# Update on Immunotherapy for NSCLC and Pathology

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## New Dimension in Lung Cancer Therapy

- Surgery
- Radiotherapy
- Chemotherapy
- Molecular targeted therapy
- Immunotherapy







## Clinically evident tumors must have evaded immune recognition/killing

## Avoided immune surveillance clearance of readily recognized tumor cell clones

<u>Structural</u> alterations of tumor antigen presentation to avoid immune recognition

#### In ~5-10% of human tumors:

- Deletion/mutation of MHC class I, b-2 microglobulin, TAP1
- Functional alterations to avoid immune recognition
  - For 90-95% of human tumors, we see:

#### Failure to induce a response

Failure of responding T cells to effectively kill tumor targets
Both soluble and cell surface immune-regulatory factors

These defects can theoretically be overcome

Tumor loss of Class I MHC presentation



#### Regulation of T Cell Responses Via Multiple Co-Stimulatory and Inhibitory Interactions

T cell response to antigen is mediated by peptide-MHC recognized by TCR (first signal – specificity)

B7 family of membrane-bound ligands bind both co-stimulatory and inhibitory receptors (second costimulatory signal)

Pardoll DM Nature Rev Cancer 12, 252, 2012





















Intra-tumoural PD-L1 expression and response to PD-1/PD-L1 blockade							
						Response side	
Minuch country	Turning	Los of bestered	Topping of all MERA 201212	226	21M	26%	Potr
MPDI 32804	Solid tumours	Linknown	Herbst et al. 4500 2013 <sup>1</sup>	140	21%	36%	13%
				240	.14	.34	
Nivolumab		221	Brahmer et al. ASCD 2014 <sup>4</sup>	129	17%	15%	14%
Nivolumab		11.	Ripri et al. CMSTO 2014 <sup>5</sup>	52	21%	315	10%
Nivolumab		31.	Ramalingam et al. CMSTO 2014 <sup>6</sup>	117	15%	24%	14%
MPDL3280A	NSCLC	Unknown	Soria et al. ESMO 20147	53	N/A	31%	20%
MEDI4736		211	Brahmer et al. ASCO 20148	155	16%	25%	3%
Pembrolizumab		211	Garon et al. ESMO 2014*	129	22%	37%	10%
Pembrolizumab		211	Garon et al. ESMO 2014*	236	21%	23%	9%
Nivolumab		221	Weber ASCO 201313	87	25%	67%	19%
Nivolumab		221.	McDermott et al. ESMO 201411	107	32%	44%	13%
Pembrolizumab	Melanoma	>2%	Daud et al. AACR 2014 <sup>13</sup> Kefford et al. ASCD 2014 <sup>13</sup>	125	40%	49%	13%
MPDL3280A		211	Hamid et al. ASCO 201314	38	29%	27%	20%
	1. Tapalan 1, et al. Nilogi Med 2012 (Med 2012) Med 2012 (Med 2012) (See al. Control of a good (12) (See al. Control of a good						
MPDL3280A	5 Rice N, et al. Poder 185 presented at CMITO 2011 (abd): 10(6); 6 Kanalingare S, et al. Citil presentation at CMITO 2011 (abd): 10(1); 7 Jona K, et al. Presented at DMITO 2011 (abd): 10(2); 8 J4%						
	Relation and Active State Stat						
Pembrolizumab	at ASICE 2011 (abov. 9000), 15. Berlinkel J, et al. Newsenie J at 1960 2011 (abov. 9800), 36. Chowled, et al. Prevented at 1980 2011 (abov. 98A10). N/A						

**PD-L1 Identifies Pts With NSCLC Most Likely to Benefit From (MK-3475) Pembrolizumab**  $h_{0}^{0}$   $h_{0}^{0}$ 













PD-L1 expression level	NIVO	DOC	Unstratified HR (95% CI)	P-value*	
05					
			0.59 (0.43, 0.82)	0.0040	- <del>-</del>
<1%	108	101	0.90 (0.66, 1.24)	0.0646	
≥5%	95	86	0.43 (0.30, 0.63)	0.0004	
<5%	136	138	1.01 (0.77, 1.34)	0.0004	
≥10%	86	79	0.40 (0.26, 0.59)	0.0000	- <del>-</del> - :
<10%	145	145	1.00 (0.76, 1.31)	0.0002	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)		<b></b> ;
PFS					
	123	123	0.70 (0.53, 0.94)	0.0007	- <u></u> i
<1%	108	101	1.19 (0.88, 1.61)	0.0227	
≥5%		86	0.54 (0.39, 0.76)	0.0004	
<5%	136	138	1.31 (1.01, 1.71)	<0.0001	· · · · · · · · · · · · · · · · · · ·
≥10%	86	79	0.52 (0.37, 0.75)	0.0000	
<10%	145	145	1.24 (0.96, 1.61)	0.0002	⊢•──
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)		



	Patie	nts, n	Unstratified		
D-L1 expression	NIVO	DOC	HR(95% CI)		
s					
≥1%	63	56	0.69 (0.45, 1.05)		
			0.58 (0.37, 0.92)		
≥5%	42	39	0.53 (0.31, 0.89)		
<5%	75	69	0.70 (0.47, 1.02)		
≥10%	36	33	0.50 (0.28, 0.89)		
<10%	81	75	0.70 (0.48, 1.01)		
Not quantifiable at baseline	18	29	0.39 (0.19, 0.82)		
FS					
≥1%	63		0.67 (0.44, 1.01)		
<1%	54	52	0.66 (0.43, 1.00)		
≥5%	42	39	0.54 (0.32, 0.90)		
<5%	75	69	0.75 (0.52, 1.08)		
≥10%	36	33	0.58 (0.33, 1.02)		
<10%	81	75	0.70 (0.49, 0.99)	-	
Not quantifiable at baseline	18	29	0.45 (0.23, 0.89)		





#### Biomarker not predictive in Squamous (CheckMate 017) but predictive in Non-Squamous (Checkmate 057)

- Same drug, same biomarker
   Current/Former smokers
   017 92% 057 9.5% (EGFR/ALK in 17.5%)
   -25-30% of 057 cases NOT tobacco driven?
- · Greater mutational load in 017 squamous cell cancers?
- Immune system and squamous versus glandular epithelia?
   Does the immune status or immune microenvironment differ between these patients?
   Immune infiltrates in and around tumours differ.
- Does the mutation burden make a difference? Are immunomodulatory mechanisms different?
- Are the cut offs correct? Are 1, 5 & 10% too low?



## POPLAR: A Randomized All-comer Phase II Study

- · Archival or fresh tissue required for pre-dose testing
- · TC scored as percentage of tumor cells positive any intensity
- · IC scored as percentage of tumor area with positive cells any intensity

ASCO A

- TC3 or IC3 = TC  $\geq$  50% or IC  $\geq$  10% PD-L1+
- TC2/3 or IC2/3 = TC or IC  $\geq$  5% PD-L1+
- TC1/2/3 or IC1/2/3 = TC or IC  $\geq$  1% PD-L1+
- TC0 and IC0 = TC and IC < 1% PD-L1+....not actually negative

PD-L1 Expression on TC and IC Were Independent Predictors of Response to Atezolizumab in NSCLC

 In PCD4989g, TC3 and IC3 represented non-overlapping populations, each benefiting from treatment with atecolizumab

PD-L1 Status	Best Overall Confirmed Response <sup>a</sup> (95% CI)				
TC3 (n = 9)	44% (14%-79%)				
IC3 (n = 12)	50% (21%-79%)				
TC3 or IC3 (n = 21)	48% (26%-70%)				
All treated patients (n = 88)	23% (14%-33%)				

 Additional data on the association between PD-L1 expression in TC or IC and response to atezolizumab to be presented by Hom et al (abstract 8029), Spigel et al (abstract 8028) and Spira et al (abstract 8010), ASCO 2015











PD-L1 immunohistochemistry as a biomarker • Is it the correct marker?





### PD-L1 immunohistochemistry as a biomarker

- Is it the correct marker?
- Does the oncology community trust immunohistochemistry? • No!
- Are our (oncologists) expectations of a biomarker in this setting reasonable?
  - No!
  - Biological continuum 'anologue' not 'digital'
  - Artificial cut offs 'noise in the system'
  - IO therapy NOT like inhibiting addictive oncogenes

## PD-L1 immunohistochemistry as a biomarker

- Is it the correct marker?
- Does the oncology community trust immunohistochemistry?
- Are our expectations of a biomarker in this setting reasonable?
- Four drugs, four biomarkers, all for 'PD-L1'

## Four drugs, Four biomarkers......

- Pros and Cons of companion diagnostics
- 'Skiing off piste'
- Programmed Death Receptor 1 and Its Ligand Immunohistochemistry in Lung Cancer In what state is this art? · Comparability of assays
  - Technically
    Qualitatively
  - Predictively
- Communication with Oncologists
- Is your lab equipped?



Kerr et al, J Thorac Oncol April, 2015









