MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

agencia española de medicamentos y productos sanitarios

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP Oncology Working Party Workshop

Histology – independent indications in Oncology

What have we learnt from the anti PD1- PDL1 story?

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Disclaimers

- the views presented are personal and may not be understood or quoted as being made on behalf of or reflecting the position of AEMPS, EMA or one of its committees or working parties

- data presented have been sourced from European Public Assessment Reports (EPARs) and published literature

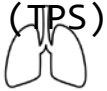
Approved PD-1 PD-L1 agents in EU

Nivolumab

- treatment of advanced (unresectable or metastatic) melanoma 
- locally advanced or metastatic non-small cell lung cancer after prior chemotherapy 
- advanced renal cell carcinoma after prior therapy 
- relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin 
- squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy 
- locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy 

Approved PD-1 PD-L1 agents in EU

Pembrolizumab

- treatment of advanced (unresectable or metastatic) melanoma 
- first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) 
- Locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen.
- relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV 
- advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (and 1L not eligible for cisplatin-containing chemotherapy) 

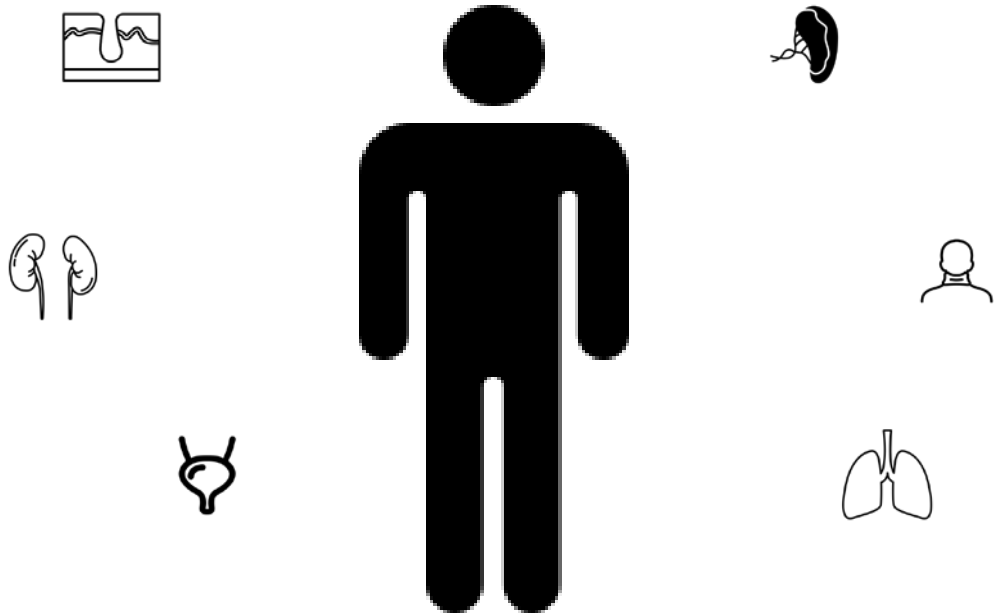
Approved PD-1 PD-L1 agents in EU

Atezolizumab

- locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible 
- locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy 

Avelumab

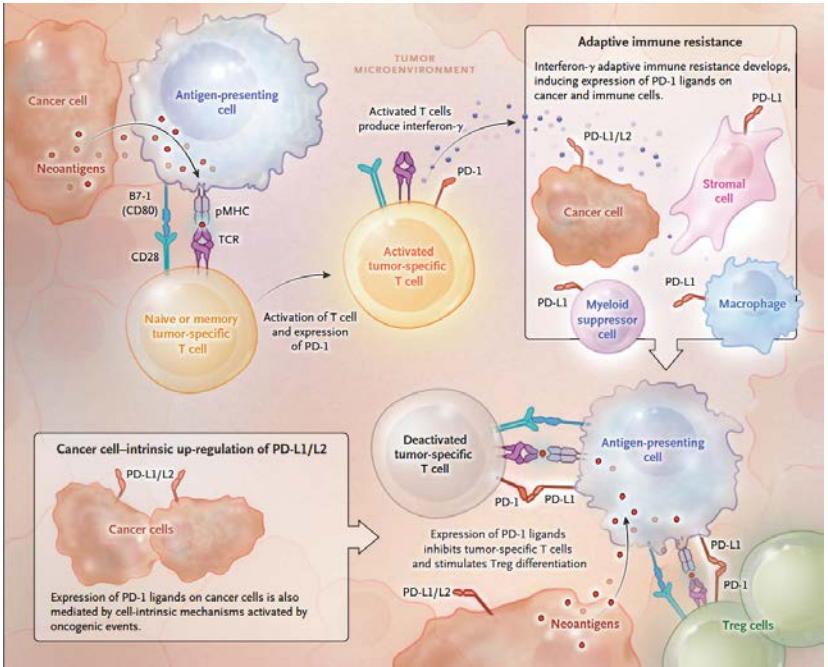
- treatment of adult patients with metastatic Merkel cell carcinoma 



Similar indications, different histologies, anything in common?

Mechanism of action

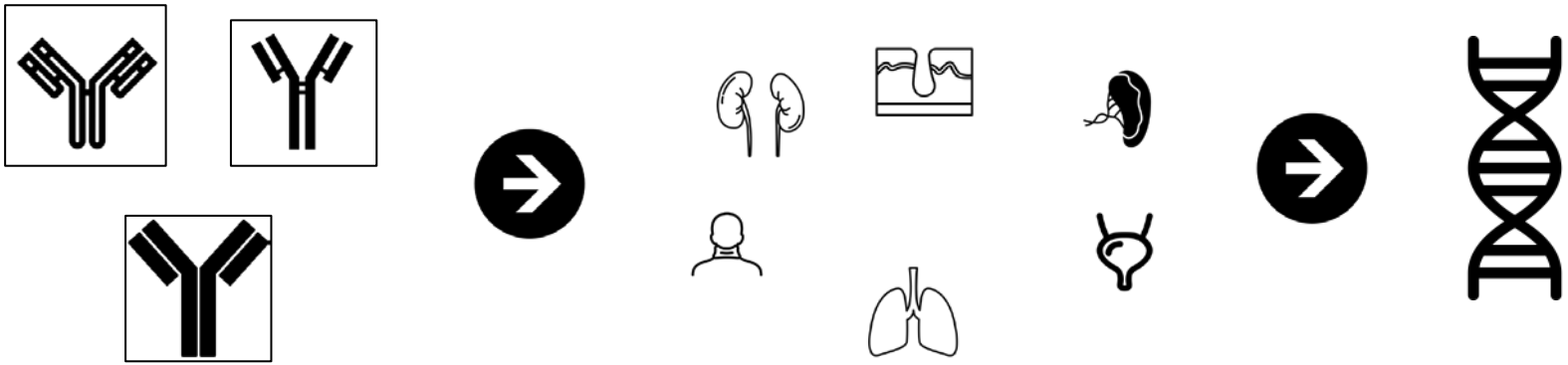
- Nivolumab and pembrolizumab. Anti PD-1
- Atezolizumab and avelumab. Anti PD-L1



removal of the coinhibitory signals that block anti- tumor T-cell responses.

N Engl J Med 2016;375:1767-78

- So, if we have 4 different products, but with a same mechanism of action (similar?), authorised in different histologies, maybe we should look for a common pattern. Biomarker? Which?



PD-L1

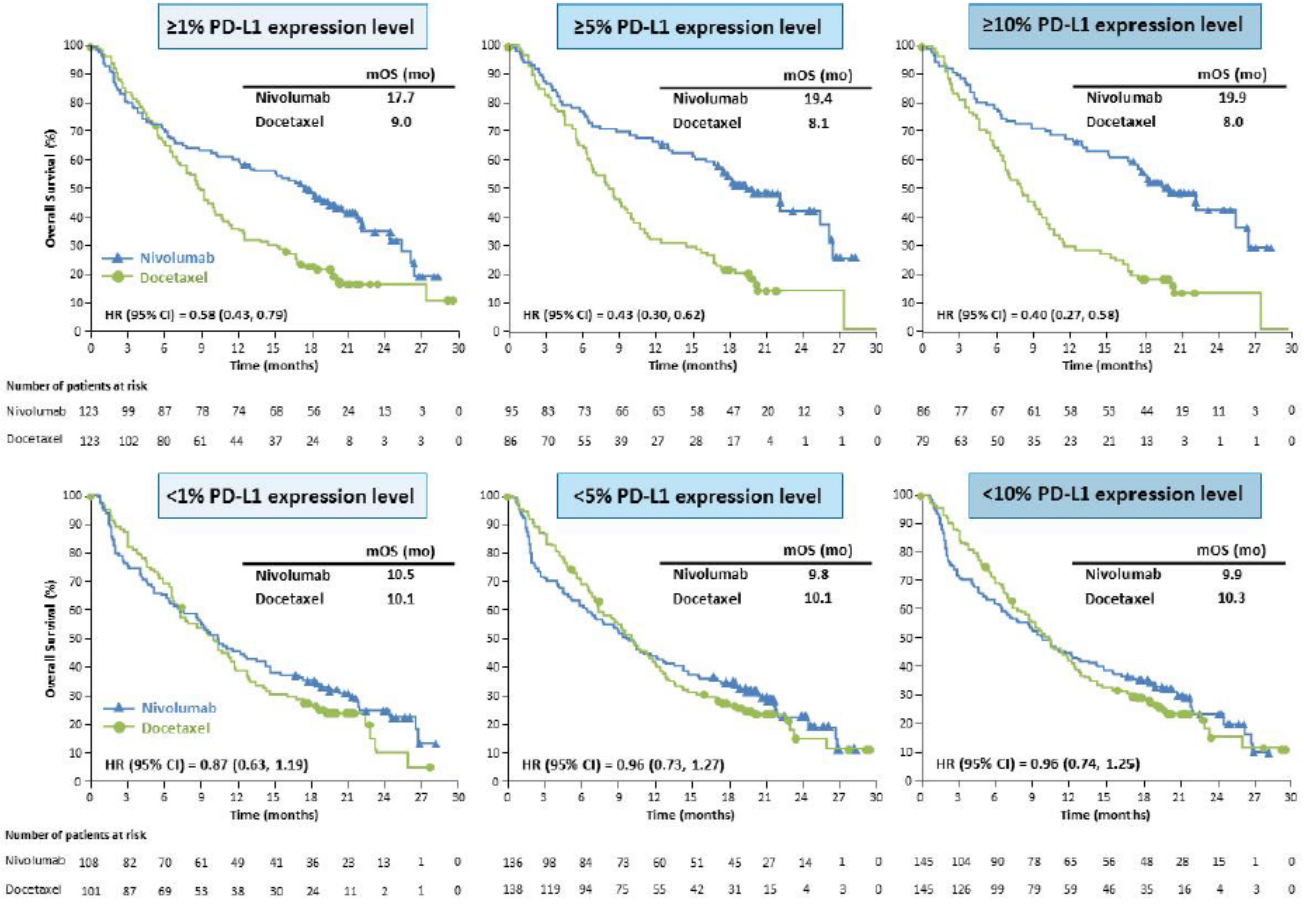
- PD-L1 is expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment
- This ligand is directly involved in the MoA of nivolumab, pembrolizumab, atezolizumab and avelumab
- PD-L1 expression could be useful as biomarker

- Different antibodies
- Different cutoffs
- Different targets

Drug	Antibody (marker)	Rx line	Tumor type	Targeted cells	Tumor specimen
Nivolumab	28-8 rabbit (Dako)	1 L	Melanoma	TCs	Archival FFPE or new biopsy
Nivolumab + ipilimumab					
Nivolumab		≥2 L			
Nivolumab + ipilimumab		1 L			
Nivolumab		1 L			
		≥2 L	NSCLC	TCs	Archival FFPE or new biopsy
		≥2 L			Archival FFPE
		≥2 L			Archival FFPE
		1 L			Archival FFPE
Nivolumab + ipilimumab		1 L			Archival FFPE
Nivolumab	5H1 and anti-PD-1 monoclonal M3	≥2 L			Archival FFPE
Pembrolizumab	22C3 mouse (Dako)	≥1 L	NSCLC	TCs and ICs	New biopsy
		1 L			New biopsy
		Any			Archival FFPE
		≥1 L			Archival FFPE
		1 L			Archival FFPE
Atezolizumab (MPDL3280A)	SP142 rabbit (Roche Ventana)	≥2 L	NSCLC	TCs and ICs	Archival FFPE and new biopsy
		≥2 L	NSCLC		
			Solid Tumor		
		≥2 L	NSCLC		

Ma et al. Journal of Hematology & Oncology (2016) 9:47

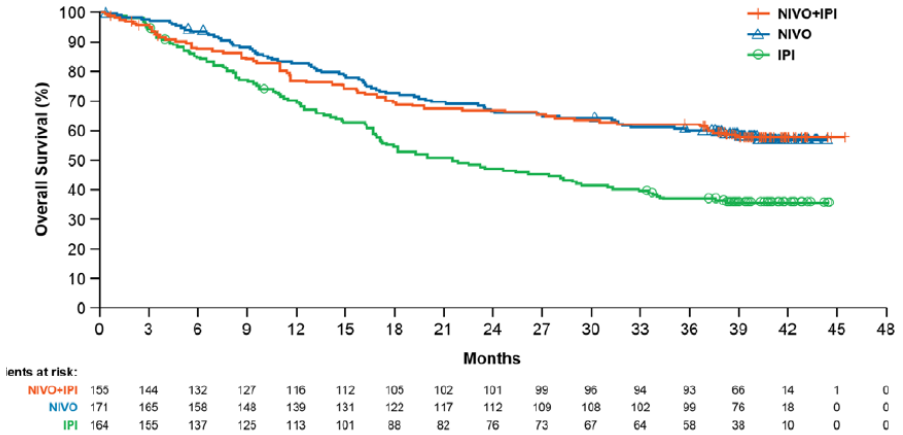
What are the data telling us?



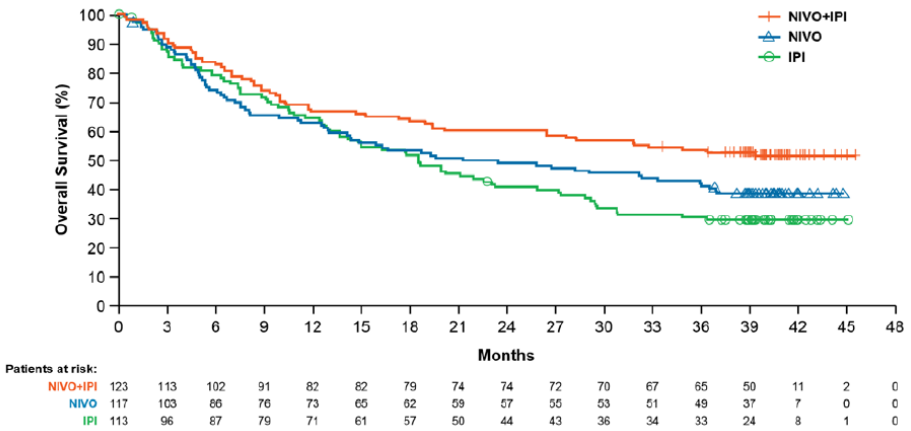
Borghaei et al. 2015.

No OS benefit in **PD-L1-positive** patients?

(C) PD-L1 expression level ≥1%



(D) PD-L1 expression level <1%



OS benefit restricted to **PD-L1-negative** patients?

Wolchok et al. 2017

CheckMate 275 a multicentre, single-arm, phase 2 trial. UC

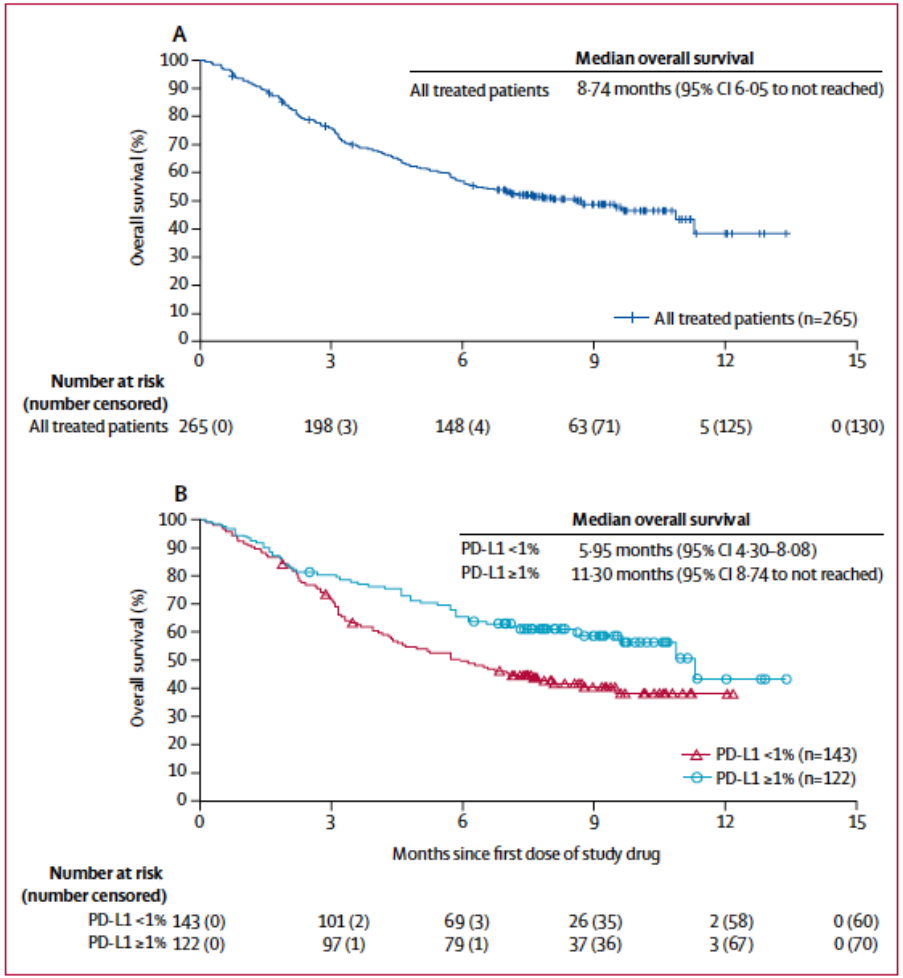


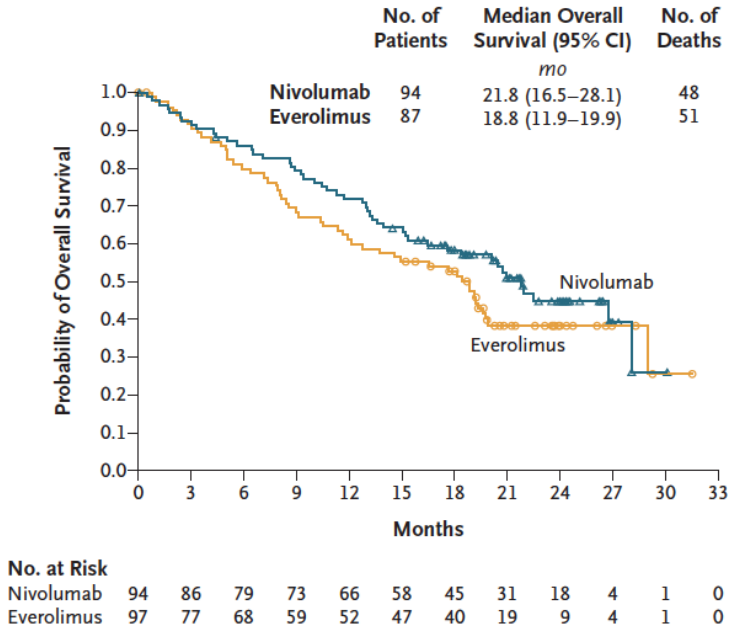
Figure 3: Median overall survival in all treated patients (A), and by PD-L1 expression (B)

Lancet Oncol 2017

PD-L1

- Apparently, the PD-L1 expression could be predictive of response, or not?

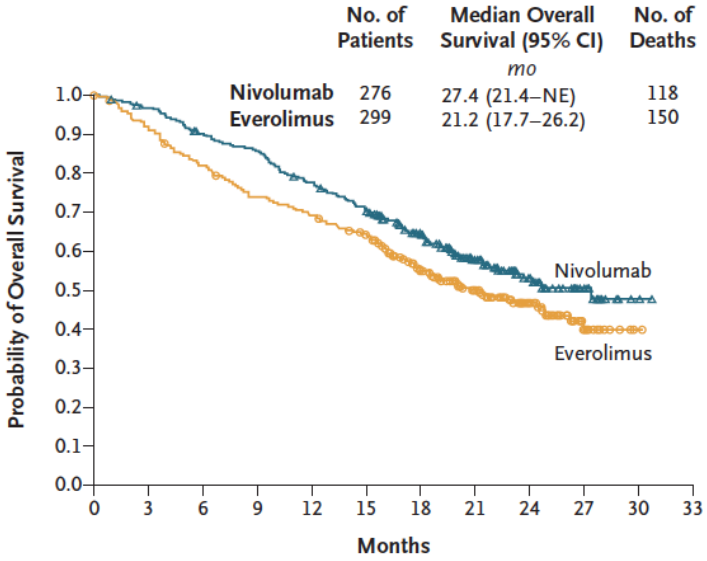
A Patients with ≥1% PD-L1 Expression



No. at Risk

Nivolumab	94	86	79	73	66	58	45	31	18	4	1	0
Everolimus	97	77	68	59	52	47	40	19	9	4	1	0

B Patients with <1% PD-L1 Expression



No. at Risk

Nivolumab	276	265	245	233	210	189	145	94	48	22	2	0
Everolimus	299	267	238	214	200	192	137	92	51	16	1	0

N Engl J Med 2015;373:1803-13

PD-L1

- The clinical utility of PD-L1 as a predictive biomarker in MCC has not been established (avelumab SPC)
- The efficacy and safety of pembrolizumab in patients with tumours that do not express PD-L1 have not been established (NSCLC)
- Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (nivolumab-melanoma)
- The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumour PD-L1 expression levels (nivolumab-H&N)

PD-L1

- The use of PD-L1 as biomarker could help to maximise the benefit. However, it does not seem very reliable at the time of the decision-making process
- Low expressors even with small (no) differences in efficacy vs SoC, could benefit of a better safety profile
- It is difficult to establish a cutoff among all the checkpoint inhibitors
- The role of the biomarkers PD-L1 or **PD-L2** expression as potential predictive or prognostic biomarkers remains undetermined

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1. To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, etc.) as predictive of nivolumab therapy efficacy. This will be provided for the approved indications:
   - Melanoma monotherapy: studies CA209038 and CA209066
   - NSCLC: studies CA209017, CA209057 and CA209026
   - RCC: studies CA209025 and CA209009
   - UC: studies CA209275 and CA209032

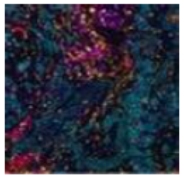
2. To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other genomic-based methods/ assays, and associated cut offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, expression of components of antigen-presentation complexes and/or other inhibitory checkpoint receptors/ligands within tumour, etc.) as predictive of nivolumab + ipilimumab combination therapy efficacy in the context of melanoma studies CA209038, CA209067, or CA209069.
In addition, levels of myeloid-derived suppressor cells in circulation will be explored in study CA209038.

7. To further explore in UC patients the early identification of those who do / do not respond to treatment with nivolumab, as well as to evaluate the association between improved clinical outcomes to nivolumab and the presence of:
   - Mutational and neoantigen load, PD-L1 expression on tumour- and tumour associated immune cells using validated approaches as feasible

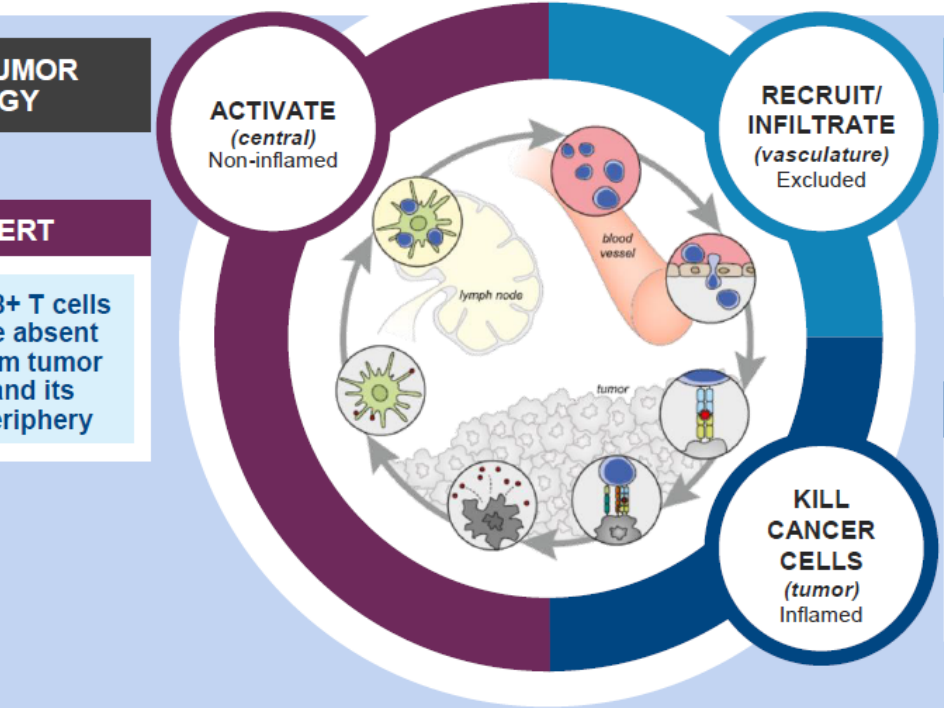
Obligation to conduct post-authorisation measures

*EVALUATE TUMOR IMMUNOLOGY

IMMUNE DESERT



CD8+ T cells are absent from tumor and its periphery



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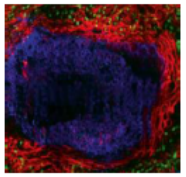
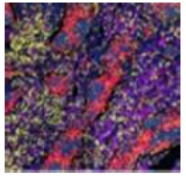


CD8+ T cells present but have not efficiently infiltrated

INFLAMED



CD8+ T cells infiltrated, but are inhibited

Modified from Chen DS, Mellman I. Immunity. 2013; Herbst et. al. Nature 2014; Hegde, Karanikas, Evers. Clin Cancer Res 2016

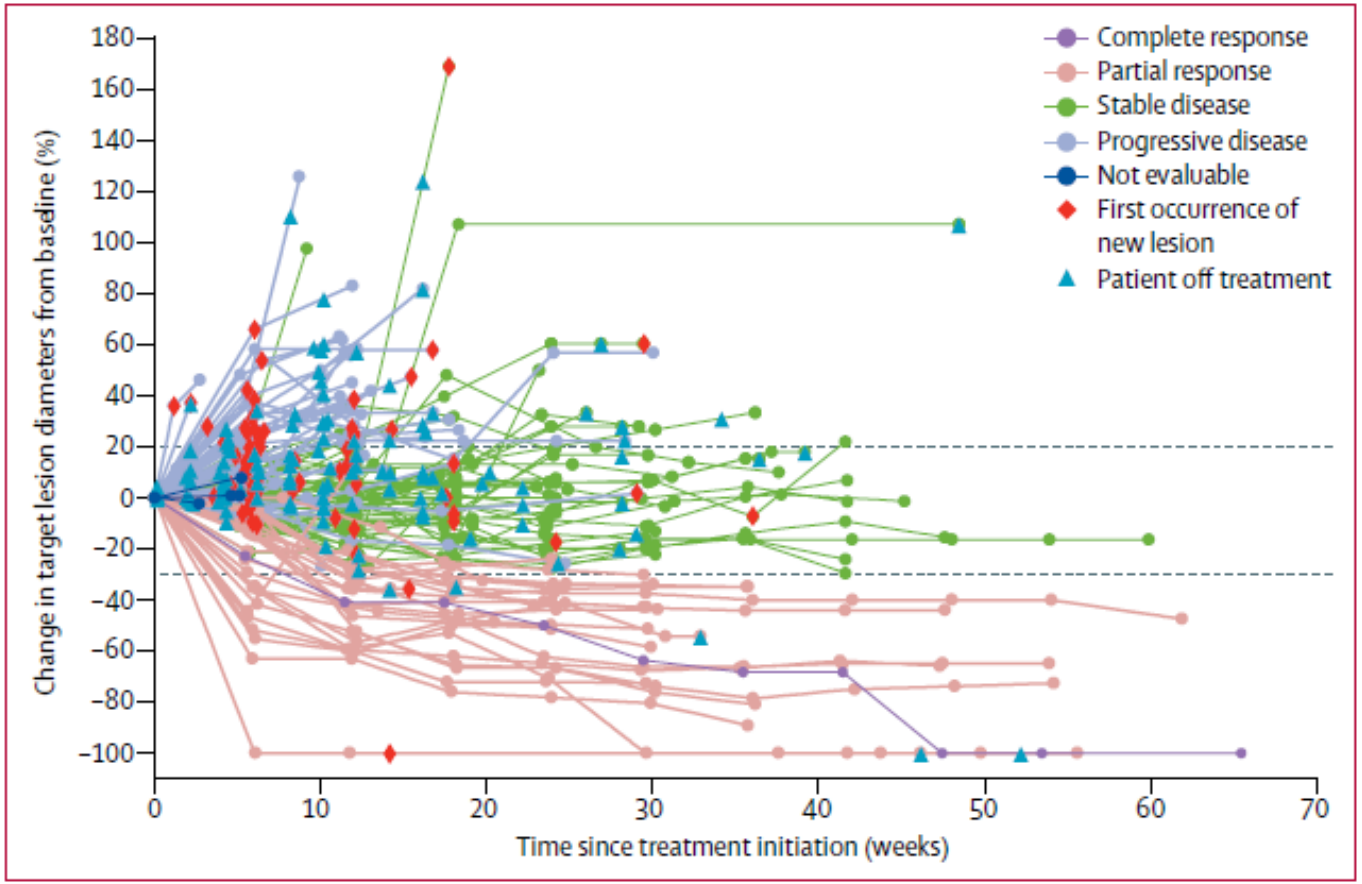
What have we learnt from the anti PD1- PDL1 story?

- PD-L1 cannot be use as biomarker so as to be the basis for Histology agnostic indication

- But this is probably the only certain we have

Uncertainties with checkpoint inhibitors

- RECIST criteria are applicable?
- Correlation between PFS and OS
- How to interpret the survival curve (long term survivors)
- Hyperprogressive disease (≥2-fold increase of the TGR) with checkpoint inhibitors
- Duration of the treatment?



Gulley et al. 2017

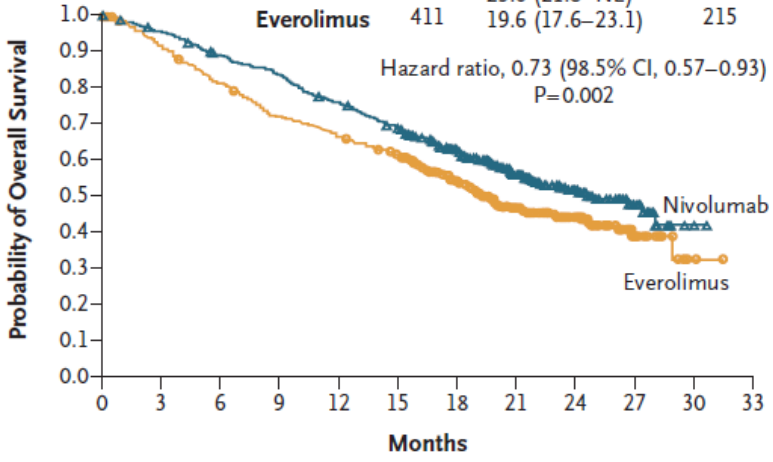
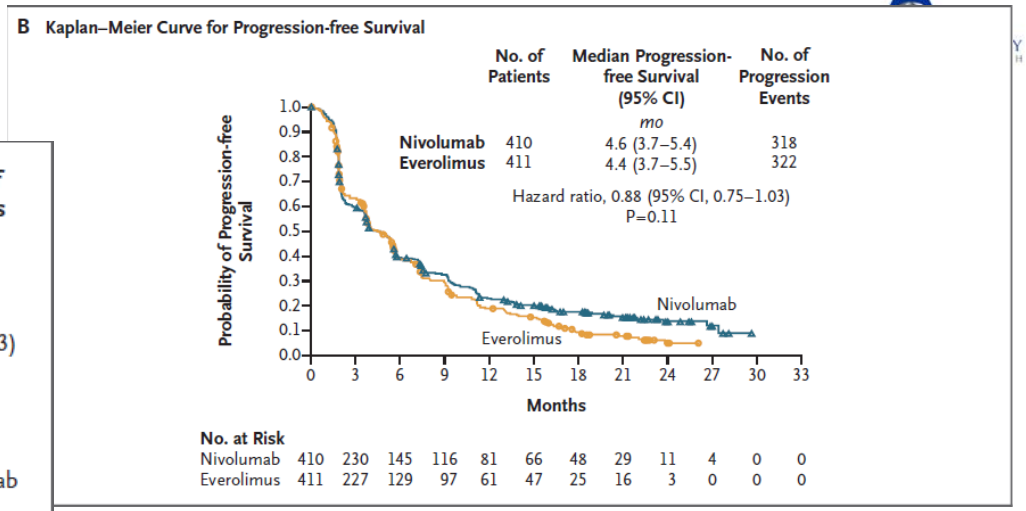


Figure 1. **Kaplan–Meier Curve for Overall Survival.**
CI denotes confidence interval, and NE not estimable.



Tumor kinetics

Pseudo-progression

PFS-OS correlation

What have we learnt from the anti PD1- PDL1 story?

- PD-L1 cannot be use as biomarker so as to be the basis for Histology agnostic indication

- But could be possible a line-agnostic?

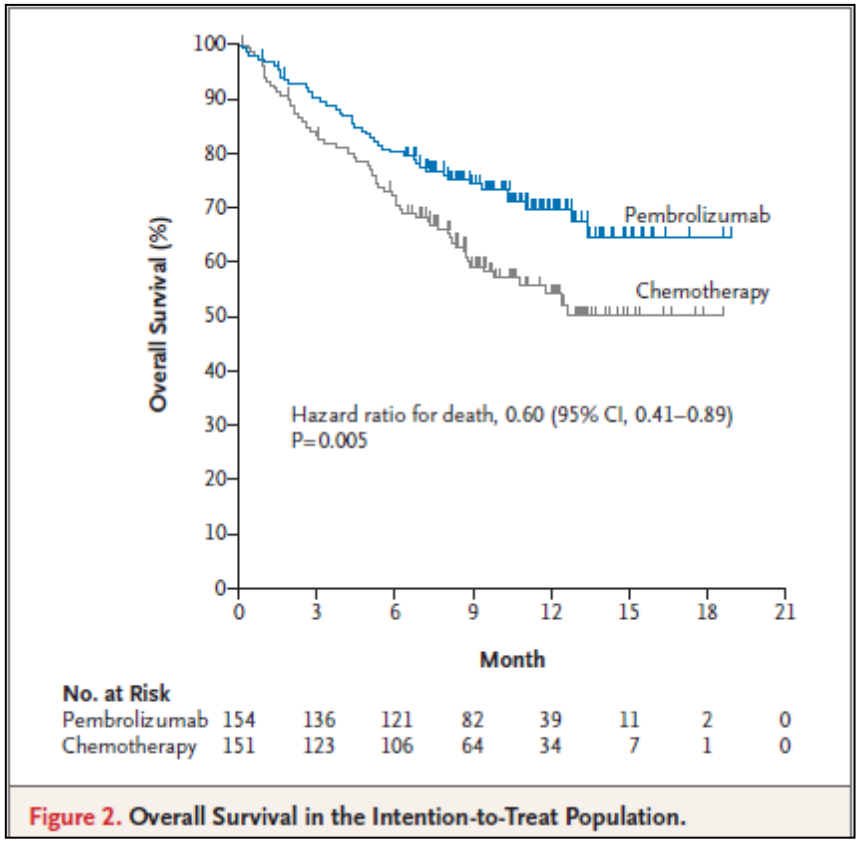


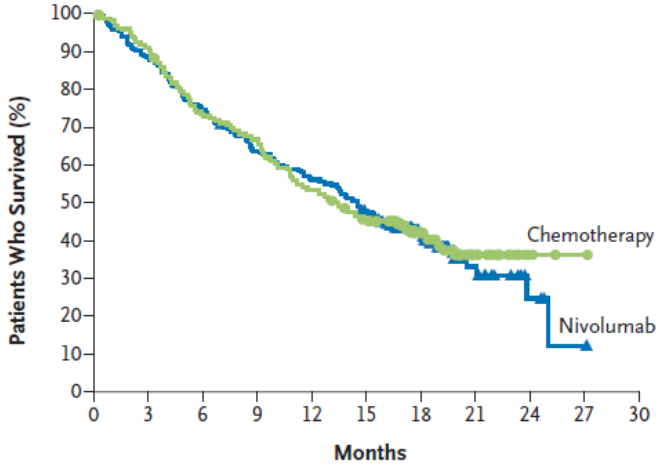
Figure 2. Overall Survival in the Intention-to-Treat Population.

Reck et al., 2016

B Overall Survival

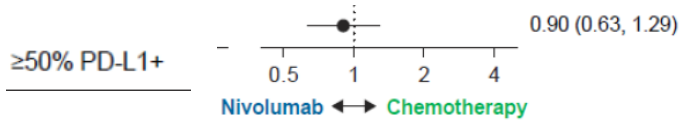
	Median Overall Survival (95% CI) *mo*	1-Yr Overall Survival Rate %
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

Hazard ratio for death, 1.02 (95% CI, 0.80–1.30)



No. at Risk

Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0



Carbone et al. 2017

Thank you!

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