Current standards and practice changing studies in stages I-III NSCLC

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Kazan, June 11, 2019

Disclosures

Consultant or Advisory Role in the last two years

I have received honoraria as a consultant at advisory boards from Abbvie, AstraZeneca, Boehringer Ingelheim, MSD, Pfizer, Roche and Takeda.

Speaker Honoraria in the last two years

I have received honoraria as a speaker from Astra Zeneca, Boehringer Ingelheim, Lilly, MSD and Roche.

DMC in the last two years

Roche and Takeda

Financial Support of ETOP trials (president and scientific chair)

AstraZeneca, BMS, Boehringer Ingelheim, Genentech, MSD, Roche, and Pfizer.

Adjuvant therapy for surgically resected NSCLC

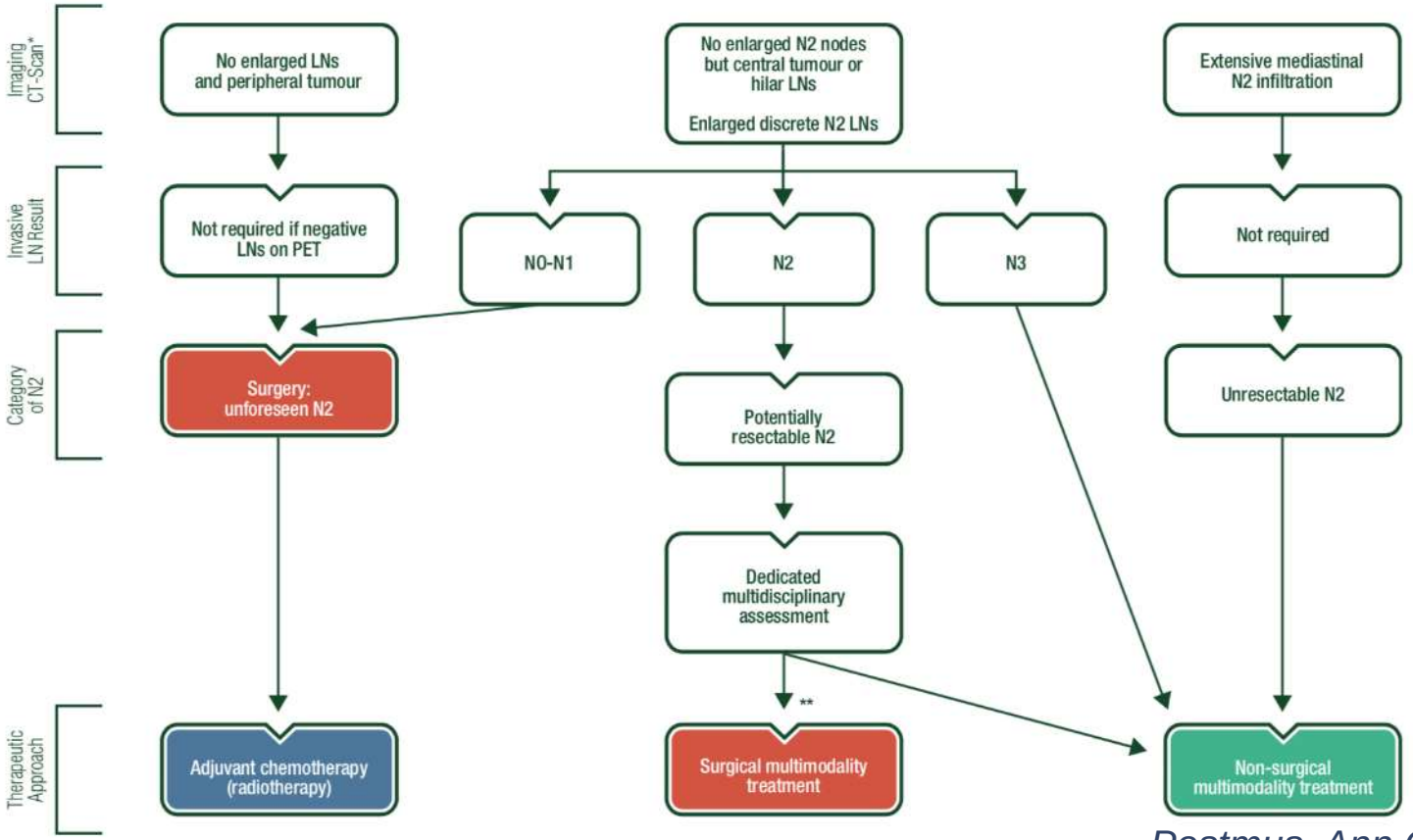
- Adjuvant ChT should be offered to patients with resected stage II and III NSCLC [I, A] and can be considered in patients with resected stage IB disease and a primary tumour >4cm [II,B].
- For adjuvant ChT, a two-drug combination with cisplatin is preferable [I, A]. In randomised studies, the attempted cumulative cis-platin dose was up to 300 mg/m2, delivered in three to four cycles. The most frequently studied regimen is cisplatin–vinorelbine.
- At the present time, the choice of adjuvant therapy should not be guided by molecular analyses [IV, B].

Postmus, Ann Oncol 2017

Adjuvant phase III clinical trials in NSCLC

			Primary endpoint	Sample size
Nivolumab After Surgery and Chemotherapy in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer (ANVIL)	Phase III	IB-IIIA	DFS OS	714
Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091) (PEARLS)	Phase III	IB-IIIA	DFS	1400
A Phase III, Open-Label, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared With Best Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy in Patients With Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer (IMpower 010)	Phase III	IB-III	DFS	1127
Double Blind Placebo Controlled Controlled Study of Adjuvant MEDI4736 In Completely Resected NSCLC	Phase III	IB-III	DFS in PD-L1 positive	1100

Treatment recommendation for locoregional NSCLC



Postmus, Ann Oncol 2017

Staging of locally advanced (stage III) NSCLC

- All patients planned for definitive stage III NSCLC treatment should undergo a diagnostic contrast-enhanced CT scan of the chest and upper abdomen followed by a PET or a combined PET-CT with a CT technique with adequately high resolution for initial staging purposes [I, A] in order to rule out detectable extrathoracic, extracranial metastasis, and to assess potential mediastinal lymph node involvement, ideally within 4 weeks before the start of treatment [III, B]
- Single PET-positive distant lesions need pathological confirmation [V, B]
- For patients with operable N2 disease, pathological staging of the mediastinum is advised [III, C]

Postmus, Ann Oncol 2017

Staging of locally advanced (stage III) NSCLC

- All patients planned for curative stage III NSCLC treatment should receive brain imaging for initial staging [III, B]. Contrast-enhanced brain MRI is the preferred method for staging of the brain in stage III disease [III, A]. If it is not possible to perform MRI, dedicated contrast-enhanced brain CT scan is advised [III, B]

Postmus, Ann Oncol 2017

Treatment of locally advanced (stage III) NSCLC

- If single station N2 disease can be demonstrated by preoperative pathological nodal analysis, resection followed by adjuvant ChT, induction ChT followed by surgery or induction CRT followed by surgery are options. If induction ChT alone is given preoperatively, PORT is not standard treatment, but may be an option based on critical evaluation of locoregional relapse risks [IV,C]
- In multistation N2 or N3, concurrent definitive CRT is preferred [I,A]. An experienced multidisciplinary team is of paramount importance in any complex multimodality treatment strategy decision, including the role of surgery in these cases [IV,C].

Postmus, Ann Oncol 2017

 # Neoadjuvant chemotherapy

Pathologic Complete Response in Advanced Non–Small-Cell Lung Cancer Following Preoperative Chemotherapy: Implications for the Design of Future Non–Small-Cell Lung Cancer Combined Modality Trials

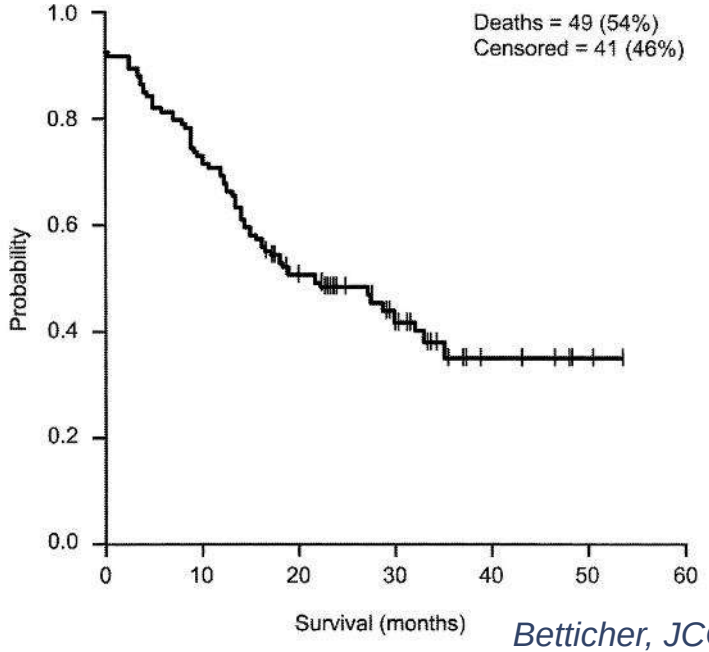
By Katherine M.W. Pisters, Mark G. Kris, Richard J. Gralla, Muhammed B. Zaman, Robert T. Heelan, and Nael Martini

Conclusion: **We have observed pathologic complete responses in approximately 12% of advanced NSCLC patients treated with preoperative MVP chemotherapy. These pathologically determined responses were seen only in patients with major objective responses clinically. Pathologic complete response predicts excellent survival and functional level and should be considered a major end point in the evaluation of preoperative chemotherapy programs.**

J Clin Oncol 11:1757-1762. © 1993 by American Society of Clinical Oncology.

Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial

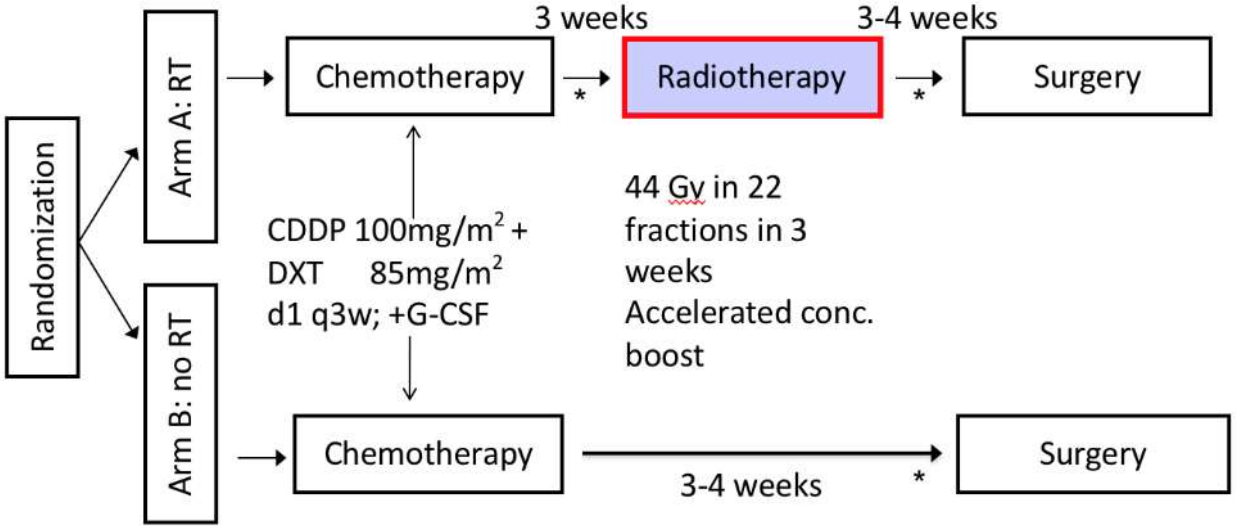
- The median EFS and OS were 14.8 months (range, 2.4 to 53.4) and 33 months (range, 2.4 to 53.4), respectively.
- Local relapse occurred in 27% of patients with tumor resection, with distant metastases in 37%.
- Multivariate analyses identified mediastinal clearance (hazard ratio,0.22; P =.0003) and complete resection (hazard ratio, 0.26; P =.0006) as strongly prognostic factors for increased survival



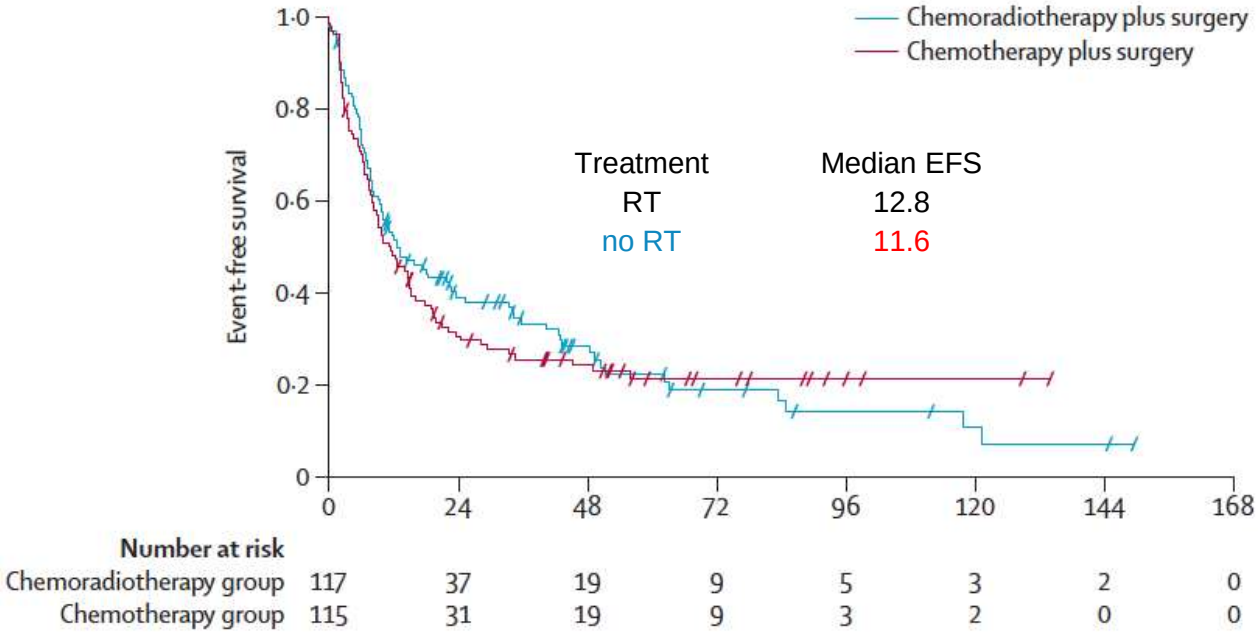
Betticher, JCO 2003

SAKK trials on neoadjuvant therapy of stage III NSCLC

SAKK 16/00 (*Pless, Lancet 2015*): Hypothesis: Neoadjuvant chemo-radiotherapy could increase nodal downstaging and R0 resection rate, resulting in an improved local control, event-free survival and overall survival



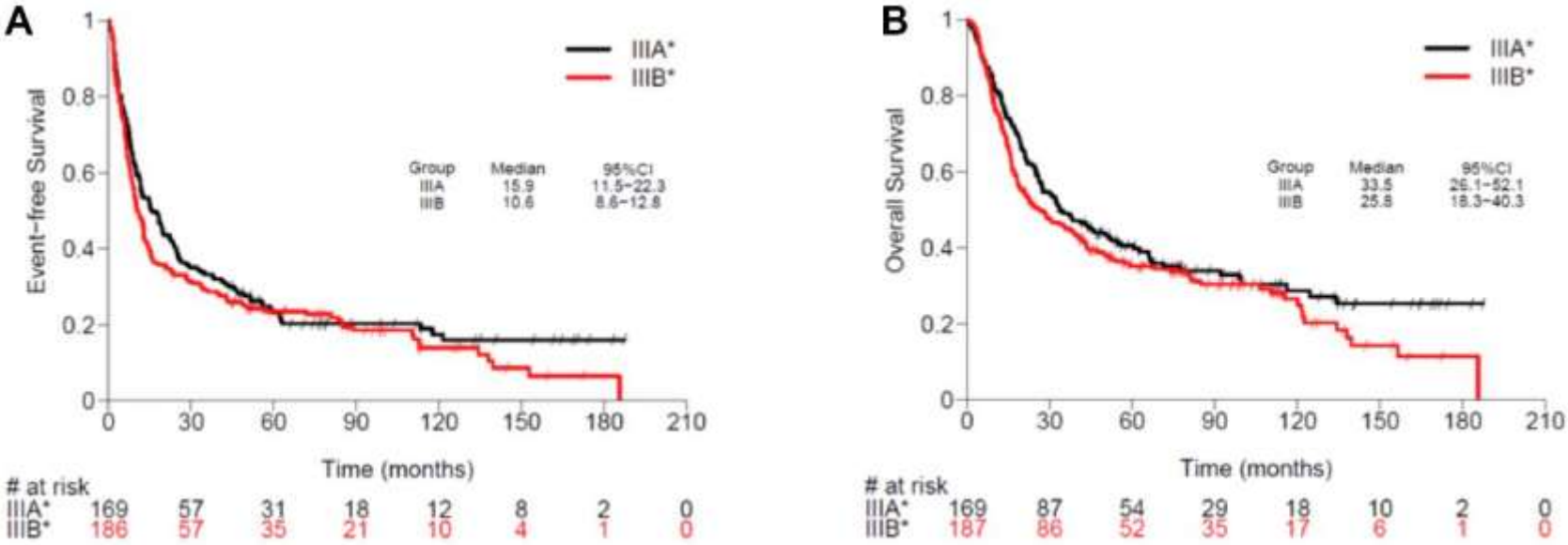
Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial (SAKK 16/00): Event-free survival



The SAKK study failed to show benefit by adding relatively low doses of RT (45 Gy) to ChT.

Pless, Lancet 2015

Multimodal treatment in operable Stage III NSCLC: A pooled analysis on long-term Results of three SAKK trials (SAKK 16/96, 16/00, 16/01)



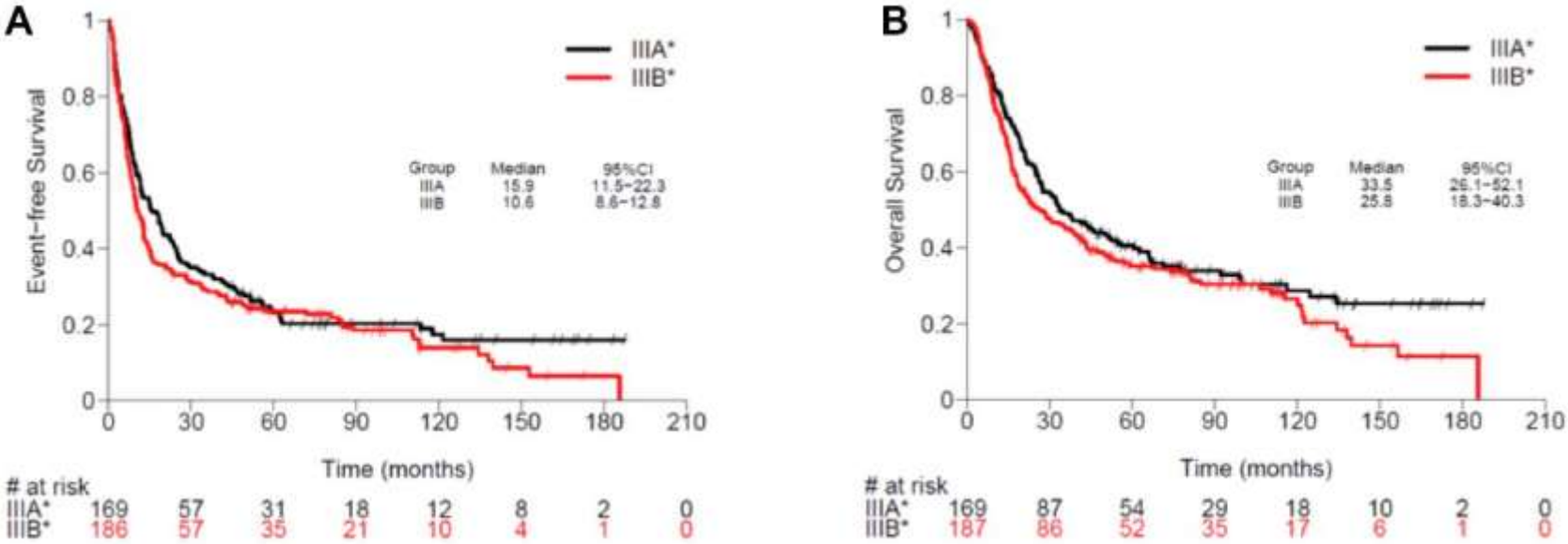
5- and 10-year survival :

Stage IIIA: 41% and 29%

Stage IIIB: 35% and 27%

Früh, JTO 2019

Multimodal treatment in operable Stage III NSCLC: A pooled analysis on long-term Results of three SAKK trials (SAKK 16/96, 16/00, 16/01)

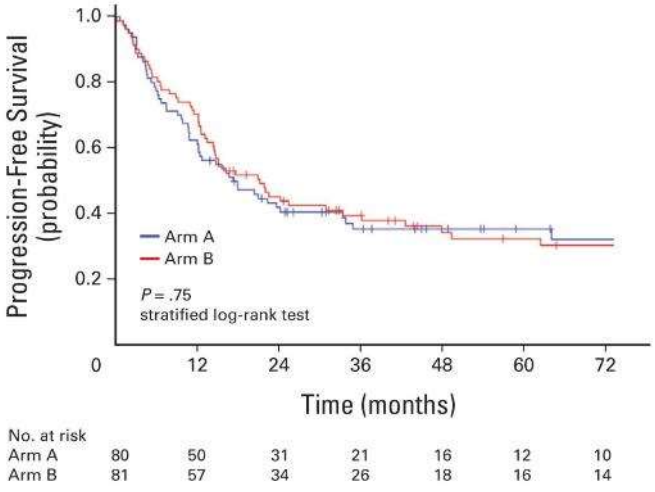


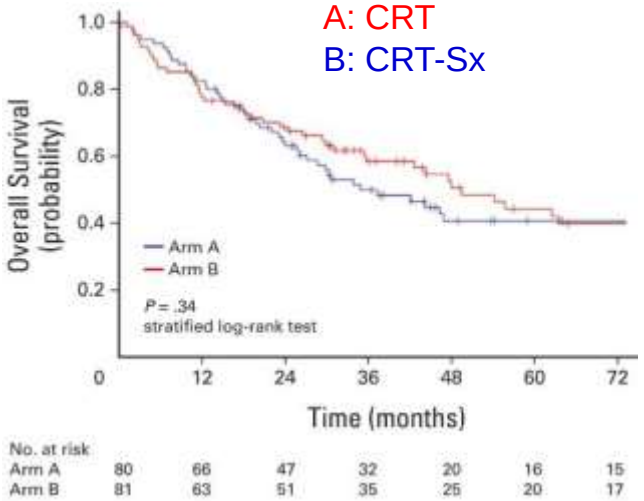
The most frequent location of relapse was distant failure in 53%, but first site of relapse was locoregional in 33%, whereas 14% had both locoregional and distant failure

Früh, JTO 2019

Phase III study of surgery versus definitive concurrent chemo-radiotherapy boost in patients with resectable Stage IIIA(N2) and selected IIIB NSCLC after induction chemotherapy and concurrent Chemoradiotherapy (ESPATUE).

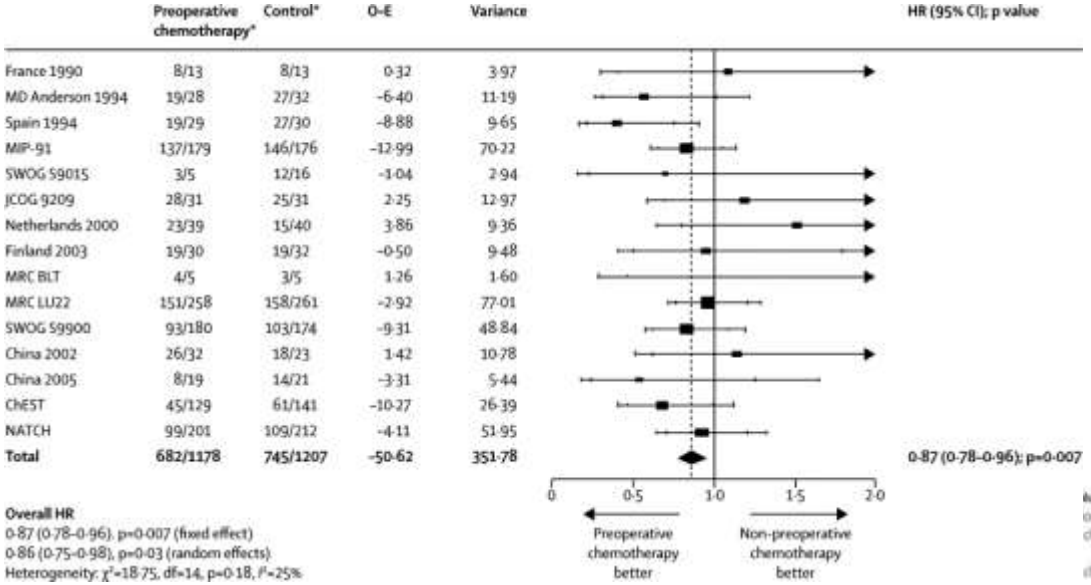
C

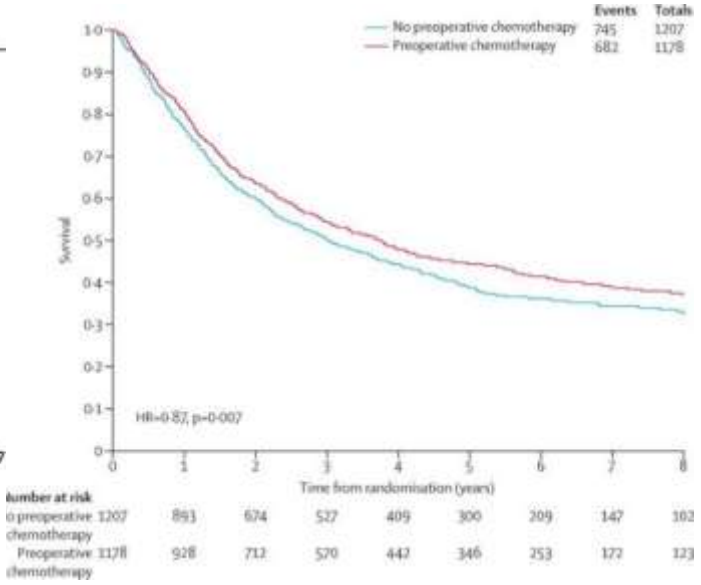




The ESPATUE trial confirmed that CRT (45 Gy) followed by surgery, is as good as CRT with definitive RT (65–71 Gy) given as a boost in the last week of CRT.

Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data





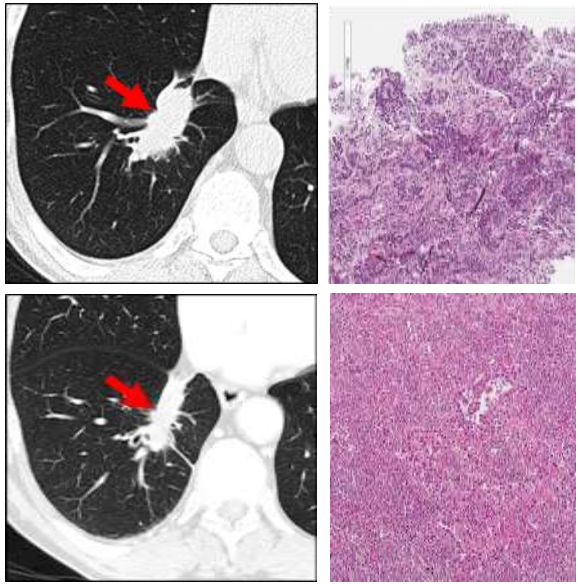
Lancet 2014

Neoadjuvant PD-1 blockade in resectable lung cancer with two infusions of nivolumab 2 weeks apart: Major pathological response

63yo M, ex-smoker, adeno, PD-L1 2%+, <10% viable tumor at resection

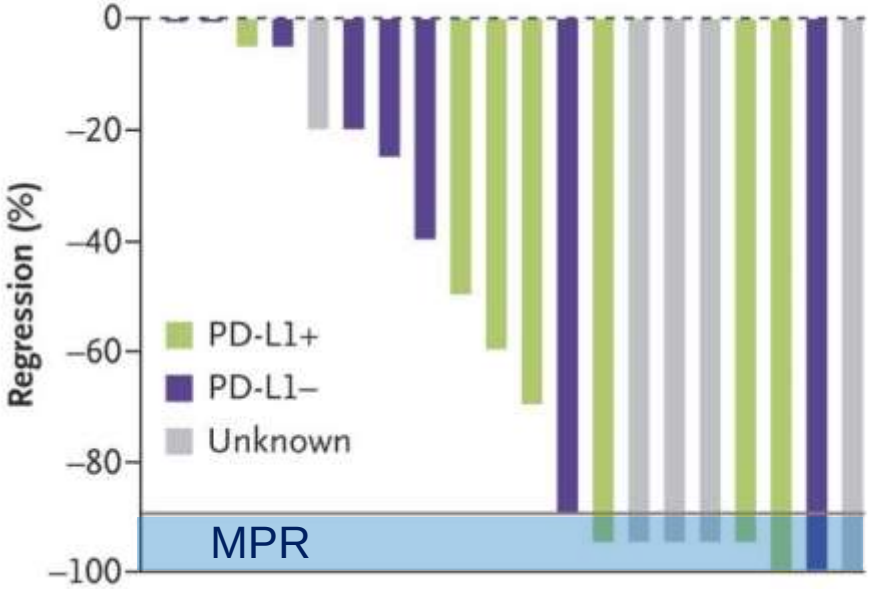
Pre-nivo

Post-nivo



Pre-nivo

% pathological regression:



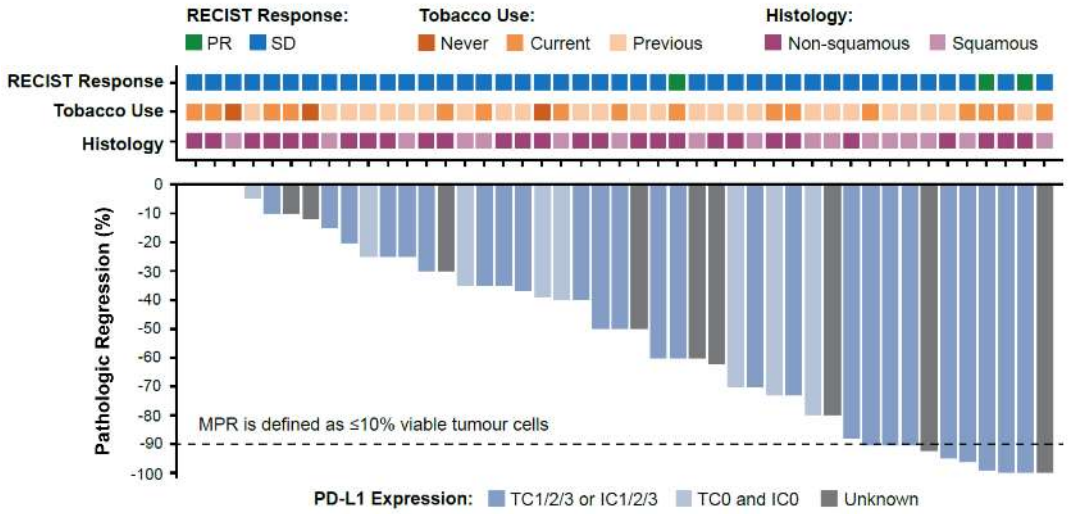
Forde, ESMO 2016 and NEJM 2018

Neoadjuvant atezolizumab

Outcome, n (%)	Efficacy Population (n=45)
MPR	10 (22%)
(95% CI)	(11%, 37%)
ORR	
PR	3 (7%)
SD	42 (93%)
PD	0

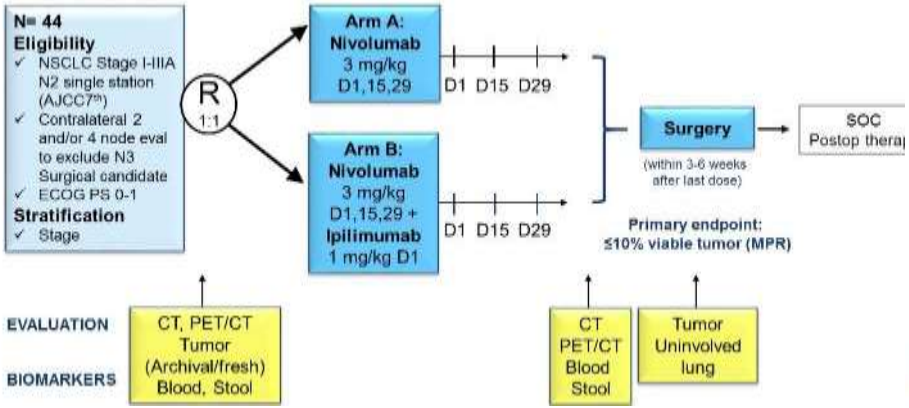
10 out of 45 patients (22% [95% CI: 11%, 37%]) without an *EGFR* or *ALK* genetic alteration treated with neoadjuvant atezolizumab had a MPR

- There was no observable correlation between pathologic and radiographic responses

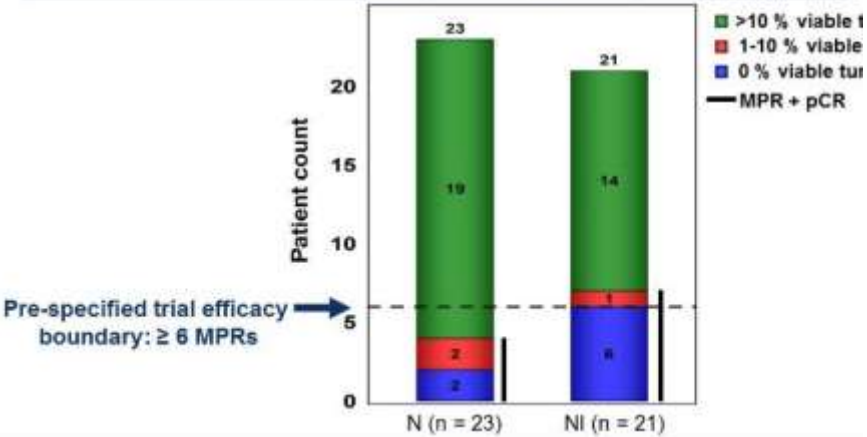


Rusch, WCLC 2018

Neoadjuvant nivolumab or nivolumab plus ipilimumab for resectable NSCLC: Clinical and correlative results from the NEOSTAR study

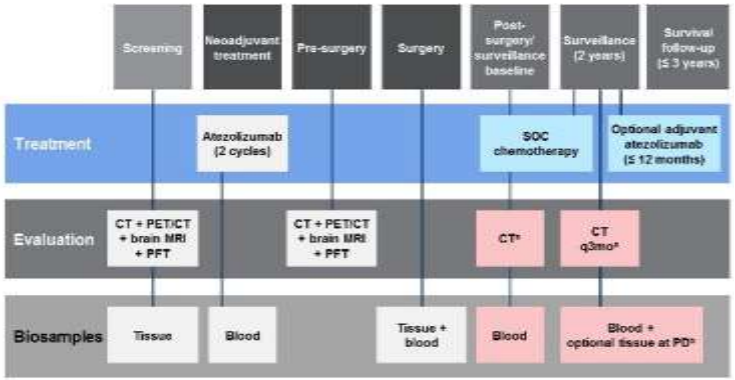


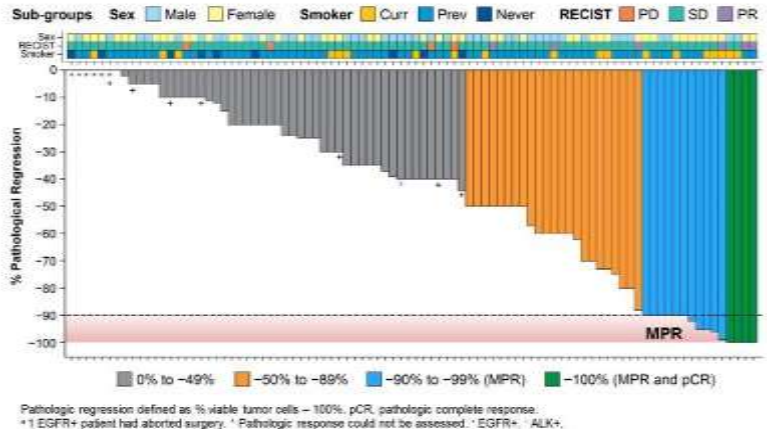
Overall ITT Resected + not resected*	Total n = 44	N n = 23	NI n = 21
MPR + pCR	11 (25%)	4 (17%) (95% CI:5%,39%)	7 (33%) (95% CI:15%,57%)
0% viable tumor (pCR)	8 (18%)	2 (9%)	6 (29%)
1-10% viable tumor	3 (7%)	2 (9%)	1 (5%)



Cascone, ASCO 2019

Neoadjuvant atezolizumab in resectable NSCLC(NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3)





Pathologic regression defined as % viable tumor cells – 100%. pCR, pathologic complete response.
[a]1 EGFR+ patient had aborted surgery. [b]Pathologic response could not be assessed. [c]EGFR+. [d]ALK+.

Patients in intended surgery population (n = 90)

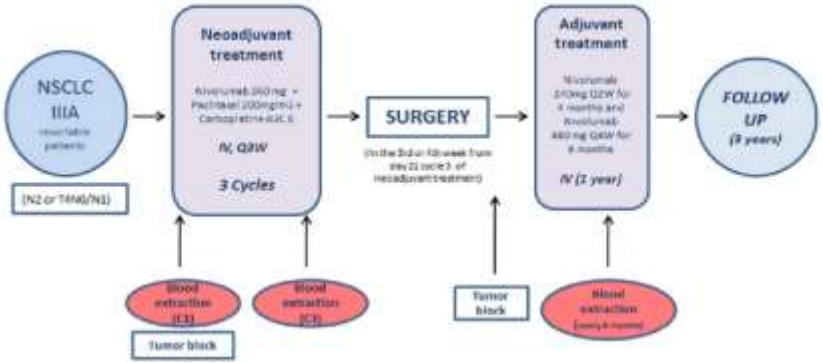
- PR: 6 (7%); SD: 80 (89%); PD: 4 (4%)
- 3 of 8 EGFR/ALK+ had 40% to 50% pathological regression

Primary efficacy population (n = 77)

- MPR: 15 of 77 (19%; 95%CI: 11%, 30%)
- pCR: 4 of 77 (5%) patients
- 38 of 77 (49%) had ≥ 50% pathological regression

Kwiatkowsky, ASCO 2019

NEO-adjuvant chemo-immunotherapy for the treatment of STAGE IIIA resectable NSCLC: A phase II multicenter exploratory study—Final data of patients who underwent surgical assessment



Clínical response after Neoadjuvant treatment (ITT)	
Complete Response (CR)	3 (6,5%)
Partial Response (PR)	33 (72%)
Stable Disease (SD)	8 (17,5%)

Table 2. Radiological response (n=46).

Pathological response afterNeoadjuvant treatment		
	N (%)	**95% IC**
Major pathological resp. (MPR)	35 (85,36%)	71-95%
Complete pathological resp.	25 (71,4%)	54-87%
Partial response	6 (14,6%)	-

Table 3. Pathological response (n=41). MPR was defined as <10% and include CPR.

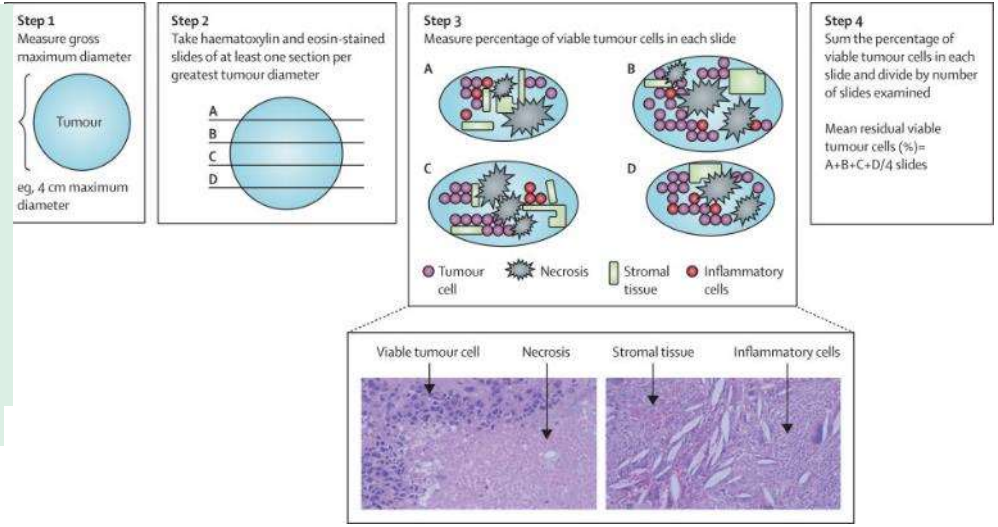
Provencio, ASCO 2019

Pathological response after neoadjuvant chemotherapy in resectable NSCLC: proposal for the use of major pathological response as a surrogate endpoint

Panel 2: Proposals

- Major pathological response, defined as less than 10% residual tumour after neoadjuvant therapy, should be adopted as an outcome measurement in non-small-cell lung cancers
- Methods for assessment of the degree of pathological response should adhere to those described by Pataer and colleagues[47]
- Future neoadjuvant clinical trials integrating prospective assessment of pathological response should be prioritised for resectable NSCLCs
- Major pathological response could ultimately be an acceptable endpoint for accelerated regulatory approval, but trials should still be designed to investigate overall survival to validate the initial findings and comprehensively assess the toxic effects

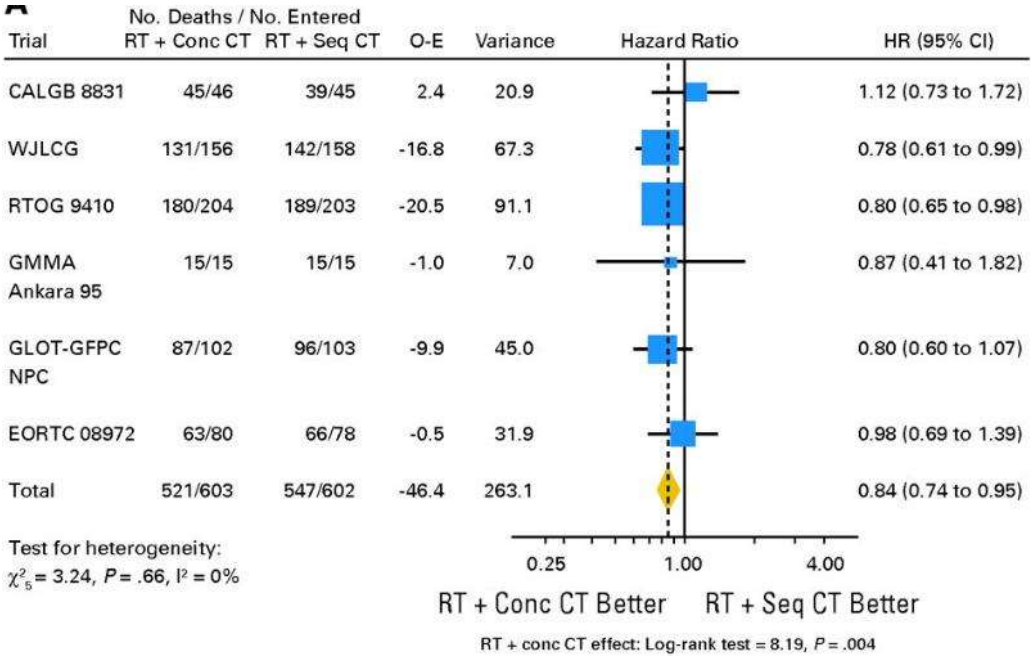
validate the initial findings and comprehensively assess the toxic effects

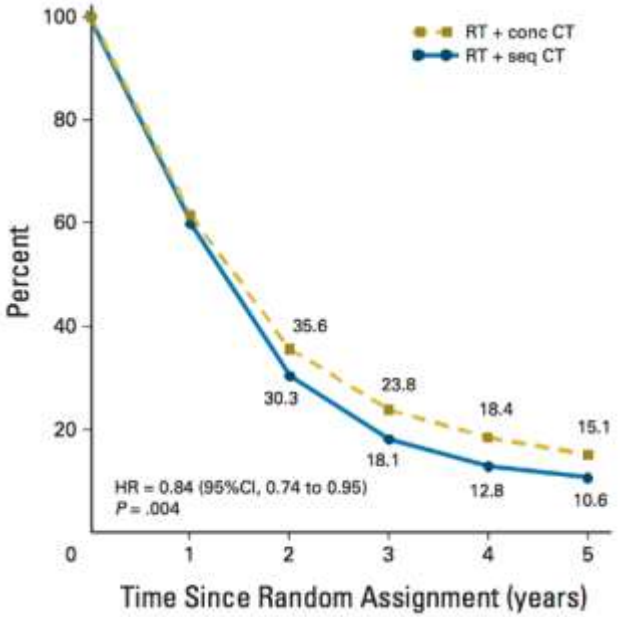


Hellmann, Lancet Oncol 2014

Chemo-radiotherapy

Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced NSCLC:

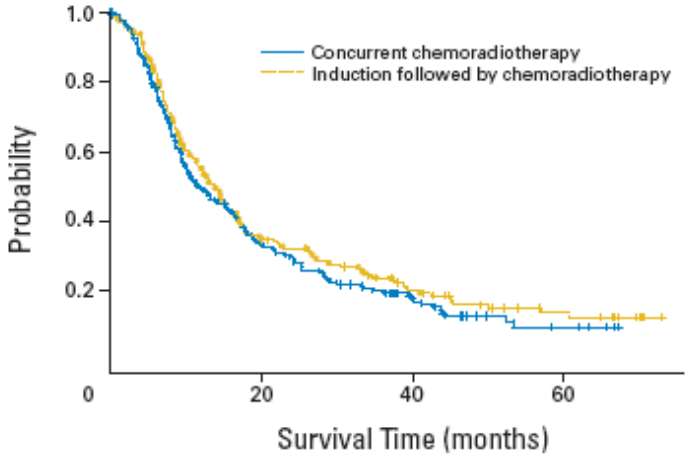




Auprin, JCO 2010

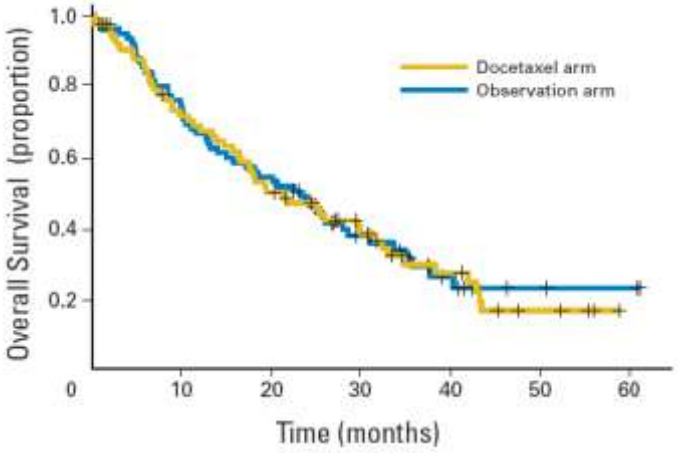
Chemo-radiotherapy: No evidence for advantage with induction or consolidation chemotherapy in stage III

Carboplatin-paclitaxel induction followed by chemo-radiotherapy



Vokes, JCO 2007

Concurrent PE chemo-radiotherapy followed by docetaxel consolidation



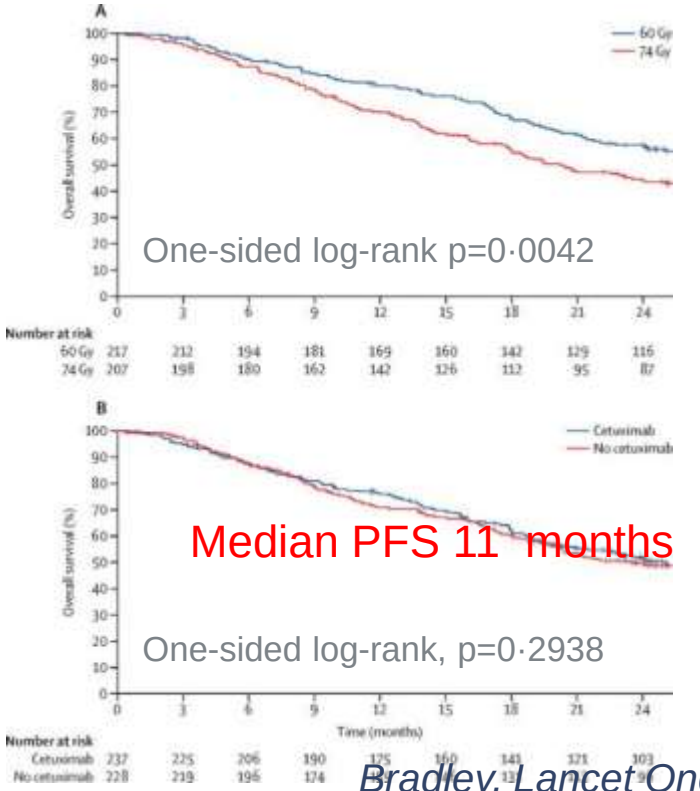
Hanna, JCO 2008

Randomized phase III comparison of standard-dose versus high-dose chemo-radiotherapy ± cetuximab for stage III NSCLC

Schema

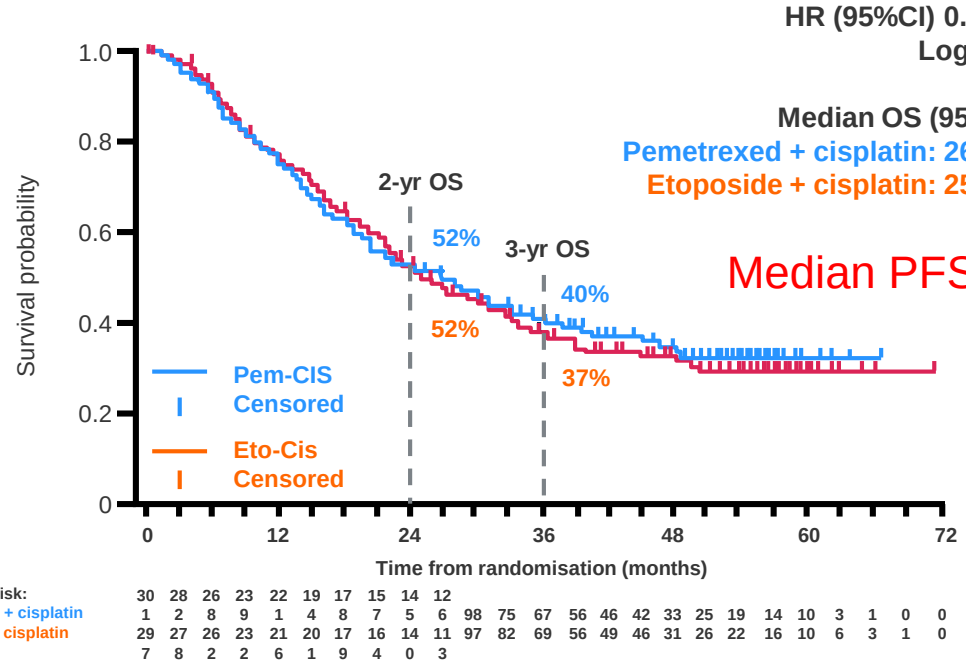
STRATIFY	RANDOMIZE	Concurrent Treatment	Consolidation Treatment
RT Technique 1. 3D-CRT 2. IMRT **Zubrod** 1. 0 2. 1 **PET Staging** 1. No 2. Yes **Histology** 1. Squamous 2. Non-Squamous		**Arm A** Concurrent chemotherapy* RT to **60 Gy**, 5 x per wk for 6 wks	Arm A Consolidation chemotherapy*
		Arm B Concurrent chemotherapy* RT to **74 Gy**, 5 x per wk for 7.5 wks	Arm B Consolidation chemotherapy*
		Arm C Concurrent chemotherapy* and **Cetuximab** RT to **60 Gy**, 5 x per wk for 6 wks	Arm C Consolidation chemotherapy* and Cetuximab
		Arm D Concurrent chemotherapy* and **Cetuximab** RT to **74 Gy**, 5 x per wk for 7.5 wks	Arm D Consolidation chemotherapy* and Cetuximab

*Carboplatin and paclitaxel



Bradley, Lancet Oncology 2015

OS results of the phase III PROCLAIM trial: Pemetrexed, cisplatin or etoposide, cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced NSCLC

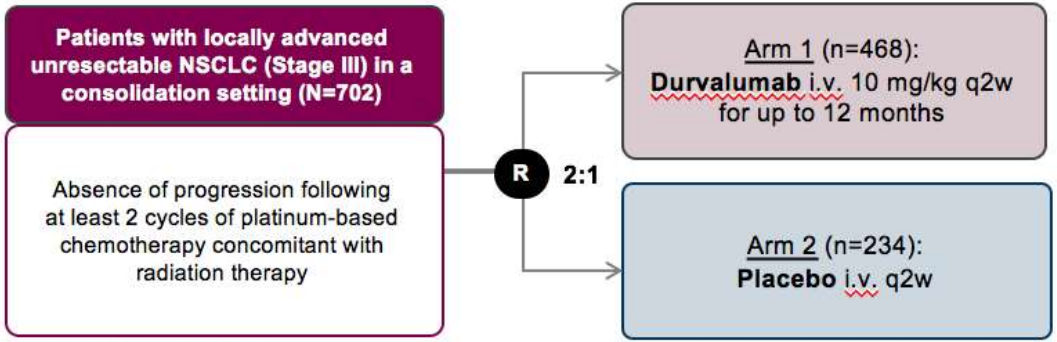


Median PFS 10 and 11 months

Senan, ASCO 29015

PACIFIC: Consolidation durvalumab for 1 year after chemo-radiotherapy of stage III NSCLC

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study (28 countries)[1-3]



Primary endpoints[3]
- PFS, OS

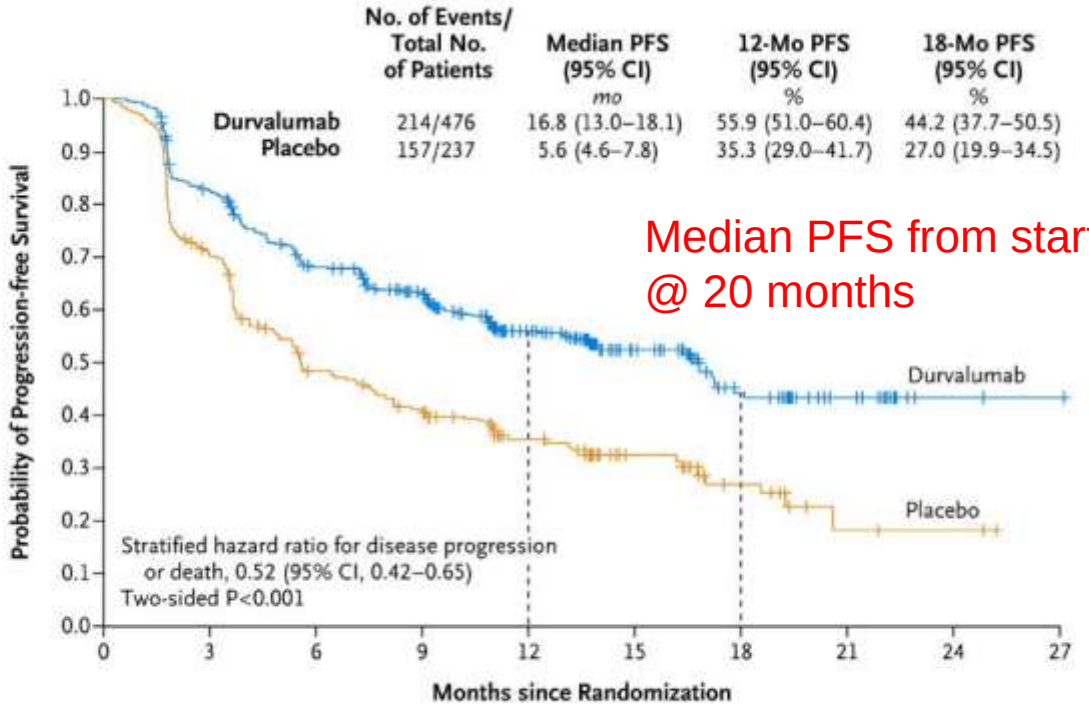
Secondary endpoints[1]
- ORR, DoR, DSR
- Safety/tolerability
- PK, immunogenicity, QoL

713 pts with stage III NSCLC after chemo-radiotherapy

2:1 durvalumab 10 mg/kg Q2w for 12 months or placebo

Paz-Ares, ESMO 2017; Antonia, NEJM 2017

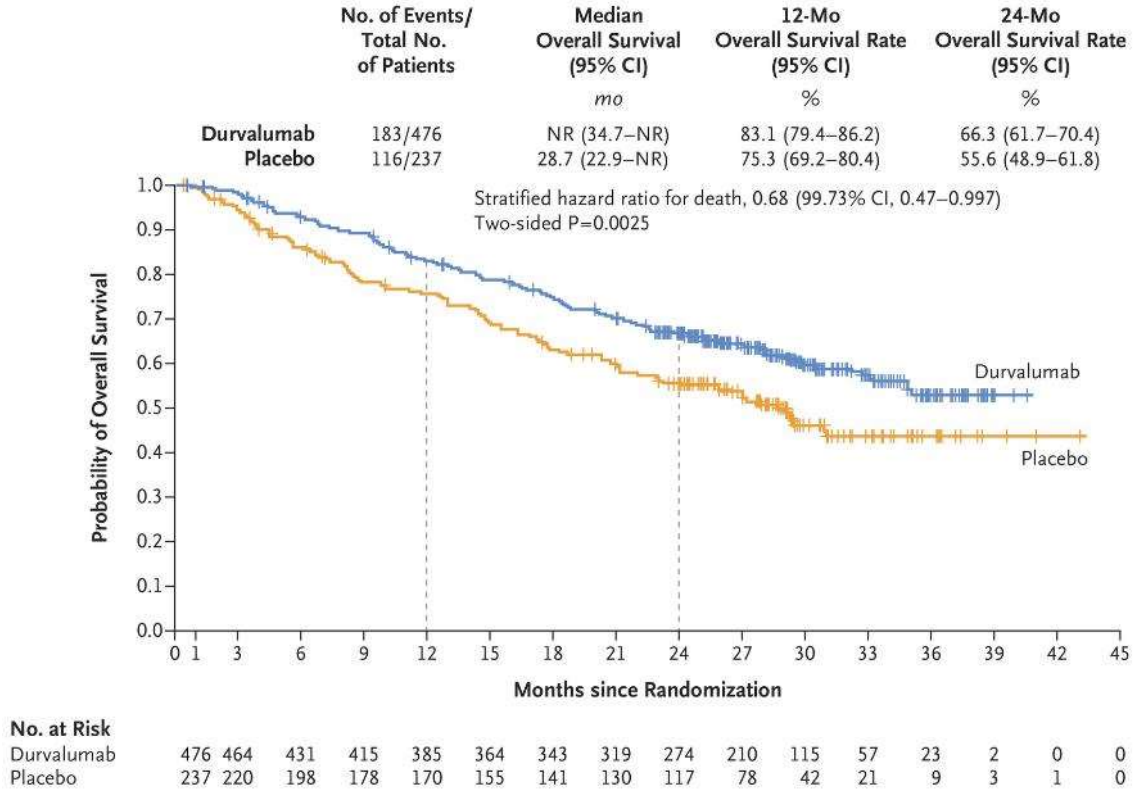
PACIFIC: Consolidation durvalumab for 1 year after chemo-radiotherapy of stage III NSCLC: Progression-free survival



Median PFS from start of therapy @ 20 months

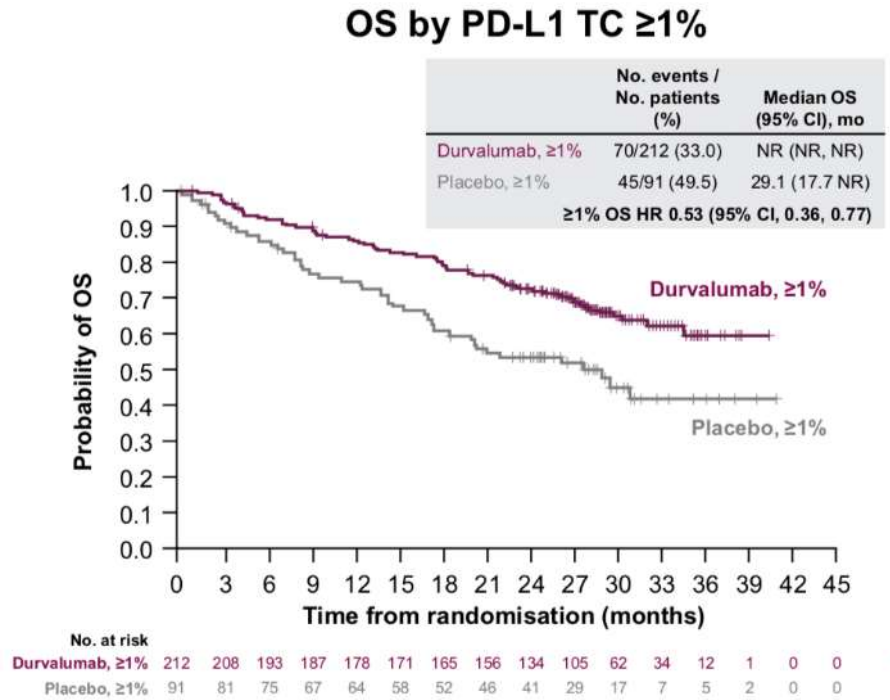
Paz-Ares, ESMO 2017; Antonia, NEJM 2017

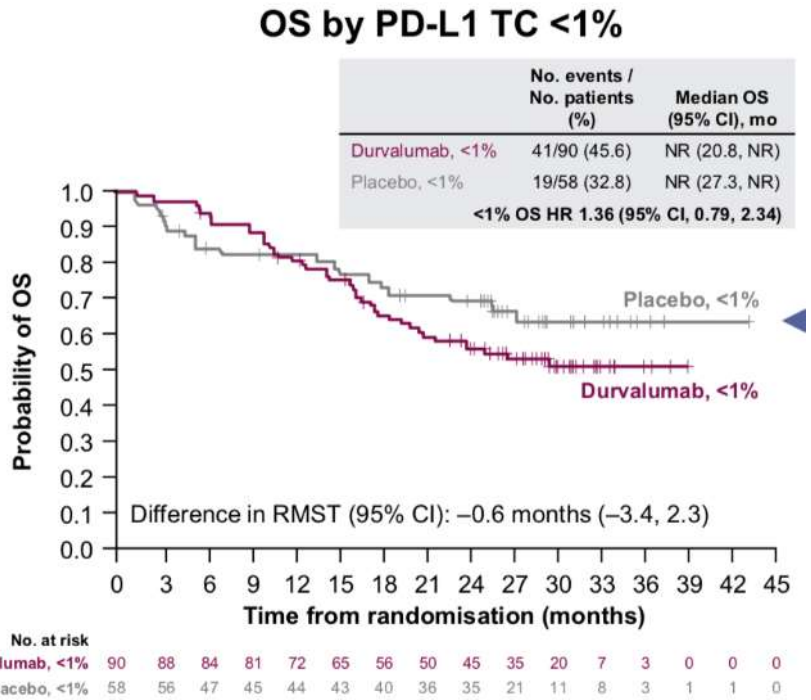
Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC



Antonia, NEJM 2018

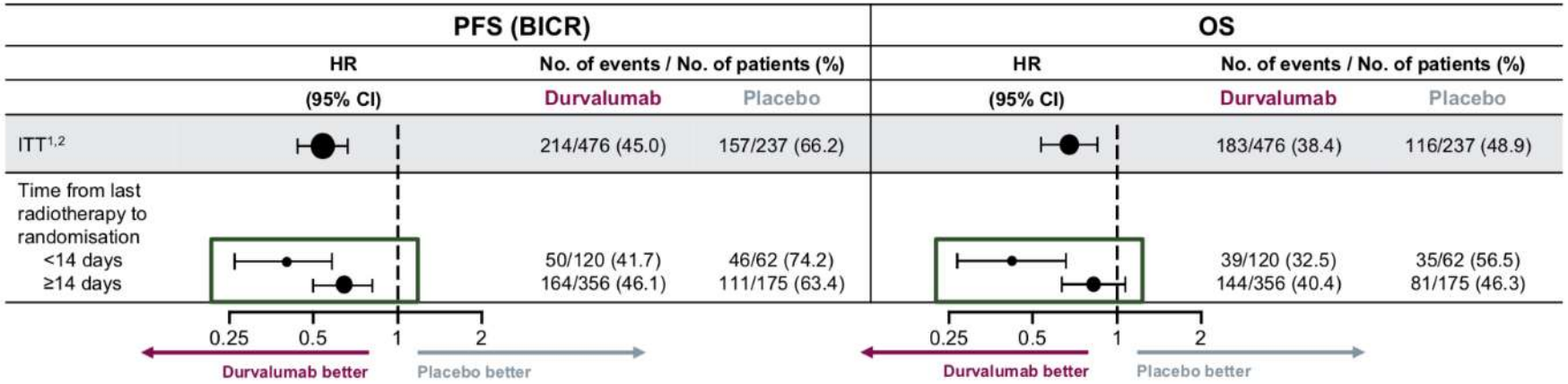
Exploratory analyses of overall survival in PACIFIC





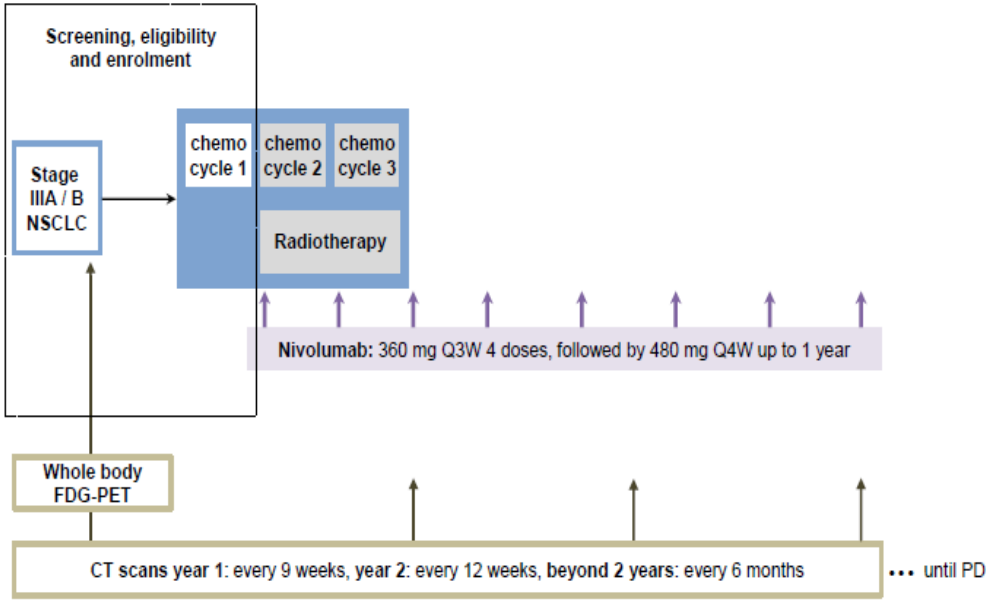
Faivre-Finn, ESMO 2018

Exploratory analyses of overall survival in PACIFIC



Faivre-Finn, ESMO 2018

NICOLAS – A phase II trial evaluating the safety and efficacy of the addition of concurrent anti-PD-1 nivolumab to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC (Amendment 2)



Primary Endpoint:

Grade ≥3 pneumonitis

Key secondary endpoint:

1-year PFS

Sample Size:

43 patients → extended to 78 patients under amendment 2

Countries:

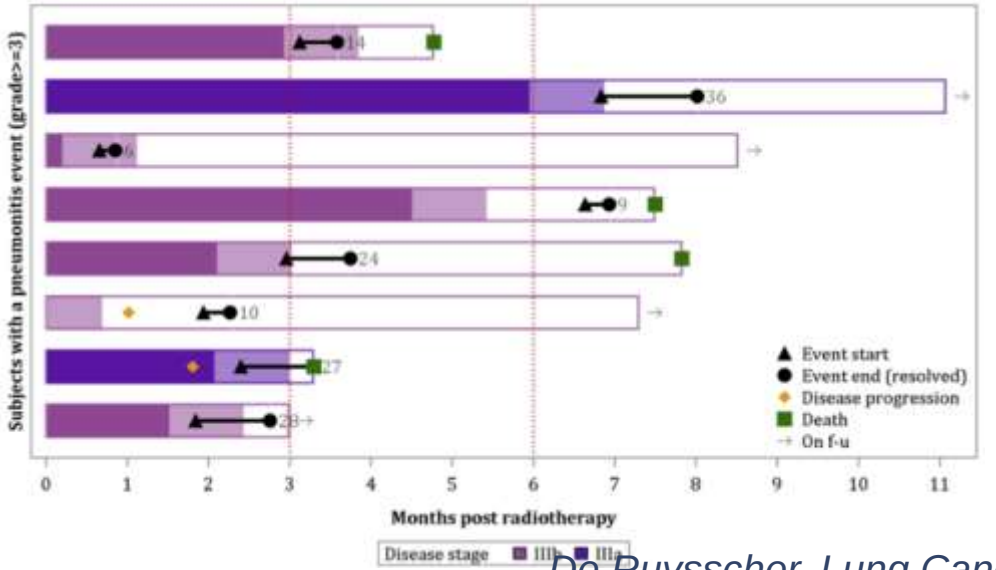
Belgium, Germany, Netherland, Spain, Switzerland

Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-radiotherapy regimen in stage III non-small cell lung cancer—The ETOP NICOLAS trial

Pneumonitis in 34 (42.5%):

- Grade 1: 7
- Grade 2: 19
- Grade 3: 8
- No association with V20 lung dose

Timing of grade ≥3 pneumonitis any time post radiotherapy



De Ruysscher, Lung Cancer 2019

Summary on systemic treatment as part of multimodality therapy of earlier stages of NSCLC

- After curative resection, 4 cycles of adjuvant cisplatin-based chemotherapy remain as standard of care in stages II and III disease
- Immune checkpoint inhibition and targeted approaches remain investigational
- Major pathological responses have been observed using neoadjuvant immune checkpoint inhibition alone or in combination. However, MPR is not approved a surrogate endpoint for survival and we have to wait for surivial data from randomized phase III trials to make a final judgment
- Durvalumab consolidation has become the standard of care after chemoradiotherapy of stage III disease. Ongoing trials are investigation the optimal timing of immunotherapy.