Locally Advanced Non-Small Cell Lung Cancer

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Disclosures

- Advisor: AbbVie, AstraZeneca, Genentech, Janssen, Lilly, Merck, Pfizer, Regeneron
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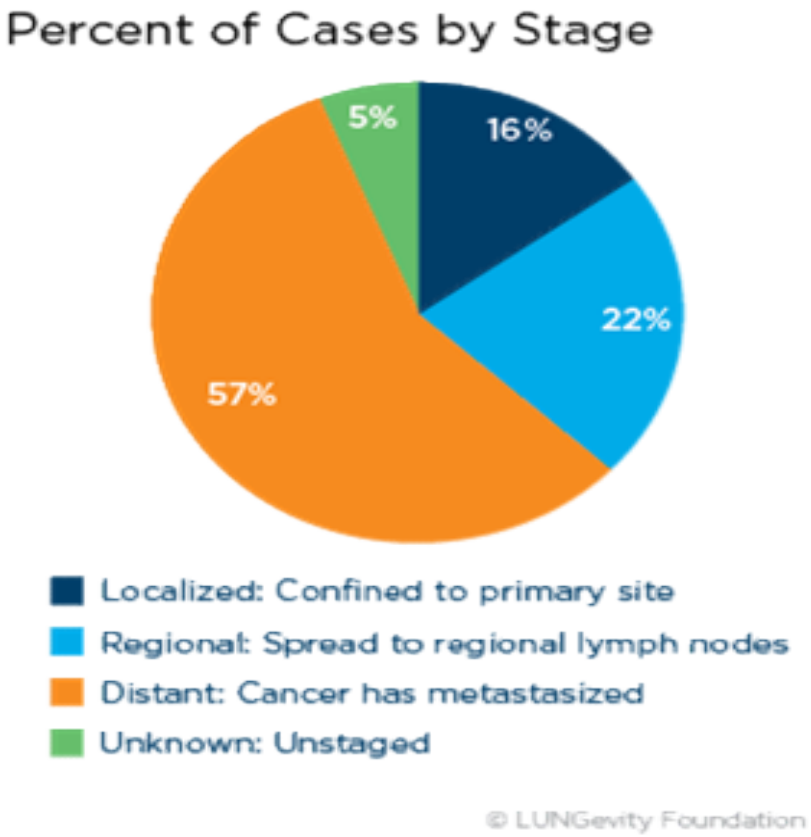
- Royalty: UpToDate Author

Stage III Lung Cancer



TNM 8th edition

Proposed		Events / N	MST	24 Month	60 Month
IA1	1 cm	68 / 781	NR	97%	92%
IA2	2 cm	505 / 3105	NR	94%	83%
IA3	3 cm	546 / 2417	NR	90%	77%
IB	4 cm	560 / 1928	NR	87%	68%
IIA	5 cm	215 / 585	NR	79%	60%
IIB	7 cm	605 / 1453	66.0	72%	53%
IIIA	>7 cm	2052 / 3200	29.3	55%	36%
IIIB		1551 / 2140	19.0	44%	26%
IIIC		831 / 986	12.6	24%	13%

Heterogeneous group of patients
- Unresectable
- Resectable
- Surprise N2

SEER Stat Fact Sheets: Lung and Bronchus Cancer. National Cancer Institute website. http://seer.cancer.gov/statfacts/html/lungb.html. Published April 2017. Accessed November 27, 2017.

Locally Advanced Unresectable NSCLC New Standard of Care PACIFIC

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1-42 days post-cCRT

R

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

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

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

Primary endpoints

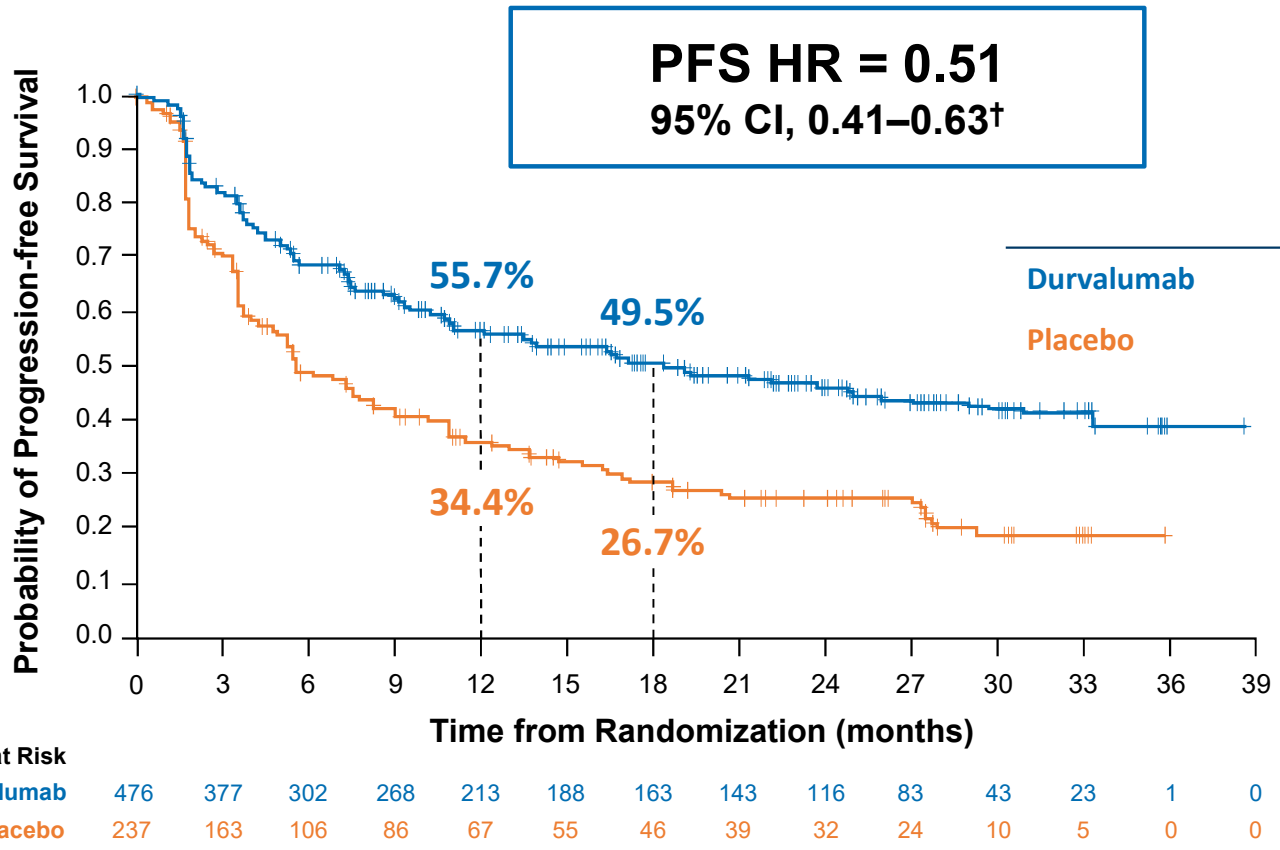
- PFS by BICR using RECIST v1.1†
- OS

Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

Antonia, SJ et al, WCLC 2018, abstr PL02.01

Updated Progression-free Survival by BICR* (ITT)

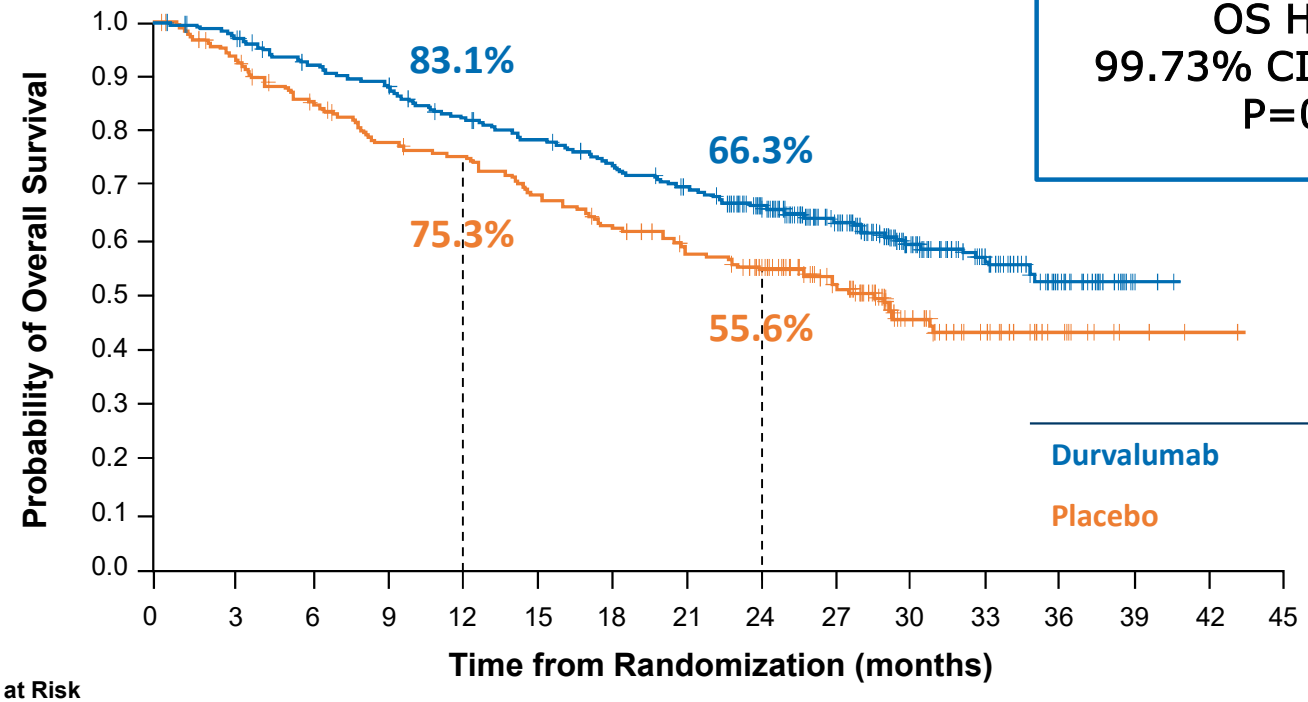


	No. of events / No. of patients (%)	Median PFS (95% CI) months
Durvalumab	243/476 (51.1)	17.2 (13.1–23.9)
Placebo	173/237 (73.0)	5.6 (4.6–7.7)

*Median duration of follow-up was 25.2 months (range 0.2–43.1)
†No formal statistical comparison was made because the study had achieved significance for PFS at the first planned IA (data cutoff of Feb 13, 2017)

Antonia, SJ et al, WCLC 2018, abstr PL02.01

Overall Survival* (ITT)



OS HR = 0.68
99.73% CI, 0.469–0.997†
P=0.00251

	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvalumab	183/476 (38.4)	NR (34.7–NR)
Placebo	116/237 (48.9)	28.7 (22.9–NR)

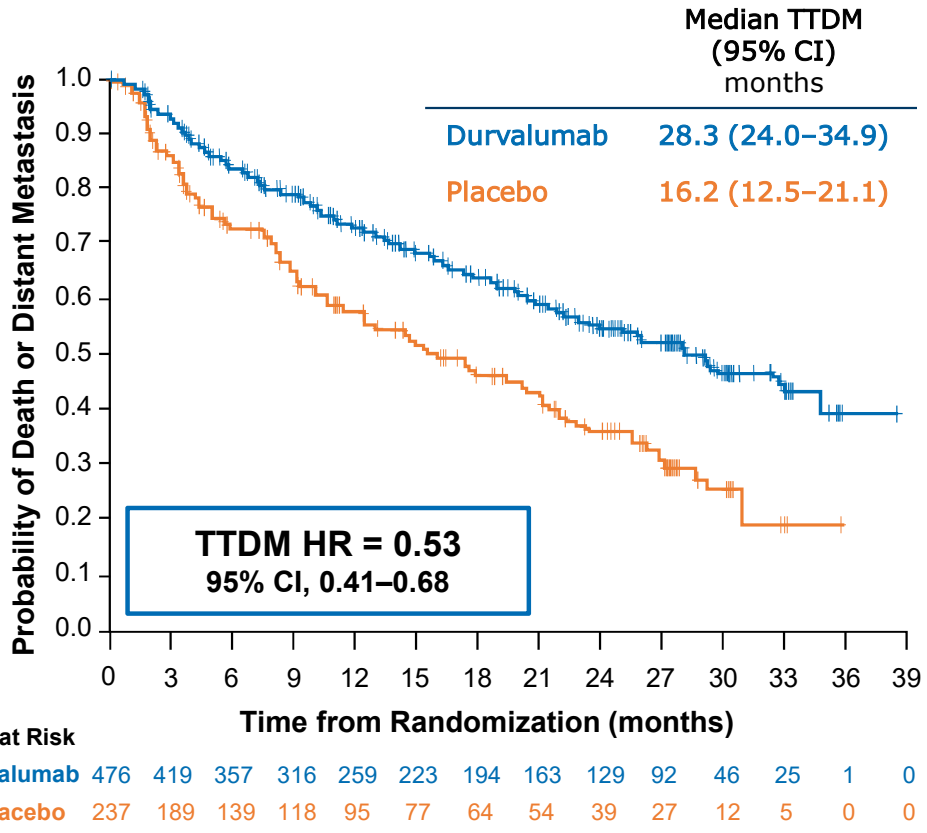
No. at Risk																
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

*Median duration of follow-up for OS was 25.2 months (range 0.2–43.1)
†Adjusted for interim analysis

NR, not reached

Antonia, SJ et al, WCLC 2018, abstr PL02.01

Updated Time to Death or Distant Metastasis (TTDM) by BICR* (ITT)



*Median duration of follow-up was 25.2 months (range 0.2–43.1)
†A patient may have had more than one new lesion site

Updated Incidence of New Lesions by BICR* (ITT)

New Lesion Site†	Durvalumab (N=476)	Placebo (N=237)
Patients with any new lesion, n (%)	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

Antonia, SJ et al, WCLC 2018, abstr PL02.01

Locally Advanced Unresectable Disease

Trial	N	Distant Metastases
RTOG 0617 Paclitaxel/Carboplatin 60 Gy	217	49%
PROCLAIM Cisplatin/Etoposide 60-66 Gy	297	29%
PACIFIC Durvalumab consolidation	476	22.5%

HOW DO WE IRRADICATE MICROMETASTATIC DISEASE?

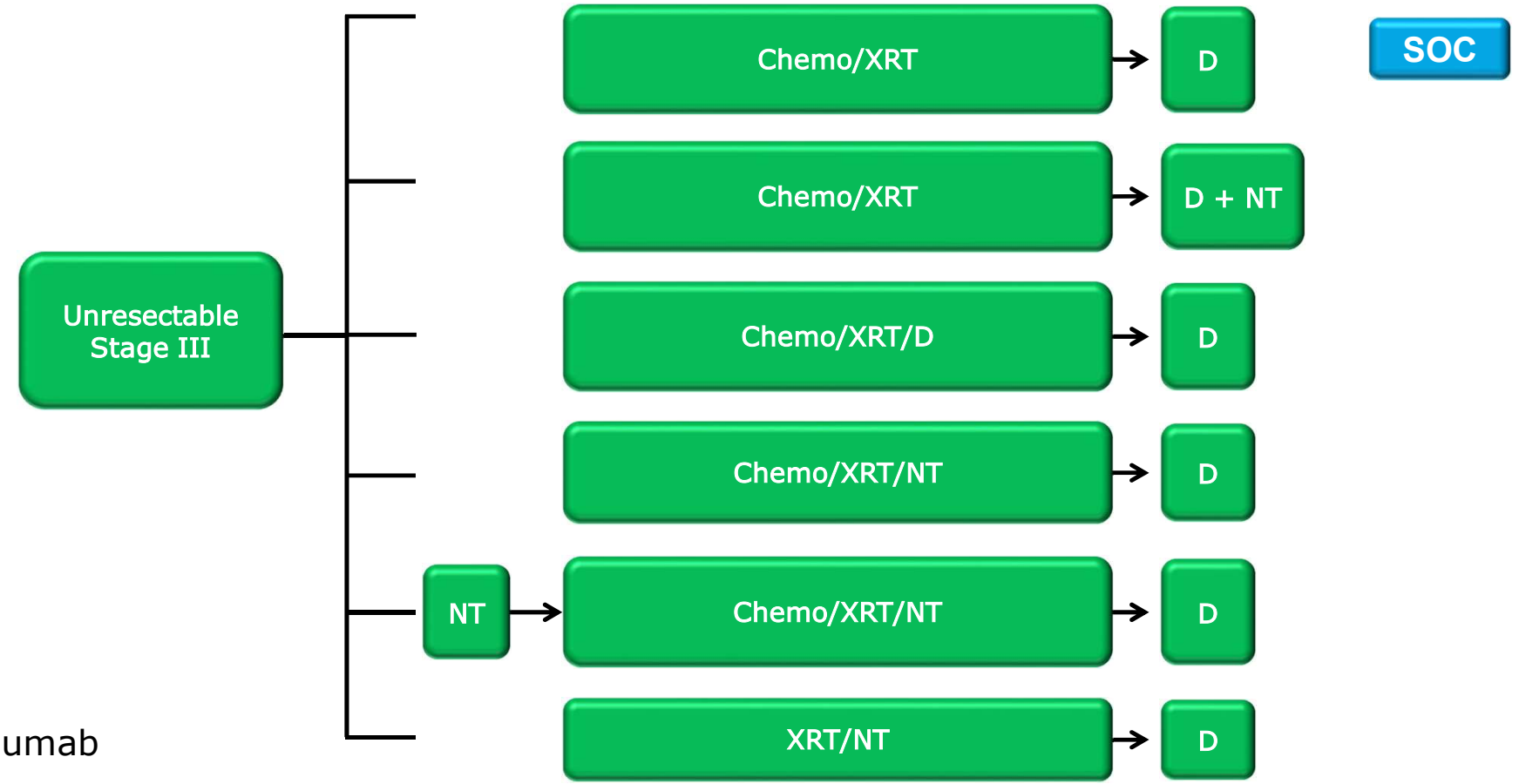
Bradley J, et al; Lancet Oncology 2015; Seenan S et al JCO 2018

Eradicating Micrometastatic Disease

- Improving treatments for micrometastatic disease
  - Molecularly targeted therapy
  - Immunotherapy

- Identifying patients with micrometastatic disease
  - ctDNA/tumor gene signatures
  - Radiomics
  - Improved imaging techniques

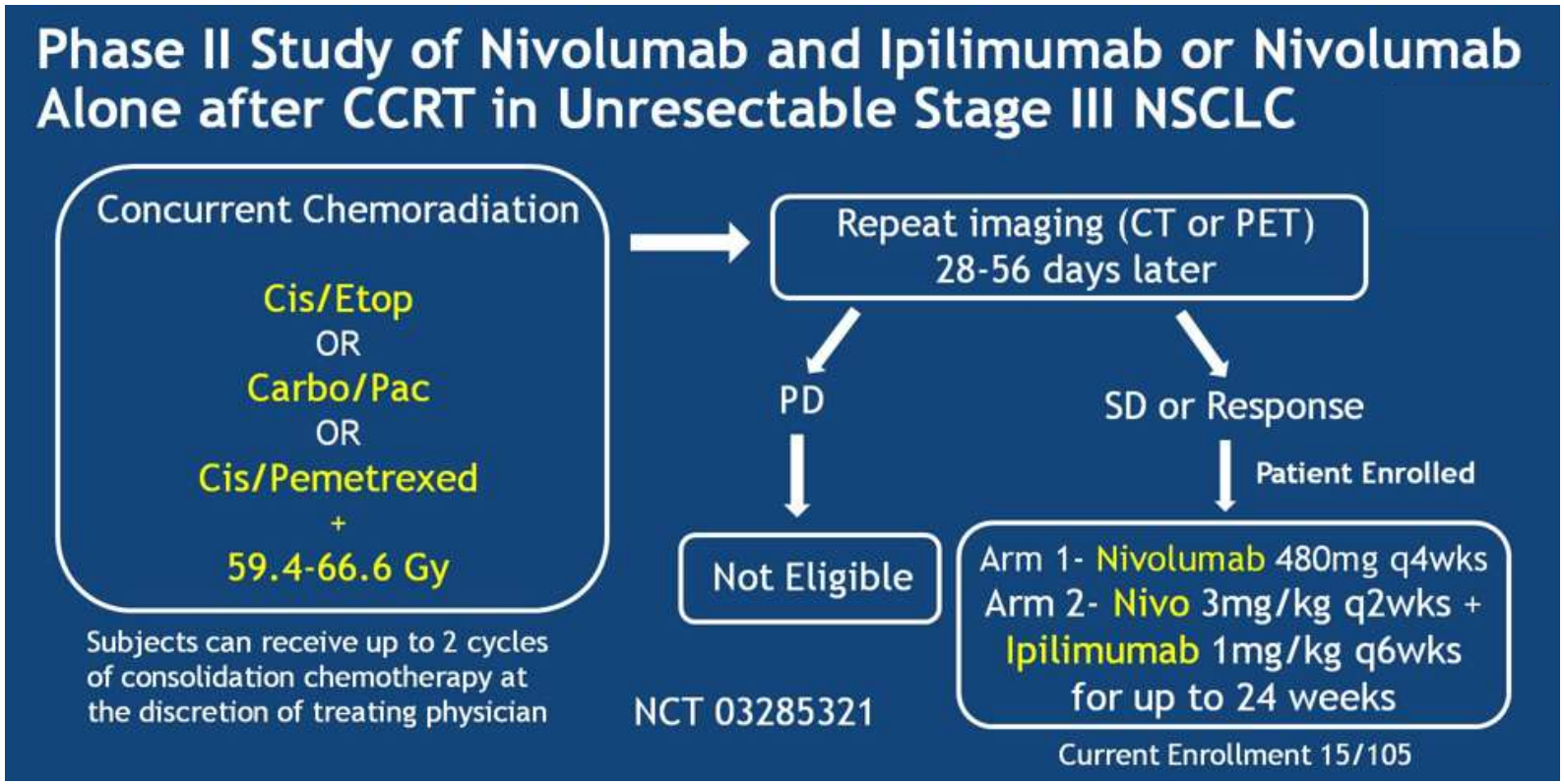
How do we incorporate novel therapies (NT) into the treatment regimens for Stage III lung cancer?



D=Durvalumab

Future Directions for Consolidation Immunotherapy

Phase II Study of Nivolumab and Ipilimumab or Nivolumab Alone after CCRT in Unresectable Stage III NSCLC



Durm G, et al. J Clin Oncol 36, 2018 (suppl; abstr 8500)

Enthusiasm for Concurrent Chemotherapy/TRT/IO

NICOLAS Trial

Cyclic Chemotherapy + TRT + Nivolumab (N=62)

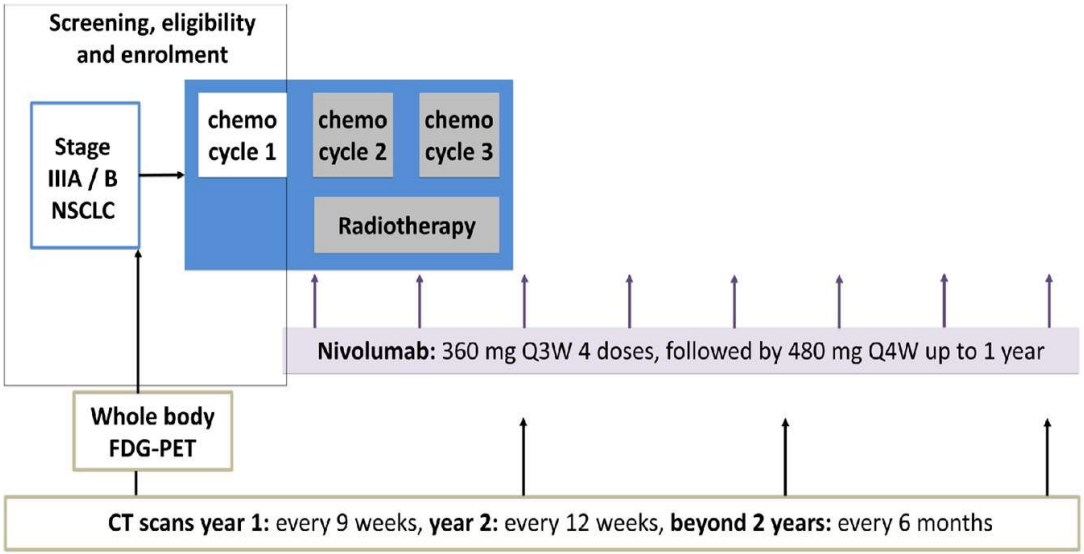


Figure 1: NICOLAS trial design

- Radiotherapy: A physical dose of ≥60 Gy.
- Nivolumab:
  - First, 4 doses at 360 mg as intravenous infusion (approx. 30 minutes) every 3-w.
  - Thereafter, 480 mg every 4-w for up to 1 year from start of nivolumab treatment, unless discontinuation occurs (due to any reason described in the protocol).

Trial treatment

- Chemotherapy consists of 3 cycles

Option	Drug		Dose	Dose frequency
1	Cisplatin plus vinorelbine			
	Cisplatin*		80 mg/m²	d1,Q3W,3 cycles**
	Vinorelbine	chemo-RT	30 mg/m²	d1+d8 cycle 1
			20 mg/m²	d1+d8 cycles 2 & 3
2	Cisplatin plus etoposide			
	Cisplatin*		80 mg/m²	d1,Q3W,3 cycles**
	Etoposide		100 mg/m²	d1-d3,Q3W,3 cycles**
3	Cisplatin plus pemetrexed (for non-squamous histological subtypes)			
	Cisplatin*		75 mg/m²	d1,Q3W,3 cycles**
	Pemetrexed		500 mg/m²	d1,Q3W,3 cycles**

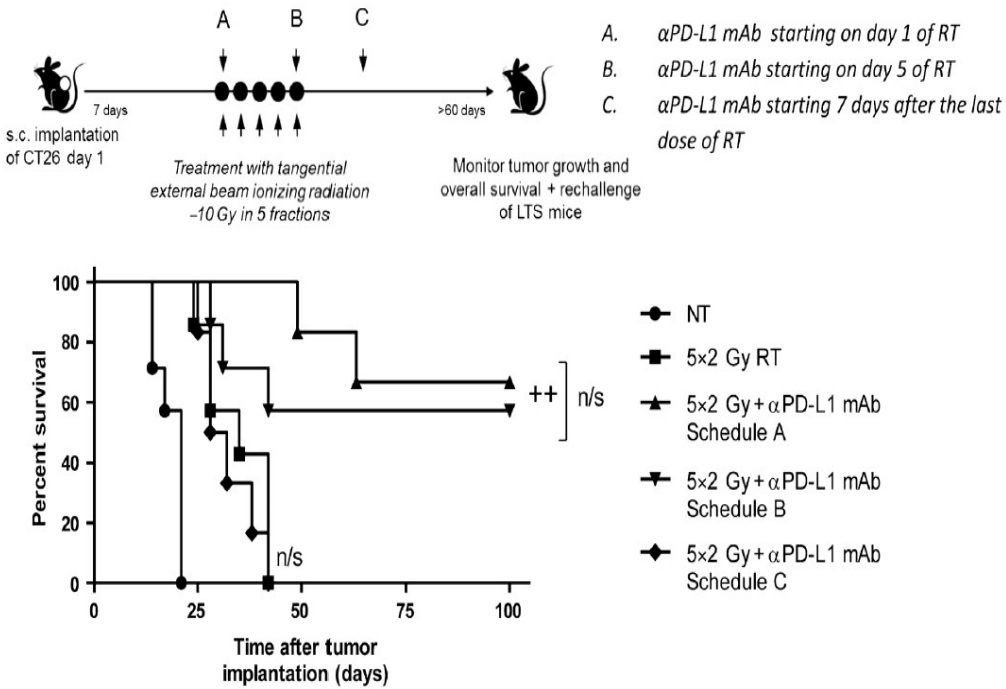
* If cisplatin cannot be used, it can be replaced by carboplatin AUC5 at d1.

** The first chemotherapy cycle is administered before enrolment.

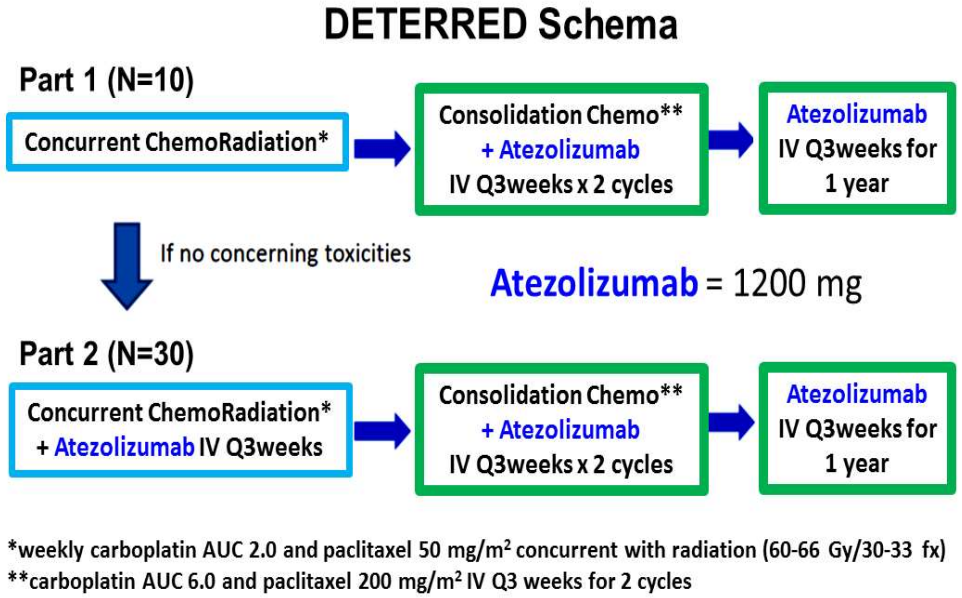
Peters, S et al. J Clin Oncol 2018 (suppl; abstr 8510)

Enthusiasm for Concurrent Chemotherapy/TRT/IO

DETERRED Trial
Weekly chemotherapy + TRT + Atezolizumab



Dovedi SJ, et al. Cancer Res 2014, 74:5458-68.



Lin SH, et al. J Clin Oncol 37, 2019 (suppl; abstr 8512)

Enthusiasm for Concurrent Chemotherapy/TRT/IO Safety

NICOLAS

Characteristic	Grade 1/2 (177/376)	Grade 3 (43/50)	Grade 4 (15/15)	Grade 5 (3/3)	# of which became SAE
Blood and lymphatic system disorders					
Anaemia	21 (36.2%)	3 (5.2%)	-	-	1 G3
Neutrophil count decrease	7 (12.1%)	4 (6.9%)	9 (15.5%)	-	2 G4
Febrile neutropenia	-	5 (8.6%)	1 (1.7%)	-	5 G3 / 1 G4
Cardiac disorders					
Heart failure	1 (1.7%)	-	-	-	1 G2
Pericarditis	1 (1.7%)	-	-	-	1 G2
Gastrointestinal disorders					
Nausea	17 (29.3%)	1 (1.7%)	-	-	1 G2 / 1 G3
Dysphagia	14 (24.1%)	1 (1.7%)	-	-	
Esophagitis	9 (15.5%)	3 (5.2%)	-	-	1 G3
Enterocolitis	-	1 (1.7%)	-	-	1 G3
Oesophageal fistula	-	-	-	1 (1.7%)	1 G5
General disorders and administration site conditions					
Fatigue	21 (36.2%)	3 (5.2%)	-	-	
Pain	9 (15.5%)	1 (1.7%)	-	-	1 G3
Fever	8 (13.8%)	1 (1.7%)	-	-	3 G2
Malaise	3 (5.2%)	-	-	-	2 G2
Infections and infestations					
Bronchial infection	6 (10.3%)	1 (1.7%)	-	-	1 G3
Lung infection	4 (6.9%)	-	-	-	1 G2
Catheter related infection	-	1 (1.7%)	-	-	1 G3
Sepsis	-	-	1 (1.7%)	-	1 G4
Investigations					
White blood cell decreased	6 (10.3%)	2 (3.4%)	1 (1.7%)	-	
Lymphocyte count decreased	-	5 (8.6%)	1 (1.7%)	-	
Platelet count decreased	5 (8.6%)	-	1 (1.7%)	-	
Lipase increased	1 (1.7%)	1 (1.7%)	1 (1.7%)	-	
Metabolism and nutrition disorders					
Hyponatremia	1 (1.7%)	1 (1.7%)	-	-	1 G3
Nervous system disorders					
Stroke	-	1 (1.7%)	-	2 (3.4%)	1 G3 / 2 G5
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	11 (19.0%)	1 (1.7%)	-	-	1 G2 / 1 G3
Pneumonitis	***13 (22.4%)***	***6 (10.3%)***	-	-	***2 G2 / 6 G3***
Cough	18 (31.0%)	-	-	-	
Pulmonary fibrosis	-	1 (1.7%)	-	-	1 G3
Respiratory insufficiency	1 (1.7%)	-	-	-	1 G2

Adverse events with G1 & G2 ≥15% (9 pts), G3 ≥3% (2 pts), and all G4, G5 and SAEs are presented.

No Unexpected AEs or Increased Safety Concerns Were Observed

Peters, S et al. J Clin Oncol 2018 (suppl; abstr 8510)

DETERRED

N=30	Part 2
All AEs	451
All Grade 3+ AEs	41
% pts developed any Grade 3+	20 of 30 (67%)
AEs leading to withdraw from tx	5 of 30 (17%)
% pts with immune-related Grade 3+ AEs	6 of 30 (20%)

Grade 2 AEs of special interest	Frequency
Nephritis	1 of 30 (3%)
Arthalgia	2 of 30 (7%)
Diarrhea	1 of 30 (3%)
Dyspnea	1 of 30 (3%)
Fatigue	1 of 30 (3%)
Hypothyroidism	1 of 30 (3%)
Pneumonitis	4 of 30 (13%)
Rash	5 of 30 (17%)

Patients with Grade 3+ AEs	Frequency
Diarrhea (Grade 3), Radiation pneumonitis (Grade 3)	1 of 30 (3%)
Nephritis (Grade 3), Fatigue (Grade 3)	1 of 30 (3%)
Fatigue (Grade 3)	2 of 30 (7%)
Heart failure (Grade 3)	1 of 30 (3%)
Respiratory failure NOS (Grade 4)	1 of 30 (3%)

Grade 3 Immune Related Toxicities Were Low

Lin SH, et al. J Clin Oncol 37, 2019 (suppl; abstr 8512)

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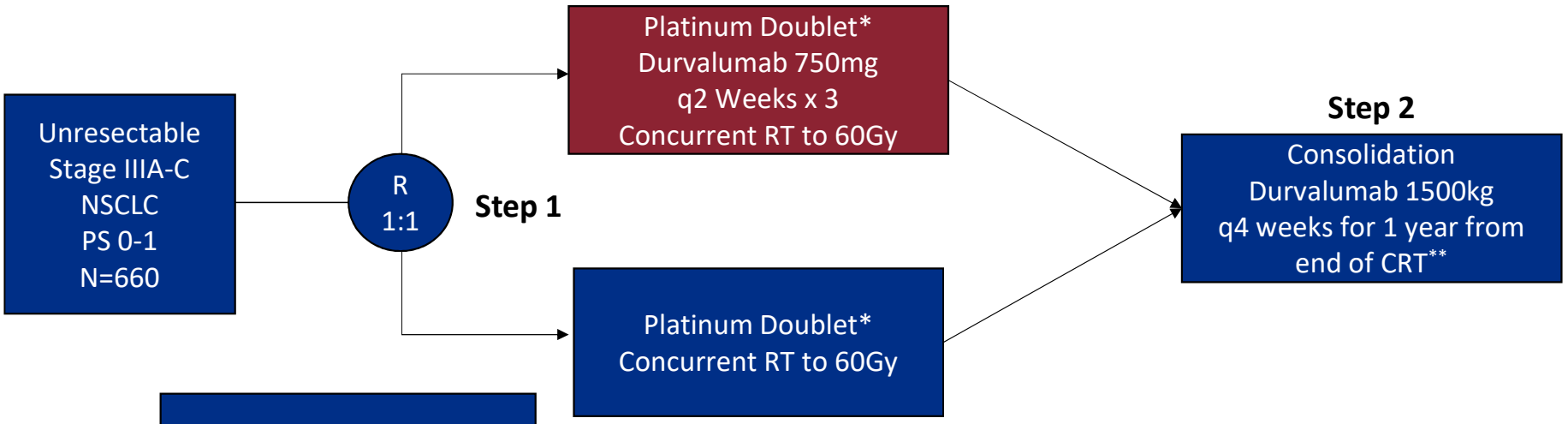


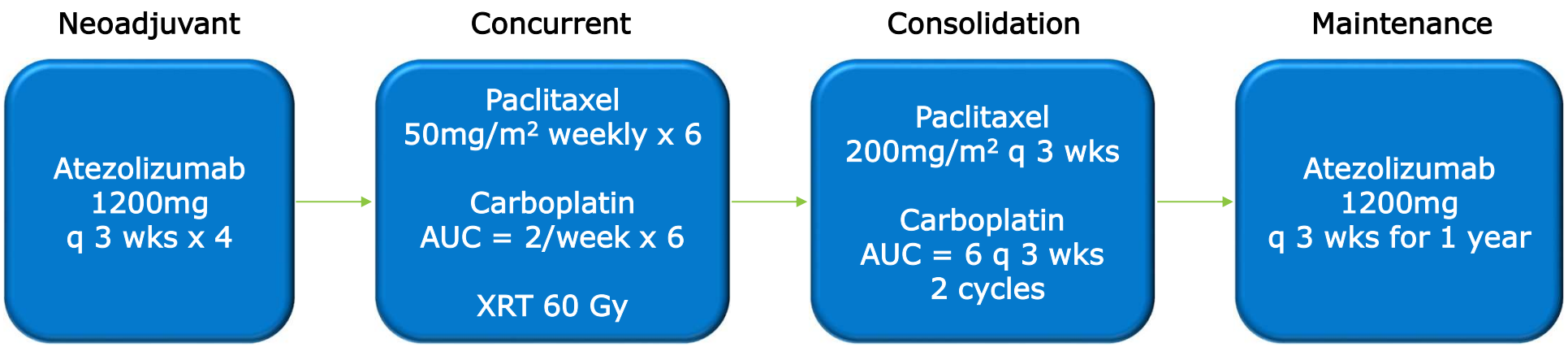
Randomization

Stratified by:
1) Planned chemotherapy
2) Age
3) Sex
4) Stage (IIIA vs IIIB vs IIIC)

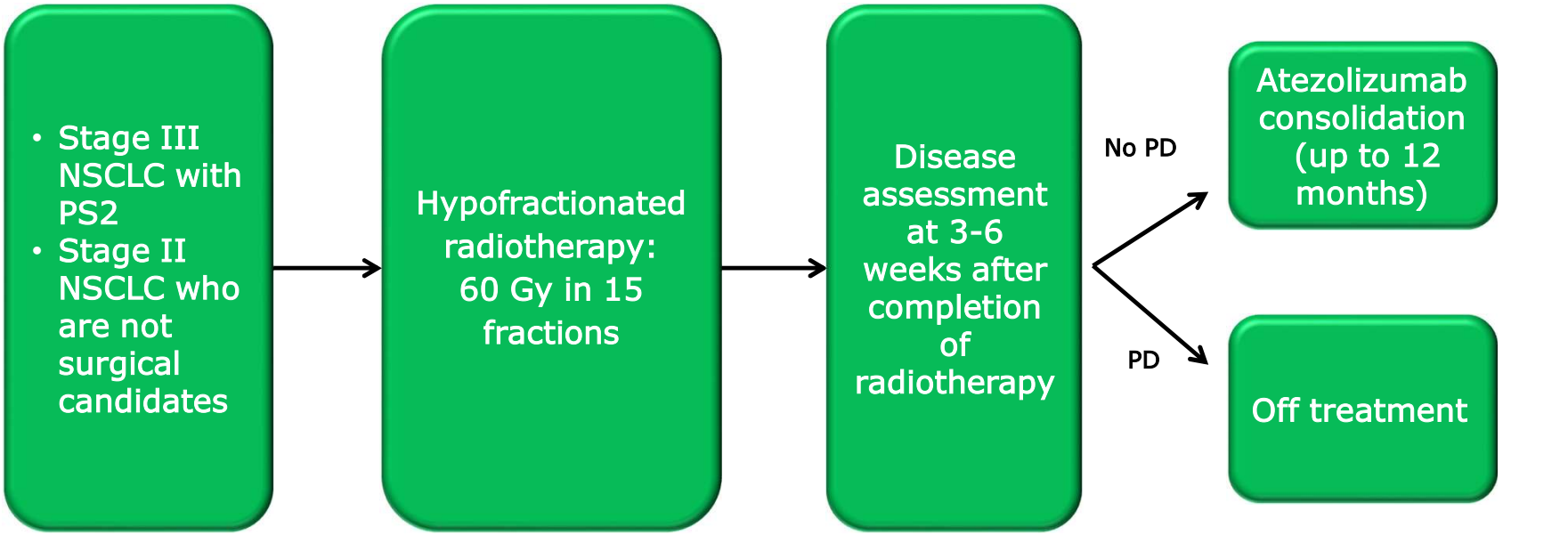
*__Investigator choice__
Cisplatin 50 mg/m2 D1, 8, 29, 36; etoposide 50 mg/m2 D1-5, 29-33
Cisplatin 75 mg/m2 D1, 22; pemetrexed 500 mg/m2 D1, 22 (nonsquamous only)
Carboplatin AUC 2 D1, 8, 15, 22, 29, 36; paclitaxel 45 mg/m2 D1, 8, 15, 22, 29, 36

**Starting within 14 days of CRT unless toxicity has not resolved to ≤ grade 2, but not later than 45 days post-CRT

Alliance Foundation Trial AFT-16 (N=63)

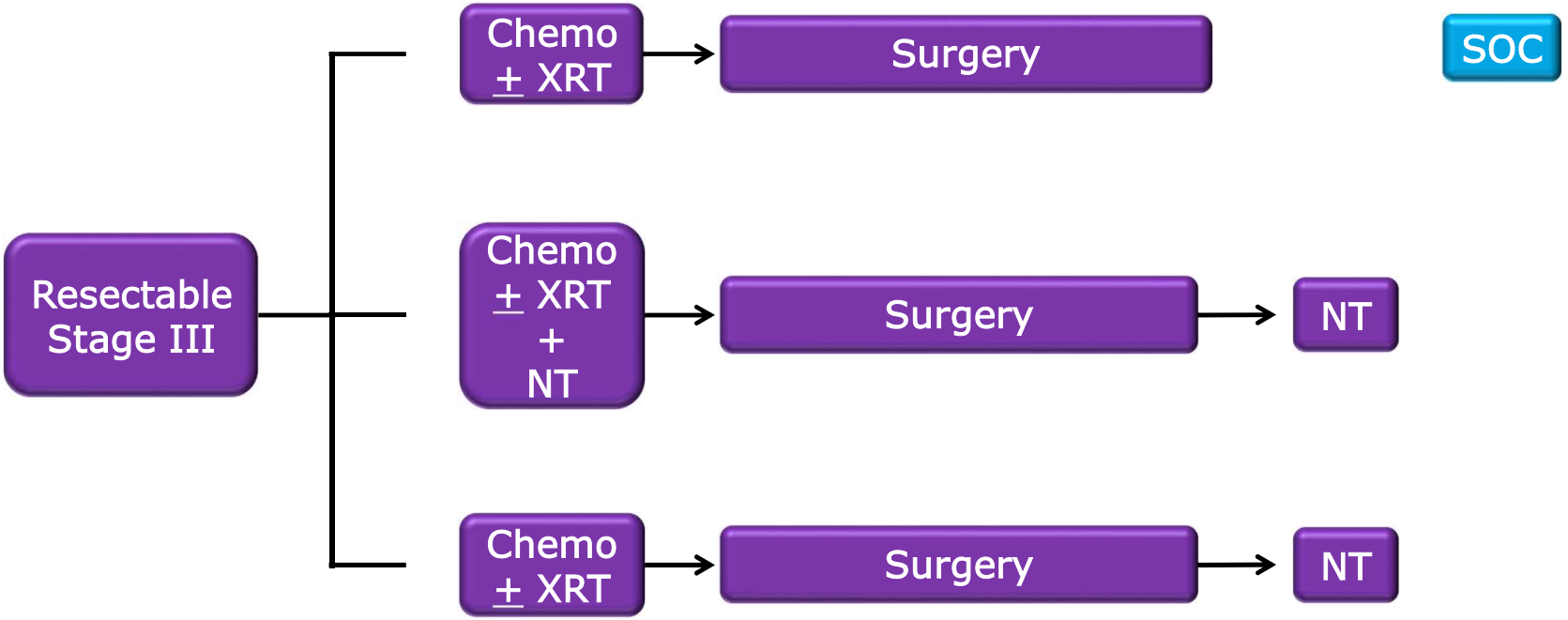


S1933: XRT Followed by Atezolizumab or Observation in Patients with Borderline PS



PI: Aljumaily

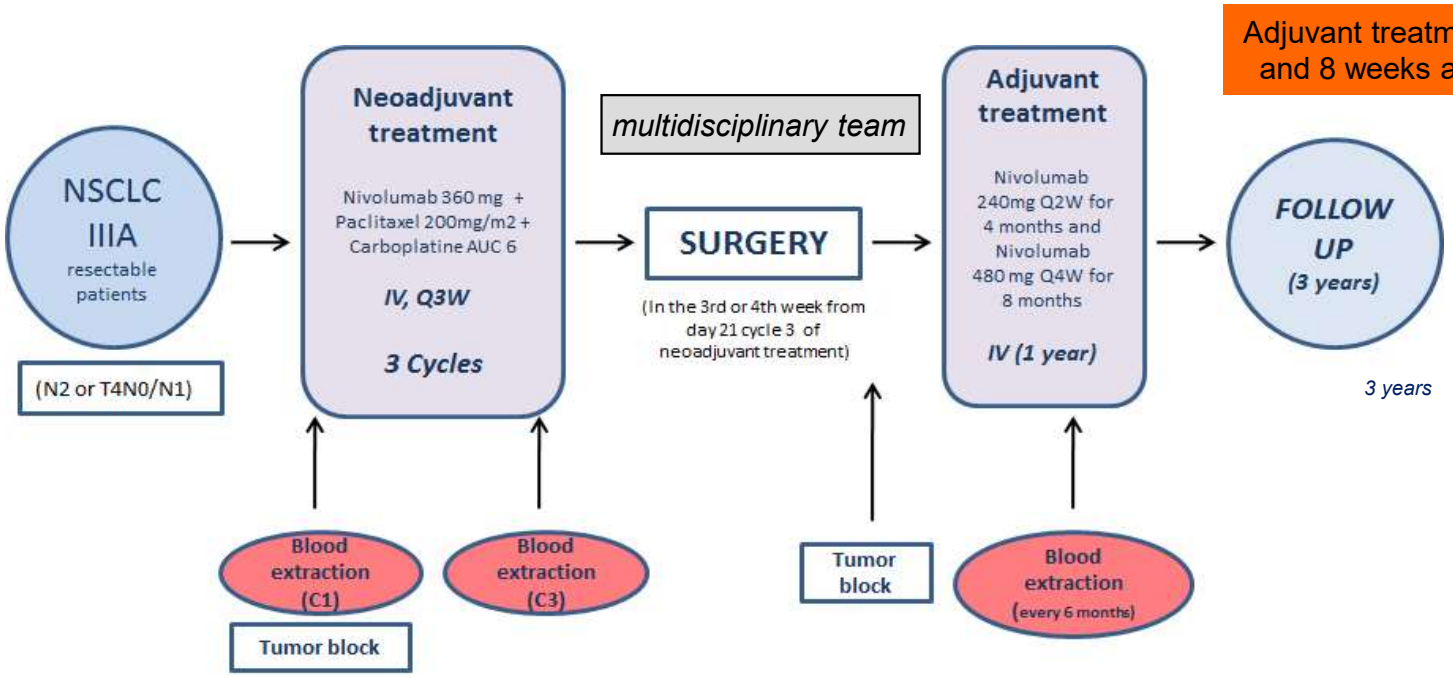
How do we incorporate novel therapies (NT) into the treatment regimens for resectable Stage III lung cancer?



± Adjuvant chemotherapy and/or XRT

NADIM: Neo-Adjuvant Immunotherapy

Study Design & Flow-Chart



- Phase II
- Single-arm
- Open-label
- Multicenter
- Resectable IIIA NSCLC
- 46 patients

M. Provencio, et al. WCLC 2018

NADIM: Neo-Adjuvant Immunotherapy

Neoadjuvant Treatment

	N	Median	Range
Cycles	45	3.0	(1.0-3.0)

CYCLES	N	%
1	3	5
3	43	95
Total	46	100.0

All patients received three neoadjuvant cycles except for the three patients still being treated.

Clinical Response

	N	%
Complete response (CR)	3	10.0
Partial response (PR)	18	60.0
Stable disease (SD)	9	30.0
Total	30	100.0

No progressive disease has been observed.

M. Provencio, et al. WCLC 2018

NADIM: Neo-Adjuvant Immunotherapy

Pathological Response

	N	%
Major response[1]	24	80.0
Complete response	18	75.0
Less < 90%	6	20.0
Total	30	100.0

[1]Major pathological response defined as <10% viable tumor cells in the resected specimen.

The following factors were considered to identify factors that potentially influence pathological response (complete and major):

- *Age*
- *Gender*
- *Performance status*
- *Smoking status*
- *Comorbidities*
- *Clinical stage*
- *Clinical response*
- *Primary tumor site (right vs left)*
- *Histology (adenocarcinoma vs squamous)*
- *Nodes involvement (yes/no)*
- *Nodes resected and hematological toxicities grade 3-4*

Each factor was compared between patients with pathological response (complete and major) vs those with no response. Factors with p<0.1 were considered potential factors for a logistic regression analysis (N=30).

No significant logistic regression models were obtained.

- *Median patient follow-up = 4.1 months, range 0.2-14.6 months.*
- *None of the patients have suffered recurrence.*

M. Provencio, et al. WCLC 2018

Alliance Foundation Trial – Neoadjuvant IO + Chemo

Stage IIIA NSCLC

-histologically proven N2, nonbulky disease, no N3 disease

-all NSCLC histologies

-negative brain imaging

-PET/CT negative for metastatic disease

-Resection by LOBECTOMY, or BEYOND STANDARD LOBECTOMY required as deemed by ABTS general thoracic surgeon

Platinum doublet
x 4 cycles
Chemotherapy
PLUS IMMUNE
CHECKPOINT INHIBITOR;

Then repeat CT (mandatory) +/- PET (encouraged) to rule out progression, repeat PFT's

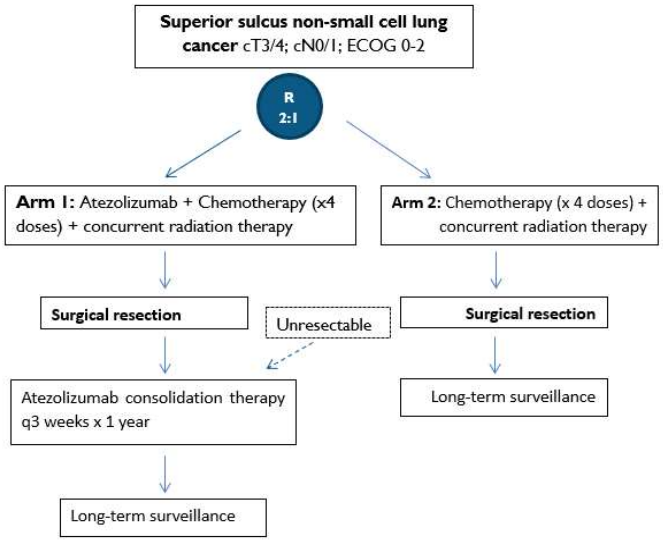
Surgery – resection; must be by ABTS surgeon

Adjuvant radiation to 50-54 Gy

Trials in Development

Concurrent Atezolizumab/Chemo/TRT

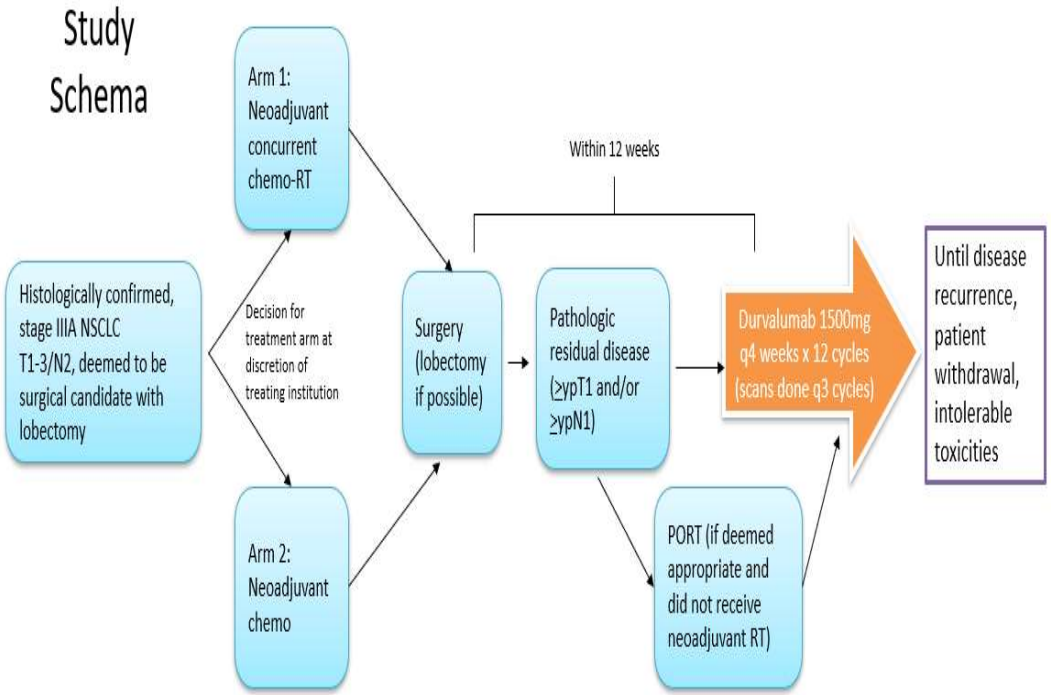
S1934 TRUST-IO Schema



Eligibility criteria: Histologically-confirmed non-small cell lung cancer, superior sulcus location, cT3/4, cN0/1, adequate organ function for all proposed modalities, no contraindications to any treatment component.

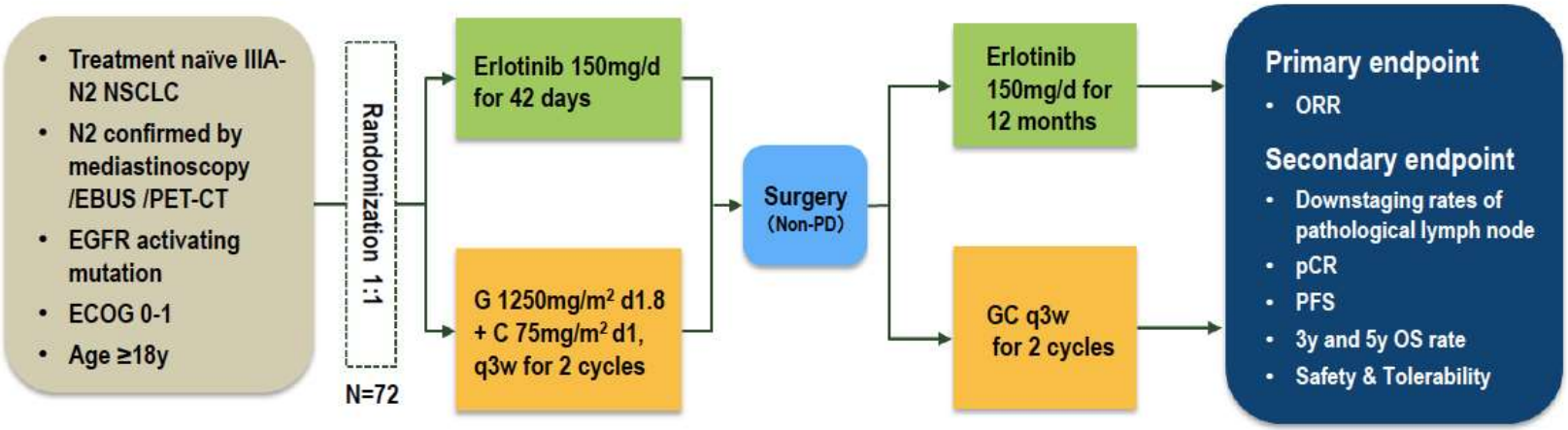
Clinical end-points: treatment intensity, toxicity, side-effects (e.g. dose-density of systemic therapy, radiation, surgery); short-term benefits (e.g. surgical resection rates, complete (R0) resection rates, pathologic complete response rates (primary end-point); long-term benefits (e.g. recurrence rates, recurrence sites, survival).

Consolidation Durvalumab



What about molecularly targeted therapies for Stage III NSCLC?

EMERGING-CTONG 1103 Study Design



- Stratification by lymph node status, histology, smoking status and sex.

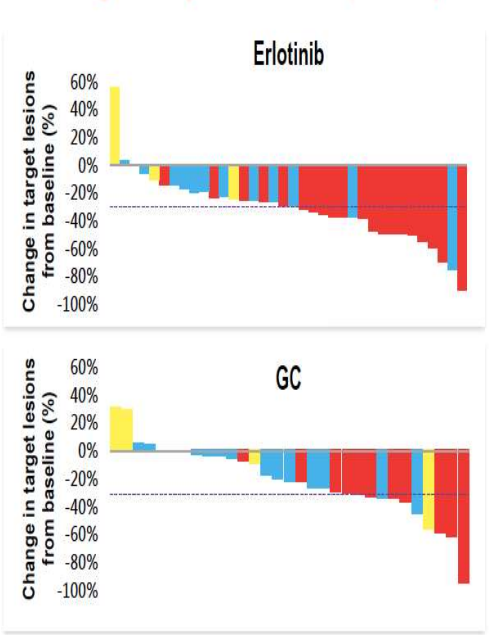
ECOG PS, Eastern Cooperative Oncology Group Performance Status; G, gemcitabine ; C, cisplatin;
ORR, objective response rate; pCR, pathological complete response; PFS, progression free survival; OS, overall survival.

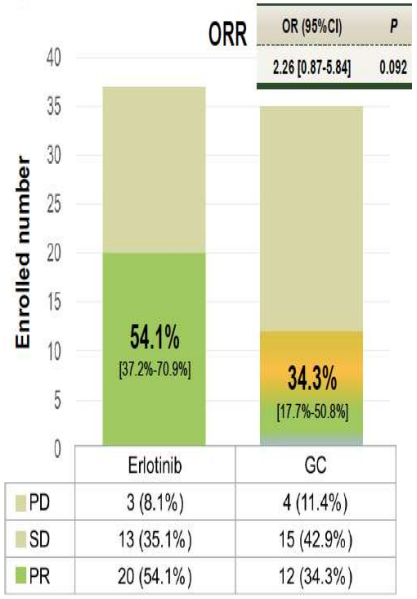
MUNICH 2018 ESMO congress

Data cut-off: April 2018 ; NCT01407822; PI:Yi-long Wu

What about molecularly targeted therapies for Stage III NSCLC?

Primary Endpoint: ORR (ITT Population)





	Erlotinib	GC
PD	3 (8.1%)	4 (11.4%)
SD	13 (35.1%)	15 (42.9%)
PR	20 (54.1%)	12 (34.3%)

MUNICH 2018 ESMO congress

ORR, objective response rate; PR, partial response; SD, stable disease; PD, progressive disease

Secondary Endpoint: Complete Resection and Lymph Node Downstage

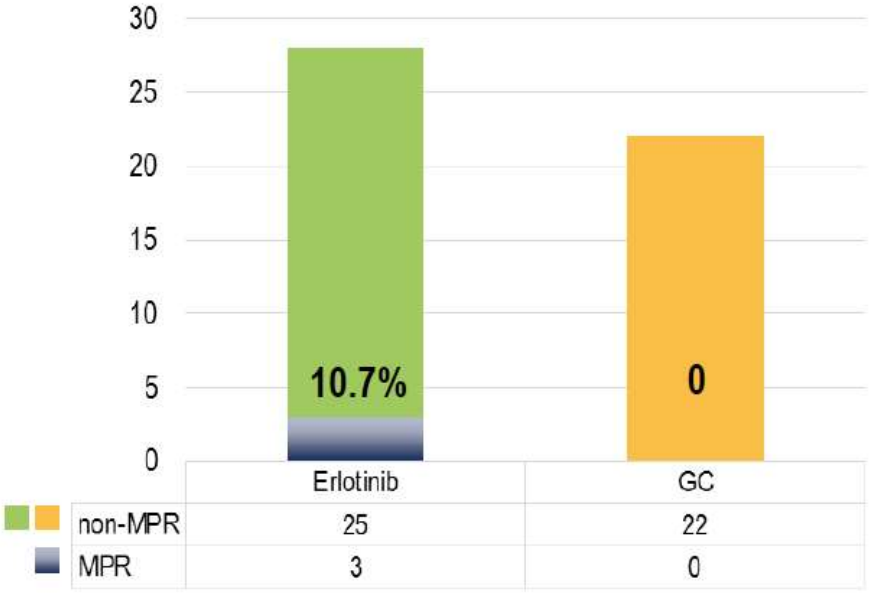
	Erlotinib group (n=37)	GC group (n=35)	P value
Surgery, n (%)	**31 (83.8)**	**24 (68.6)**	0.129
Complete resection, n (%)	**27 (73.0)**	**22 (62.9)**	0.358
R0	27 (73.0)	22 (62.9)	
R1	1 (2.7)	1 (2.9)	
R2	3 (8.1)	1 (2.9)	
Lymph node downstage,n (%)	**4 (10.8)**	**1 (2.9)**	0.185
N2→ pN0	3 (8.1)	1 (2.9)	
N2→ pN1	1 (2.7)	0 (0)	
N2→ pN2	27 (73.0)	23 (65.7)	
Type of resection, n(%)	24(64.9)	19(54.3)	0.308
Lobectomy	5(13.5)	5(14.3)	
Bilobectomy	2(5.4)	0	
Pneumonectomy			

What about molecularly targeted therapies for Stage III NSCLC?

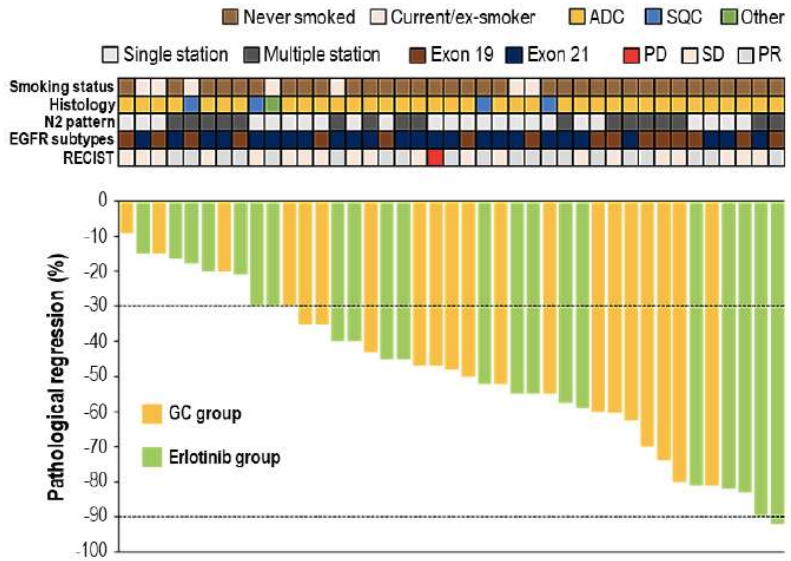
Secondary Endpoint: Pathological Complete Response (pCR) Rate

50 surgical resected specimens were available, No pCR cases in both groups.

The major pathological response (MPR)

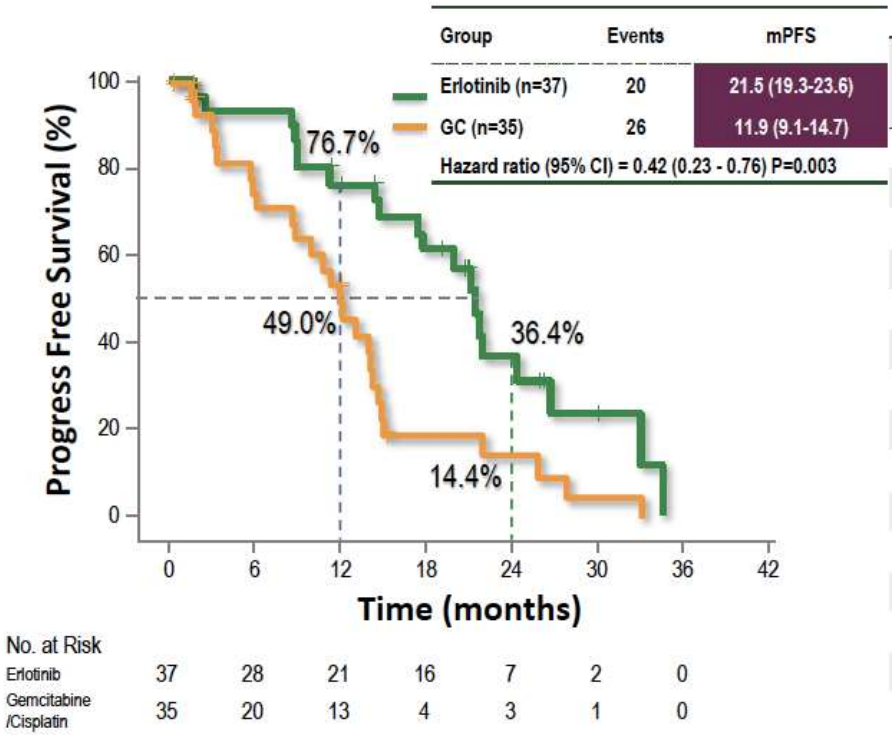


Pathological regression

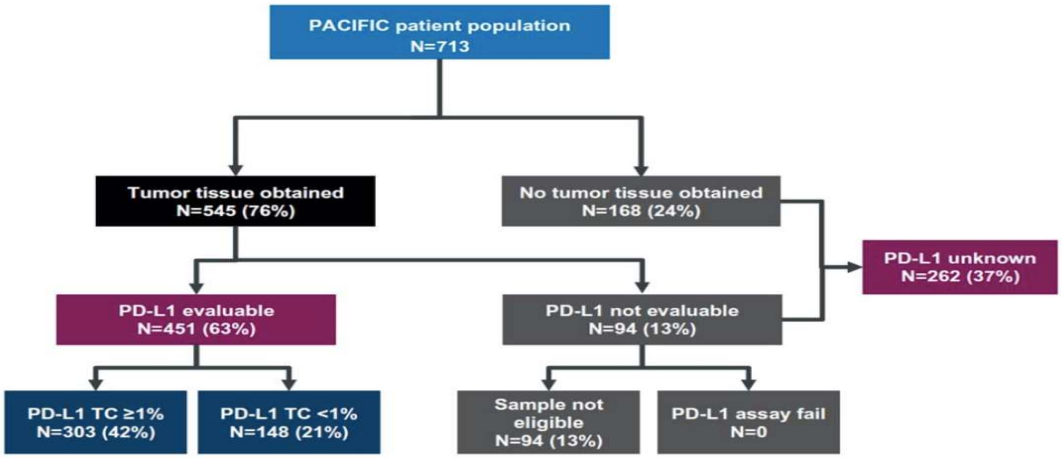


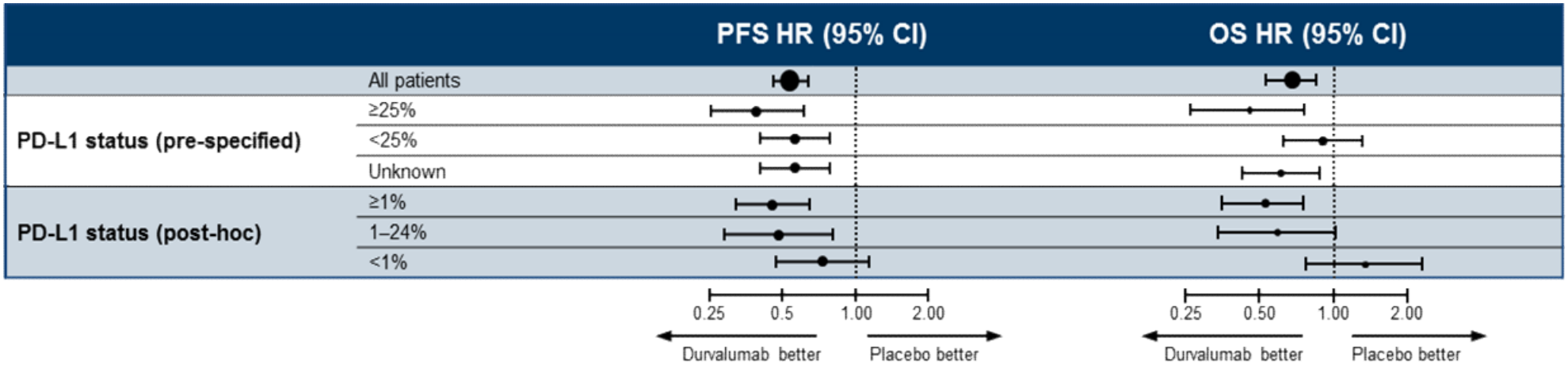
What about molecularly targeted therapies for Stage III NSCLC?

Secondary Endpoint: PFS (ITT population)



Will We Have Predictive Biomarkers?



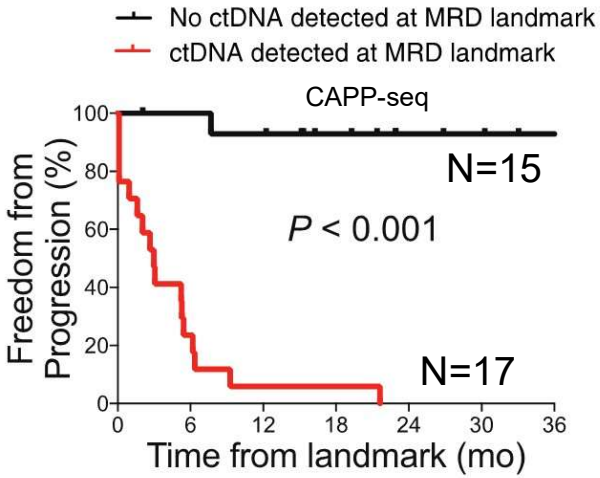


Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of March 22, 2018

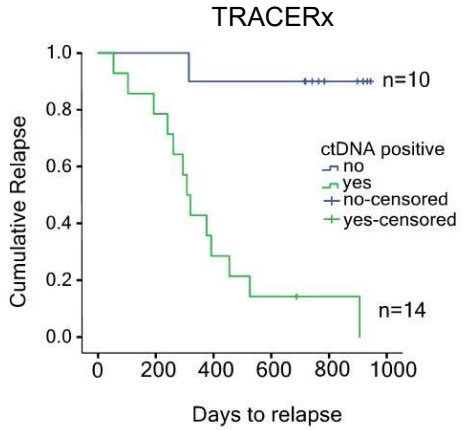
Antonia, SJ et al, WCLC 2018, abstr PL02.01

Molecular Residual Disease (MDR)

ctDNA Identifies Patients with Molecular Residual Disease (MRD) after Surgery or Radiotherapy



Chaudhuri et al. *Cancer Discovery* 2017



Abbosh et al. *Nature* 2017

ctDNA MRD analysis after local therapy is highly prognostic

Summary

1. Durvalumab consolidation is the new standard of care for patients with unresectable stage III NSCLC.

2. Multiple trial designs to further integrate immune checkpoint inhibitors into this new regimen have been launched.

3. Trials integrating immune checkpoint inhibitors into the treatment of resectable stage III NSCLC are being pursued.

4. How to incorporate targeted therapies into the regimens remains challenging but important.

5. Prognostic and predictive biomarker are needed.