The Royal Marsden NHS
NHS Foundation Trust

Biomarkers and New Drugs for Melanoma Immunotherapy

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Disclosures

Institutional research support: AZ, BMS, MSD, Novartis, Pfizer

Consulting: AZ, BMS, Eisai, EUSA Pharma, GSK, Ibsen, iOnctura, Kymab, MSD, Nektar, Novartis, Pierre Fabre, Pfizer, Roche / Genentech, Secarna

Support from NIHR RM/ICR Biomedical Research Centre for Cancer

Background

Lots of different types of immunotherapy e.g. cytokines, vaccines, checkpoint inhibitors (CPIs)

I will concentrate on approved checkpoint inhibitors i.e. anti-CTLA4 and anti-PD1/PD-L1

Q: What do we want to get from a biomarker in cancer medicine?

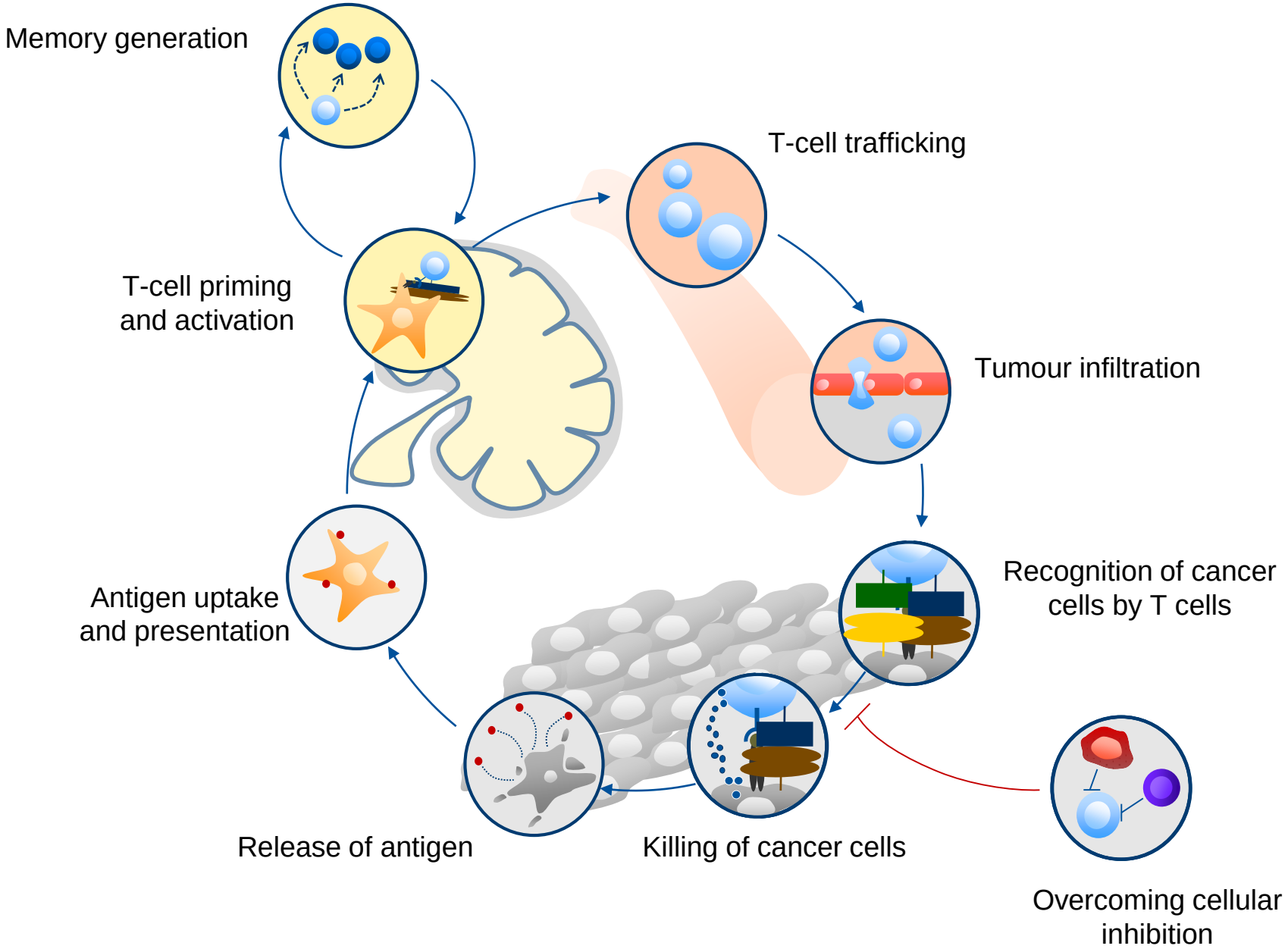
This is linked to: what are our clinical questions?

Background

Clinical questions include:

- how to select patients for treatment e.g. targeted therapy vs CPI, single agent vs combination, adjuvant therapy versus observation
- tailoring duration of therapy
- profiling risk of side effects

Cancer Immunity Cycle



What is a biomarker?

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

Types: Molecular, histologic, radiographic, and physiologic characteristics are types of biomarkers.

Examples:

- Blood glucose (molecular)
- Tumor size (radiographic)
- Blood pressure (physiologic)

DIFFERENT CATEGORIES OF BIOMARKERS

Biomarkers in melanoma implicated as being prognostic/predictive for response to therapy

- **Biomarkers for BRAF targeted therapy:**

- $BRAF^{v600}$ mutational status
- Tumour mutational burden (TMB)
- PD-L1 expression
- Immune gene expression signature

- ctDNA
- Serum LDH

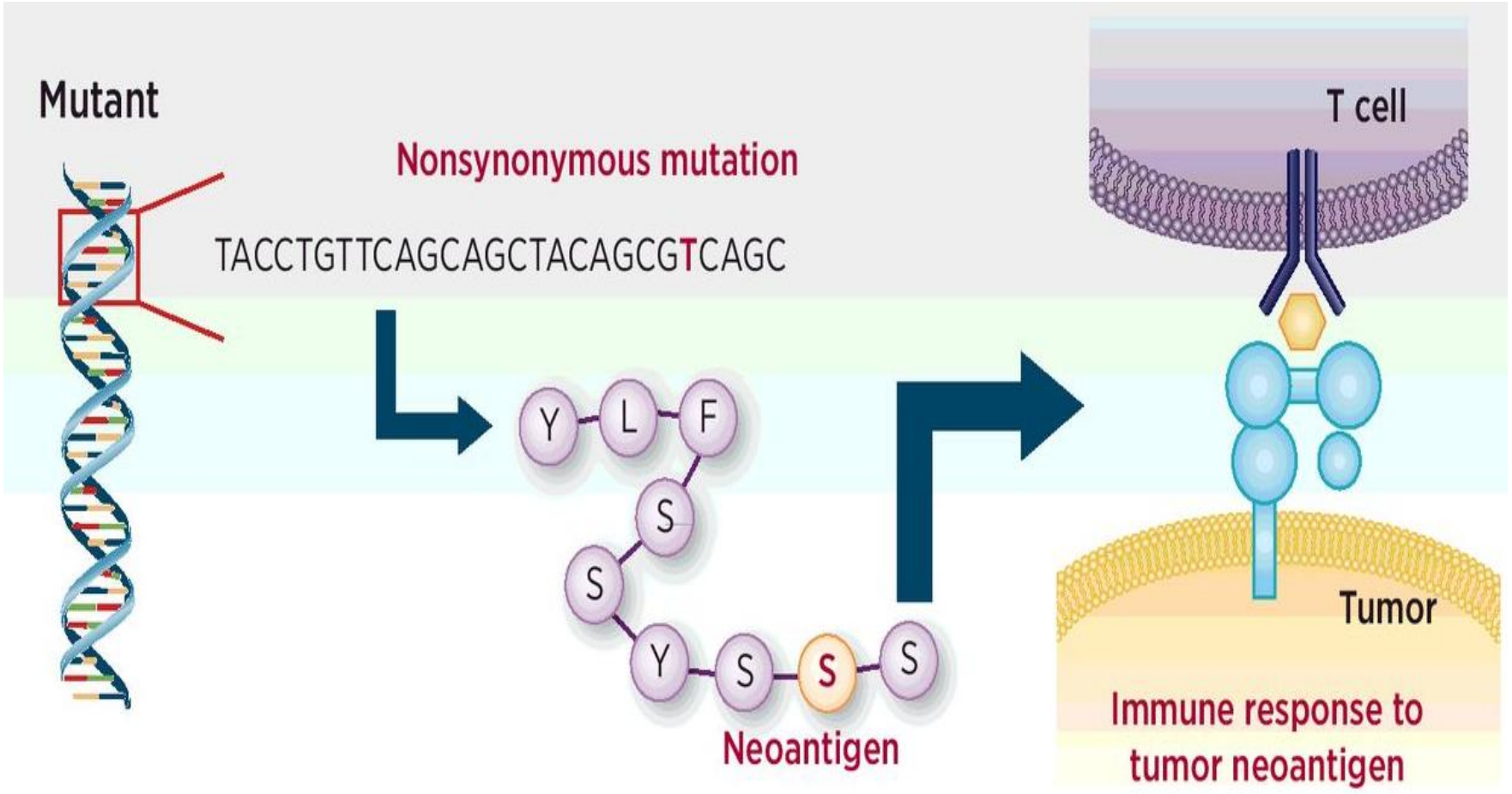
- **Biomarkers for immunotherapy**

- CD8+, tumour infiltrating lymphocyte (TIL) – immune cell infiltration
- Tumour mutational burden (TMB)
- PD-L1 expression
- Immune gene expression signature

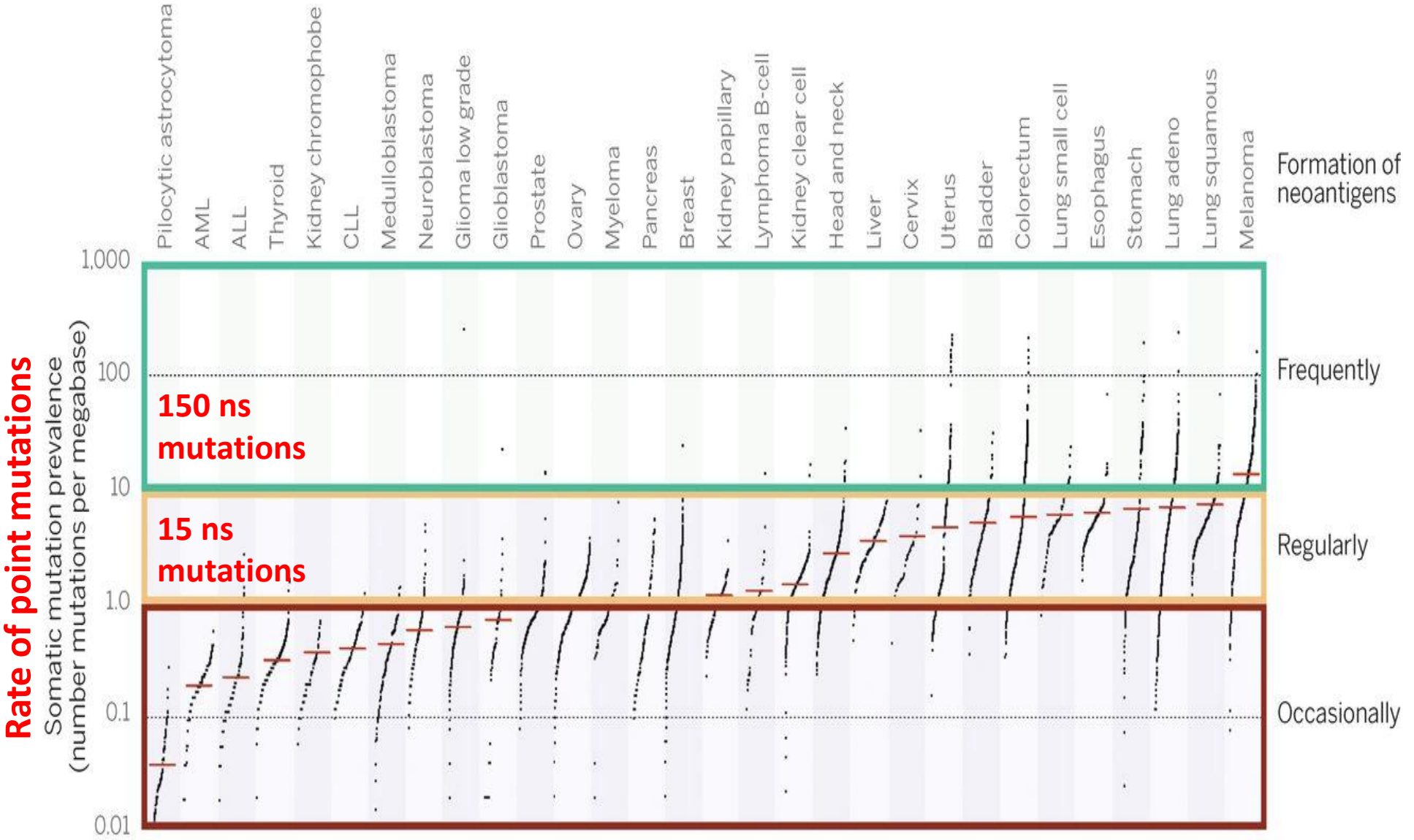
- ctDNA
- Serum LDH

Tumour

Tumour mutational burden as a biomarker of response to immunotherapy: neoantigen hypothesis

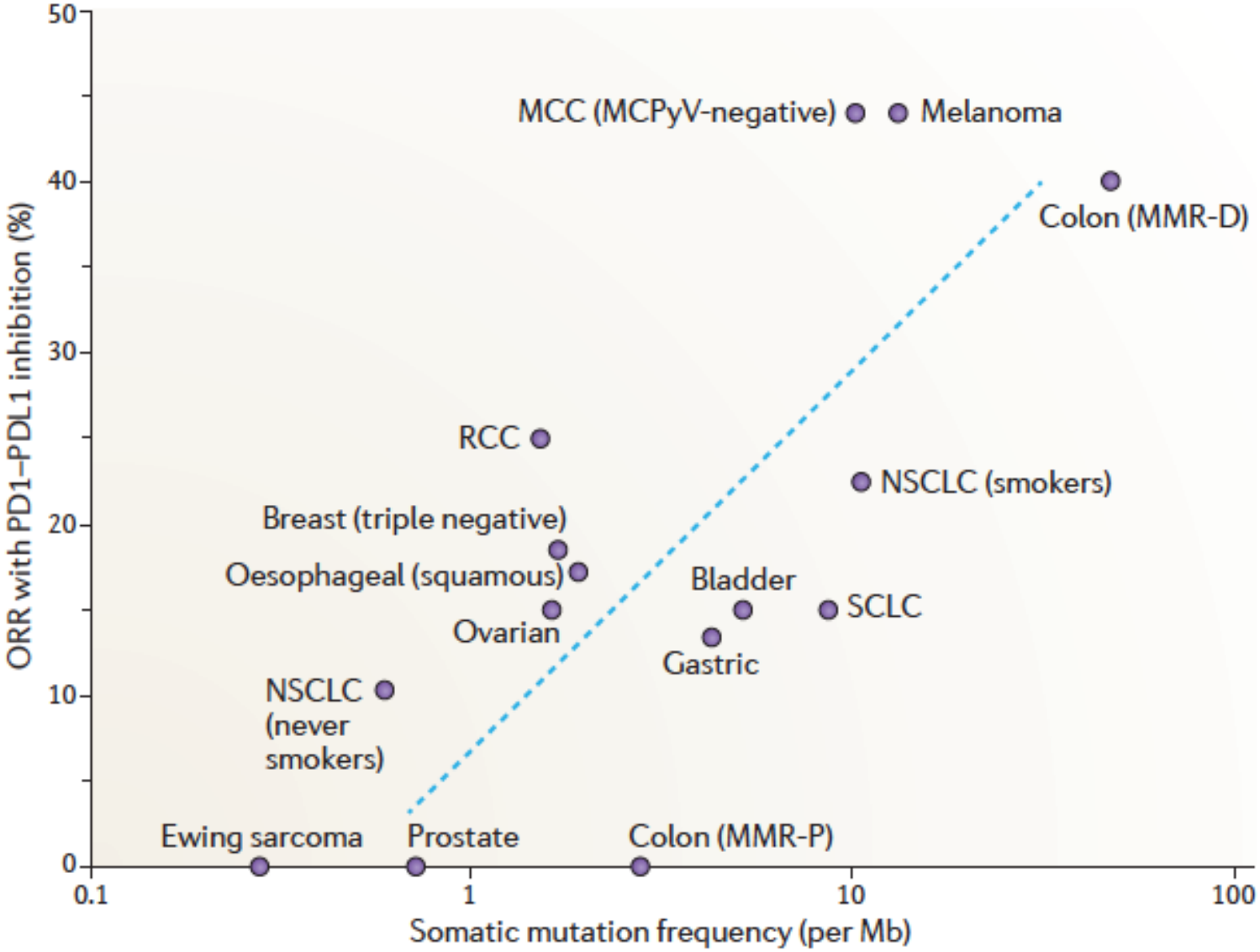


Tumour mutational burden as a biomarker of response to immunotherapy: melanoma



Alexandrov et al. Nature 2013, Schumacher and Schreiber, Science 2015

TMB and response to checkpoint inhibition



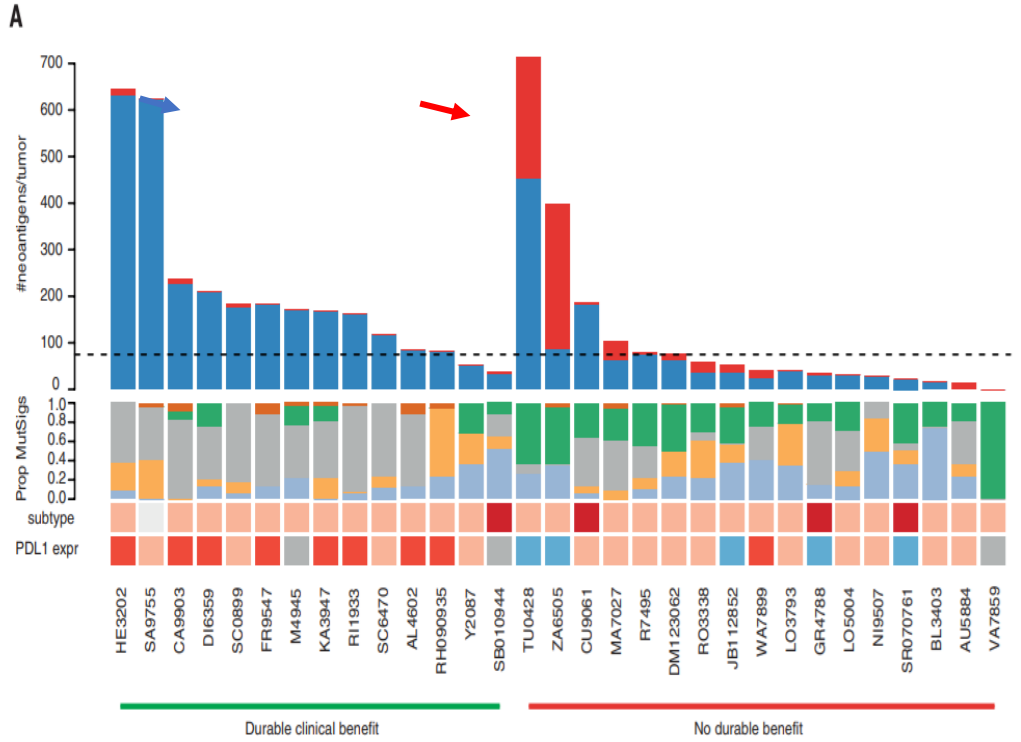
Yarchoan et al. Nat Rev Cancer 2017

Clonal neoantigen load as a biomarker of response to immunotherapy

NSCLC and Melanoma

Clonal neoantigens

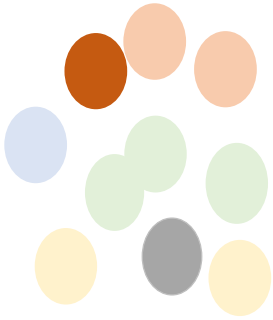
Subclonal neoantigens



clinical benefit no clinical benefit

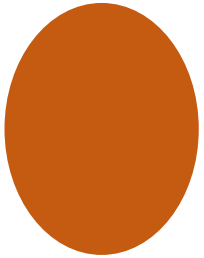
McGranahan et al. Science 2016

Clonal evolution under immunotherapy: resistance via escape mutations



Tumour at the start of therapy

Bottlenecking



JAK1/2→loss of response to IFN signaling

TAP
HLA
B2M
→loss of antigen presentation

Zaretsky et al. 2016 Shin et al. 2017 Sucker et al 2017

Tumour site agnostic approval

For Immediate Release:
May 23, 2017
The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

"This is an important first for the cancer community," said Richard Pazdur, M.D., acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research and director of the FDA's Oncology Center of Excellence. "Until now, the FDA has approved cancer treatments based on where in the body the cancer started—for example, lung or breast cancers. We have now approved a drug based on a tumor's biomarker without regard to the tumor's original location."

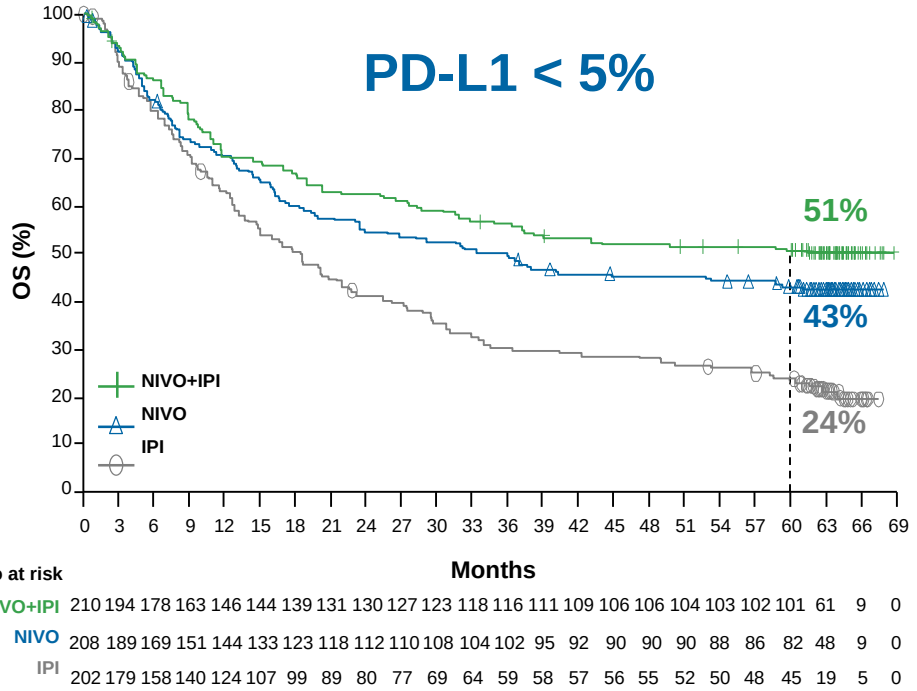
PD-L1

OS by Tumor PD-L1 Expression, 5% Cutoff

- Improved OS with NIVO+IPI and NIVO vs IPI regardless of baseline tumor PD-L1 expression

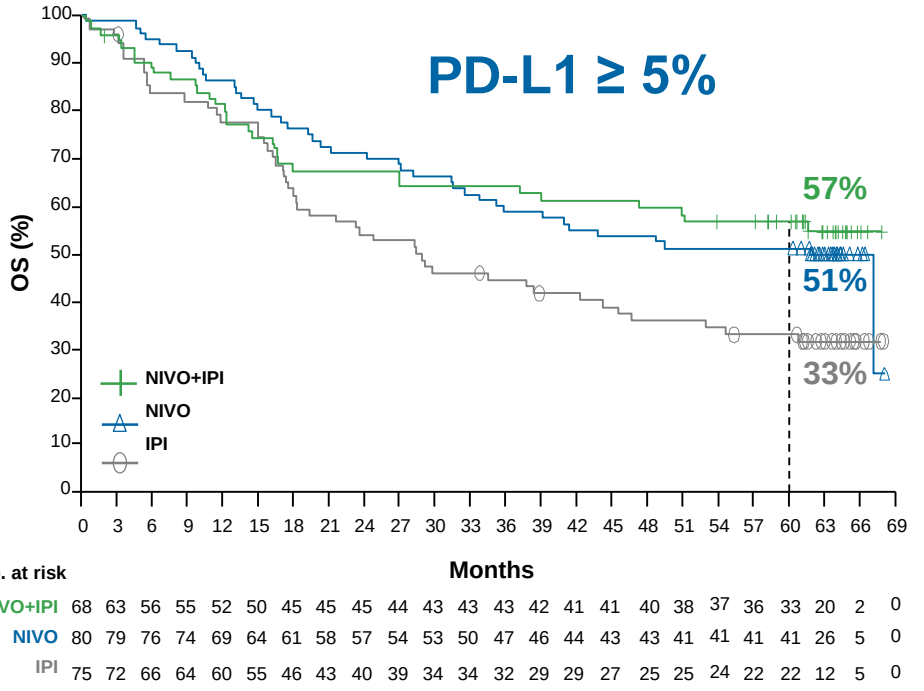
	NIVO+IPI (n = 210)	NIVO (n = 208)	IPI (n = 202)
Median, mo (95% CI)	NR (32.7–NR)	35.9 (23.1–59.2)	18.4 (13.7–22.5)
HR (95% CI) vs IPI	0.50 (0.39–0.65)	0.62 (0.49–0.79)	–
HR (95% CI) vs NIVO[a]	0.81 (0.62–1.06)	–	–

	NIVO+IPI (n = 68)	NIVO (n = 80)	IPI (n = 75)
Median, mo (95% CI)	NR (39.1–NR)	61.6 (33.6–NR)	28.9 (18.1–44.2)
HR (95% CI) vs IPI	0.58 (0.37–0.91)	0.63 (0.42–0.96)	–
HR (95% CI) vs NIVO[a]	0.91 (0.57–1.46)	–	–



No at risk

NIVO+IPI	210	194	178	163	146	144	139	131	130	127	123	118	116	111	109	106	106	104	103	102	101	61	9	0
NIVO	208	189	169	151	144	133	123	118	112	110	108	104	102	95	92	90	90	90	88	86	82	48	9	0
IPI	202	179	158	140	124	107	99	89	80	77	69	64	59	58	57	56	55	52	50	48	45	19	5	0



No. at risk

NIVO+IPI	68	63	56	55	52	50	45	45	45	44	43	43	43	42	41	41	40	38	37	36	33	20	2	0
NIVO	80	79	76	74	69	64	61	58	57	54	53	50	47	46	44	43	43	41	41	41	41	26	5	0
IPI	75	72	66	64	60	55	46	43	40	39	34	34	32	29	29	27	25	25	24	22	22	12	5	0

[a]Descriptive analysis.

What about other cancers?

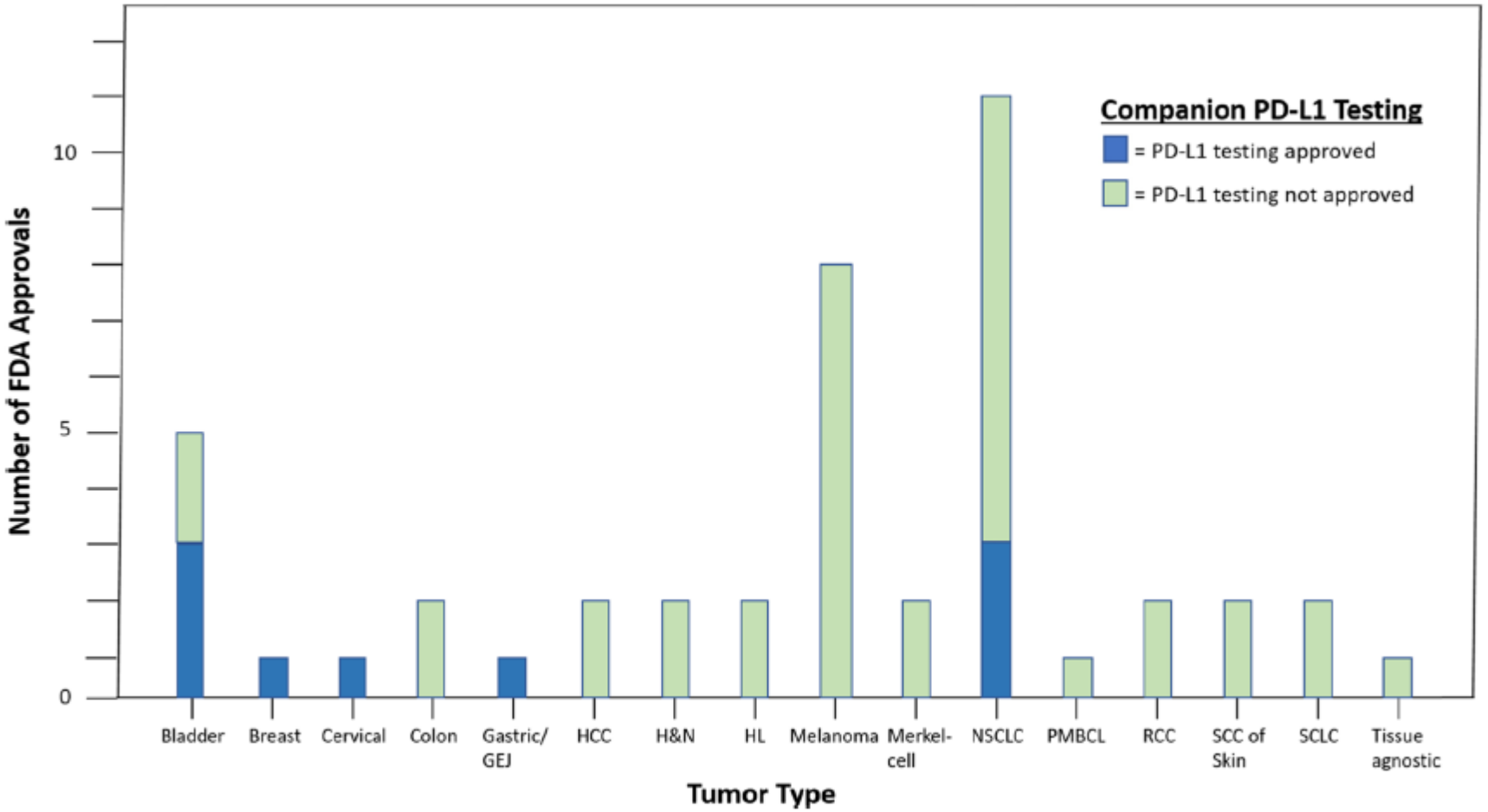


Fig. 1 Number of immune checkpoint inhibitor FDA approvals by tumor type: The colors in the key denote whether PD-L1 testing was approved (blue) or not approved (green) as a companion diagnostic. Abbreviations: GEJ = gastro-esophageal junction; HCC = hepatocellular carcinoma; HL = Hodgkin's Lymphoma; NSCLC = non-small cell lung cancer; PMBCL = primary mediastinal B-cell lymphoma; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; SCLC = small cell lung cancer

Davis JITC 2019

What about other cancers?

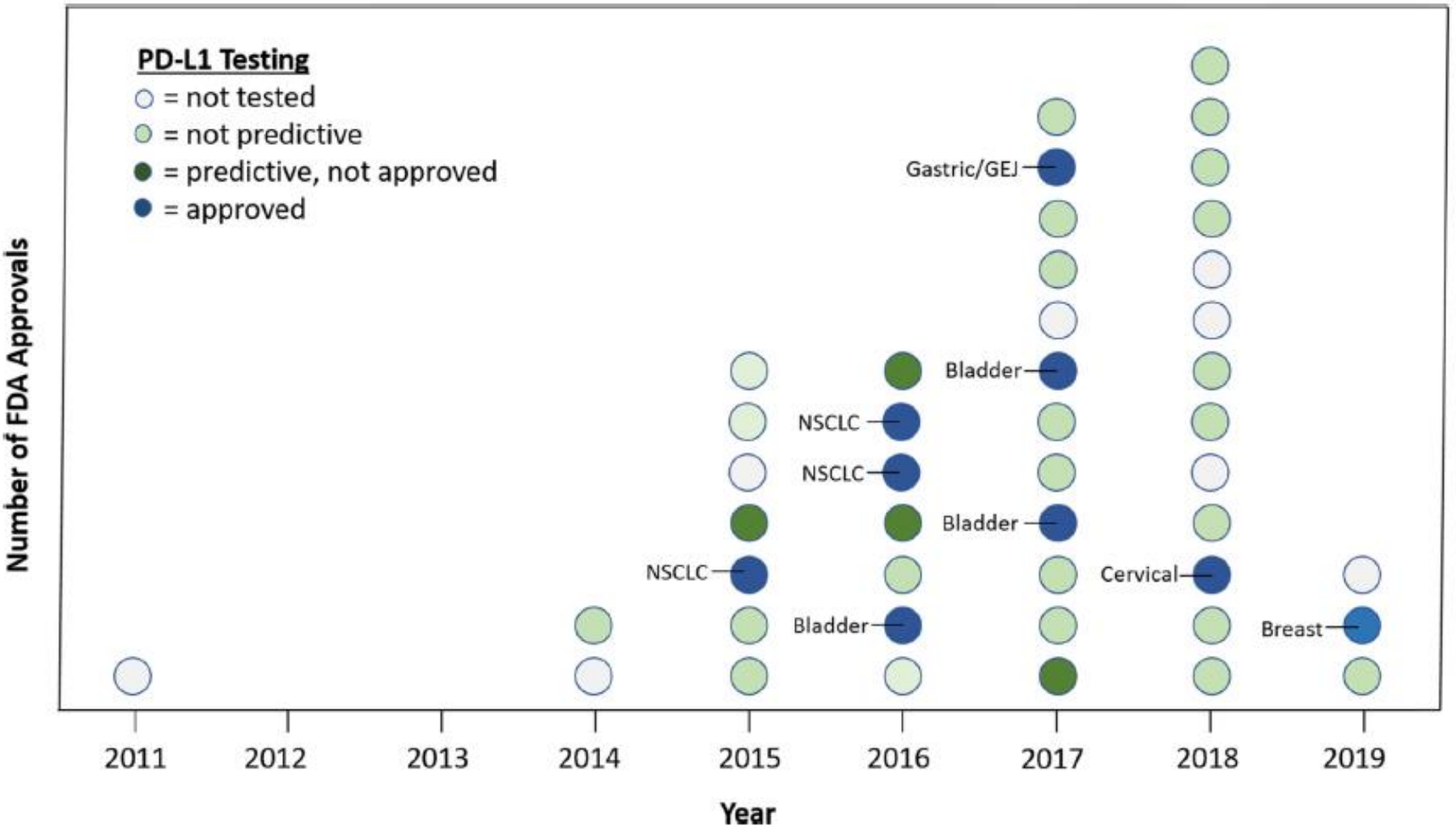


Fig. 2 Number of immune checkpoint inhibitor FDA approvals by year: The colors in the key denote the predictiveness and approval status of PD-L1 status as a companion diagnostic. The labeled tumor types (in blue) represent approvals with PD-L1 testing as a companion diagnostic. Abbreviations: GEJ = gastroesophageal junction, NSCLC = non-small cell lung cancer

Davis JITC 2019

Factors predicting response to CPIs

Factor	Association with favourable clinical outcome	Validated in phase III clinical trial?	Predictive versus prognostic[a]	Cancer type	Tissue type for biomarker assessment[b]	Possible assay type for biomarker assessment
Tumour mutation burden	Positive	Yes	Predictive	Multiple cancer types	Blood or tumour tissue	NGS WES or targeted gene panel sequencing
PDL1 expression	Positive	Yes	Predictive	Multiple cancer types	Tumour tissue	Immunohistochemistry
Copy number variation	Negative	TBD	Prognostic, predictive or both	Multiple cancer types	Tumour tissue	NGS WES or targeted gene panel sequencing
HLA class I diversity	Positive	TBD	Predictive	Melanoma and NSCLC	Blood	NGS WES or PCR-based typing
LOH at HLA class I alleles	Negative	TBD	Predictive	Melanoma	Tumour tissue	TBD
T cell repertoire clonality change	Positive	TBD	Predictive	Melanoma	Tumour tissue or blood	TBD
T cell-inflamed microenvironment	Positive	TBD	Prognostic, predictive or both	Multiple cancer types	Tumour tissue	NGS RNA-seq or immunostaining
SERPINB3 or *SERPINB4* mutations	Positive	TBD	Predictive	Melanoma	Tumour tissue	NGS WES
Gut microbial diversity	Positive	TBD	Predictive	Melanoma	Oral or gut	PCR or NGS
Specific gut microbial species	Positive or negative	TBD	Predictive	Melanoma	Oral or gut	PCR or NGS
TGFβ expression	Negative	TBD	Predictive	Colon cancer and urothelial cancer	Tumour tissue	NGS RNA-seq or expression panel
Mutations in the β-catenin pathway	Negative	TBD	Predictive	Melanoma	Tumour tissue or blood	NGS WES, targeted gene panel sequencing or RNA-seq
JAK2 mutations (rare)[c]	Negative	TBD	Predictive	Melanoma	Tumour tissue or blood	NGS WES or targeted gene panel sequencing
B2M mutations (rare)[c]	Negative	TBD	Predictive	Melanoma	Tumour tissue or blood	NGS WES or targeted gene panel sequencing
STK11 mutations (common)	Negative	TBD	Predictive	NSCLC	Tumour tissue or blood	NGS WES or targeted gene panel sequencing

Havel et al. 2019 NRC

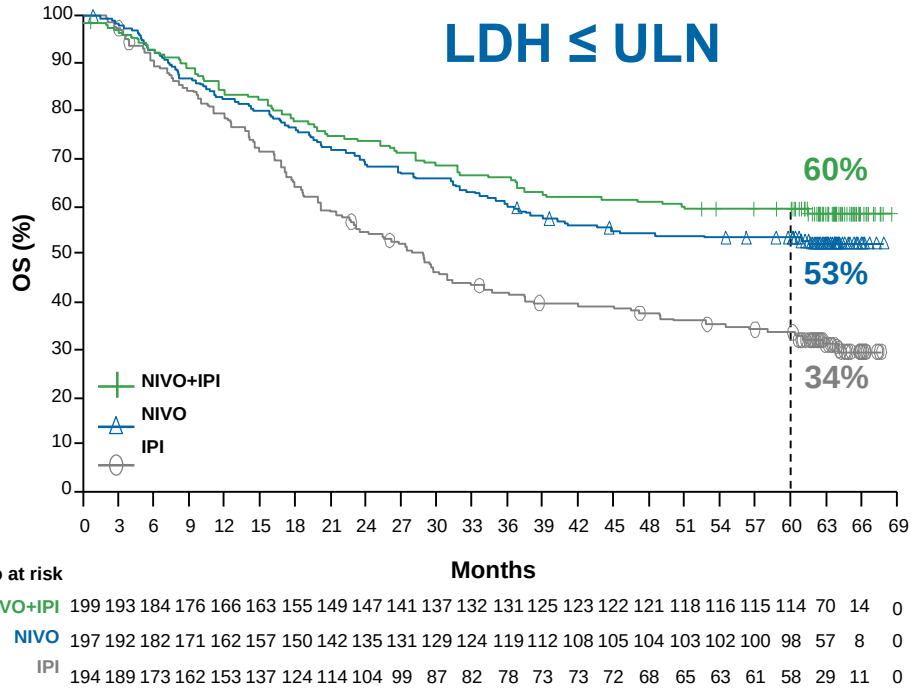
Systemic

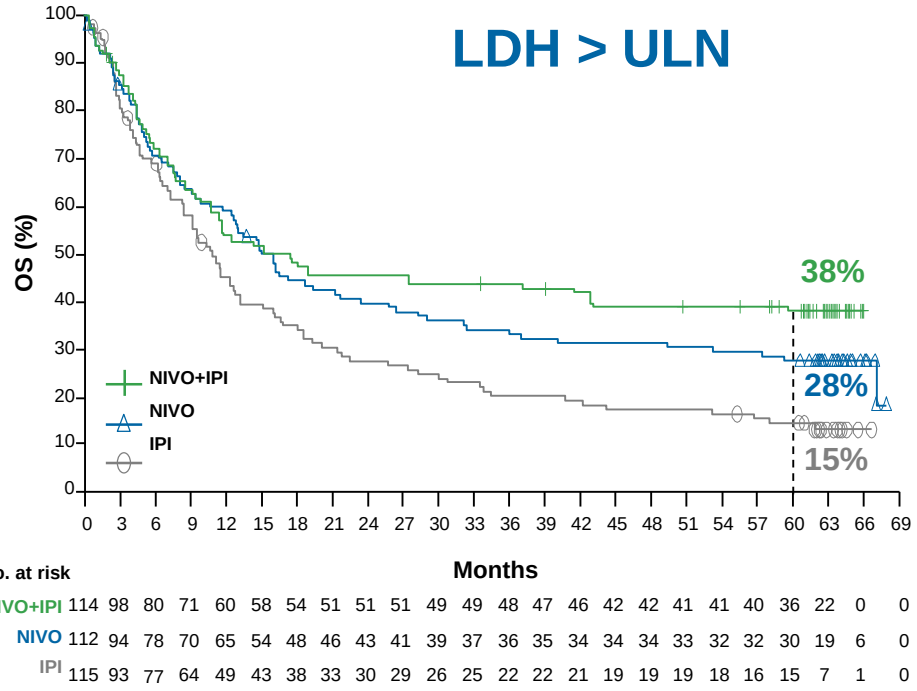
OS by LDH Level

- Improved OS with NIVO+IPI and NIVO vs IPI regardless of baseline LDH levels

	NIVO+IPI (n = 199)	NIVO (n = 197)	IPI (n = 194)
Median, mo (95% CI)	NR	NR (40.2–NR)	28.8 (22.7–34.0)
HR (95% CI) vs IPI	0.48 (0.37–0.64)	0.58 (0.44–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.62–1.12)	–	–

	NIVO+IPI (n = 114)	NIVO (n = 112)	IPI (n = 115)
Median, mo (95% CI)	17.4 (10.7–42.6)	16.0 (11.7–21.7)	10.9 (8.4–13.1)
HR (95% CI) vs IPI	0.58 (0.43–0.79)	0.71 (0.53–0.96)	–
HR (95% CI) vs NIVO[a]	0.82 (0.59–1.13)	–	–





[a]Descriptive analysis. LDH, lactate dehydrogenase; ULN, upper limit of normal.

Special mention: neoadjuvant therapy

- **Can we identify molecular predictors of response/resistance to drug therapy?**
- What other questions to ask? For example:
- Is drug treatment better before surgery than after?
- Are there differences in side effects?
- Can we switch those that fail one neoadjuvant therapy (e.g. CPI) to another one (e.g. targeted or investigational) and improve efficacy overall?
- Can we efficiently test new drugs?
- Can we avoid surgery altogether in those with an excellent response to drug therapy?
- pCR rate correlate with efficacy? (cf breast cancer)

Biomarkers: not discussed

Predicting side effects

Copy number variation/aneuploidy and immunotherapy response

Tumour microenvironment including the role of spatial patterns of T cells and other lineages, especially macrophages

T cell states- progenitor versus exhausted

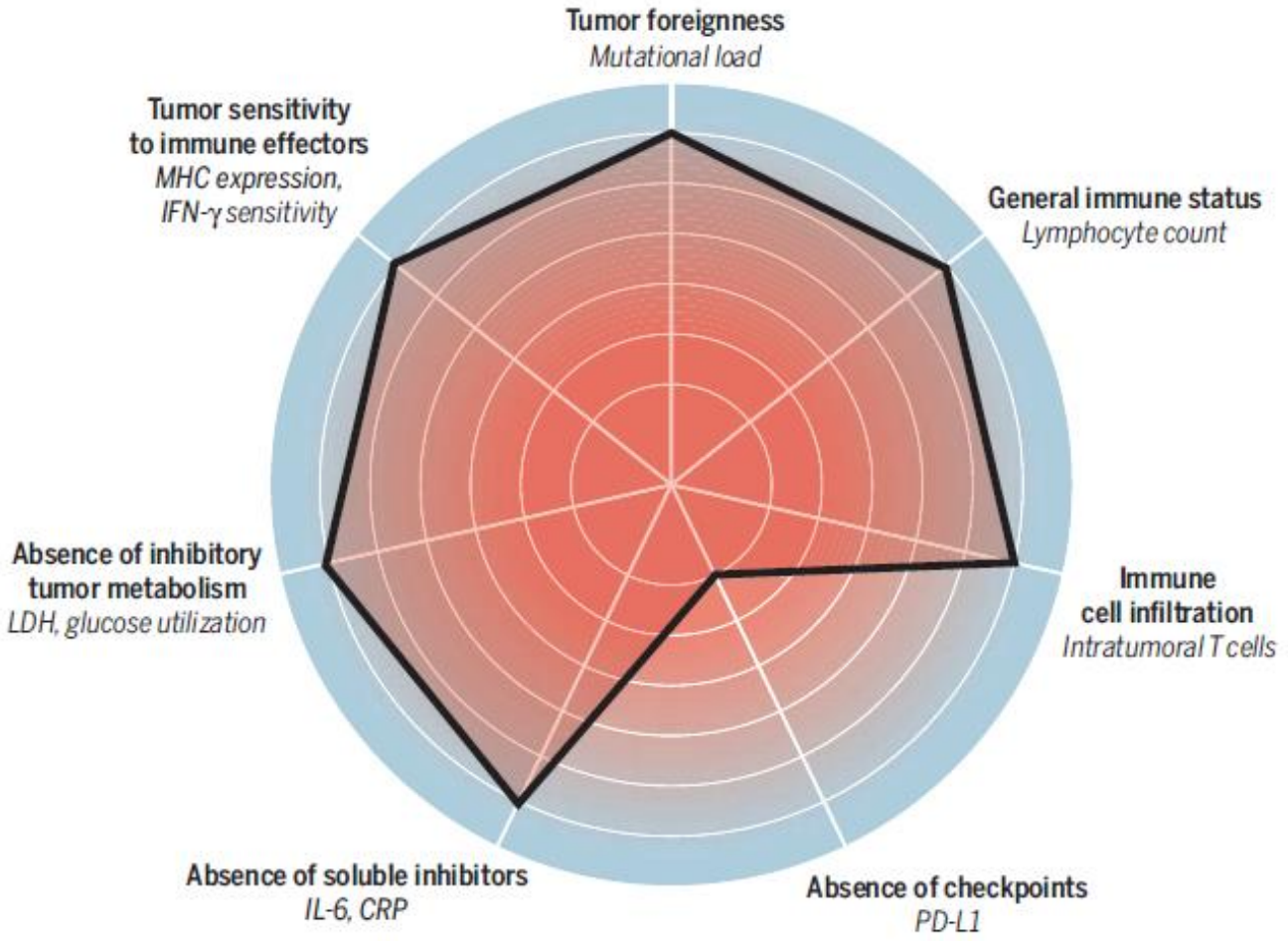
TCR sequencing

Use of cell-free tumour DNA

Static vs dynamic e.g. PD-L1 expression inducible / variable over space/time (cf BRAF mutation); imaging biomarkers dynamic e.g. change of tumour volume/achievement of CR (CT or PET)

How do we capture all this information in routine clinical samples…?!

Cancer Immunogram

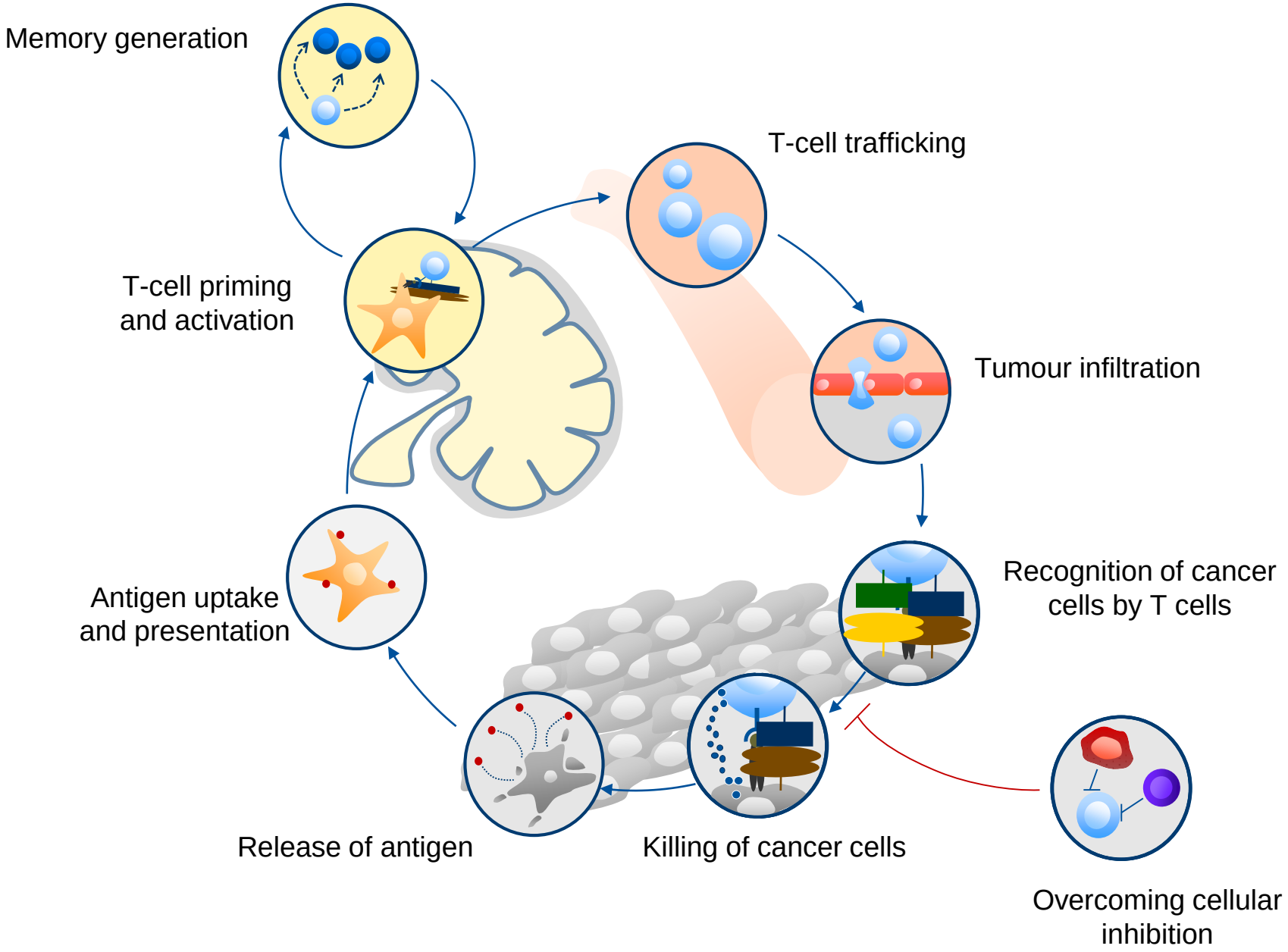


The cancer immunogram. The radar plot depicts the seven parameters that characterize aspects of cancer-immune interactions for which biomarkers have been identified or are plausible. Potential biomarkers for the different parameters are shown in italics. Desirable states are located in blue; progressively undesirable states are shown in the red gradient. The black line connecting the data values for each parameter represents a plot for a single hypothetical patient. In the case shown, it may be argued that single-agent PD-1 blockade, rather than combined PD-1 and CTLA-4 blockade, could be a first treatment of choice. For details on this case and other hypothetical patient cases, see (*2*).

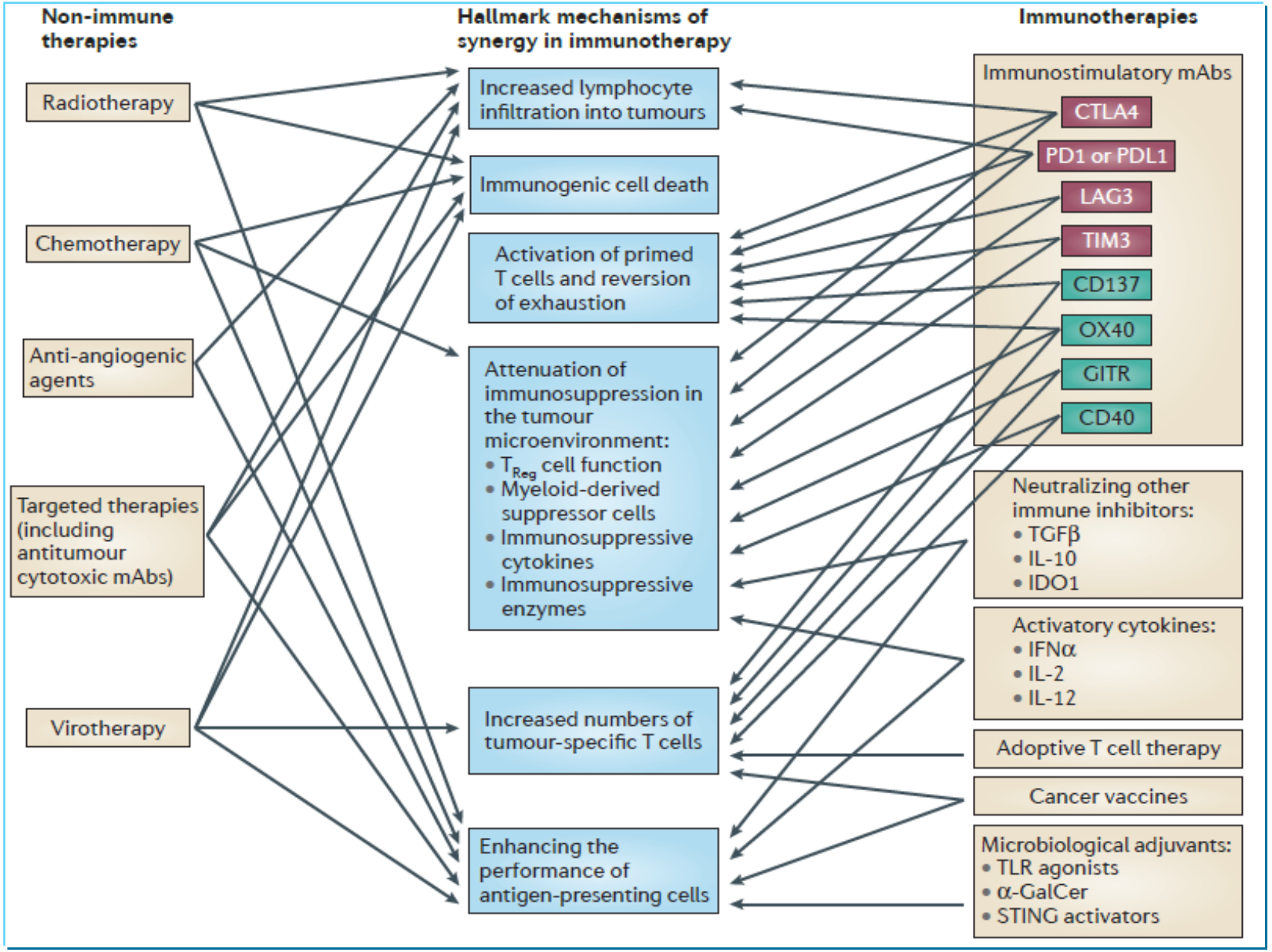
Blank Science 2016

New Immunotherapy Drugs

Cancer Immunity Cycle



New Immunotherapy Drugs and Combinations



Melero Nature Reviews Cancer 2015

Summary

- Developing biomarkers critical for patients to make our treatments work better and avoid overtreatment
- Lots of possibilities and lots of early data
- Thorough validation required if clinical decisions are to be based on biomarkers; withholding a potentially effective treatment or giving a futile treatment based on a poor biomarker is a disaster
- I think a multidimensional immunogram/fingerprint based on host and tumour factors is a definite possibility for checkpoint inhibitors
- Multiple new immunotherapy approaches under investigation; difficult to pick a winner at this stage…

Thank you