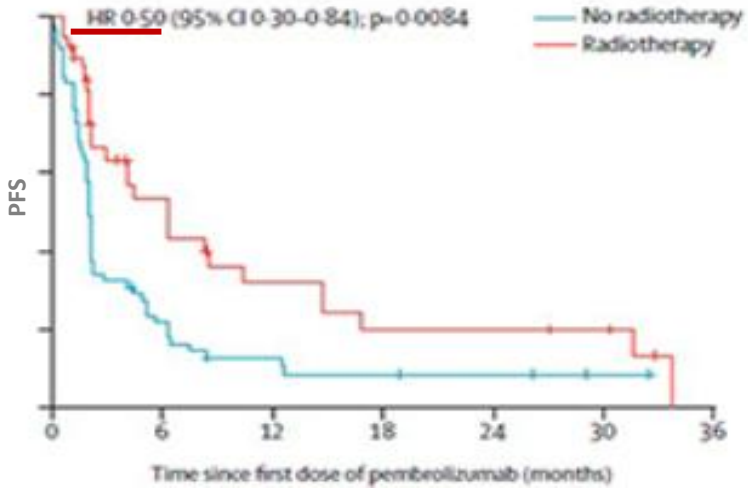
CHEMORADIATION **ICI (ANTI PD-L1)**

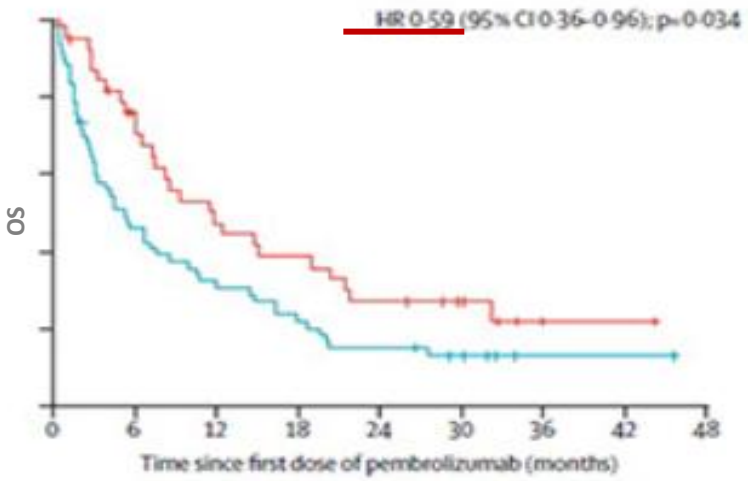
Deng. J Clin Invest. 2014;124:687. Dovedi. Cancer Res. 2014;74:5458. Chacon. Vaccines. 2016;4:E43.
Formenti. J Natl Cancer Inst. 2013;105:256. Funaki. Oncol Rep. 2017;38:2277. Antonia. NEJM. 2017;377:1919.

Stage III NSCLC unresectable- The role of ICIs

Justification of the use Radiotherapy Prior to I-O

Keynote -001: Subgroup secondary analysis for pembrolizumab after extra-cranial RT





Shaveridan N, et al Lancet Oncol 2017; 18:895-903

Stage III NSCLC unresectable - The role of ICIs

MADRID 2017 ESMO congress

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

Chemo 2c or more: platinum-based with: etoposide, vinblastine, vinorelbine, taxanes[carbo-taxol] or pemetrexed
RT:54-66Gy

Antonia SJ et al New Engl J Med 2017; Sep 8

Stage III NSCLC unresectable - The role of ICIs

PACIFIC Trial: IIT patients characteristics

Characteristic	Durvalumab (n = 476)	Placebo (n = 237)
Median age, yrs (range)	64 (31-84)	64 (23-90)
Male, %	70.2	70.0
WHO PS 0/1*, %	49.2/50.4	48.1/51.5
Smoking status, %		
▪ Current	16.6	16.0
▪ Former	74.4	75.1
▪ Never	9.0	8.9
Disease stage†, %		
▪ IIIA	52.9	52.7
▪ IIIB	44.5	45.1
Histology, %		
▪ Squamous	47.1	43.0
▪ Nonsquamous	52.9	57.0

*Missing data (durvalumab, placebo): WHO PS (0.4% each), prior RT (0.2%, 0.4%). †Other: durvalumab, 2.5%; placebo, 2.1%. ‡Non-evaluable/applicable: durvalumab, 1.1%; placebo, 1.3%

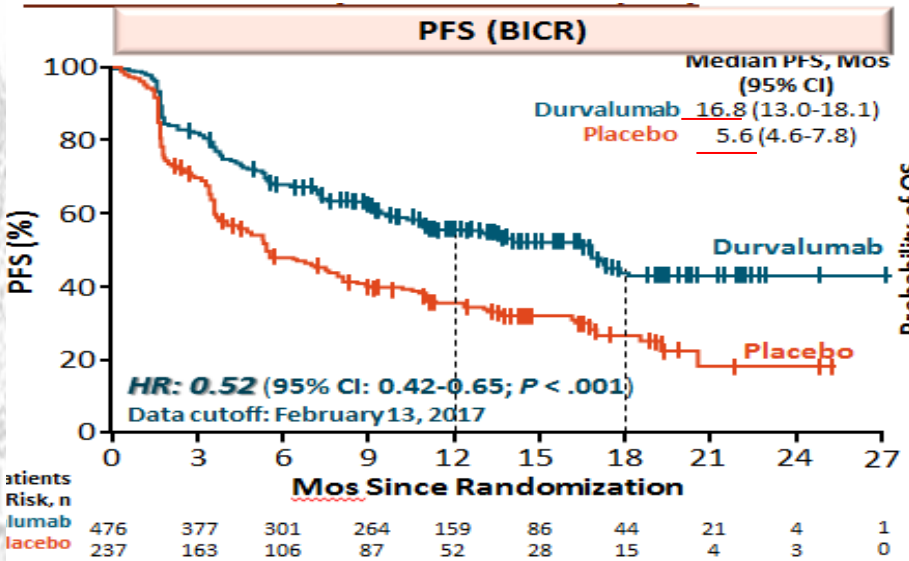
Characteristic	Durvalumab (n = 476)	Placebo (n = 237)
PD-L1 expression level, %		
▪ < 25%	39.3	44.3
▪ ≥ 25%	24.2	18.6
▪ Unknown	36.6	37.1
Prior CT, %		
▪ Induction	25.8	28.7
▪ Definitive cCRT	99.8	99.6
Prior RT*, %		
▪ < 54 Gy	0.6	0
▪ 54 to ≤ 66 Gy	92.9	91.6
▪ > 66 Gy to ≤ 74 Gy	6.3	8.0
Best response to prior cCRT‡, %		
▪ CR	1.9	3.0
▪ PR	49.8	47.3
▪ SD	46.8	48.5
▪ PD	0.4	0

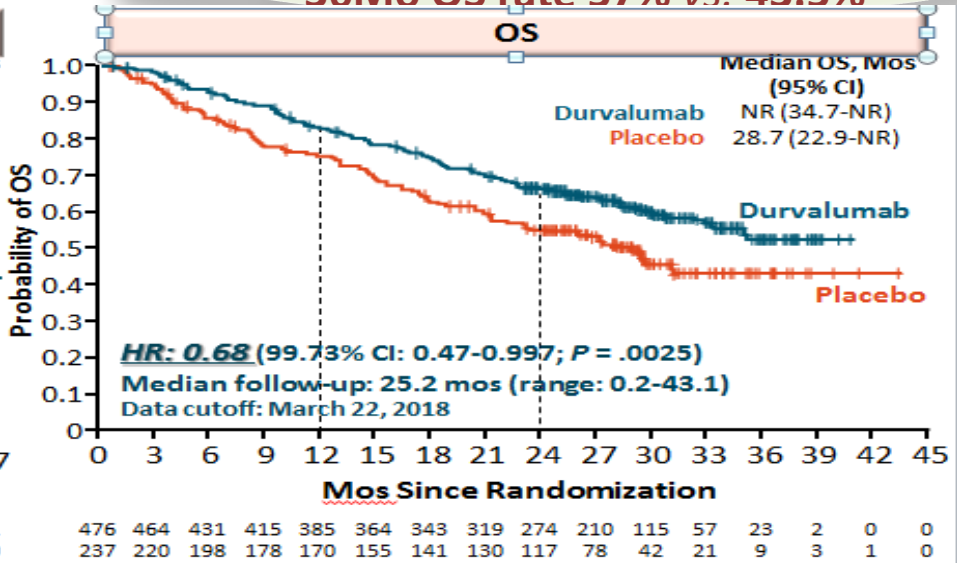
Antonia. N Engl J Med. 2017;377:1919. Antonia. WCLC 2018. Abstract PL02.01. Antonia. N Engl J Med. 2018;379:2342.

Stage III NSCLC unresectable - The role of ICIs

PACIFIC: Efficacy PFS and OS (ITT)

32% improvement in OS
36Mo OS rate 57% *vs.* 43.5%

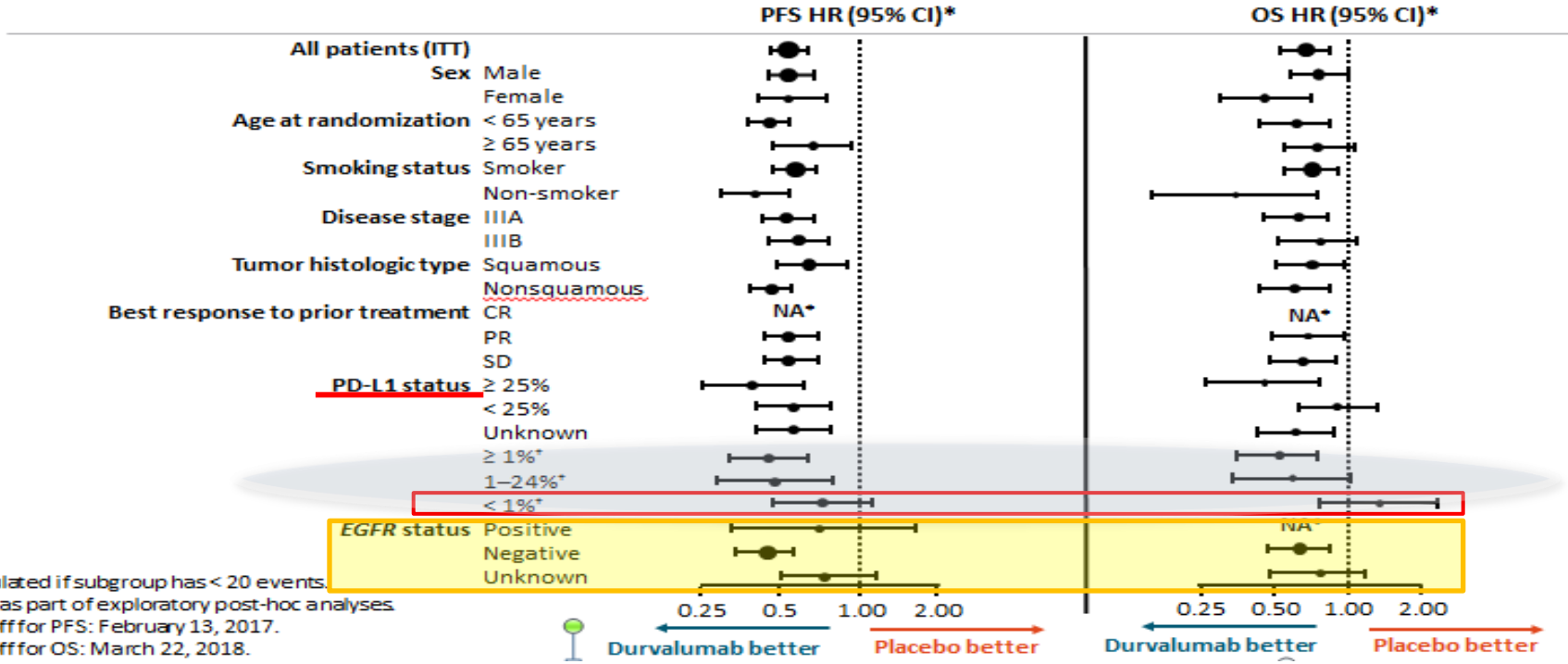




Antonia NEJM 2017;377:1919. Antonia NEJM 2018;379:2342

Stage III NSCLC unresectable - The role of ICIs

PACIFIC: Efficacy Subgroup analysis PFS and OS (ITT)

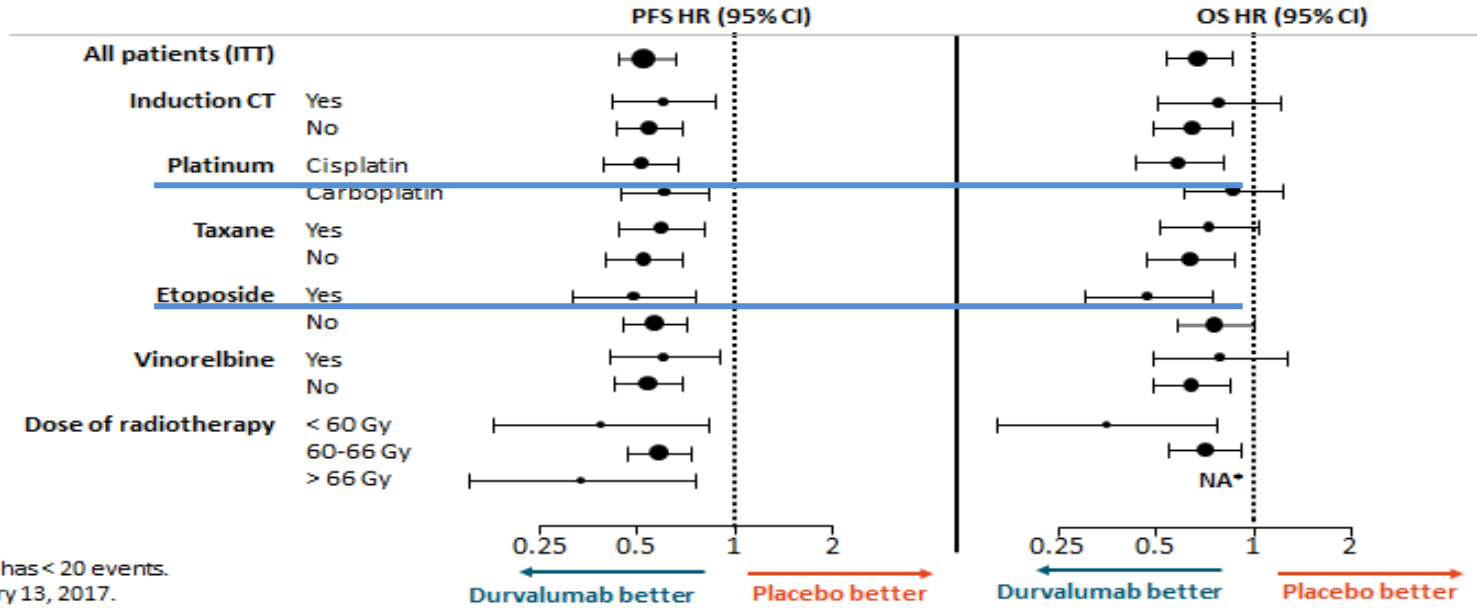


*Not calculated if subgroup has < 20 events.
†Assessed as part of exploratory post-hoc analyses.
Data cut-off for PFS: February 13, 2017.
Data cut-off for OS: March 22, 2018.

Antonia. WCLC 2018. Abstract PL02.01. Antonia. N Engl J Med. 2018;379:2342. Antonia. N Engl J Med. 2017;377:1919.

Stage III NSCLC unresectable - The role of ICIs

PACIFIC: Efficacy Impact of Prior CT and Dose of RT on PFS and OS (ITT)



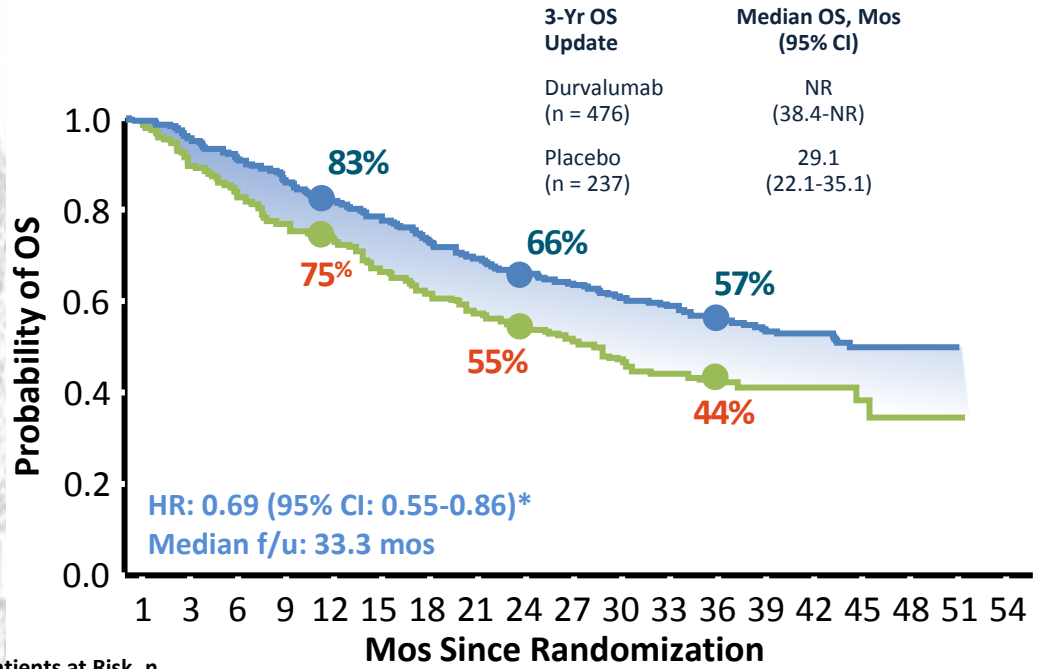
*Not calculated if subgroup has < 20 events.
Data cut-off for PFS: February 13, 2017.
Data cut-off for OS: March 22, 2018

Antonia NEJM 2017;377:1919. Antonia NEJM 2018;379:2342

Faivre-Finn. ESMO 2018. Abstract 1363O.

Stage III NSCLC unresectable - The role of ICIs

PACIFIC: OS with Durvalumab at 3 Years



Patients at Risk, n

Durvalumab	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1	0

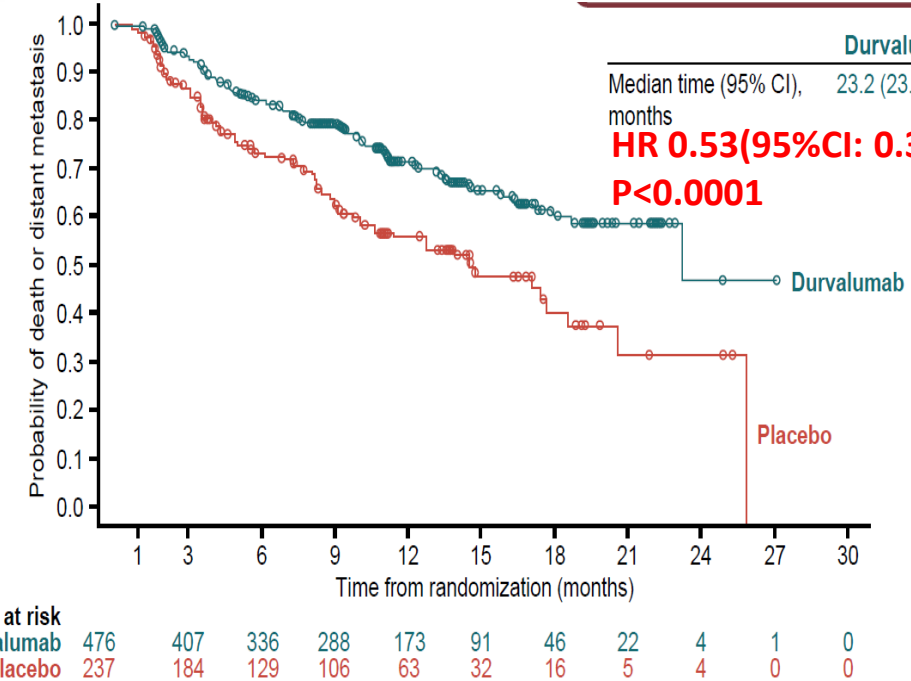
- Primary 2-yr OS analysis of durvalumab vs placebo
  - Conducted at 42% maturity
  - Median OS: NR vs 28.7 mos (P = .0025)
  - 32% reduction in the risk of death (HR: 0.68)
  - Median f/u: 25.2 mos

*3-yr post-hoc OS analysis conducted at 70% maturity, not powered to show statistical significance; 31% reduction in risk of death with durvalumab vs placebo.

Gray. ASCO 2019. Abstract 8526. Antonia. N Engl J Med. 2018;379:2342.

Stage III NSCLC unresectable - The role of ICIs

PACIFIC trial: Results – Efficacy: Time to Distant Metastasis or Death



	Durvalumab	Placebo
Median time (95% CI), months	23.2 (23.2–NR)	14.6 (10.6–18.6)

HR 0.53(95%CI: 0.39-0.69)

P<0.0001

BICR, blinded independe

LOCAL
DISTANT

New lesion Site	Durva (N=476)	Placebo(N=237)
Patients with any new lesion, n(%)	107 (22.5)	80 (33.8)
Lung	56(11.8)	41(17.3)
Lymph nodes	27(5.7)	27(11.4)
Brain	26(5.5)	26(11.0)
Liver	9(1.9)	8(3.4)
Bone	8(1,7)	6(2.5)
Adrenal	3(0.6)	5(2.1)
Other	9(1.9)	5(2.1)

Antonia. WCLC 2018. Abstract PL02.01. Antonia. N Engl J Med. 2018;379:2342. Antonia. N Engl J Med. 2017;377:1919.

Stage III NSCLC unresectable - The role of ICIs

PACIFIC: Updated Safety

AE, n (%)	Durvalumab (n = 475)	Placebo (n = 234)
Any-grade, all-causality AE	**460 (96.8)**	**222 (94.9)**
▪ Grade 3/4	145 (30.5)	61 (26.1)
▪ Outcome of death	21 (4.4)	15 (6.4)
▪ Leading to discontinuation	73 (15.4)	23 (9.8)
Serious AEs	138 (29.1)	54 (23.1)
Any-grade pneumonitis/radiation pneumonitis	161 (33.9)	58 (24.8)
▪ Grade 3/4	**17 (3.6)**	**7 (3.0)**
▪ Outcome of death	5 (1.1)	5 (2.1)
▪ Leading to discontinuation	30 (6.3)	10 (4.3)

- No clinically important differences in key PROs identified between durvalumab and placebo arms

Antonia. WCLC 2018. Abstract PL02.01. Antonia. N Engl J Med. 2018;379:2342. Hui. Lancet Oncol. 2019;[Epub ahead of print].

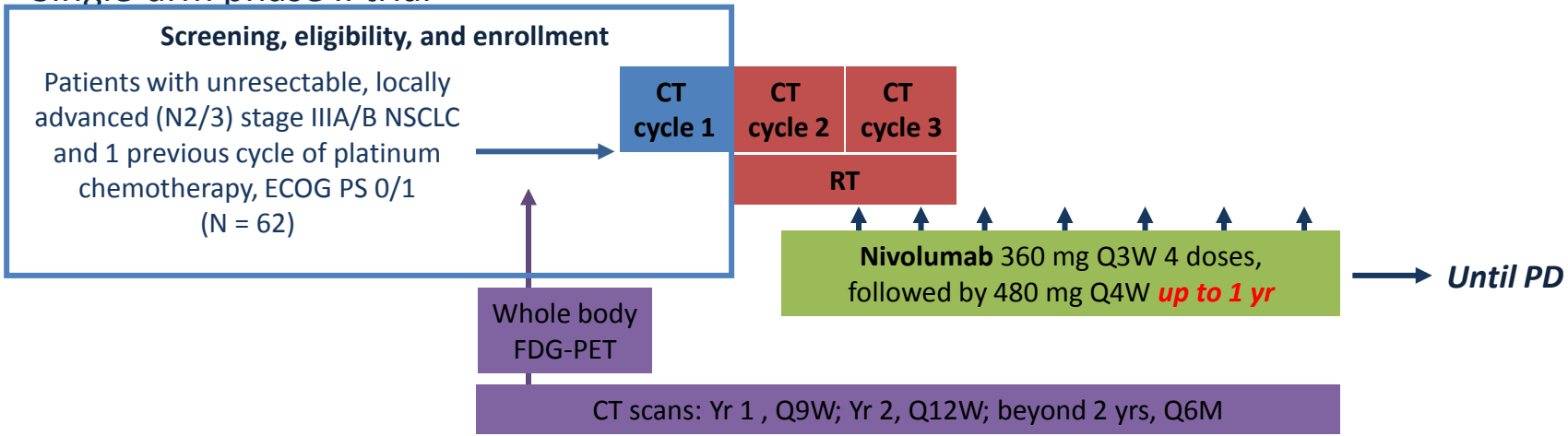
Stage III NSCLC

- Stage III NSCLC unresectable - The role of ICIs
- Can we improve the PACIFIC in locally advanced NSCLC?
- What about moving immunotherapy into earlier stages of disease?
- How we can identify patients who will benefit most from immunotherapy?

Stage III future of ICIs

ETOP 6-14 NICOLAS: Concurrent CRT + Nivolumab in Unresectable Stage III NSCLC

Single-arm phase II trial



*Platinum CT: cisplatin/vinorelbine, cisplatin/etoposide, or cisplatin/pemetrexed (can substitute carboplatin in cisplatin-ineligible patients). †Cycle 1 is CT only and is administered prior to enrollment. ‡RT dose ≥ 60 Gy.

Primary endpoint: rate of grade ≥ 3 pneumonitis at 6 mos post RT

Secondary endpoints: 1-yr PFS, time to first grade ≥ 3 pneumonitis, ORR, TTF, OS, safety

Peters. ASCO 2018. Abstr 8510. NCT02434081.

Stage III future of ICIs

NICOLAS: Overall Adverse Events for the Safety Cohort, N=58

- At DCO, February 20, 2018, 62 patients were recruited, with a median follow-up of 6.6 months (95% CI, range 5.6-7.8).
- The safety cohort included all patients who had received ≥1 dose of trial treatment, N = 58.
  - Patients received a median of 8 cycles of nivolumab therapy (range, 1-17).
  - 89.7% of patients (n=52) reported an AE.
  - 41.4% of patients (n=24) developed a SAE.
- The most frequently observed AEs were
  - Fatigue in 41.4% of patients (n=24)
  - Anemia in 41.4% of patients (n=24), of which one was an SAE
  - Pneumonitis in 32.7% of patients (n=19), of which 8 were SAEs (discussed in detail on the previous slide)
  - Nausea in 31.0% of patients (n=18), of which two were SAEs

Conclusion

- No new safety signals were identified in this trial.
- The safety analysis indicates a tolerable safety profile for the nivolumab-CRT combination.
- Safety of the nivolumab-CRT combination is established in this trial. The 6 month pneumonitis rate is consistent with the expected rate for this patient population.
- The pneumonitis rate is acceptable for the nivolumab-CRT combination used in this trial.

AE = adverse event; CRT = chemoradiotherapy;
DCO = data cutoff; SAE = serious adverse event.

Peters et al. Poster presented at: ASCO 2018; June 1-5, 2018; Chicago, IL. Abs 8510.

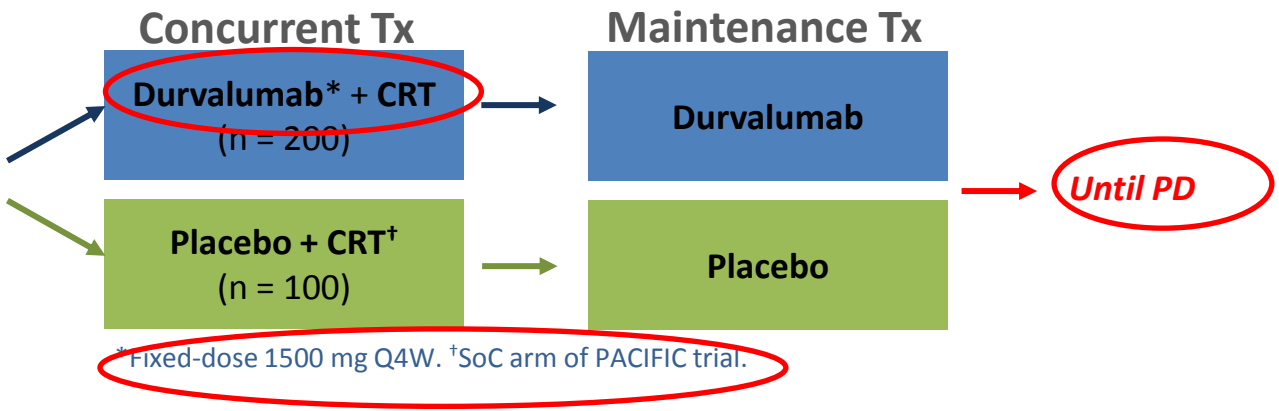
Stage III future of ICIs

PACIFIC 2:

Concurrent CRT + Durvalumab vs CRT Alone in Locally Advanced Stage III NSCLC

Randomized, double-blind, placebo-controlled phase III trial

Patients with unresectable stage III NSCLC (per PET/CT, MRI), with ECOG PS 0/1 (Planned N = 390)



Primary endpoints: PFS, ORR

Secondary endpoints: OS

Stage III future of ICIs

RTOG 3505: CRT ± Adjuvant Nivolumab in Unresectable Stage III NSCLC

- *Randomized, double-blind phase III study*

Patients with unresectable stage IIIA/B NSCLC, any histology, no *EGFR* mutation or *ALK* rearrangement, no prior treatment, ECOG PS 0/1 (planned N = 660)

Concurrent CRT
Cisplatin 50 mg/m^2
Days 1, 8, 29, 36
Etoposide 50 mg/m^2
Days 1-5, 29-33
+ 60 Gy RT

→ **Adj Nivolumab** 240 mg Q2W

→ **Adj Placebo** Q2W

→ ***Until PD, unacceptable toxicity, or up to 1 yr***

Primary endpoints: OS, PFS

Secondary endpoints: safety, PROs, QoL, OS, and PFS in PD-L1 ≥ 1% vs PD-L1 < 1%

Gerber. Clin Lung Cancer. 2017;18:333. NCT02768558.

Stage III future of ICIs

CA209 73L: Study Design

Screening

Key Eligibility Criteria:

- Stage III NSCLC amenable to CCRT
- No prior systemic therapy
- ECOG PS 0–1

- **Stage (IIIA / IIIB / IIIC)**
- **PD-L1 (≥1% / <1%, indeterminate, not evaluable)**

R 1:1:1

n=888

	CCRT	Recovery	Maintenance
A	Nivolumab 360 mg q3w (cycles 1-3) + Chemotherapy q3w (cycles 1-3) + Radiotherapy 60-66 Gy (cycles 2-3)	*Recovery (2-6 wks)*	Nivolumab 360 mg q3w + Ipilimumab 1 mg/kg q6w (Up to 1 year)
B	Nivolumab 360 mg q3w (cycles 1-3) + Chemotherapy q3w (cycles 1-3) + Radiotherapy 60-66 Gy (cycles 2-3)	*Recovery (2-6 wks)*	Nivolumab 480 mg q4w (Up to 1 year)
C	Chemotherapy q3w (cycles 1-3) + Radiotherapy 60-66 Gy (cycles 2-3)	*Recovery (2-6 wks)*	Durvalumab 10 mg/kg q2w (Up to 1 year)

Follow-Up

- Safety monitoring
- Survival monitoring
- Tumor imaging until confirmed PD
- Monitoring of subsequent therapy/ PD

- CCRT will be up to 3 cycles with 21 days per cycle
- Radiotherapy will start at cycle 2
- Recovery period will last up to 42 days
- Maintenance therapy will last up to 12 months

Stage III NSCLC

- Stage III NSCLC unresectable - The role of ICIs
- Can we improve the PACIFIC in locally advanced NSCLC?
- What about moving immunotherapy into earlier stages of disease?
- How we can identify patients who will benefit most from immunotherapy?

ICIs in early stage I-IIIA

Ongoing Phase III Trials of Adj Anti–PD-1/PD-L1 Abs in Resectable Stage IB-IIIA NSCLC

Trial	Study Arms	Study Population	PD-L1 Expression	Primary Endpoint(s)
ANVIL (of ALCHEMIST)*[1]	Nivolumab vs observation	US NCI; stage IB (≥ 4 cm) to IIIA; after surgery and adj CT and/or RT	Any	OS, DFS
IMpower010[2]	Atezolizumab vs BSC	Global; stage IB (≥ 4 cm) to IIIA; after surgery and adj CT	Any	DFS
CCTG BR.31*[3]	Durvalumab vs placebo	Global; stage IB (≥ 4 cm) to IIIA; after surgery ± adj CT	Any	DFS
KEYNOTE-091/ PEARLS*[4]	Pembrolizumab vs placebo	ETOP/EORTC; stage IB (≥ 4 cm) to IIIA; after surgery ± adj CT	Any	DFS

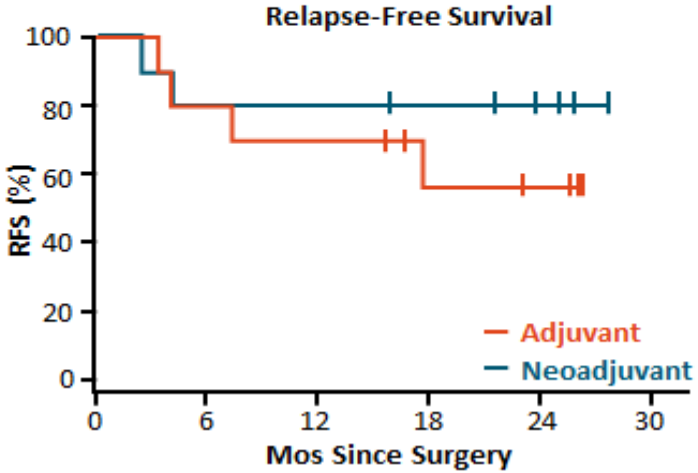
*Recruiting as of November 2018.

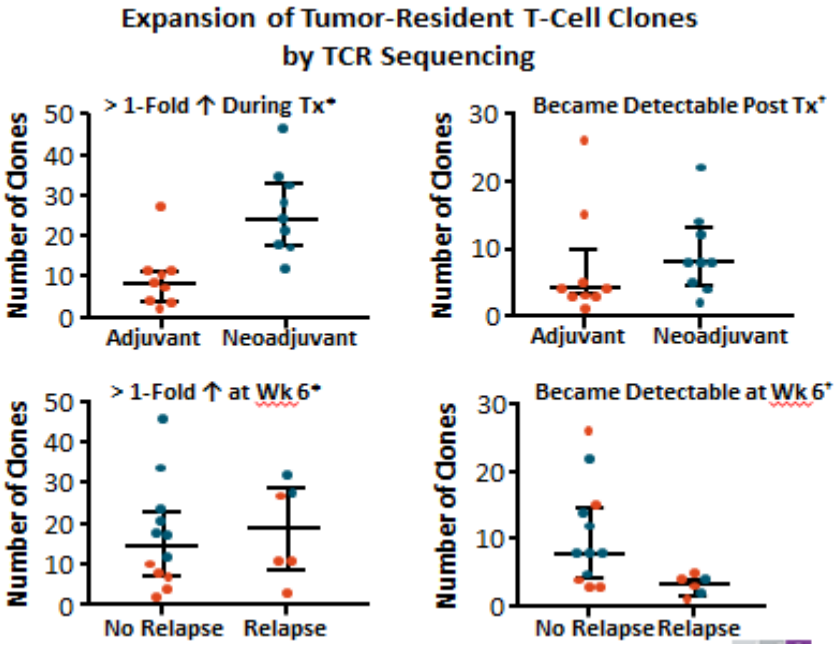
1. NCT02595944. 2. NCT02486718. 3. NCT02273375. 4. NCT02504372.

ICIs in early stage I-IIIA

Efficacy of Neoadjuvant Immunotherapy in Melanoma Suggests Promise in Early-Stage NSCLC

- Phase Ib OpACIN: neoadjuvant vs adjuvant nivolumab + ipilimumab in palpable stage III melanoma (N = 20)

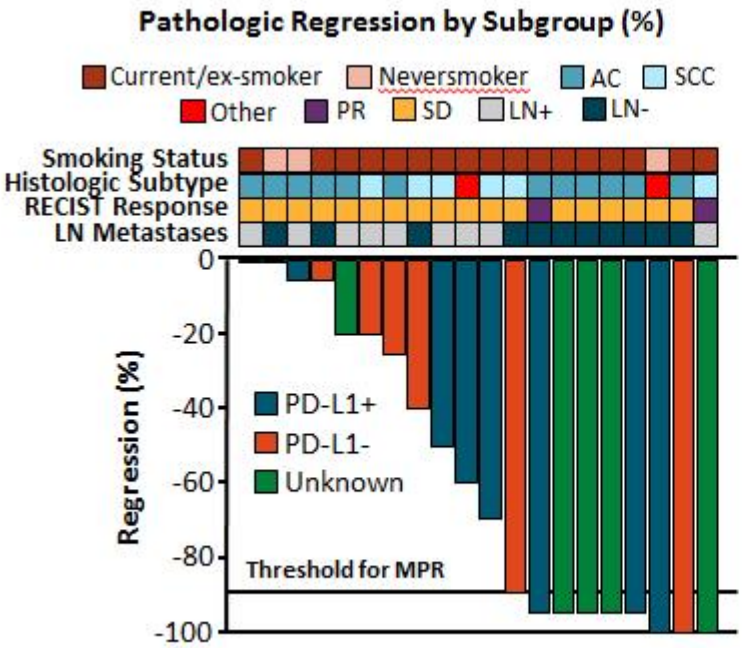


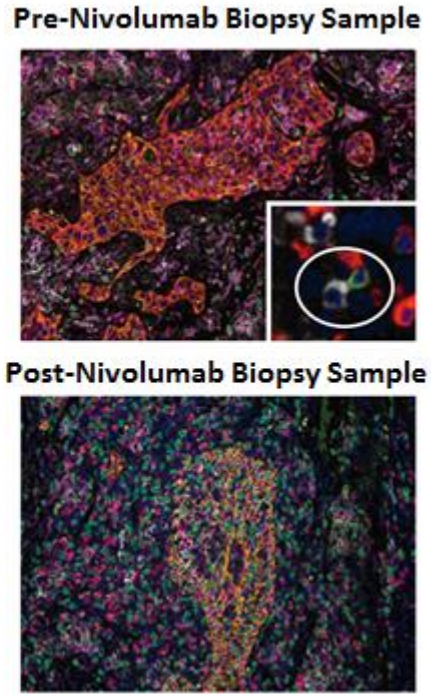


Blank. Nat Med. 2018;[Epub].

ICIs in early stage I-IIIA

Neoadjuvant Nivolumab in Stage I-IIIA NSCLC (Pilot Study)



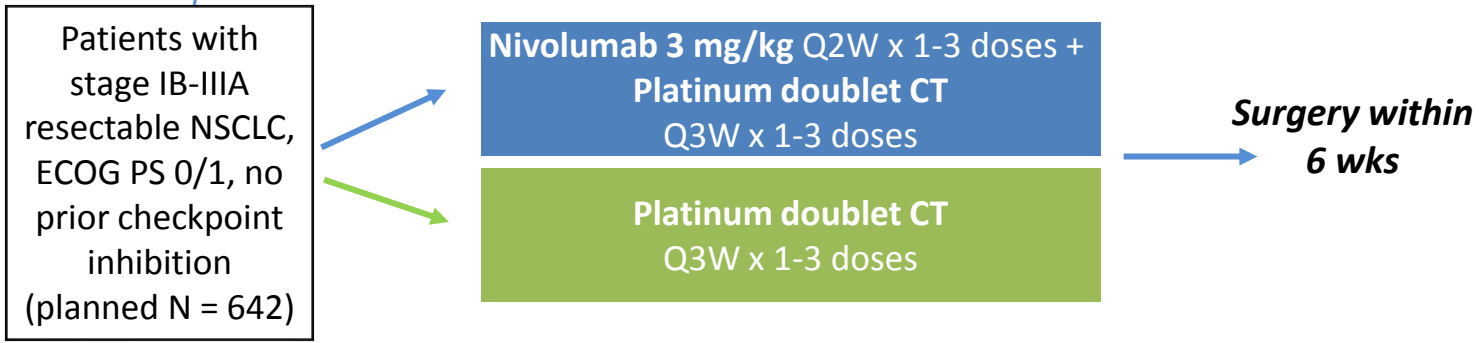


Forde. NEJM. 2018;378:1976.

ICIs in early stage I-IIIA

CheckMate 816: Neoadjuvant Nivolumab in Resectable Stage IB-IIIA NSCLC

- *Randomized phase III trial*



- Primary endpoints: EFS, pCR rate
- Secondary endpoints: MPR rate (≤ 10% residual tumor in lung and LN), OS, TTDM

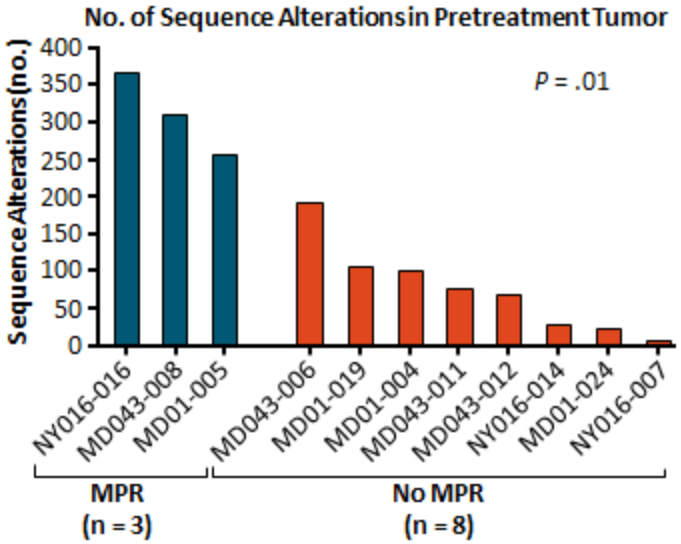
Felip. WCLC 2018. Abstr P2.16-03. Forde. ASCO 2017. Abstr TPS8577. NCT02998528.

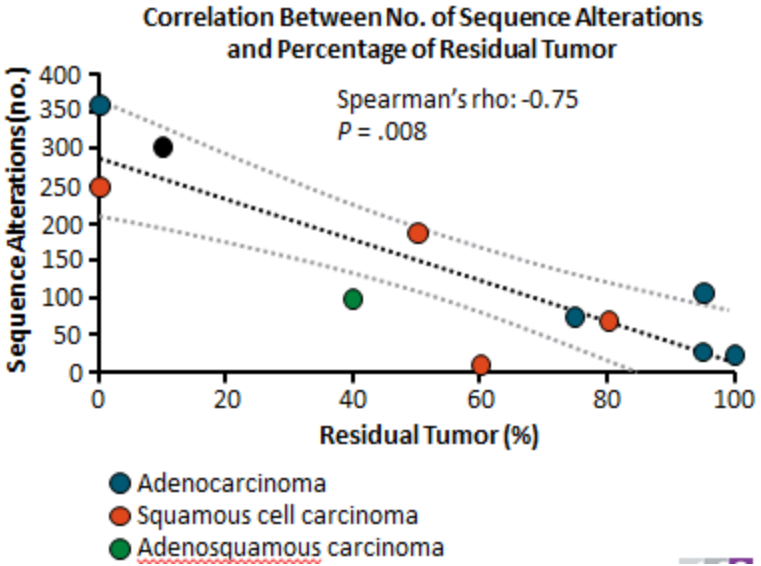
Stage III NSCLC

- Stage III NSCLC unresectable - The role of ICIs
- Can we improve the PACIFIC in locally advanced NSCLC?
- What about moving immunotherapy into earlier stages of disease?
- How we can identify patients who will benefit most from immunotherapy?

Tumor Mutation Burden Is Associated With Pathologic Response to Neoadjuvant Nivolumab

Pilot study of neoadjuvant nivolumab for resectable early-stage NSCLC (N = 20)

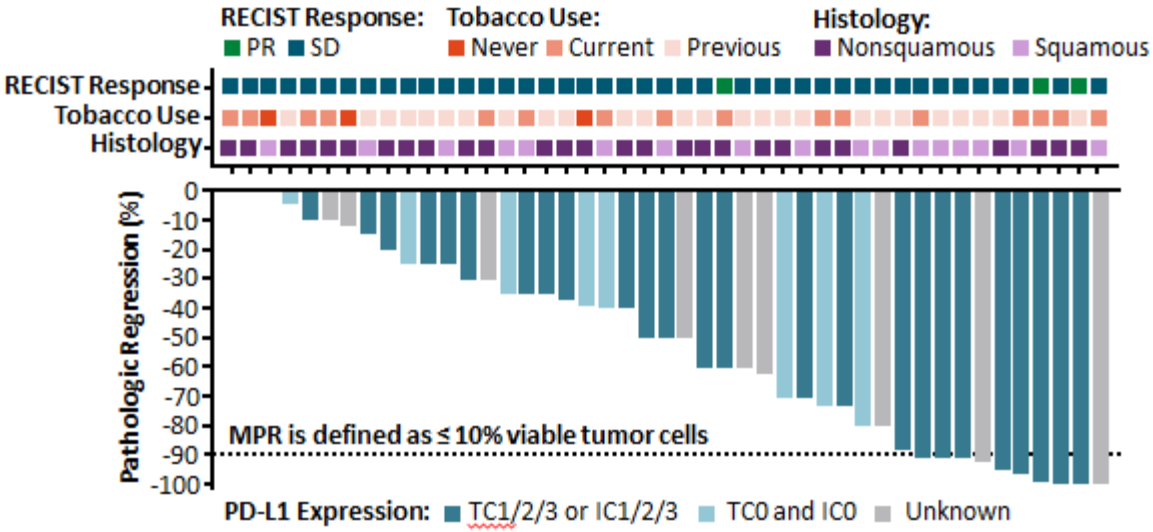




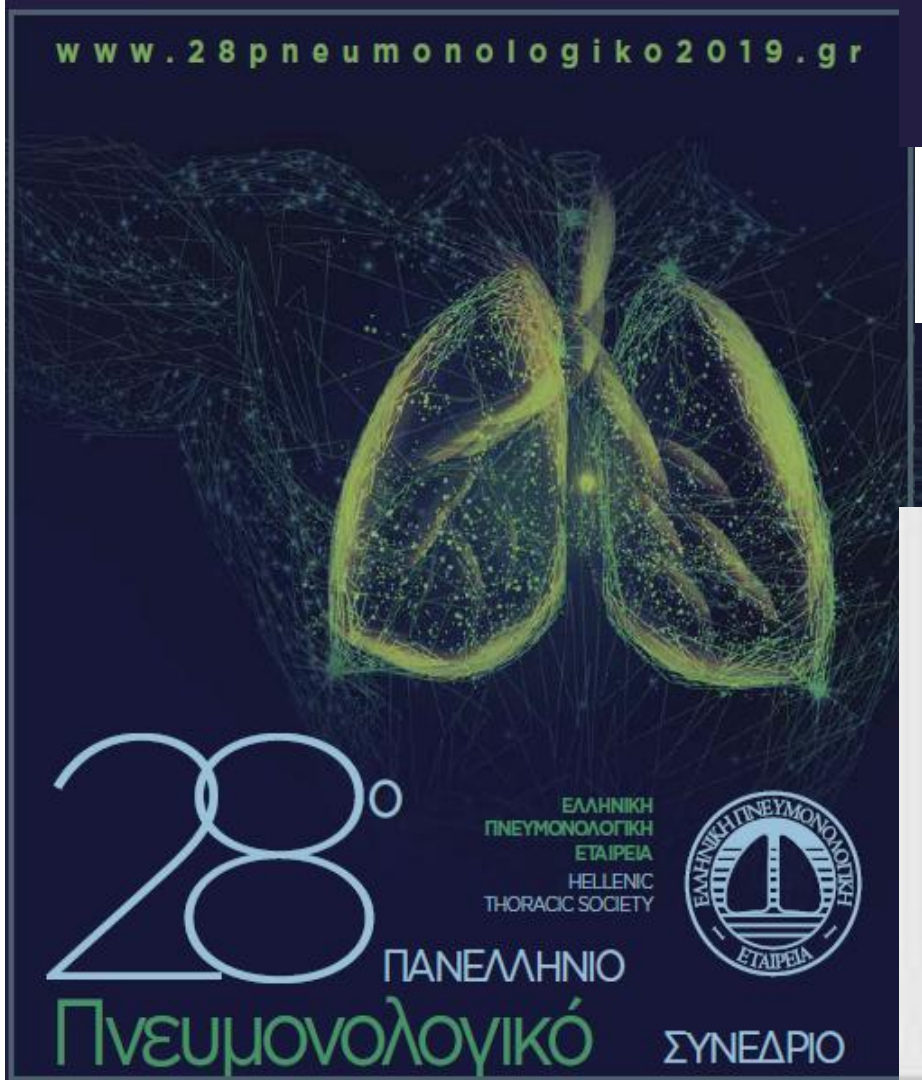
Forde. NEJM. 2018;21:1976.

PD-L1–Negative Tumors
No Major Pathologic Response With Neoadjuvant Atezolizumab

LCMC3: open-label, single-arm, multicenter phase II study of neoadjuvant atezolizumab in resectable early-stage NSCLC (N = 45)



Rusch. WCLC 2018. Abstr MA04.09.



28ο ΠΑΝΕΛΛΗΝΙΟ Πνευμονολογικό ΣΥΝΕΔΡΙΟ

Μη Μικροκυτταρικός καρκίνος σταδίου ΙΙΙ: Συνδυασμένη θεραπευτική προσέγγιση

Ο ρόλος της Ανοσοθεραπείας στην αντιμετώπιση του σταδίου ΙΙΙ