Integrated Medicines Ltd

Immuno-Oncology Biomarkers in Clinical Development and Patient Selection

NIHR DEC UK Diagnostics Forum: *"Diagnostics in Times of Change"*

Tuesday 16th May 2017, Lady Margaret Hall, Oxford

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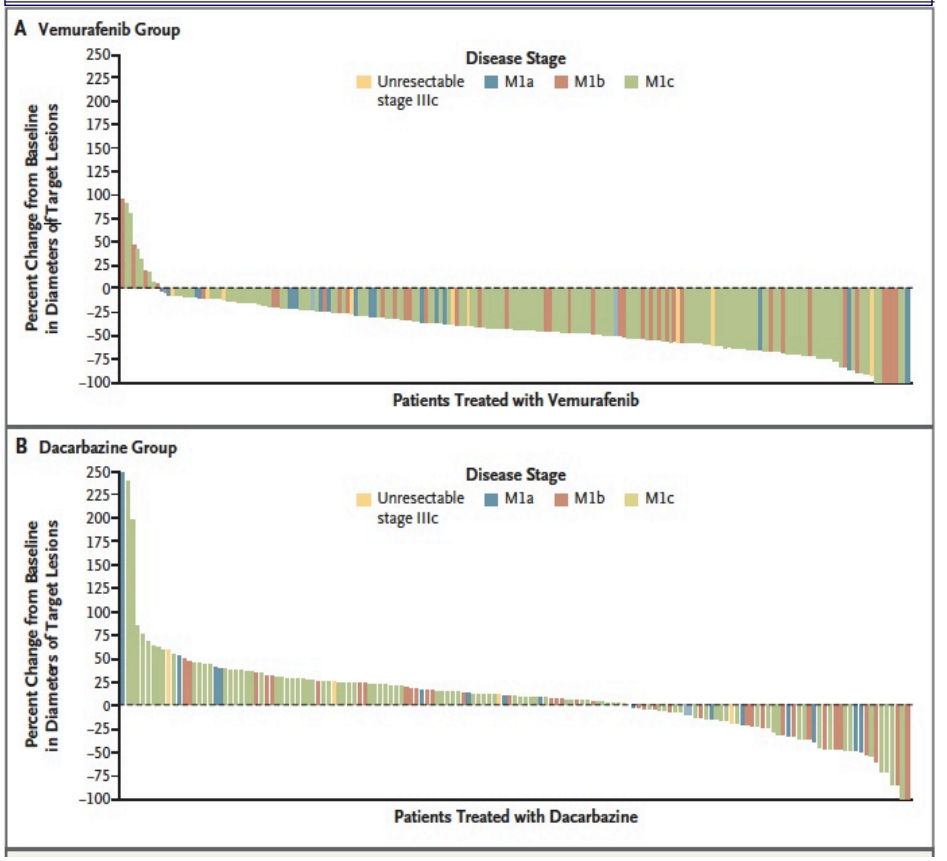
Integrated Medicines



Targeted Therapies: Expedited Development and Approval Timelines[1,2,3]

- Roche co-developed PLX4032/ vemurafenib with Plexxikon from October 2006[1] subsequent to IND filing; consequent Phase 1 study shows a 81% response rate in 38 metastatic melanoma patients with **BRAF^{V600E}** mutation
- Clinical development proceeded directly to Phase 3; widely anticipated efficacy and limited trial crossover opportunity slowed enrollment; trial modified to reach 675 total patients[1]
- FDA review of drug (Rx) and companion diagnostic (CDx) completed in 3.6 months with approval on 17th August 2011[3]
- Approval credits coordination of Rx-CDx regulatory submissions and clear efficacy of drug in *target* population[3]

Best Tumour Response for Each Patient[2,*]

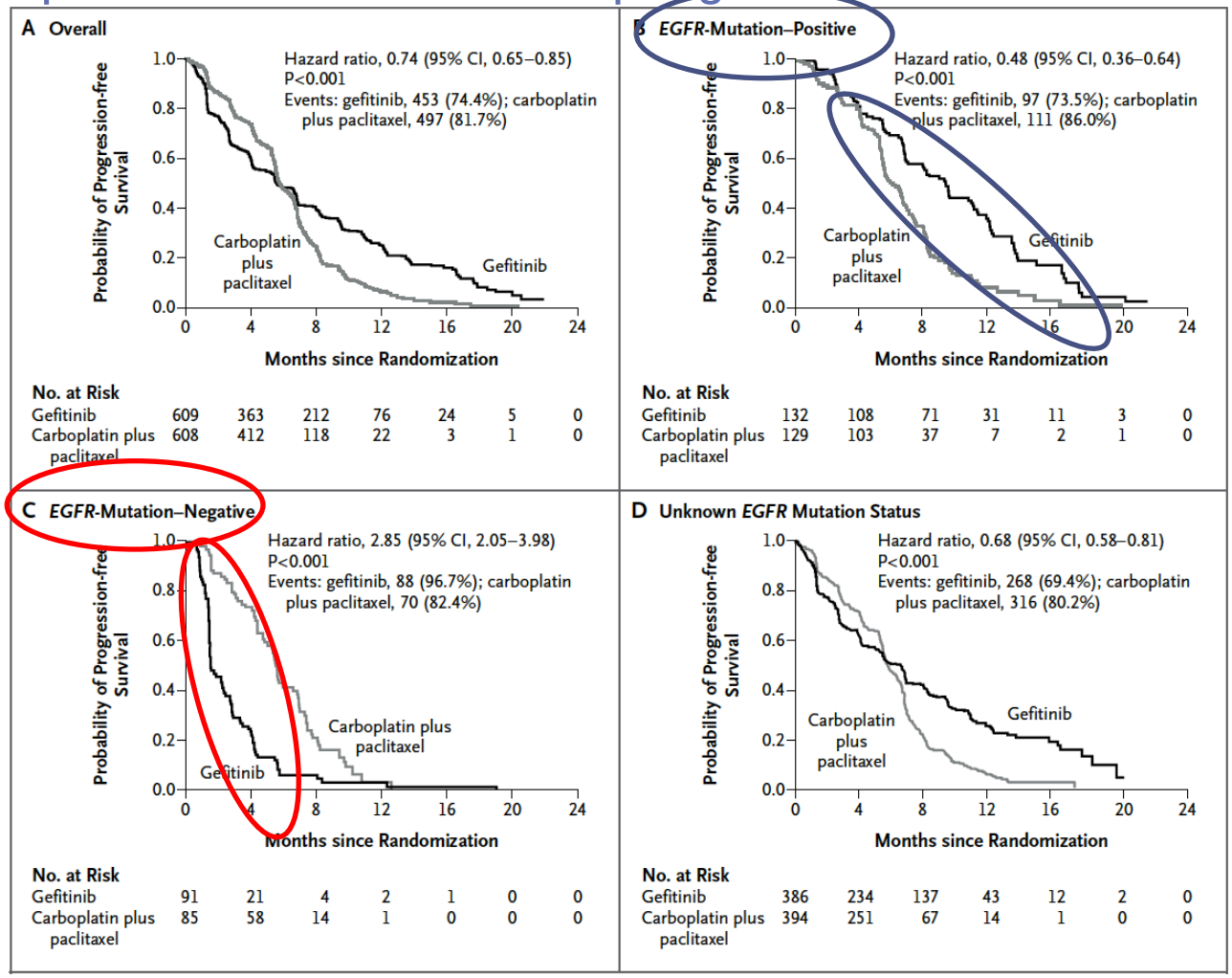


*Data for 209 patients in the vemurafenib group (Panel A) and 158 patients in the dacarbazine group (Panel B). Each bar represents data for an individual patient. Colours indicate the tumour sub-stage for each patient. The percent change from baseline in the sum of the diameters of the target lesions is shown on the y axis. *Negative values indicate tumour shrinkage.*

1. http://www.roche.com/investors/updates/inv-update-2006-10-05.htm, accessed 11th October 2016
2. Chapman et. al NEJM 364;26 30 June 2011
3. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm268241.htm , accessed 11th October 2016

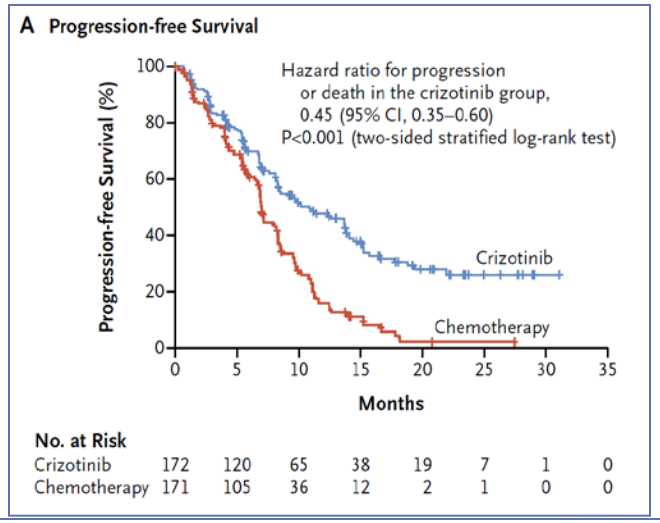
Targeted Therapies Only Provide Benefit When Target is Present[1,2]

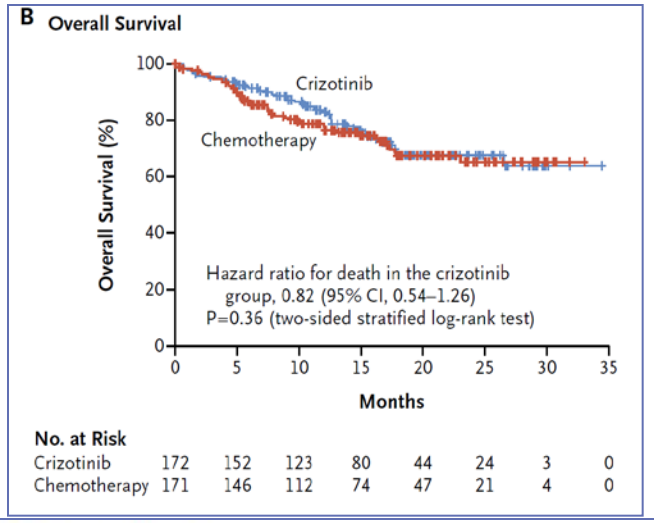
Kaplan–Meier curves for progression-free survival[2]

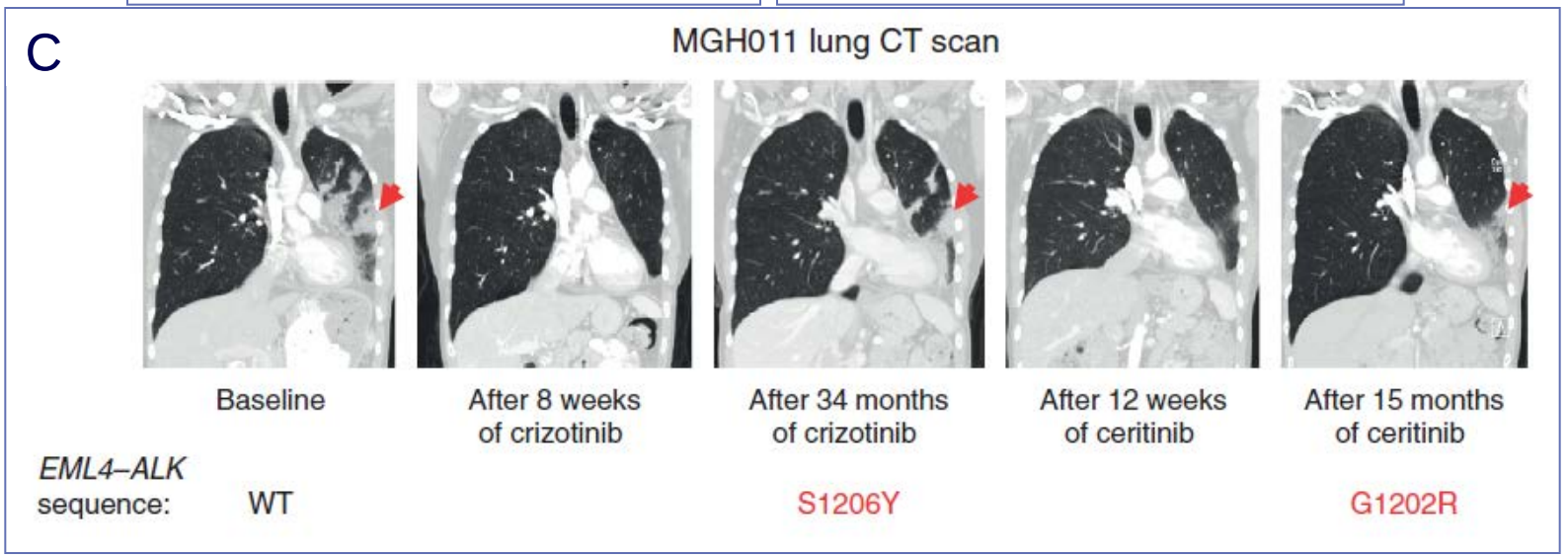


1. Professor Ken Bloom, LSO3 Roche Diagnostics Symposium "From testing to therapy – the PD-L1 continuum". European Society of Pathology 28th Congress (2016),
2. Adapted from Mok TS, et al. N Engl J Med 2009

Targeted therapies work rapidly but may show little long-term benefit[1,2,3]







1. Professor Ken Bloom, LSO3 Roche Diagnostics Symposium "From testing to therapy – the PD-L1 continuum". European Society of Pathology 28th Congress (2016),
2. Solomon BJ, et al. N Engl J Med 2014;371:2167 (Figures A & B)
3. Friboulet L et al. *Cancer Discovery* 2014;4:662-673 (Figure C)

Key Differences Between Targeted Therapy and Immunotherapy[1]

Targeted Therapy

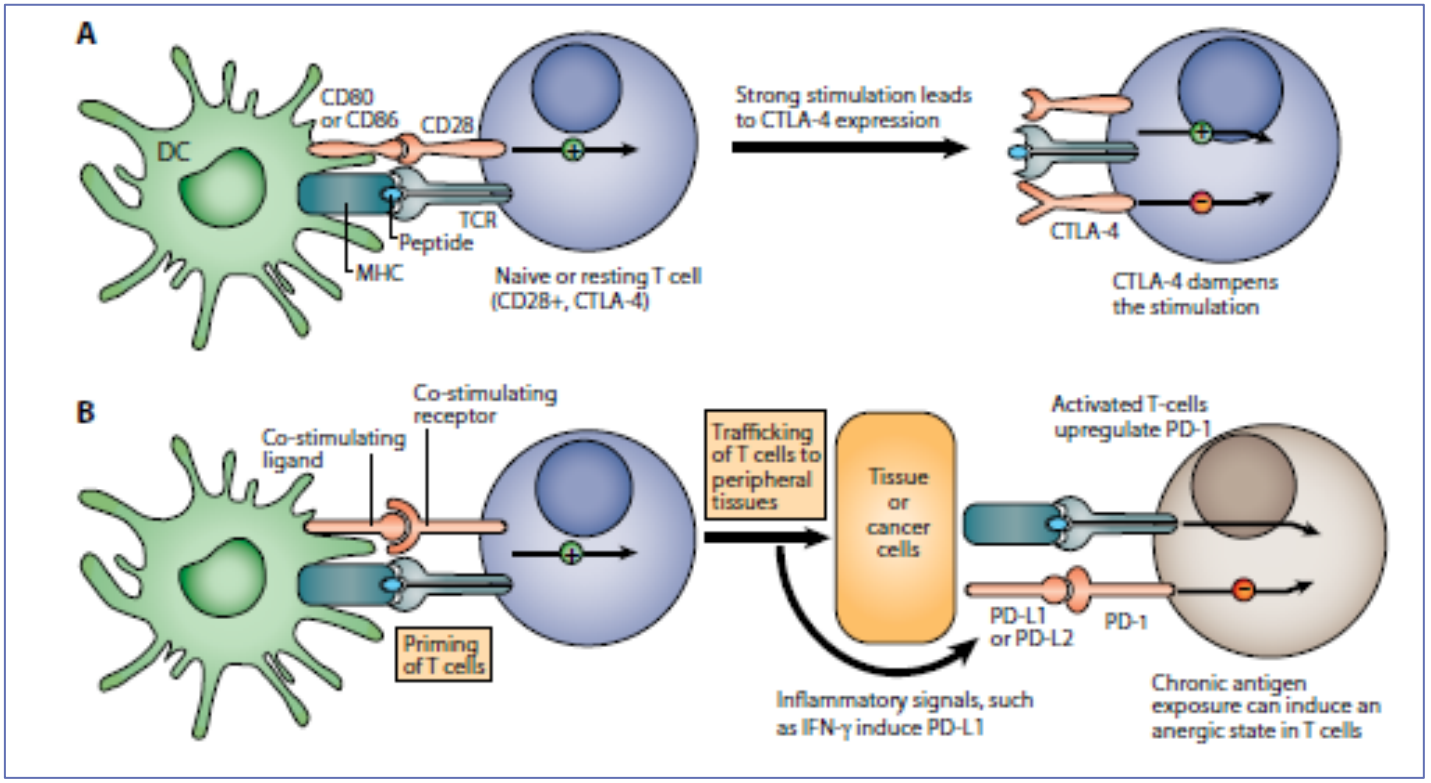
- Tends to be organ specific?
- Patients negative for biomarker get no benefit
- Benefits seen early
- *Duration of benefit limited*
- Impact on survival limited
- Biomarker in tumour cells

Immuno Therapy

- Pan tumor potential
- Patients negative for biomarker still get benefit
- Benefit not always seen early
- *Extended duration of benefit*
- Impact on overall survival
- Biomarker on tumour cells and other cells in tumour microenvironment

1. Professor Ken Bloom, LSO3 Roche Diagnostics Symposium “From testing to therapy – the PD-L1 continuum”. European Society of Pathology 28th Congress (2016)

Regulating the T-cell Response: Immune Checkpoints and Checkpoint Inhibitors[1]



anti–CTLA-4

ipilimumab

anti–PD-1

nivolumab

pembrolizumab

anti–PD-L1

atezolizumab

durvalumab

CD28 = cluster of differentiation 28; CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed death receptor-1; PD-L1 = Programmed Death Ligand 1

CD80 & CD86 = Ligands for CD28 (+ve) and CTLA4 (-ve)

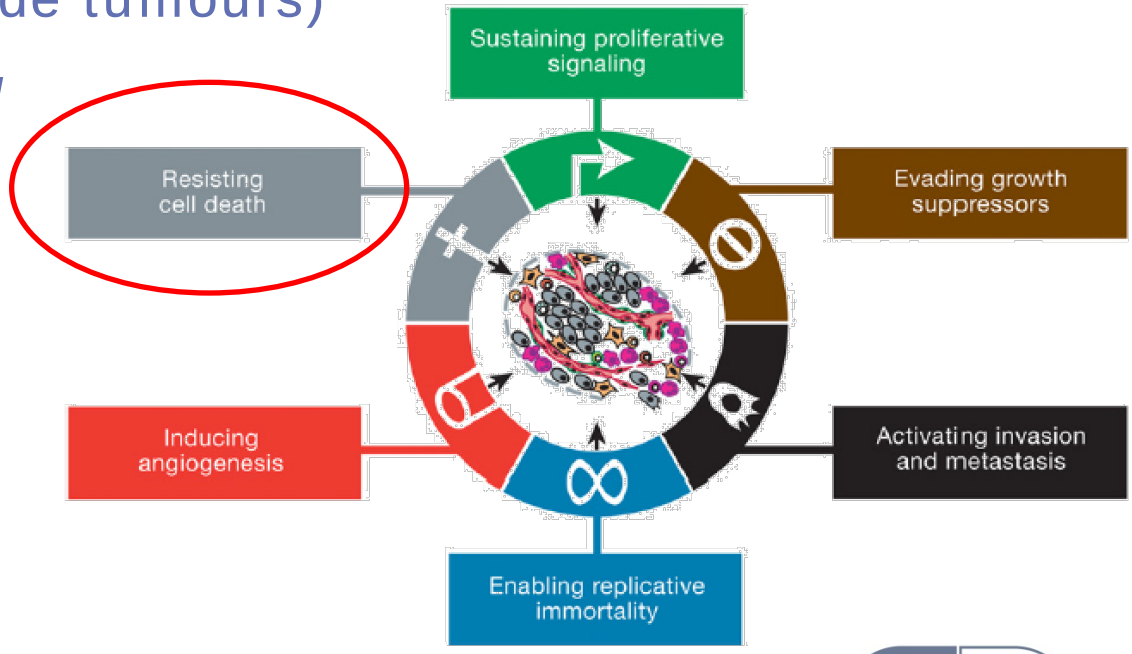
1. Tsao MS et al (2017) IASLC Atlas of PD-L1 Immunohistochemistry Testing in Lung Cancer

Resisting Cell Death is one Hallmark of Cancer[1,2,3]

The tumour cell releases antigens, presumably altered proteins due to expressed mutations (frameshifts and truncations), that are presented to dendritic cells that prime and activate T cells which then traffick to the tumour

This is more likely with higher mutational burden (pleomorphic/higher grade tumours)

Tumour may look inflamed but is not ablated



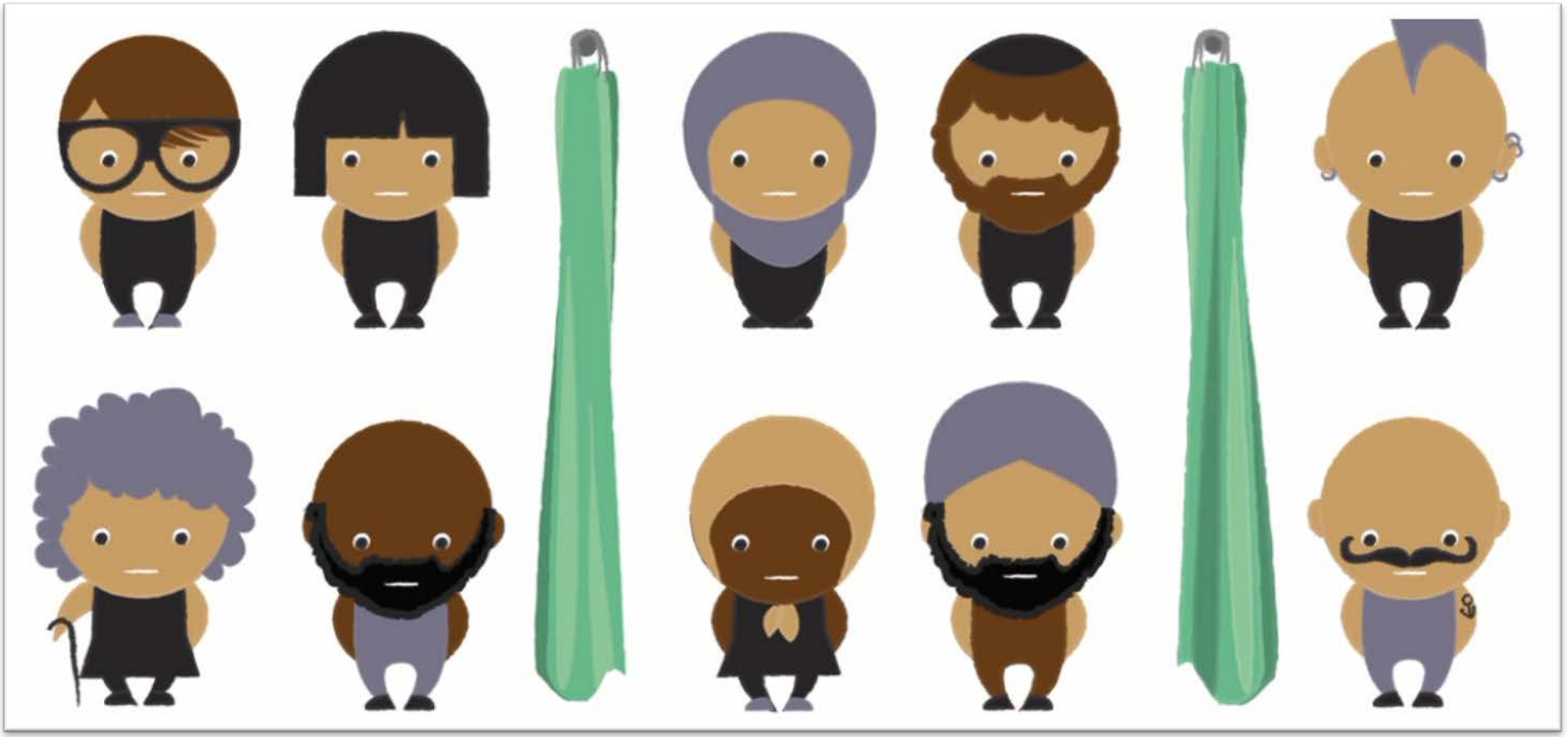
1. Professor Ken Bloom LSO3 Roche Diagnostics Symposium "From testing to therapy – the PD-L1 continuum". European Society of Pathology 28th Congress (2016).
2. Adapted from Hanahan & Weinberg, Cell (2011) **144**, 646–674.
3. Text adapted by E Blair

Patterns of immune cell infiltration[1]

immune desert

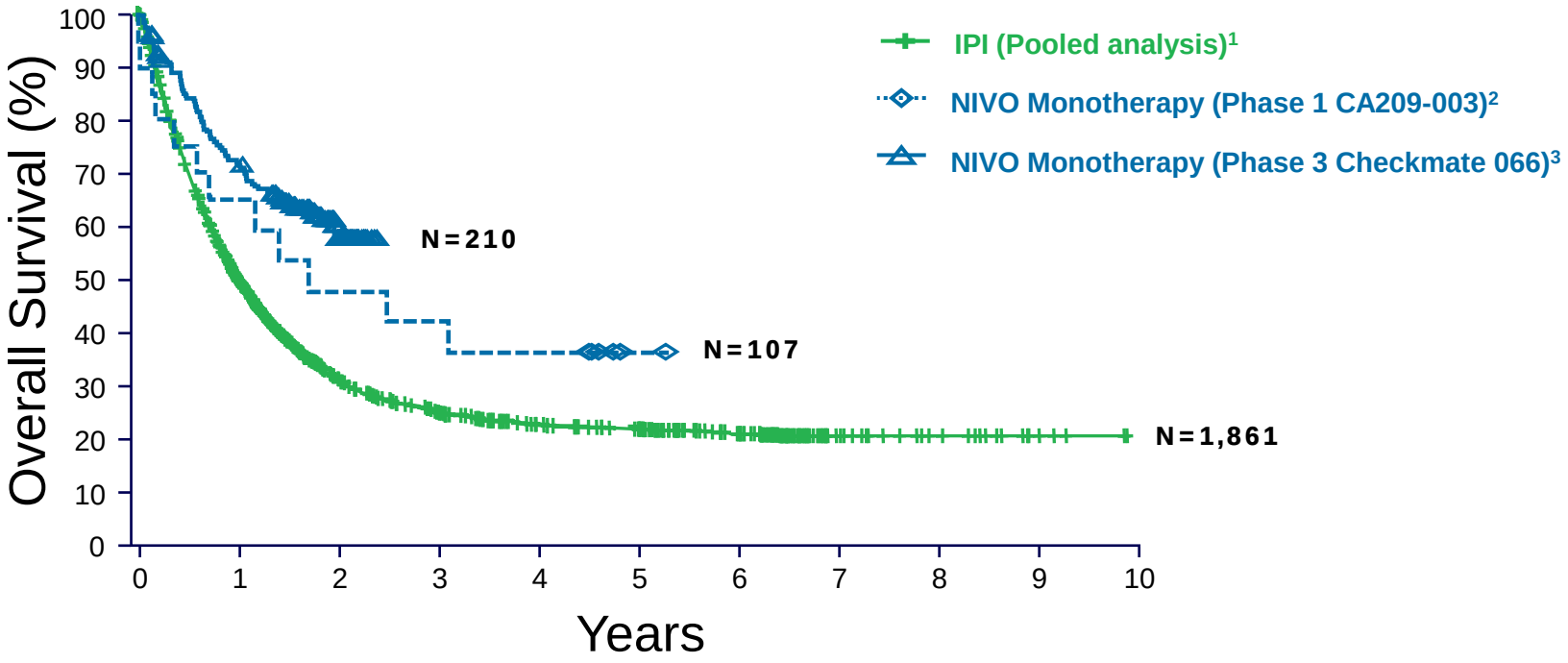
immune excluded

immune infiltrated



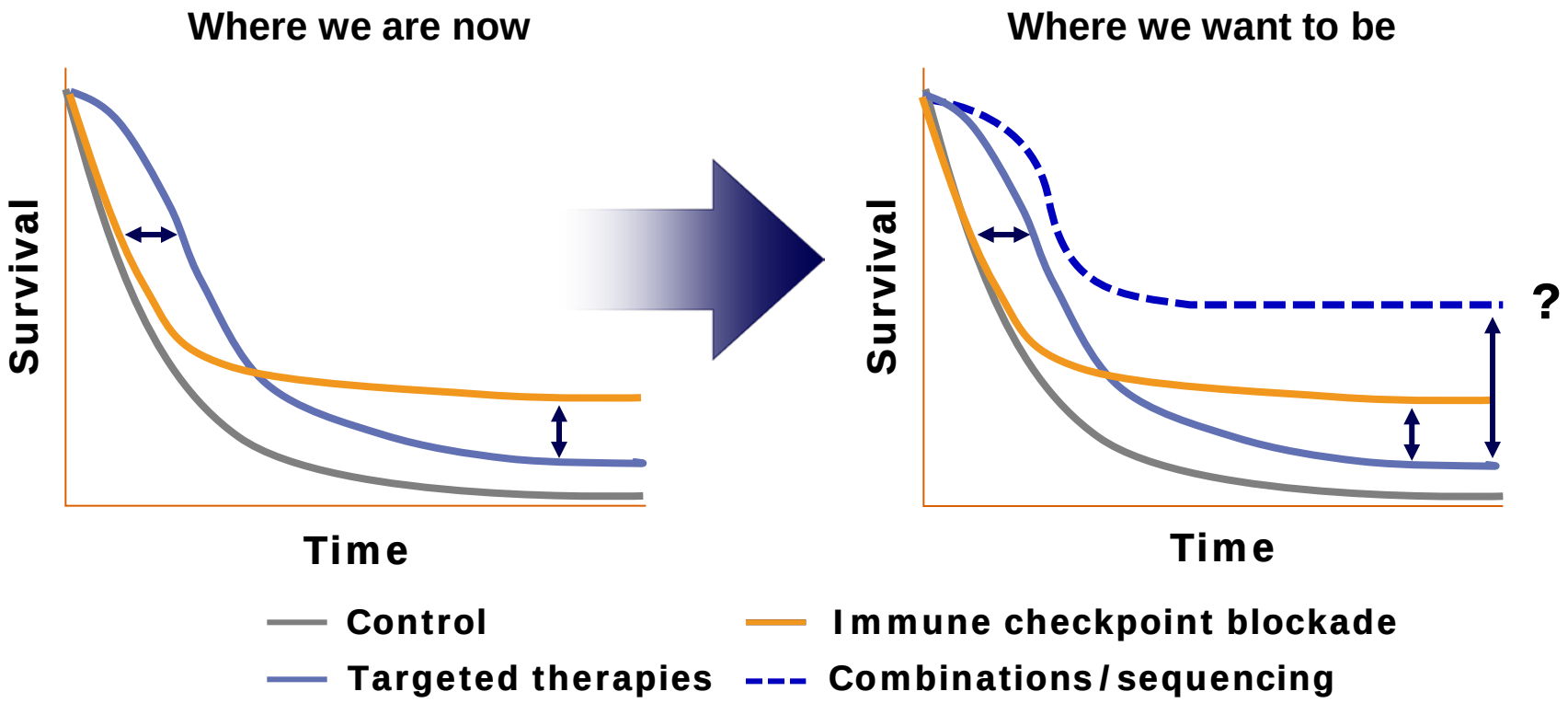
1. Professor John Gosney, 11th October 2016, personal communication and used with permission.

Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma



1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894;
2. Hodi SF et al (2016) AACR Presentation 001;
3. Atkinson V et al (2015) SMR International Congress.

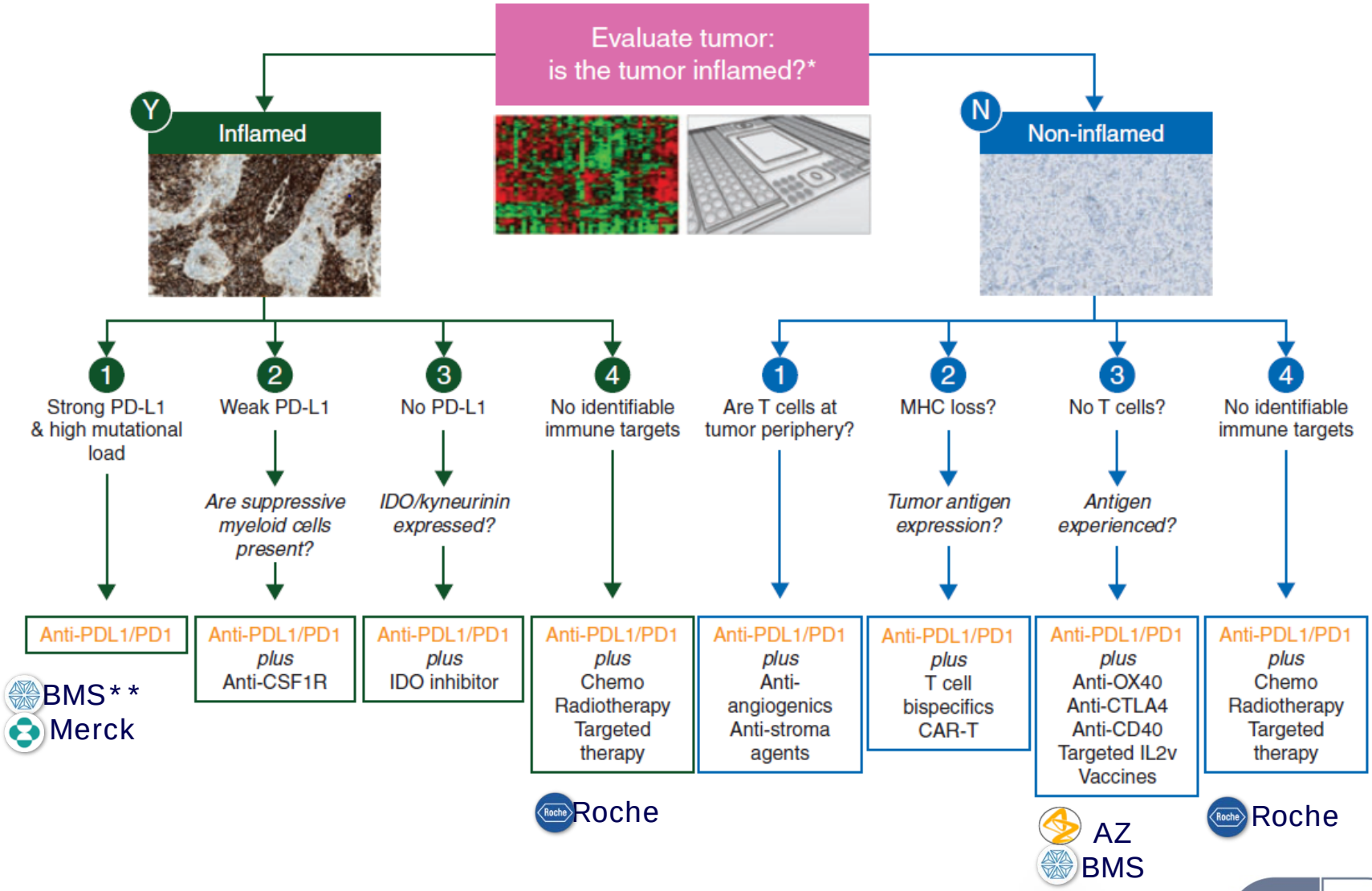
Combination Therapies: A Promising Treatment Strategy*[1]



*Hypothetical slide illustrating a scientific concept that is beyond data available so far. These charts are not intended to predict what may actually be observed in clinical studies.

1. Adapted from Sharma P, Allison JP. *Cell*. 2015;161(2):205-214.

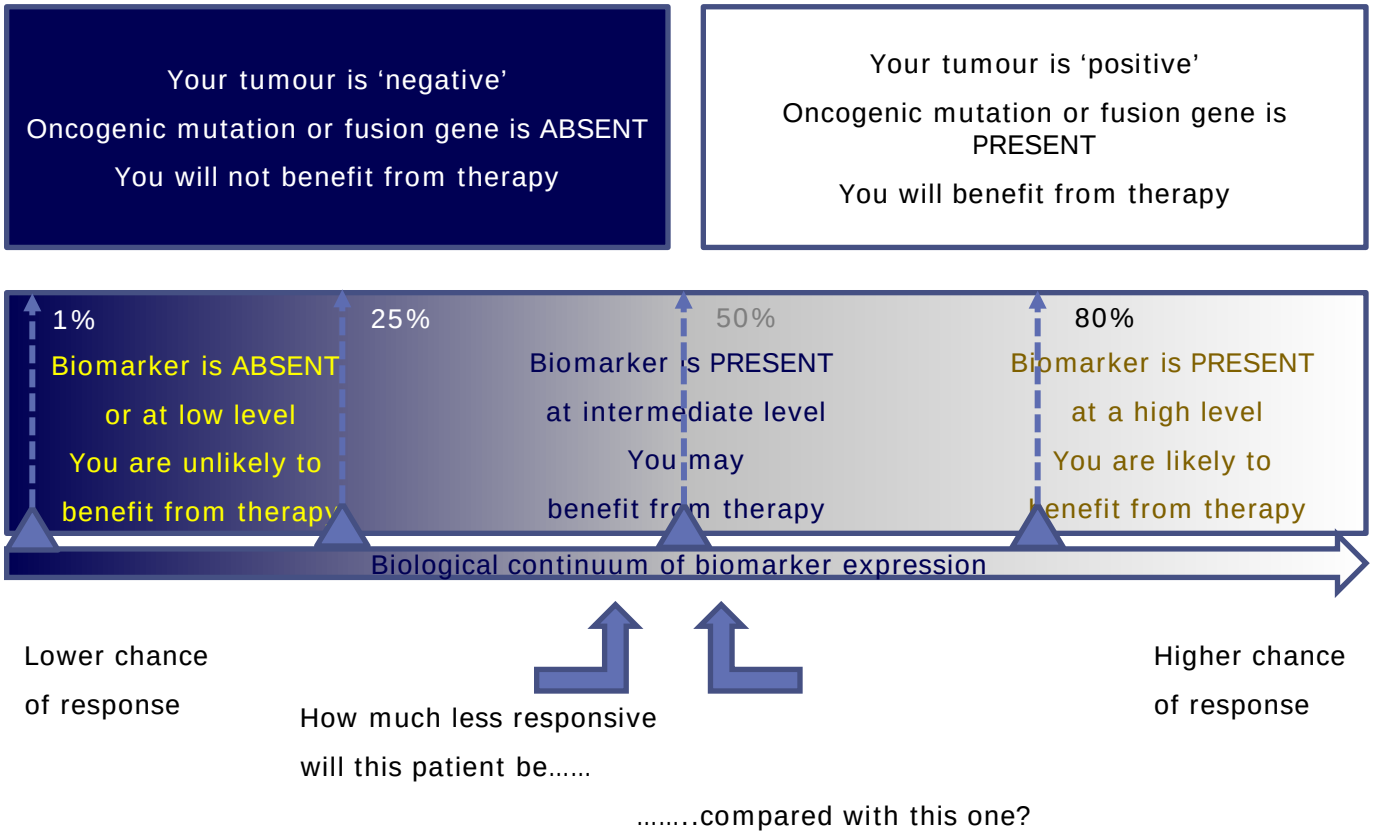
Towards Precision Immuno-Therapy[1]



1. Kim JM & Chen DS (2016) Immune escape to PD-L1/ PD-1 blockade: seven steps to success (or failure) Annals Oncology 27: 1492 – 1504.

** EB superficial interpretation

Biomarker 'Positivity' in Targeted Therapy and Immunotherapy: Present, Absent or Graduated?[1]



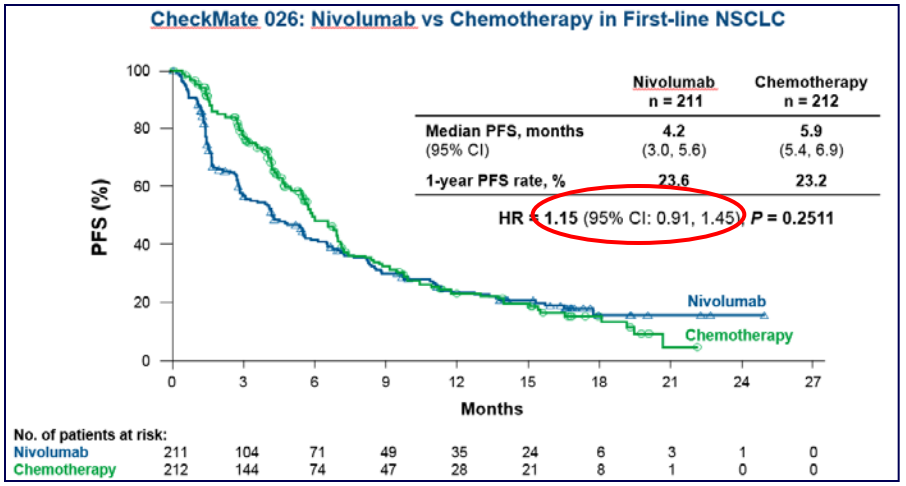
* PD-L1 = Programme Death Receptor Ligand 1

1. Professor Keith Kerr, ESMO 2016 Controversy of the Day Session 8th October 2016: The current way to measure PD-L1 biomarkers will not stand the test of time, "No"

First-Line Monotherapy in PD-L1 Expressing NSCLC

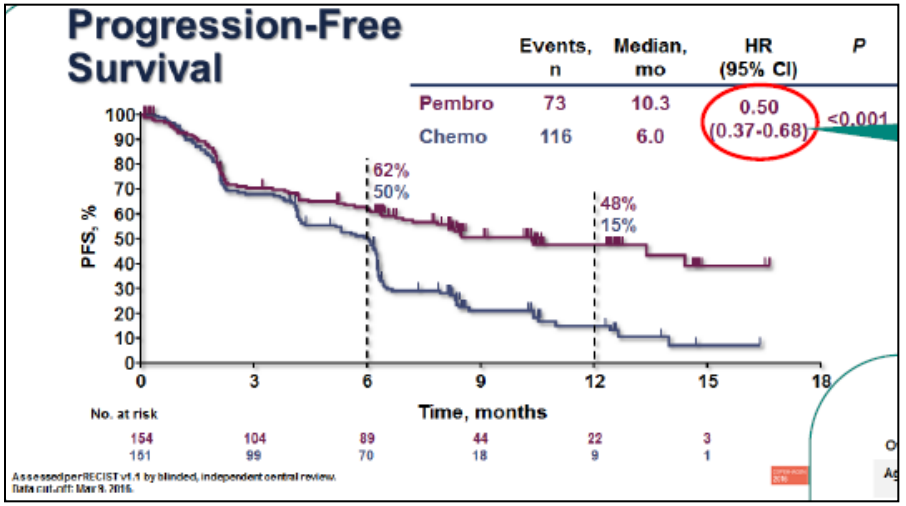
BMS CheckMate 026 Press Release[1,3]

- *"CheckMate 026, a trial investigating the use of OPDIVO® (nivolumab) as monotherapy, did not meet its primary endpoint of progression-free survival in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed PD-L1 at ≥ 5%."*



Merck KEYNOTE-024 Press Release[2,4]

- *"KEYNOTE-024 trial investigating the use of KEYTRUDA® (pembrolizumab), in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1 (tumor proportion score of 50 percent or more), met its primary endpoint (PFS)."*



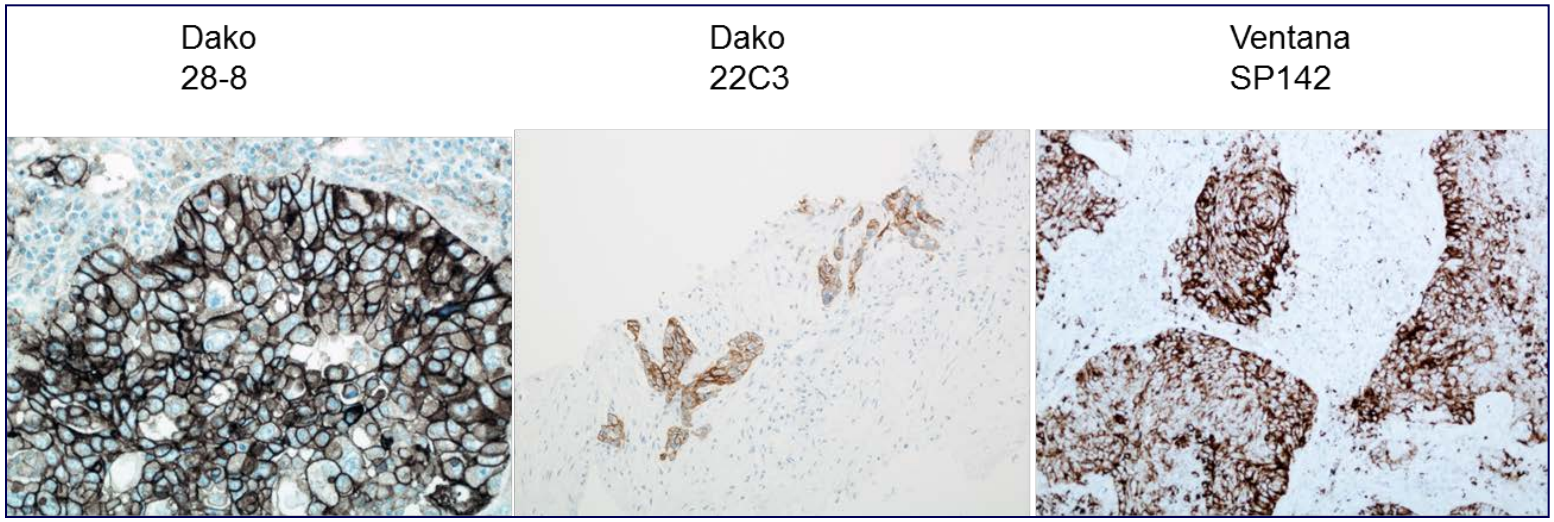
1. Bristol-Myers Squibb Press Release 5th August, 2016. Accessed 31st October, 2016.
2. Merck Sharp & Dohme Press Release 16th June 16, 2016. Accessed 31st October, 2016.
3. Socinski et al ESMO 2016,
4. Reck et al ESMO 2016, NEJM.org.

Problems with PD-L1 and IHC*,[1,2]

Not a 'perfect' biomarker:

- Responses seen in patients below selected thresholds – 'negative', aka 'low expressors'
- Affected by prior radiation and chemotherapy[2]
- Expression is dynamic over time (archival 2L vs fresh 1L)[2]
- Expression is heterogeneous – biopsy sampling "error"[2]

Consequently, there is 'noise', 'variability', 'error' around the specific value, including the selected threshold (cut off)



*IHC = Immunohistochemistry; staining of tissue sections with specific antibodies & detection by 2^0 reagents, may be based on counting of tumour and/ or immune cells

1. Professor Keith Kerr, ESMO 2016 Controversy of the Day Session 8th October 2016: The current way to measure PD-L1 biomarkers will not stand the test of time, "No".
2. Kerr KM et al. Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer: what state is this art? *J Thorac Oncol.* 2015;10: 985–989.

Beyond PDL1 – Tumour Mutation Burden (TMB[1]) Analysis in Failed Checkmate 026[2]

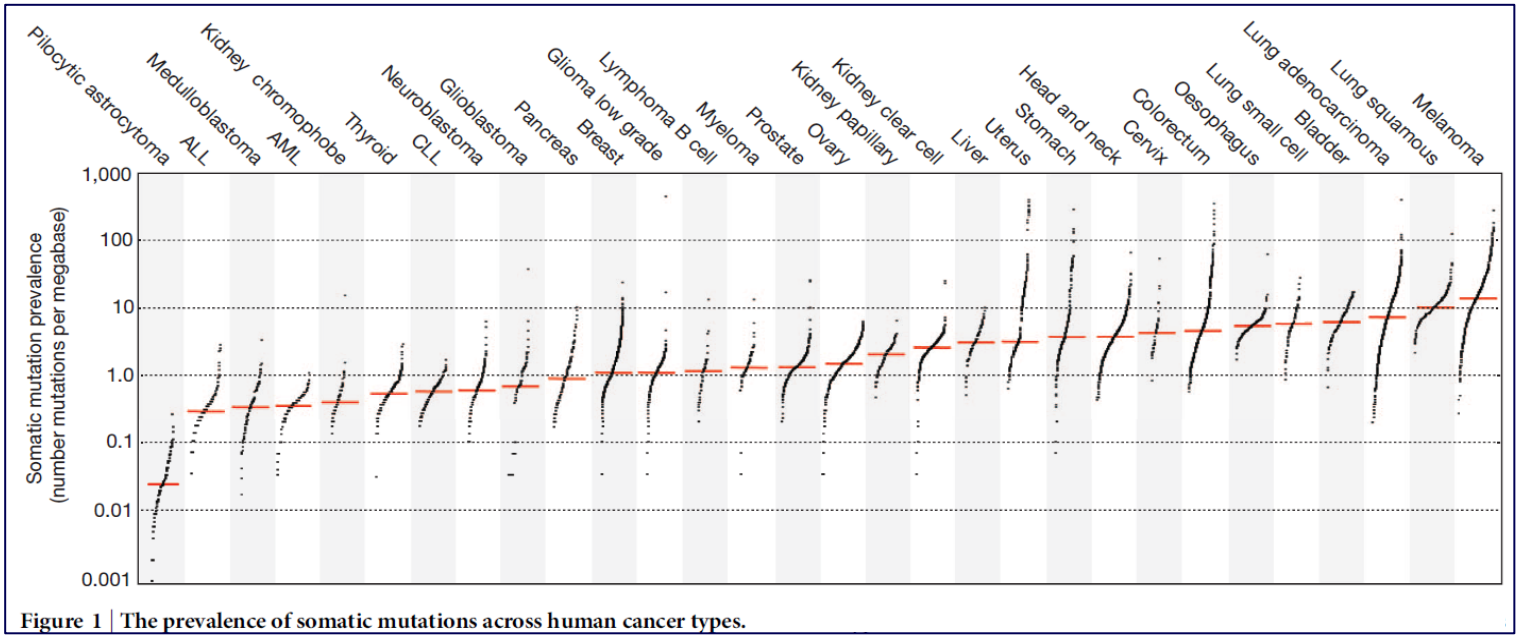


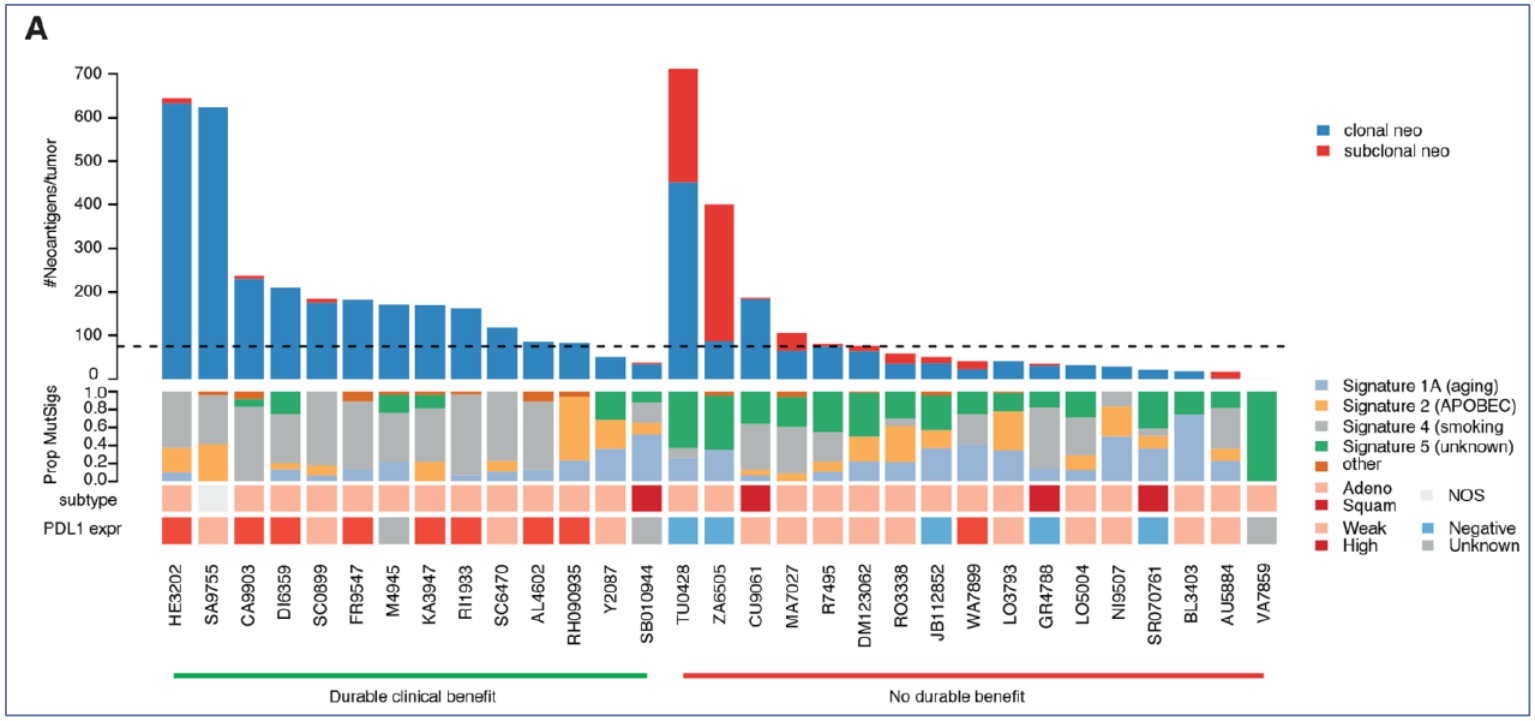
Figure 1 | The prevalence of somatic mutations across human cancer types.

[2]TMB	Nivolumab mPFS (mo)	Chemo mPFS (mo)	Nivolumab ORR (%)	Chemo ORR (%)
Low (<99 mutations detected)	4.2 (HR 1.82)	6.9	23	33
Medium (100 – 242)	3.6 (HR 1.82)	6.5	23	33
High (≥243 mutations)	*9.7 (HR 0.62 [95% CI; 0.38 – 1])*	*5.8*	46.8	28.3

[1]LB Alexandrov et al (2013) "Signatures of mutational processes in human cancer" *Nature* 500: 415 - 421

[2]Peters S (2017) Impact of tumor mutation burden on the efficacy of first-line nivolumab in stage IV or recurrent non-small cell lung cancer: an exploratory analysis of CheckMate -026 AACR Abstract # CT082

Biomarkers Associated with Tumour Genetic Instability 1 – Results[1]

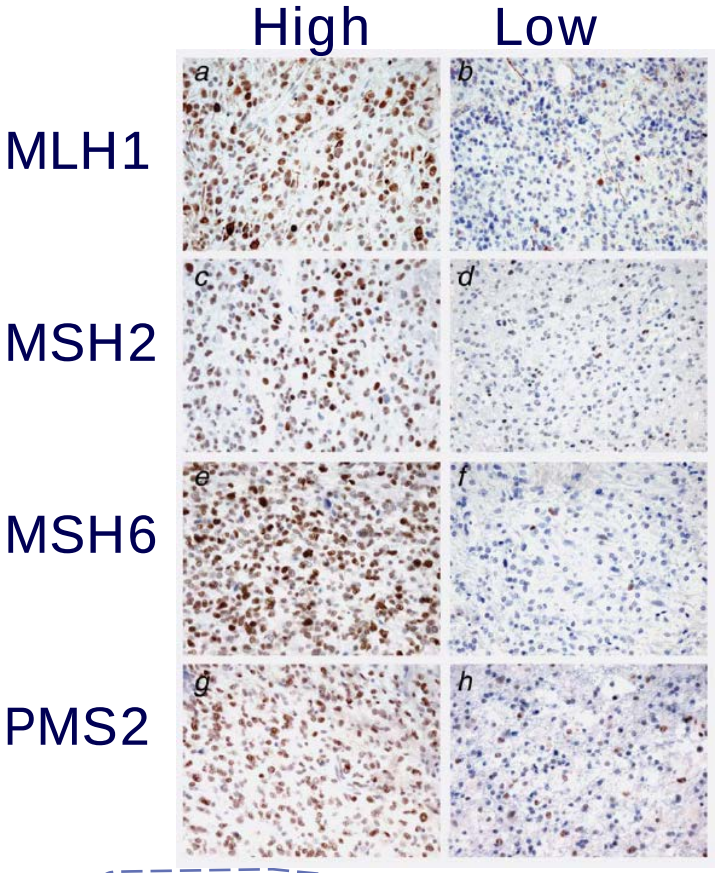


- High mutational burden creates neo-antigens (clonal > sub-clonal) that attract immune cells that give strong response to checkpoint inhibitors[1]
- This activation, expansion and differentiation of T-cells and other cytotoxic immune cells is reflected by immuno-profiling of cell-associated and soluble factors[2] [in liquid biopsies]

[1]N McGranahan et al (2016) "Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade" *Science* 351 (6280) 1463-1469

[2]A Huang et al (2017) "T-cell invigoration to tumour burden ratio associated with anti-PD-1 response" *Nature*

Biomarkers Associated with Tumour Genetic Instability 2 – Causal Events



- Hereditary: [1]High Microsatellite Instability (MSI) due to poor MMR from absent MLH1, MSH2, MSH6 or PMS2[a] (CRC)
- Epigenetic: Methylation of MGMT[a] promoter leads to poor MMR (GBM) as expression blocked
- Environmental: [2]Smoking, diet and other factors induce certain types of mutation (lung, bladder)

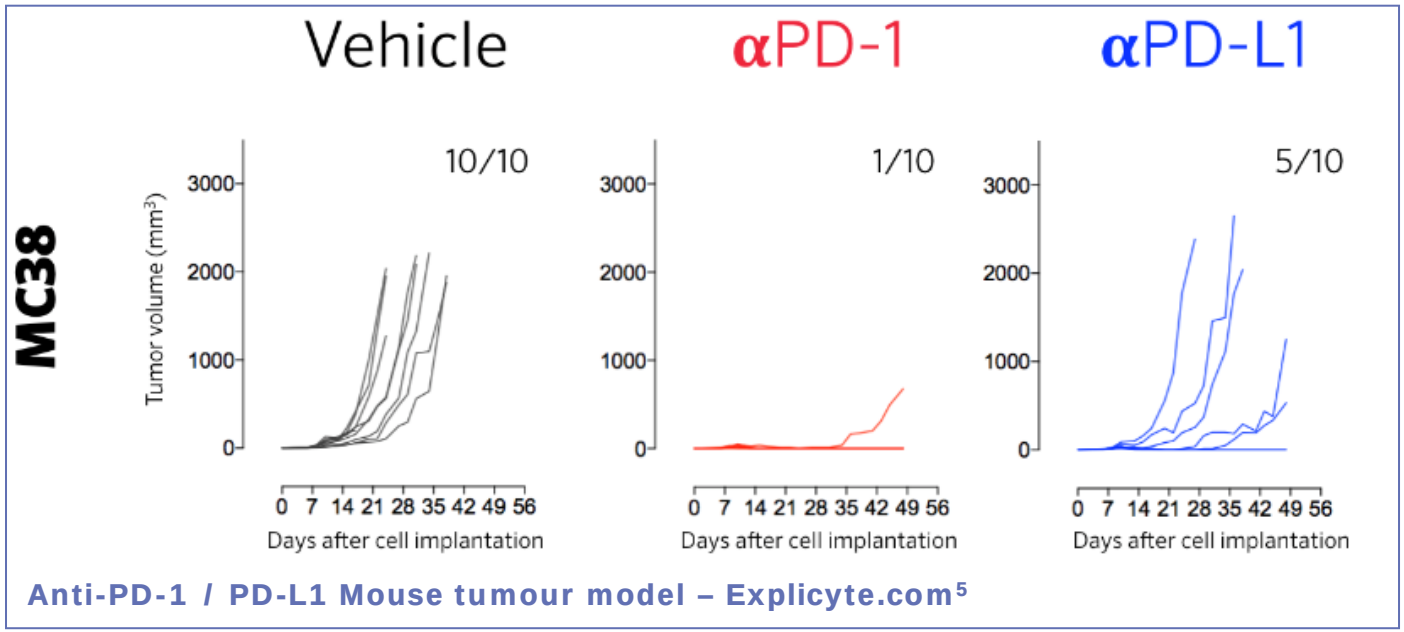
[1]Leads to high tumour mutational burden (TMB)

[1]GM Frampton et al (2016) "Assessment and comparison of tumour mutational burden and microsatellite instability status in >40,000 cancer genomes" Annals of Oncology 27 (Supplement 6): vi15–vi42

[2]LB Alexandrov et al (2013) "Signatures of mutational processes in human cancer" *Nature* 500: 415 – 421

[a]*O6-methylguanine-DNA methyltransferase* (*MGMT*); MutL homolog 1 (MLH1); MutS homolog 2 (MSH2); MutS homolog 6 (MSH6); PMS1 endonuclease homolog 2 (PMS2)

Acquired resistance to IO Products 1: Direct Effects[1]

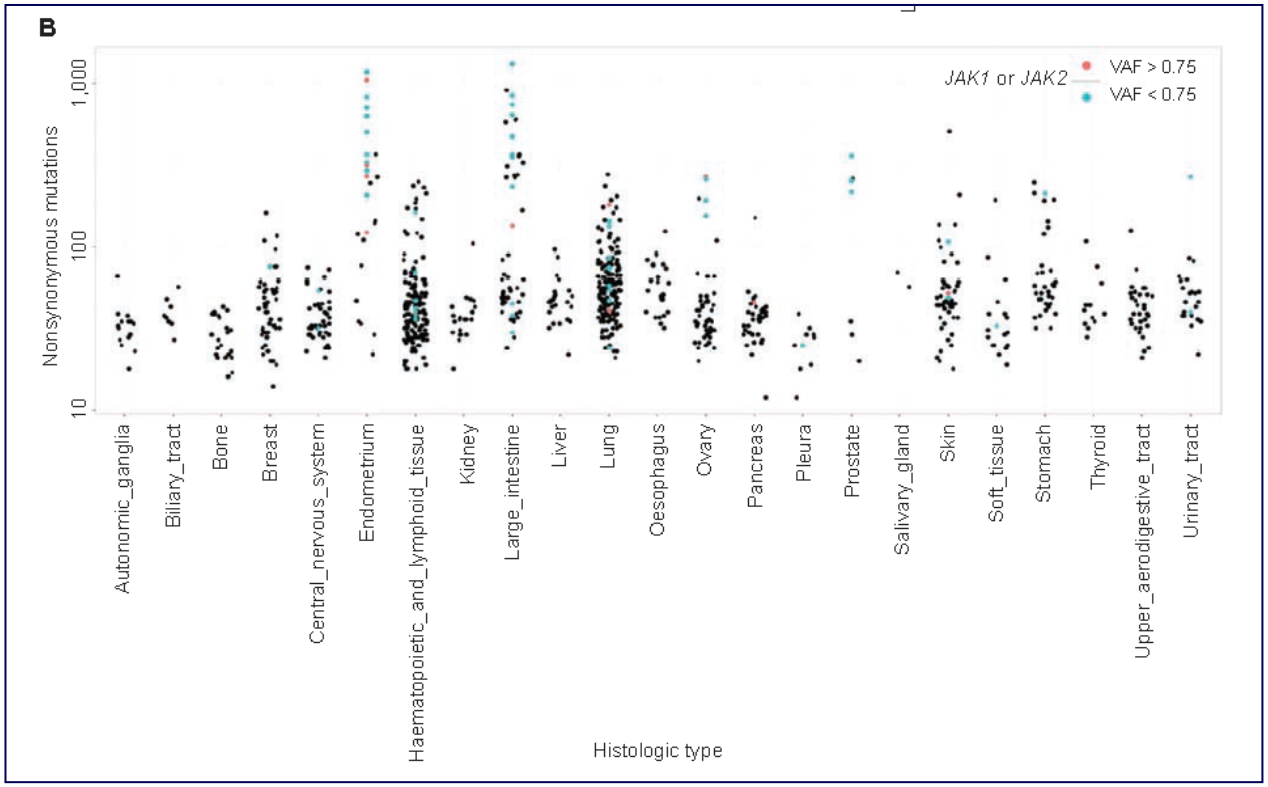


Anti-PD-1 / PD-L1 Mouse tumour model – Explicyte.com[5]

- Anti-PDL1 targets ligand on tumour cells; opportunity for changes to PDL1 that affect Mab binding
- Anti-PD1 targets receptor on immune cells; changes to PD1 not universal but impact of receptor density known

[1]E Blair hypothesising without licence

Acquired resistance to IO Products 2: Indirect Effects[1,2,3]



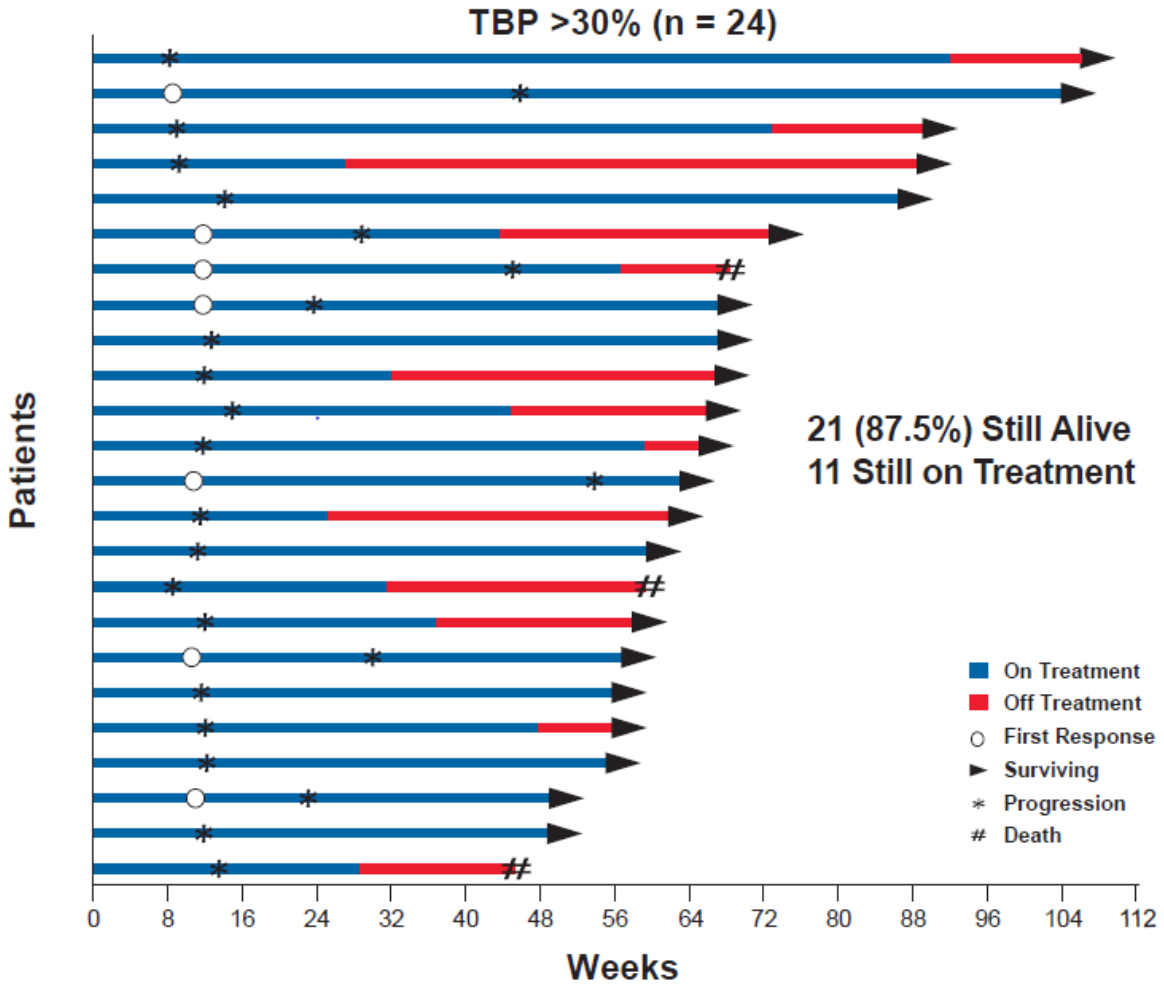
- Gene cluster approach – immune cells (CD8, DØ, MØ) vs DNA regulation & repair
- Regulatory pathways - Jak1,2; B2M; IFNγ; GBP1

[1]DS Shin et al (2016) "Primary Resistance to PD-1 Blockade Mediated by JAK1/2 Mutations" *Cancer Discov; 7(2); 1–14*

[2]L Verlingue et al (2017) "RNAseq Analysis of MATCH-R Trial Tumour Biopsies" (*sic*) *AACR Abstract #1011*

[3]JM Zaretsky et al (2016) "Mutations Ascociated with Acquired Resistance to PD1 Blockade in Melanoma" NEJM 3759: 819 - 829

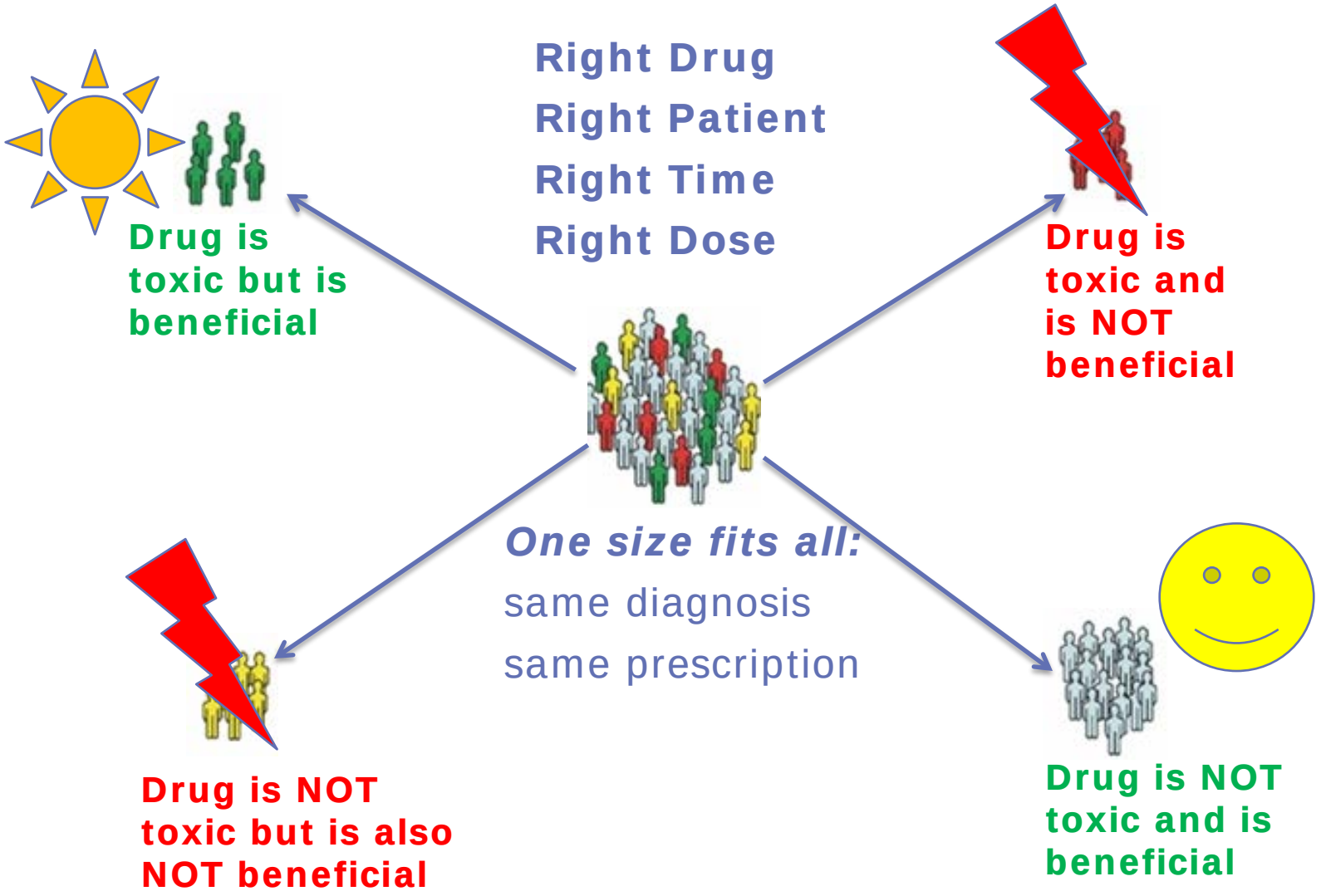
Other key questions in IO*



1. Why do some patients survive and some die after stopping treatment?
2. How long do patients need to be treated for sustained response?
3. Can predictive biomarkers be found to aid patient selection?

*Data from Long GV et al (2016) SMR

Precision Medicine Requires Precision Diagnosis[1]



1. Professor Ken Bloom, LSO3 Roche Diagnostics Symposium "From testing to therapy – the PD-L1 continuum". European Society of Pathology 28th Congress (2016), adapted by E Blair

Thank you and….

….Any questions?

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