Ruolo emergente dell'immunoterapia nello stadio III

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Disclosures

- Advisory Boards / Honoraria / Speakers' fee / Consultant for:
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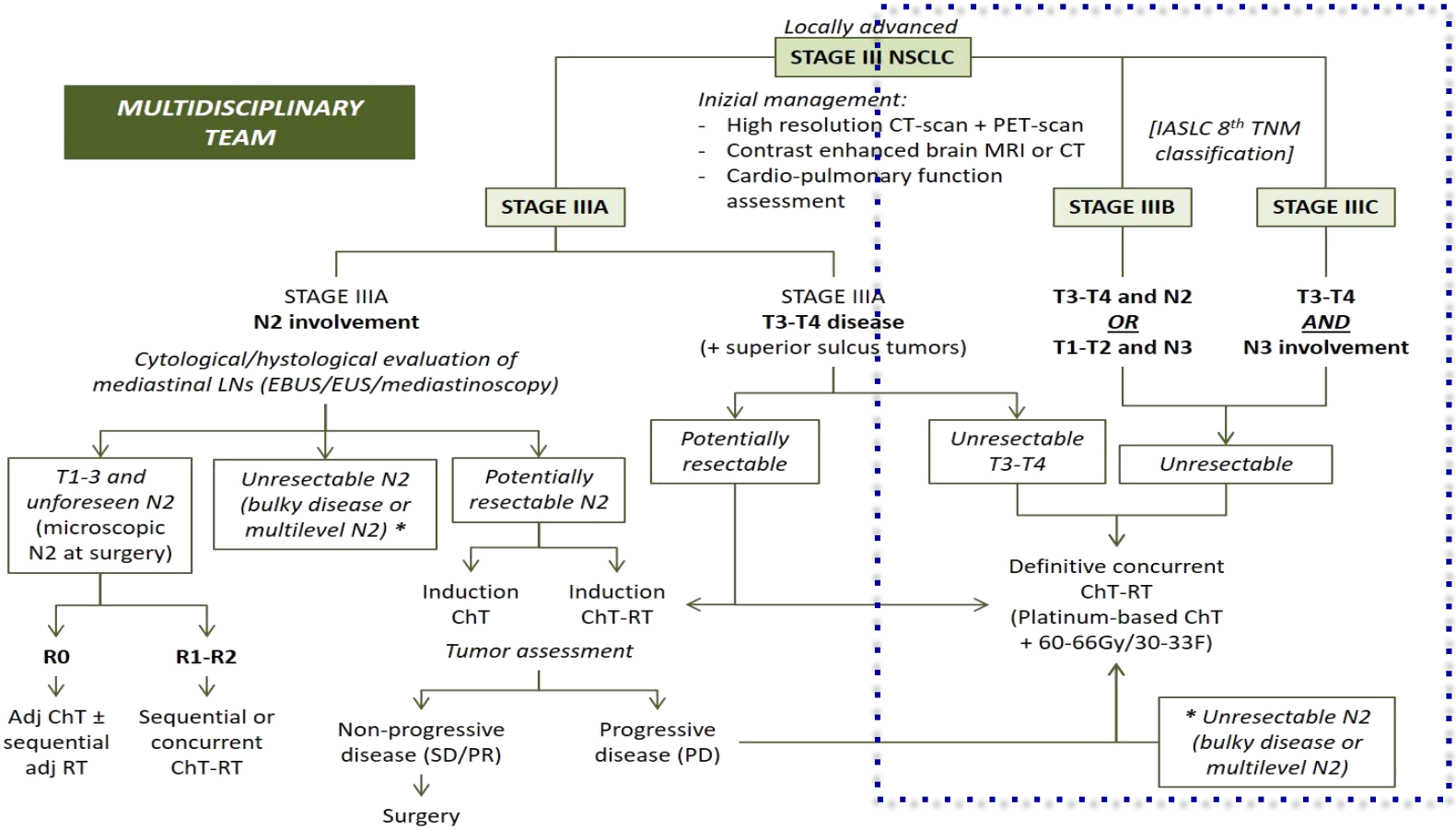
  - AIRC (Associazione Italiana Ricerca sul Cancro)
  - ESMO (European Society for Medical Oncology)

Stage III NSCLC: a heterogeneous picture



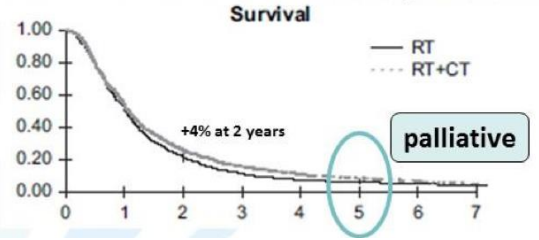
Unresectable stage III NSCLC

- 1980: radiotherapy alone: median OS 10 m
- 1990: chemotherapy added: median OS 14 m

Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients

A. Aupérin[1*], C. Le Péchoux[2], J. P. Pignon[1], C. Koning[4], B. Jeremic[5], G. Clamon[6], L. Einhorn[7], D. Ball[8], M. G. Trovo[9], H. J. M. Groen[10], J. A. Bonner[11], T. Le Chevalier[3] & R. Arriagada[2,12]
On behalf of the Meta-Analysis of Cisplatin/carboplatin based Concomitant Chemotherapy in non-small cell Lung Cancer (MAC3-LC) Group

Annals of Oncology 17: 473–483, 2006



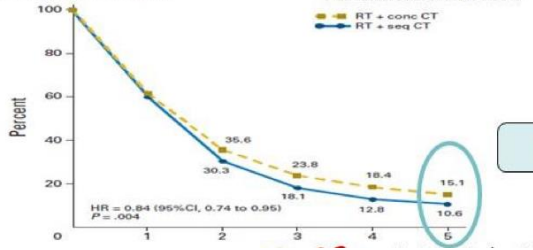
palliative

- 2000: concurrent chemoradiotherapy: median OS 18 m

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

Anne Aupérin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon

J Clin Oncol 28:2181-2190. © 2010



cure

	Regimen	Median OS	2y OS	5y OS
Meta-analysis 2006				
RT alone	-	(12 mo)	21.4%	6%
Concurrent CTRT	cisplatin alone carboplatin-etoposide	(14 mo)	25.4%	8.2%
Meta-analysis 2010				
Sequential CTRT	cisplatin-vinca cisplatin-etoposide cisplatin-vinorelbine	(14 mo)	30.3%	10.6%
Concurrent CTRT		(18 mo)	35.6%	15.1%

Vansteenkiste JF, ESMO 2017

Unresectable stage III NSCLC

2 cycles of cis-etoposide

Radiotherapy 60 / 2 Gy

1/ Improve local therapy ?

- Failure of RTOG 0617 (ASCO 2013) [1]
  - ➢ 74 Gy not better than 60 Gy

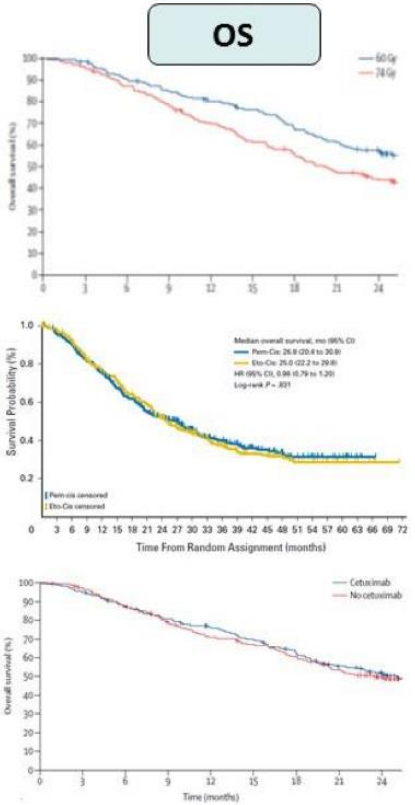
2/ Improve chemotherapy ?

- Failure of PROCLAIM (ASCO 2015) [2]
  - ➢ Cis-pemetrexed no better OS

3/ Targeted therapy ?

- Failure of RTOG 0617 (WCLC 2013) [3]
  - ➢ Cetuximab not better than placebo

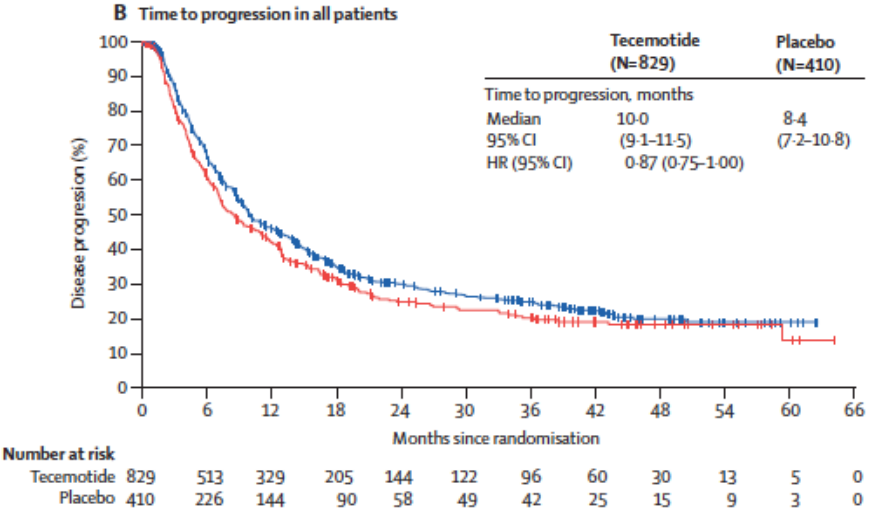
➢ **Benefits in stage IV are NOT translated in stage III**



1 Bradley et al, ASCO 2013 *and* Lancet Oncol 16:187-199, 2015
2 Senan et al, ASCO 2015 and J Clin Oncol
3 Bradley et al, WCLC 2013 *and* Lancet Oncol 16:187-199, 2015

Vansteenkiste JF, ESMO 2017

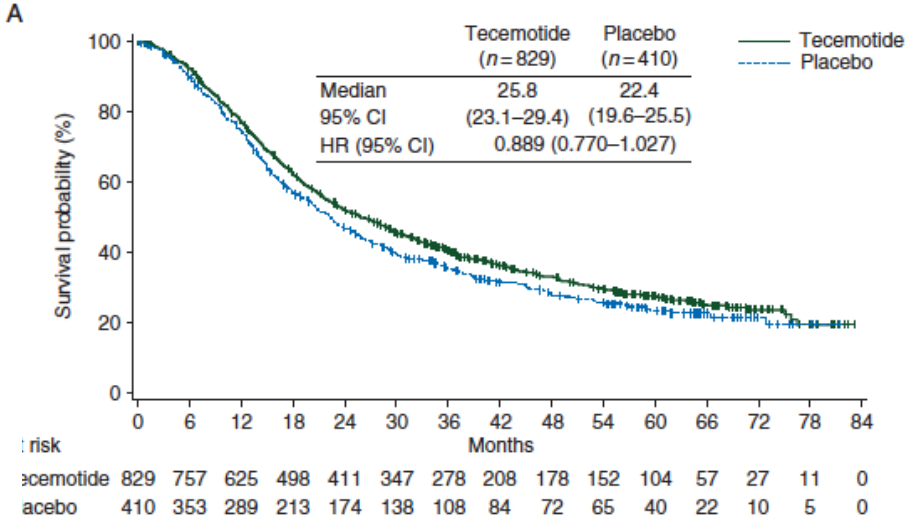
Tecemotide (L-BLP25) *vs*. placebo in unresectable stage III NSCLC



cCTRT	Tecemotide ($n=538$)	Placebo ($n=268$)
Median	29.4	20.8
95% CI	(25.7–35.4)	(17.8–24.2)
HR (95% CI)	0.814 (0.678–0.976)	

Tecemotide
Placebo

p:0.02



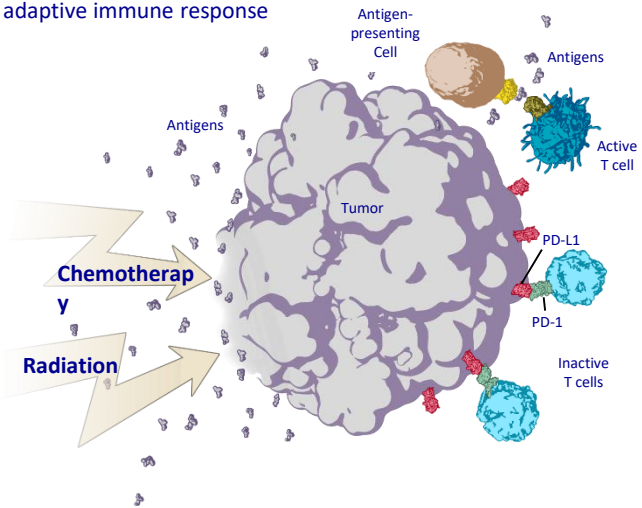
Butts C, Lancet Oncol 2014; Mitchell P Ann Oncol 2015

The rationale for PD1/PD-L1 ICI in unresectable stage III NSCLC

CHEMORADIATION

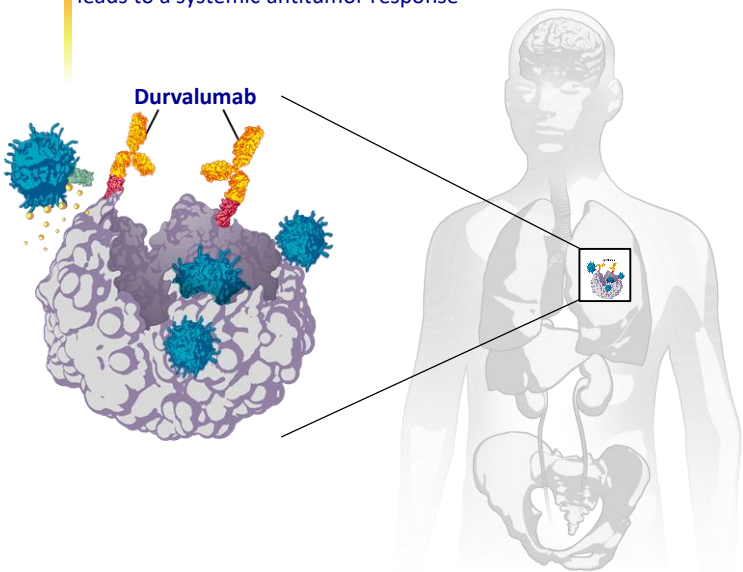
Chemoradiation induces tumor antigen release and an adaptive immune response

PD-L1 overexpression leads to immune cell evasion



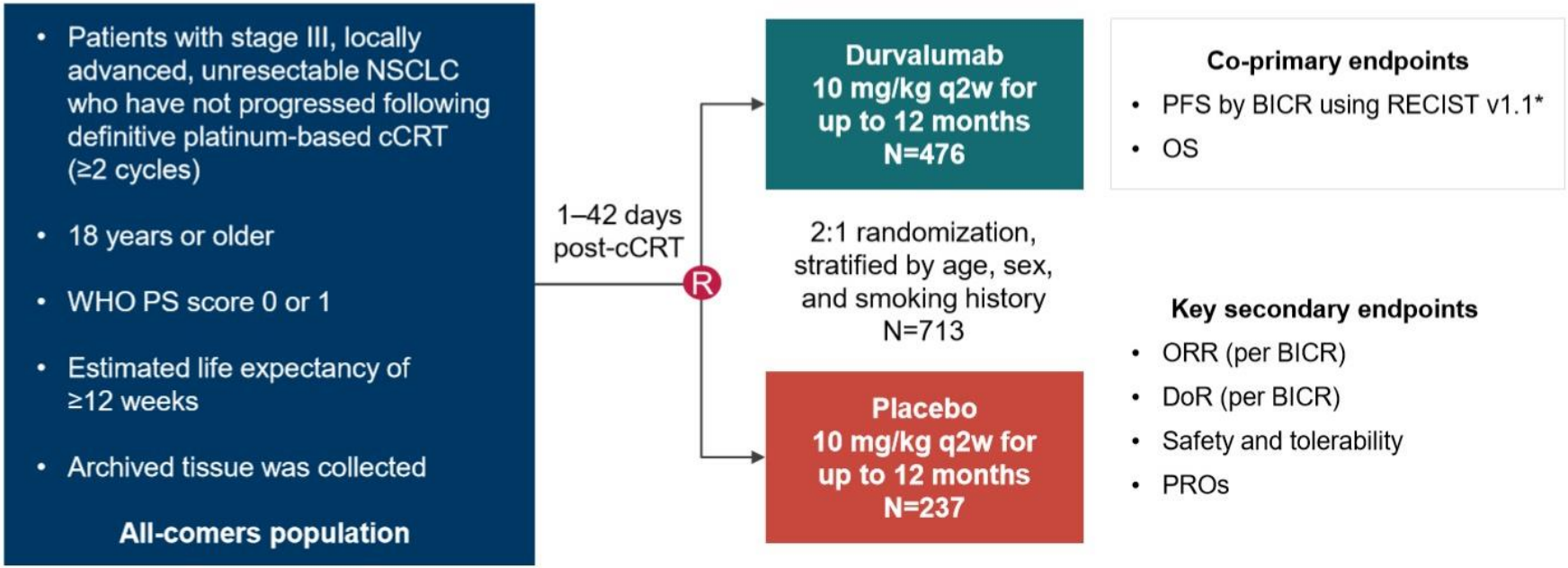
DURVALUMAB

Durvalumab reverses immune suppression and leads to a systemic antitumor response



Deng L, J Clin Invest 2014; Dovedi SJ, Cancer Res 2014; Chacon JA, Vaccines (Basel) 2016; Formenti SC, J Natl Cancer Inst 2013; Funaki S, Oncol Rep 2017; Antonia SJ, N Engl J Med 2017

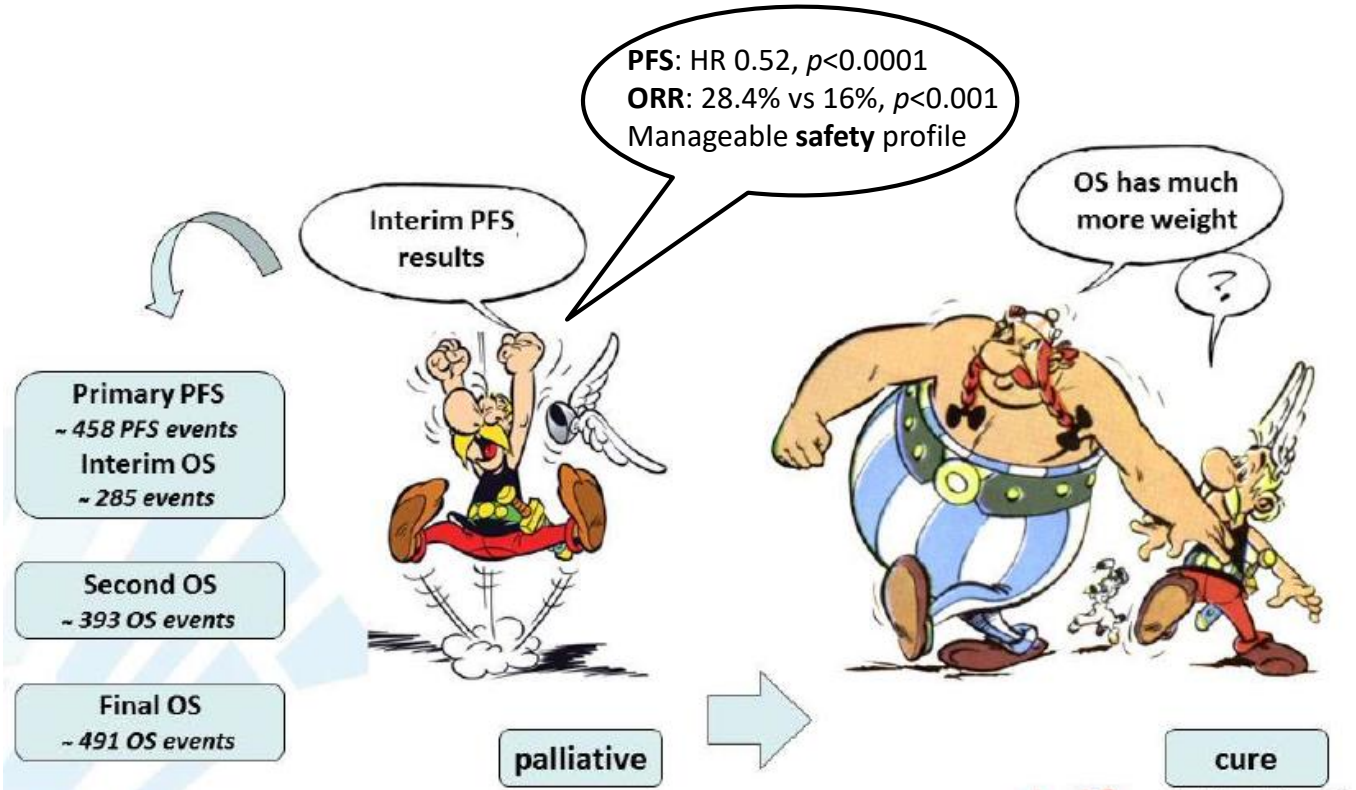
Durvalumab *vs.* placebo in unresectable stage III NSCLC



*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

Paz-Ares L, ESMO 2017

Durvalumab *vs.* placebo in unresectable stage III NSCLC

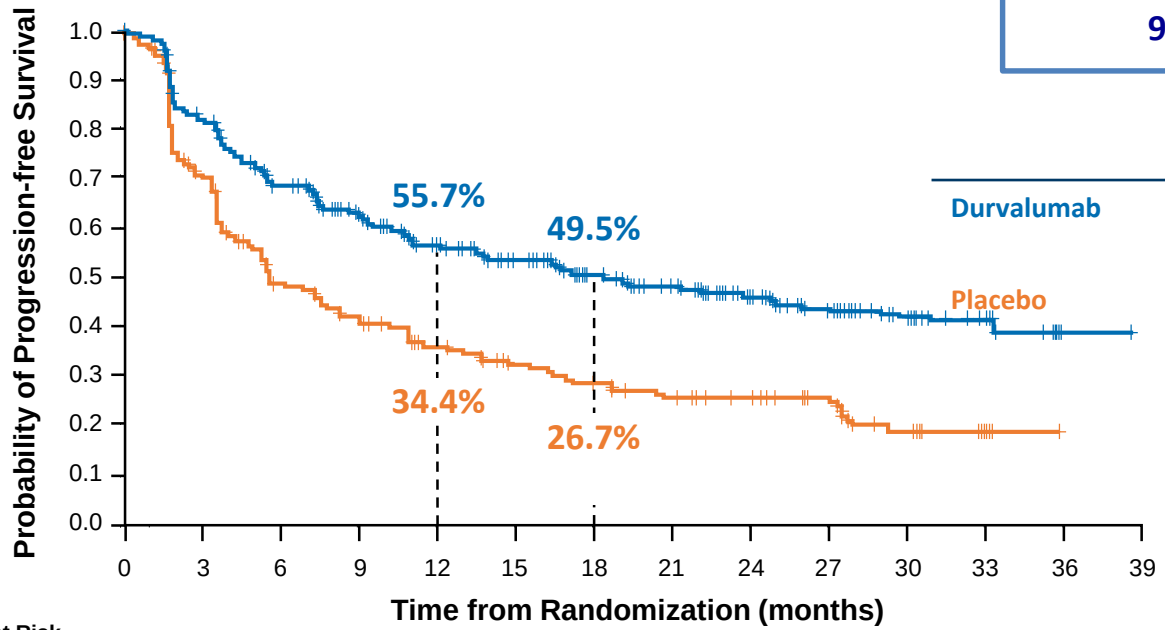


Vansteenkiste JF, ESMO 2017

Durvalumab *vs.* placebo in unresectable stage III NSCLC

Updated Progression-free Survival by BICR* (ITT)

PFS HR = 0.51
95% CI, 0.41–0.63†



	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)

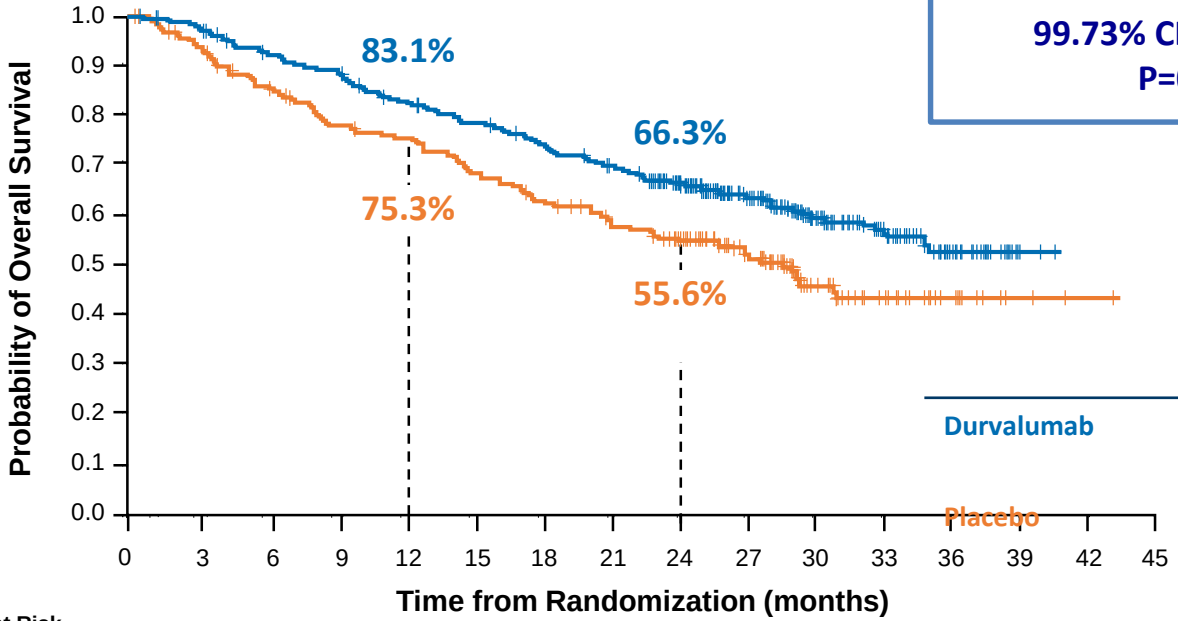
No. at Risk														
Durvalumab	476	377	302	268	213	188	163	143	116	83	43	23	1	0
Placebo	237	163	106	86	67	55	46	39	32	24	10	5	0	0

Scott A, WCLC 2018

Durvalumab *vs.* placebo in unresectable stage III NSCLC

Overall Survival* (ITT)

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



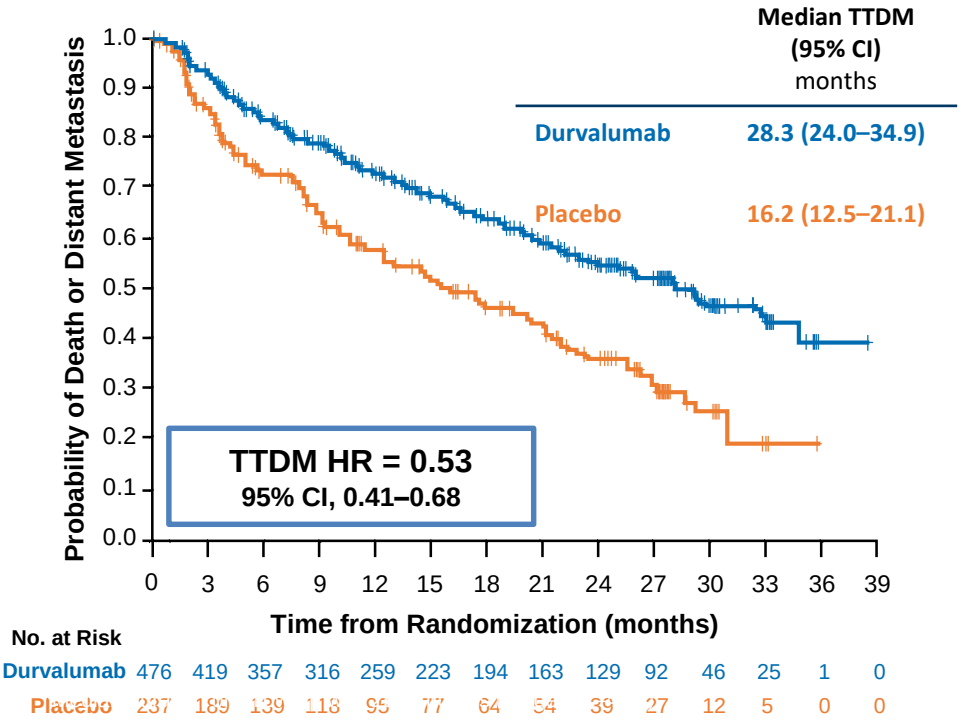
	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvalumab	183/476 (38.4)	NR (34.7–NR)
Placebo	116/237 (48.9)	28.7 (22.9–NR)

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

Scott A, WCLC 2018

Durvalumab *vs.* placebo in unresectable stage III NSCLC

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



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)

Scott A, WCLC 2018

Durvalumab *vs.* placebo in unresectable stage III NSCLC

Updated Safety Summary

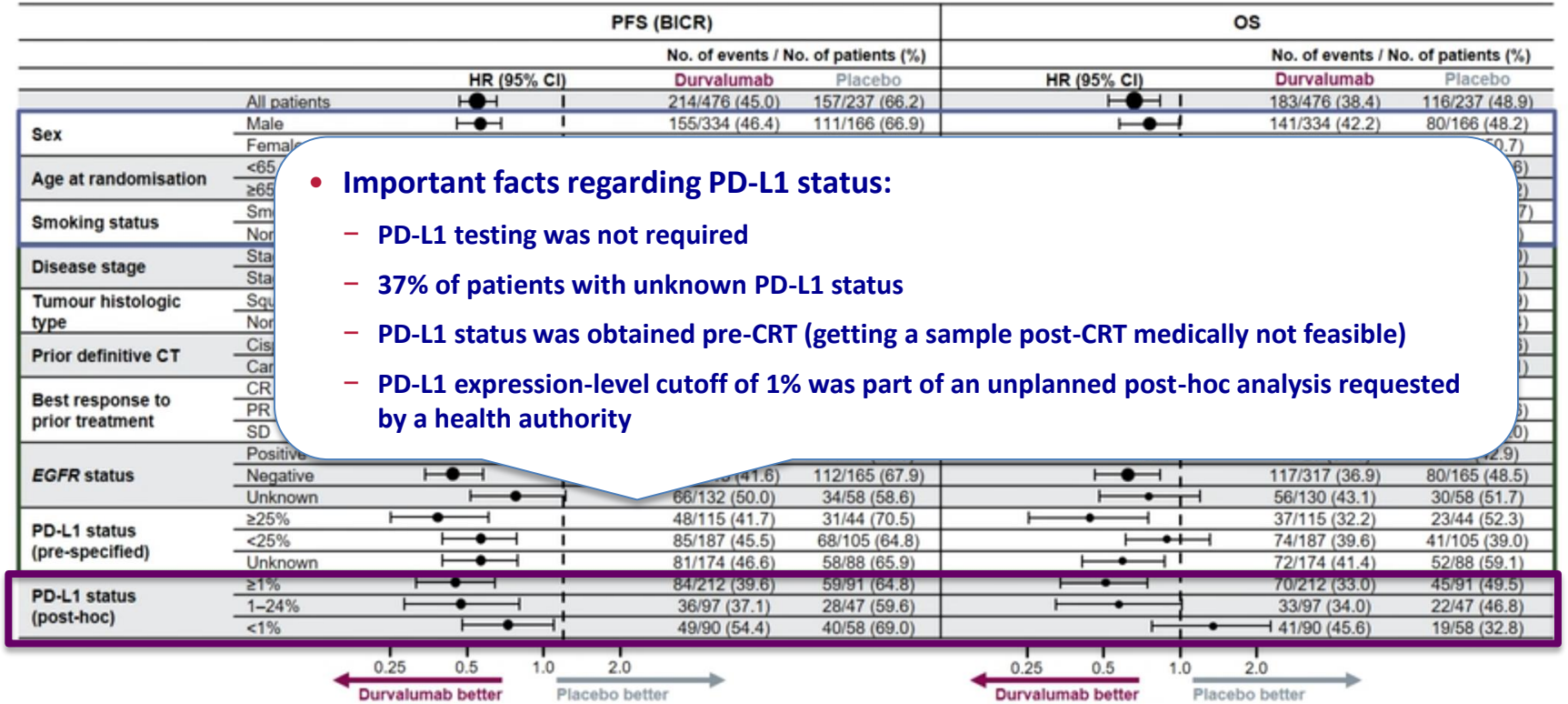
	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	145 (30.5)	61 (26.1)
Outcome of death	21 (4.4)	15 (6.4)
Leading to discontinuation	73 (15.4)	23 (9.8)
Serious AEs, n (%)	138 (29.1)	54 (23.1)
Any-grade pneumonitis/radiation pneumonitis, n (%)	161 (33.9)	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)

- **Similar safety profiles in different PD-L1 expression subgroups and according to time from radiation**

Scott A, WCLC 2018
Faivre-Finn C, ESMO 2018

Durvalumab *vs.* placebo in unresectable stage III NSCLC

Progression-free and Overall Survival by Subgroup (ITT)

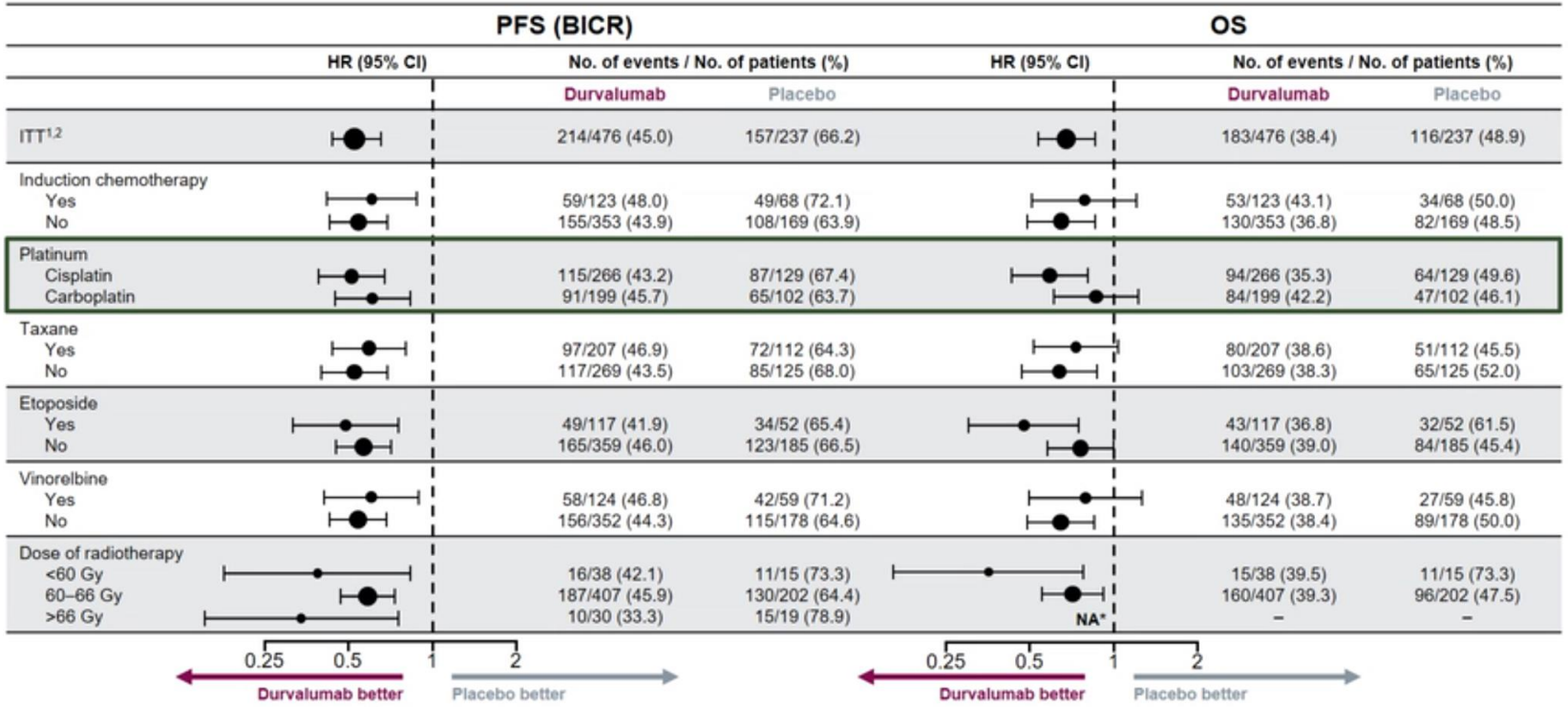


- **Important facts regarding PD-L1 status:**
  - **PD-L1 testing was not required**
  - **37% of patients with unknown PD-L1 status**
  - **PD-L1 status was obtained pre-CRT (getting a sample post-CRT medically not feasible)**
  - **PD-L1 expression-level cutoff of 1% was part of an unplanned post-hoc analysis requested by a health authority**

Faivre-Finn C, ESMO 2018

Durvalumab *vs.* placebo in unresectable stage III NSCLC

Impact of previous treatment



Faivre-Finn C, ESMO 2018

Durvalumab *vs.* placebo in unresectable stage III NSCLC

Impact of time to radiation

	PFS (BICR)			OS		
	HR	No. of events / No. of patients (%)		HR	No. of events / No. of patients (%)	
	(95% CI)	Durvalumab	Placebo	(95% CI)	Durvalumab	Placebo
ITT[1,2]		214/476 (45.0)	157/237 (66.2)		183/476 (38.4)	116/237 (48.9)
Time from last radiotherapy to randomisation						
<14 days		50/120 (41.7)	46/62 (74.2)		39/120 (32.5)	35/62 (56.5)
≥14 days		164/356 (46.1)	111/175 (63.4)		144/356 (40.4)	81/175 (46.3)

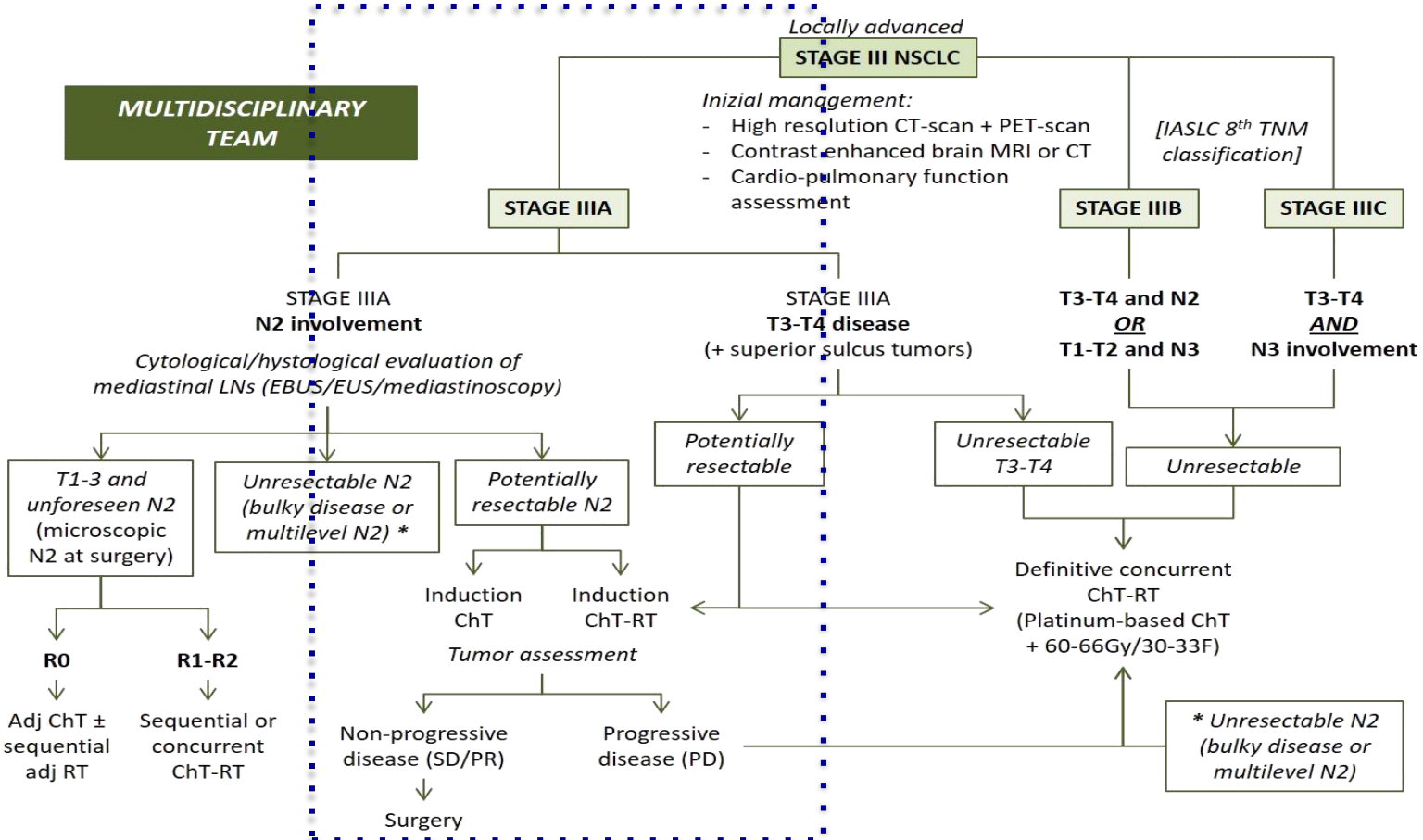
	TTDM (BICR)			ORR (BICR)	
	HR	No. of events / No. of patients (%)		%	
	(95% CI)	Durvalumab	Placebo	Durvalumab	Placebo
ITT[1]	0.52 (0.39, 0.69)	131/476 (27.5)	98/237 (41.4)	28.4	16.0
Time from last radiotherapy to randomisation					
<14 days	0.33 (0.20, 0.55)	30/120 (25.0)	34/62 (54.8)	34.2	16.4
≥14 days	0.70 (0.51, 0.95)	101/356 (28.4)	64/175 (36.6)	26.5	15.8

Faivre-Finn C, ESMO 2018

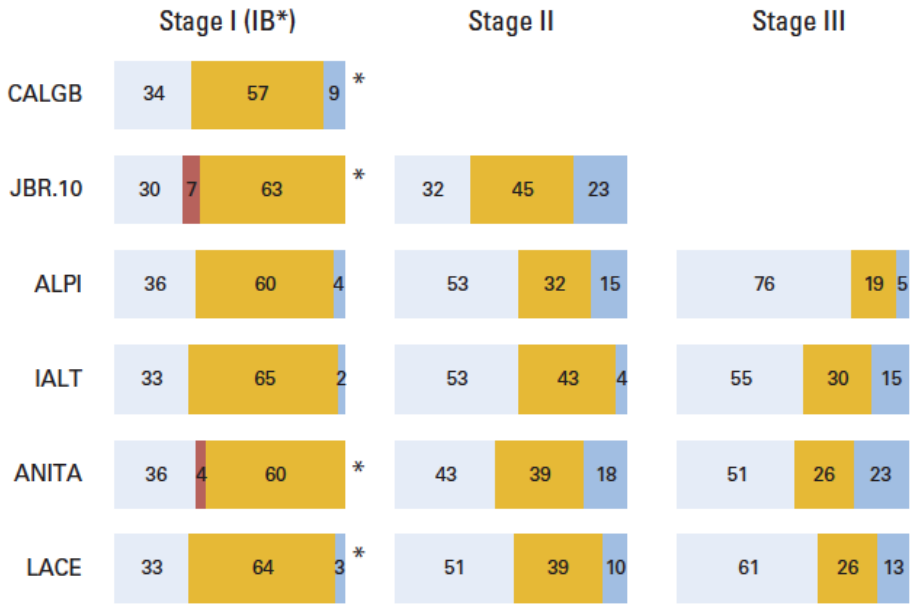
Critical issues

- **Randomization** of patients who experienced **clinical benefit after** cCTRT
- **Consolidation chemo** not allowed
- Chemoradiation **regimen** not predefined
- **Staging** procedures?
- **PD-L1 tested before** chemo-radiation

Stage III NSCLC: a heterogeneous picture



Early stage NSCLC: an unmet medical need



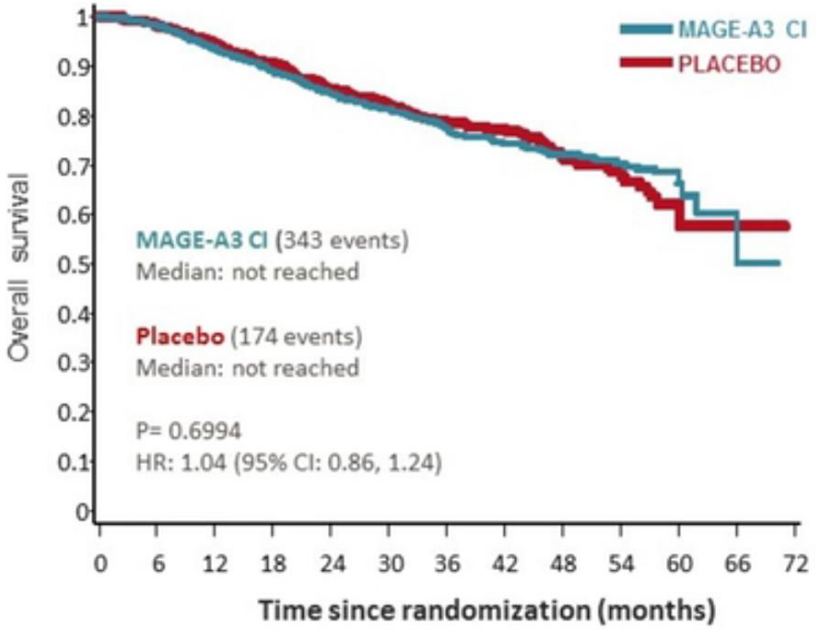
- Platinum-based adjuvant chemotherapy in NSCLC: **5 years survival benefit 4%** with or without adj. RT
- Most benefit achieved in stage IV not translated in stage III (chemotherapy or local treatment optimization)

Pisters KMW, JCO 2007; NSCLC Meta-analysis Collaborative Group, Lancet 2010; Vansteenkiste JF, ESMO 2017

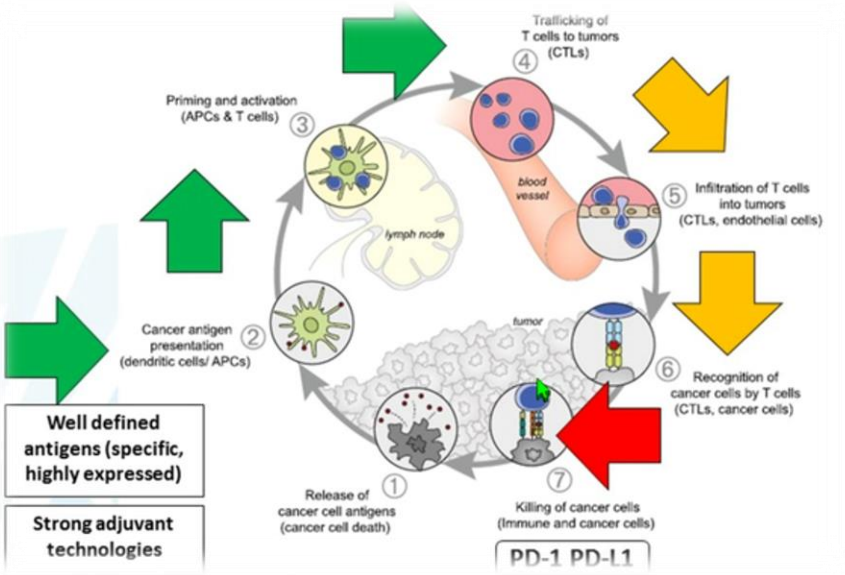
ICI in early stage: neoadjuvant *vs.* adjuvant setting

	adjuvant	neoadjuvant
Delay of surgery	+	-
Amount of tissue for translational studies	+	-
Pathological TNM	+	-
Earlier immune priming to tumor antigen and micrometastasis eradication	-	+
(Earlier) clinical benefit evaluation	-	+
Higher tumor mutation burden and neoantigen presentation	-	+
Post-treatment tissue availability for pCR assessment and additional translational studies	-	+
Compliance	-	+

MAGE-A3 *vs*. placebo as adjuvant treatment in early stage NSCLC



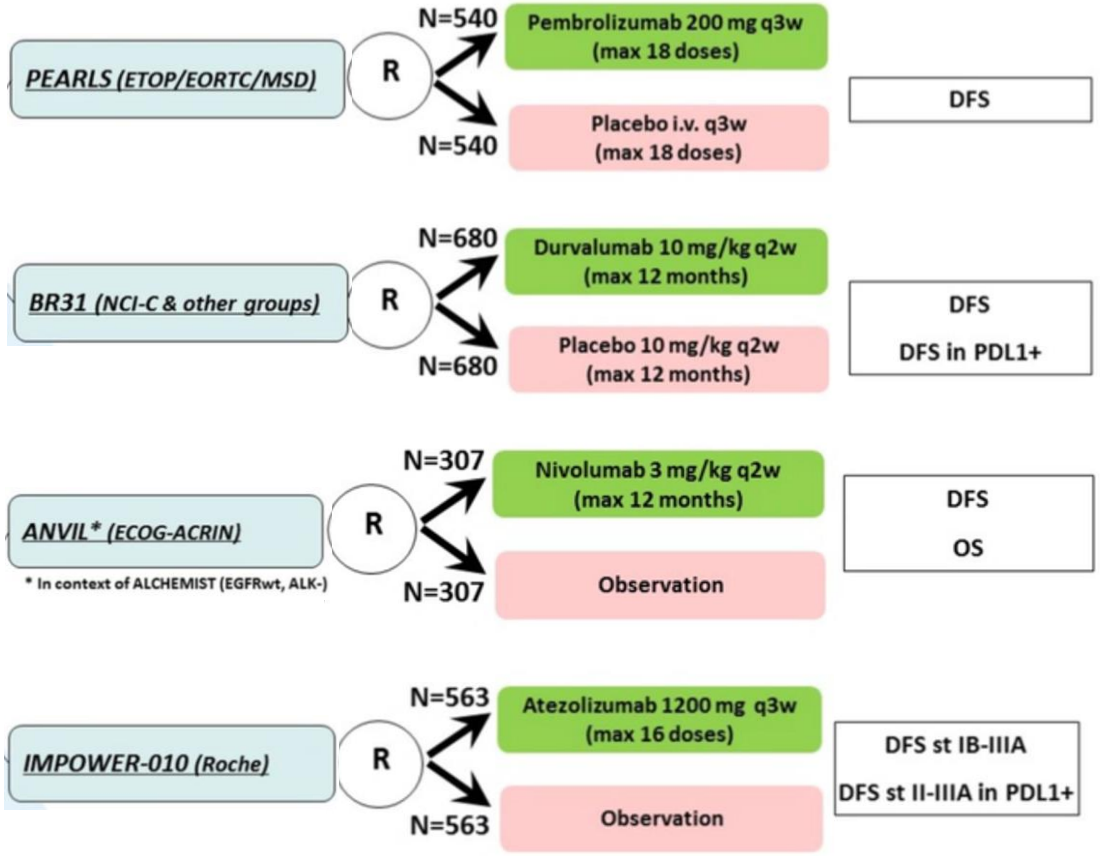
Vansteenkiste et al, Lancet Oncol 17:822-835, 2016



Vansteenkiste JP, Lancet Oncol 2016; Chen, Immunity 2013

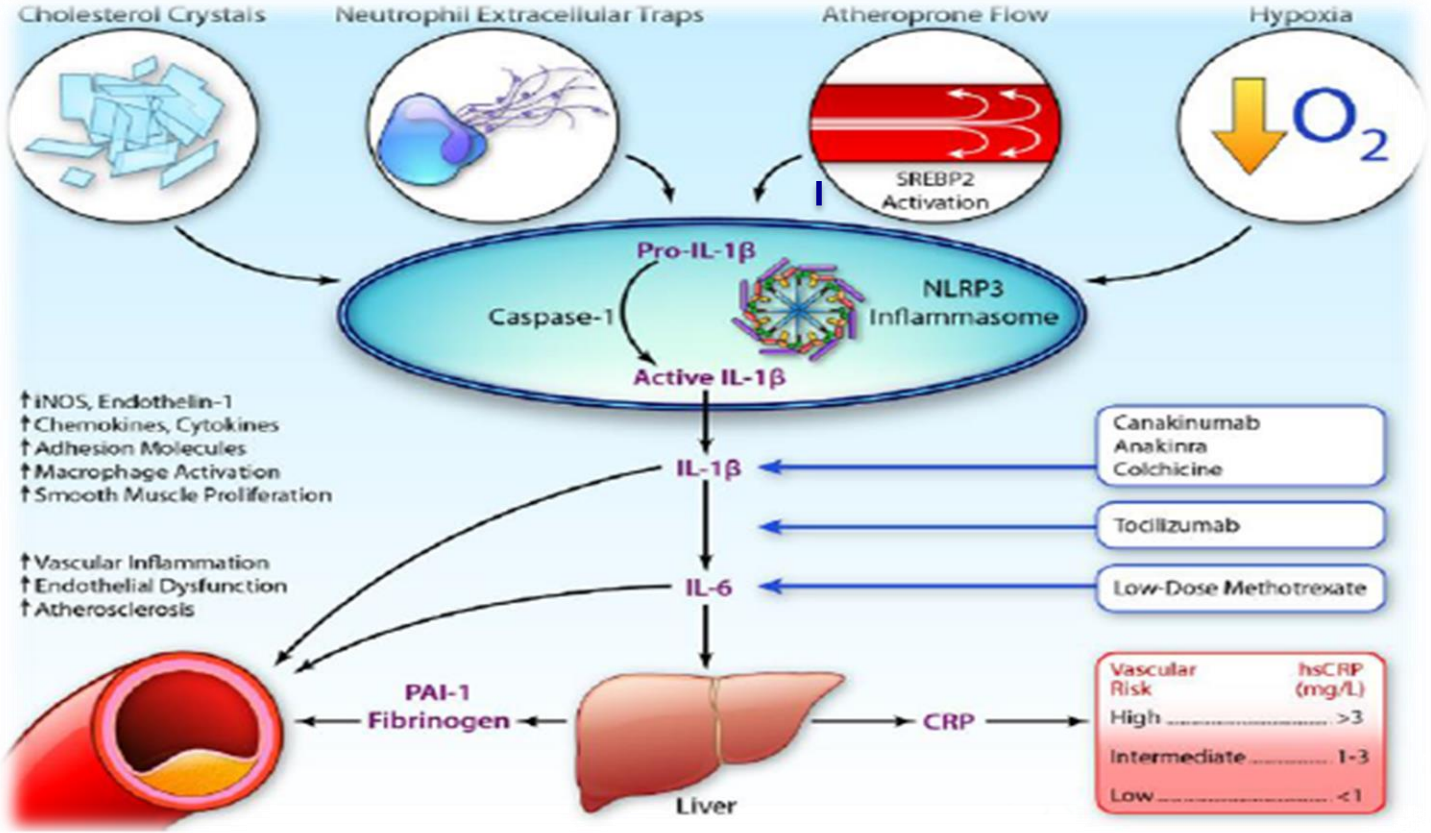
Phase III adjuvant IO trials

Post R0 surgery
Stage IB(>4cm), II, IIIA
ECOG PS 0-1
ACT as indicated



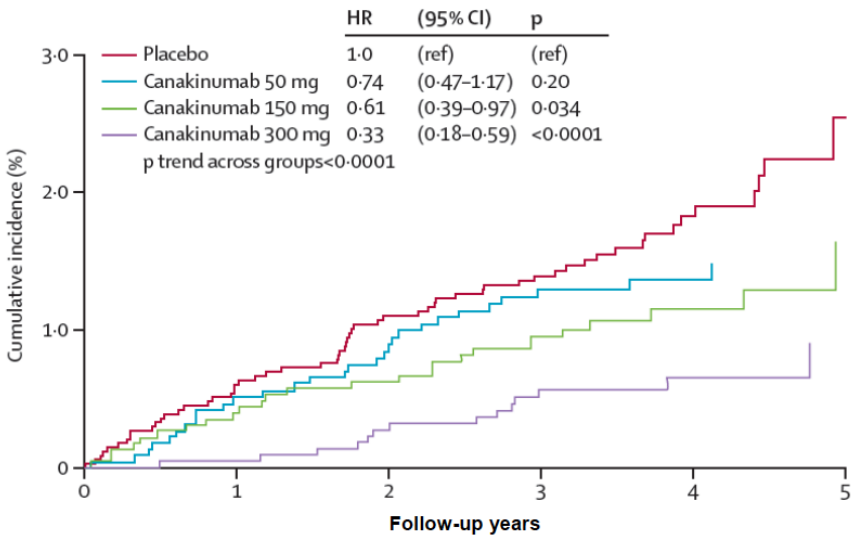
Modified from Vansteenkiste JP, ESMO 2018

New immuno-options in the adjuvant setting: the Canakinumab story

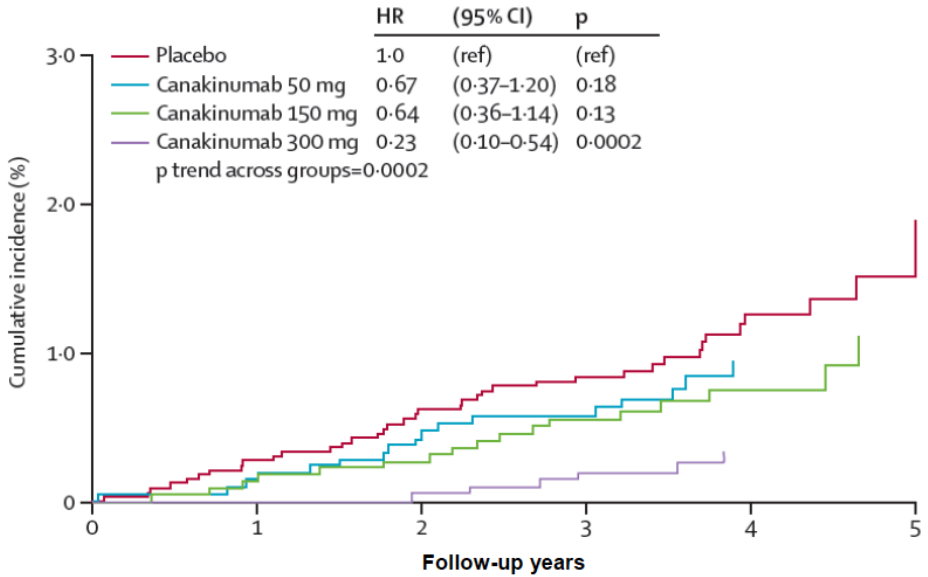


New immuno-options in the adjuvant setting: the Canakinumab story

LC incidence



LC mortality

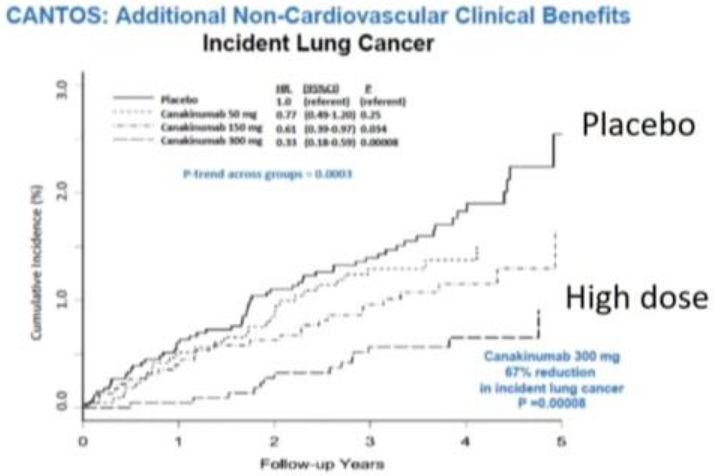


Ridker PM, Lancet 2107

From CANTOS to CANOPY trials

CANTOS trial

- Canakinumab (Novartis)
- Reduced lung cancer incidence by 67 % and death by 77 %.



Canakinumab phase 3 trials

Adjuvant NSCLC
After surgery, no mets, placebo control
1500 patients, recruitment ongoing
Completion 2021/22

First line (CANOPY-1)
Untreated locally advanced/metastatic
Combination Pembro/Platinum doublet
627 patients, start Dec 2018
Completion 2021/22

Second line metastatic (CANOPY-2)
Previously treated loc adv/metastatic
Combination Docetaxel
240 patients, start Dec 2018

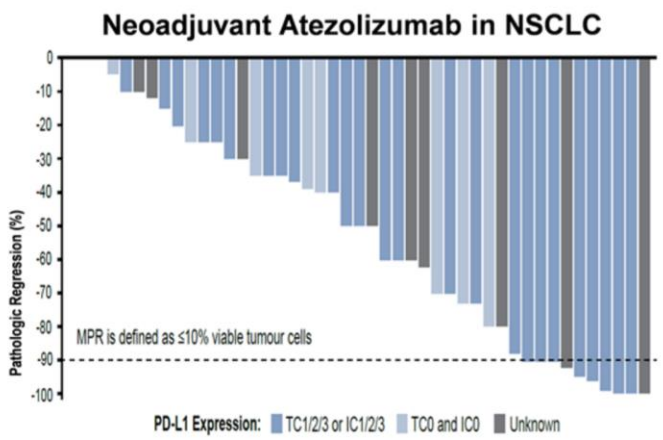
Ongoing trials with neoadjuvant anti-PD1/PD-L1 treatment in early stage NSCLC

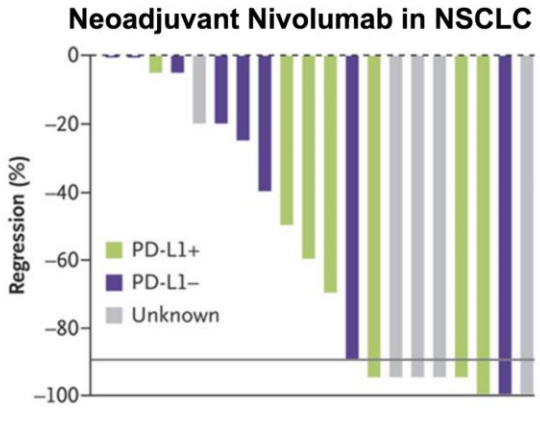
	Phase	Patients	N	Primay endpoint	Sponsor	Name	Register
Nivo	Ph2	IB-IIIA	30	Surg feasibility	Johns Hopkins		NCT02259621
Nivo *or* Nivo-Ipi	Ph2	IA-IIIA	66	MPR	MD Anderson + BMS	NEOSTAR	NCT 03158129
Nivo + ChT	Ph2	IIIA	46	PFS	SLCG + BMS		NCT 03081689
Pembrolizumab	Ph1	I-II	28	Safety	Sheba + MSD		NCT 02938624
Pembrolizumab	Ph1	IB-IIIA	32	Surg feasibilty	Duke + MSD	TOP 1501	NCT 02818920
Durva + ChT	Ph2	IIIA	68	EFS	SAKK		NCT 02572843
Durvalumab	Ph2	IB-II	81	R0 resection	IFCT	IONESCO	NCT 03030131
Atezolizumab	Ph2			Safety	Roche		NCT 02927301
Atezolizumab	Ph2	IA-IIIA	60	Surg feasibilty	Gustave-Roussy	PRINCEPS	NCT 02994576
Atezo + ChT	Ph2	IB-IIIA	30	MPR	Columbia Univ	MAC	NCT 02716038
Atezo	Ph2	IB-IIIA	180	MPR	Genentech	LCMC3	NCT 02927301

Vansteenkiste JP, ESMO 2018

Anti PD1/PD-L1 in the neoadjuvant setting

Neoadjuvant anti-PD1/PD-L1 blockade is safe and active in resectable NSCLC patients

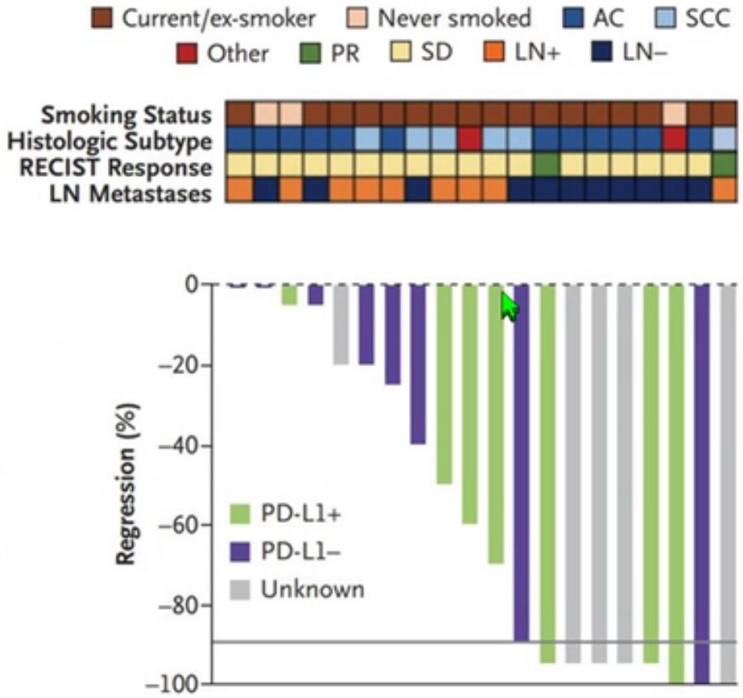


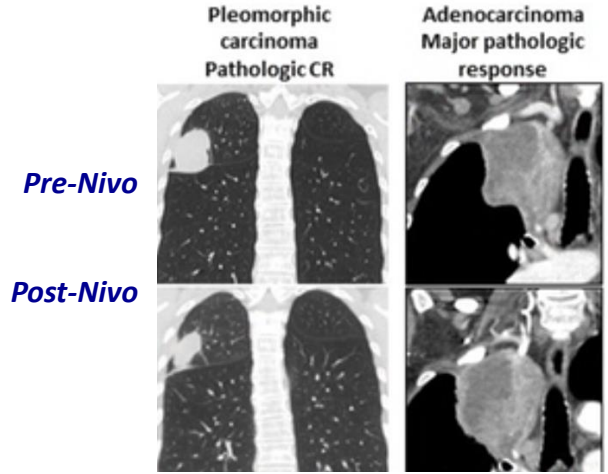


- No delay of surgery (*surgical feasibility*)
- No new AEs, no TR-AEs leading to post-operative mortality

Cascone, ESMO 2018

Discordance between MPR and RECIST response

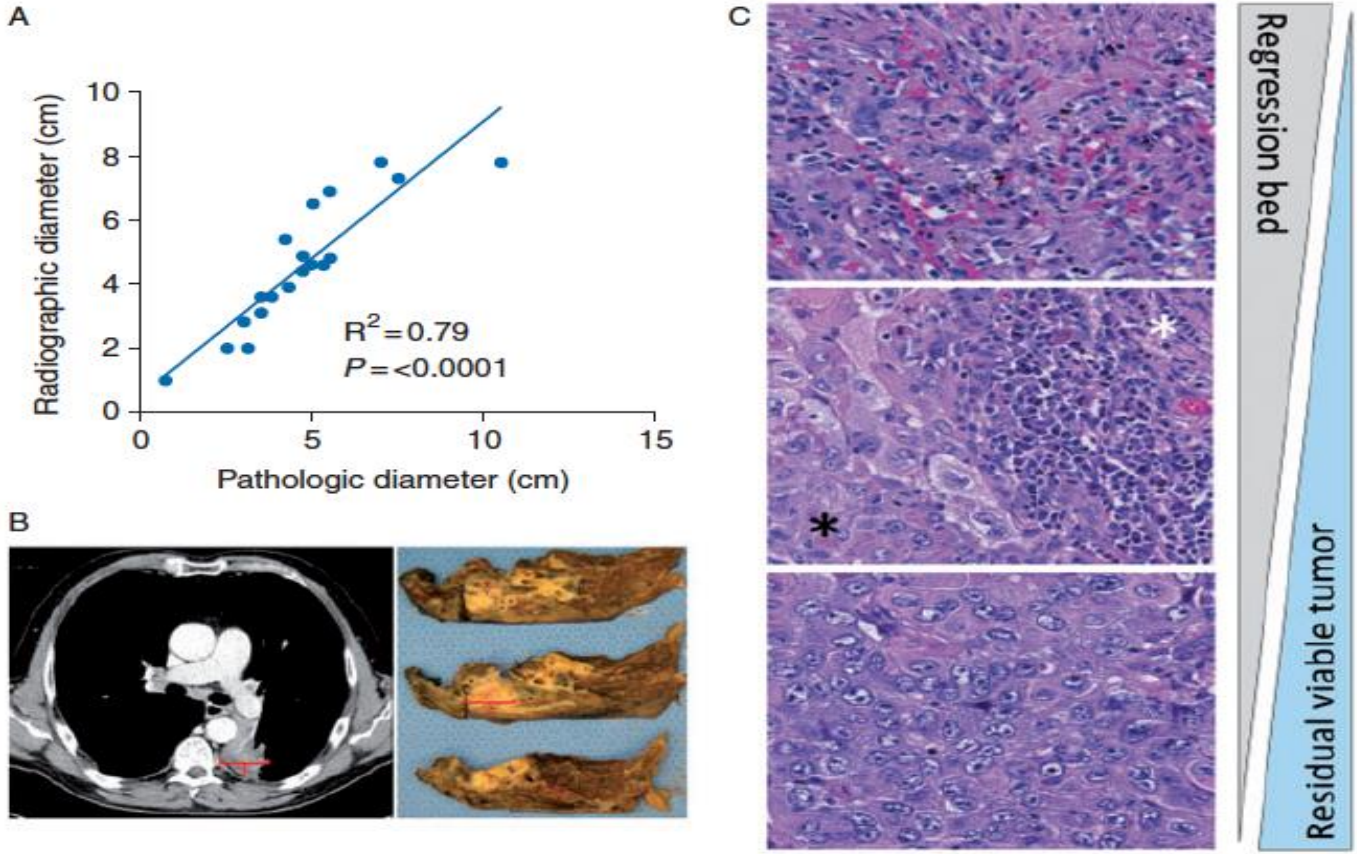




RECIST*	N(%)
PR	2 (10%)
SD	18 (85%)
PD	1 (5%)

Forde P, NEJM 2018

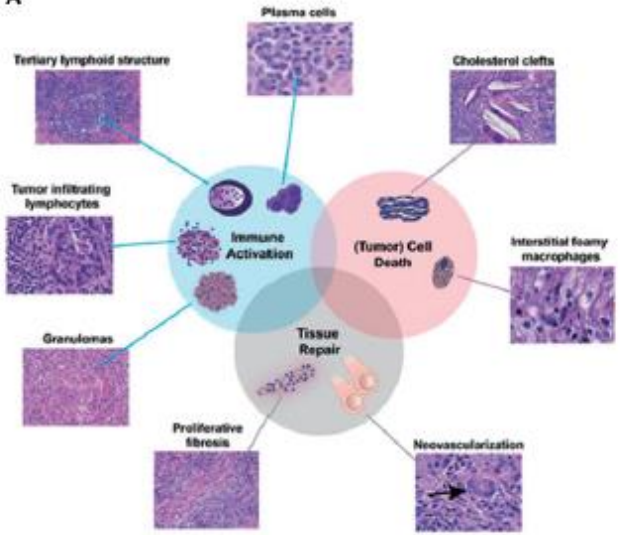
Immune-related pathologic response criteria (irPRC)



Cottrell TR, Ann Oncol 2018

Immune-related pathologic response criteria (irPRC)

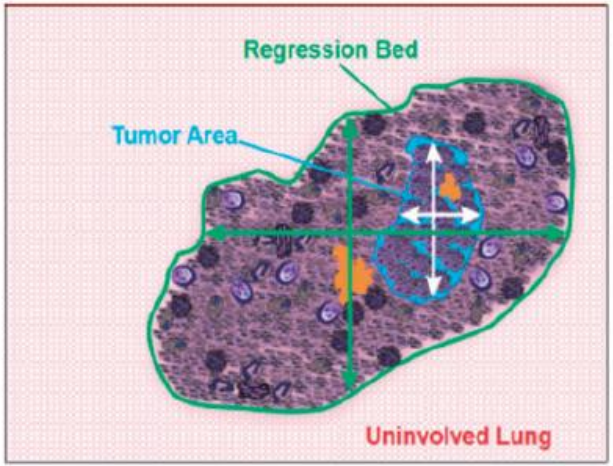
A



B

Feature, *n* (%)[a]	cMPR (*n* = 9)	cNR (*n* = 4)	*P* value[b]
Fibrosis			
% Fibrosis, Median (range)	75 (40-96.5)	0 (0-0)	2.2e-05[c]
Proliferative Fibrosis	7 (78)	0 (0)	0.021
Mature Fibrosis	1 (11)	0 (0)	1
Mixed Fibrosis	1 (11)	0 (0)	1
Neovascularization	9 (100)	0 (0)	0.0014
Cholesterol clefts	8 (89)	0 (0)	0.007
TIL score			
Low (1+)	0 (0)	3 (75)	0.014
High (3+)	7 (78)	0 (0)	0.021
Tertiary lymphoid structures	7 (78)	0 (0)	0.021
Dense plasma cells	6 (67)	0 (0)	0.07
Granulomas	5 (56)	0 (0)	0.1
Foamy macrophages			
Interstitial	4 (44)	0 (0)	0.23
Alveolar	8 (89)	2 (50)	0.2
Giant cells	7 (78)	1 (25)	0.22
Lymphoid aggregates	9 (100)	3 (75)	0.31
Necrosis	3 (33)	0 (0)	0.5
Hemosiderin	5 (56)	2 (50)	1
Neutrophils	3 (33)	1 (25)	1

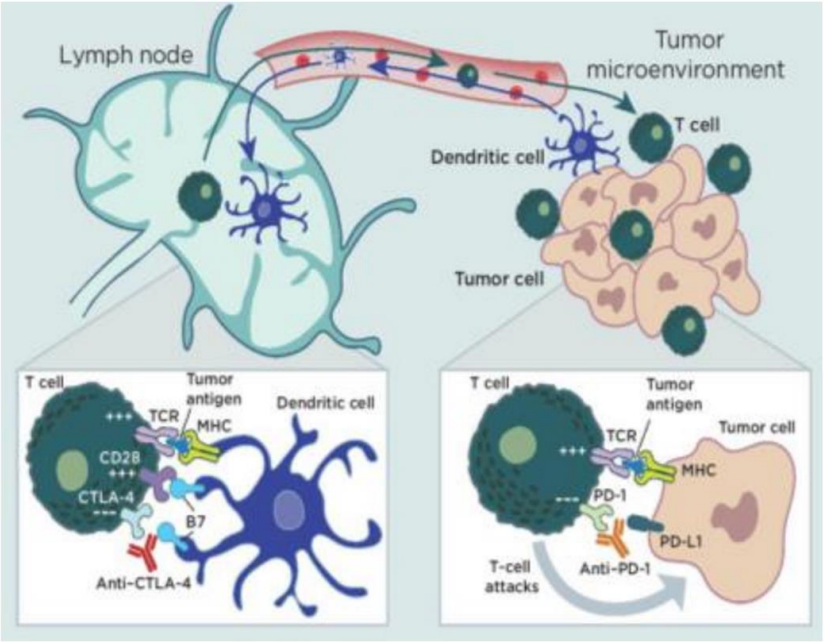
[a]All features are reported as *n* (%) of patients with the feature present, unless otherwise noted.
[b]Fisher's Exact test, unless otherwise noted.
[c]Student's t-test



$$\%irRVT = \frac{\text{Total area involved by tumor}}{\text{Total tumor bed area}} \times 100$$

Cottrell TR, Ann Oncol 2018

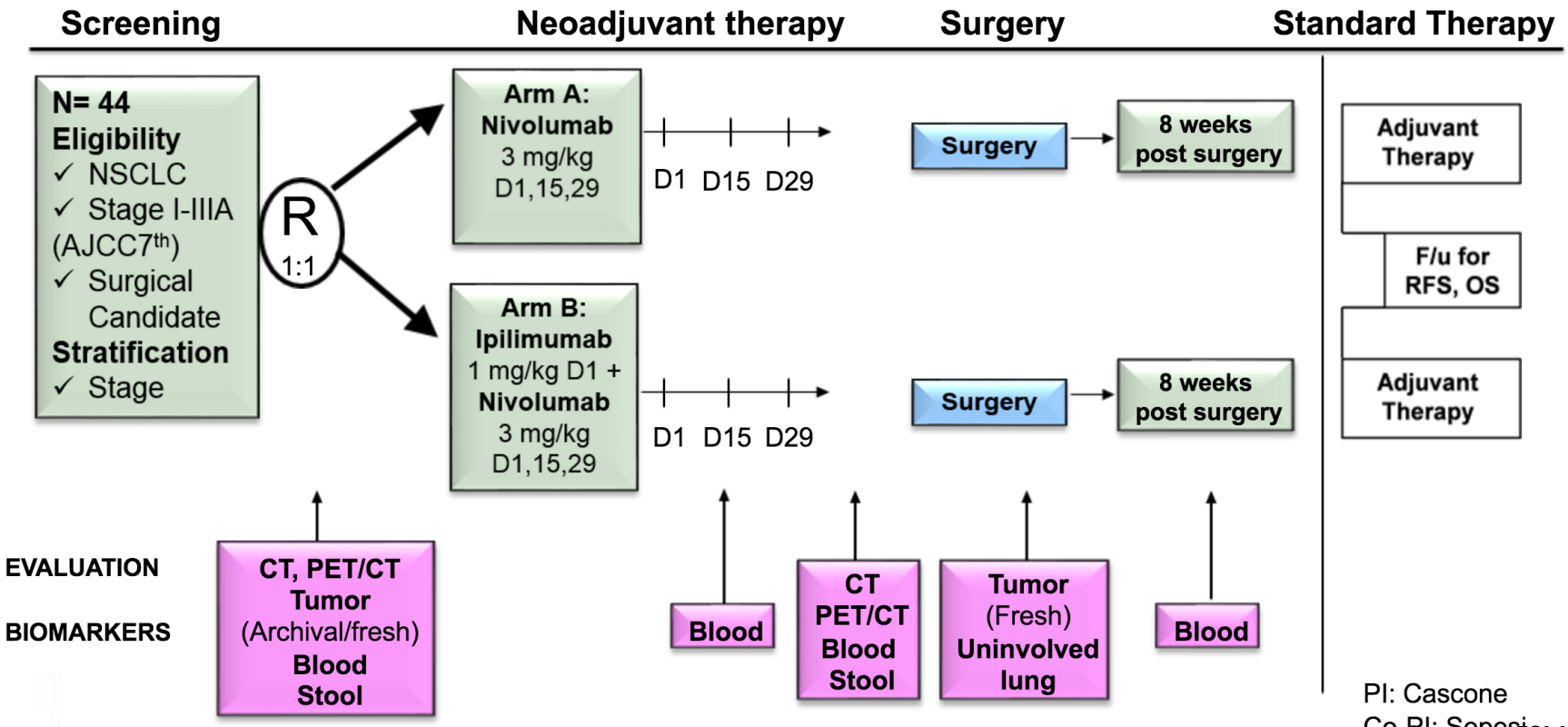
Rationale for anti-PD1 and anti-CTLA4 combination as neoadjuvant treatment in early stage NSCLC



- Nivolumab (anti-PD-1) primarily acts at the effector phase of the T cell response within the tumor microenvironment
- Ipilimumab (anti-CTLA-4) acts during the T-cell priming phase in the lymphoid tissues
- Combining anti-PD-1 and anti-CTLA-4 therapies may be additive and/or synergistic.

Carlino M, Clin Cancer Res 2016

Neoadjuvant anti-PD1 + anti-CTLA4: the phase II NEOSTAR study



PI: Cascone
Co-PI: Sepesi

Cascone, ESMO 2018

Neoadjuvant anti-PD1 + anti-CTLA4: the phase II NEOSTAR study

Major pathologic response (≤10% viable tumor cells)

Evaluable* (Resected)	n=26	N n=14	NI n=12
MPR + pCR	**8 (31%)**	**4 (28%)**	**4 (33%)**
0% viable tumor cells (pCR)	5 (19%)	2 (14%)	3 (25%)
1-10% viable tumor cells	3 (11%)	2 (14%)	1 (8%)

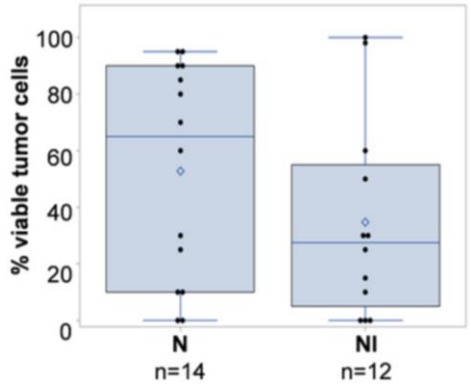
*5 no surgery (2 N, 3 NI)

Overall** Resected + unresectable	n=31	N n=16	NI n=15
MPR + pCR	**8 (26%)**	**4 (25%)**	**4 (27%)**
0% viable tumor cells (pCR)	5 (16%)	2 (13%)	3 (20%)
1-10% viable tumor cells	3 (10%)	2 (13%)	1 (7%)
Path response pending	5**	2	3

**5 pending (2 N, 3 NI)

Evaluable (resected)	N n=14*	NI n=12**	p-value
	Median (min, max)	Median (min, max)	
% viable tumor cells	65 (0, 95)	27.5 (0, 100)	0.364

* 2 no surgery;1 awaiting surgery; 1 on therapy
** 3 no surgery; 1 awaiting surgery; 2 on therapy



MUNICH 2018 ESMO congress

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Neoadjuvant anti-PD1 + anti-CTLA4: the phase II NEOSTAR study

Radiografic responses

Evaluable*	n=32*	N n=16	NI n=16
Response (RECIST)	n (%)	n (%)	n (%)
CR	1 (3)	0 (0)	1 (6)
PR	6 (19)	5 (31)	1 (6)
SD	19 (59)	8 (50)	11 (69)
PD	6 (19)	3 (19)	3 (19)
Not yet evaluable	4	2*	2**

* 1 pending, 1 on therapy; ** 2 on therapy

ORR (CR+PR): 22%(7/32)

ORR by Arm:
N: 31% (5/16)
NI: 12% (2/16)

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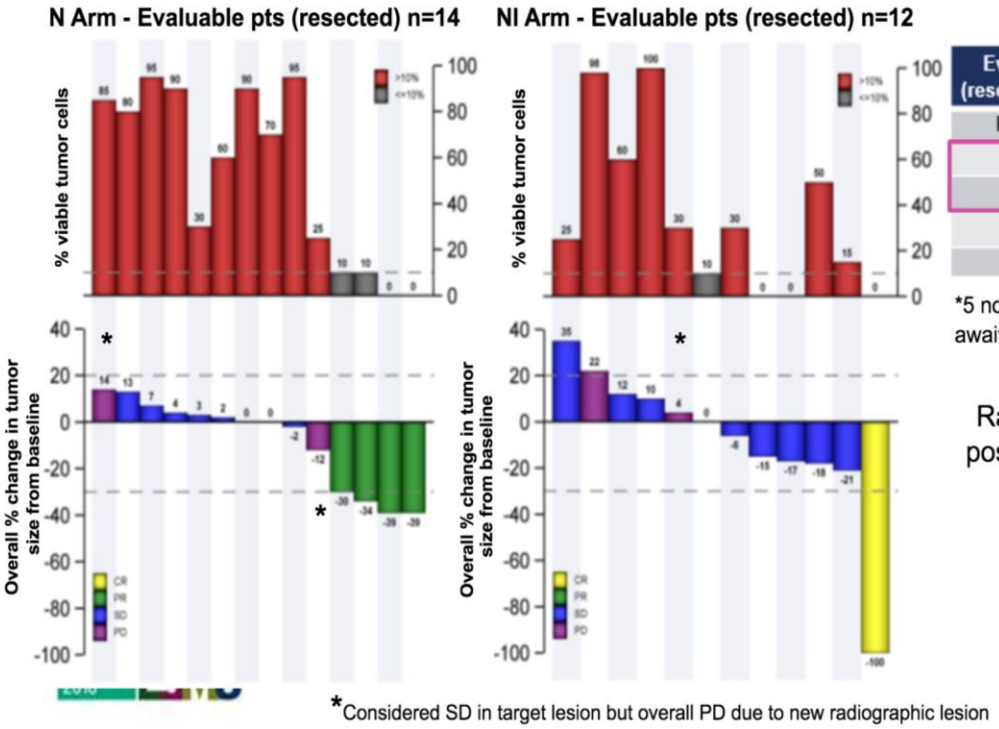
Association with MPR



Evaluable* (resected) n=26	No MPR* n=18	MPR n=8	p-value
RECIST	n (%)	n (%)	
CR	0 (0)	1 (13)	0.002
PR	0 (0)	4 (50)	
SD	14 (78)	3 (37)	
PD	4 (22)	0 (0)	

*5 no surgery; 5 path responses N/A: 2 awaiting surgery, 3 on therapy

Radiographic responses were positively associated with major pathological responses (p<0.002)

*Considered SD in target lesion but overall PD due to new radiographic lesion

Cascone, ESMO 2018

Neoadjuvant anti-PD1 + anti-CTLA4: the phase II NEOSTAR study

Treatment-related adverse events (TRAEs) and surgical complications

	N		NI		
Grade 1-2 TRAE*	n	%	n	%	Total N
Increased Alanine Aminotransferase	1	1.7	1	1.7	2
Chills	0	0	2	3.4	2
Cough	1	1.7	5	8.5	6
Diarrhea	0	0	3	5.1	3
Dyspnea	1	1.7	1	1.7	2
Fatigue	5	8.5	7	11.9	12
Hemoptysis	1	1.7	1	1.7	2
Hyperthyroidism	0	0	3	5.1	3
Hypomagnesemia	2	3.4	0	0	2
Hypothyroidism	1	1.7	1	1.7	2
Myalgia	1	1.7	1	1.7	2
Nausea	0	0	6	10.2	6
Pruritus	0	0	2	3.4	2
Rash acneiform	1	1.7	8	13.6	9
Sinus tachycardia	1	1.7	1	1.7	2
Increased WBC	1	1.7	1	1.7	2
Total	16	27.1	43	72.9	59

*Total reported G1-2 TRAEs include toxicities that occurred in >1 pt

	N		NI		
Grade 3-5 TRAE	n	%	n	%	Total N
Hypoxia	1 (G3)	33.3	0	0	1
Pneumonia**	1 (G3)	33.3	0	0	1
Pneumonitis**	1 (G5)	33.3	0	0	1
Total	3	100	0	0	3

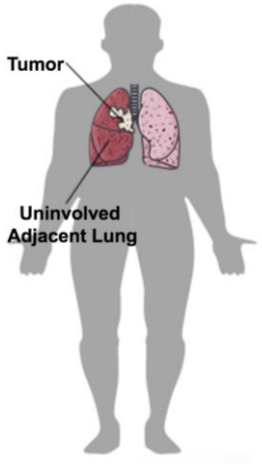
**Pneumonia and pneumonitis occurred in the same pt.

Surgical complication (n=26 resected)	N (Arm)
Broncho-pleural Fistula (BPF)**	1 (N)
Air Leak > 5 days	1 (NI)
Pneumonia**	1 (N)
Pneumonitis**	1 (N)

**BPF, pneumonia and pneumonitis occurred in the same pt.

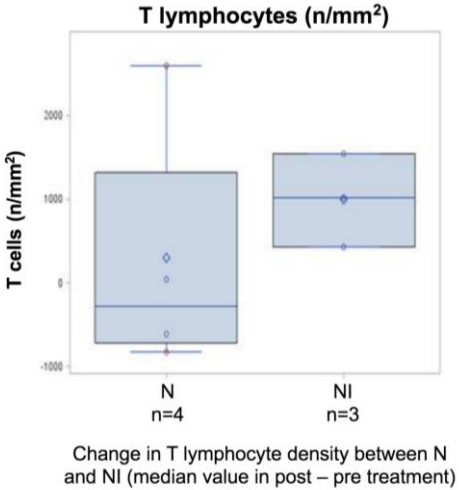
Cascone, ESMO 2018

Neoadjuvant anti-PD1 + anti-CTLA4: the phase II NEOSTAR study

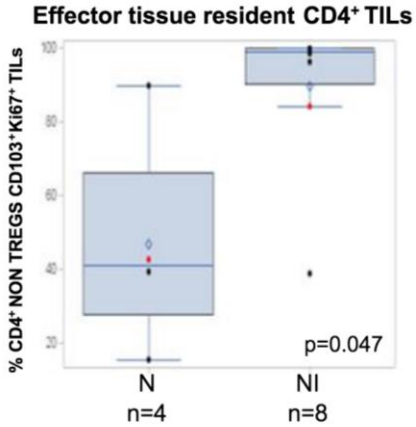


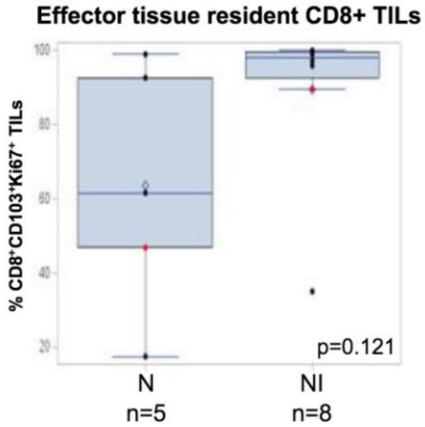
- **Neoadjuvant N and NI increase proliferative and activated effector TILs vs. untreated lung tumors**

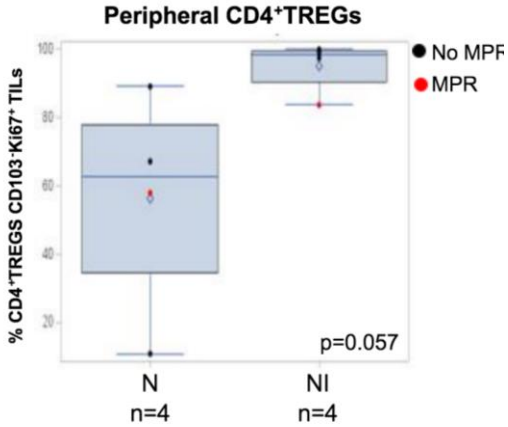
T-cell infiltration



Different T-cell subsets proliferation

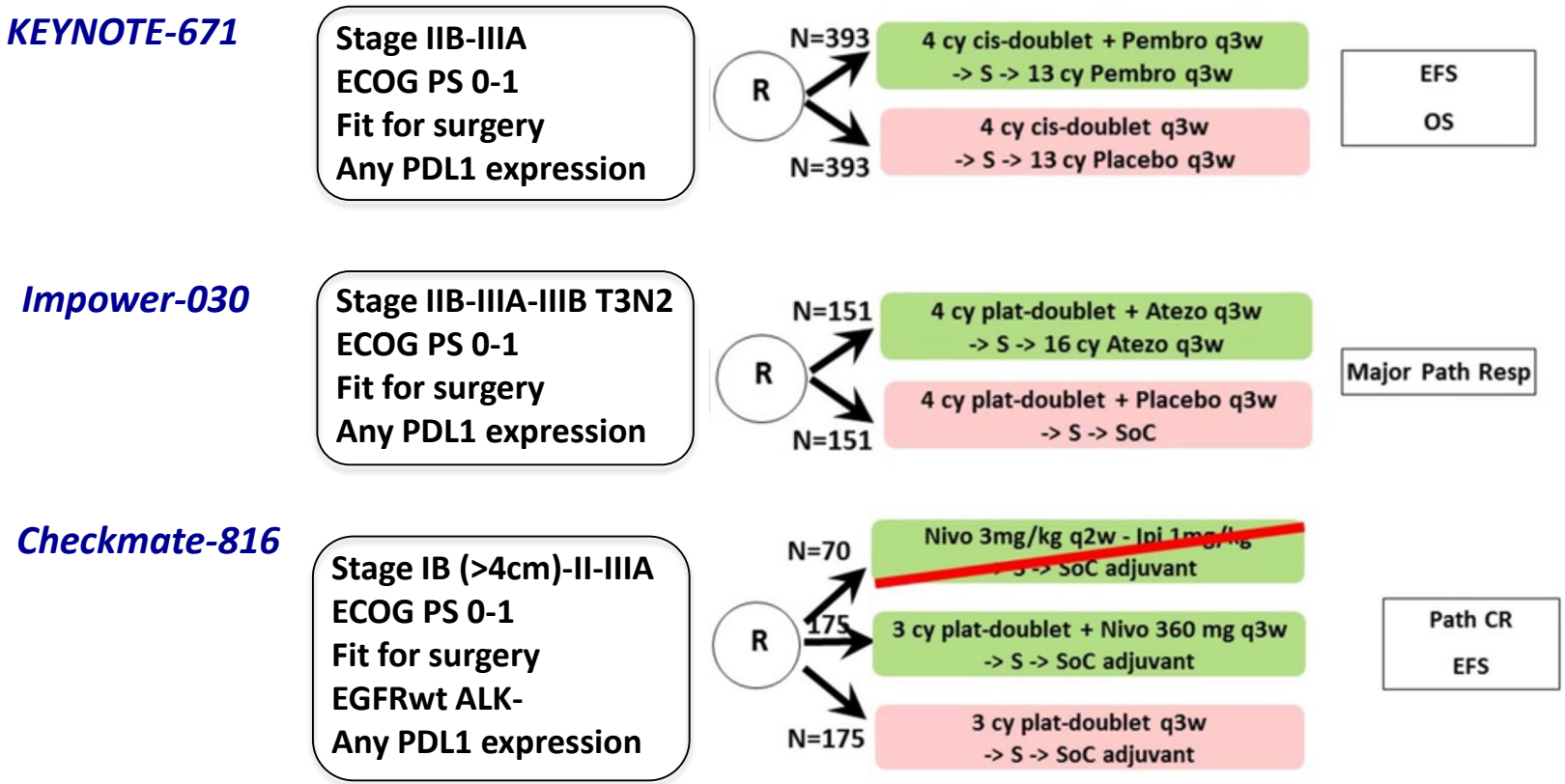






Cascone, ESMO 2018

Phase III neoadjuvant CT+IO trials



Modified from Vansteenkiste JP, ESMO 2018

Take home messages

- Although with some method limitation of the PACIFIC phase III trial, **durvalumab as consolidation after cCTRT** might be considered as new standard of care in unresectable stage III NSCLC

- **Adjuvant IO**: **long time** results, difficult assessment of clinical benefit, lower compliance

- **Neoadjuvant IO**: the **ideal setting** for early **micrometastasis eradication**, clinical benefit evaluation and **translational pre-post** surgery studies.

- **CT+IO**: a promising future

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