Combination cancer immunotherapy tailored to the tumour microenvironment

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Disclosure Slide

- I have no disclosures to declare.

Talk Outline

1. Conceptual Developments in Cancer Immunology
2. Tailoring combination immunotherapies to the tumour microenvironment

Conceptual Developments in Cancer Immunology

[1]Cancer immunoediting

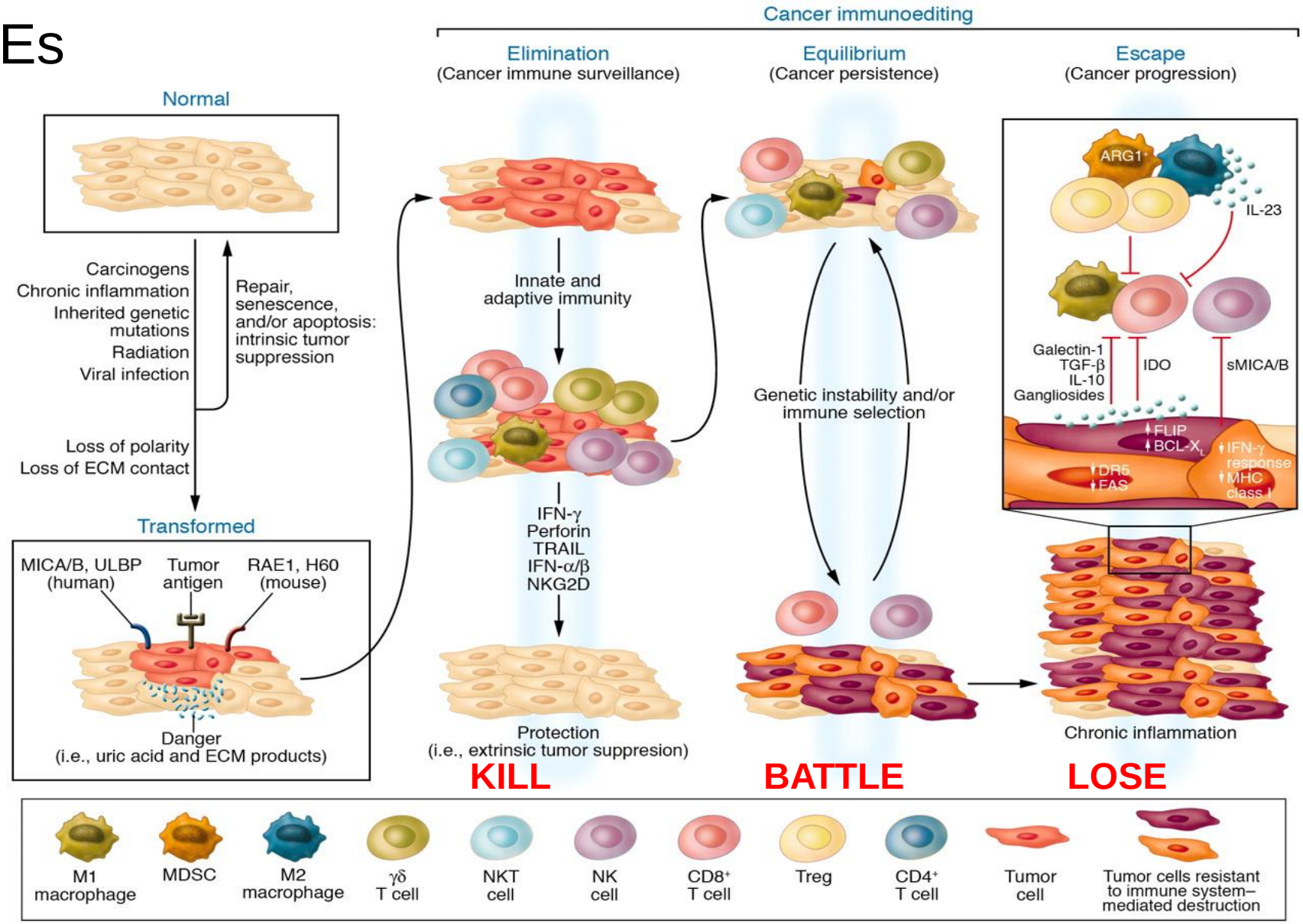
[2]Tumour Neoantigen

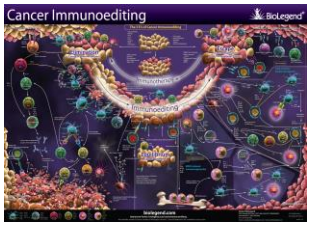
[3]Immune Reaction

[4]Combination mAb-based therapy

[5]Tumour induced Immune suppression

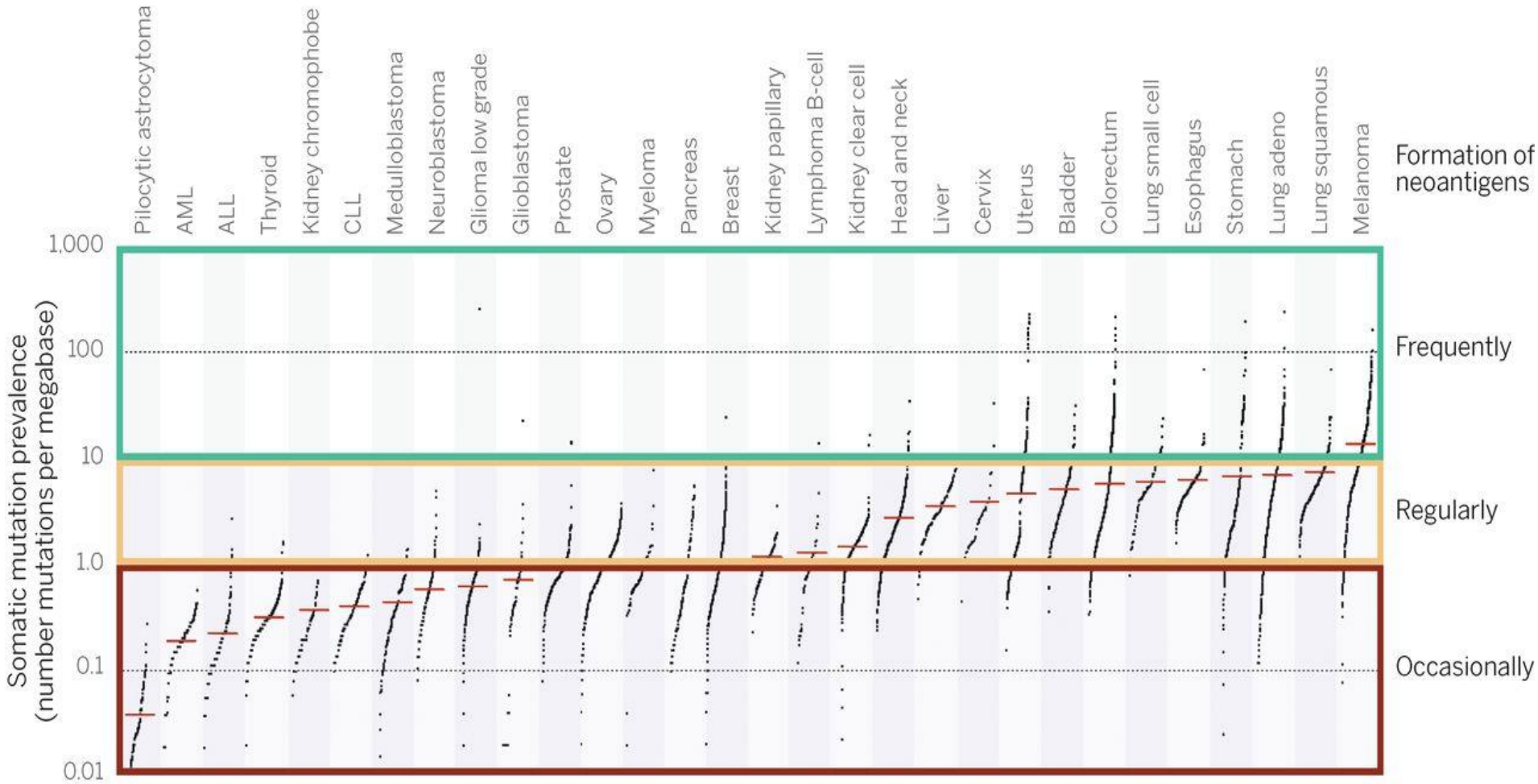
1 3Es





Smyth et al. JEM 2000, Shankaran et al. Nature 2001
Swann et al. J. Clin. Invest. 2007, Koebel et al. Nature 2007
Teng et al., JLB 2008; Schreiber..Smyth. Science 2011
Teng et al., Cancer Res 2012, Teng et al., JCI 2015

[2]Mutational load correlates with frequency of tumour neoantigens



Estimate of the neoantigen repertoire in human cancer

QIMR Berghofer Medical Research Institute

Ton N. Schumacher, and Robert D. Schreiber Science 2015;348:69-74

Immune contexture correlates with clinical outcome

Immune contexture associated with good prognosis in CRC

Chemokine
↑CXCL9 ↑CX3CL1
↑ CXCL10 ↑ CCL2
↑ CCL5 ↑ CXCL13

Adhesion
↑MADCAM1
↑ ICAM1
↑ VCAM1

Cytotoxic
↑ Granzymes
↑ Perforin
↑ Granulysin

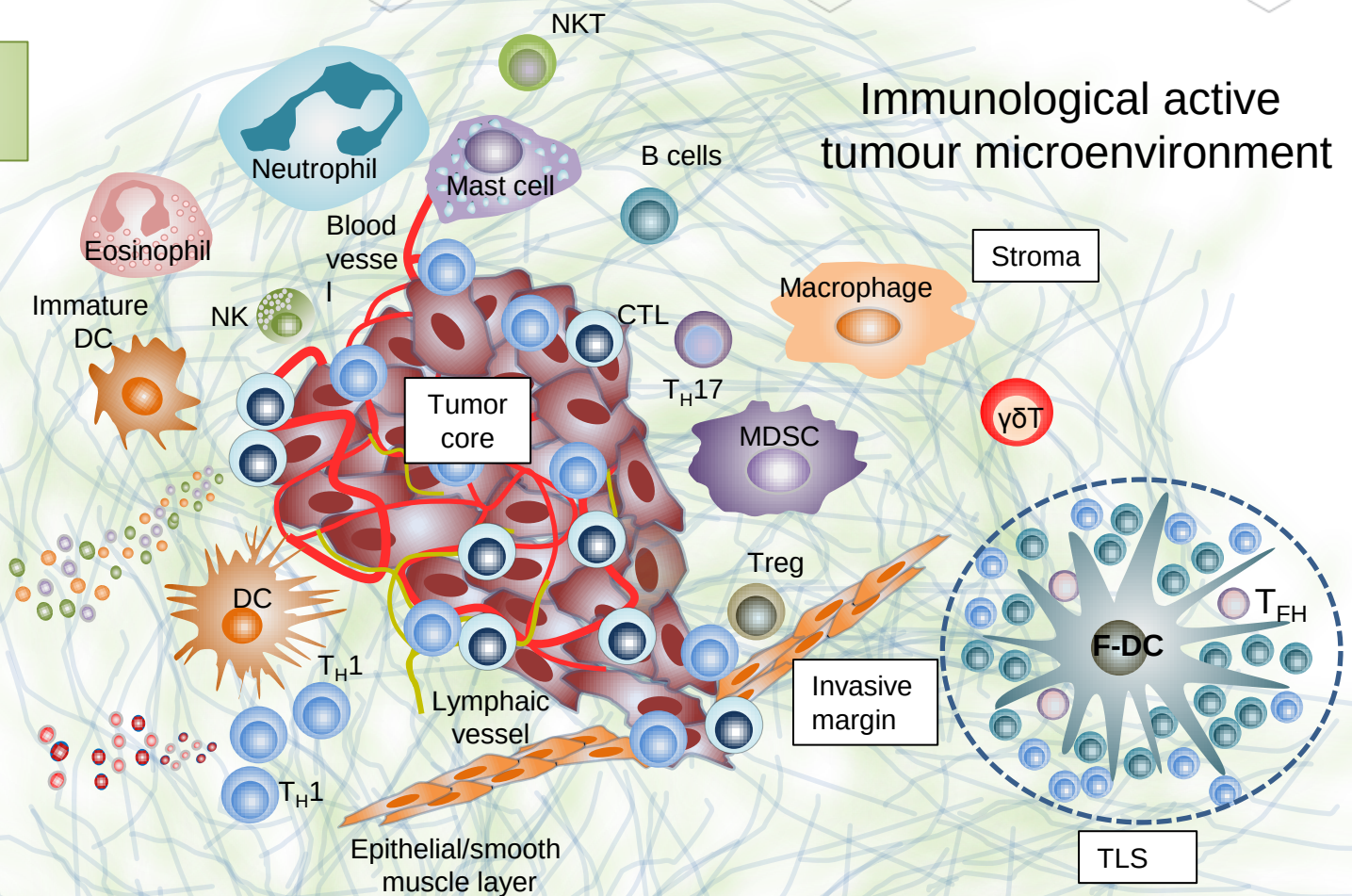
T_H1
↑T-bet
↑ IRF1
↑ STAT1

T_H1
↑ IL-12
↑ IFN-γ
↑IL-15

T_{FH}
↑ IL21

B cells

Tumor margin
↑ CD3+, CD8+, CD45RO+ T cells



Galon et al., 2006 Science
Pages et al., 2005 NEJM
Bindea el al., 2013 Immunity
Fridman et al., 2012 NRC

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nature medicine

Eradication of established tumors in mice by a combination antibody-based therapy (trimAb)

Tomoyasu Uno[1,2], Kazuyoshi Takeda[1,3], Yuko Kojima[4], Hirohisa Yoshizawa[5], Hisaya Akiba[1], Robert S Mittler[6], Fumitake Gejyo[2], Ko Okumura[1], Hideo Yagita[1] & Mark J Smyth[3]

trimAb

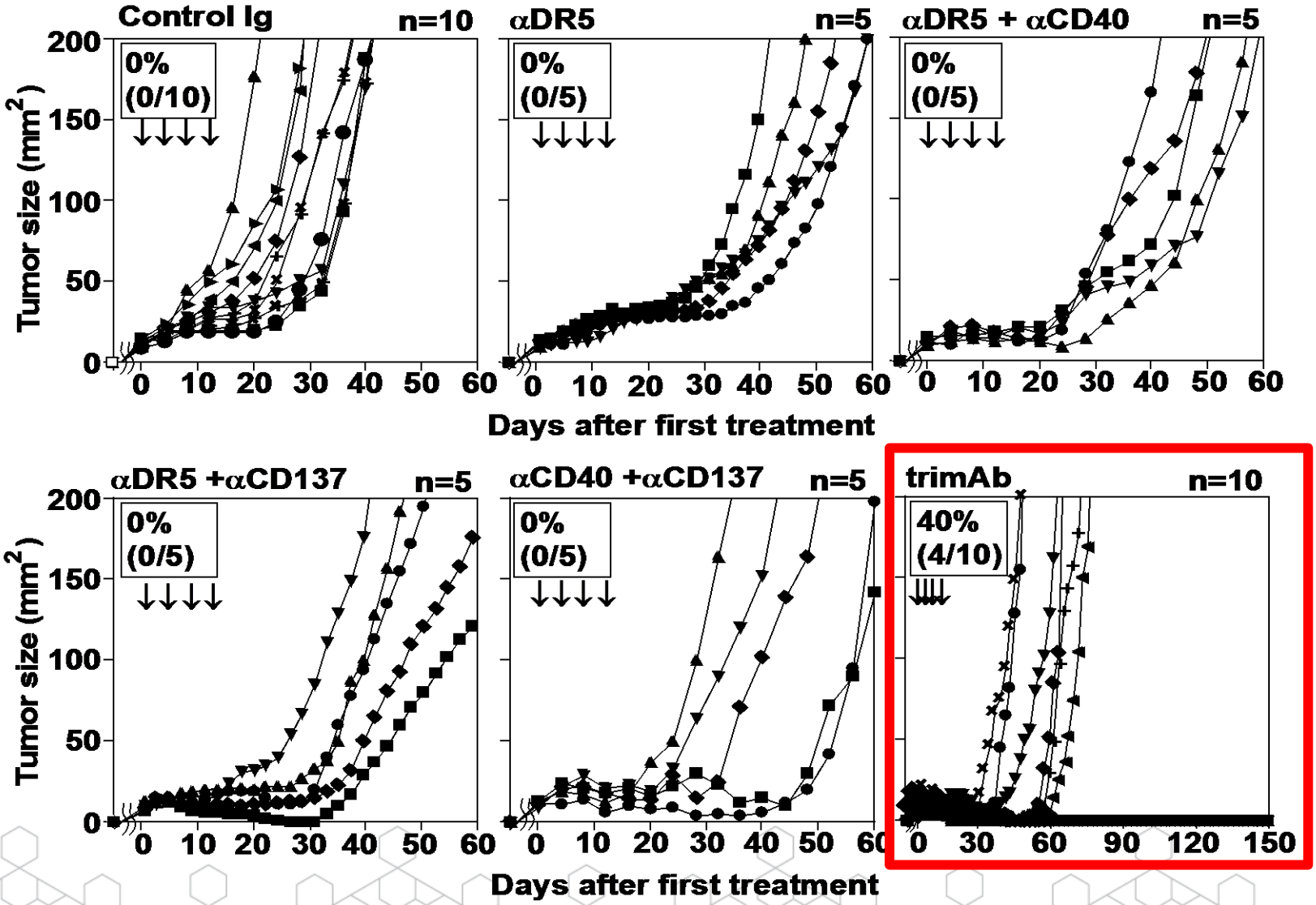
anti-DR5 (immunogenic cell death)
anti-CD40 (activate APC)
anti-CD137 (enhance effector T cell function and survival)

MCA induced fibrosarcoma model

WT or KO mouse

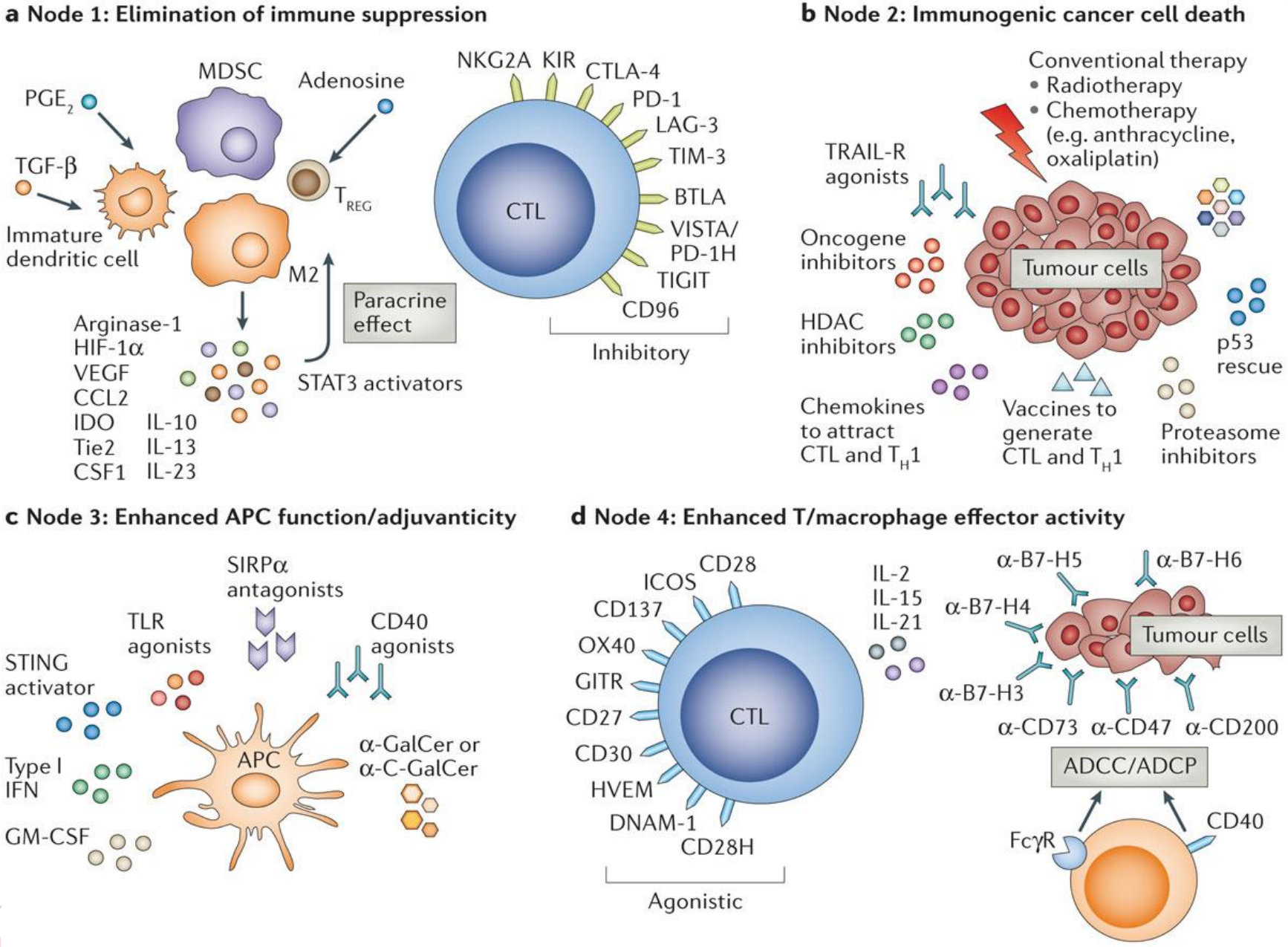
Detect sarcoma
Measure growth
Commence treatment

Rejection of carcinogen-induced established tumors by trimAb



Uno et al. Nature Medicine, 2006

The four nodes to target for inducing maximal anti-tumour immunity

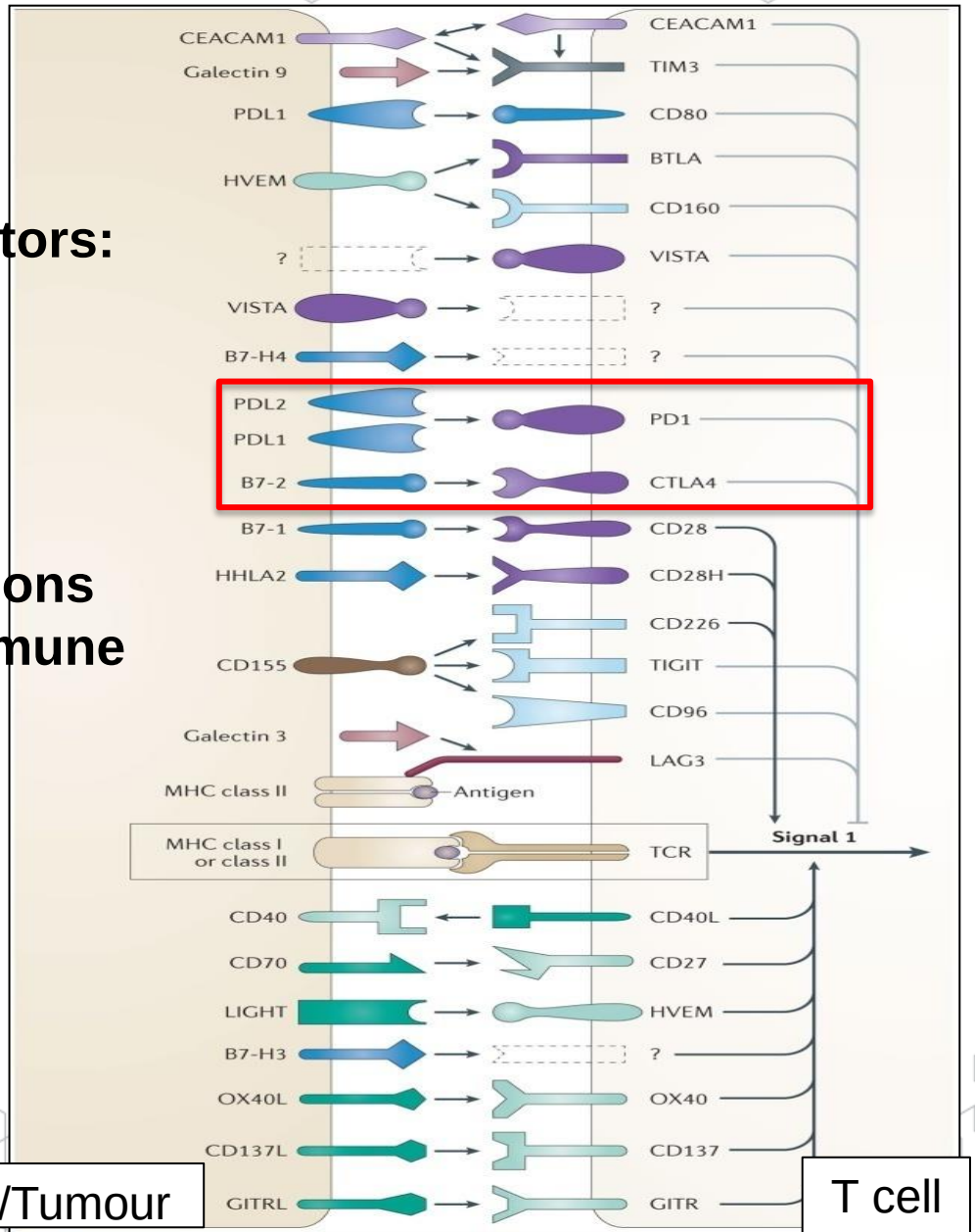


Smyth et al., NRCO 2015

Engagement of checkpoint receptors represents a major mechanism of tumour-induced immunosuppression

Checkpoint receptors: Brakes to limit overzealous T cell activation

About 20 interactions regulate T cell immune response



Melero I et al.
Nat Rev Cancer 2015

Checkpoint blockade can unleash endogenous anti-tumour response

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

ORR – 10% **2010**

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORR – 31% **2012**

Nivolumab plus Ipilimumab in Advanced Melanoma

ORR – 53% **2013**

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

ORR – 61% **2015**

Anti-PD-1 to be used as standard of care and in combination immunotherapies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab versus Ipilimumab in Advanced Melanoma

ORR – 33.7% vs 11.9%

2015

Lancet Oncol 2015; 16: 375–84

Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial

ORR – 31.7% vs 10.6%

2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

ORR – 20% vs 9%

2015

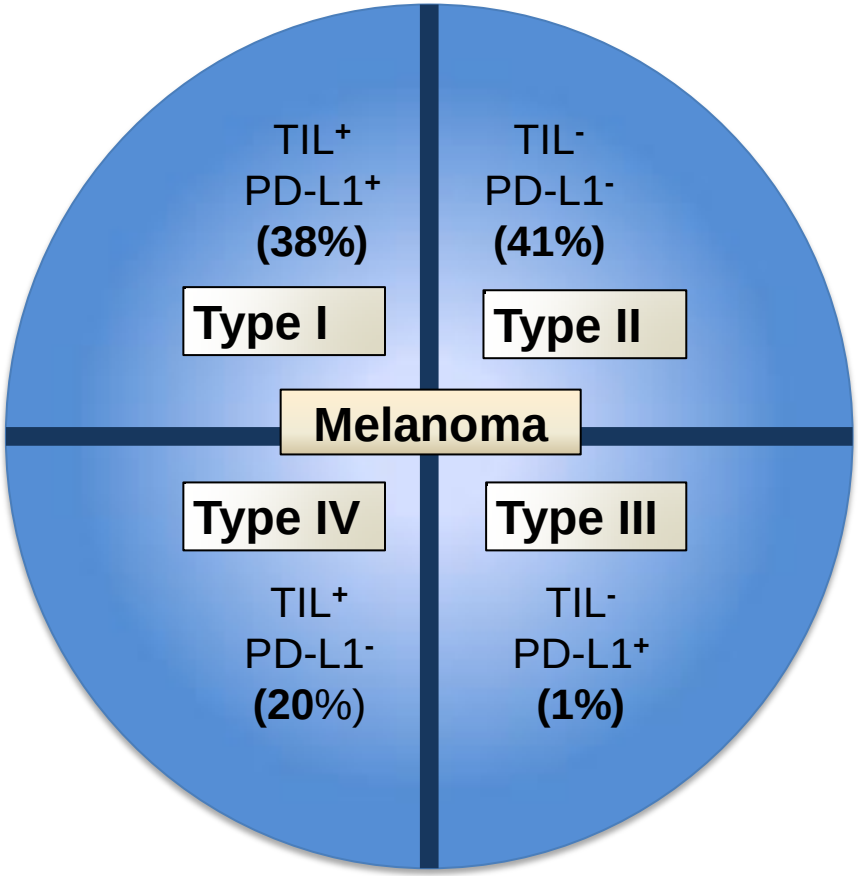
Moving Forward…

Key issues in cancer immunotherapy

1) **Identifying biomarkers to predict what cancers will respond to anti-PD-1/PD-L1**
2) **How do we increase the proportion of patients who respond to anti-PD-1/PD-L1?**
3) **What therapies do we use to treat cancers with tumour microenvironments that are resistant to anti-PD-1/PD-L1?**
4) **What do we do for patients who develop acquired resistance to anti-PD-1 therapies?**
5) **What is the optimal scheduling for administration of combination immunotherapy?**
6) **How to assess the therapeutic index (anti-tumour efficacy/irAEs) of combination immunotherapies?**

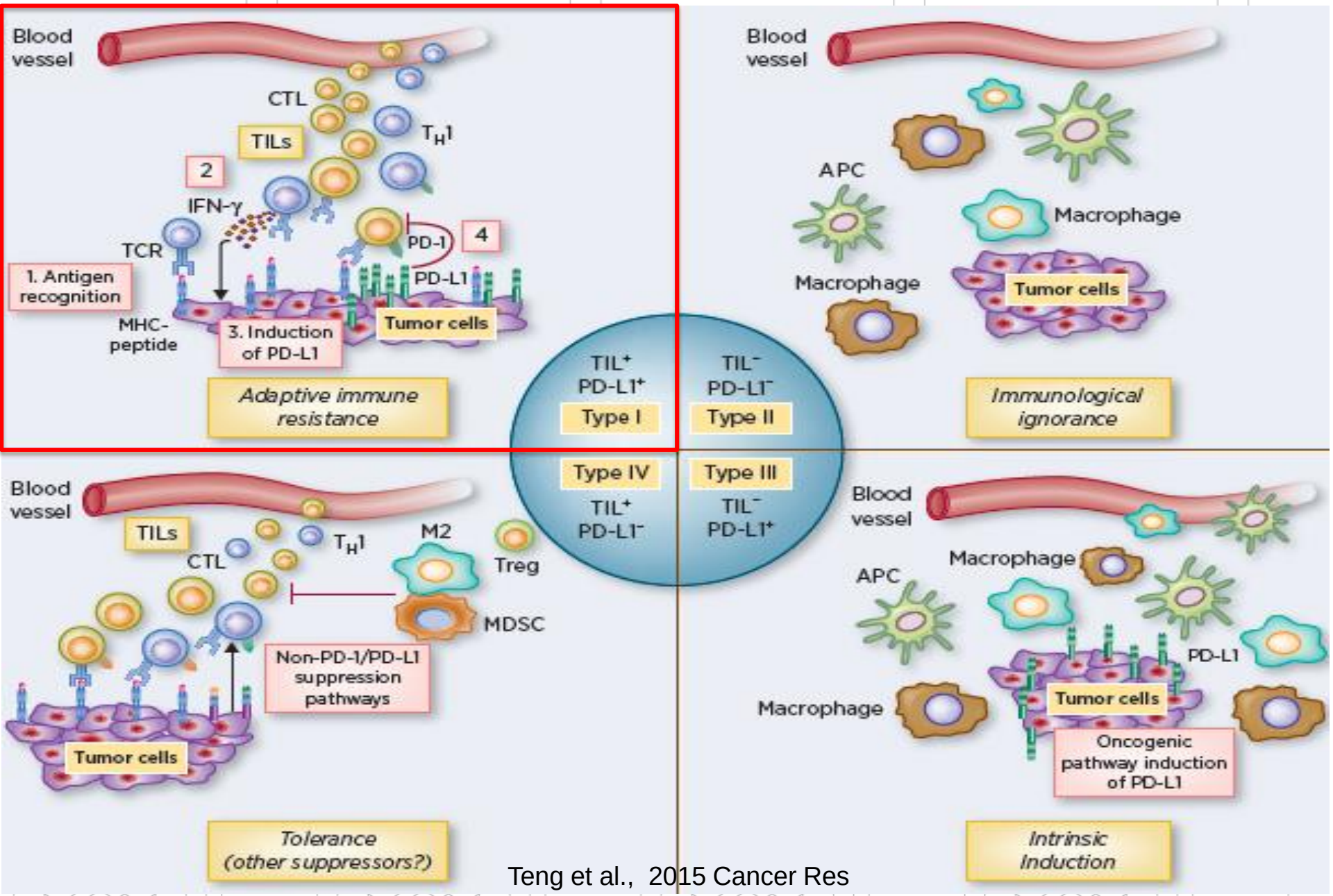
Tailoring combination immunotherapies to the tumour microenvironment

Tumour microenvironment can be stratified into 4 types based on TILs and PD-L1 expression in tumours



Taube et al. Sci Transl Med 2012, CCR 2014

Tumour microenvironment can be stratified into 4 types based on TILs and PD-L1 expression in tumours



Teng et al., 2015 Cancer Res

Association of anti-PD-L1 response and tumour-infiltrating immune cell PD-L1 expression

LETTER

doi:10.1038/nature14011

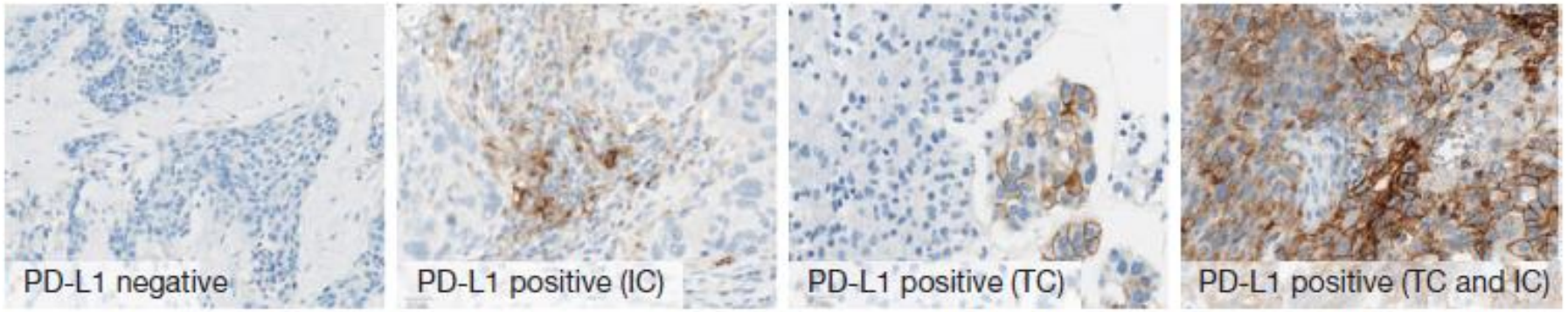
Predictive correlates of response to the anti–PD–L1 antibody MPDL3280A in cancer patients

Roy S. Herbst[1], Jean-Charles Soria[2], Marcin Kowanetz[3], Gregg D. Fine[3], Omid Hamid[4], Michael S. Gordon[5], Jeffery A. Sosman[6], David F. McDermott[7], John D. Powderly[8], Scott N. Gettinger[1], Holbrook E. K. Kohrt[9], Leora Horn[10], Donald P. Lawrence[11], Sandra Rost[3], Maya Leabman[3], Yuanyuan Xiao[3], Ahmad Mokatrin[3], Hartmut Koeppen[3], Priti S. Hegde[3], Ira Mellman[3], Daniel S. Chen[3] & F. Stephen Hodi[12]

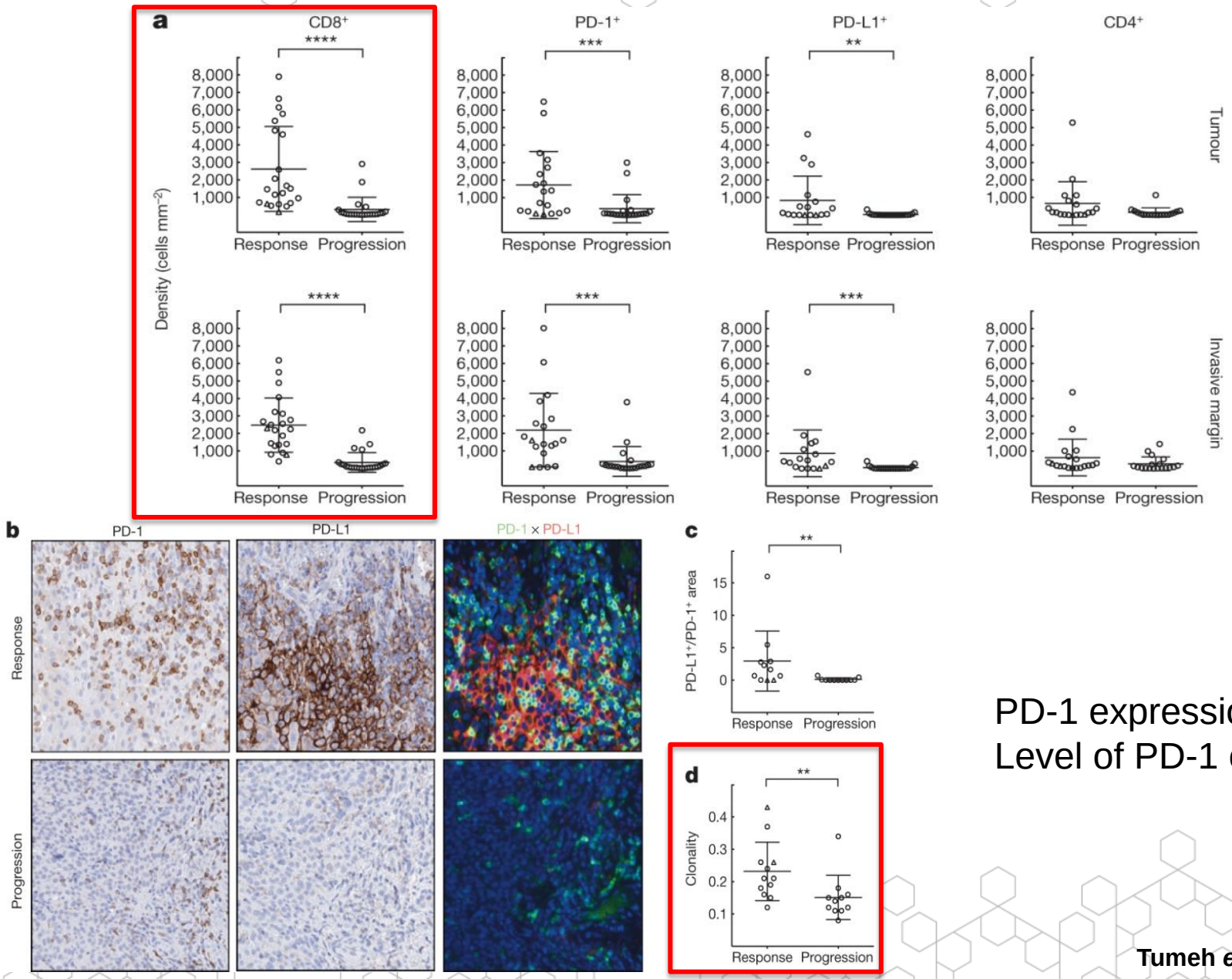
a PD-L1 prevalence determined with a Genentech/Roche anti-PD-L1 IHC assay

Indication	*n*	Percentage of PD-L1 positive (IC)	Percentage of PD-L1 positive (TC)
NSCLC	184	26	24
RCC	88	25	10
Melanoma	58	36	5
HNSCC	101	28	19
Gastric cancer	141	18	5
CRC	77	35	1
Pancreatic cancer	83	12	4

b



Cancers with type I TME containing CD8+ T cells and PD-L1 most likely to respond to anti-PD-1/PD-L1



PD-1 expression on cancer
Level of PD-1 expression

Tumeh *et al. Nature* (2014)

What other cancers should we treat with anti-PD-1/PD-L1?

PD-1 & PD-L1 expression in various types of solid tumours

Table 1. Overview of PD-1 and PD-L1 expression in various types of solid tumors

Tumor types (n = 437 total)	PD-1 expression (% and range)	PD-L1 (tumor cells; %)	Concurrent PD-1 and PD-L1 expression (%)
Carcinomas (n = 380 total)			
Breast (n = 116)	51% (1–20)	45%	29%
Colon (n = 87)	50% (1–>20)	21%	12%
NSCLC (n = 44)	75% (1–20)	50%	43%
Pancreas (n = 23)	43% (1–16)	23%	9%
Prostate (n = 20)	35% (1–6)	25%	5%
Merkel cell carcinoma (n = 19)	17% (1–4)	0%	0%
Endometrium (n = 16)	86% (1–13)	88%	79%
Ovary (n = 14)	93% (1–16)	43%	36%
Liver (n = 13)	38% (1–5)	8%	0%
Bladder (n = 11)	73% (1–10)	55%	55%
Kidney (n = 11)	36% (1–3)	67%	33%
CUP (n = 6)	50% (1–4)	33%	33%
Sarcomas (n = 33 total)	30% (1–>10)	97%	30%
Melanoma (n = 24 total)	58% (1–15)	92%	58%

Table 2. PD-1 and PD-L1 expression in breast cancers, according to the molecular subtype

Breast cancer subtypes ($n = 116$)	PD-1 expression/hpf (TILs; % and range)	PD-L1 (tumor cells; %)	Concurrent PD-1 and PD-L1 expression (%)
Luminal tumors ($n = 58$)			
Luminal A ($n = 33$)	25% (1–>10)	33%	13%
Luminal B ($n = 25$)	44% (1–20)	33%	17%
HER2 positive ($n = 5$)	60% (1–9)	20%	20%
Triple-negative ($n = 53$)	70% (1–20)[a]	59%[a]	45%[a]

Abbreviation: hpf, high-power fields.
[a]Significantly higher than in luminal tumors.

Table 3. PD-1 and PD-L1 expression in colorectal carcinomas in relationship to the microsatellite instability status

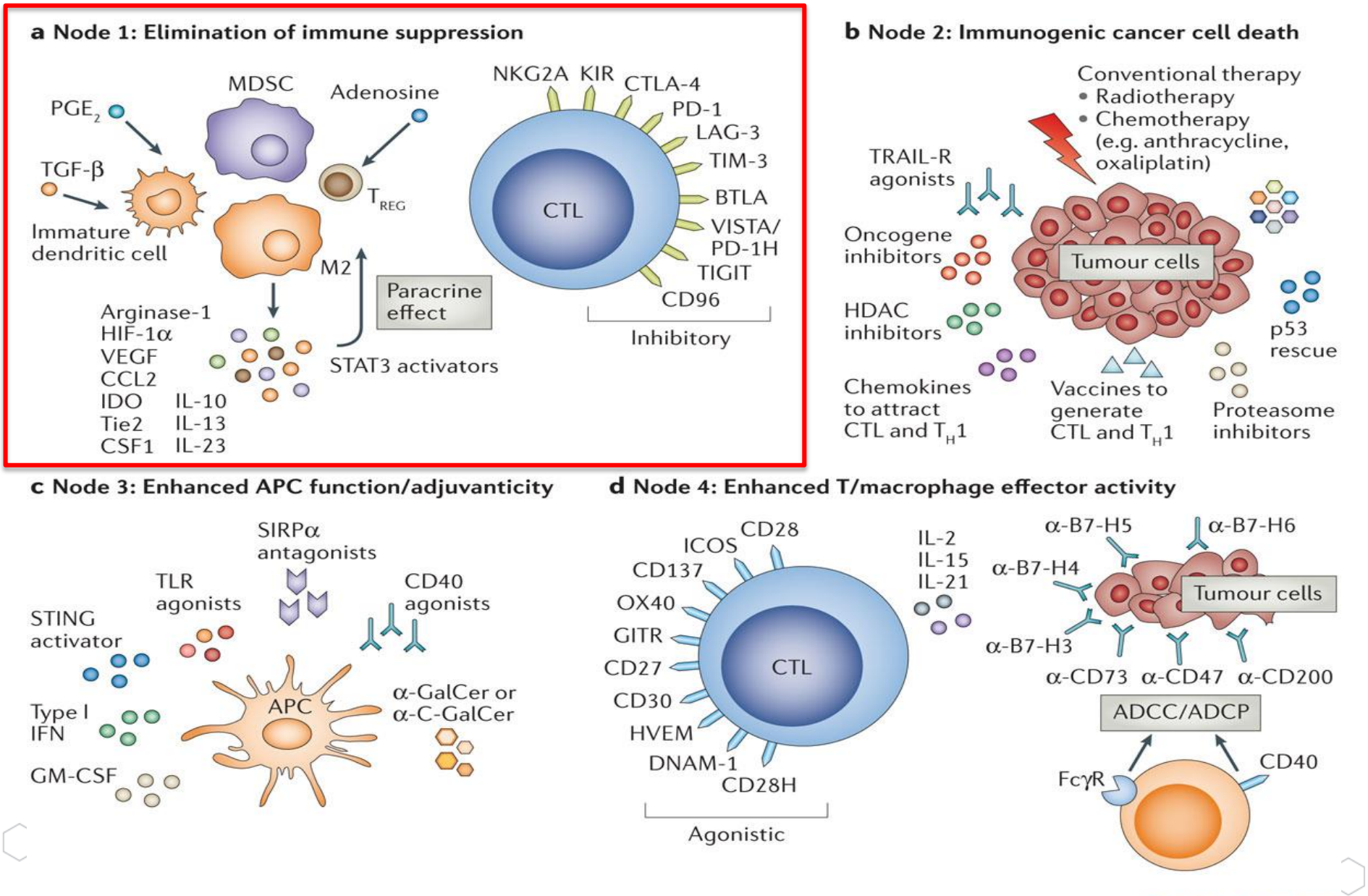
Colon cancer subtypes ($n = 87$)	PD-1 expression/hpf (TILs; % and range)	PD-L1 (tumor cells; %)	Concurrent PD-1/ PD-L1 expression (%)
MSS colon cancers ($n = 60$)	39% (1–11)	13%	4%
MSI-H colon cancers ($n = 27$)	77% (1–>20)[a]	38%[a]	32%[a]

Abbreviation: hpf, high-power fields.
[a]Significantly higher.

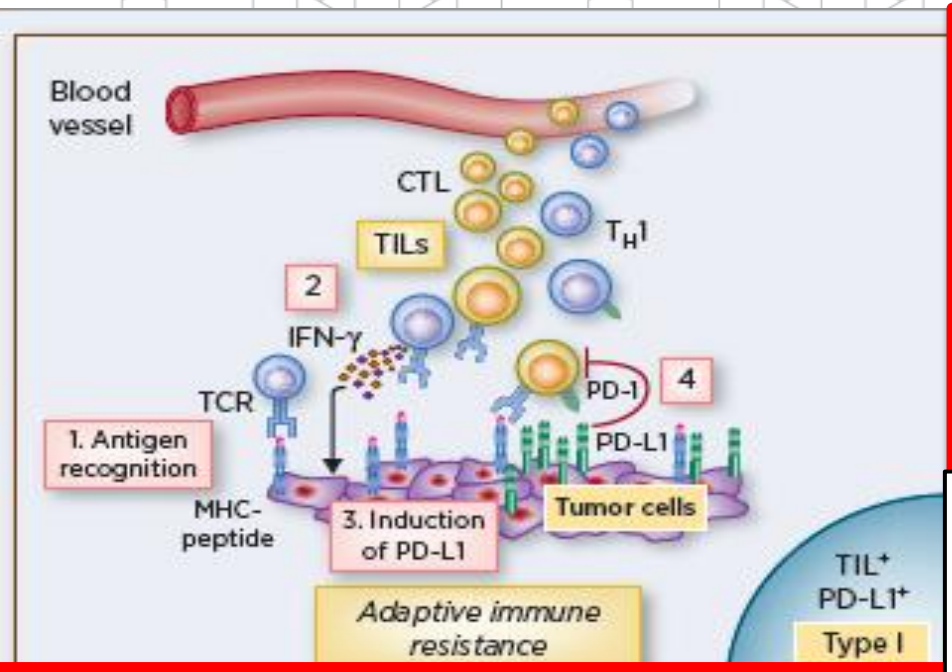
PD-1^{+} TILs expression correlates with increasing mutational load
Le et al., NEJM, 2015; Maby et al., Cancer Res, 2015

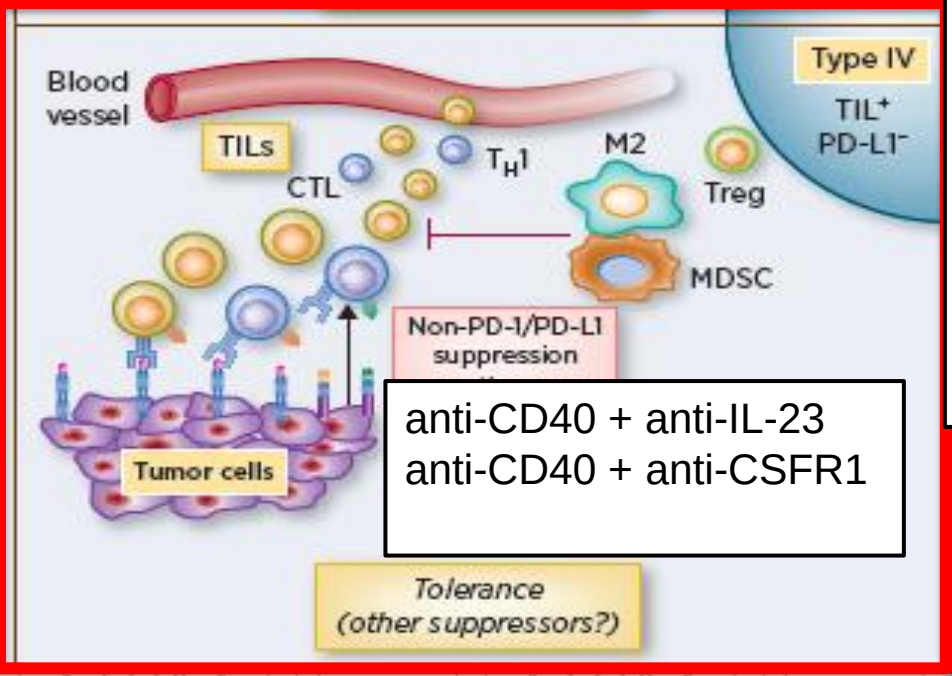
How do we increase the proportion of responders with type I (PD-L1+TIL+) tumour microenvironment?

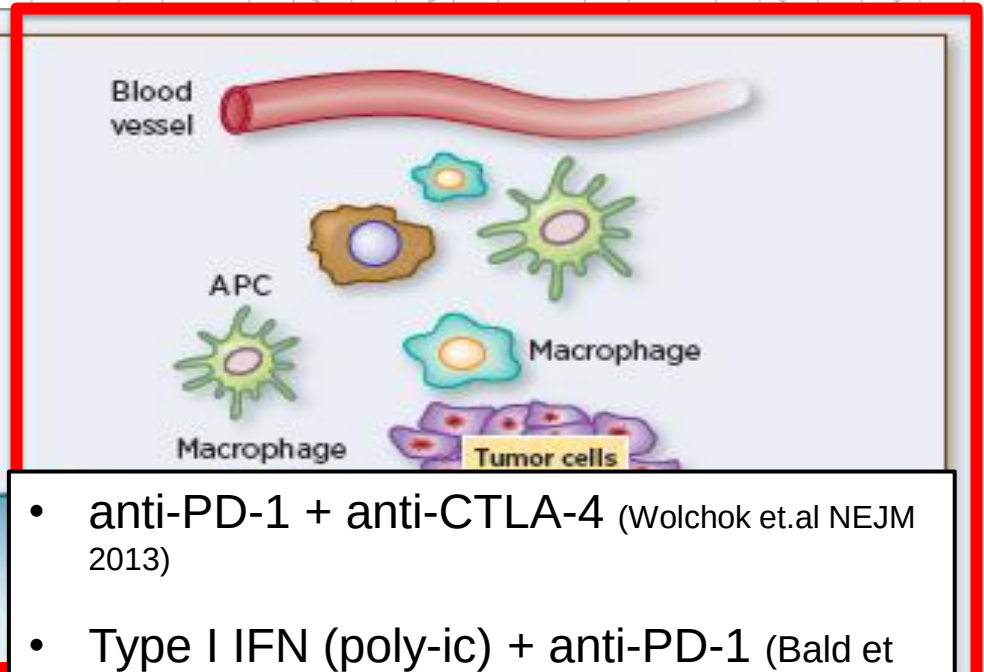
Can we improve above the 50% ORR induced by anti-CTLA-4 & anti-PD-1?



What therapies do we use to treat cancers with TME that are resistant to anti-PD-1/PD-L1?







- anti-PD-1 + anti-CTLA-4 (Wolchok et.al NEJM 2013)
- Type I IFN (poly-ic) + anti-PD-1 (Bald et al. Cancer Discovery 2014)
- Chemotherapy or targeted therapy + anti-PD-1
- Radiotherapy + anti-CTLA-4 + anti-
- PD-1(Twyman-Saint Victor et al., Nature 2015)
- CAR-T + anti-PD-1
- microbiota

anti-CD40 + anti-IL-23
anti-CD40 + anti-CSFR1

Summary

- **Anti-PD-1/PD-L1 - will become the immunotherapeutic backbone of future cancer treatments**
- **Cancers can be divided into four type**
  - absence or presence of TILs and PD-L1 expression
- **Efficient anti-tumour strategies must focus on hitting different targets concurrently**
- **Key nodes to target in combination treatment**
  - abrogating immune suppression
  - inducing immunogenic cancer-cell death,
  - enhancing antigen presentation/adjuvanticity
  - inducing activation and survival of immune-effector cells

Summary

- **Exome-sequencing data can be mined to**
  - identify unique neoantigen profile of tumours
  - guide future personalized vaccine design for use in combination treatments

- **A large proportion of patients have ‘immune ignorant’ tumours,**
  - predicted to have a poor prognosis regardless of any current intervention
  - novel therapies have to be developed

Thank You

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