IMMUNE CHECK POINT INHIBITORS IN NSCLC & THEIR TOXICITY

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Immune check point inhibitors

- Introduction
- Role in previously Rxed NSCLC
- Role as first line agent
- Role as combination Rx
- PDL 1 testing
- Toxicity & Management

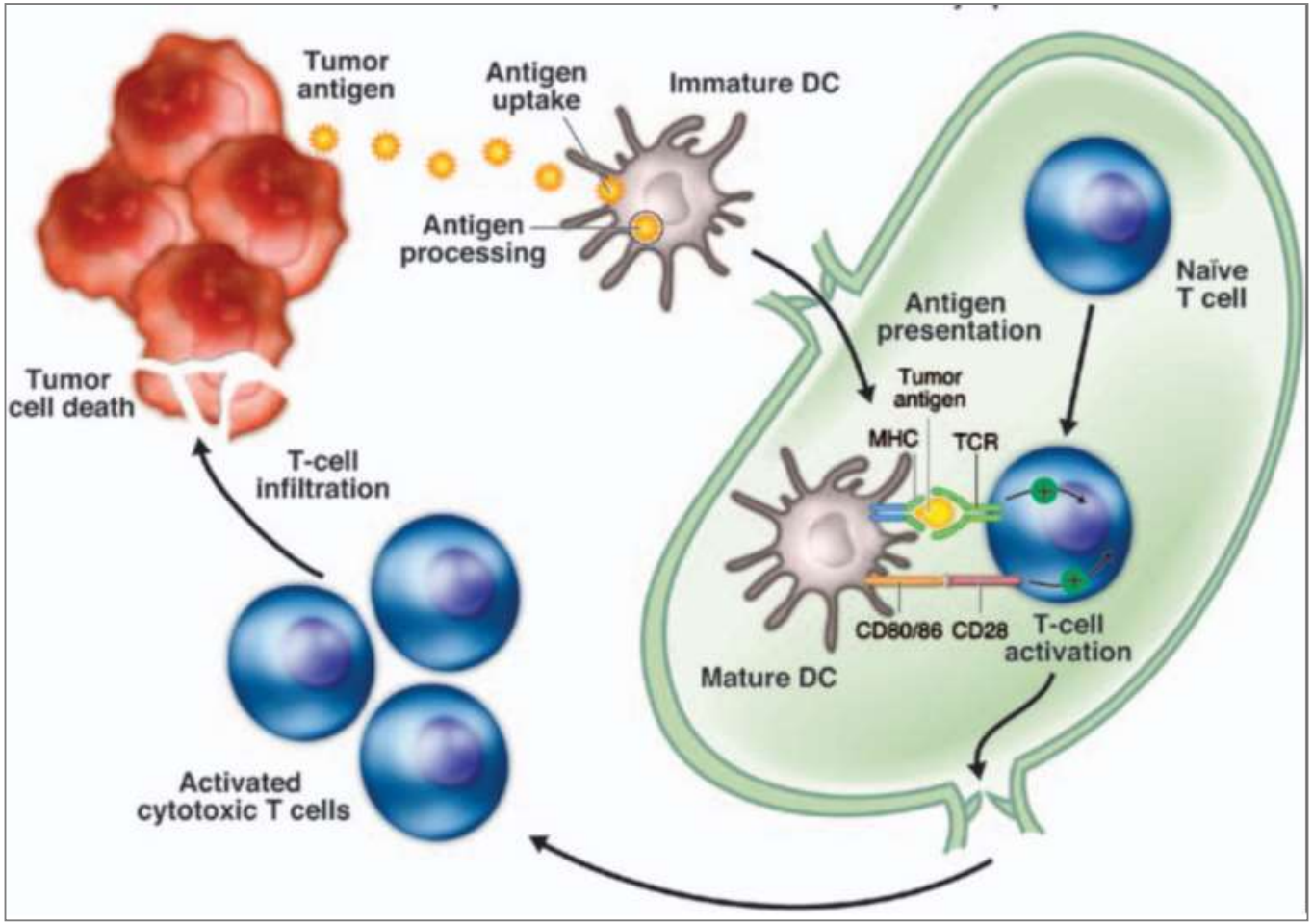
INTRODUCTION

Anti cancer immunity

- Anti tumour immune response – innate and adaptive
- Adaptive immunity offers durable and robust anti cancer immune response
- Immune system is capable of not only inhibiting but also promoting tumor growth through either the selection of tumor cells that are better able to survive in an immunocompetent host

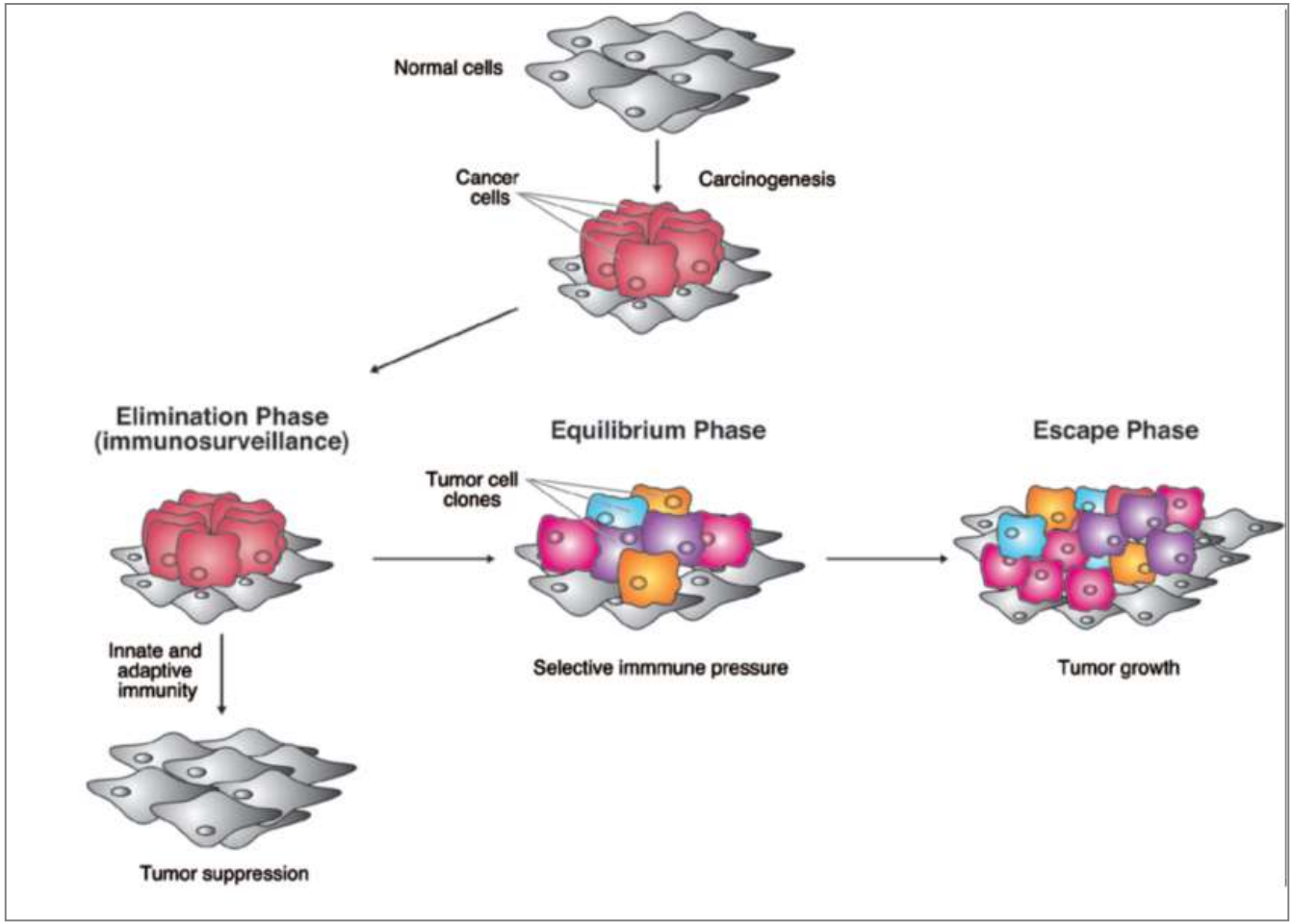
David P. Carbone et al, J Thorac Oncol. 2015

Anti cancer immunity



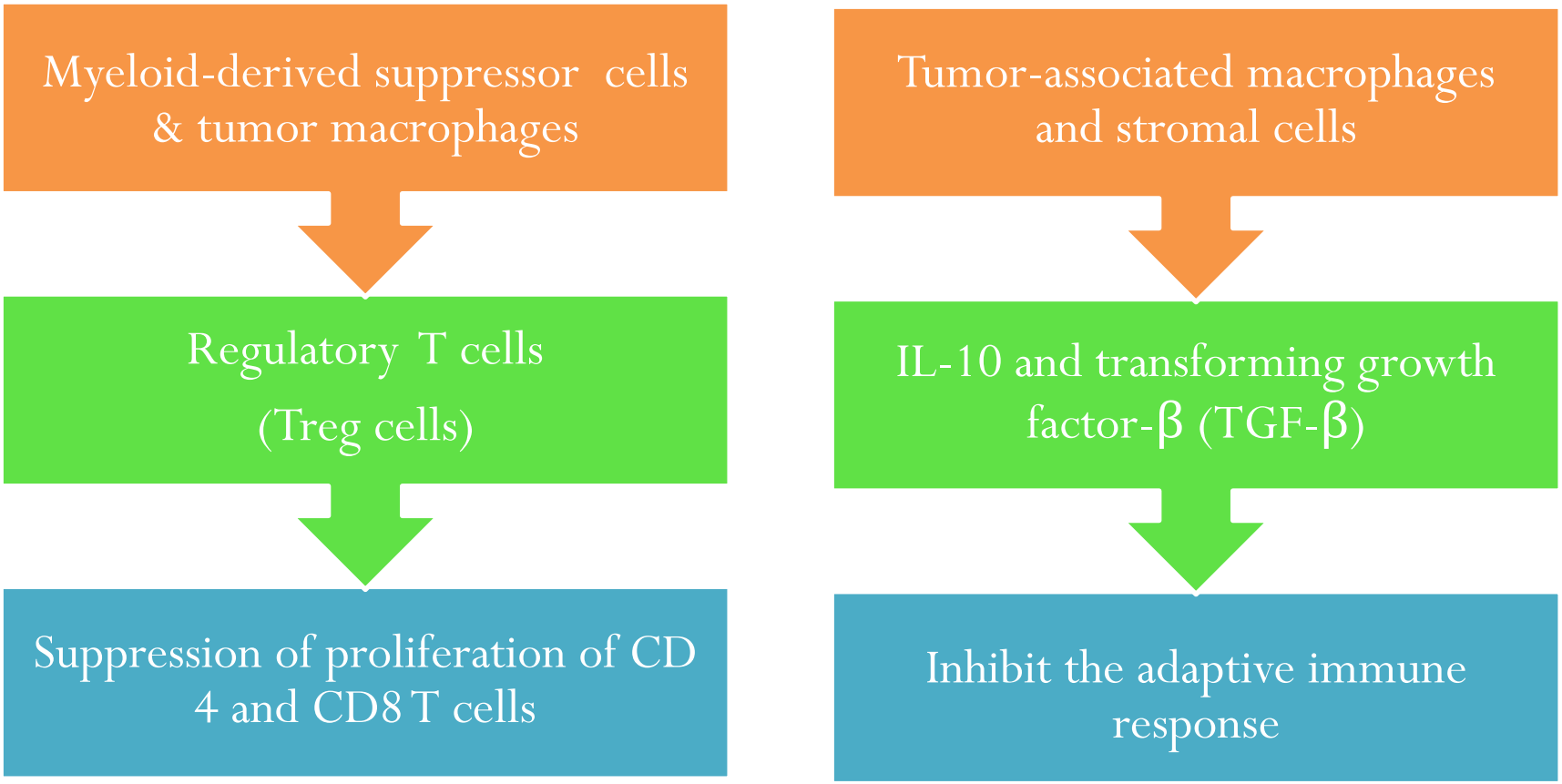
David P. Carbone et al, J Thorac Oncol. 2015

Cancer immuno editing



David P. Carbone et al, J Thorac Oncol. 2015

Escape of immunity



David P. Carbone et al, J Thorac Oncol. 2015

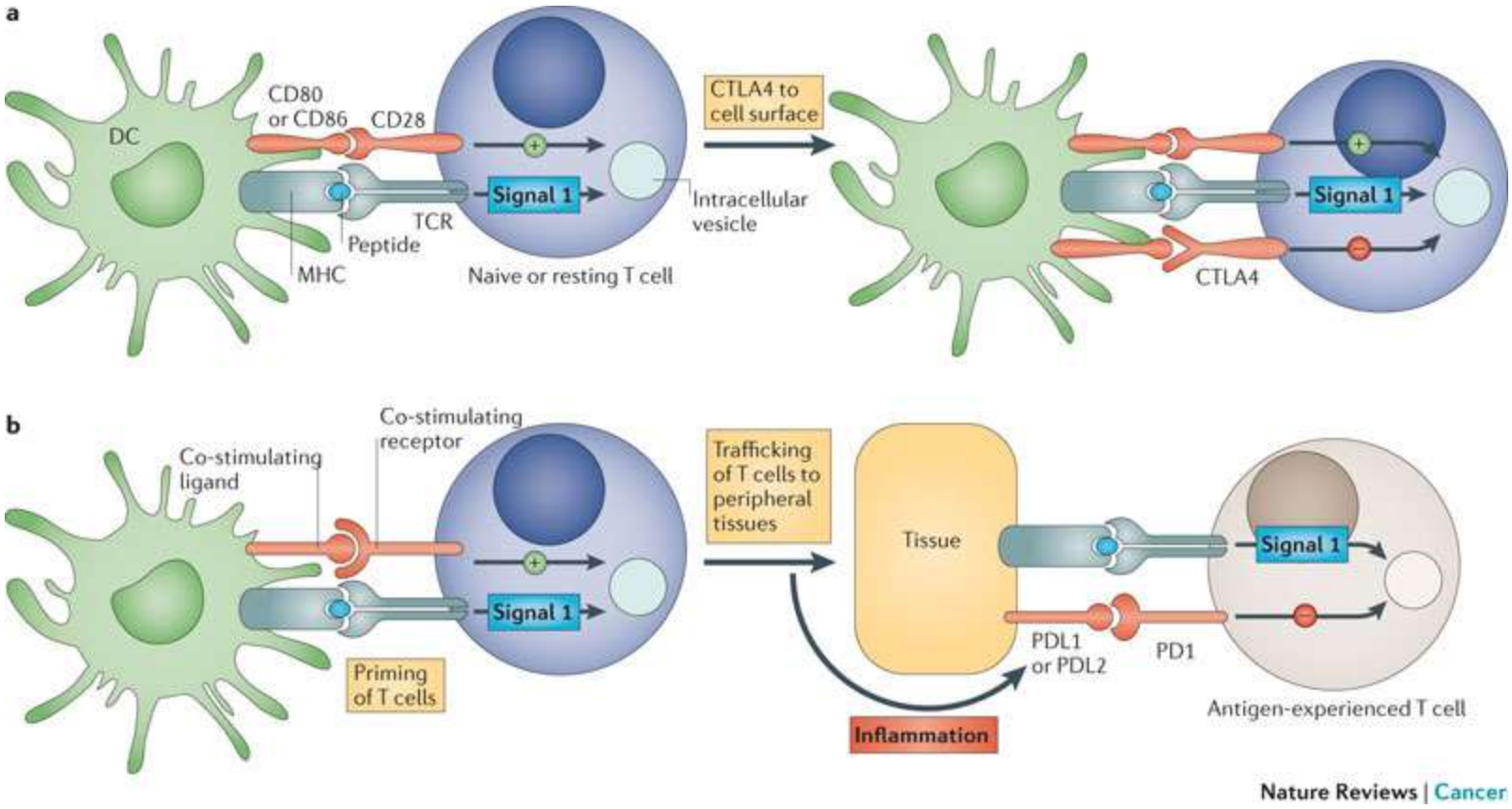
Immune check points

- Immune checkpoints - variety of inhibitory pathways that are crucial in regulating the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage

- However, these immune checkpoint pathways can be co-opted by cancer cells, thus circumventing immune destruction

Nat Rev Cancer 2012;12:252–264

Immune check points



Nat Rev Cancer 2012;12:252–264

Immunotherapy

- Aid in the recognition of cancer as foreign by the immune system
- Stimulate immune responsiveness
- Relieve inhibition of the immune system that allows tolerance of tumor growth

Immune check point inhibitors

- Antibodies to PD – 1 (IgG4)
  - Nivolumab (BMS-936558; MDX-1106)
    Pembrolizumab (MK-3475)
- Antibodies to PD - L1 (IgG1)
  - Atezolizumab (MPDL3280A)
  - Durvalumab
  - BMS-936559
- Antibodies to CTLA 4
  - Ipilimumab
  - Tremelimumab

IN PREVIOUSLY TREATED NSCLC

NIVOLUMAB

Nivolumab

- 296 patients with melanoma, NSCLC, prostate cancer, renal cancer, or colorectal cancer were treated with doses of 1 mg/kg, 3 mg/kg, or 10 mg/kg every 2 weeks for up to 96 weeks
- 76 pts of NSCLC at 24 weeks
- ORR -18%
- SD -7%
- PFS at 24 weeks - 26%
- Better OR was seen with dose of 3 mg/kg
- Grade 3 /4 AEs – 14%

Topalian SL, N Eng J Med 2012, 366:2443-54

Checkmate 017 & 057

- Stage IIIB & IV NSCLC
- Progression during or after initial platinum based CT
- ECOG 0 & 1
- Stable and treated brain metastases
- Regardless of PDL 1 expression
- Excluded are patients with autoimmune disease, symptomatic ILD, on systemic immunosuppression, prior therapy with targeted agents

H. Borghaei et al, N Engl J Med 2015;373:1627-39
Julie Brahmer et al, N Engl J Med 2015;373:123-35

Nivolumab vs Docetaxel

	Checkmate 017 (Squamous NSCLC)	Checkmate 057 (Non Squamous NSCLC)
No of subjects	135 vs 137	292 vs 290
Dose	Nivolumab 3 mg/kg q 2 weekly vs	Docetaxel 75 mg/sq.m q 3 weekly
OS	**9.2 months** (95% CI, 7.3 to 13.3) vs **6.0 months** (95% CI, 5.1 to 7.3) **HR, 0.59**; (0.44 to 0.79; P<0.001)	**12.2 months** (95% CI, 9.7 to 15.0) vs **9.4 months** (95% CI, 8.1 to 10.7) **HR, 0.73;** (0.59 to 0.89;P=0.002)
PFS	**3.5 months** (95% CI, 7.3 to 13.3) vs **2.8 months** (95% CI, 5.1 to 7.3) **HR, 0.62**; (0.47 to 0.81; P<0.001)	2.3 months (95% CI, 2.2 to 3.3) vs 4.2 months (95% CI, 3.5 to 4.9) HR, 0.92; (0.77 to 1.1; P<0.001)

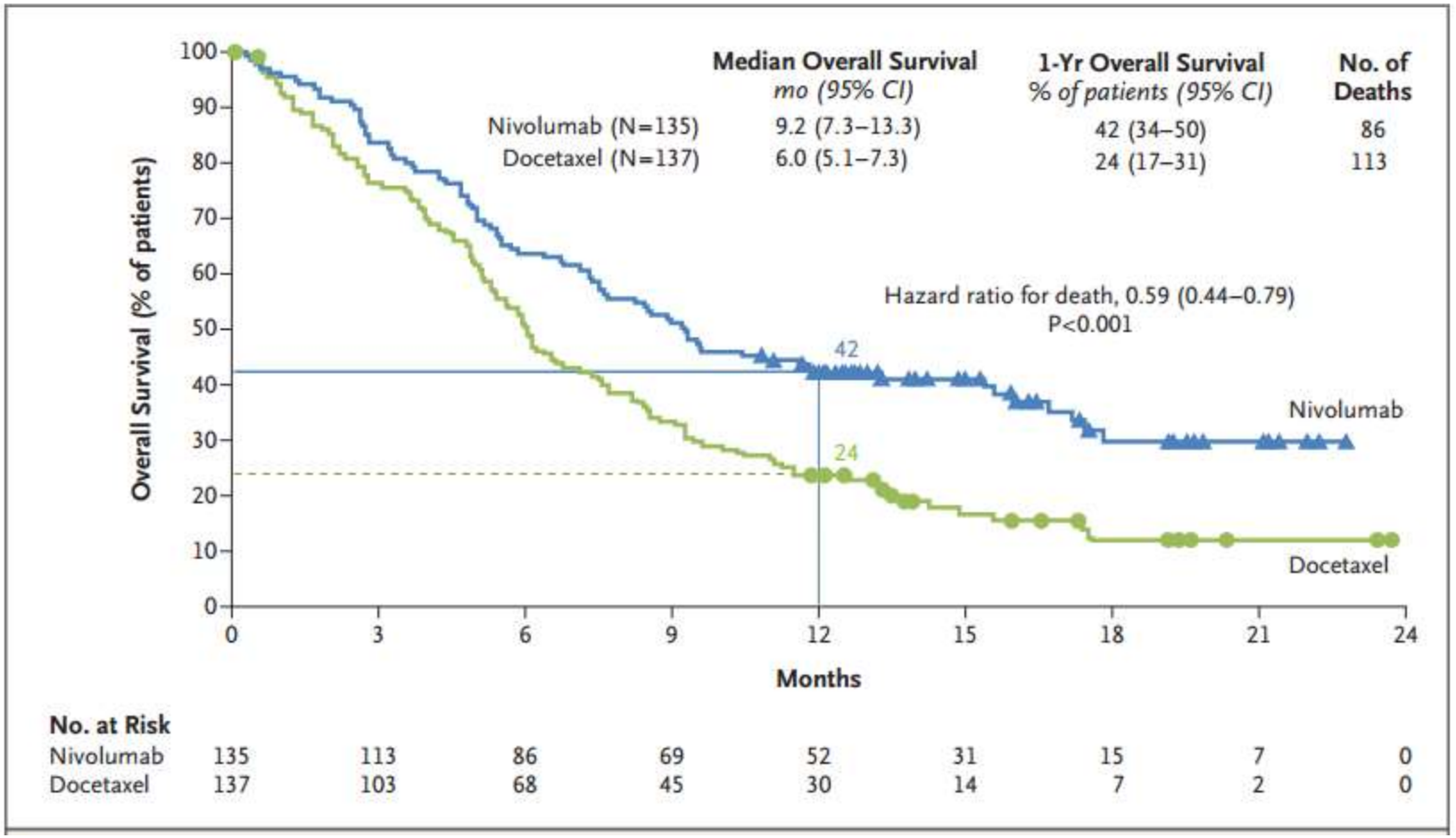
H. Borghaei et al, N Engl J Med 2015;373:1627-39
Julie Brahmer et al, N Engl J Med 2015;373:123-35

Nivolumab vs Docetaxel

	Checkmate 017 (Squamous NSCLC)	Checkmate 057 (Non Squamous NSCLC)
Overall survival rate at 1 yr	**42%** (95% CI, 34 to 50) Vs **24%** (95% CI, 17 to 31)	**51%** (95% CI, 45 to 56) Vs **39%** (95% CI, 33 to 45)
Objective response rate	**20 %** vs **9 %**	**19 %** vs **12 %**
Time to res	2.2 m vs 2.1 m	2.1 m vs 2.6 m
Duration of res	NR vs 8.4 m	17.2 m vs 5.6 m
AEs 3/4	7 % vs 55 %	10 % vs 54 %

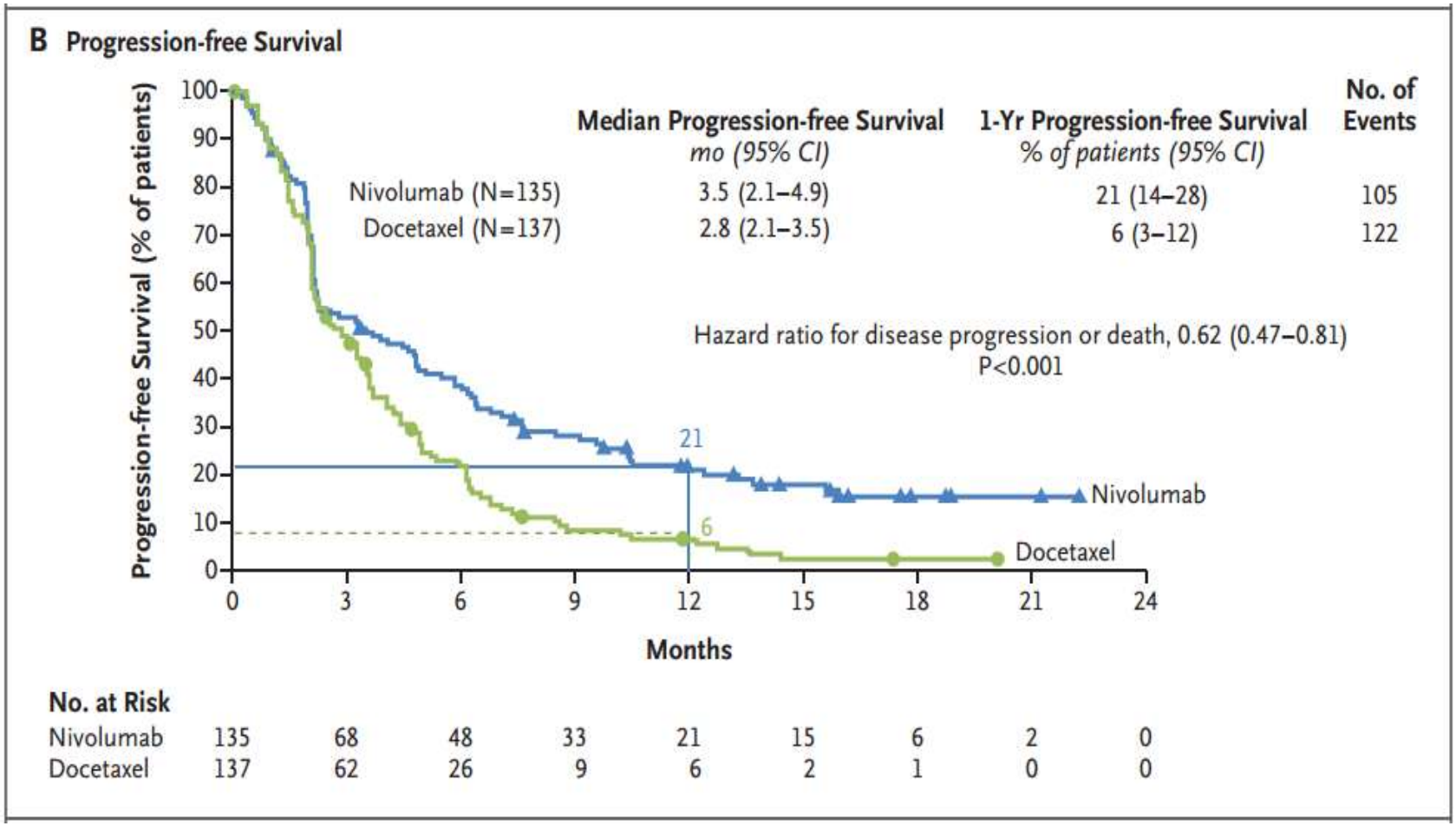
H. Borghaei et al, N Engl J Med 2015;373:1627-39
Julie Brahmer et al, N Engl J Med 2015;373:123-35

Checkmate 017 (Squamous NSCLC)



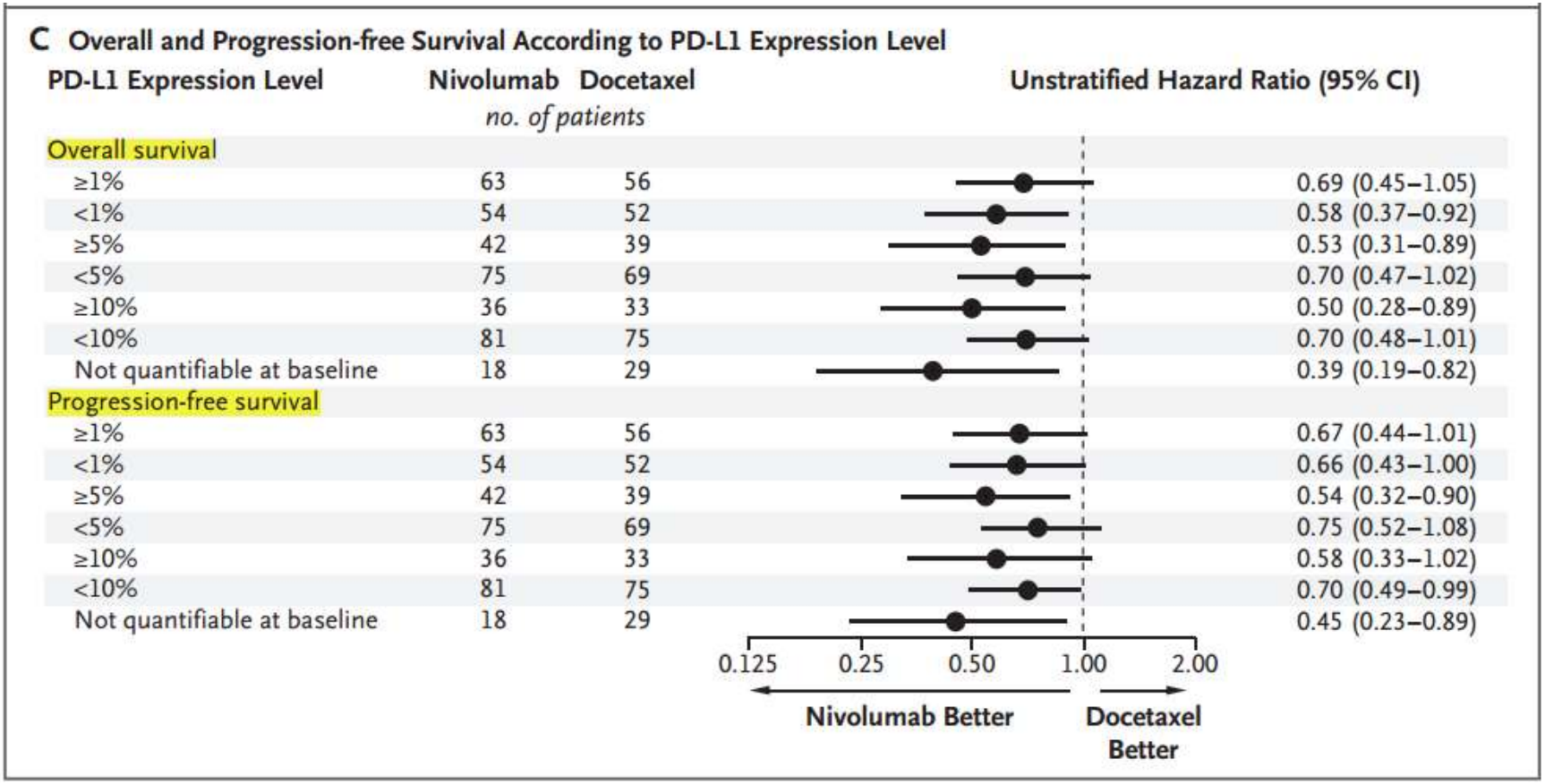
Overall survival better with Nivolumab

Checkmate 017 (Squamous NSCLC)



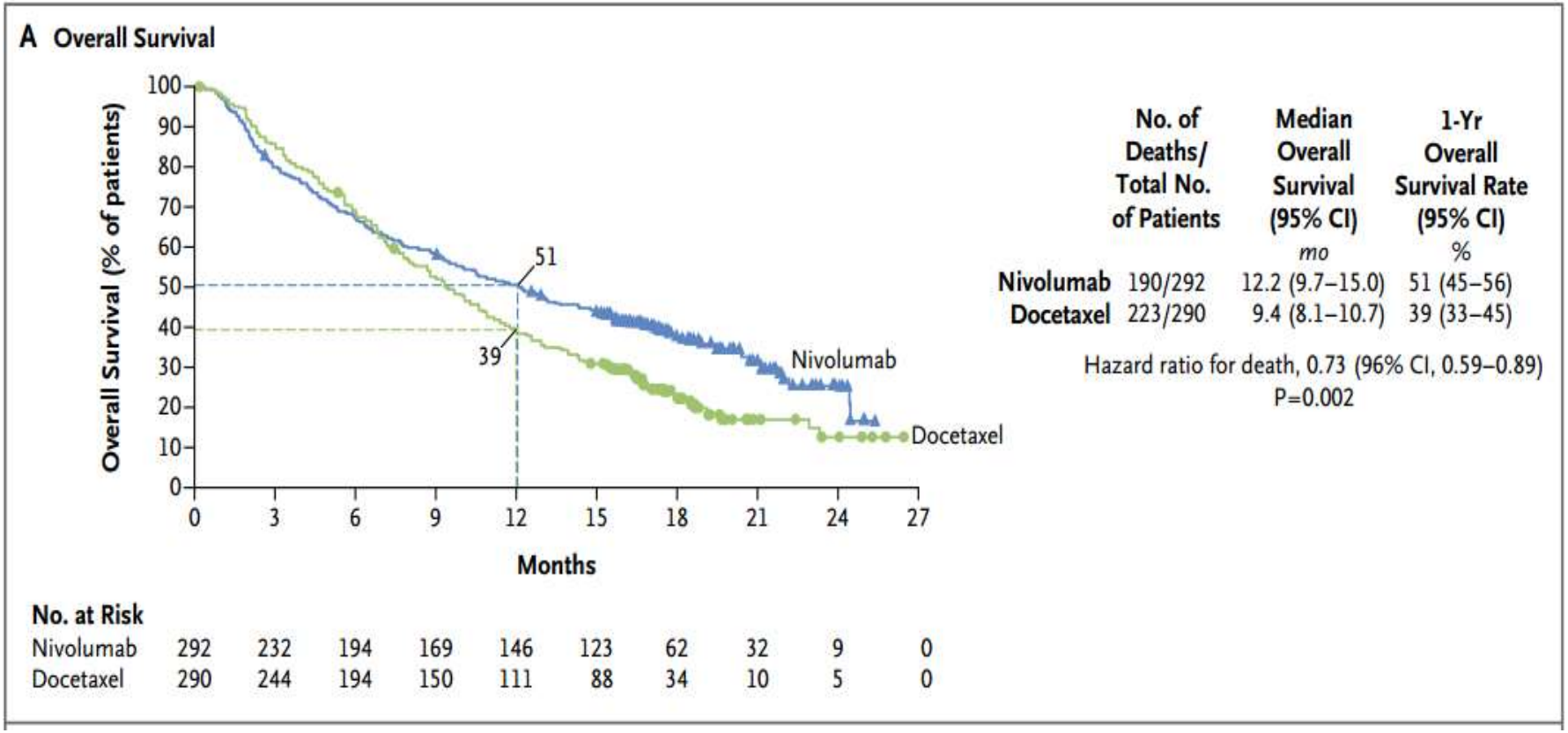
Progression free survival better with Nivolumab

Checkmate 017 (PDL1 expression)



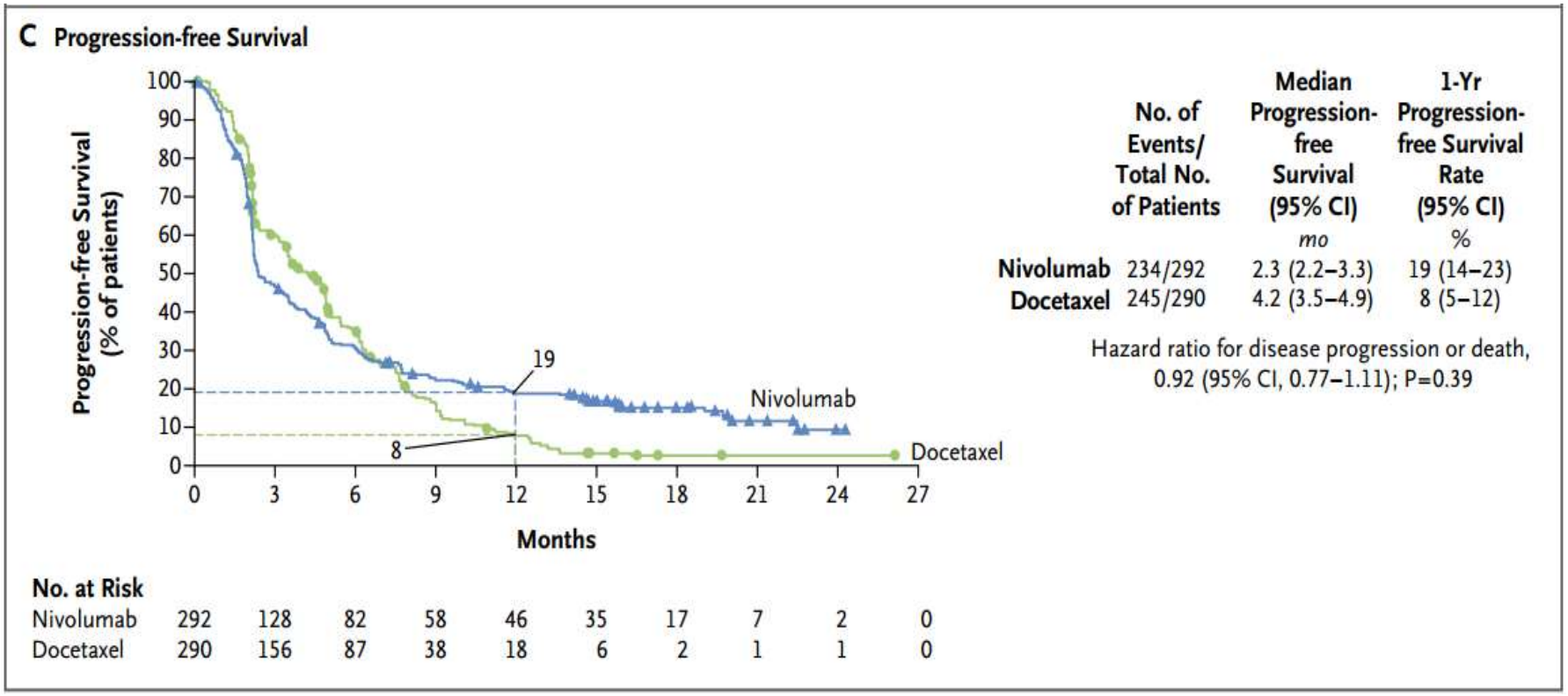
PDL1 expression didn't appear to influence the survival benefit

Checkmate 057 (Non Squamous NSCLC)



Overall survival better with Nivolumab

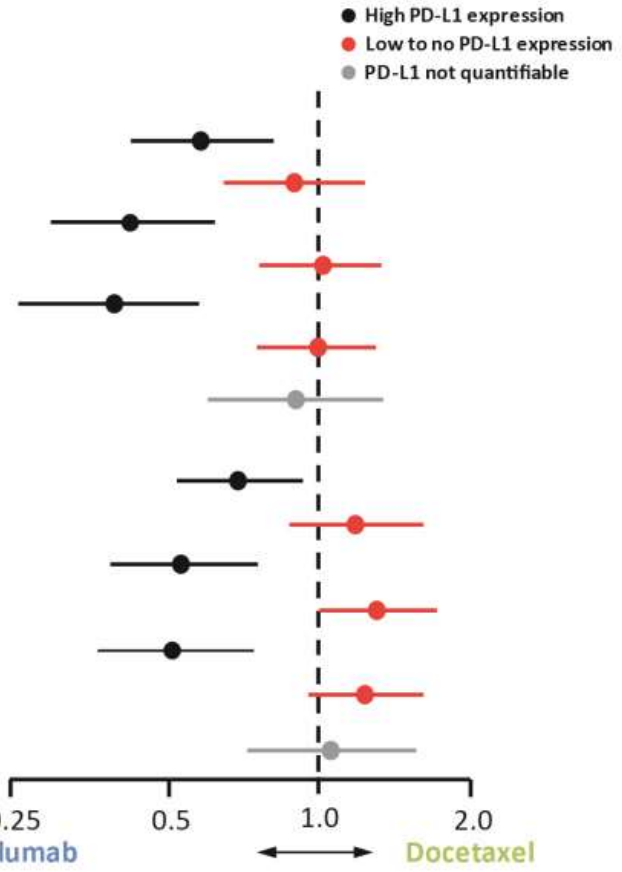
Checkmate 057 (Non Squamous NSCLC)



Progression free survival didn't favour nivolumab over docetaxel

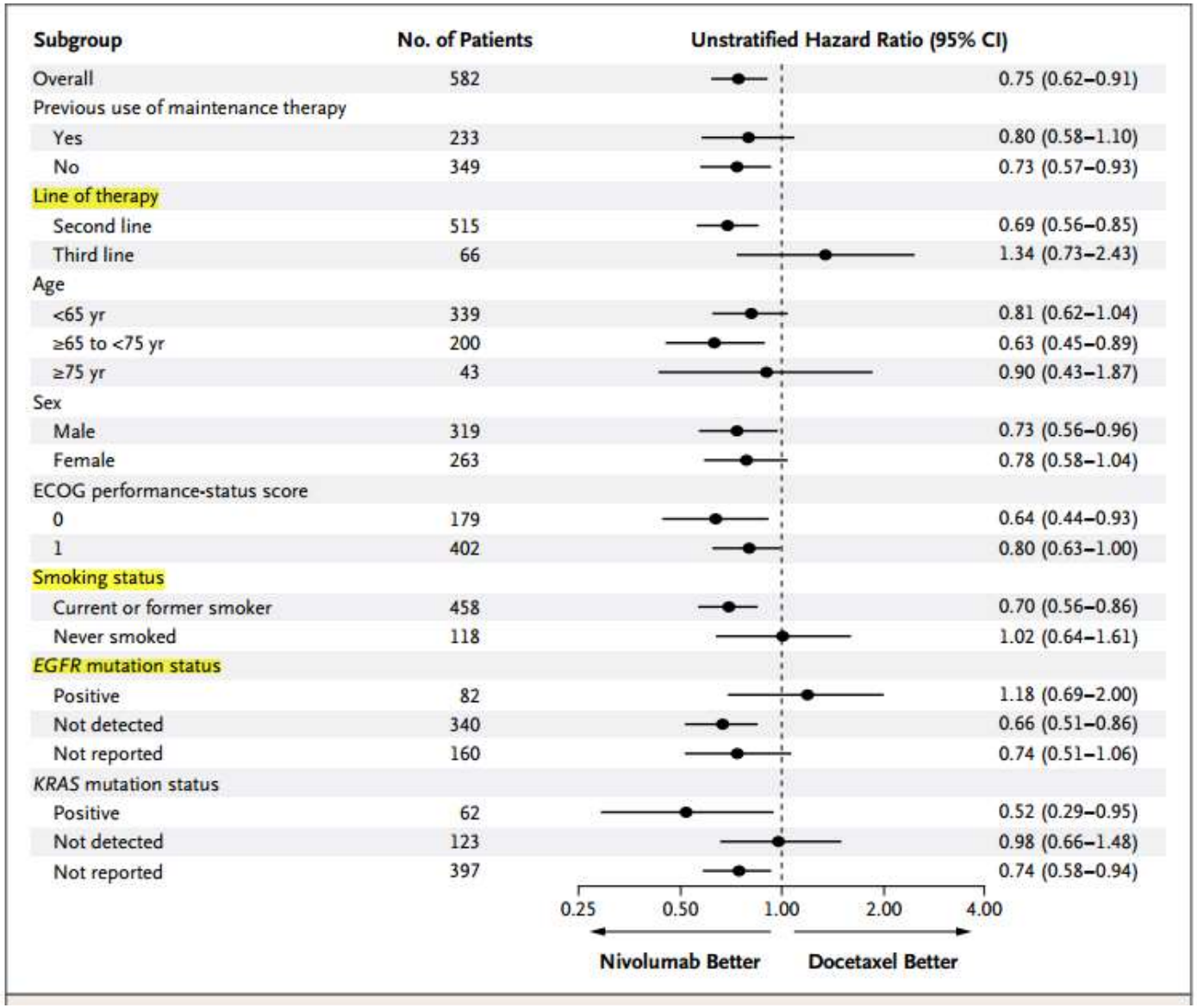
Checkmate 057 (PDL1 expression)

PD-L1 expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.06
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	<0.001
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	<0.001
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥1%	123	123	0.70 (0.53, 0.94)	0.02
<1%	108	101	1.19 (0.88, 1.61)	
≥5%	95	86	0.54 (0.39, 0.76)	<0.001
<5%	136	138	1.31 (1.01, 1.71)	
≥10%	86	79	0.52 (0.37, 0.75)	<0.001
<10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	



PDL1 expression a/w improved survival with nivolumab

Checkmate 057



Checkmate 057 (Non Squamous NSCLC)

- Nivolumab doesn't improve survival in specific subgroups like
  - EGFR mutation positive status
  - Never smokers
  - Those with CNS metastases
  - On 3rd line therapy

H. Borghaei et al, N Engl J Med 2015;373:1627-39

Nivolumab

- FDA approved for the treatment of patients with advanced NSCLC who experience disease progression on or after standard platinum based chemotherapy
- Dosage - 3 mg/kg iv q 2 weekly

PEMBROLIZUMAB

Keynote 001

- Phase 1 clinical trial in chemotherapy naive and previously treated locally advanced or metastatic NSCLC
- Pembrolizumab (n=495)
  - 10 mg/kg q 2 wks
  - 10 mg/kg q 3 wks
  - 2 mg/kg q 3 wks

- Efficacy and safety
- Validate PD-L1 expression level that is a/w the likelihood of clinical benefit

Edward B. Garon et al, N Engl J Med 2015;372:2018-28

Keynote 001

	Previously Rxed (n = 394)	Previously un Rxed (n = 101)
Over all response rate	19.9 % (16.0 to 23.2)	
	18.0 % (14.4 to 22.2)	24.8 % (16.7 to 34.3)
Median DOR	12.5 months (range, 1.0 to 23.3)	
	10.4 months (range, 1.0 to 10.4)	23.3 months (range, 1.0 to 23.3)
Median PFS	3.0 months (95% CI, 2.2 to 4.0)	6.0 months (95% CI, 4.1 to 8.6)
Median OS	9.3 months (95% CI, 8.4 to 12.4)	16.2 months (95% CI, 16.2 to not reached)

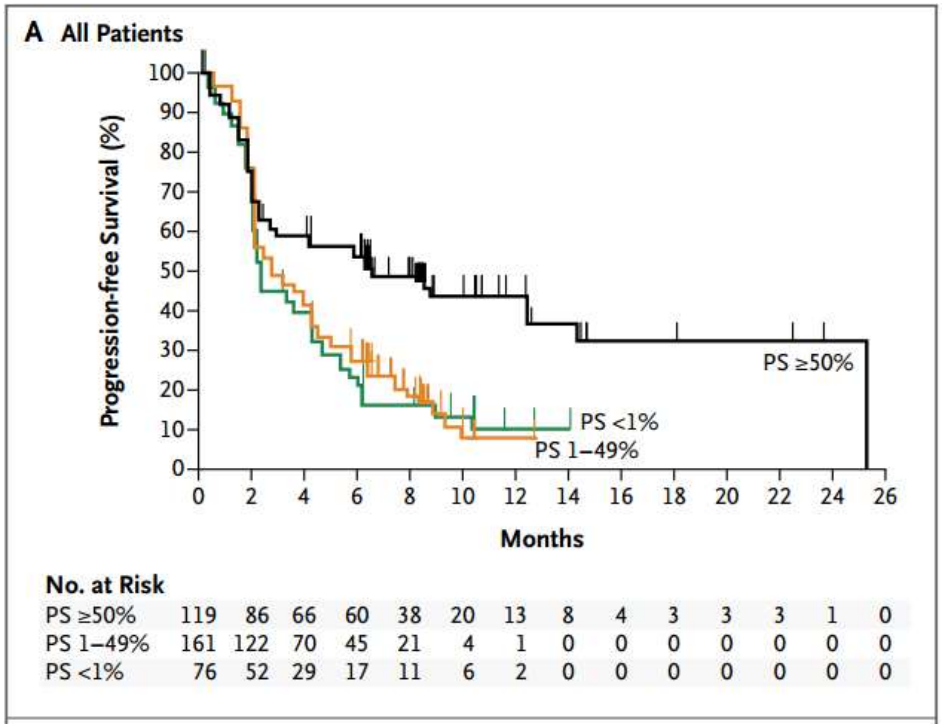
Edward B. Garon et al, N Engl J Med 2015;372:2018-28

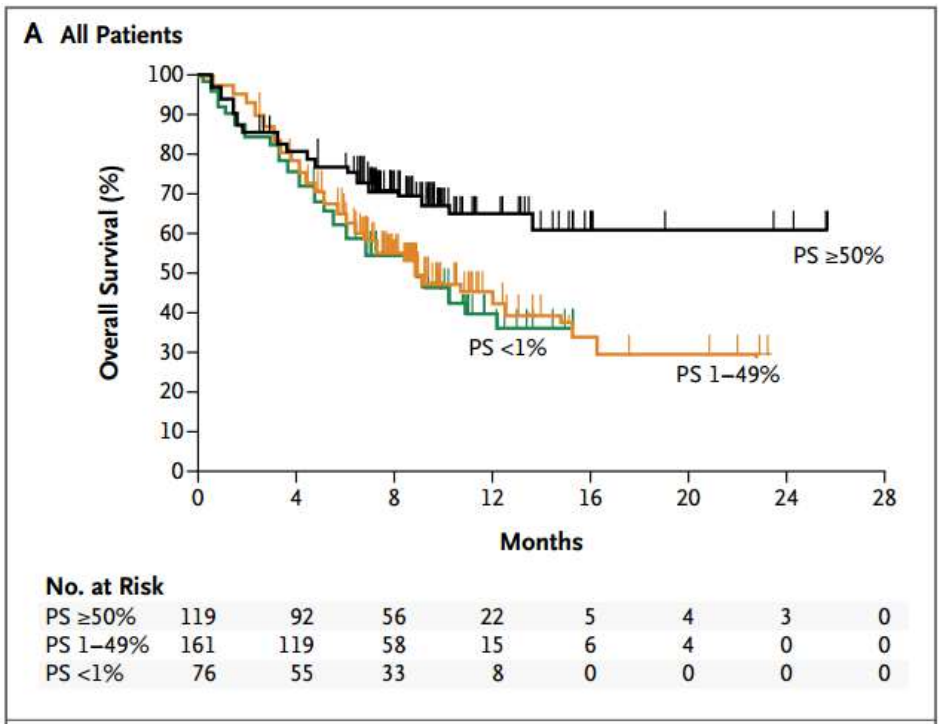
Keynote 001

- Treatment-related AEs occurred in 351/495 patients (70.9%)
- Grade 3 or higher in 47 of 495 patients (9.5%)
- No clear difference according to dose or schedule
- Common S/E were fatigue, pruritus and anorexia
- Response rate was independent of the dose and histology of NSCLC
- Higher response rate in TPS > 50 % (45.2%)

Edward B. Garon et al, N Engl J Med 2015;372:2018-28

Keynote 001





PD-L1 expression ≥ 50% of tumor cells correlated with improved efficacy of pembrolizumab

Edward B. Garon et al, N Engl J Med 2015;372:2018-28

Keynote 010

- Progression after two or more cycles of platinum-doublet chemotherapy as well as an appropriate TKI for those with an EGFR-sensitising mutation or ALK gene rearrangement
- Measurable disease as per investigator-assessed RECIST
- ECOG of 0 or 1
- PD-L1 expression on at least 1% of tumour cells

Roy S Herbst et al, Lancet 2015

Keynote 010

1034 (PDL 1 ≥ 1%) , 442 (PDL 1≥ 50 %)				
		Pembrolizumab 2 mg/kg	**Pembrolizumab 10 mg/kg**	**Docetaxel**
PDL 1 ≥ 1% (345/ 346/ 343)	**OS**	**10·4 months** **HR 0·71** 95% CI 0·58–0.88	**12·7 months** **HR 0·61** 95 % CI 0·49–0·75	8·5 months
	PFS	3·9 months HR 0·88, 95% CI 0·74–1·05	4·0 months HR 0·79, 95% CI 0·66–0·94	4·0 months
PDL 1 ≥ 50 % (139/ 151/ 152)	**OS**	**14.9 months** **HR 0·54** 95% CI 0·38–0.77	**17.3 months** **HR 0·50** 95 % CI 0·36–0·70	8·2 months
	PFS	**5.0 months** **HR 0·59** 95% CI 0·44–0·78	**5.2 months** **HR 0·59** 95% CI 0·45–0·78	4·1 months

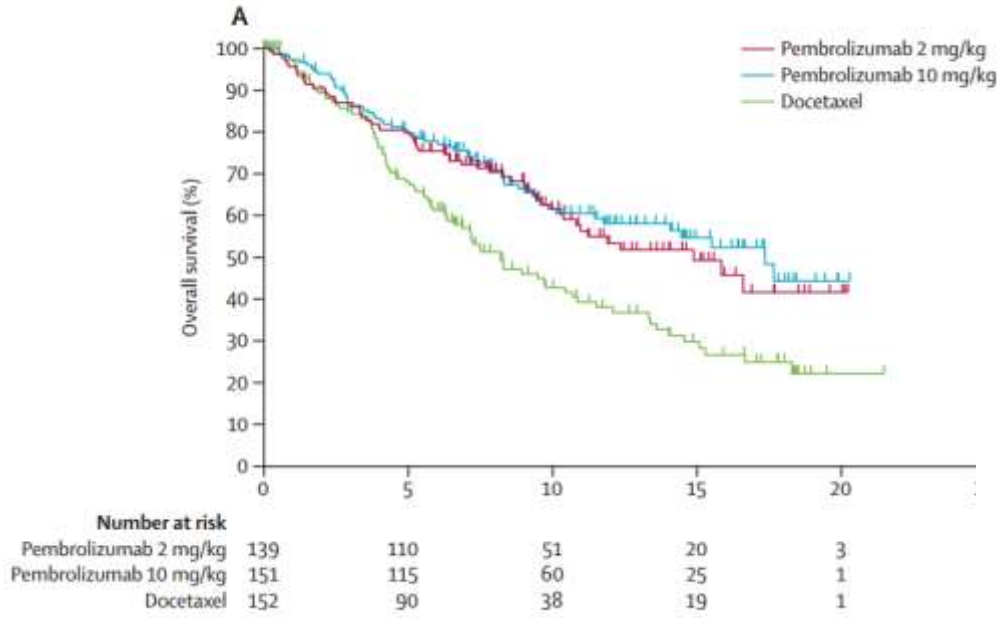
Roy S Herbst et al, Lancet 2015

Keynote 010

	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Docetaxel
ORR in TPS ≥ 1%	62 (18%)	64 (18%)	32 (9%)
ORR in TPS ≥ 50 %	42 (30%)	44 (29%)	12 (8%)
Median time to response	9 weeks	9 weeks	9 weeks
Duration of response	NR	NR	8 months (≥50%) 6 months (≥ 1%)

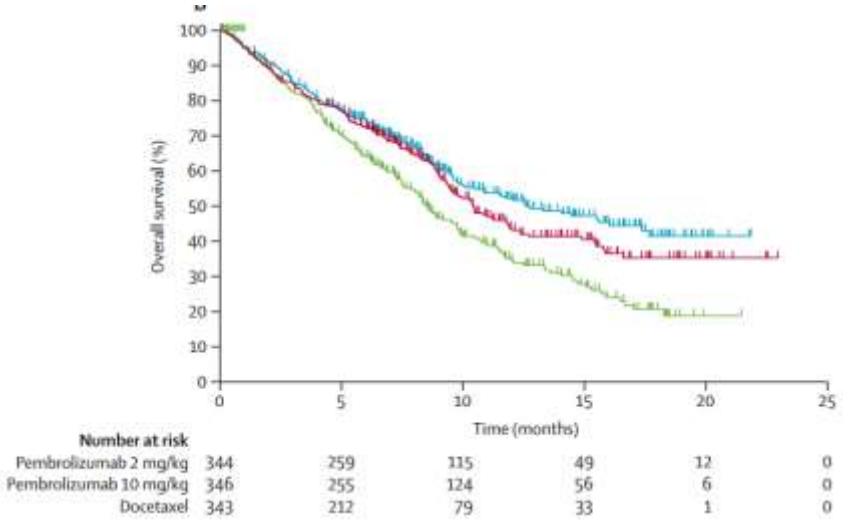
Roy S Herbst et al, Lancet 2015

Keynote 010



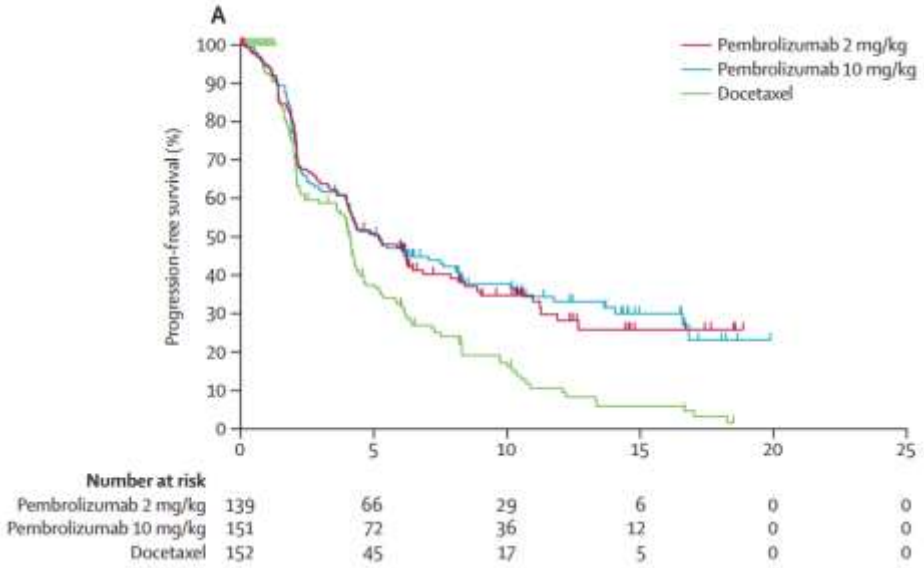
TPS ≥50%

TPS ≥1 %



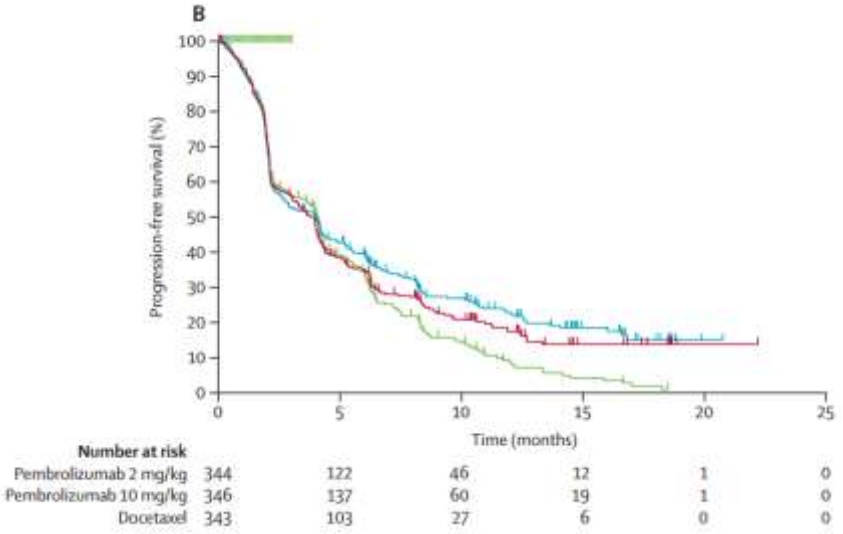
Roy S Herbst et al, Lancet 2015

Keynote 010



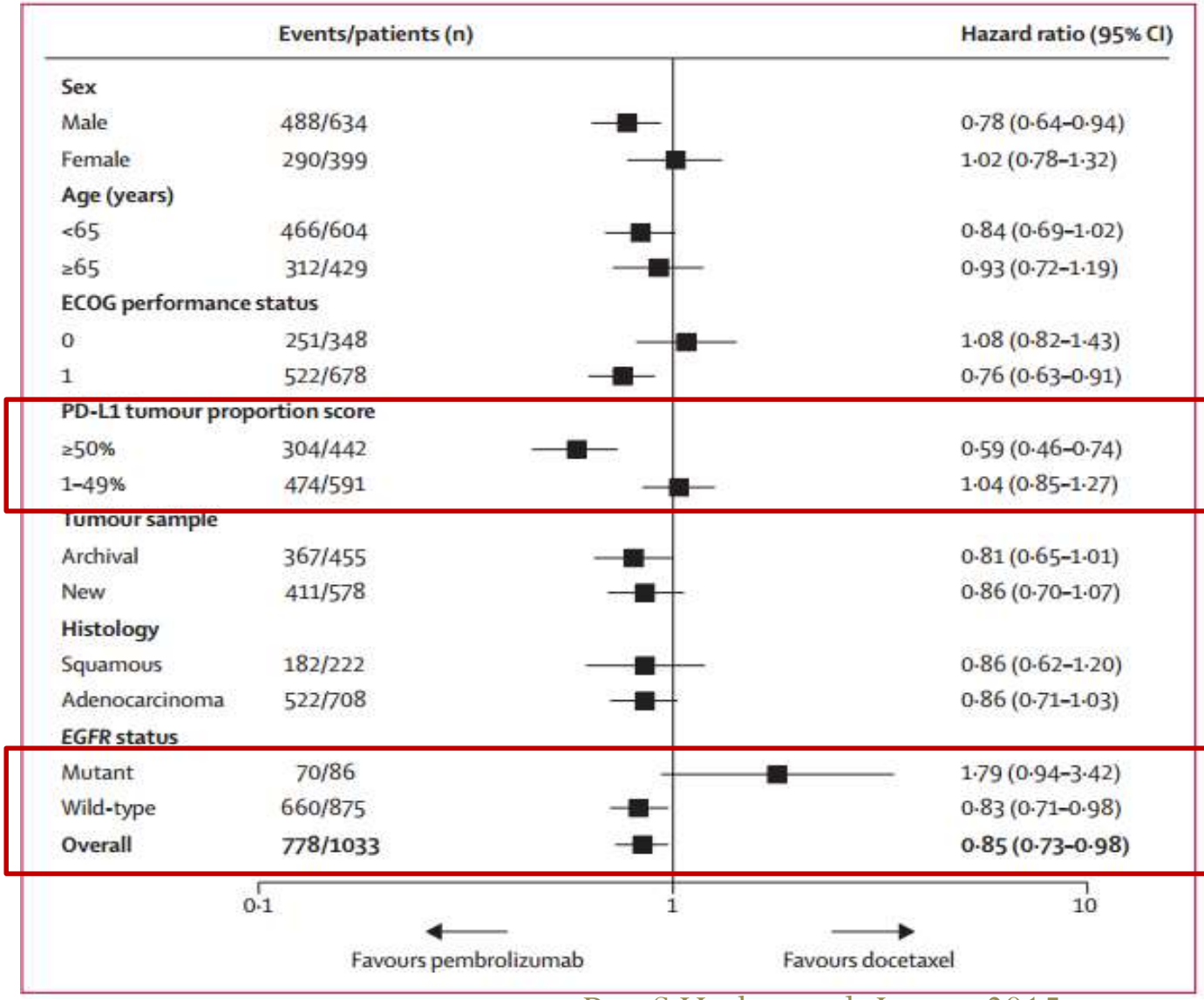
TPS ≥50%

TPS ≥1 %



Roy S Herbst et al, Lancet 2015

Keynote 010



Roy S Herbst et al, Lancet 2015

Keynote 010

- Greatest improvement in overall survival was in patients with a TPS of $\geq 50\%$ for pembrolizumab compared with docetaxel
- Patients with a score of 1–49% also benefited
- Because patients with TPS < 1% were excluded from this study, it is unclear whether such patients would have a different response to pembrolizumab compared with the 1–49% subgroup
- Equally efficacious doses of 2 mg/kg and 10 mg/kg

Roy S Herbst et al, Lancet 2015

Brain metastases

- Typically portend a poor prognosis
- Significant morbidity
- Patients with untreated brain metastases are excluded in most clinical trials
- Only included asymptomatic, treated and documented stable before enrollment
- Pembrolizumab (10 mg/kg q 2wkly) was studied in a phase 2 trial in NSCLC and melanoma patients with brain mets

Sarah B Goldberg et al,Lancet Oncol 2016; 17: 976–83

Untreated progressive brain mets

- 36 patients (18 melanoma and 18 NSCLC)
- 18 NSCLC were positive for PDL1
- Atleast one brain metastasis between 5 mm and 20 mm that was untreated or that was unequivocally progressing after radiation
- Excluded patients with neurological symptoms attributable to brain mets or who required steroids, patients with leptomeningeal disease

Sarah B Goldberg et al,Lancet Oncol 2016; 17: 976–83

Untreated progressive brain mets

- ORR of brain mets was 22% for melanoma and 33% for NSCLC with durable response
- Strong concordance with systemic response
- It is unknown whether pembrolizumab is effective or safe in patients with symptomatic or larger brain metastases
- Immature survival data and small sample size
- Requires further studies for validation

Sarah B Goldberg et al, Lancet Oncol 2016; 17: 976–83

ATEZOLIZUMAB

PDL 1 testing in Atezolizumab trials

PD-L1 tumour cell scoring		PD-L1 tumour-infiltrating immune cell scoring	
Score	Percentage of PD-L1-expressing cells	Score	Percentage of PD-L1-expressing cells
TC3	≥50%	IC3	≥10%
TC2	≥5% and <50%	IC2	≥5% and <10%
TC1	≥1% and <5%	IC1	≥1% and <5%
TC0	<1%	IC0	<1%

POPLAR trial - Atezolizumab

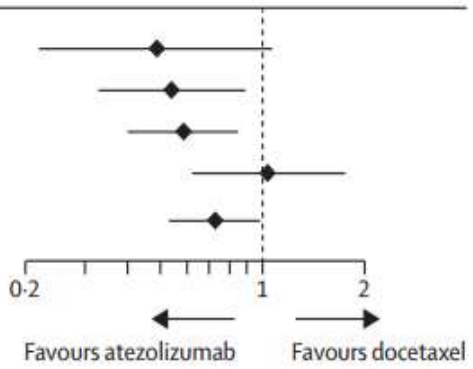
- Randomised, open-label phase 2 trial
- Previously treated NSCLC
- ECOG 0 or 1
- 287 patients
- Atezolizumab 1200 mg (n= 144) or docetaxel 75 mg/m²(n =143) once every 3 weeks
- Benefit in overall survival but not in PFS or ORR
- Overall survival improvement was significant in the TC2/3 or IC2/3

Louis Fehrenbacher et al, Lancet 2016; 387: 1837–46

POPLAR trial - Atezolizumab

B

	n (%)	HR*	95% CI	p value	Median overall survival (months [95% CI])	
					Atezolizumab (n=144)	Docetaxel (n=143)
TC3 or IC3	47 (16%)	0·49	0·22–1·07	0·068	15·5 (9·8–NE)	11·1 (6·7–14·4)
TC2/3 or IC2/3	105 (37%)	0·54	0·33–0·89	0·014	15·1 (8·4–NE)	7·4 (6·0–12·5)
TC1/2/3 or IC1/2/3	195 (68%)	0·59	0·40–0·85	0·005	15·5 (11·0–NE)	9·2 (7·3–12·8)
TC0 and IC0	92 (32%)	1·04	0·62–1·75	0·871	9·7 (6·7–12·0)	9·7 (8·6–12·0)
Intention to treat	287	0·73	0·53–0·99	0·040	12·6 (9·7–16·4)	9·7 (8·6–12·0)



Overall survival benefit from atezolizumab increased with increasing PD-L1 expression on tumour cells, tumour infiltrating immune cells, or both

PD-L1 expression is predictive of OS benefit

Louis Fehrenbacher et al, Lancet 2016; 387: 1837–46

OAK trial - Atezolizumab

- Randomised, open-label, phase 3 trial
- Stage III/IV non-small-cell lung cancer
- One to two previous cytotoxic chemotherapy regimens
- ECOG 0 or 1
- Measurable disease by RECIST
- 850 patients (425 in each group)

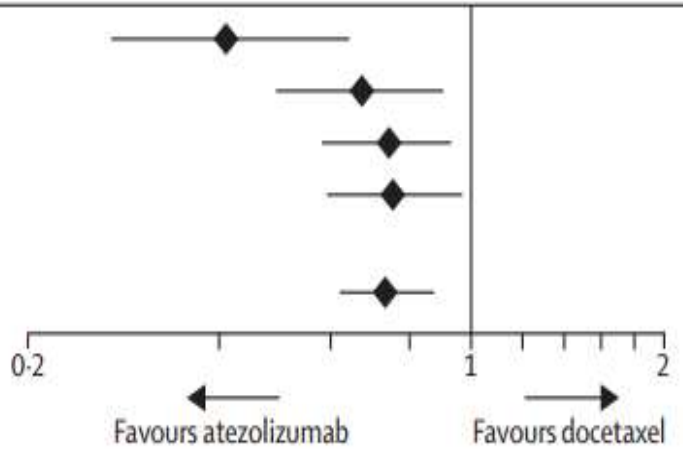
Achim Rittmeyer et al, Lancet 2017; 389: 255–65

OAK trial - Atezolizumab

- Atezolizumab 1200 mg vs Docetaxel 75 mg/m^2
- Over all survival

F

	n (%)	Median overall survival (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
TC3 or IC3	137 (16)	20·5	8·9	0·41 (0·27–0·64)
TC2/3 or IC2/3	265 (31)	16·3	10·8	0·67 (0·49–0·90)
TC1/2/3 or IC1/2/3	463 (54)	15·7	10·3	0·74 (0·58–0·93)
TC0 and IC0	379 (45)	12·6	8·9	0·75 (0·59–0·96)
ITT	850 (100)	13·8	9·6	0·73 (0·62–0·87)

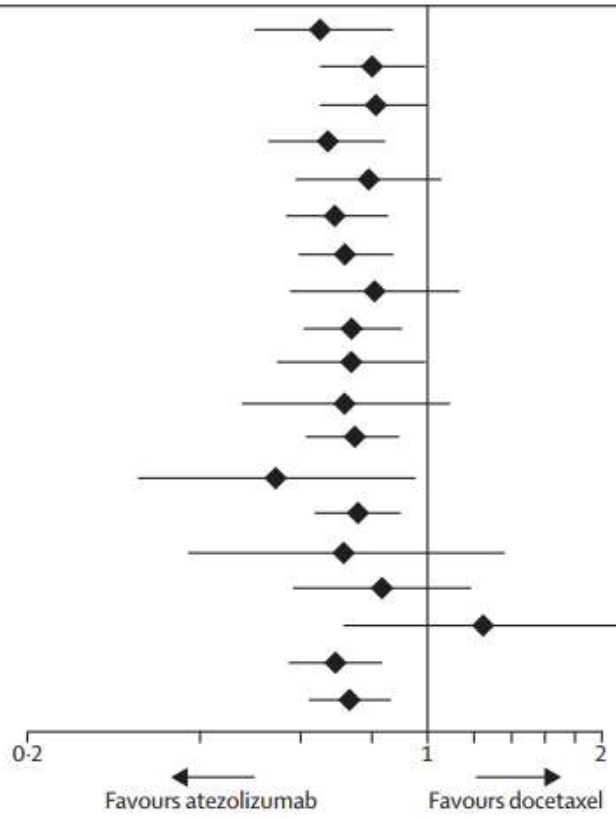


Achim Rittmeyer et al, Lancet 2017; 389: 255–65

OAK trial - Atezolizumab

A

	n (%)	Median overall survival (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
Female	330 (39)	16·2	11·2	0·64 (0·49–0·85)
Male	520 (61)	12·6	9·2	0·79 (0·64–0·97)
<65 years old	453 (53)	13·2	10·5	0·80 (0·64–1·00)
≥65 years old	397 (47)	14·1	9·2	0·66 (0·52–0·83)
ECOG PS 0	315 (37)	17·6	15·2	0·78 (0·58–1·04)
ECOG PS 1	535 (63)	10·6	7·6	0·68 (0·56–0·84)
1 previous therapy	640 (75)	12·8	9·1	0·71 (0·59–0·86)
2 previous therapies	210 (25)	15·2	12·0	0·80 (0·57–1·12)
Non-squamous	628 (74)	15·6	11·2	0·73 (0·60–0·89)
Squamous	222 (26)	8·9	7·7	0·73 (0·54–0·98)
Never smokers	156 (18)	16·3	12·6	0·71 (0·47–1·08)
Current or previous smokers	694 (82)	13·2	9·3	0·74 (0·61–0·88)
CNS metastases	85 (10)	20·1	11·9	0·54 (0·31–0·94)
No CNS metastases	765 (90)	13·0	9·4	0·75 (0·63–0·89)
KRAS mutant	59 (7)	17·2	10·5	0·71 (0·38–1·35)
KRAS wildtype	203 (24)	13·8	11·3	0·83 (0·58–1·18)
EGFR mutant	85 (10)	10·5	16·2	1·24 (0·71–2·18)
EGFR wildtype	628 (74)	15·3	9·5	0·69 (0·57–0·83)
ITT	**850 (100)**	**13·8**	**9·6**	**0·73 (0·62–0·87)**



Achim Rittmeyer et al, Lancet 2017; 389: 255–65

OAK trial - Atezolizumab

	Atezolizumab (n = 425)	Chemotherapy (n = 425)	HR
Median PFS	2·8 months (2·6–3·0)	4·0 months (3·3–4·2)	0.95 (0·82–1·10)
Objective response rate	58 (14%)	57 (13%)	0.34 (0·21–0·55)
Objective response rate in TC3/IC3	**22 /72 (31%)**	**7 /65 (11%)**	
Median duration of response	16.3 months	6.2 months	-

Achim Rittmeyer et al, Lancet 2017; 389: 255–65

OAK trial - Atezolizumab

- Over all survival benefit – irrespective of the histology and PDL-1 expression
- Benefit in all the subgroups except for EGFR mutant NSCLC
- In contrast to other trials of immune check point inhibitors, no benefit on PFS was found

Achim Rittmeyer et al, Lancet 2017; 389: 255–65

BIRCH - Atezolizumab

- Efficacy of atezolizumab across all the lines of therapy
- Phase II clinical trial in 659 patients
- In PDL -1 expressors $\geq$ 5% of TC or IC
- Atezolizumab 1,200 mg iv q 3 wkly
- Divided into three cohorts based on line of therapy, C1 (1st line), C2 (2nd line), C3 (3rd line)

Solange Peters et al, J Clin Oncol 35:2781-2789

BIRCH - Atezolizumab

TC or IC 2/3	ORR	Median PFS (m)	Median OS (m)
Cohort 1 (139)	30 (22 %)	5.4	20.1
Cohort 2 (268)	52 (19 %)	2.8	15.5
Cohort 3 (252)	45 (18%)	2.8	13.2

TC or IC 3	ORR	Median PFS (m)	Median OS (m)
Cohort 1 (65)	20 (31 %)	5.6	NE
Cohort 2 (122)	32 (26 %)	4.0	15.1
Cohort 3 (115)	31 (27 %)	4.1	17.5

Solange Peters et al, J Clin Oncol 35:2781-2789

BIRCH - Atezolizumab

- Clinically meaningful efficacy of atezolizumab across all lines of therapy
- In PD-L1 expressing tumors, response rates were higher with atezolizumab versus historical chemotherapy
- Patients with TC3 or IC3 tumors had higher ORRs versus those with TC2/3 or IC2/3 tumors

Solange Peters et al, J Clin Oncol 35:2781-2789

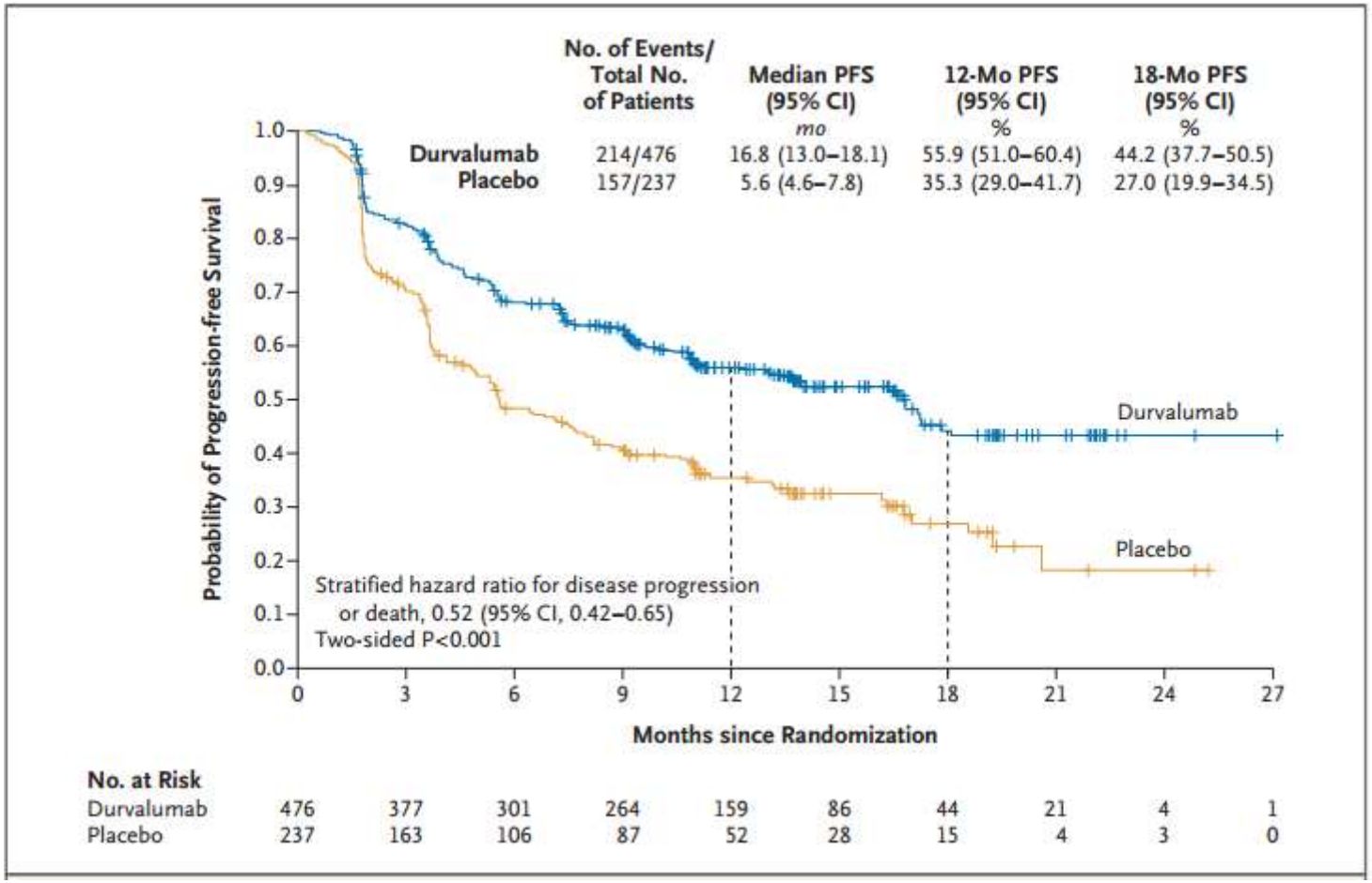
DURVALUMAB

PACIFIC study - Durvalumab

- Stage III locally advanced unresectable NSCLC
- With no disease progression after two or more cycles of chemoradiotherapy
- Durvalumab at a dose of 10 mg/kg iv or matching placebo every 2 weeks as a consolidation therapy for up to 12 months
- 709 patients were included
- Optional PDL1 testing of archived samples

S.J. Antonia et al, N Eng J Med 2017

PACIFIC study - Durvalumab



S.J. Antonia et al, N Eng J Med 2017

PACIFIC study - Durvalumab

Subgroup	Durvalumab	Placebo
	no. of patients	
All patients	476	237
Sex		
Male	334	166
Female	142	71
Age at randomization		
<65 yr	261	130
≥65 yr	215	107
Smoking status		
Smoker	433	216
Nonsmoker	43	21
NSCLC disease stage		
IIIA	252	125
IIIB	212	107
Tumor histologic type		
Squamous	224	102
Nonsquamous	252	135
Best response		
Complete response	9	7
Partial response	232	111
Stable disease	222	114
PD-L1 status		
≥25%	115	44
<25%	187	105
Unknown	174	88
EGFR mutation		
Positive	29	14
Negative	315	165
Unknown	132	58

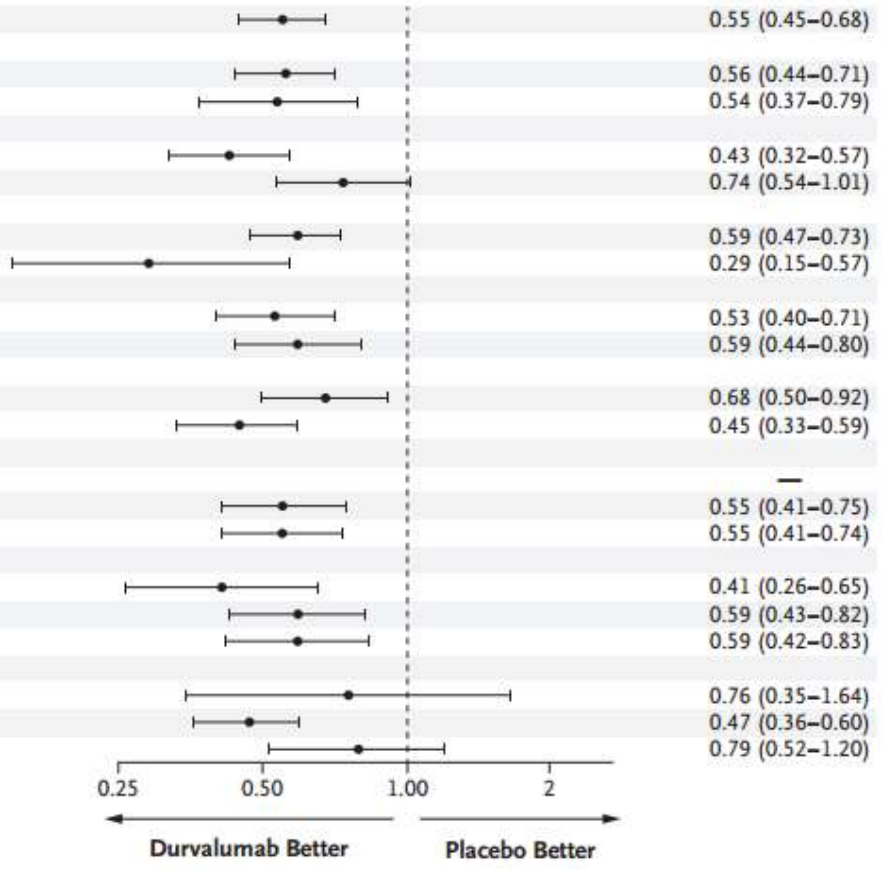


Figure 2. Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.

S.J. Antonia et al, N Eng J Med 2017

PACIFIC study - Durvalumab

	Durvalumab (N = 443)	Placebo (N =213)	HR
Median PFS	16.8 months (13.0–18.1)	5.6 months (4.6–7.8)	0.52 (0·42–0.65)
12-month PFS rate	55.9% (51.0 to 60.4)	35.3% (29.0 to 41.7)	-
18-month PFS rate	44.2% (37.7 to 50.5)	27.0% (19.9 to 34.5)	-
ORR	28.4%	16.0% P<0.001	

S.J. Antonia et al, N Eng J Med 2017

Difference b/n PFS & OS

- Standard radiographic endpoints might underestimate treatment benefit with ICPis
  - initial increase in tumour volume from increased immune infiltration
- Delayed anticancer immune effects after RECIST-defined progression
- Anti tumour immune activation beyond progression that might be sustained by continued treatment

Summary of phase III trials

	OS	PFS	ORR	Benefit in PDL 1
Nivolumab Checkmate 017	✓	✓	✓	Independent of PDL1
Nivolumab Checkmate 057	✓	✗	✓	Predictive association
Pembrolizumab Key note 010	✓	✗	✓	More OS /PFS benefit in PDL 1 ≥ 50 %
Atezolizumab OAK	✓	✗	✗	Independent of PDL1
Durvalumab PACIFIC	✓	✓	✓	Independent of PDL1

AS FIRST LINE THERAPY NSCLC

Untreated NSCLC

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

KEYNOTE 024, NEJM November 2016

First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer

D.P. Carbone, M. Reck, L. Paz-Ares, B. Creelan, L. Horn, M. Steins, E. Felip, M.M. van den Heuvel, T.-E. Ciuleanu, F. Badin, N. Ready, T.J.N. Hiltermann, S. Nair, R. Juergens, S. Peters, E. Minenza, J.M. Wrangle, D. Rodriguez-Abreu, H. Borghaei, G.R. Blumenschein, Jr., L.C. Villaruz, L. Havel, J. Krejci, J. Corral Jaime, H. Chang, W.J. Geese, P. Bhagavatheeswaran, A.C. Chen, and M.A. Socinski, for the CheckMate 026 Investigators*

CHECKMATE 026, NEJM June 2017

Keynote 024

- Untreated stage IV NSCLC with no sensitizing EGFR mutation / ALK translocation
- PD-L1 tumor-expression level of 50 % or more
- ECOG - 0 or 1
- Measurable disease according to RECIST
- No previous systemic anticancer therapy as primary therapy for advanced or metastatic disease

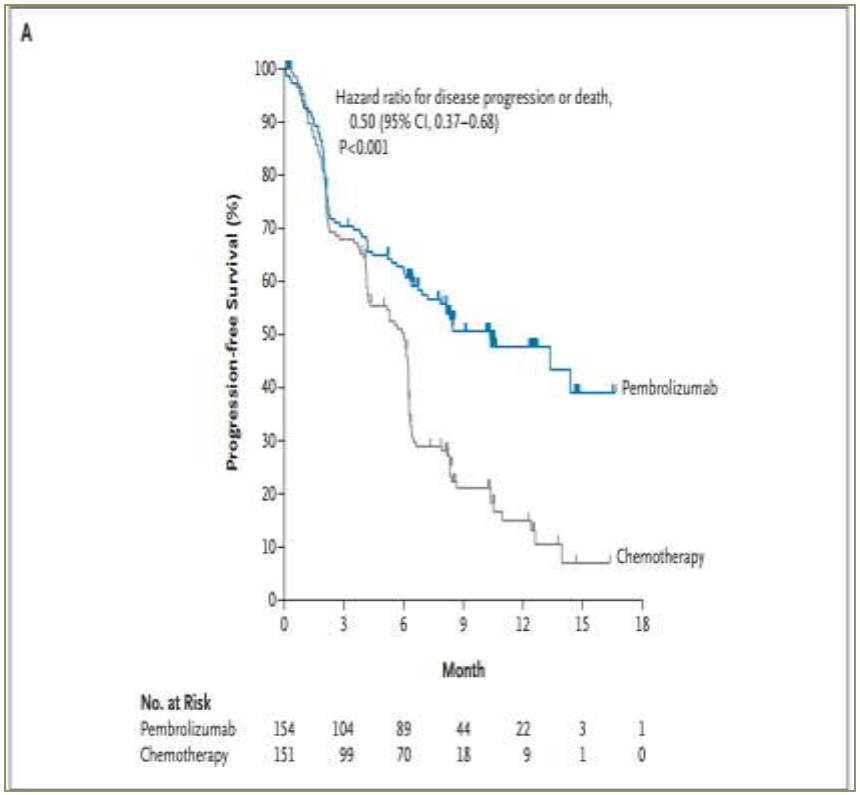
Martin Reck et al, N Engl J Med 2016;375:1823-33

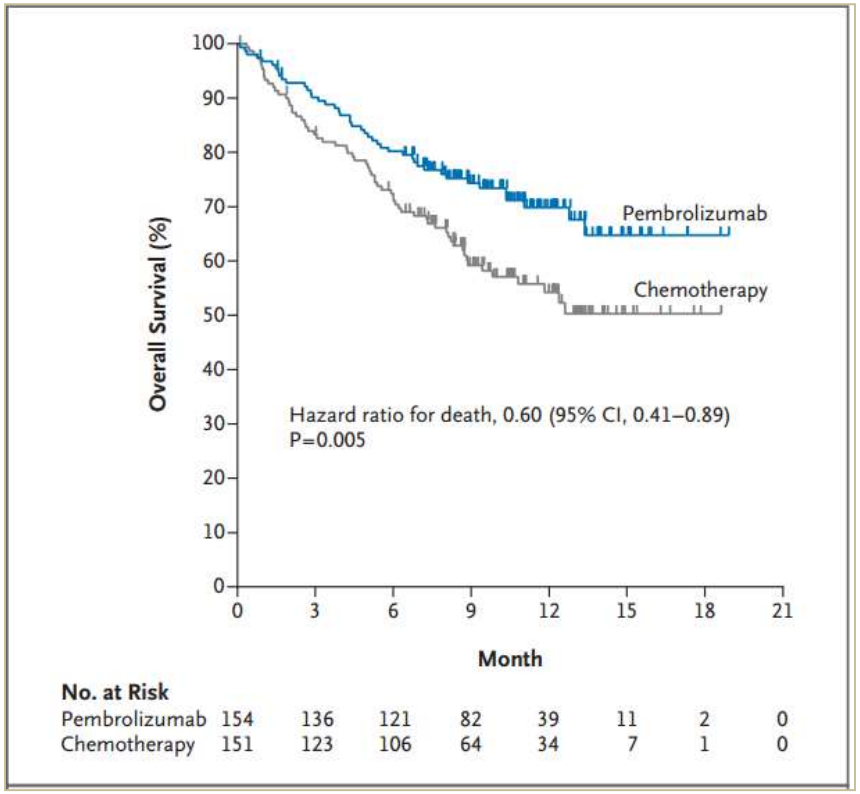
Keynote 024

	Pembrolizumab (n = 154) 200 mg q3 wkly	Platinum based Chemotherapy (n= 151)	HR
Median PFS	10.3 months (6.7 to NR)	6 months (4.2 to 6.2)	0.50 (0.37 – 0.68)
Rate of OS at 6 months	80.2 %	72.4 %	0.60 (0.41 - 0.89)
Rate of OS at 12 months	70%	54%	
Median duration of response	Not reached	6.3 months	-
Objective response rates	44.8 %	27.8 %	-
AEs/ Gr 3,4 AEs	73 %/27 %	90 %/53 %	

Martin Reck et al, N Engl J Med 2016;375:1823-33

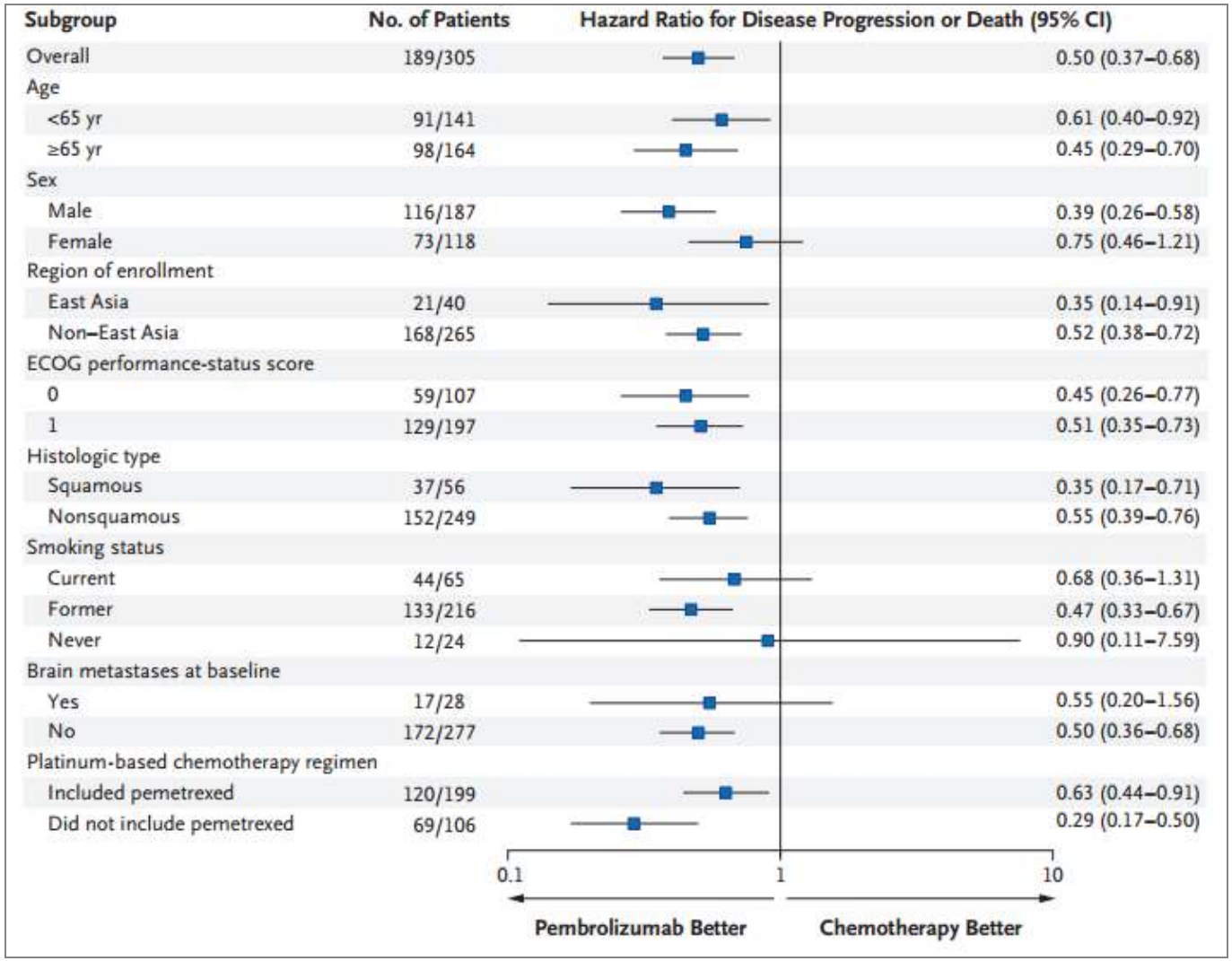
Keynote 024





Martin Reck et al, N Engl J Med 2016;375:1823-33

Keynote 024



Martin Reck et al, N Engl J Med 2016;375:1823-33

Keynote 024

- Longer progression-free and overall survival in patients with previously untreated advanced NSCLC and a PD-L1 ≥ 50% or greater
- Fixed dosage of pembrolizumab 200 mg q 3weeks

Pembrolizumab has survival benefit over chemotherapy in untreated NSCLC in high PDL 1 expressors

Martin Reck et al, N Engl J Med 2016;375:1823-33

Check mate 026

Untreated stage IV or recurrent NSCLC

- PD-L1 tumor-expression level of 1% or more
- ECOG - 0 or 1
- Measurable disease according to RECIST
- No previous systemic anticancer therapy as primary therapy for advanced or metastatic disease

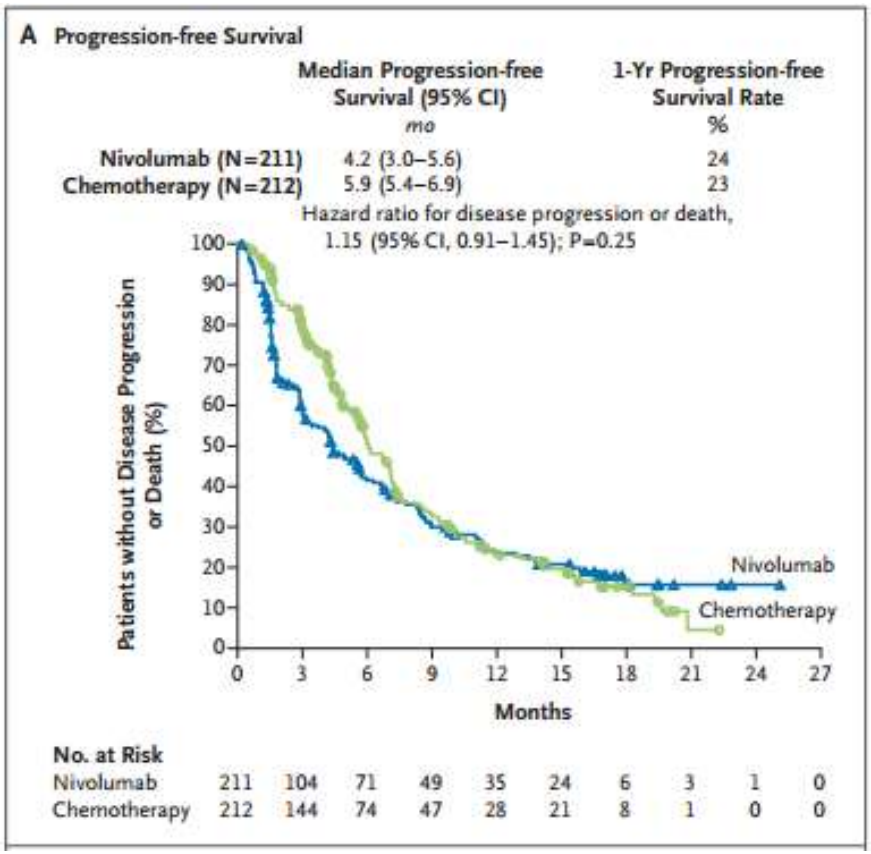
D.P. Carbone et al, N Engl J Med 2017;376:2415-26c

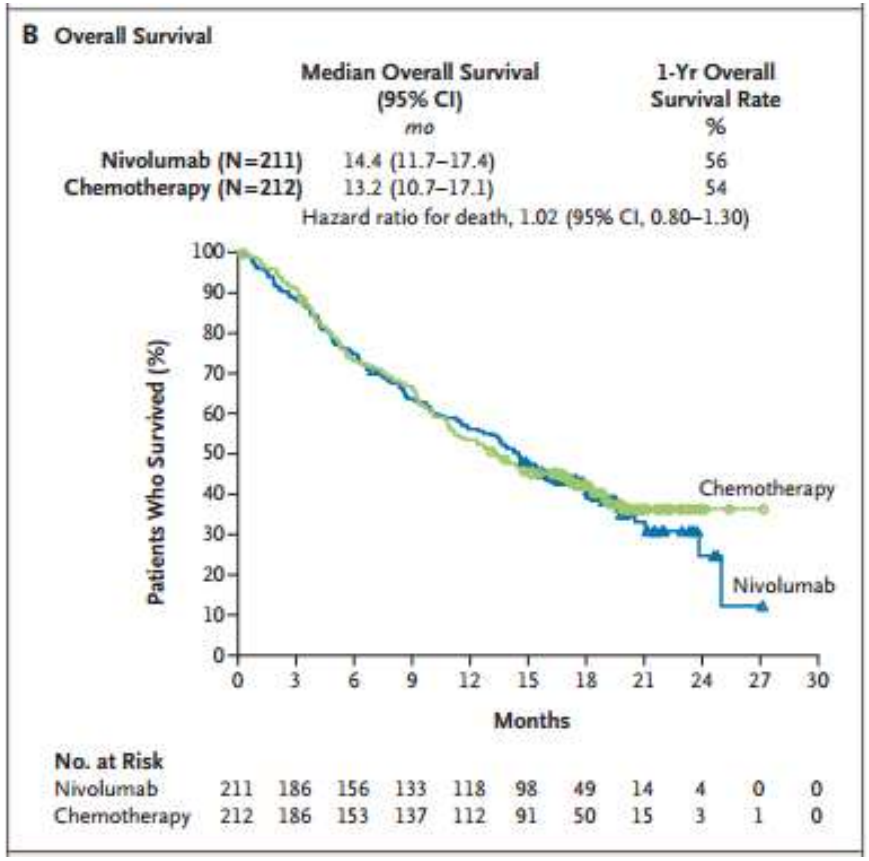
Check mate 026

	Nivolumab (n = 211)	Chemotherapy (n= 212)	HR
Median PFS	4.2 months (3.0 to 5.6)	5.9 months (5.4 to 6.9)	1.15 (0.91 – 1.45)
Median OS	14.4 months (11.7 to 17.4)	13.2 months (10.7 to 17.1)	1.02 (0.80 -1.30)
Median duration of response	12.1 months	5.7 months	-
Objective response rates	26 %	33 %	-
AEs / Gr3, 4 AEs	71 % /18 %	92 % /51 %	

D.P. Carbone et al, N Engl J Med 2017;376:2415-26c

Check mate 026

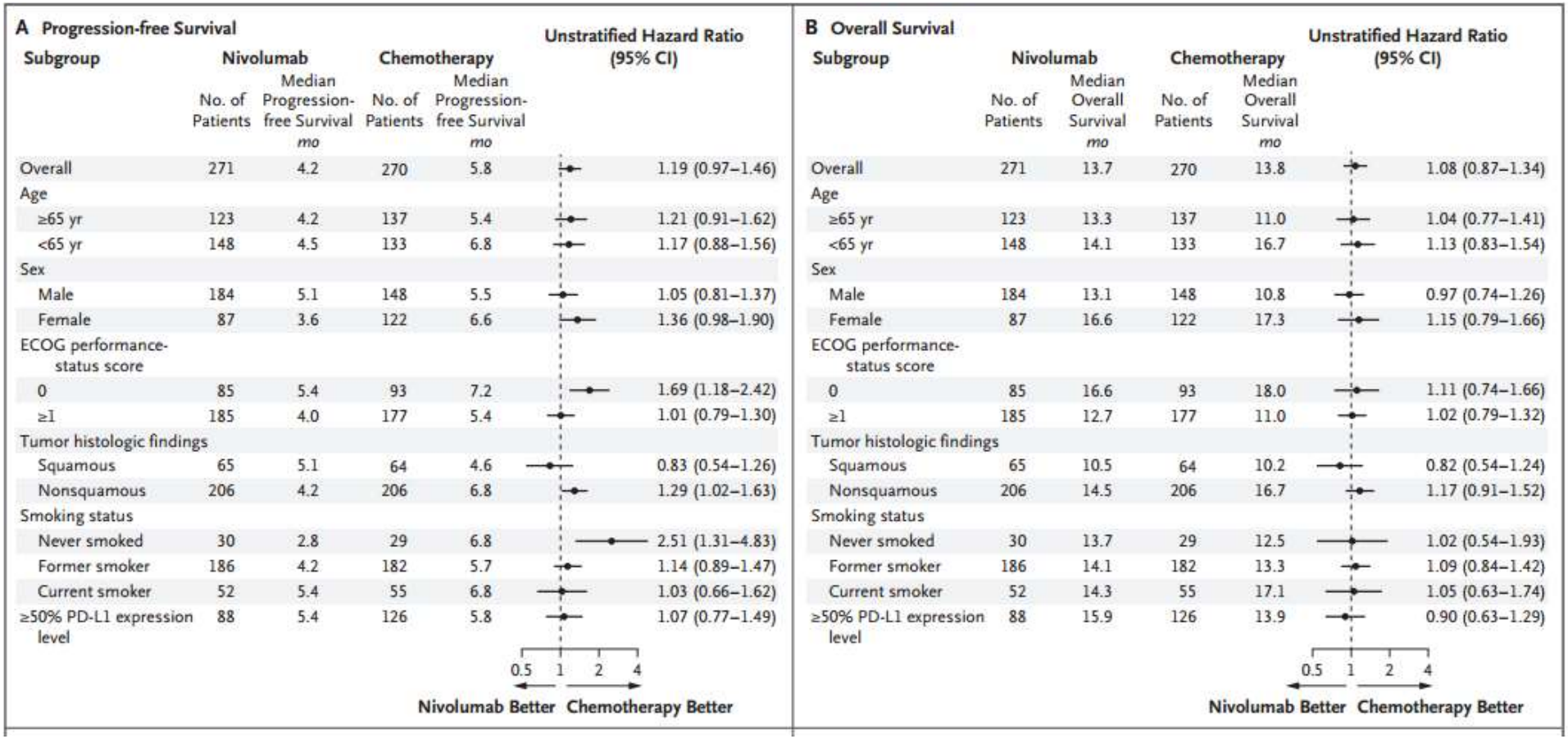




PFS and OS was similar in both the groups (in PDL1 ≥ 5 %)

D.P. Carbone et al, N Engl J Med 2017;376:2415-26c

Check mate 026



A Progression-free Survival

Subgroup	Nivolumab No. of Patients	Nivolumab Median Progression-free Survival mo	Chemotherapy No. of Patients	Chemotherapy Median Progression-free Survival mo	Unstratified Hazard Ratio (95% CI)
Overall	271	4.2	270	5.8	1.19 (0.97–1.46)
Age					
≥65 yr	123	4.2	137	5.4	1.21 (0.91–1.62)
<65 yr	148	4.5	133	6.8	1.17 (0.88–1.56)
Sex					
Male	184	5.1	148	5.5	1.05 (0.81–1.37)
Female	87	3.6	122	6.6	1.36 (0.98–1.90)
ECOG performance-status score					
0	85	5.4	93	7.2	1.69 (1.18–2.42)
≥1	185	4.0	177	5.4	1.01 (0.79–1.30)
Tumor histologic findings					
Squamous	65	5.1	64	4.6	0.83 (0.54–1.26)
Nonsquamous	206	4.2	206	6.8	1.29 (1.02–1.63)
Smoking status					
Never smoked	30	2.8	29	6.8	2.51 (1.31–4.83)
Former smoker	186	4.2	182	5.7	1.14 (0.89–1.47)
Current smoker	52	5.4	55	6.8	1.03 (0.66–1.62)
≥50% PD-L1 expression level	88	5.4	126	5.8	1.07 (0.77–1.49)

B Overall Survival

Subgroup	Nivolumab No. of Patients	Nivolumab Median Overall Survival mo	Chemotherapy No. of Patients	Chemotherapy Median Overall Survival mo	Unstratified Hazard Ratio (95% CI)
Overall	271	13.7	270	13.8	1.08 (0.87–1.34)
Age					
≥65 yr	123	13.3	137	11.0	1.04 (0.77–1.41)
<65 yr	148	14.1	133	16.7	1.13 (0.83–1.54)
Sex					
Male	184	13.1	148	10.8	0.97 (0.74–1.26)
Female	87	16.6	122	17.3	1.15 (0.79–1.66)
ECOG performance-status score					
0	85	16.6	93	18.0	1.11 (0.74–1.66)
≥1	185	12.7	177	11.0	1.02 (0.79–1.32)
Tumor histologic findings					
Squamous	65	10.5	64	10.2	0.82 (0.54–1.24)
Nonsquamous	206	14.5	206	16.7	1.17 (0.91–1.52)
Smoking status					
Never smoked	30	13.7	29	12.5	1.02 (0.54–1.93)
Former smoker	186	14.1	182	13.3	1.09 (0.84–1.42)
Current smoker	52	14.3	55	17.1	1.05 (0.63–1.74)
≥50% PD-L1 expression level	88	15.9	126	13.9	0.90 (0.63–1.29)

D.P. Carbone et al, N Engl J Med 2017;376:2415-26c

Check mate 026

- No definite benefit of survival was found even in any of the subgroups (histology or PDL1 ≥ 50 %)
- Chemotherapy group has less tumor burden and less liver mets
- High frequency of subsequent nivolumab therapy (58 % cross over) may have contributed to favourable OS in chemotherapy group

Nivolumab has no benefit over chemotherapy in untreated NSCLC

D.P. Carbone et al, N Engl J Med 2017;376:2415-26c

Differences in both the trials

- Although the precise reasons for the divergent outcomes of the KEYNOTE 024 trial and the CHECK MATE 026 trial remain unclear
- Cannot be attributed to a single factor
- Subtle differences are present which may be contributing factors

Remon J et al, BMC Medicine (2017) 15:55

Differences in both the trials

	KEYNOTE 024 (Pembrolizumab)	CHECKMATE 026 (Nivolumab)
PD L1 cut off	≥ 50%	≥ 5%
High PDL 1 ≥ 50% expression	No difference in both the groups	Higher proportion in the control arm compared to the nivolumab arm (126 vs 88) **Analysis was not prespecified*
Assay for PDL 1 expression	Anti–PD-L1 antibody (22 C3 antibody)	Anti–PD-L1 antibody (28-8 antibody)
	Sensitivity of the relevant clones used to define PD-L1 status is potentially different	
Tumor sample for testing	Tissue resected at the time the metastatic disease was diagnosed	Fresh or archival tumor-biopsy specimens obtained within 6 months

Remon J et al, BMC Medicine (2017) 15:55

Differences in both the trials

	KEYNOTE 024 (Pembrolizumab)	CHECKMATE 026 (Nivolumab)
% never smokers in study group	3 %	11 %
	Never smokers have low mutational load Efficacy of immune checkpoint inhibitors is lower among never smokers	
% RT before enrollment	Previous RT within 6 months is an exclusion criteria	37.6%
	Previous RT can have major consequences on the tumor microenvironment and potentially lead to decreased activity of inhibitors in previously irradiated areas	
Systemic GC Rx	Ineligible	Concomitant GC Rx was allowed

Remon J et al, BMC Medicine (2017) 15:55

First line Rx

- Pembrolizumab – received FDA approval in October 2016
- Only ICPi approved alone as a first line therapy in metastatic NSCLC with TPS ≥ 50 % with no EGFR or ALK genomic tumour aberrations

IN COMBINATION WITH CHEMOTHERAPY

As a combination 1st line

Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

*Corey J Langer, Shirish M Gadgeel, Hossein Borghaei, Vassiliki A Papadimitrakopoulou, Amita Patnaik, Steven F Powell, Ryan D Gentzler, Renato G Martins, James P Stevenson, Shadia I Jalal, Amit Panwalkar, James Chih-Hsin Yang, Matthew Gubens, Lecia V Sequist, Mark M Awad, Joseph Fiore, Yang Ge, Harry Raftopoulos, Leena Gandhi, for the KEYNOTE-021 investigators**

KEYNOTE 021, Lancet Oncol 2016

Synergy with chemotherapy

Immunologic effects of chemotherapy

- Induction of PD-L1 expression on tumour cells
- Reducing the regulatory T cell activity
- Killing the tumour cells
  - improves the T cell to tumour ratio
  - reduces barriers to T-cell migration into the tumour
  - diminishes immunosuppressive substances release

Key note 021

- Addition of pembrolizumab to platinum-doublet chemotherapy improves efficacy in patients with advanced non-squamous NSCLC
- Randomised, open-label, phase 2 trial
- Chemotherapy-naive, stage IIIB or IV, non-squamous NSCLC without targetable EGFR or ALK genetic aberrations

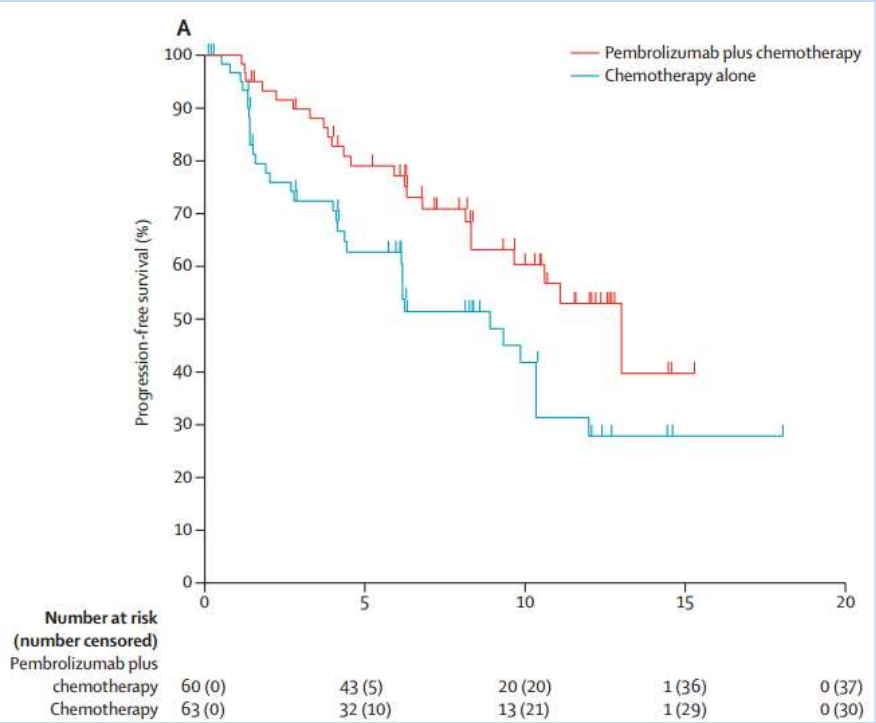
Corey J Langer et al, Lancet Oncol 2016

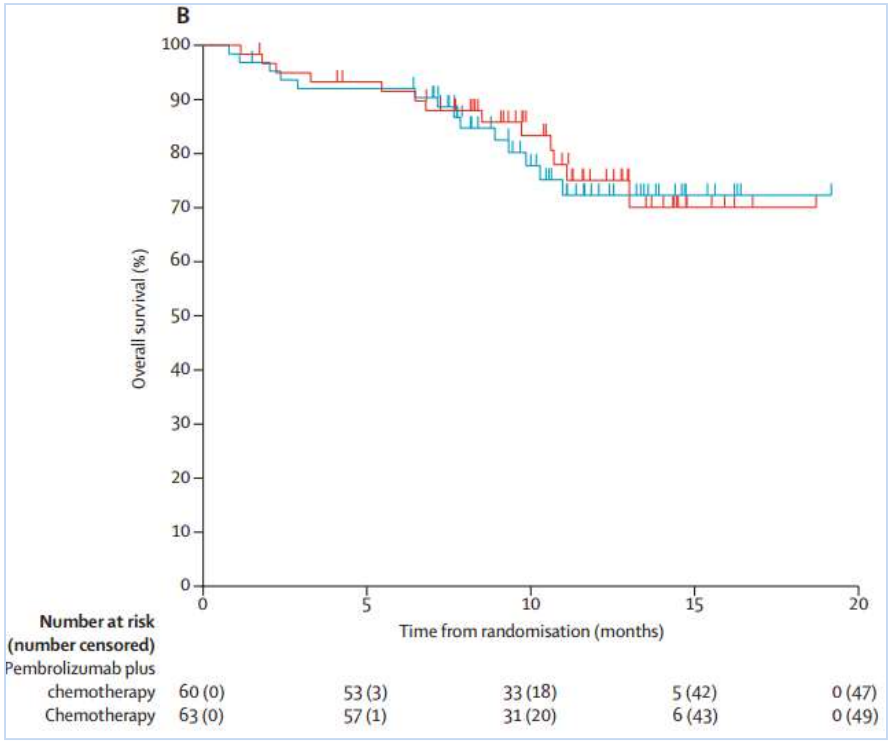
Key note 021

	Pembrolizumab + Carboplatin/pemetrexed (n = 60)	Carboplatin/pemetrexed (n= 63)	HR
Objective response	**33 (55%)** **95 % CI 42–68**	**18 (29%)** **95 % CI 18–41** **p 0.0016**	
Median PFS	**13·0 months** **(95% CI 8·3 to NR)**	**8·9 months** **(95% CI 4·4–10·3)**	0.53 (0.31 – 0.91)
Rate of deaths at data cut off	13 (22%)	14 (22%)	0.90 (0.42 –1.91)
Median time to response	1·5 (1·4–2·8)	2·7 (1·4–2·8)	
Response PD L1 <1 % 1- 49% ≥ 50 %	 **57 %** **26 %** **80 %**	 **13 %** **39 %** **35 %**	

Corey J Langer et al, Lancet Oncol 2016

Key note 021





Corey J Langer et al, Lancet Oncol 2016

Key note 021

- Benefit in progression free survival but no difference in overall survival
- Objective response was similar in patients with a PD-L1 TPS < 1% and those with a score of ≥ 1%
- Possibly higher proportion of responses in patients with a tumour proportion score of 50% or greater

Corey J Langer et al, Lancet Oncol 2016

Key note 021

- Small sample sizes of the individual subgroups - relationship between PD-L1 expression and efficacy in patients treated with pembrolizumab plus chemotherapy inconclusive
- FDA approval in May 2017 – as a first line therapy in combination with chemotherapy in non squamous NSCLC regardless of the PDL 1 expression with no EGFR or ALK genomic tumour aberrations

Corey J Langer et al, Lancet Oncol 2016

PDL -1 TESTING

Does PDL-1 testing really needed?

- Potential predictive biomarker for efficacy from anti–PD-1 and PD-L 1 targeted agents
- Improved response rates in PDL-1 expressors
- But efficacy also seen in patients with PD-L1–negative tumors, albeit at a lower rate

PDL-1 testing

	PDL-1 testing	Results
Check mate 017 (Squamous NSCLC)	Retrospective in archival samples (83 %) Clone 28-8	**No difference in OS, PFS, ORR in all the prespecified PDL 1 subgroup analyses**
Checkmate 057 (Non squamous NSCLC)	Retrospective in archival samples (78 %) Clone 28-8	**PDL 1 expressors has better OS, PFS and ORR with Nivolumab than docetaxel at all prespecified PDL -1 levels (≥ 1 %, ≥ 5%, ≥ 10 %) PDL 1 non expressors have equal ORR, PFS and OS b/n docetaxel and nivolumab**
Checkmate 026 (NSCLC) 1st line Rx	Fresh or archival tumor-biopsy Clone 28-8 **Only PDL 1 ≥ 5 %**	**No definite association was seen with PDL-1 expression and efficacy**

***Previously treated Squamous NSCLC – independent of PDL1**
***Previously treated Non squamous NSCLC – better in PDL1 expressors, but in non expressors equivalent to chemotherapy**

PDL-1 testing

	PDL-1 testing	Results
KEYNOTE 001 (phase I) PD-L1 ≥ 1%	Contemporaneous sample anti–PD-L1 antibody clone 22C3	**PDL1 ≥ 50 % had better median OS and PFS** But no comparator group prevents the assessment of the prognostic implications of PD-L1 expression
KEYNOTE 010 PD-L1 ≥ 1%	Archival/new sample antibody clone 22C3	**PDL1 ≥ 50 % had better PFS than over all** **OS and ORR no difference**
KEYNOTE 024 PD-L1 ≥ 50 %	Fresh sample antibody clone 22C3	**Better PFS, OS and ORR** **But all patients were PDL1 ≥ 50 %**
KEYNOTE 021 Combi with CT	**Had response in all the subgroups and on PDL 1 expressors as a first line in combination with chemo Rx**	

***Trials of Pembrolizumab didnt include non PDL expressors & the benefit of it in them is not known**

***But it has shown benefit in combination with chemotherapy as 1st line**

PDL-1 testing

	PDL-1 testing	Results
POPLAR Phase II	VENTANA SP142 PD-L1 IHC assay	**OS benefit increased with increasing PD-L1 expression** on tumour cells, tumour infiltrating immune cells, or both **PD-L1 expression is predictive of OS benefit**
OAK trial Phase III		**OS benefit is independent of PDL 1expression** But better response rates in high PDL1 expressors (TC 3/IC 3)

***Previously treated NSCLC – different in both the trials**

Companion diagnostic assays comparison

Agent	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Primary antibody clone used in the assay system	28-8 (Dako)	22C3 (Dako)	SP142 (Ventana)	SP263 (Ventana)
Interpretive scoring	Tumor cell membrane	Tumor cell membrane	Tumor cell membrane Infiltrating immune cells	Tumor cell membrane
Instrument and detection systems required	EnVision Flex on AutostainerLink 48	EnVision Flex on AutostainerLink 48	OptiView detection and amplification on Benchmark ULTRA	OptiView detection on Benchmark ULTRA
Therapeutic developer	Bristol-Myers Squibb	Merck	Genentech	AstraZeneca

Different definition of PD-L1 positivity
Different antibody & different techniques
All PD-L1 IHC assays are aligned with regard to PD-L1 expression on TCs except for Ventana , SP 142
Greater variability among the immune cell staining
Interchanging assays and cut offs would lead to "misclassification" of PD-L1 status for some patients

Fred R. Hirsch, et al, Journal of Thoracic Oncology 2017

PDL-1 testing

- Lack of uniform assay
- Dynamic nature of PD-L1 expression

- **"PD-L1 positivity may predict those more likely to respond, it does not capture all of those who benefit from treatment"**

TOXICITY OF ICPI

Toxicities (ICPis)

- Infusion reactions
- Immune-related adverse events (irAEs) or adverse events of special interest (AEoSI)

ESMO clinical practice guidelines, Annals of Oncology 2017
Celine Boutros et al; Nat Rev Clin Oncol vol 13, 2016

irAE

- Block the negative regulators of immunity that are normally important for maintaining immunologic homeostasis
- Distinct both in mechanism and management from adverse effects commonly associated with chemotherapy
- Majority of data documenting irAEs come from large published trials, mostly in patients with advanced melanoma, NSCLC, and renal cell carcinoma

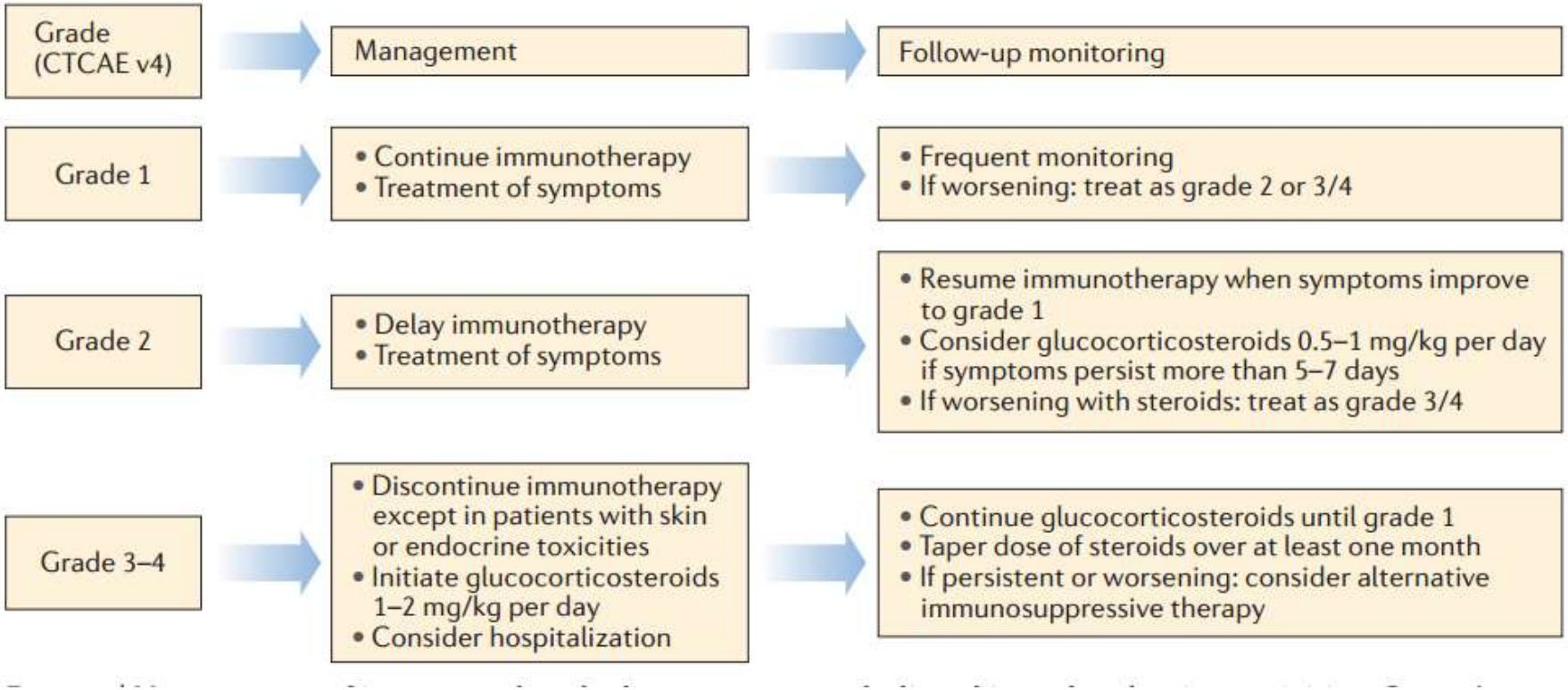
ESMO clinical practice guidelines, Annals of Oncology 2017
Celine Boutros et al; Nat Rev Clin Oncol vol 13, 2016

Toxicities (ICPis)

	AEs	Grade 3,4 AEs
anti-CTLA4	60 % - 85 %	10 % - 25 %
Nivolumab		
Squamous NSCLC	58 %	7 %
Non squamous NSCLC	69 %	10 %
Pembrolizumab		
2 mg/kg	63 %	13 %
10 mg/kg	66 %	16 %
200 mg	73.4 %	26.6 %
Combination Rx	95 %	55 %

More severe and early onset in combination Rx

Toxicities (ICPis)



Alternate immunosuppression – Infliximab, Cyclophosphamide, MMF, Tacrolimus

Celine Boutros et al; Nat Rev Clin Oncol vol 13, 2016

Fatigue

- Most common side effect
- PD-1 & anti-PD-1 ligand agents - 16 to 24 %
- Ipilimumab - 40 %
- Generally mild, and severe fatigue is rare
- Exclude thyroid, pituitary, and other endocrine disorders

ESMO clinical practice guidelines, Annals of Oncology 2017
Celine Boutros et al; Nat Rev Clin Oncol vol 13, 2016

Skin irAE

- CTLA4 (ipilimumab) 43% - 45%
- PD-1 (nivolumab and pembrolizumab) ~ 34%
- Develop early in the course of treatment
- Rash, pruritus and vitiligo
- Serious skin AEs (SJS, TEN, DRESS) are rare
- Rule out any other aetiology of the skin
- Evaluation of the severity of the disease

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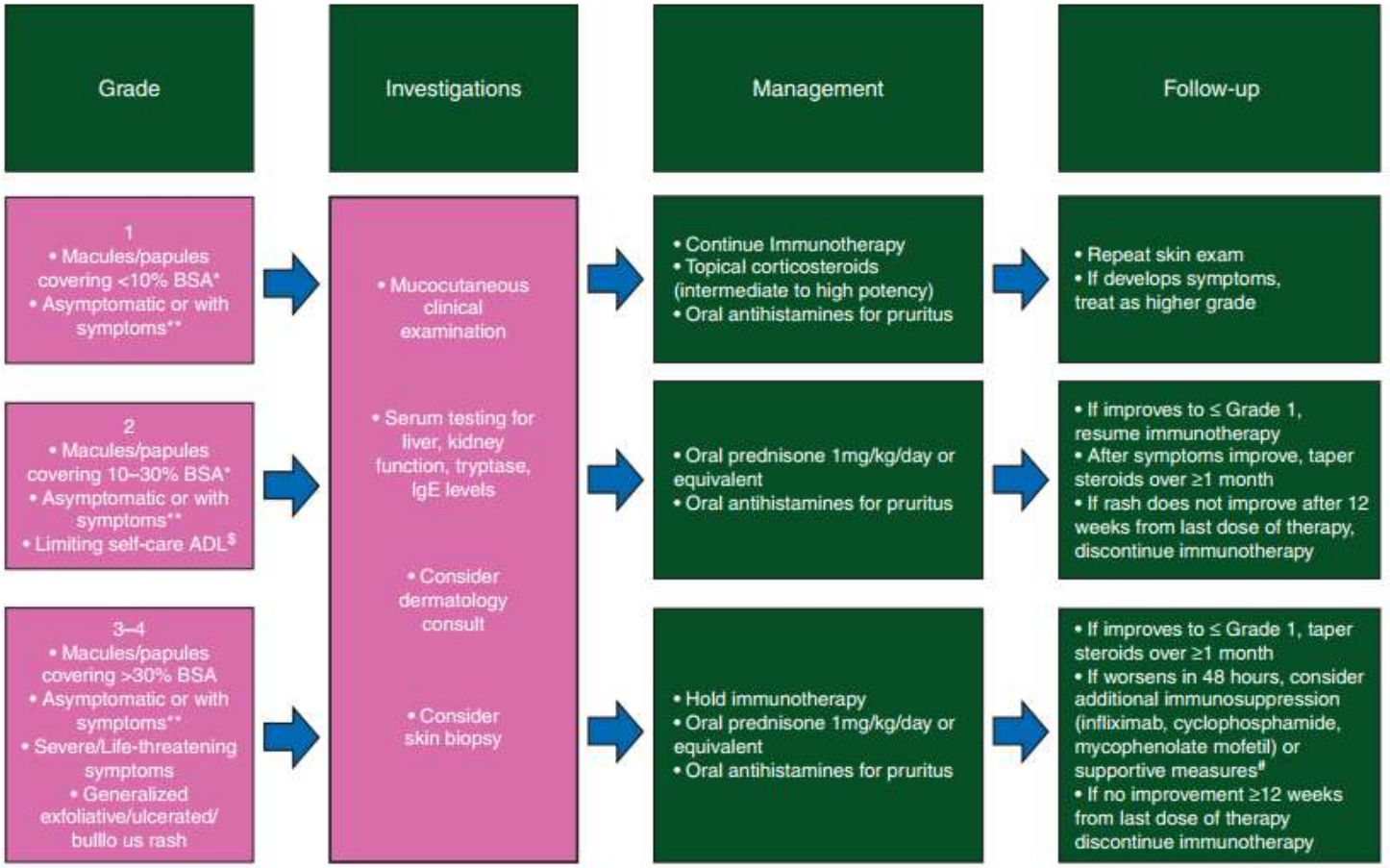
Skin irAE


Grade
Investigations
Management
Follow-up
1
• Macules/papules covering <10% BSA*
• Asymptomatic or with symptoms**
2
• Macules/papules covering 10–30% BSA*
• Asymptomatic or with symptoms**
• Limiting self-care ADL$
3–4
• Macules/papules covering >30% BSA
• Asymptomatic or with symptoms**
• Severe/Life-threatening symptoms
• Generalized exfoliative/ulcerated/ bulllo us rash
• Mucocutaneous clinical examination
• Serum testing for liver, kidney function, tryptase, IgE levels
• Consider dermatology consult
• Consider skin biopsy
• Continue Immunotherapy
• Topical corticosteroids (intermediate to high potency)
• Oral antihistamines for pruritus
• Oral prednisone 1mg/kg/day or equivalent
• Oral antihistamines for pruritus
• Hold immunotherapy
• Oral prednisone 1mg/kg/day or equivalent
• Oral antihistamines for pruritus
• Repeat skin exam
• If develops symptoms, treat as higher grade
• If improves to ≤ Grade 1, resume immunotherapy
• After symptoms improve, taper steroids over ≥1 month
• If rash does not improve after 12 weeks from last dose of therapy, discontinue immunotherapy
• If improves to ≤ Grade 1, taper steroids over ≥1 month
• If worsens in 48 hours, consider additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil) or supportive measures#
• If no improvement ≥12 weeks from last dose of therapy discontinue immunotherapy

Endocrine irAE

- Unlike others, they are permanent
- Require permanent hormone replacement Rx
- Hypophysitis & pituitary dysfunction
- Hypo > hyperthyroidism
- Potential for permanent HPG axis dysfunction, should be counselled appropriately future fertility
- Adrenal crisis – most severe
- Type 1 diabetes mellitus

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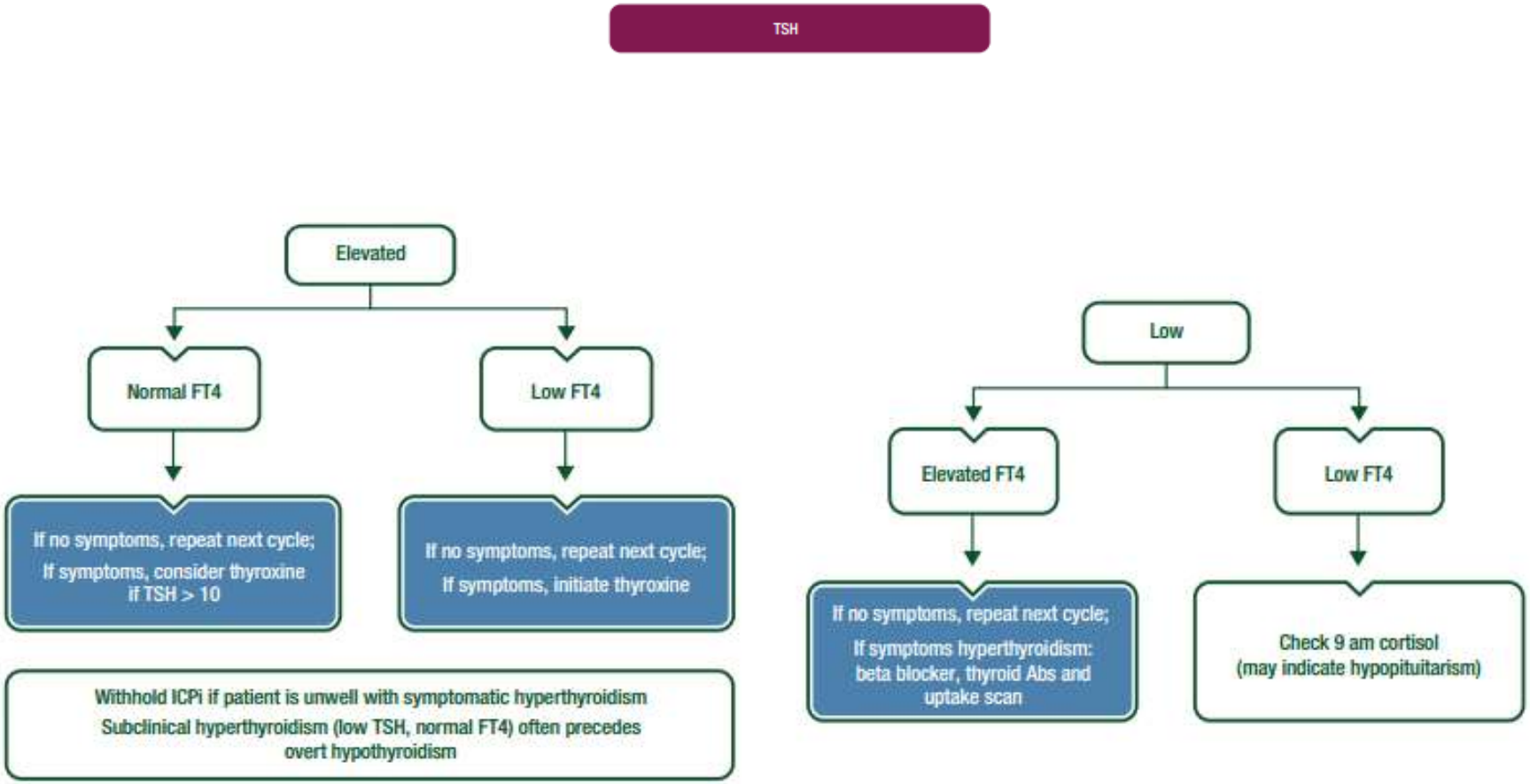
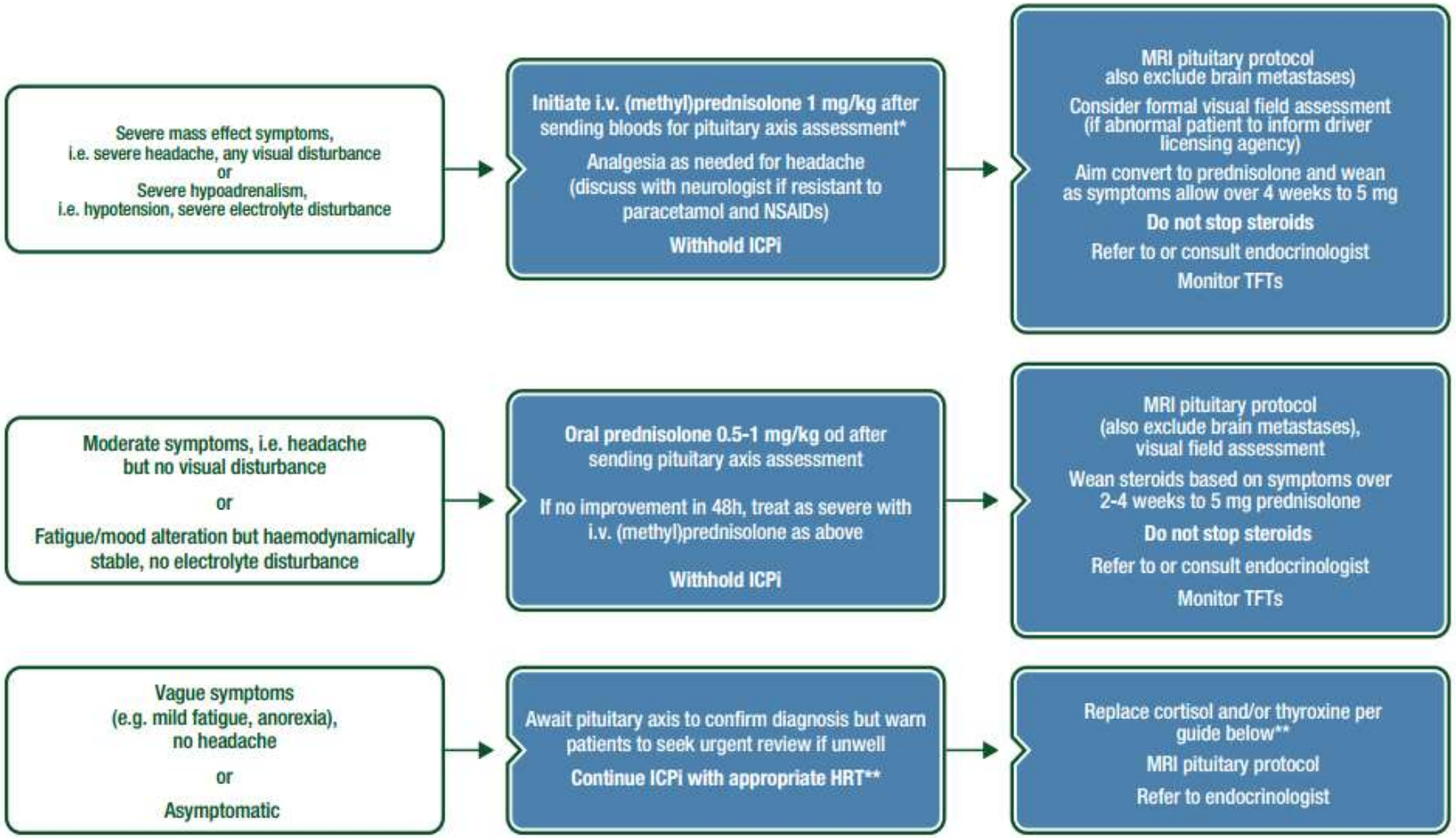
Thyroid dysfunction



Pituitary dysfunction



Endocrine irAE

- Thyroid dysfunction is found by routine blood tests (TSH and FT4)
- TFTs every cycle for first 3 months, every second cycle thereafter
- Cortisol as indicated by symptoms/falling TSH
- Comprehensive metabolic profile including glucose for the first 12 weeks of therapy

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Hepatotoxicity

- Most episodes are asymptomatic
- Radiology may show mild hepatomegaly, peri-portal edema, or periportal lymphadenopathy
- Biopsy – severe panlobular hepatitis with prominent perivenular infiltrate with endothelitis
- Infliximab should not be given to patients with elevated AST/ALT since it carries a risk of hepatotoxicity

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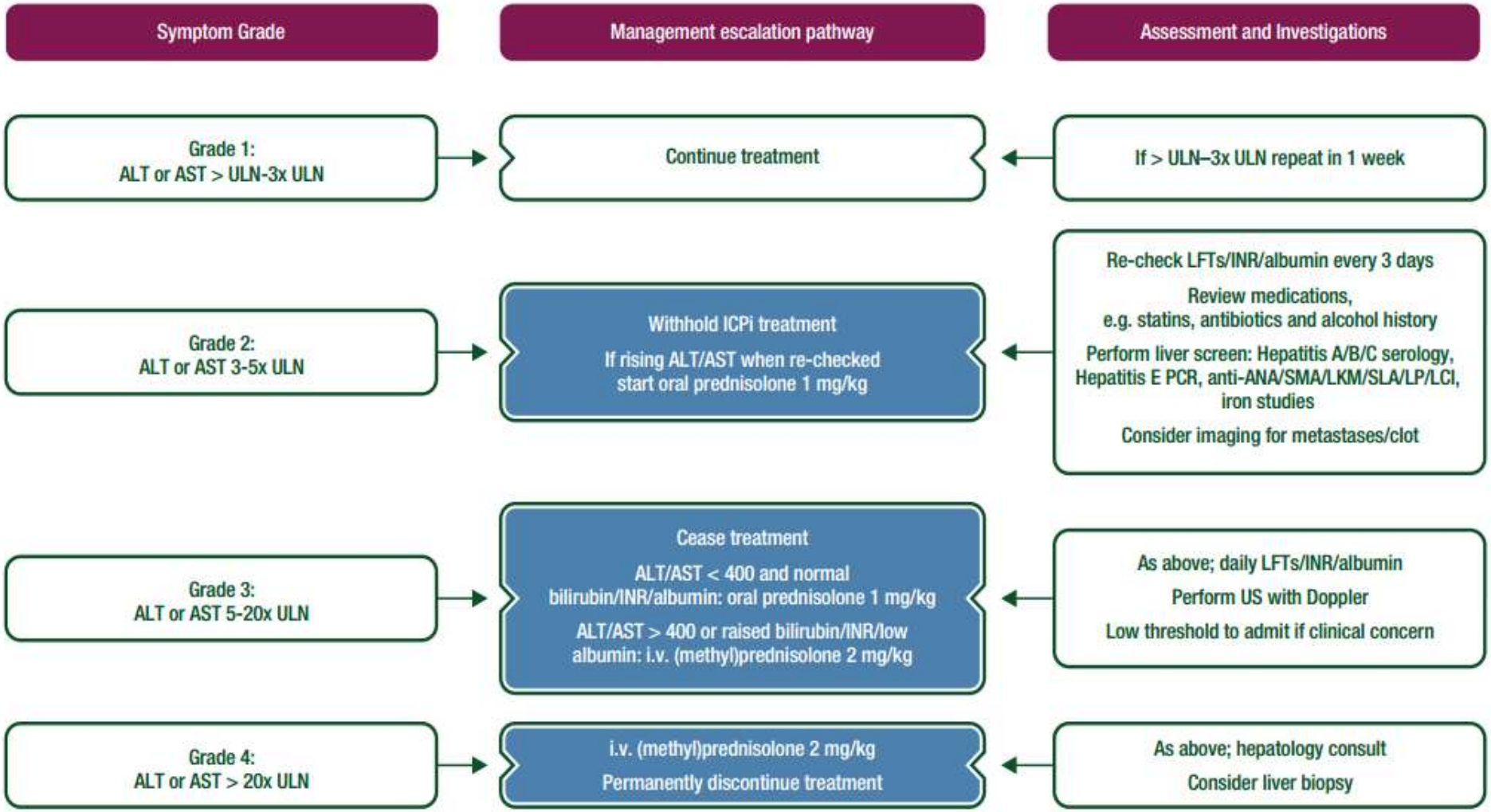
Hepatotoxicity



Diarrhoea/colitis

- 27 – 54 % in ipilimumab recipients
- Less common with PD 1 and PDL 1 agents
- A/w abdominal pain, hematochezia, weight loss, fever & vomiting
- Stool analyses for enteropathogens
- Confirmed by flexible sigmoidoscopy or colonoscopy with biopsies if grade 2 or higher

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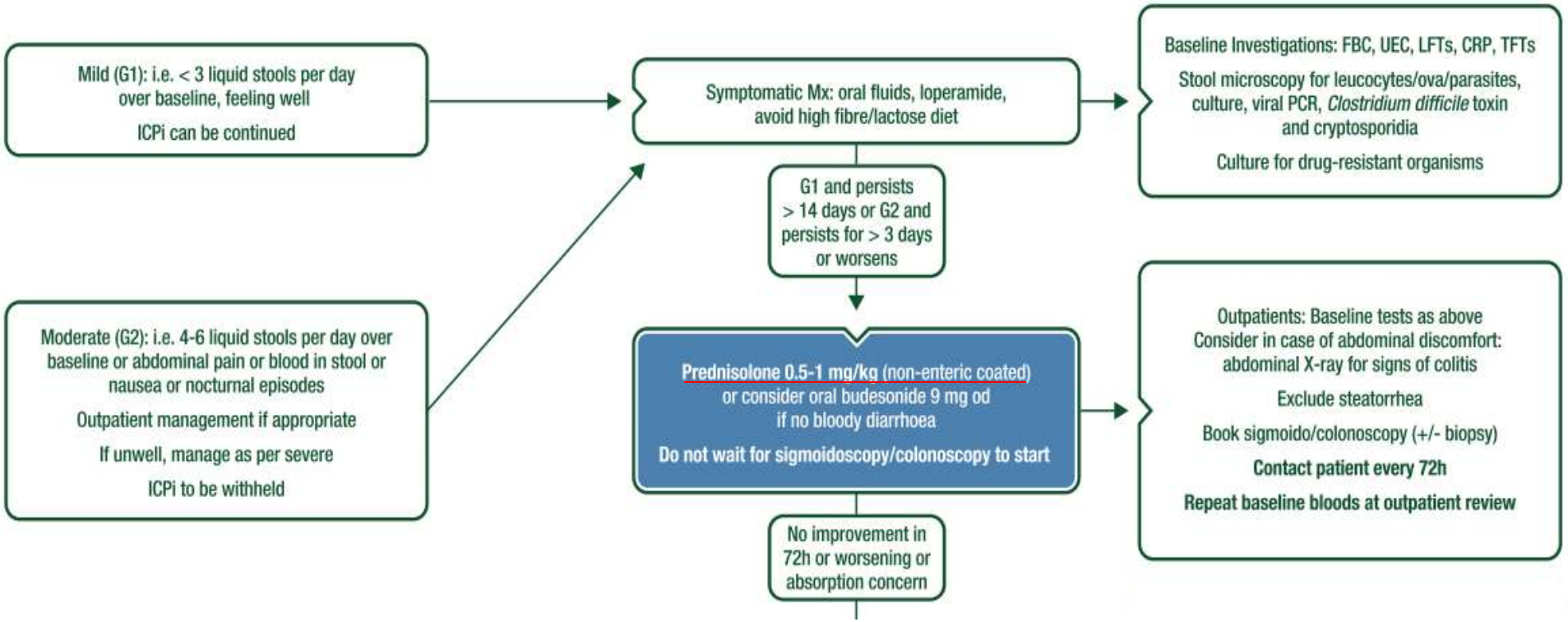
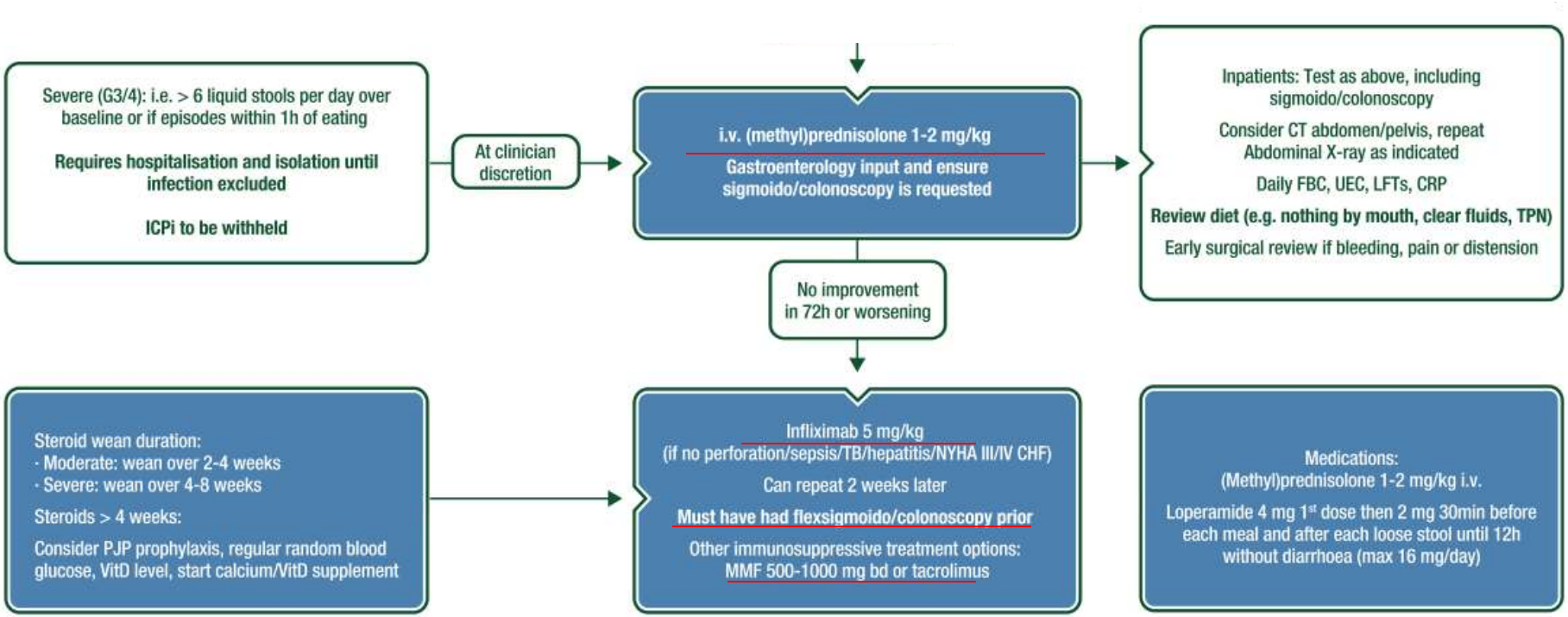
Diarrhoea/colitis



Diarrhoea/colitis



Pneumonitis

- 5% of patients treated with anti–PD-1/PD-L1 mAbs
- 1 % grade 3 and higher pneumonitis

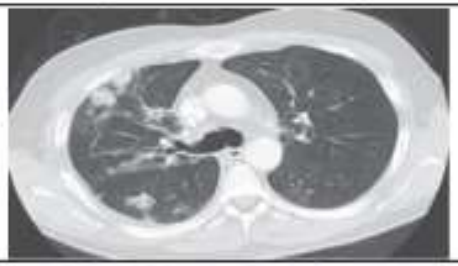
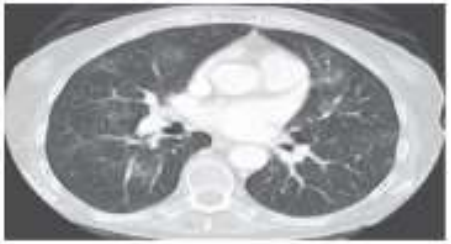
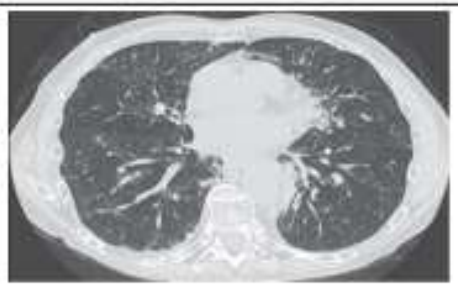
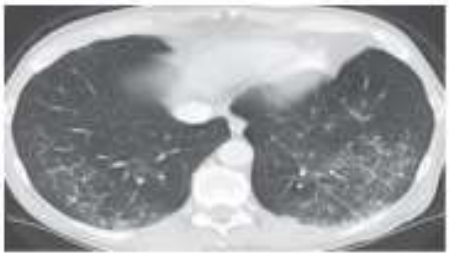
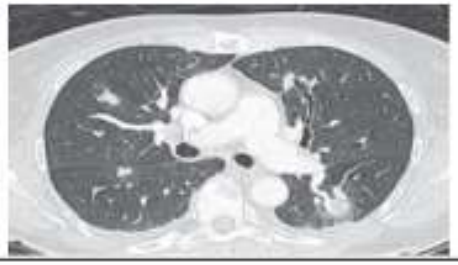
- Single case series of 43 patients of PD/ PDL-1 pneumonitis
- 72 % (31 of 43) of cases were grade 1 to 2
- Median of 2.8 months (9 days - 19 months) of Rx
- 1/3rd identified incidentally by imaging.
- 1/4th cases - CXR did not detect a new abnormality

Naidoo J eta l, J Clin Oncol 2016

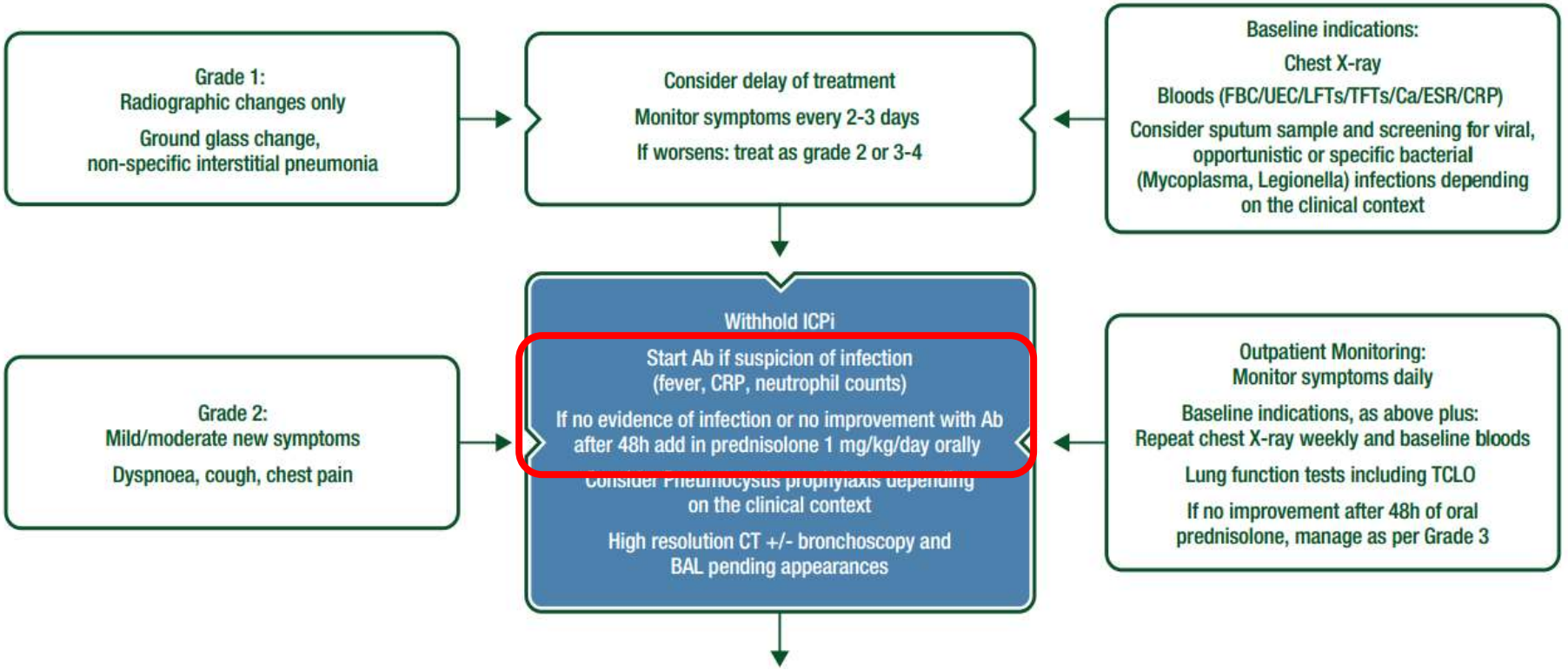
Pneumonitis

- 37 of 43 (86 %) improved by simply withholding ICPi or treating with immunosuppression
- Worse in current/former smokers
- 12 (all with grade 1 to 2) underwent re challenge and recurrent pneumonitis occurred in three (25%)
- *Diagnosis of exclusion and requires consideration of competing diagnoses, including infection and malignant lung infiltration*
- *Diagnostic bronchoscopy with lung biopsy play an important role*

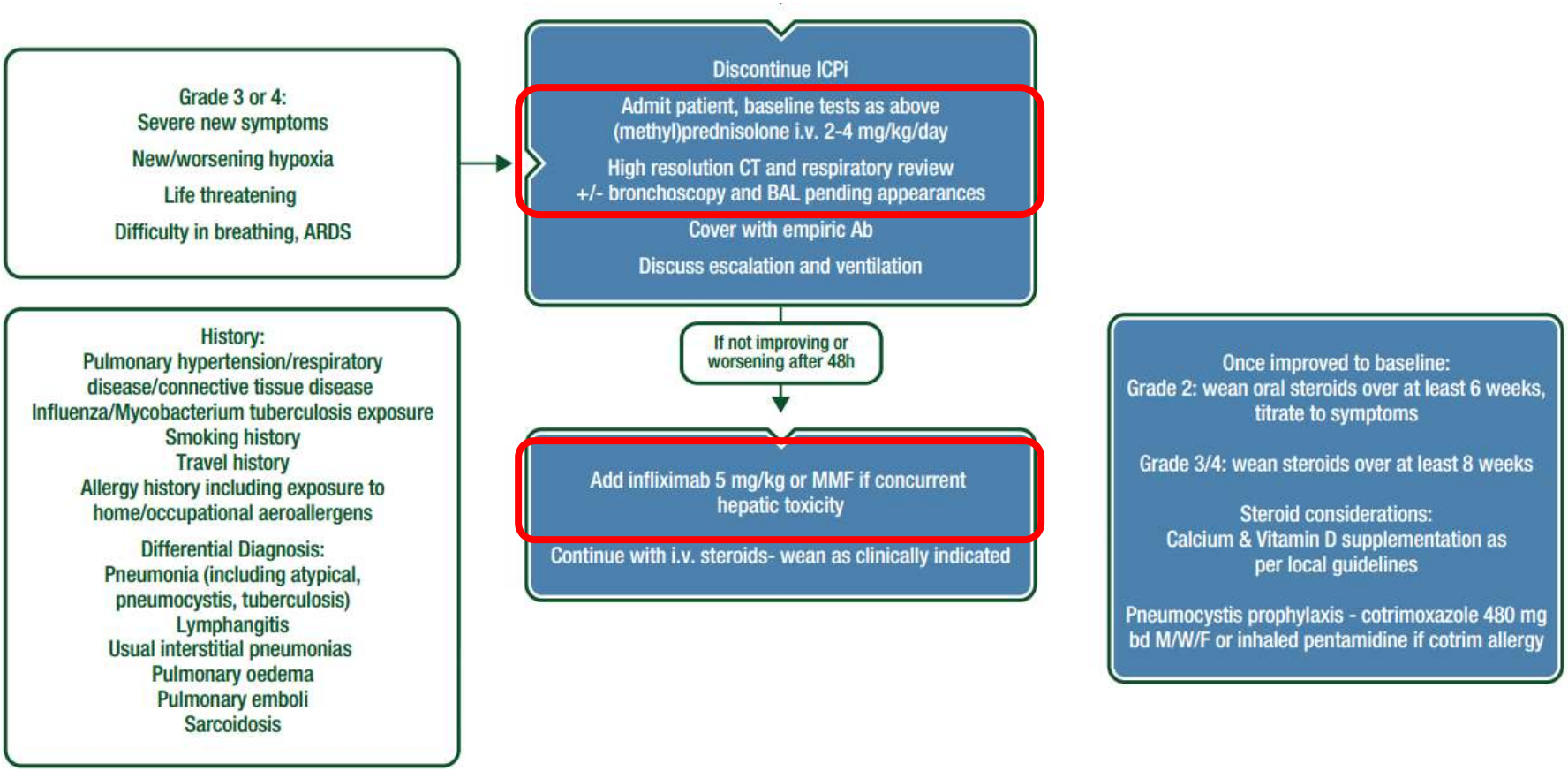
Naidoo J eta l, J Clin Oncol 2016

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

Pneumonitis



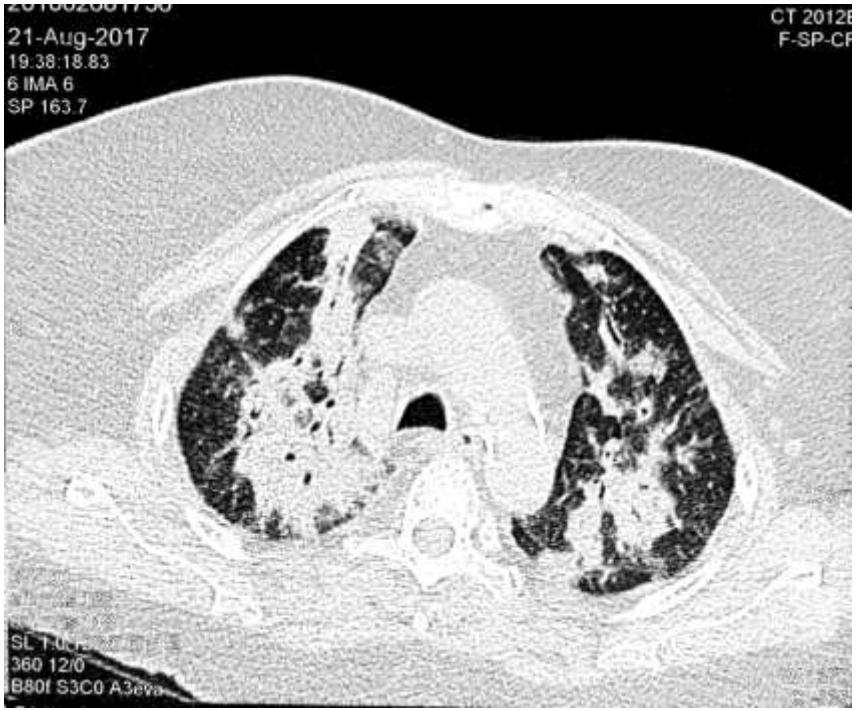
Pneumonitis

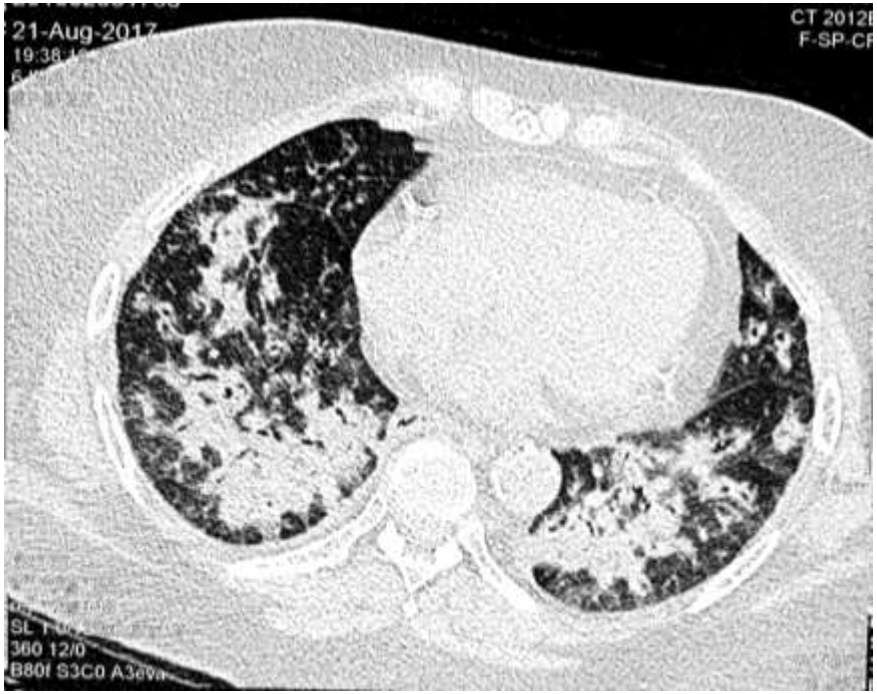


CPI should be delayed until the daily dose of steroids ≤ 10 mg of oral prednisone/day in Grade 1 and 2 pneumonitis

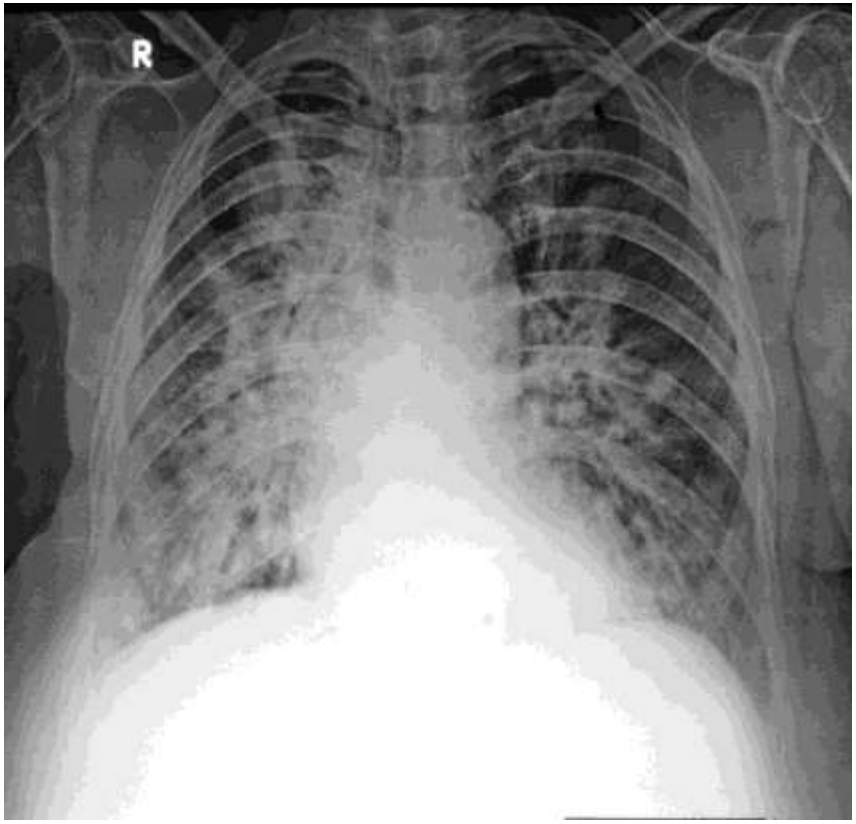
Naidoo J eta l, J Clin Oncol 2016

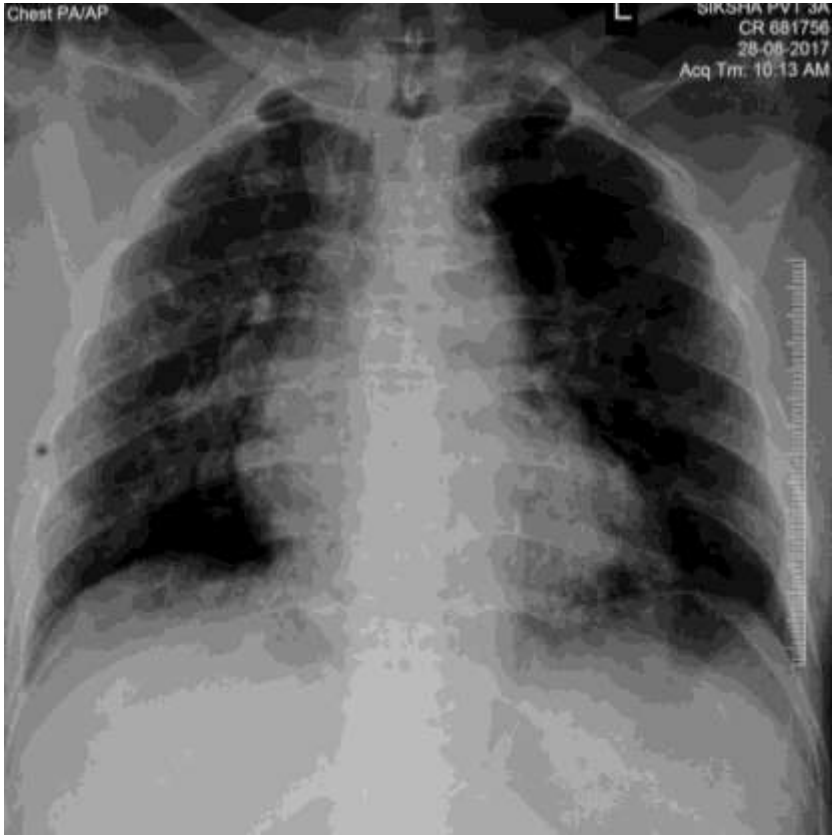
Pneumonitis





Pneumonitis





Rare irAEs

- Neurologic toxicity -polyneuropathy, facial nerve palsy, demyelination, myasthenia gravis, LGBS, posterior reversible leuko- encephalopathy, transverse myelitis, enteric neuropathy, encephalitis and aseptic meningitis
- Rheumatologic toxicity - mild or moderate myalgias and arthralgia
- Cardiac toxicity -myocarditis, pericarditis, arrhythmias, cardiomyopathy and impaired ventricular function

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Rare irAEs

- Ocular toxicity - keratitis, uveitis, orbital inflammation, including thyroid- opthalmopathy and idiopathic orbital inflammation and retinal and choroidal disease (choroidal neovascularisation and melanoma associated retinopathy)

- Renal toxicity
- Hematologic toxicity - rare

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Take home message

ICPIs act by enhancing tumour immunity

PDL 1 is predictor of responsiveness to ICPis

Immune related adverse events – requires stoppage/ withholding Rx and immunosuppression

Agent	FDA approval
Nivolumab	Previously treated NSCLC irrespective of PDL 1 expression
Pembrolizumab	Previously treated NSCLC (PDL1 ≥ 1%) As a first line agent in NSCLC (PDL 1 ≥ 50 %) As combination with chemotherapy in nonsquamous NSCLC irrespective of PDL1 expression
Atezolizumab	Previously treated NSCLC irrespective of PDL 1 expression

THANK YOU