Immunotherapy: the quest for a biomarker

Prof Keith M Kerr

Department of Pathology,

Aberdeen University School, Aberdeen Royal Infirmary, UK

Disclosures

- I have acted as consultant for Roche Genentech, Astra Zeneca, Pfizer, Eli Lilly, Novartis, Boehringer Ingelheim, Clovis, Bristol Myers Squibb, Merck Sharp Dohme

- I have received honoraria for speaker bureau from Roche Genentech, Astra Zeneca, Pfizer, Eli Lilly, Novartis, Boehringer Ingelheim, Bristol Myers Squibb

Biomarkers

- Biological features which are associated with disease behaviour
- Predictive biomarkers ‘predict’ the likely outcome from a therapy

- The ideal biomarker: always correct
  - Easy and practical to measure
  - Present or absent
  - Stable and functionally unique
  - 100% predictive

- Usually biologically related to the system being examined
  - The drug target
  - A co-factor of the drug target
  - A factor negating drug effect

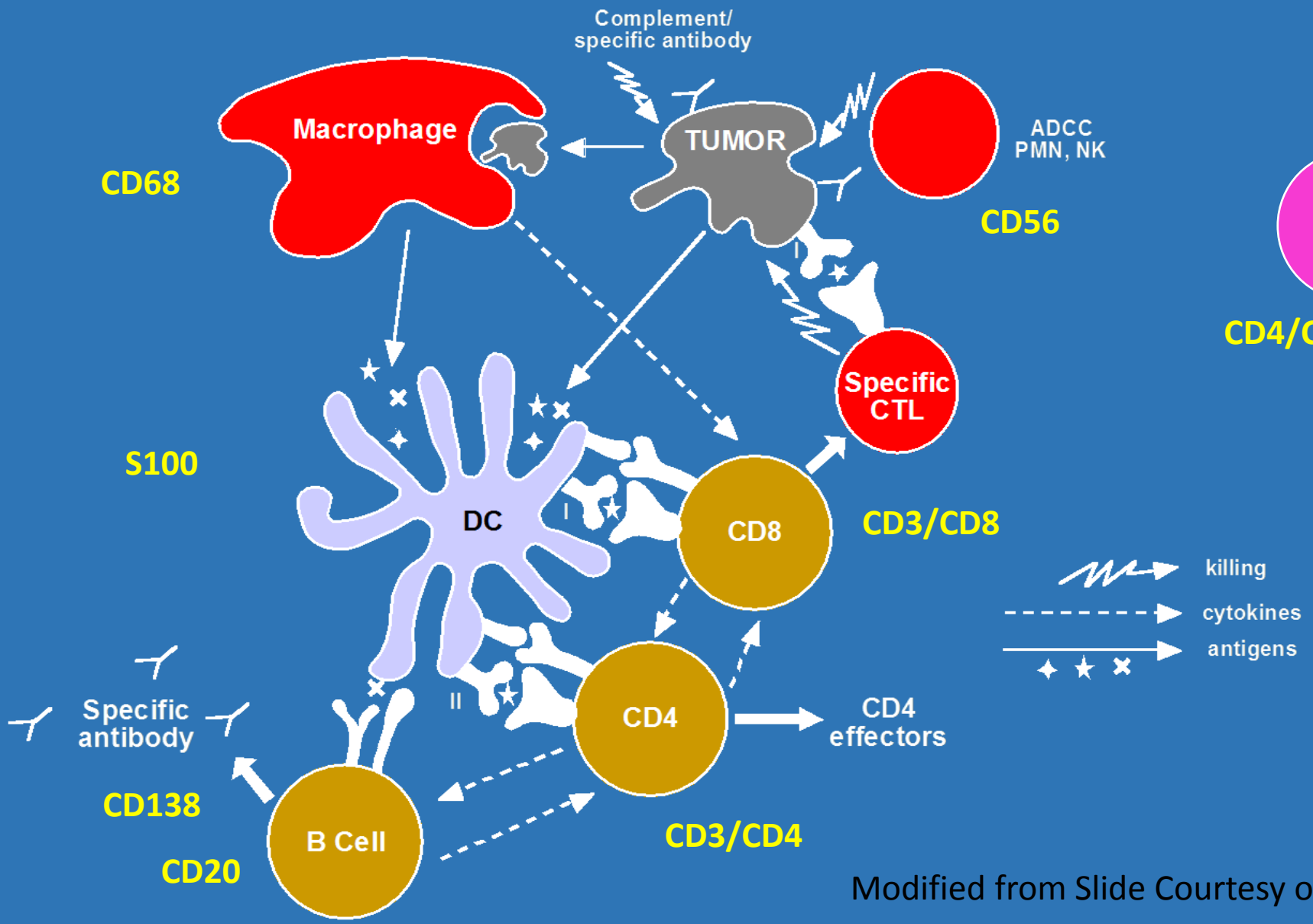
A biological rationale makes us more confident?

Biomarkers in lung cancer (so far……)

- Our experience is with the ‘low hanging fruit’
- Addictive oncogenes
  - Main driver of tumour
  - Mutation or translocation: relatively easy to measure
  - ‘Present or Absent’ at least in terms of current thinking

- And yet……
  - Best response rates are 60-70%
  - Testing is not ‘fool-proof’

Tumour immune response are VERY complex and involve many factors

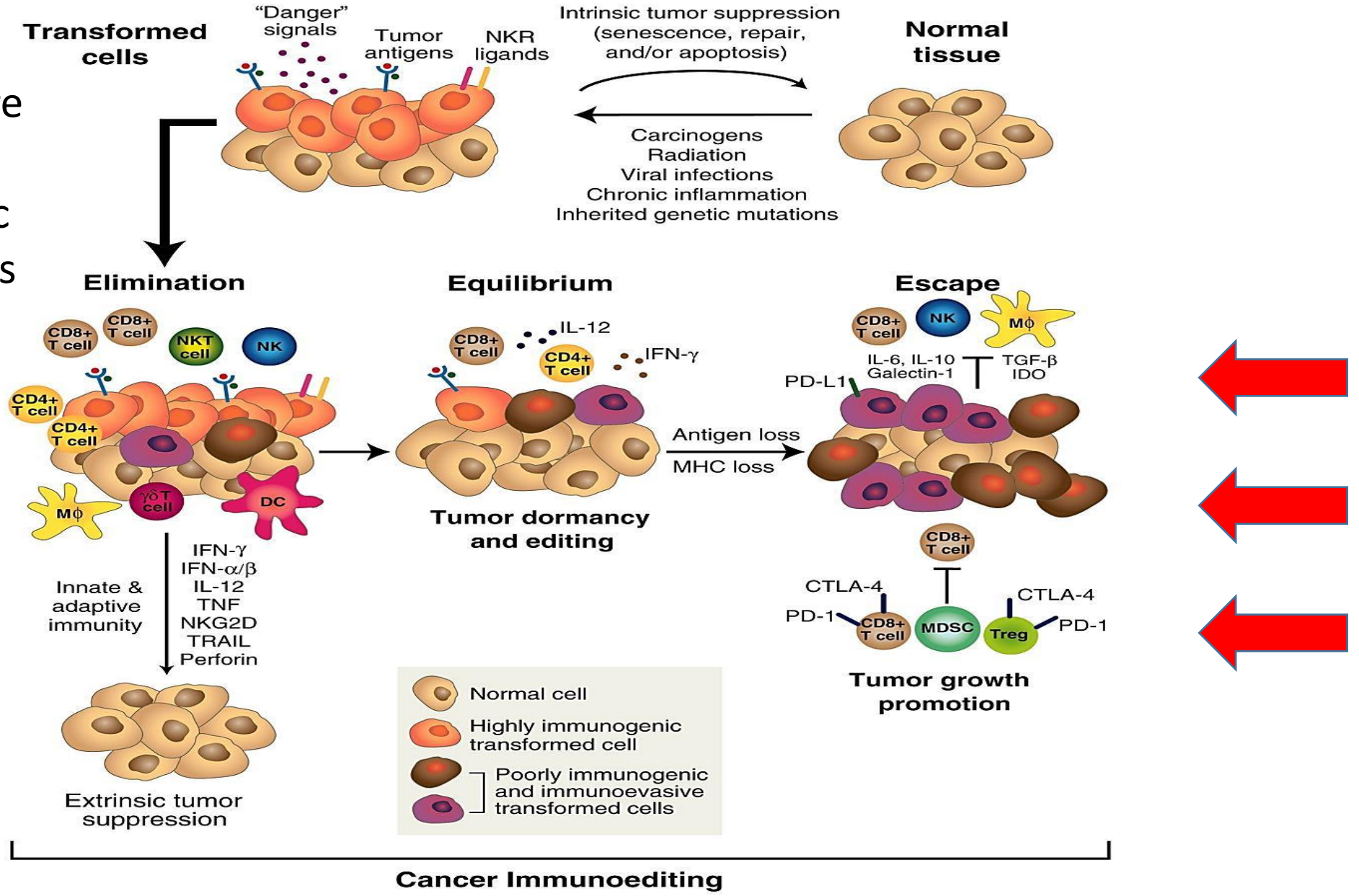


Modified from Slide Courtesy of Dr D Carbone, MD

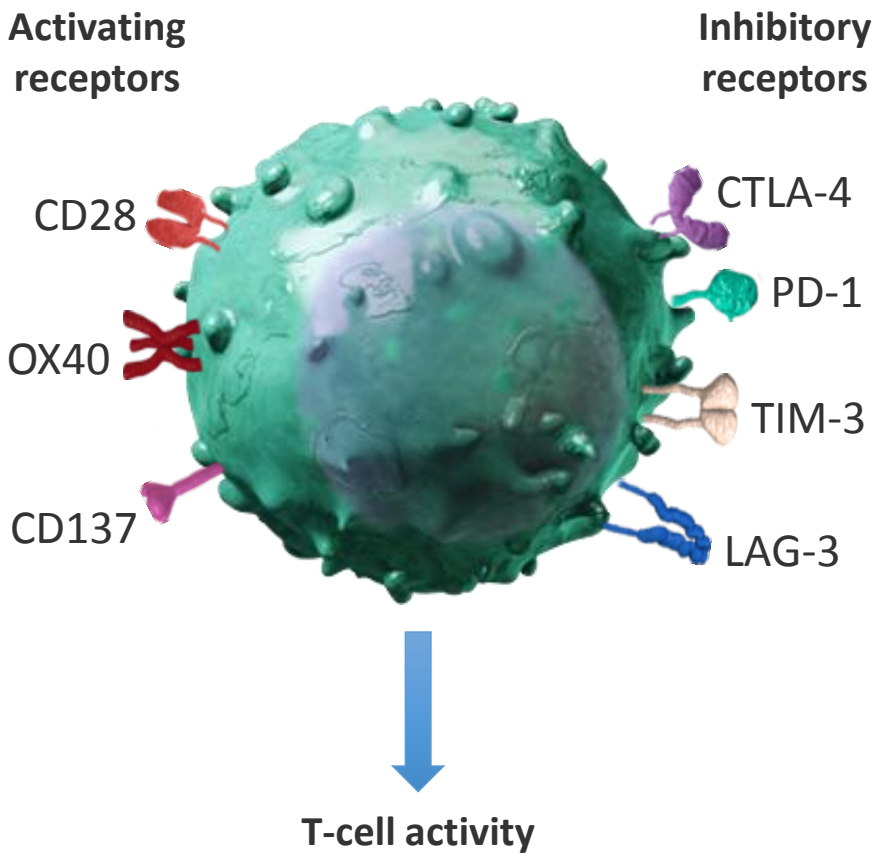
The Concept of Immune Surveillance and Escape

Schreiber RD et al. *Science*. 2011;25:331:1565-70.

Lung cancers are amongst the MOST Antigenic of solid tumours



Tumours may alter T cell activation through immune checkpoint signaling

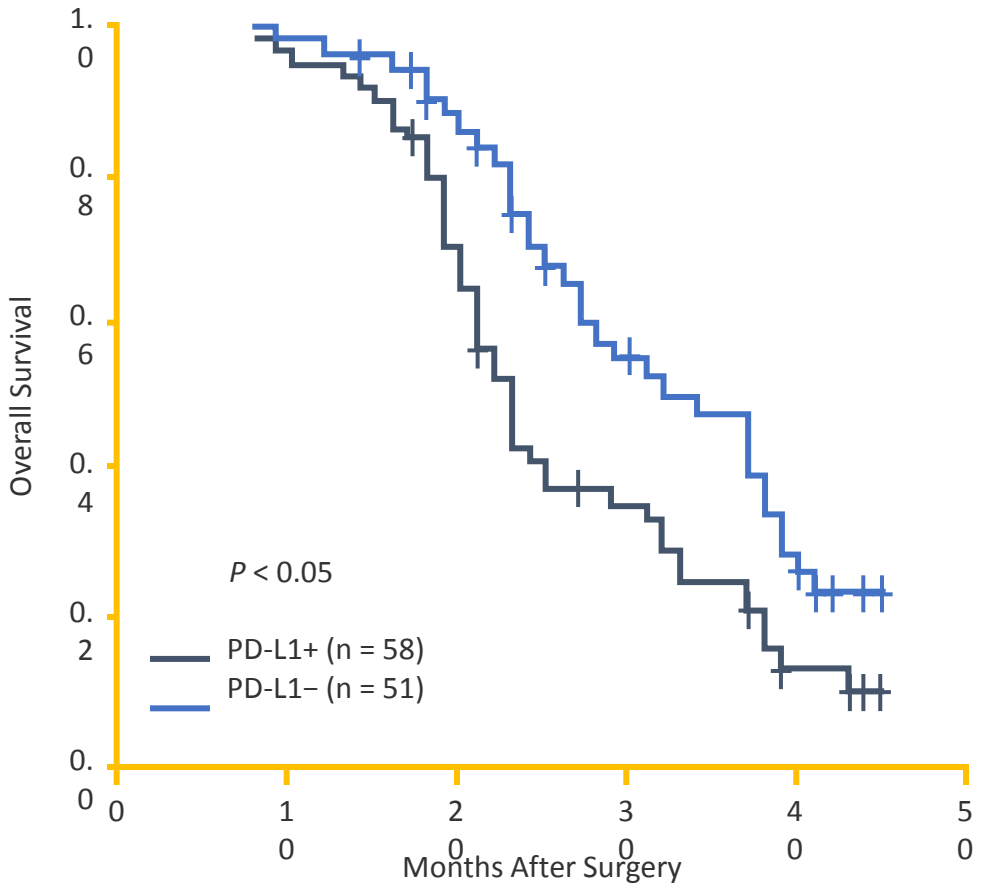


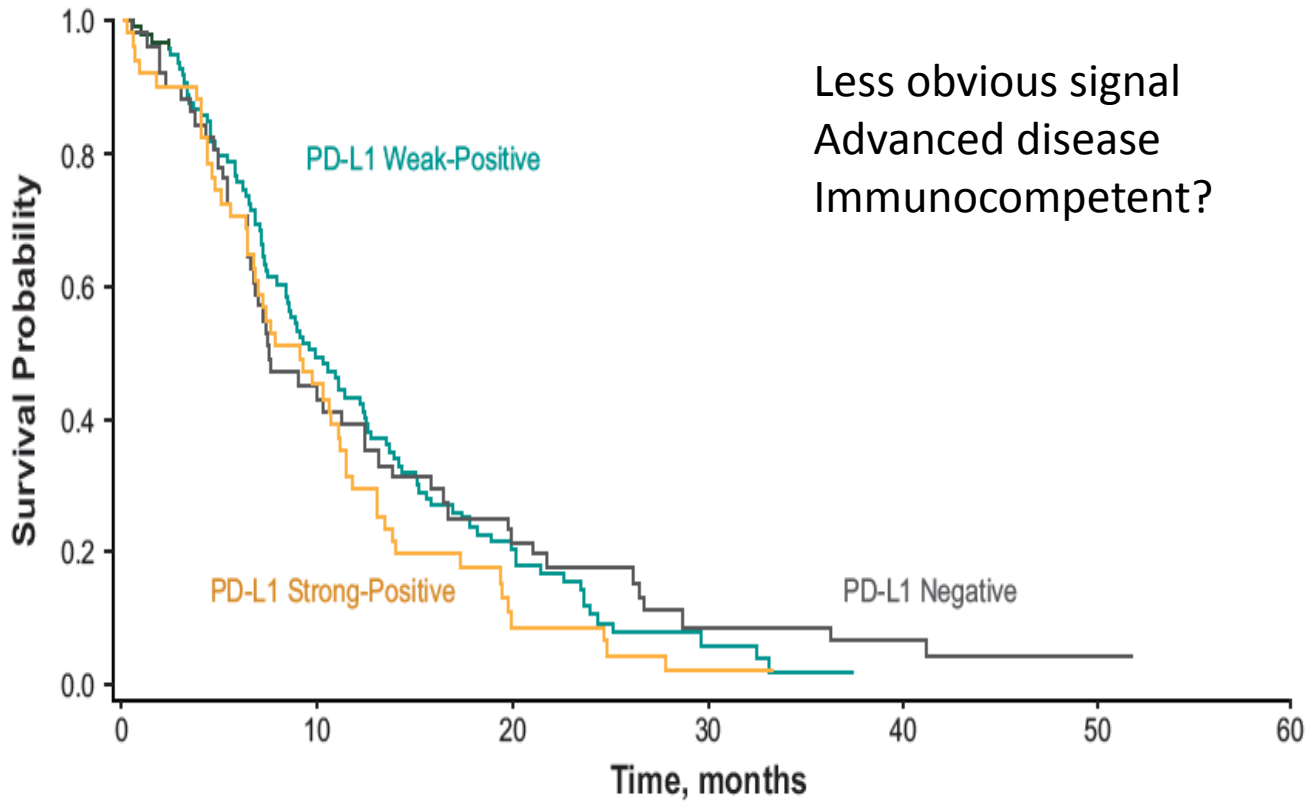
- These inhibitory checkpoints probably help host (normal) tissues avoid autoimmune responses
- Tumours can dysregulate checkpoints and activating pathways, and consequently inhibit the immune response
- Targeting checkpoints can reactivate an immune response

Adapted from Mellman I, et al. *Nature* 2011:480;481–9; Pardoll DM. *Nat Rev Cancer* 2012;12:252–64

The inhibitory (checkpoint) molecule PD-L1 is associated with poor prognosis in patients with resected NSCLC[1,2]

PD-L1 = programmed death-ligand 1.



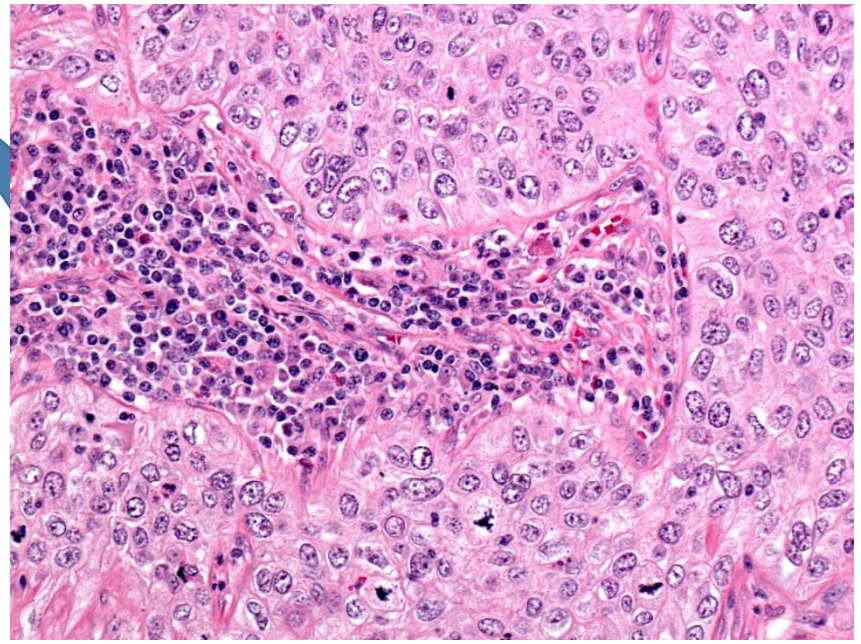


Less obvious signal
Advanced disease
Immunocompetent?

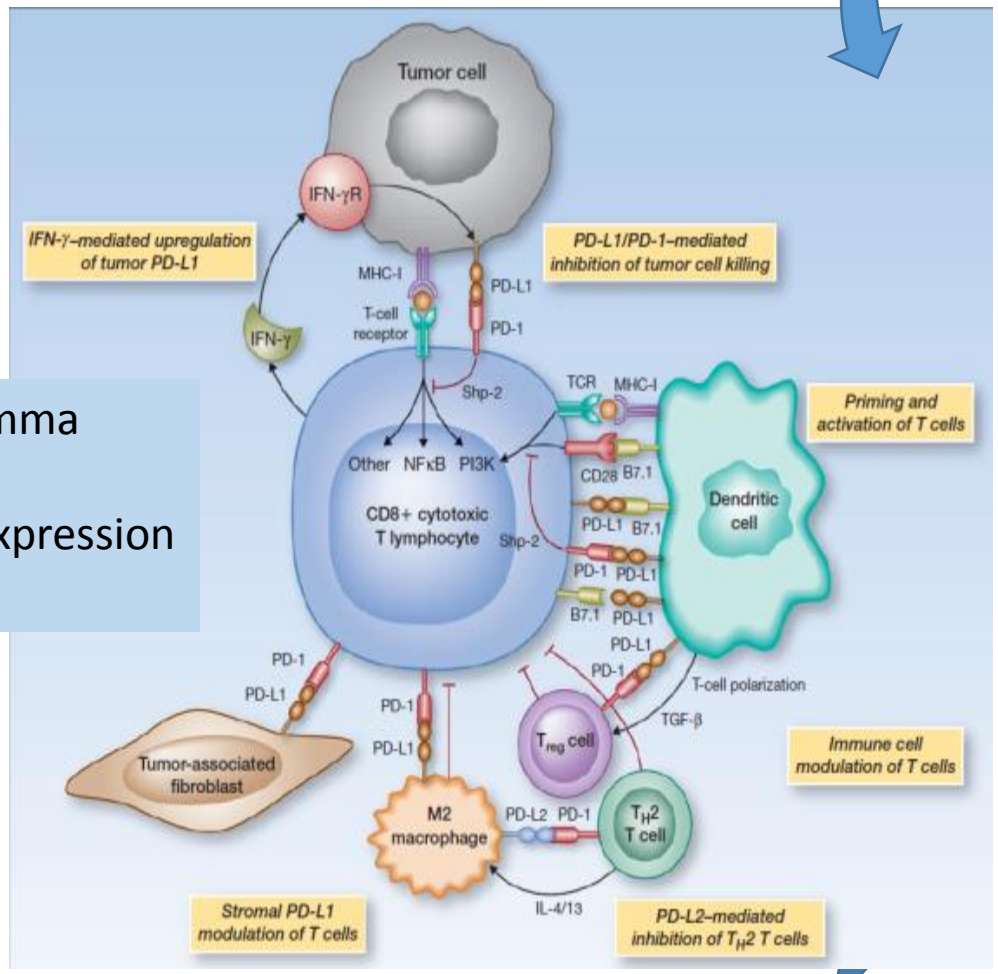
1. Chen YB, et al. *Tumori* 2012;98:751–5. 2. Mu CY, et al. *Med Oncol* 2011;28:682–88

Sorensen SF, et al ESMO 2014

High levels if PD1 or PDL1
protein expression (IHC) may inhibit
Immune response

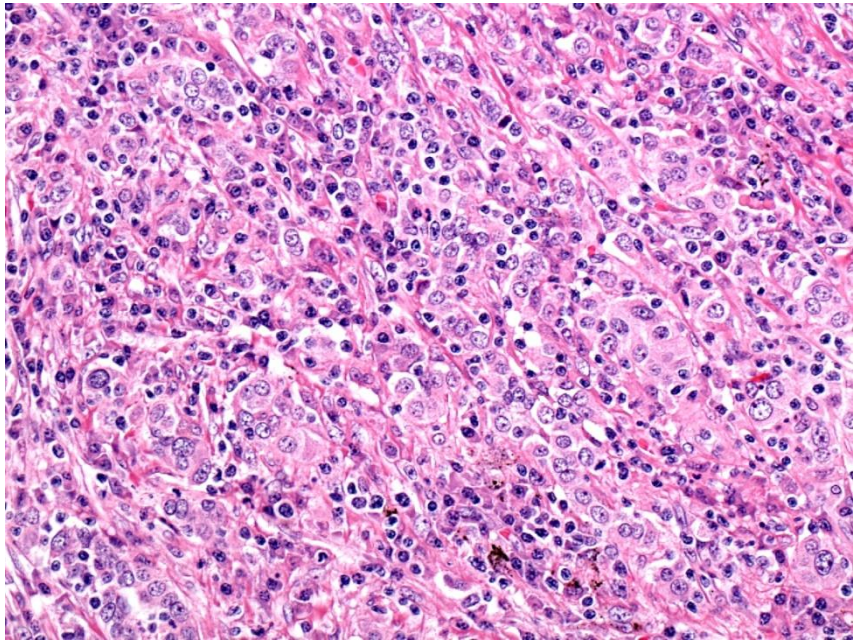


Interferon gamma
upregulates
Tumour cell expression
of PD-L1



Chen, et al. Clin Cancer Res 2012

Block PD1 or PDL1
Immune damage to tumour



Headline studies: Outcomes and PD-L1 expression

Agent	Study	Study Design	Treatment Line	Histology	PD-L1 Positive Definition	PD-L1 positive, %	ORR, % (n/N)		Median PFS, months		Medain OS, months	
							Positive	Negative	Positive	Negative	Positive	Negative
Nivolumab	CheckMate 063 [Rizvi 2015]	Phase 2, single arm	≥3rd	Squamous	≥5% in ≥100 cells	33	**24 (6/25)**	**14 (7/51)**	**NA**	**NA**	**NA**	**NA**
Nivolumab	CheckMate 017 [Brahmer NEJM 2015]	Phase 3, randomized, open-label versus docetaxel	2nd	Squamous	≥1% in ≥100 cells ≥5% in ≥100 cells ≥10% in ≥100 cells	47 31 27	**17 (11/63)** **21 (9/42)** **19 (7/36)**	**17 (9/54)** **15 (11/75)** **16 (13/81)**	**3.3** **4.8** **3.7**	**3.1** **2.2** **2.3**	**9.3** **10.0** **11.0**	**8.7** **8.5** **8.2**
Nivolumab	CheckMate 057 [Borghaei 2015]	Phase 3, randomized, open-label versus docetaxel	2nd	Non-squamous	≥1% in ≥100 cells ≥5% in ≥100 cells ≥10% in ≥100 cells	53 41 37	**31 (38/123)** **36 (34/95)** **37 (32/86)**	**9 (10/108)** **10 (14/136)** **11 (16/145)**	**4.2** **5.0** **5.0**	**2.1** **2.1** **2.1**	**17.7** **19.4** **19.9**	**10.5** **9.8** **9.9**
Nivolumab + ipilimumab	CA209-012 [Antonia SJ ASCO 2014]	Phase 1, multi-cohort	1st	Any	≥5% in ≥100 cells	42	**19 (3/16)**	**14 (3/22)**	**3.3**	**3.1**	**NR**	**NR**
Pembrolizumab	KEYNOTE-001 [Garon NEJM 2015]	Phase 1, multi-cohort	≥1st	Any	≥50% (strong); 1–49% (weak)	23 38	**45 (33/73); 17 (17/103)**	**11 (3/28)**	**6.4** **4.1**	**4.0**	**NR** **10.6**	**10.4**
Atezolizumab	POPLAR study [Spira ASCO 2015]	Phase 2, randomized versus docetaxel	2nd or 3rd	Any	TC staining: ≥50%; ≥5%; ≥1% IC staining: ≥10%; ≥5%; ≥1%	TC/IC:[a] 16, 37, 68	**TC data[a]: 38; 22; 18** **IC data[a]: 13; 15; 18**	**TC/IC: 8**	**7.8; 4.0; 3.3**	**1.9**	**NR: 13.0; NR**	**9.7**
Durvalumab	[Rizvi ASCO 2015 Abst 8032]	Phase 1, dose-escalation, cohort expansion	Any	Any	≥25% tumor cells staining at any intensity	48	**27 (23/84)**	**5 (5/92)**	**NA**	**NA**	**NA**	**NA**
Durvalumab + tremelimumab	[Antonia ASCO 2015]	Phase 1b dose-escalation, dose expansion	≥2nd	Any	NA	29	**33 (6/18)**	**27 (9/33)**	**NA**	**NA**	**NA**	**NA**
Avelumab	JAVELIN study [Gulley ASCO 2015]	Phase 1, dose-escalation, cohort expansion	≥2nd	Any	≥1% tumor cells staining at any intensity	86	**16 (19/122)**	**10 (2/20)**	**2.8**	**1.4**	**8.9**	**4.6**

Headline studies: Outcomes and PD-L1 expression

Agent	Study	Study Design	Treatment Line	Histology	PD-L1 Positive Definition	PD-L1 positive, %	ORR, % (n/N)		Median PFS, months		Medain OS, months	
							Positive	Negative	Positive	Negative	Positive	Negative
Nivolumab	CheckMate 063 [Rizvi 2015]	Phase 2, single arm	≥3rd	Squamous	≥5% in ≥100 cells	33	**24 (6/25)**	**14 (7/51)**	**NA**	**NA**	**NA**	**NA**
Nivolumab	CheckMate 017 [Brahmer NEJM 2015]	Phase 3, randomized, open-label versus docetaxel	2nd	Squamous	≥1% in ≥100 cells ≥5% in ≥100 cells ≥10% in ≥100 cells	47 31 27	**17 (11/63)** **21 (9/42)** **19 (7/36)**	**17 (9/54)** **15 (11/75)** **16 (13/81)**	**3.3** **4.8** **3.7**	**3.1** **2.2** **2.3**	**9.3** **10.0** **11.0**	**8.7** **8.5** **8.2**
Nivolumab	CheckMate 057 [Borghaei 2015]	Phase 3, randomized, open-label versus docetaxel	2nd	Non-squamous	≥1% in ≥100 cells ≥5% in ≥100 cells ≥10% in ≥100 cells	53 41 37	**31 (38/123)** **36 (34/95)** **37 (32/86)**	**9 (10/108)** **10 (14/136)** **11 (16/145)**	**4.2** **5.0** **5.0**	**2.1** **2.1** **2.1**	**17.7** **19.4** **19.9**	**10.5** **9.8** **9.9**
Nivolumab + ipilimumab	CA209-012 [Antonia SJ ASCO 2014]	Phase 1, multi-cohort	1st	Any	≥5% in ≥100 cells	42	**19 (3/16)**	**14 (3/22)**	**3.3**	**3.1**	**NR**	**NR**
Pembrolizumab	KEYNOTE-001 [Garon NEJM 2015]	Phase 1, multi-cohort	≥1st	Any	≥50% (strong); 1–49% (weak)	23 38	**45 (33/73); 17 (17/103)**	**11 (3/28)**	**6.4** **4.1**	**4.0**	**NR** **10.6**	**10.4**
Atezolizumab	POPLAR study [Spira ASCO 2015]	Phase 2, randomized versus docetaxel	2nd or 3rd	Any	TC staining: ≥50%; ≥5%; ≥1% IC staining: ≥10%; ≥5%; ≥1%	TC/IC:[a] 16, 37, 68	**TC data[a]: 38; 22; 18** **IC data[a]: 13; 15; 18**	**TC/IC: 8**	**7.8; 4.0; 3.3**	**1.9**	**NR: 13.0; NR**	**9.7**
Durvalumab	[Rizvi ASCO 2015 Abst 8032]	Phase 1, dose-escalation, cohort expansion	Any	Any	≥25% tumor cells staining at any intensity	48	**27 (23/84)**	**5 (5/92)**	**NA**	**NA**	**NA**	**NA**
Durvalumab + tremelimumab	[Antonia ASCO 2015]	Phase 1b dose-escalation, dose expansion	≥2nd	Any	NA	29	**33 (6/18)**	**27 (9/33)**	**NA**	**NA**	**NA**	**NA**
Avelumab	JAVELIN study [Gulley ASCO 2015]	Phase 1, dose-escalation, cohort expansion	≥2nd	Any	≥1% tumor cells staining at any intensity	86	**16 (19/122)**	**10 (2/20)**	**2.8**	**1.4**	**8.9**	**4.6**

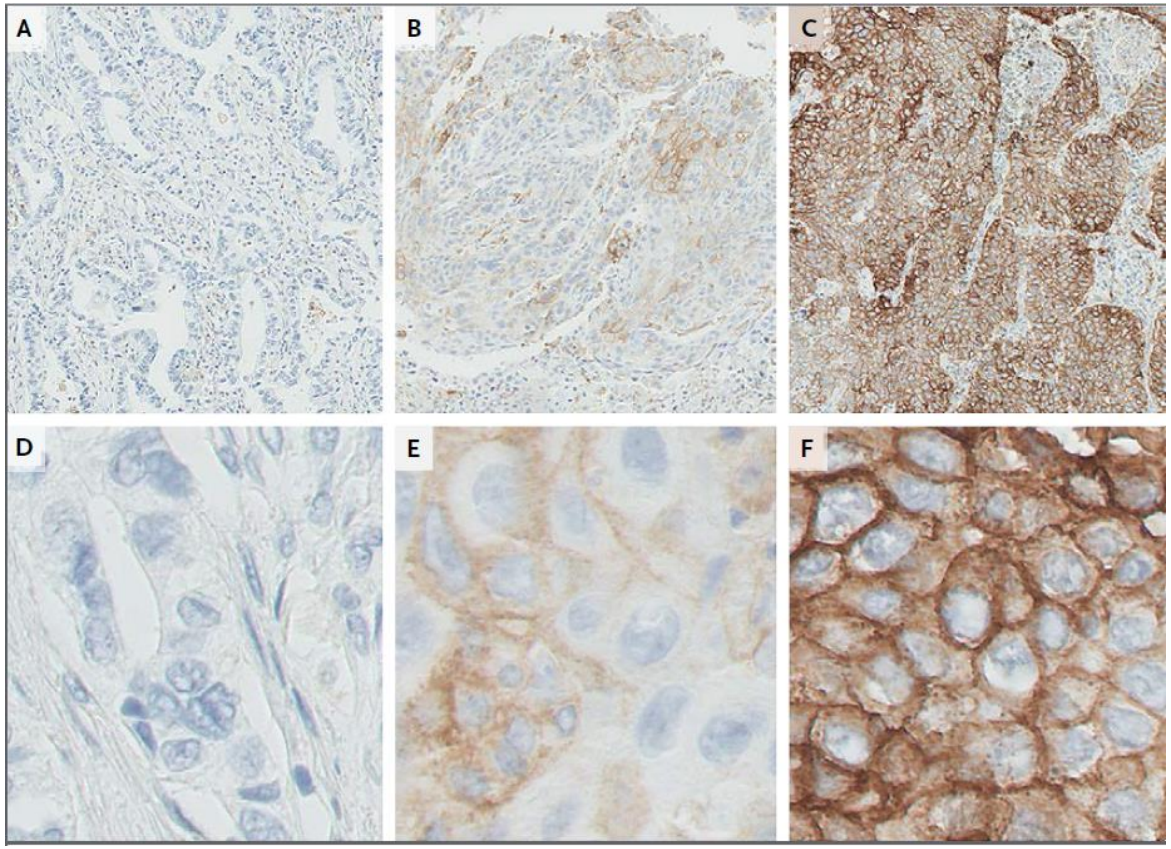
Headline studies: Outcomes and PD-L1 expression

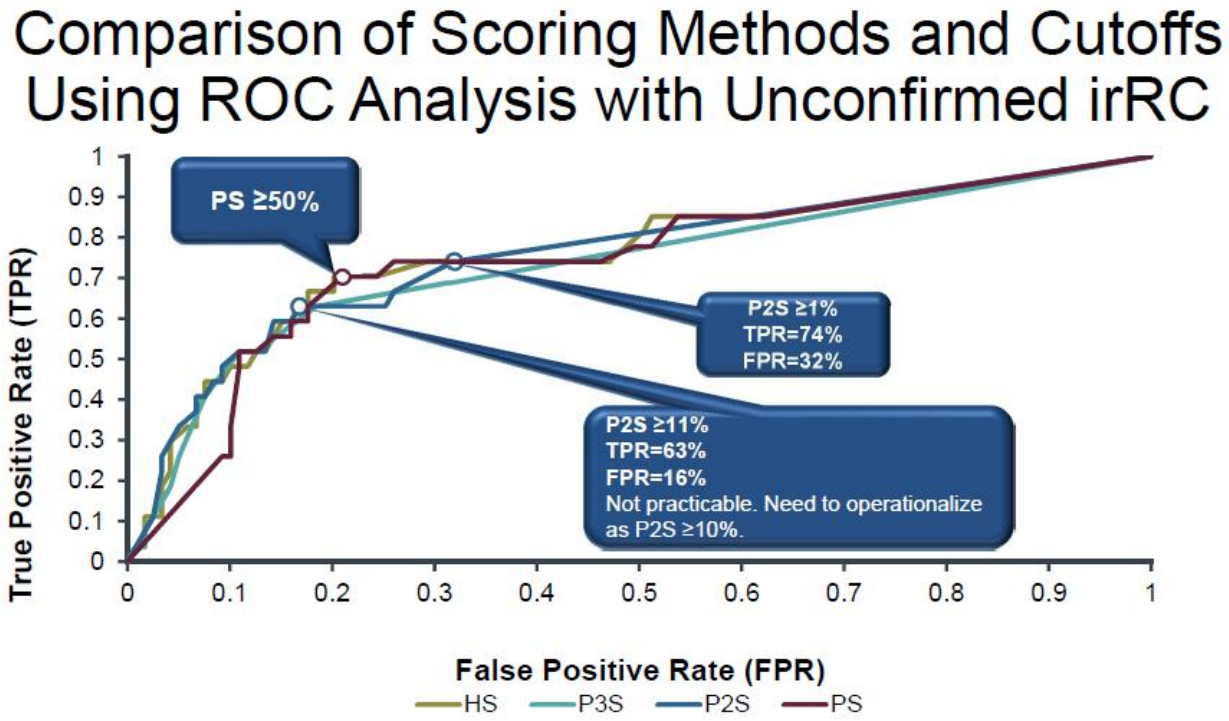
Agent	Study	Study Design	Treatment Line	Histology	PD-L1 Positive Definition	PD-L1 positive, %	ORR, % (n/N)		Median PFS, months		Medain OS, months	
							Positive	Negative	Positive	Negative	Positive	Negative
Nivolumab	CheckMate 063 [Rizvi 2015]	Phase 2, single arm	≥3rd	Squamous	≥5% in ≥100 cells	33	**24 (6/25)**	**14 (7/51)**	**NA**	**NA**	**NA**	**NA**
Nivolumab	CheckMate 017 [Brahmer NEJM 2015]	Phase 3, randomized, open-label versus docetaxel	2nd	Squamous	≥1% in ≥100 cells ≥5% in ≥100 cells ≥10% in ≥100 cells	47 31 27	**17 (11/63)** **21 (9/42)** **19 (7/36)**	**17 (9/54)** **15 (11/75)** **16 (13/81)**	**3.3** **4.8** **3.7**	**3.1** **2.2** **2.3**	**9.3** **10.0** **11.0**	**8.7** **8.5** **8.2**
Nivolumab	CheckMate 057 [Borghaei 2015]	Phase 3, randomized, open-label versus docetaxel	2nd	Non-squamous	≥1% in ≥100 cells ≥5% in ≥100 cells ≥10% in ≥100 cells	53 41 37	**31 (38/123)** **36 (34/95)** **37 (32/86)**	**9 (10/108)** **10 (14/136)** **11 (16/145)**	**4.2** **5.0** **5.0**	**2.1** **2.1** **2.1**	**17.7** **19.4** **19.9**	**10.5** **9.8** **9.9**
Nivolumab + ipilimumab	CA209-012 [Antonia SJ ASCO 2014]	Phase 1, multi-cohort	1st	Any	≥5% in ≥100 cells	42	**19 (3/16)**	**14 (3/22)**	**3.3**	**3.1**	**NR**	**NR**
Pembrolizumab	KEYNOTE-001 [Garon NEJM 2015]	Phase 1, multi-cohort	≥1st	Any	≥50% (strong); 1–49% (weak)	23 38	**45 (33/73); 17 (17/103)**	**11 (3/28)**	**6.4** **4.1**	**4.0**	**NR** **10.6**	**10.4**
Atezolizumab	POPLAR study [Spira ASCO 2015]	Phase 2, randomized versus docetaxel	2nd or 3rd	Any	TC staining: ≥50%; ≥5%; ≥1% IC staining: ≥10%; ≥5%; ≥1%	TC/IC:[a] 16, 37, 68	**TC data[a]: 38; 22; 18** **IC data[a]: 13; 15; 18**	**TC/IC: 8**	**7.8; 4.0; 3.3**	**1.9**	**NR: 13.0; NR**	**9.7**
Durvalumab	[Rizvi ASCO 2015 Abst 8032]	Phase 1, dose-escalation, cohort expansion	Any	Any	≥25% tumor cells staining at any intensity	48	**27 (23/84)**	**5 (5/92)**	**NA**	**NA**	**NA**	**NA**
Durvalumab + tremelimumab	[Antonia ASCO 2015]	Phase 1b dose-escalation, dose expansion	≥2nd	Any	NA	29	**33 (6/18)**	**27 (9/33)**	**NA**	**NA**	**NA**	**NA**
Avelumab	JAVELIN study [Gulley ASCO 2015]	Phase 1, dose-escalation, cohort expansion	≥2nd	Any	≥1% tumor cells staining at any intensity	86	**16 (19/122)**	**10 (2/20)**	**2.8**	**1.4**	**8.9**	**4.6**

Headline studies: Outcomes and PD-L1 expression

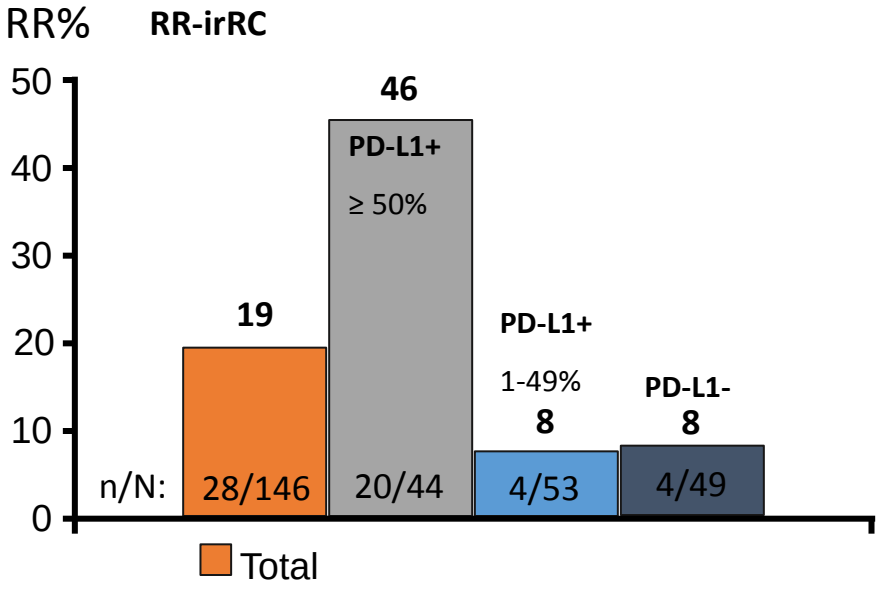
Agent	Study	Study Design	Treatment Line	Histology	PD-L1 Positive Definition	PD-L1 positive, %	ORR, % (n/N)		Median PFS, months		Medain OS, months	
							Positive	Negative	Positive	Negative	Positive	Negative
Nivolumab	CheckMate 063 [Rizvi 2015]	Phase 2, single arm	≥3rd	Squamous	≥5% in ≥100 cells	33	**24 (6/25)**	**14 (7/51)**	**NA**	**NA**	**NA**	**NA**
Nivolumab	CheckMate 017 [Brahmer NEJM 2015]	Phase 3, randomized, open-label versus docetaxel	2nd	Squamous	≥1% in ≥100 cells ≥5% in ≥100 cells ≥10% in ≥100 cells	47 31 27	**17 (11/63)** **21 (9/42)** **19 (7/36)**	**17 (9/54)** **15 (11/75)** **16 (13/81)**	**3.3** **4.8** **3.7**	**3.1** **2.2** **2.3**	**9.3** **10.0** **11.0**	**8.7** **8.5** **8.2**
Nivolumab	CheckMate 057 [Borghaei 2015]	Phase 3, randomized, open-label versus docetaxel	2nd	Non-squamous	≥1% in ≥100 cells ≥5% in ≥100 cells ≥10% in ≥100 cells	53 41 37	**31 (38/123)** **36 (34/95)** **37 (32/86)**	**9 (10/108)** **10 (14/136)** **11 (16/145)**	**4.2** **5.0** **5.0**	**2.1** **2.1** **2.1**	**17.7** **19.4** **19.9**	**10.5** **9.8** **9.9**
Nivolumab + ipilimumab	CA209-012 [Antonia SJ ASCO 2014]	Phase 1, multi-cohort	1st	Any	≥5% in ≥100 cells	42	**19 (3/16)**	**14 (3/22)**	**3.3**	**3.1**	**NR**	**NR**
Pembrolizumab	KEYNOTE-001 [Garon NEJM 2015]	Phase 1, multi-cohort	≥1st	Any	≥50% (strong); 1–49% (weak)	23 38	**45 (33/73); 17 (17/103)**	**11 (3/28)**	**6.4** **4.1**	**4.0**	**NR** **10.6**	**10.4**
Atezolizumab	POPLAR study [Spira ASCO 2015]	Phase 2, randomized versus docetaxel	2nd or 3rd	Any	TC staining: ≥50%; ≥5%; ≥1% IC staining: ≥10%; ≥5%; ≥1%	TC/IC:[a] 16, 37, 68	**TC data[a]: 38; 22; 18** **IC data[a]: 13; 15; 18**	**TC/IC: 8**	**7.8; 4.0; 3.3**	**1.9**	**NR: 13.0; NR**	**9.7**
Durvalumab	[Rizvi ASCO 2015 Abst 8032]	Phase 1, dose-escalation, cohort expansion	Any	Any	≥25% tumor cells staining at any intensity	48	**27 (23/84)**	**5 (5/92)**	**NA**	**NA**	**NA**	**NA**
Durvalumab + tremelimumab	[Antonia ASCO 2015]	Phase 1b dose-escalation, dose expansion	≥2nd	Any	NA	29	**33 (6/18)**	**27 (9/33)**	**NA**	**NA**	**NA**	**NA**
Avelumab	JAVELIN study [Gulley ASCO 2015]	Phase 1, dose-escalation, cohort expansion	≥2nd	Any	≥1% tumor cells staining at any intensity	86	**16 (19/122)**	**10 (2/20)**	**2.8**	**1.4**	**8.9**	**4.6**

22C3 assay and Pembrolizumab





Pembrolizumab in NSCLC: OS Per Proportional Scores (TPS)

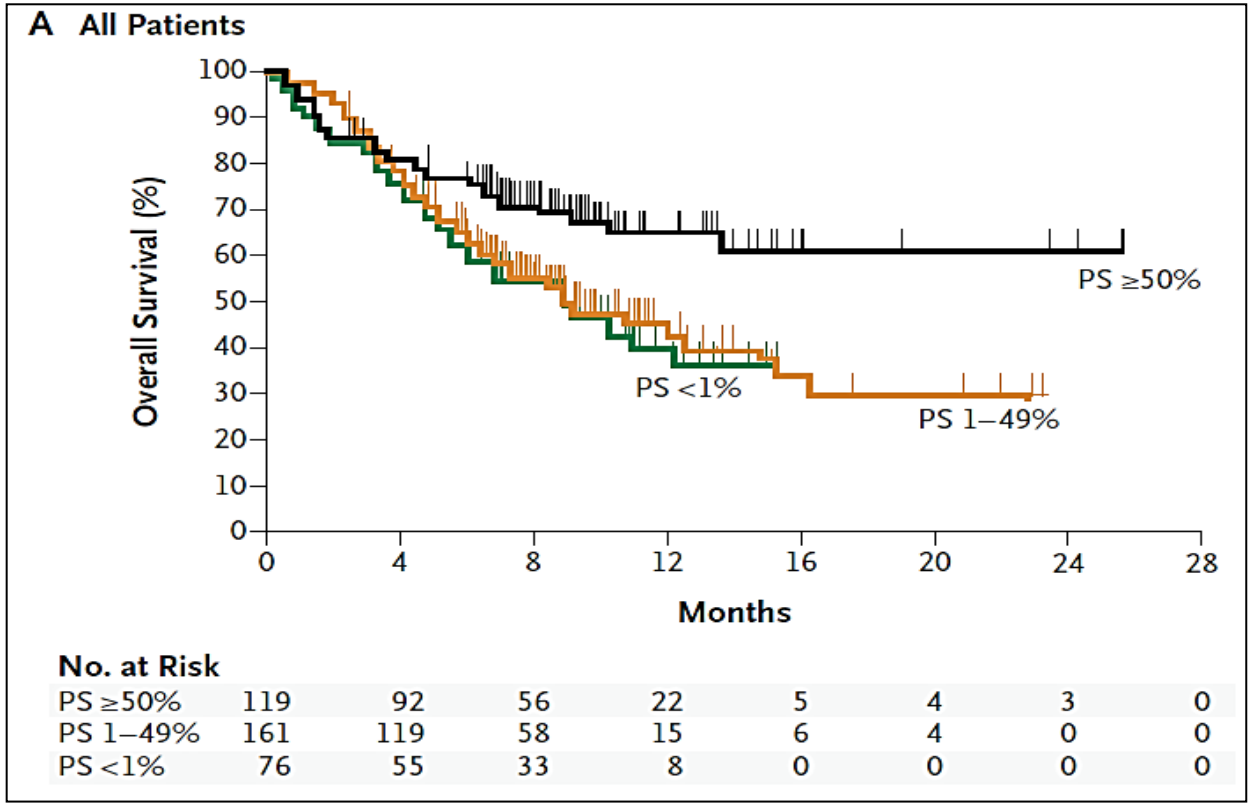


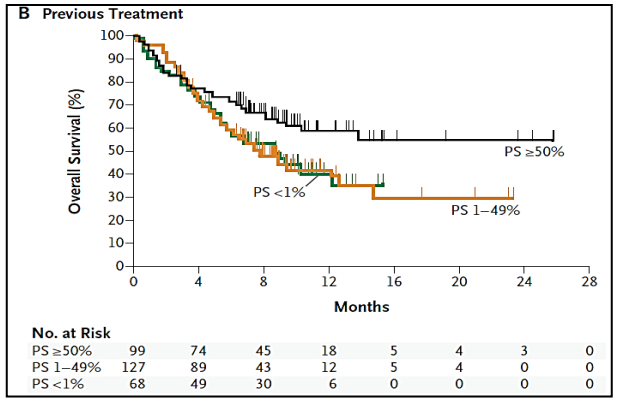
Gandhi L, et al. AACR 2014. Abstract CT105.

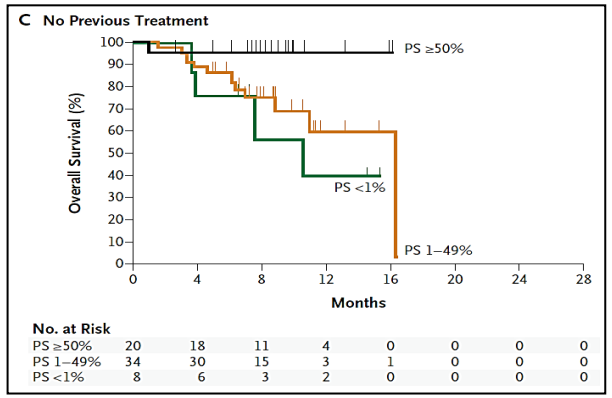
≥50% IHC cut off Tumour cell expression

22C3 clone IHC based assay

Expression in TILs added no predictive value

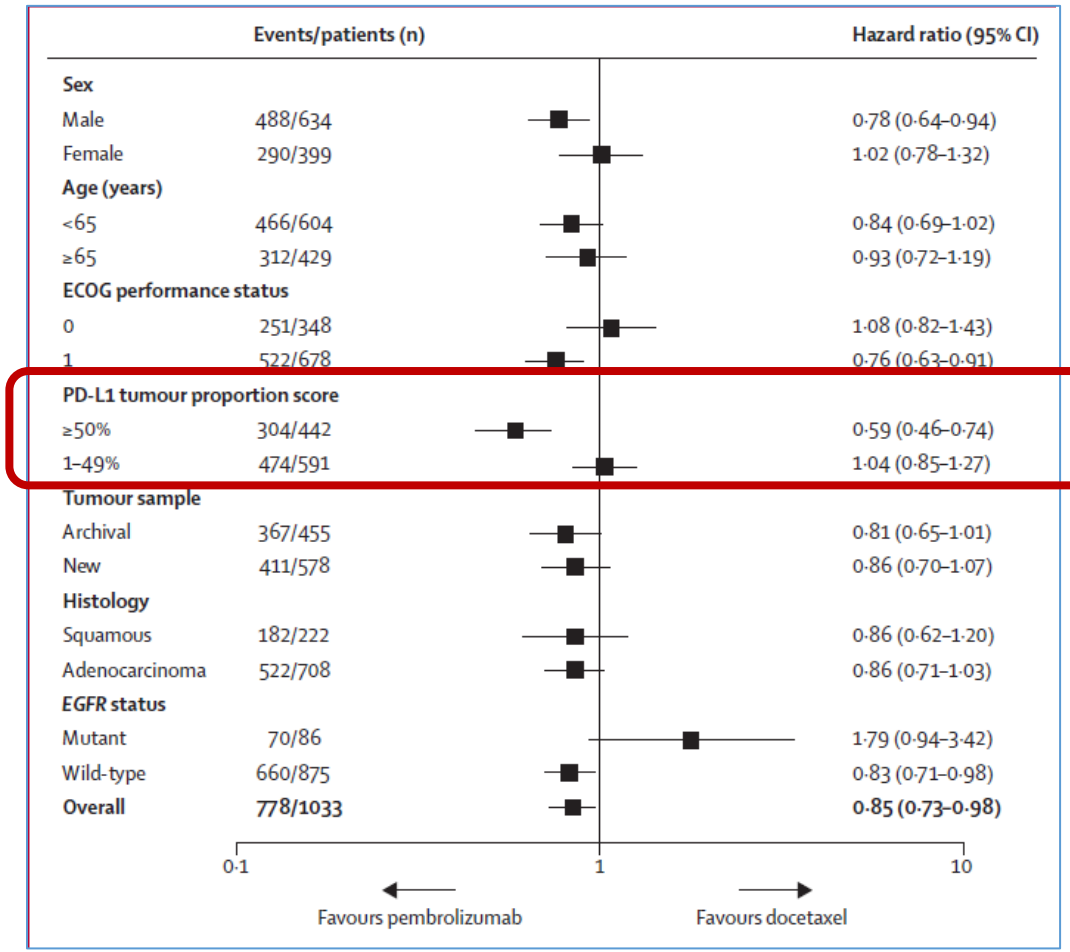


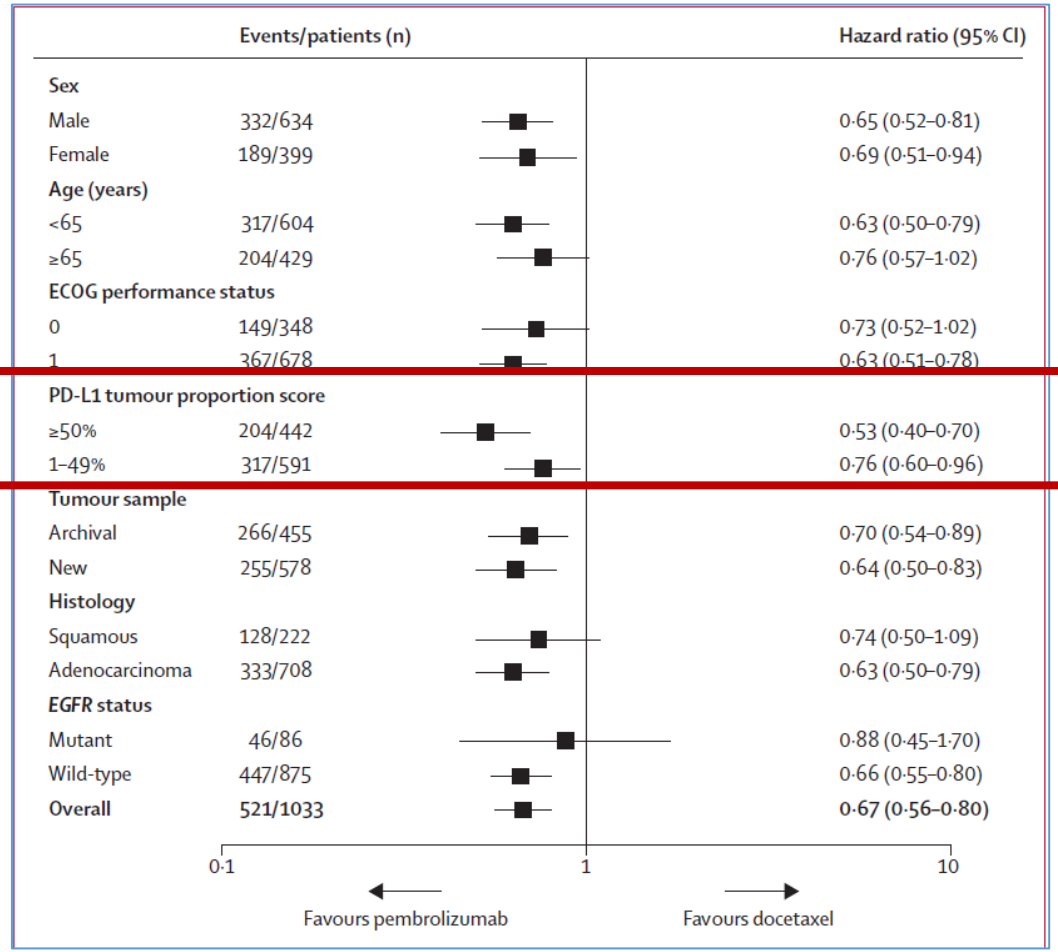




Garon EB et al NEJM 2015

Keynote 010: Pembrolizumab Phase2/3 trial



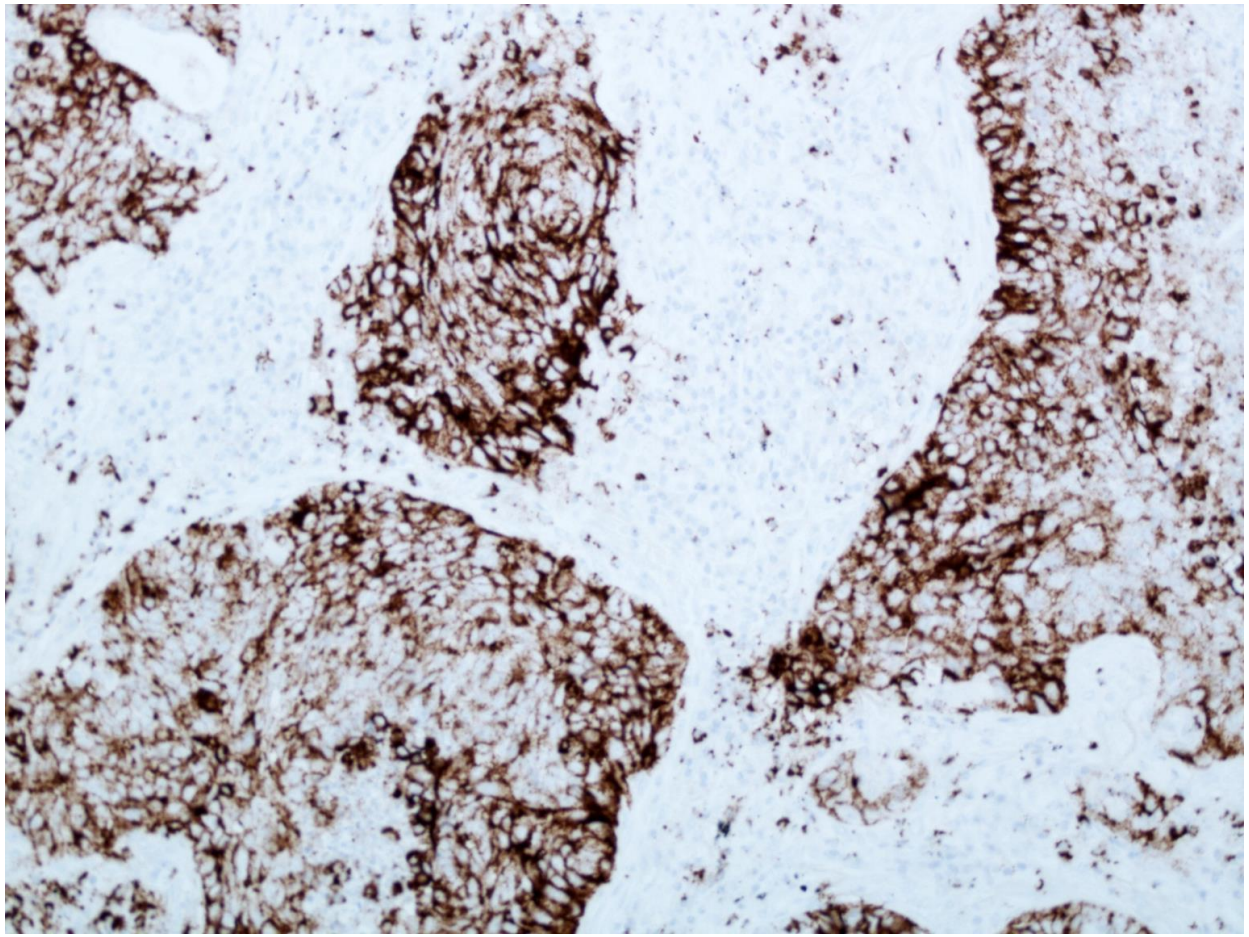


Progression Free Survival

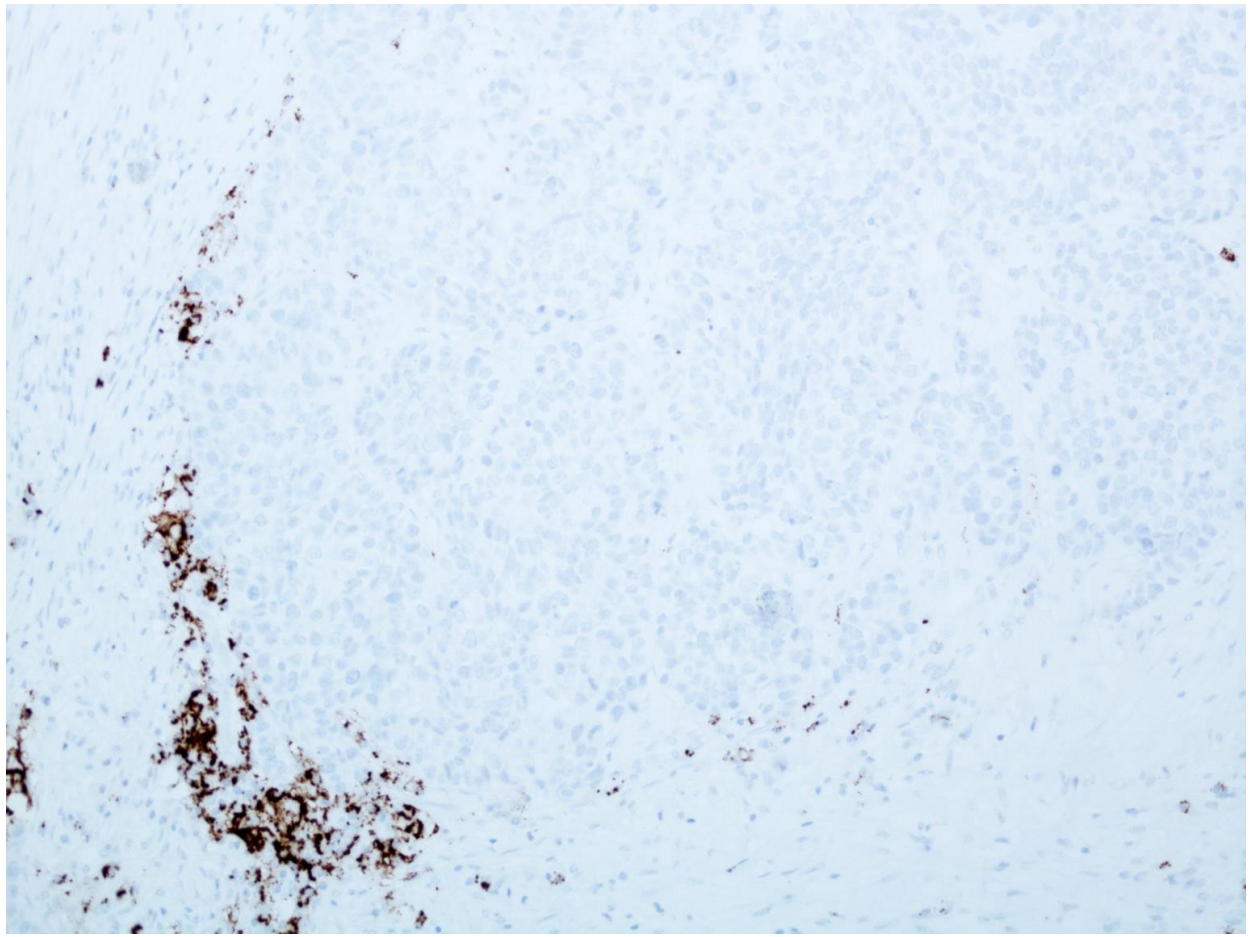
Overall Survival

Herbst RS et al. Lancet 2015

Atezolizumab & anti-PD-L1 SP142 clone based assay

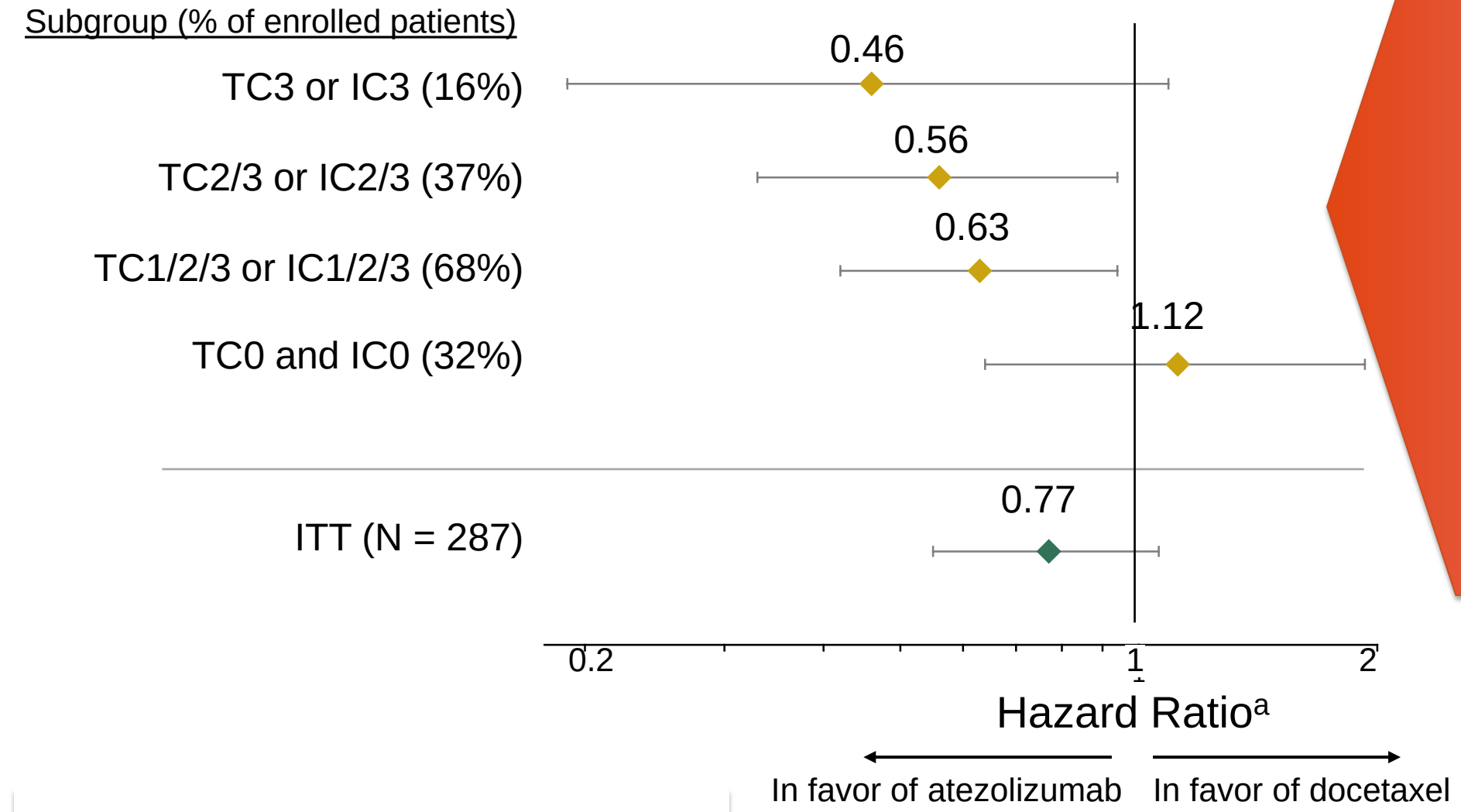


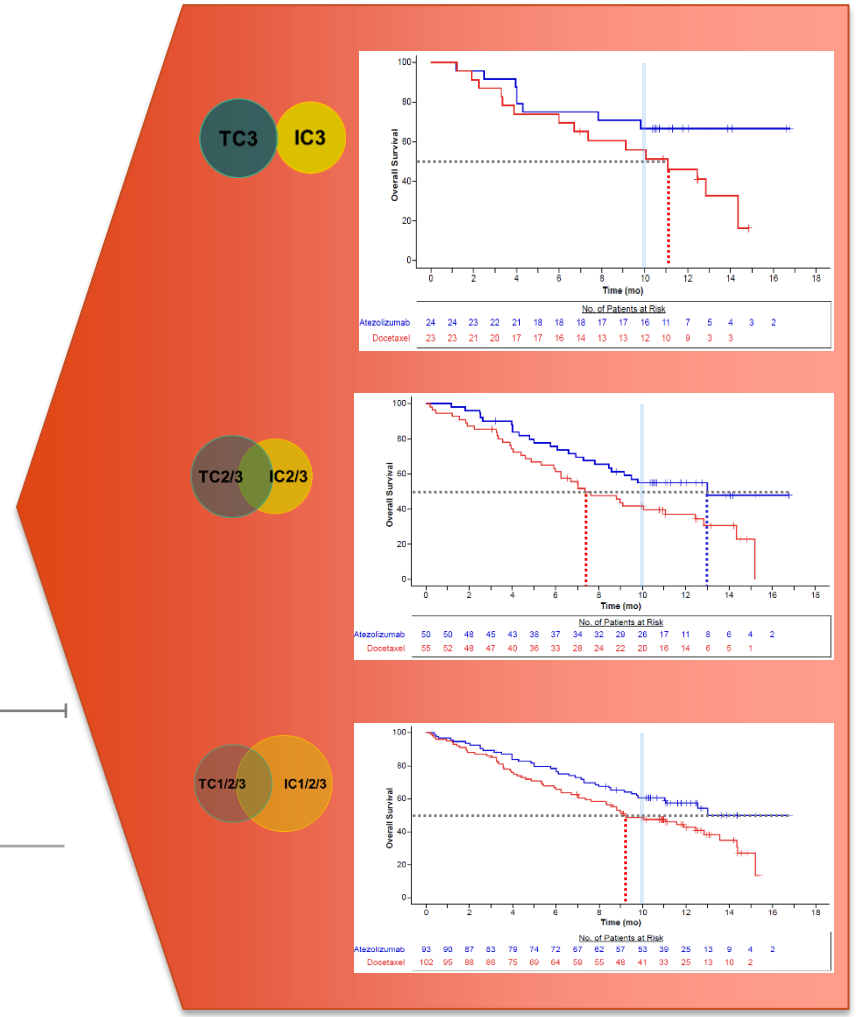
Tumour cells: % TC positive



Immune cells: % area of tumour infiltrated

POPLAR: PD-L1 Expression Subgroups
Interim OS Atezolizumab >1L





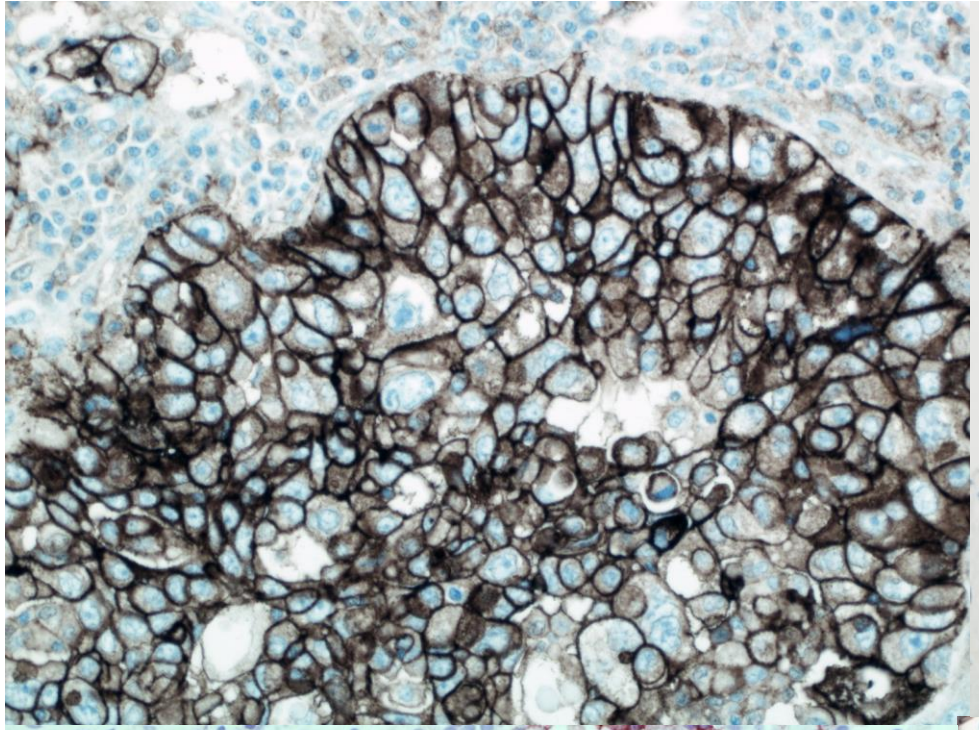
Spira A et al, ASCO June 2015

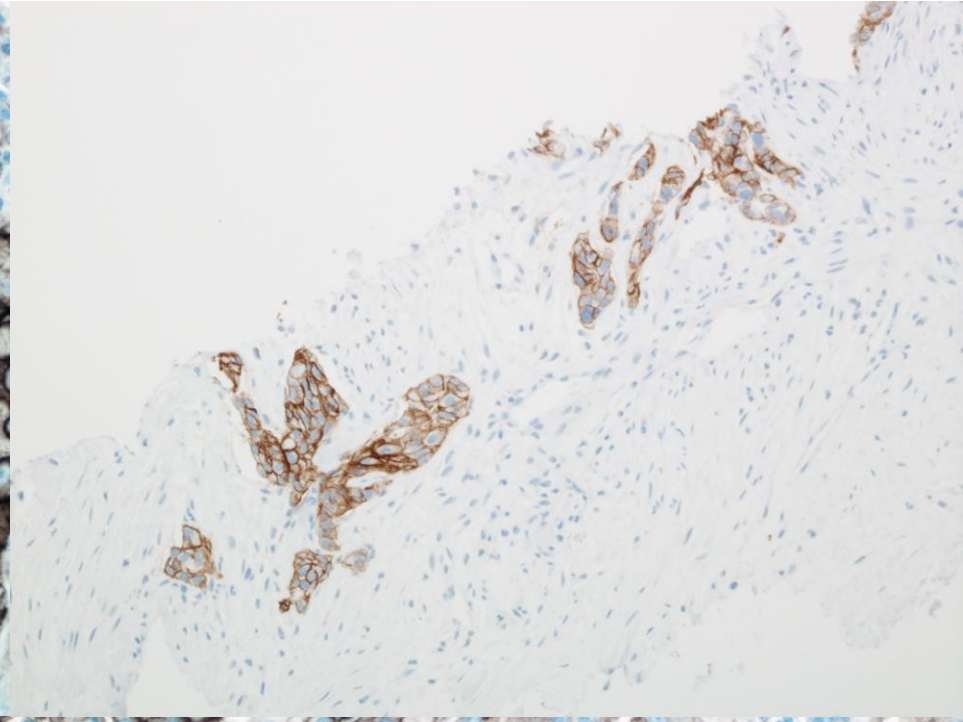
Nivolumab

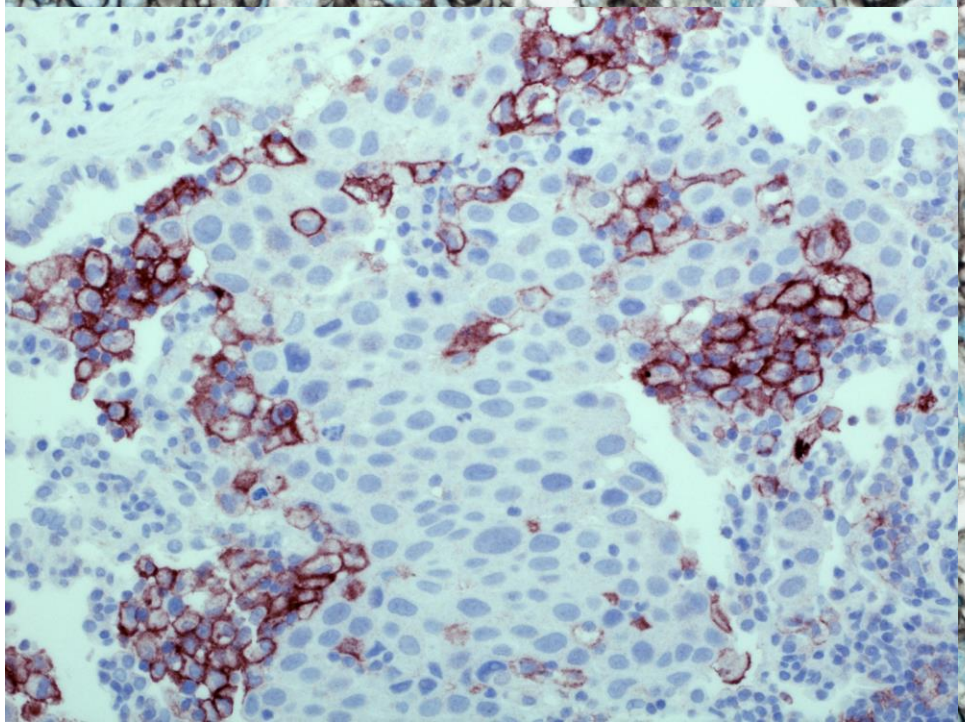
28-8 clone assay

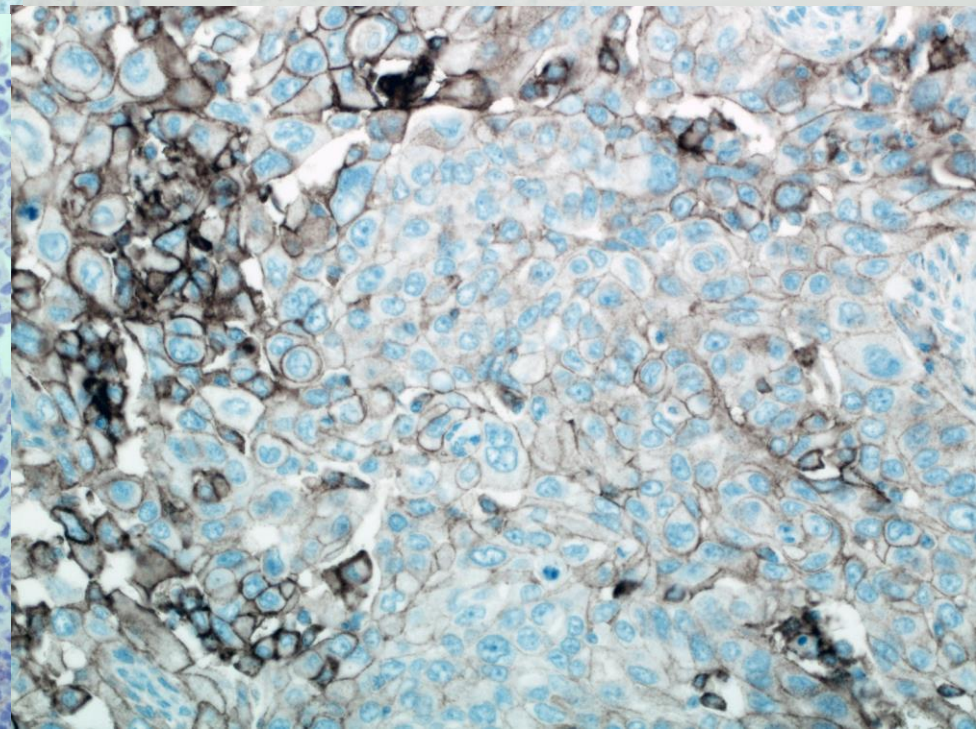
Complimentary or Companion diagnostic Assay?

1% threshold is ‘positive’



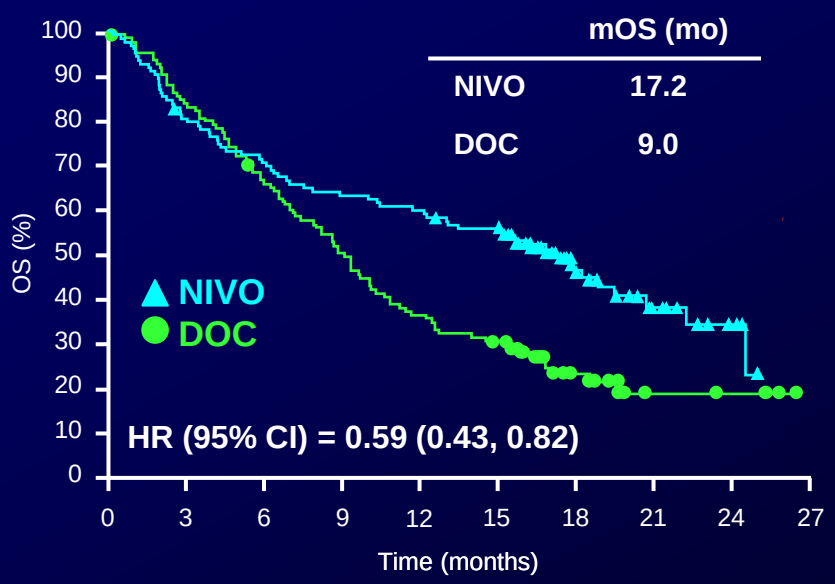




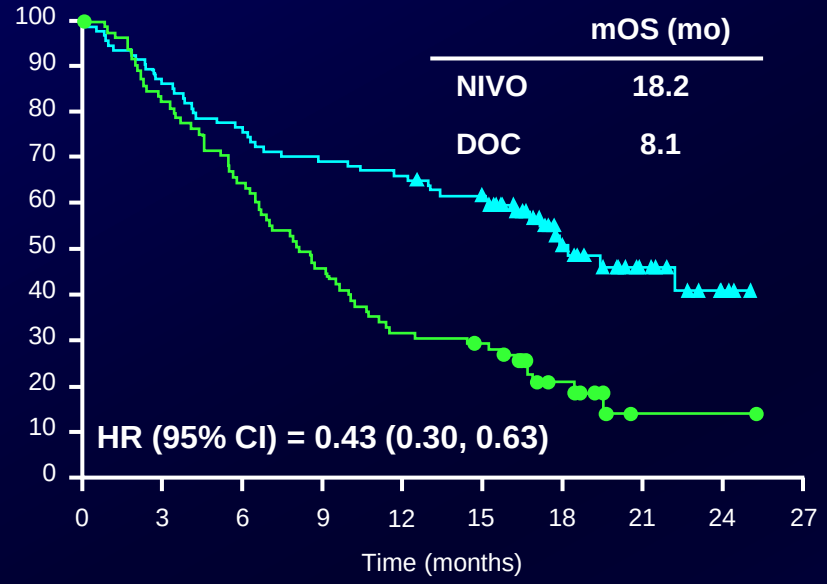


CheckMate 057: Non-Squamous - OS by PD-L1 Expression

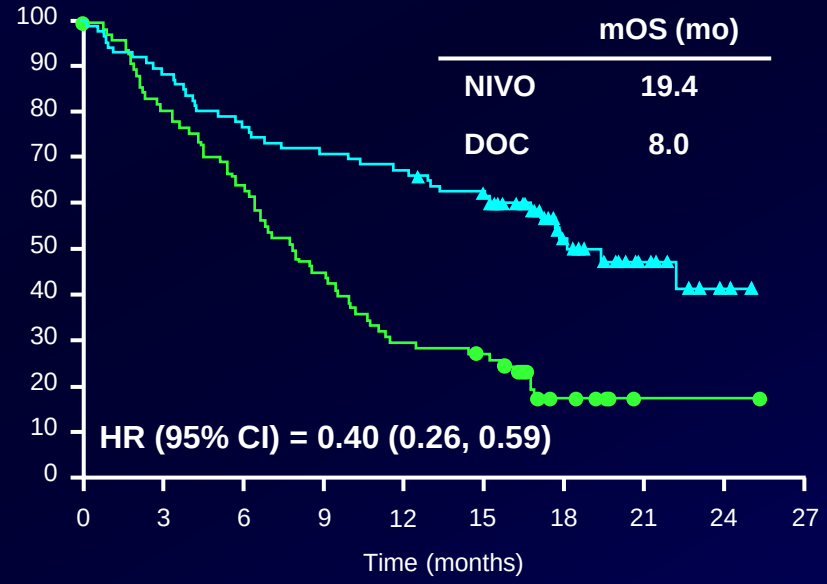
≥1% PD-L1 expression level



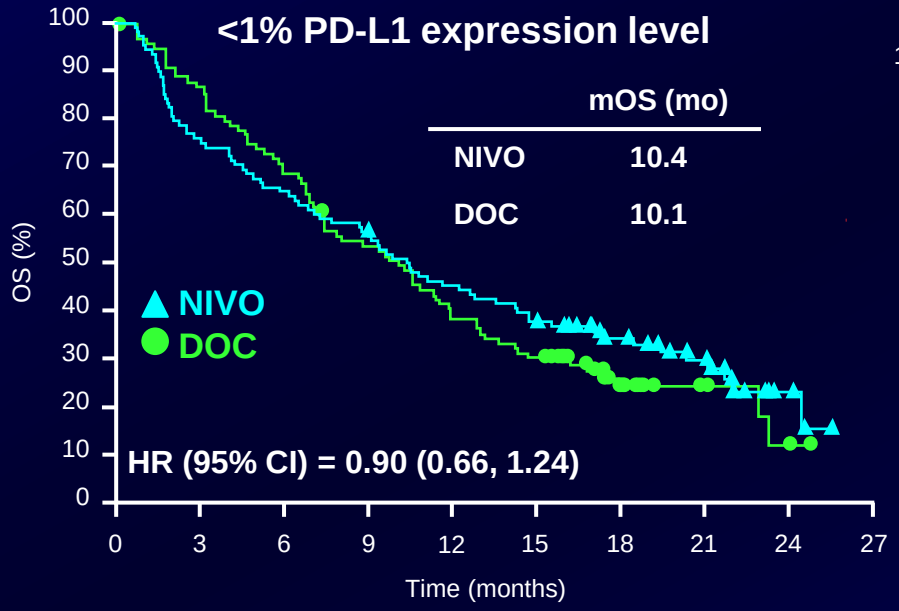
≥5% PD-L1 expression level



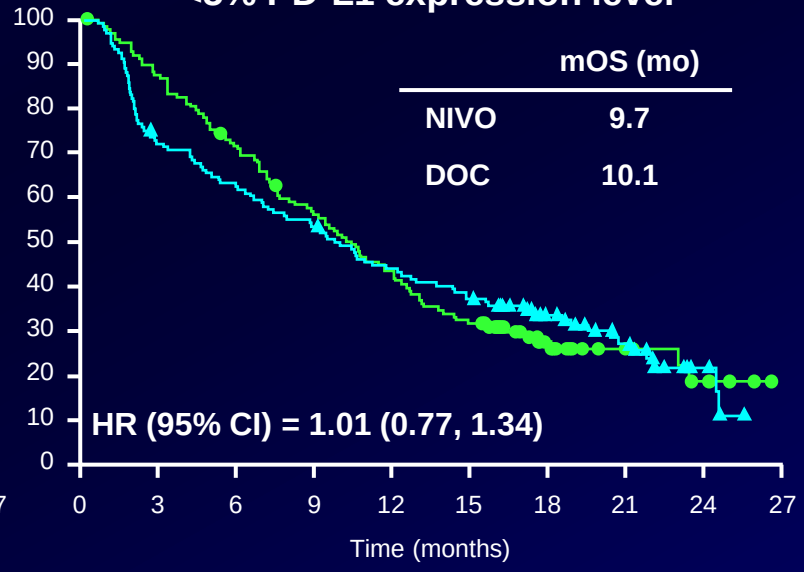
≥10% PD-L1 expression level



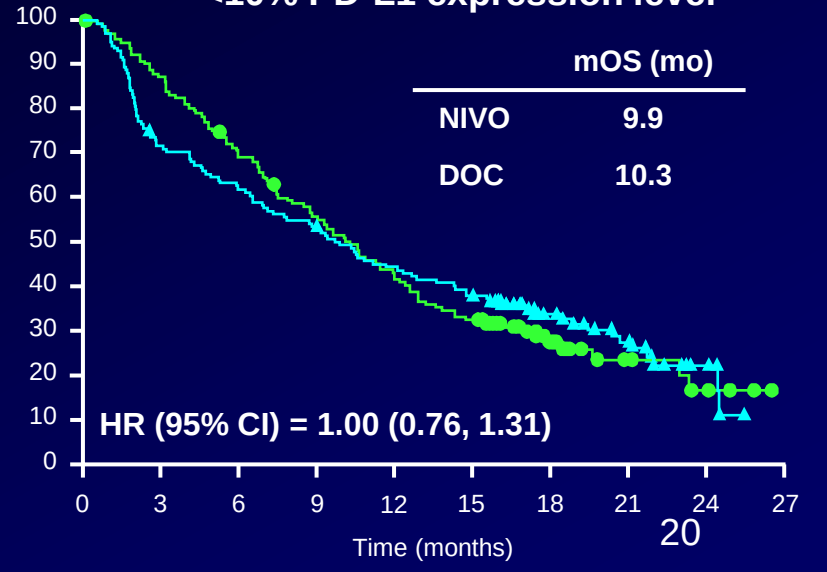
<1% PD-L1 expression level



<5% PD-L1 expression level



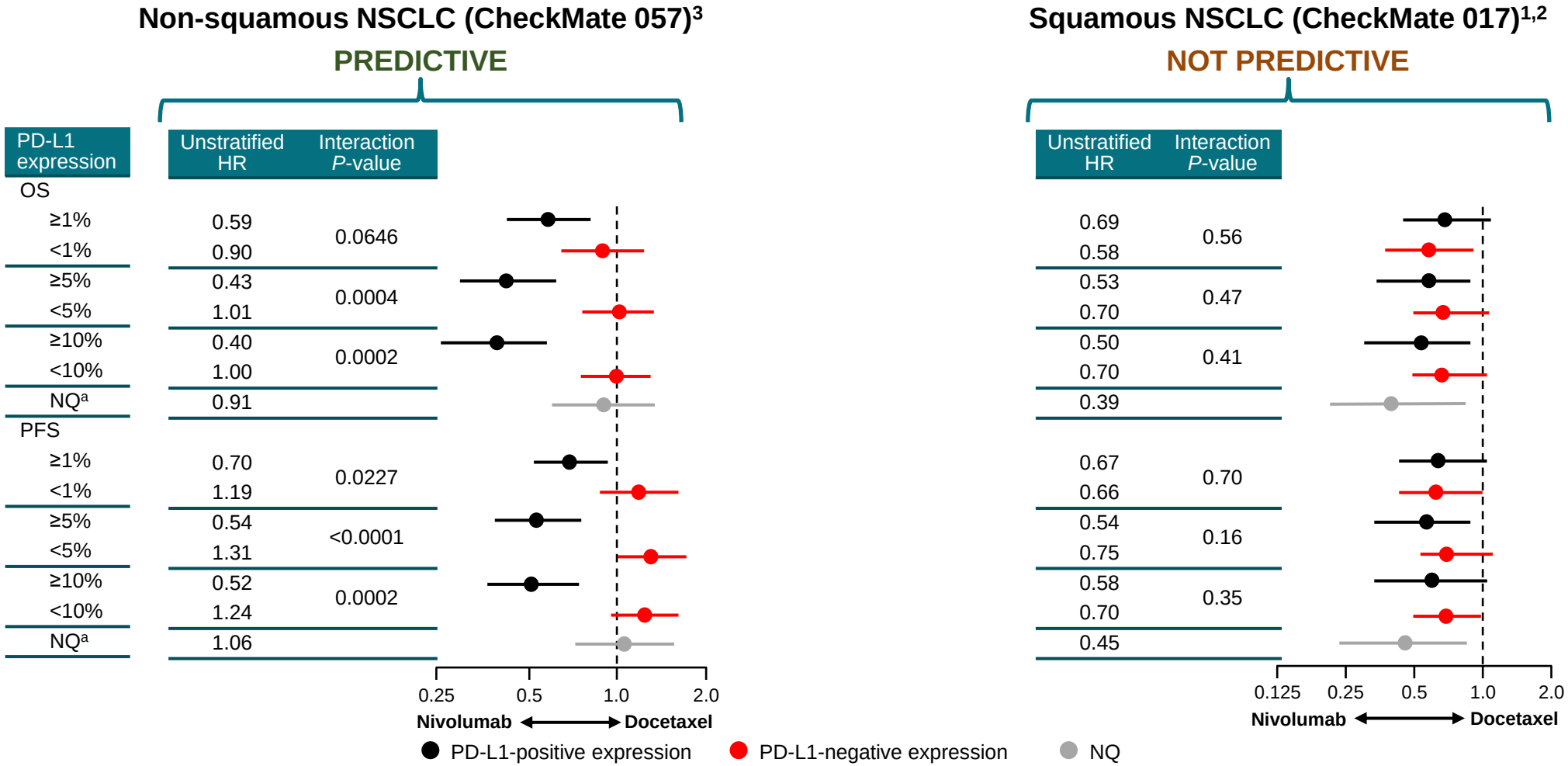
<10% PD-L1 expression level



Symbols represent censored observations. mOS = median OS.

Paz-Ares et al, ASCO 2015

PD-L1 Expression and Outcome in Nivolumab Phase 3 Trials



Alternative Potential Biomarkers for Response?

- **Immune gene signatures**

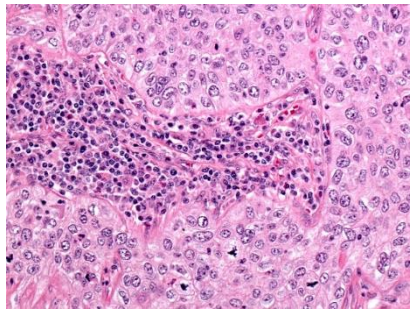
- **Immune cells**
  - Overall infiltrate
  - Specific cell types

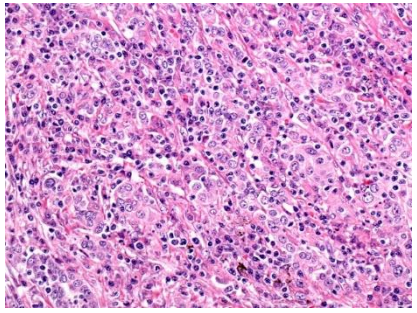
- **Other Immune checkpoints**
  - **PD-L2, IDO, etc**

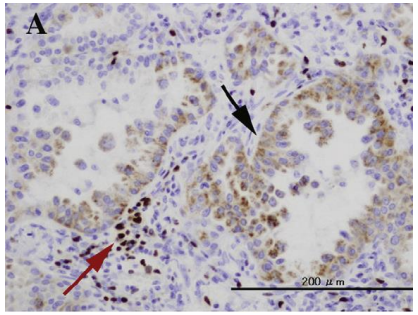
- **Mutational Burden**

Alternative Potential Biomarkers for Response?

- **Immune gene signatures**
- **Immune cells**
  - Overall infiltrate
  - Specific cell types
- Other Immune checkpoints
  - PD-L2, IDO, etc
- Mutational Burden

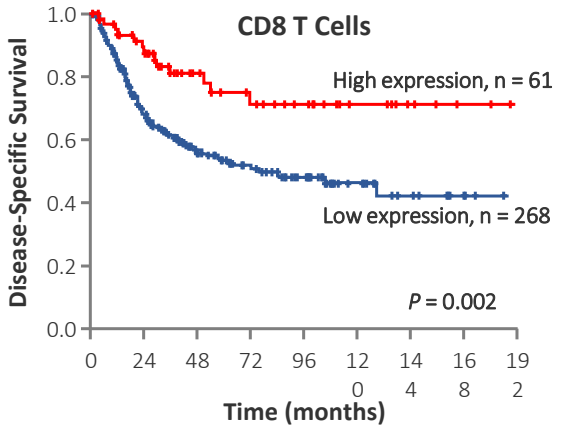




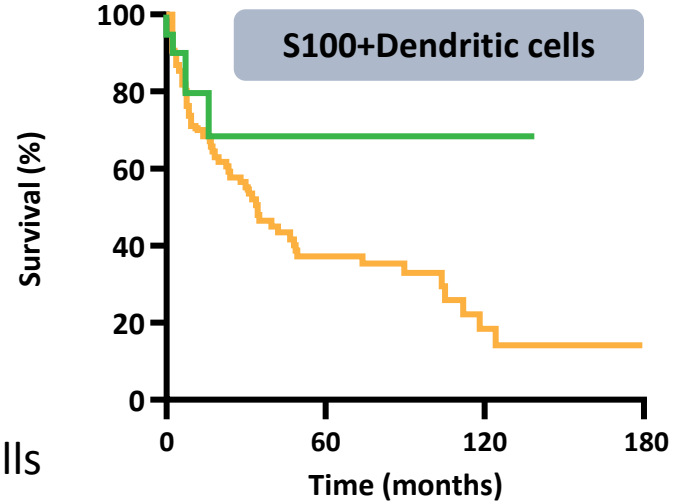


Where is the infiltrate?

FoxP3+ Tregs



Or CD4+ or CD56+ lymphoid cells



Kerr, et al Histopathol 1998; Johnson, et al. Lung Cancer 2000;
Suzuki, et al. Clin Can Res 2011; Bremnes, et al. J Thorac Oncol 2011; Tao et al. Lung cancer 2012, Al-Shibli KI, et al. *Clin Cancer Res* 2008;14:5220–7; Al-Shibli KI, et al. *Histopathol* 2009;55:301–12; Shimizu K, et al. J *Thorac Oncol* 2010;5:585–90.

Alternative Potential Biomarkers for Response?

- **Immune gene signatures**
- **Immune cells**
  - Overall infiltrate
  - Specific cell types
- **Other Immune regulators**
  - **PD-L2, IDO, LAG3,**
  - **Interferon gamma**
- **Mutational Burden**

Anti-PD-L1 therapy – Durvalumab

PD-L1 protein AND
interferon gamma mRNA expression

Higher RR (46%) in combined expression versus

Interferon gamma (33%) or PL-L1 (27%) alone

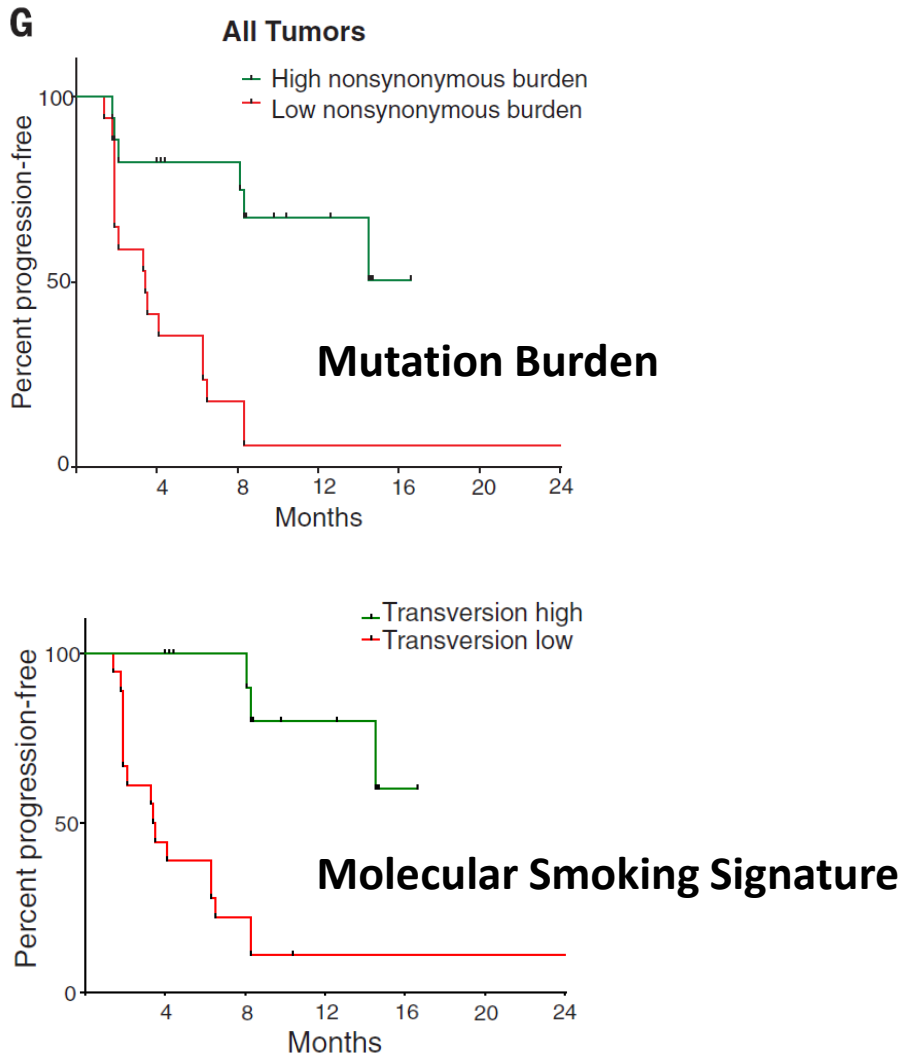
Higgs et al, 15LBA, ECCO 2015

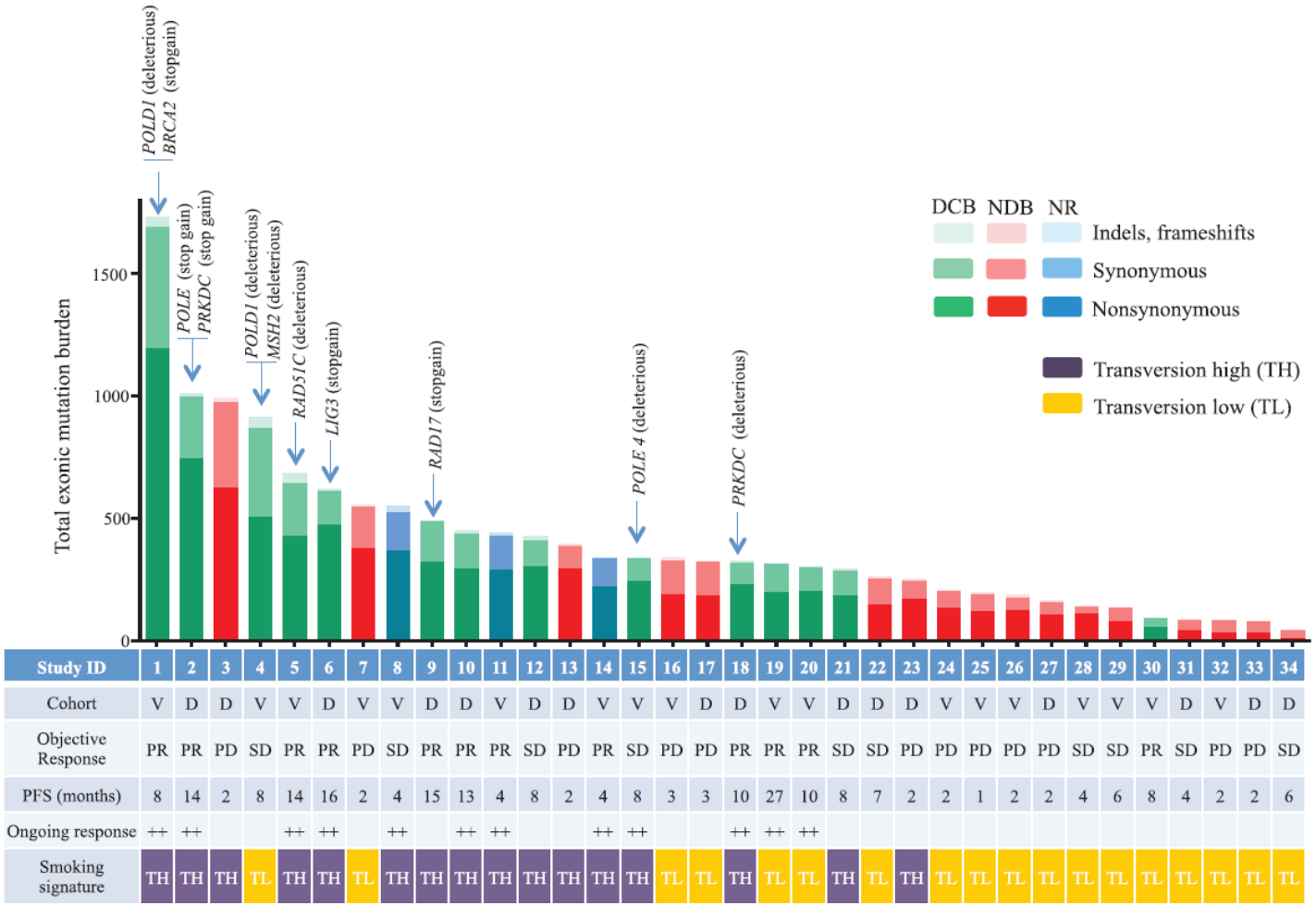
Anti-PD-1 therapy – Pembrolizumab

PD-L1 & PD-L2 IHC better than either alone

Crowley et al. LBA, ECCO 2015

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer





Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective Response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL

Rizvi NA, et al. *Science*. 2015;348:124–128.

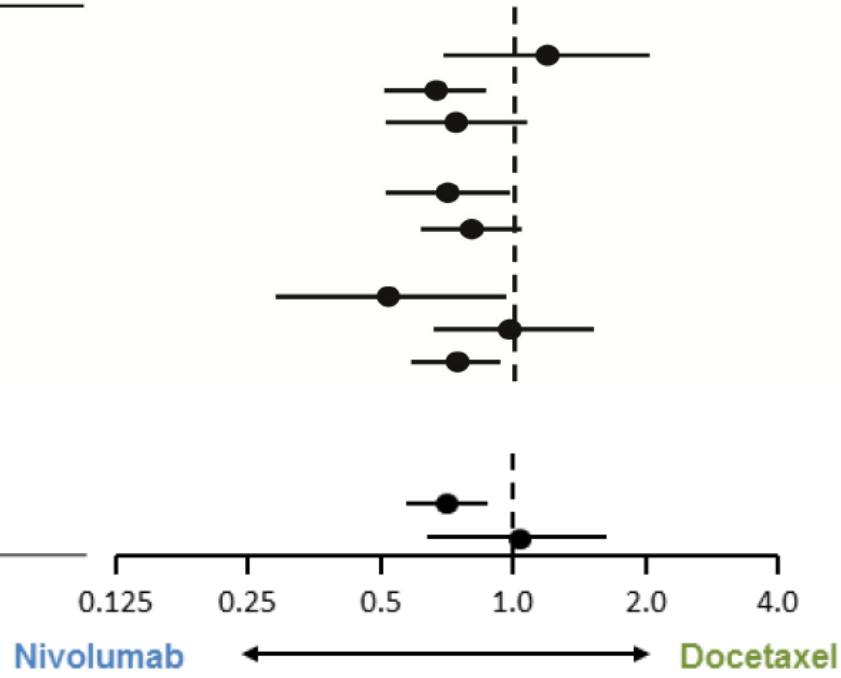
Other factors related to genomic instability

- Polymerase E (POLE) mutations
- Mismatch repair genes (MMR)
- Microsatellite Instability (MSI)

- Smoking signatures in mutations
- Smoking

Smoking and Mutational status: Checkmate 057 – Nivolumab – non-squamous tumours

	N	Unstratified HR (95% CI)
***EGFR* Mutation Status**		
Positive	82	1.18 (0.69, 2.00)
Not Detected	340	0.66 (0.51, 0.86)
Not Reported	160	0.74 (0.51, 1.06)
***ALK* Translocation Status**		
Not Detected	243	0.71 (0.52, 0.96)
Not Reported	318	0.80 (0.62, 1.04)
***KRAS* Mutation Status**		
Positive	62	0.52 (0.29, 0.95)
Not Detected	123	0.98 (0.66, 1.48)
Not Reported	397	0.74 (0.58, 0.94)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)



Borghaei H et al. NEJM 2015

Biomarker ‘positivity’: present or absent?

Your tumour is ‘negative’
Addictive oncogenic mutation or fusion gene is ABSENT
You will not benefit from therapy

Your tumour is ‘positive’
Addictive oncogenic mutation or fusion gene is PRESENT
You will benefit from therapy

Biomarker ‘positivity’: present, absent or graduated?

Your tumour is ‘negative’
Addictive oncogenic mutation or fusion gene is ABSENT
You will not benefit from therapy

Your tumour is ‘positive’
Addictive oncogenic mutation or fusion gene is PRESENT
You will benefit from therapy

Biomaker is ABSENT
or at low level
You are unlikely to
benefit from therapy

Biomaker is PRESENT
at intermediate level
You may
benefit from therapy

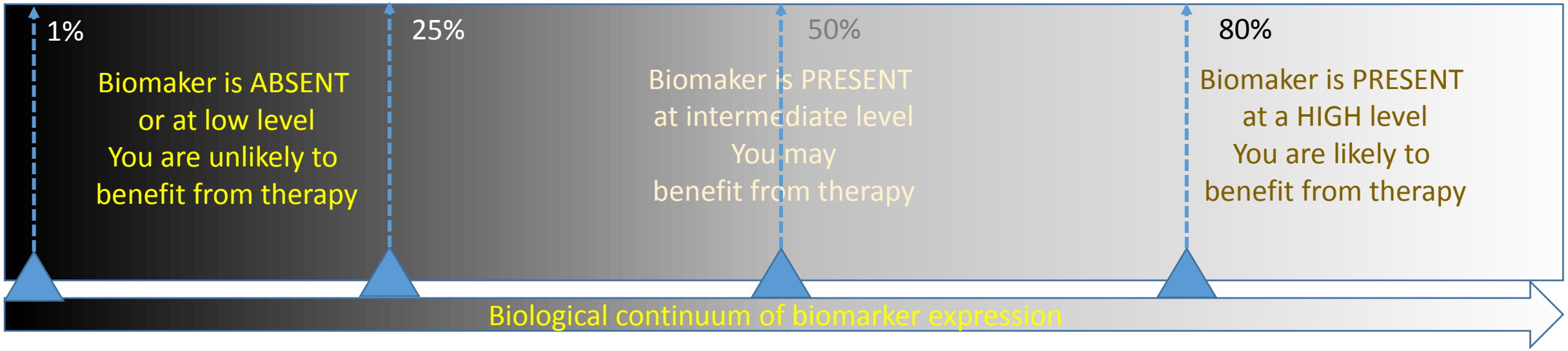
Biomaker is PRESENT
at a HIGH level
You are likely to
benefit from therapy

Biological continuum of biomarker expression

Biomarker ‘positivity’: present, absent or graduated?

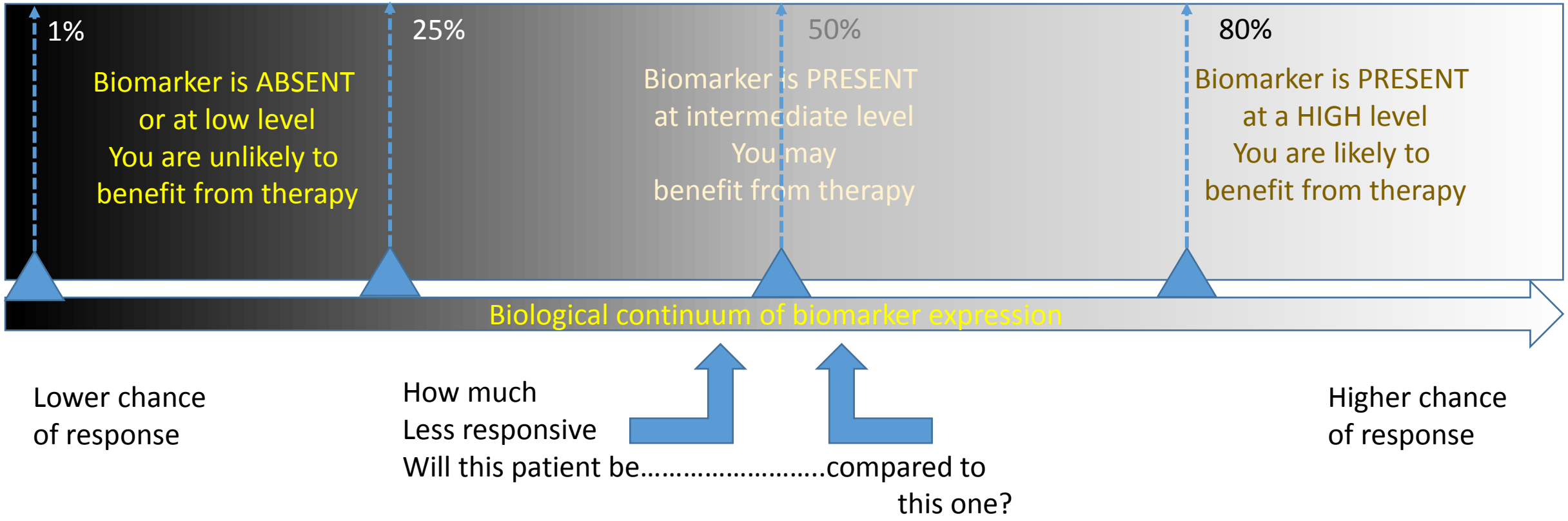
Your tumour is ‘negative’
Addictive oncogenic mutation or fusion gene is ABSENT
You will not benefit from therapy

Your tumour is ‘positive’
Addictive oncogenic mutation or fusion gene is PRESENT
You will benefit from therapy



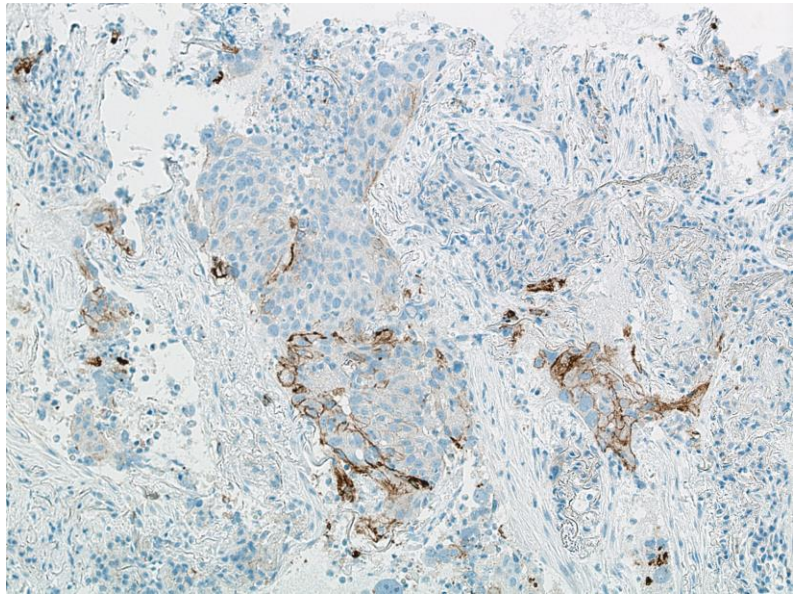
How do we define ‘positive’? Where do we set the cut-off value?

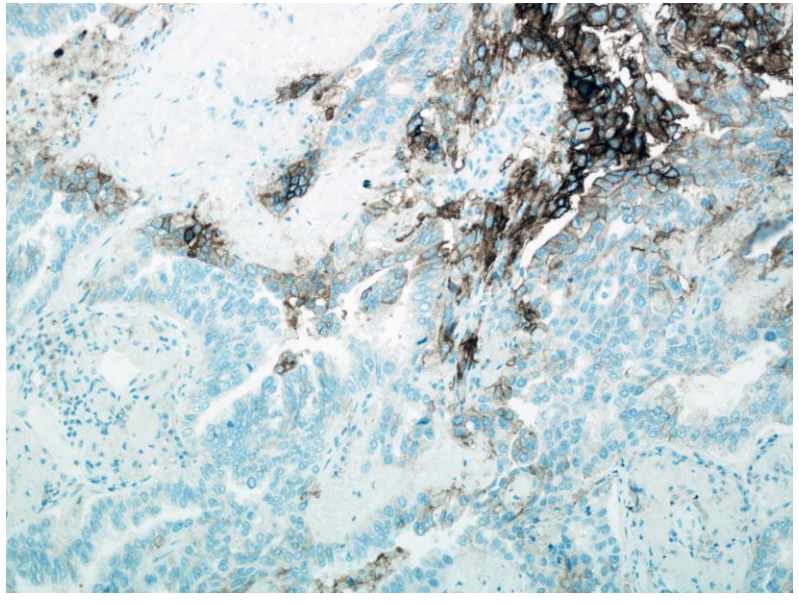
Clinical efficacy versus PD-L1 positivity……



Differential effects depend upon the Dose-response relationship

Heterogeneity and PD-L1





- Expression is dynamic
- Expression is heterogeneous
- Sampling ‘error’ must occur
- Greater impact at lower thresholds

- Part of the reason why the biomarker appears worse than it is
- Trials ‘control’ for heterogeneity to some extent

PD-L1 immunohistochemistry as a biomarker

- **Is the drug target a ‘singular’ factor in the target system?**
- **Is the biomarker present or absent?**
- **Is the biomarker stable and functionally unique?**
- **Is the biomarker easily measured?**
- **Is the biomarker 100% predictive?**

- **But it is all we currently have and what chance anything else is better?**

It depends how you look at this.
What ‘odds’ of success are you willing to accept?

PD-L1 as a predictive immune biomarker: assays, sample collection and analysis in NSCLC studies

	Pembrolizumab Merck	Nivolumab Bristol-Myers Squibb	Atezolizumab Roche/Genentech	Durvalumab AstraZeneca	Avelumab Pfizer/Merck Serono
PD-L1 Assay	• Prototype or clinical trial IHC assay (**22C3** Ab)	• Dako automated IHC assay • (**28-8** Ab)	• Central laboratory IHC assay • Ventana PD-L1 (**SP142**)	• Ventana automated IHC (BenchMark ULTRA using Ventana PD-L1 (**SP263**) clone)	• Dako assay • Clone not known
Sample Source and Collection	• Surface expression of PD-L1 on tumour specimen	• Surface expression of PD-L1 on tumour cells	• Surface expression of PD-L1 on TILs or tumour cells	• Surface expression of PD-L1 on tumour cells	• Surface expression of PD-L1 on tumour cells
	• Ph I: Fresh or archival tissue	• Archival or fresh tissue	• Archival or fresh tissue	• Unknown	• Unknown
Definition of Positivity[†]	**IHC Staining:** • Strong vs weak expression • PD-L1 expression required for NSCLC for enrollment • Note that one arm of KEYNOTE 001 trial requires PD-L1$^-$ tumours **Tumour PD-L1 expression:** • ≥50% PD-L1$^+$ cut-off: 32% (41/129) • 1–49% PD-L1$^+$ cut-off: 36% (46/129)	**IHC Staining:** • Strong vs weak expression • Patients not restricted by PD-L1 status in 2nd- & 3rd-line • Ph III 1st-line trial in PD-L1+ **Tumour PD-L1 expression:** • 1% PD-L1 + cut off • 5% PD-L1$^+$ cut-off: 59% (10/17) • 5% PD-L1$^+$ cut-off: 49% (33/68 • 10% PD-L1 + cut off	**IHC Staining Intensity (TC: 0, 1, 2, 3):** • IHC 3 (≥50% PD-L1$^+$) • IHC 2,3 (≥5% PD-L1$^+$) • IHC 1,2,3 (≥1% PD-L1$^+$) • IHC 0,1,2,3 (all patients with evaluable status)[6,7] • PD-L1 expression required for NSCLC for enrolment in Ph II trials **IC: TIL PD-L1 expression:** • IHC 3 (≥10% PD-L1$^+$): 11% (6/53) • PD-L1 low (IHC 1, 0): 62% (33/53)	**IHC Staining Intensity:** • Not presented to date **Tumour PD-L1 expression:** • PD-L1 + cut off 25% • PD-L1$^+$: 34% (20/58) • PD-L1$^-$: 50% (29/58)	**IHC Staining Intensity:** • Not presented to date **Tumour PD-L1 expression (all doses):** • PD-L1 + cut off 1% • PD-L1$^+$: 34% (20/58) • PD-L1$^-$: 50% (29/58)

PD-L1 IHC: what chance one test?

- Is all anti-PD-L1 IHC the same?
- Are all the Companion Diagnostics the same?
- **Can we use any IHC for any drug?**
  - No evidence to support this practice
  - One IHC – multiple scoring definitions
  - Implications for how PD-L1 IHC would be reported by pathologists
    - % cells positive
    - Indicate different thresholds?
    - Mention actual drugs in report?
- **How far is it safe to deviate from trial-validated practice?**

Immunotherapy and Biomarkers

- Biologically rational therapeutic approach
- Biomarkers based upon a putative understanding of
  - Likelihood of antigenicity and therefore an immune response
  - Evidence of an immune response
  - Evidence of an inhibitory mechanism
  - Evidence of the specific target – PD-L1
- PD-L1 is a realistic biomarker
  - Nature of this biomarker presents issues
  - Complex environment with multiple drugs and assays