IEO
Istituto Europeo di Oncologia

Immunoterapia

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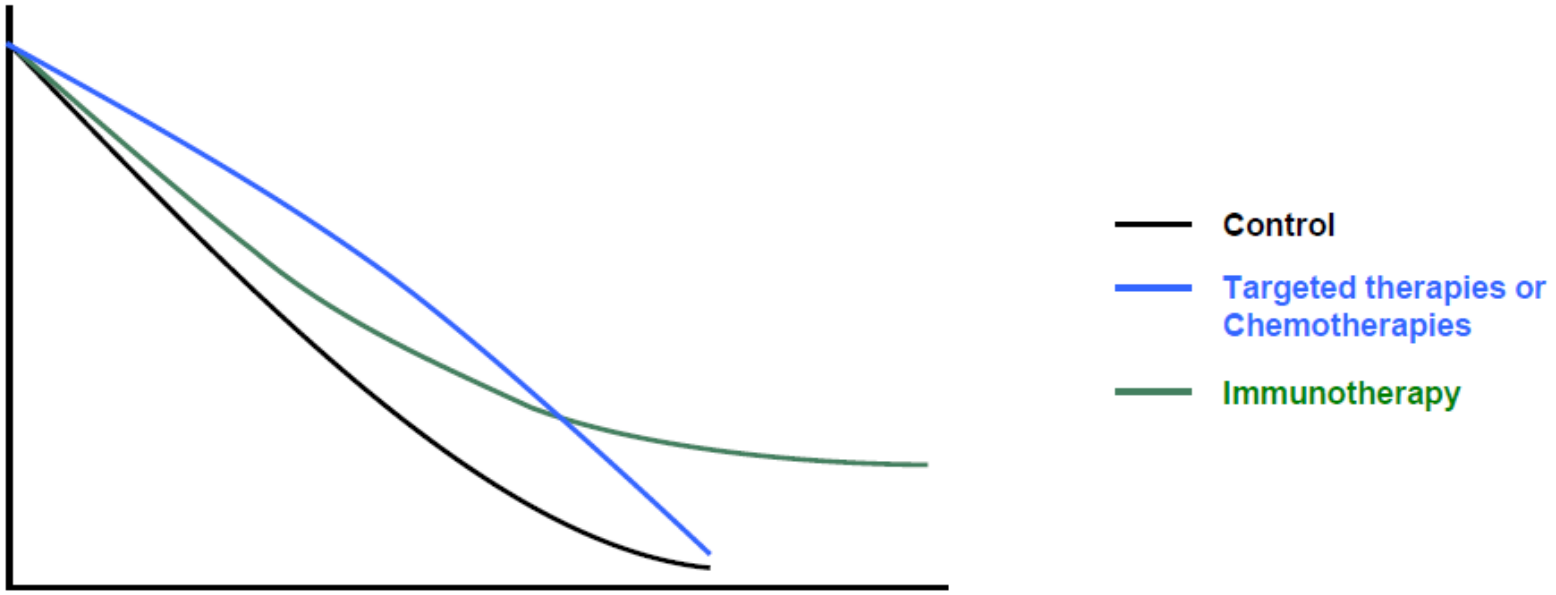
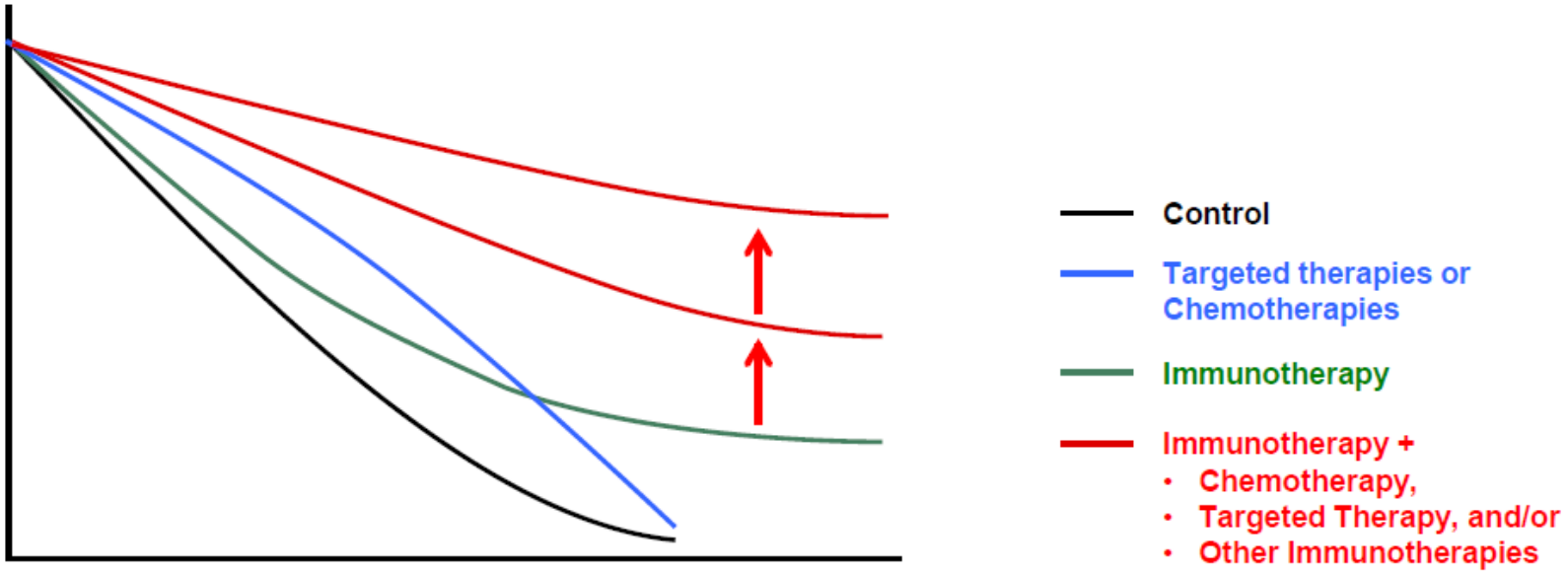
Immunotherapy in combination

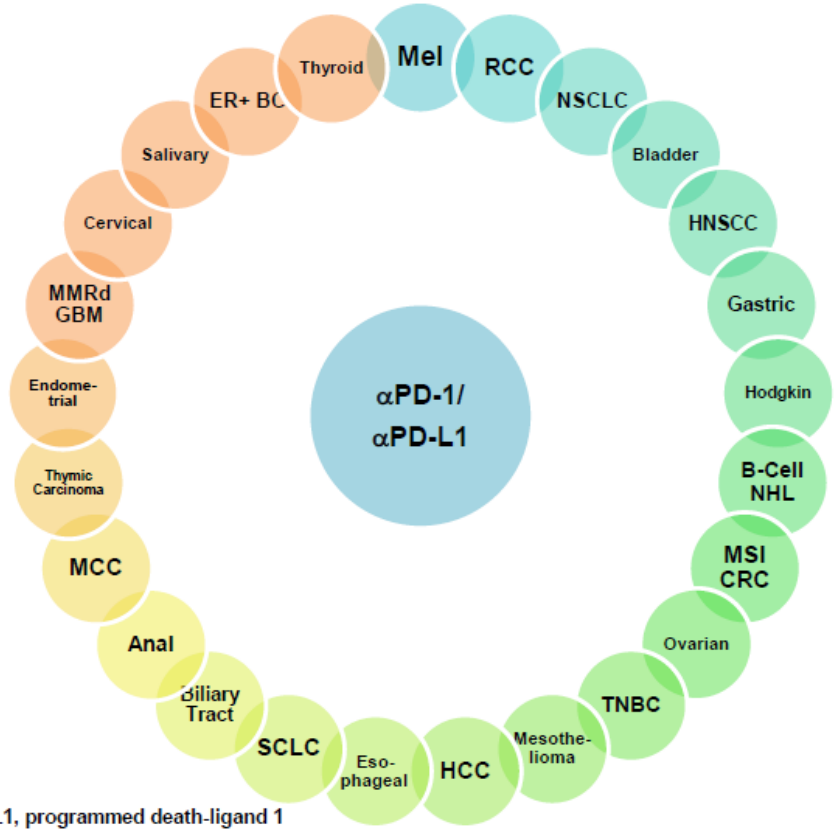


Immunotherapy in combination



- **Agents must be safe in combination**
- **The additional therapy should not interfere with the immunotherapeutic mechanism of action that is driving the antitumor response**

PD1-PDL1 spectrum of activity

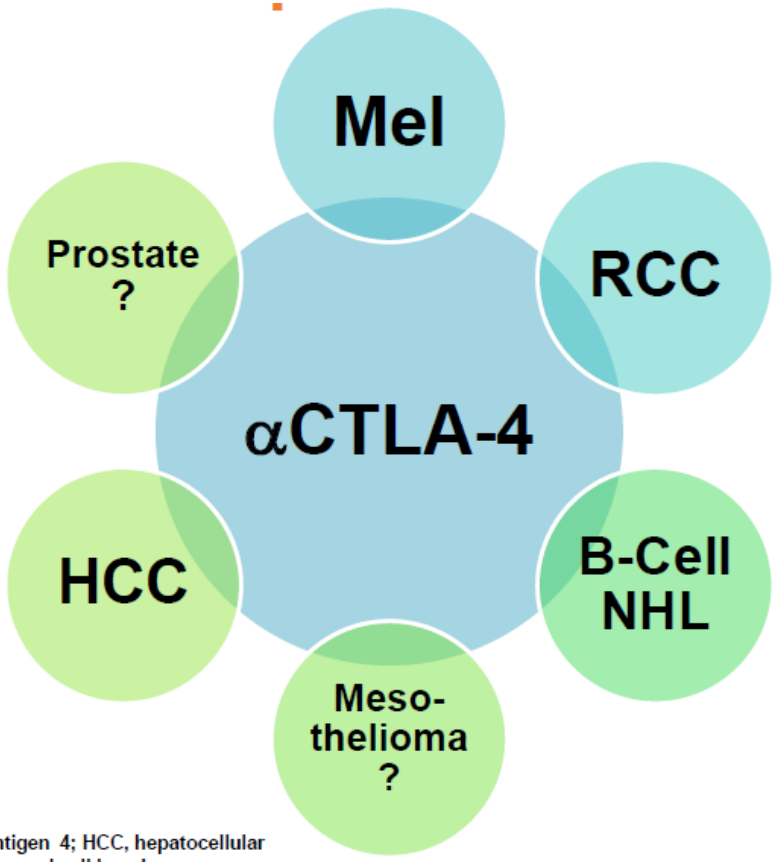


Grade 3-4 related adverse events (AEs): 10% to 15%

PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1

Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

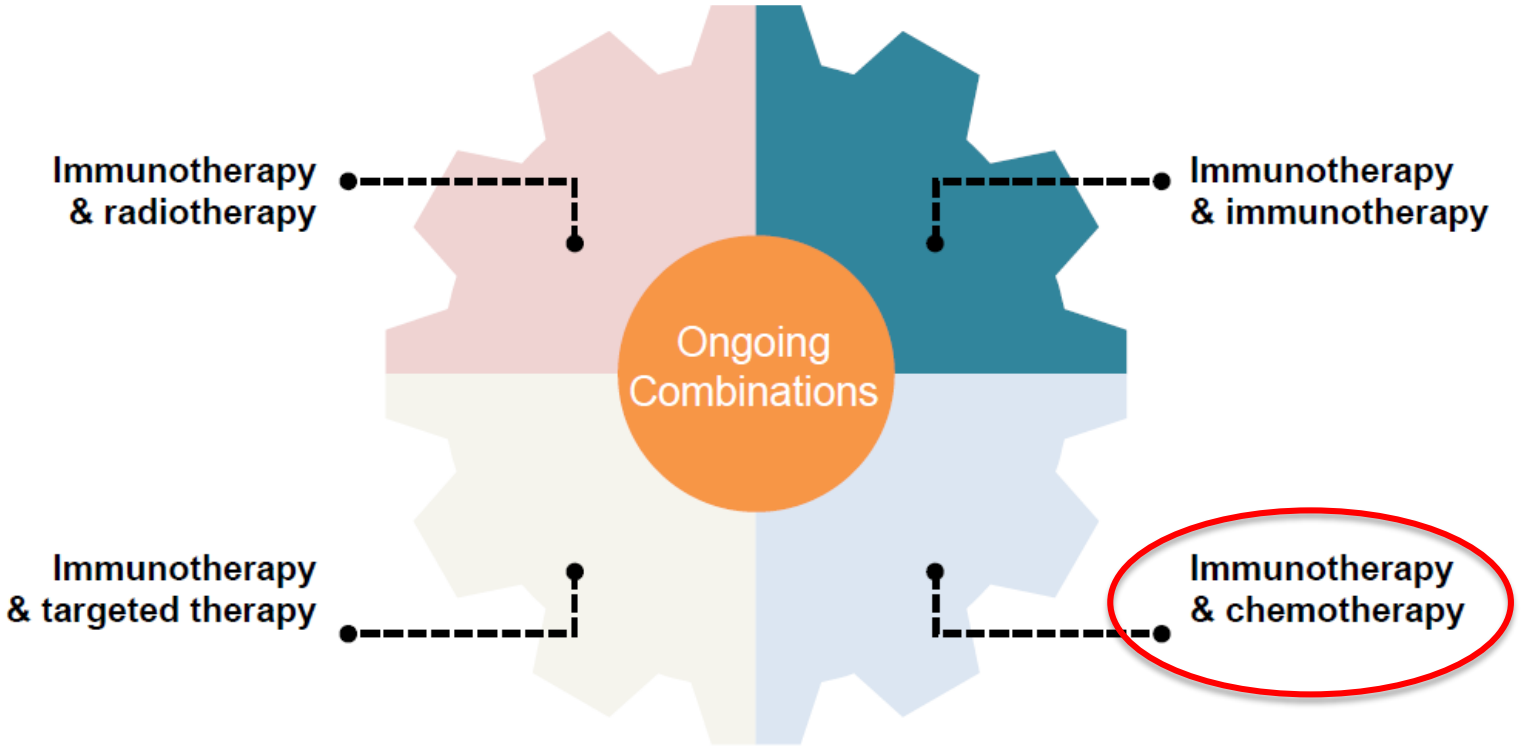
CTLA-4 spectrum of activity



Grade 3-4 related AEs: 25% to 30%

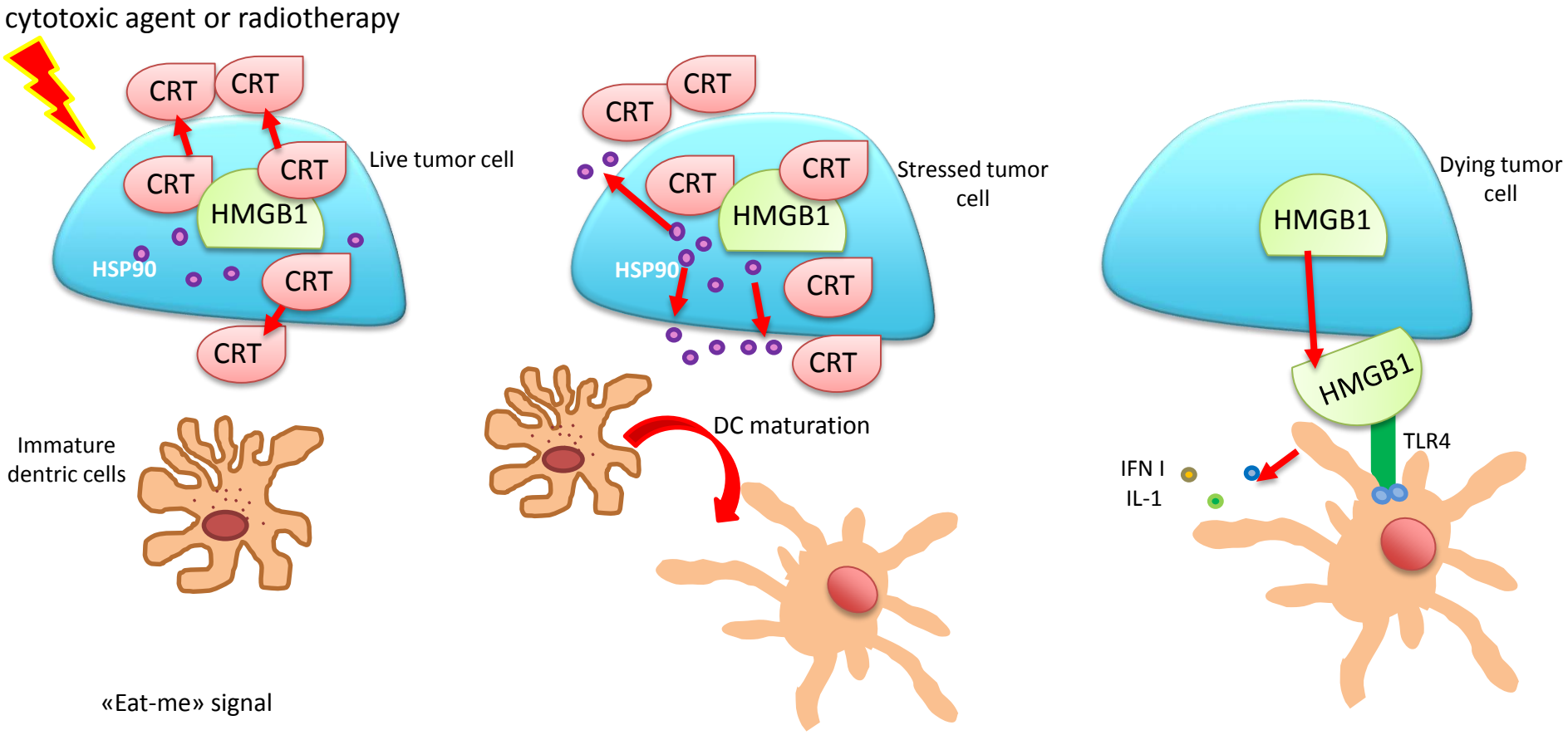
CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; HCC, hepatocellular carcinoma; NHL, non-Hodgkin lymphoma; RCC, renal cell lymphoma

Potential I-O combinations



1. Lu H. *Front Immunol.* 2014;5:1-5. 2. Melero I, et al. *Nat Rev Cancer.* 2015;15(8):457-472. 3. Drake CG. *Ann Oncol.* 2012;23 Suppl 8:viii41-viii46, 4. Vanneman M, et al. *Nat Rev Cancer.* 2012;12(4):237-251. 5. Sznol M, et al. *Clin Cancer Res.* 2013;19(19):5542. 6. Formenti SC, et al. *J Natl Cancer Inst.* 2013;105(4):256-265. 7. Kang J, et al. *J ImmunoTher Cancer.* 2016;4:51.

“Priming” with CT or RT

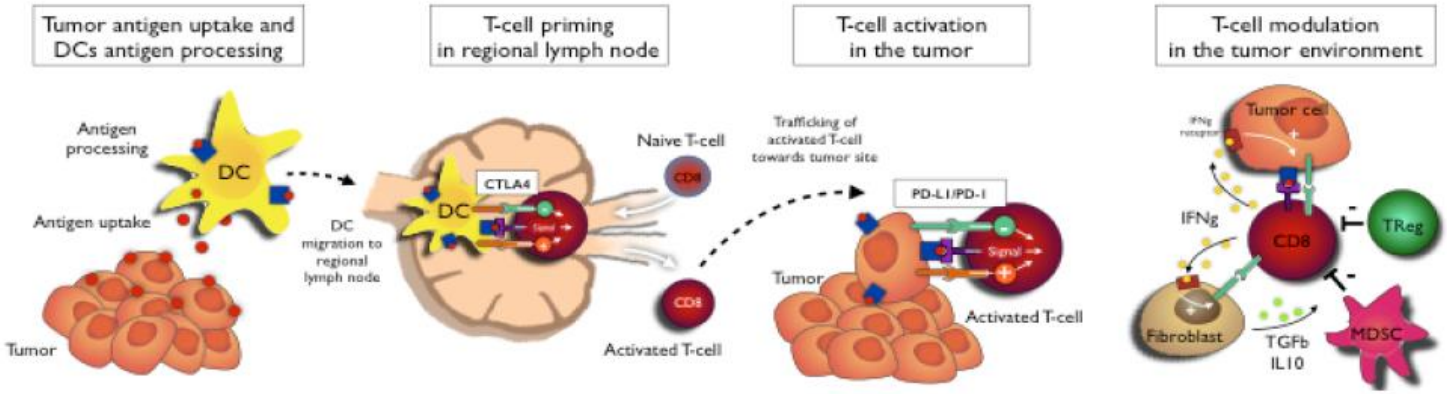


Translocation of Calreticulin to the cell surface

Activation of HSP90

Release of High Mobility Group Box 1 protein

Effect of chemotherapy



Immunogenic cell death
CT, RT

Up-regulation of MHCI
Paclitaxel, gemcitabine, erlotinib

DC maturation
Paclitaxel, docetaxel, bevacizumab

Up-regulation of PD-L1
Paclitaxel, etoposide

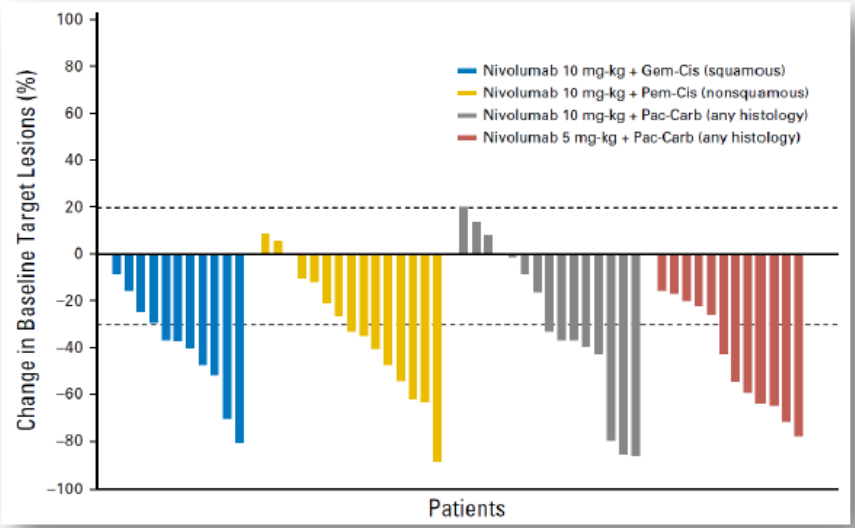
T-Reg inhibition
Cisplatin, paclitaxel, bevacizumab

Down-regulation of PD-L1
Pi3K? MEKi? crizotininb

CT, chemotherapy; DC, dendritic cell; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; RT, radiotherapy; TReg, T regulatory cells
Champiat S, et al. *J Thorac Oncol.* 2014;9(2):144-153. Galluzzi L, et al. *Cancer Cell.* 2015;28(6):690-714.

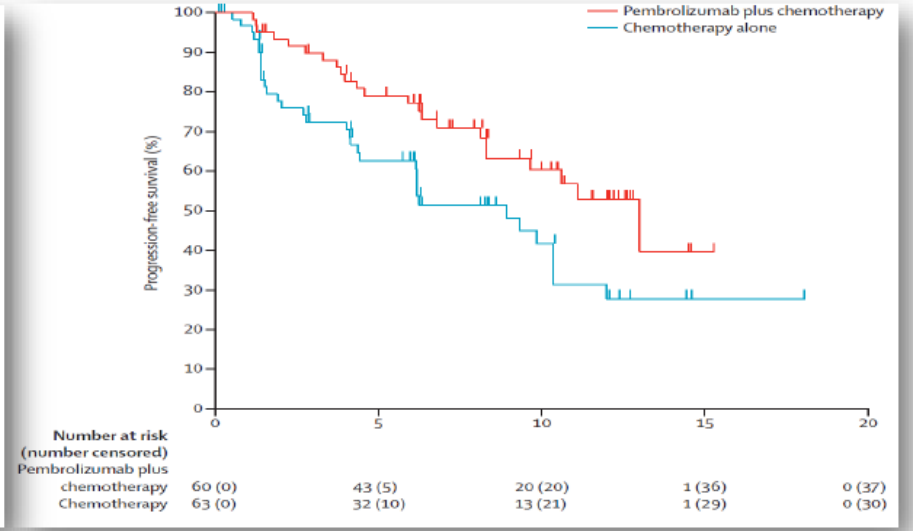
Effect of chemotherapy

Nivolumab + Platinum-Based Doublet Chemotherapy



Rizvi NA, et al. *J Clin Oncol.* 2016;34(25):2969-2979.

KEYNOTE-021:Carboplatin/Pemetrexed ± Pembrolizumab in Nonsquamous Advanced NSCLC



Langer CJ, et al. *Lancet Oncol.* 2016;17(11):1497-1508.

The TONIC trial

Short-term 'induction' or "priming" with radiation or chemotherapy can modulate the anticancer immune response resulting in an increased activity of anti-PD1

- Irradiation can induce immunogenic cell death, overcome T-cell exclusion and promote antigen presentation[1]
- Doxorubicin increases production of interferons, reduces myeloid-derived suppressor cells (MDSC)-induced immune suppression[2,3]
- Cyclophosphamide (low dose) depletes Tregs in human breast tumors[4]
- Cisplatin stimulates class I HLA and vulnerability of tumor cells for T cell killing[5,6]

M.Kok et al. abstract LBA14

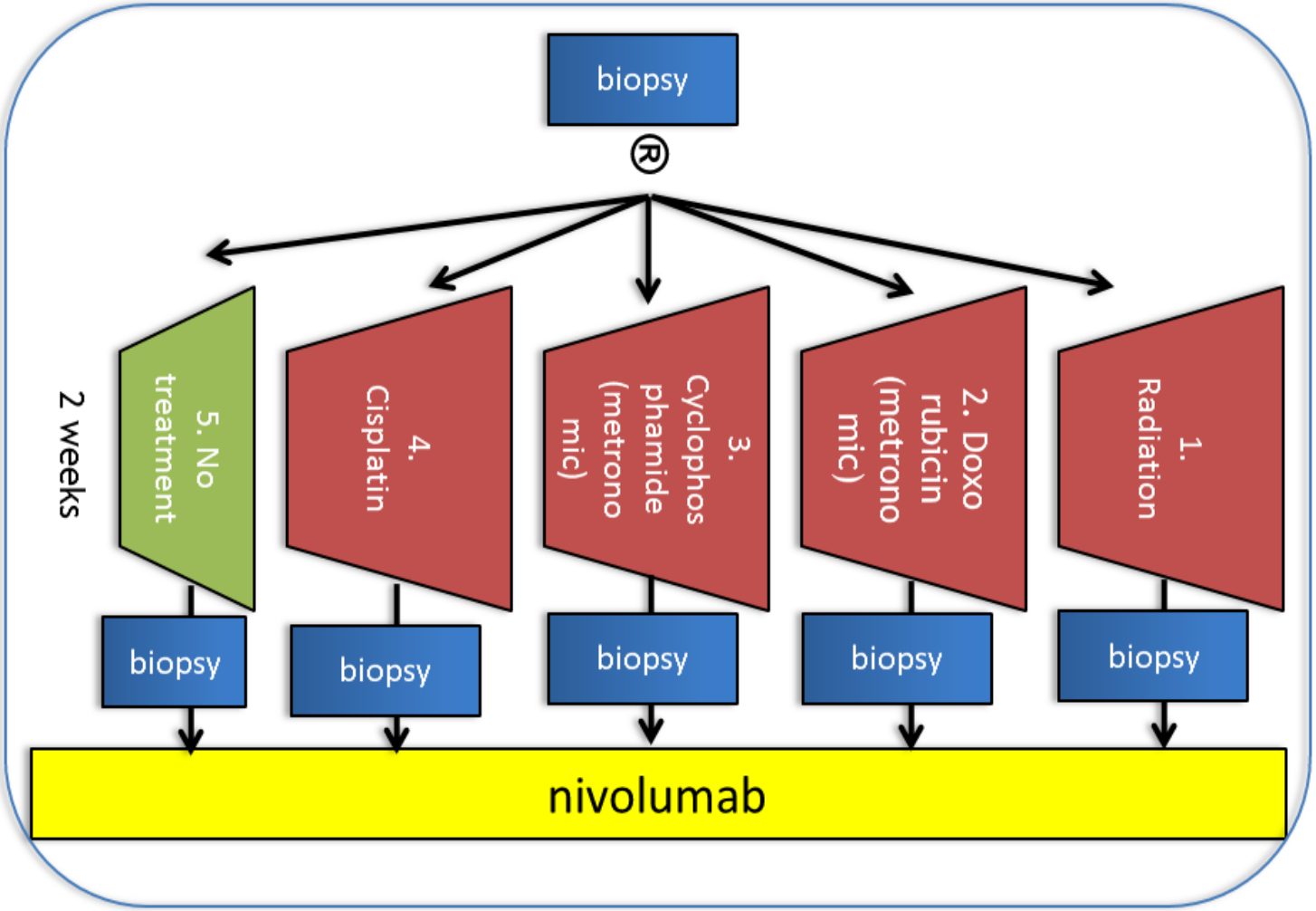
1. Vanpouille-Box et al. Clin Cancer Res 2017, 2. Sistigu et al. Nature Med 2014, 3. Alizadeh et al. Cancer Res 2014, 4. Ghiringhelli et al. CII 2007, 5. Lesterhuis et al. JCI 2011, 6. Ramakrishnan et al. JCI 2010

Inclusion criteria

- Metastatic TNBC (ER<10%, HER2 negative)
- Max 3 lines of chemotherapy for metastatic disease
- LDH < 2x ULN
- Accessible lesion for biopsy and radiation
- WHO PS 0-1
- Evaluable disease
- No history of leptomeningeal disease, no symptomatic CNS disease

M.Kok et al. abstract LBA14

Study design



M.Kok et al. abstract LBA14

“Boosting” after “priming”

	total (n = 50)
best objective response rate (ORR=CR+PR) iRECIST	**24%**
clinical benefit rate (CR+PR+SD)	**26%**
complete response (CR)	1 (2%)
partial response (PR)	11 (22%)
stable disease ≥24weeks (SD)	1 (2%)
ORR RECIST1.1	22%
median progression-free survival (PFS) [95% CI]	3.4 months [2.5-3.7]
median time to response (TTR) [range]	8.4 weeks [2-14]
median duration of response (DOR) [95% CI]	9 months [5.5 – NA]

M.Kok et al. abstract LBA14

PACIFIC: A DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY OF DURVALUMAB AFTER CHEMORADIATION THERAPY IN PATIENTS WITH STAGE III, LOCALLY ADVANCED, UNRESECTABLE NSCLC

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[1]Hospital Universitario 12 de Octubre, CiberOnc, Universidad Complutense and CNIO, Madrid, Spain; [2]Cancer Specialists of North Florida, Jacksonville, FL, USA; [3]Tennessee Oncology, Chattanooga, TN, and Sarah Cannon Research Institute, Nashville, TN, USA; [4]Hospital Universitario Virgen Macarena, Seville, Spain; [5]Kanagawa Cancer Center, Yokohama, Japan; [6]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [7]Kansai Medical University Hospital, Hirakata, Japan; [8]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [9]Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea; [10]Vivantes Klinikum Neukoelln, Berlin, Germany; [11]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea; [12]Centre Hospitalier Universitaire de Liège, Liège, Belgium; [13]CHU Montpellier and ICM Val d'Aurelle, Montpellier, France; [14]Kurume University Hospital, Kurume, Japan; [15]Florida Hospital Cancer Institute, Orlando, FL, USA; [16]Gustave Roussy, Villejuif, France; [17]AstraZeneca, Gaithersburg, MD, USA; [18]Istanbul University Cerrahpasa School of Medicine, Istanbul, Turkey

Acknowledgement: Dr. Scott J. Antonia of H. Lee Moffitt Cancer Center and Research Institute is the lead author for this study; Dr. Paz-Ares is presenting on his behalf

PACIFIC: Study Design

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks

All-comers population (i.e. any PD-L1 status)

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

Durvalumab 10 mg/kg q2w for up to 12 months N=476

Placebo 10 mg/kg q2w for up to 12 months N=237

Co-primary endpoints

- Progression-free survival (PFS) by BICR using RECIST v1.1*
- Overall survival (OS)

Secondary endpoints

- Proportion of patients alive and progression-free at 12 and 18 months (per BICR)
- ORR (per BICR)
- DoR (per BICR)
- OS at 24 months
- Safety and tolerability
- Health-related quality of life
- Pharmacokinetics
- Immunogenicity

*Defined as the time from randomization (which occurred up to 6 weeks post-cCRT) to the first documented event of tumor progression or death in the absence of progression.

ClinicalTrials.gov number: NCT02125461 BICR, blinded independent central review; cCRT, concurrent chemoradiation therapy; DoR, duration of response; HR, hazard ratio; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; ORR, objective response rate; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

Patient Disposition

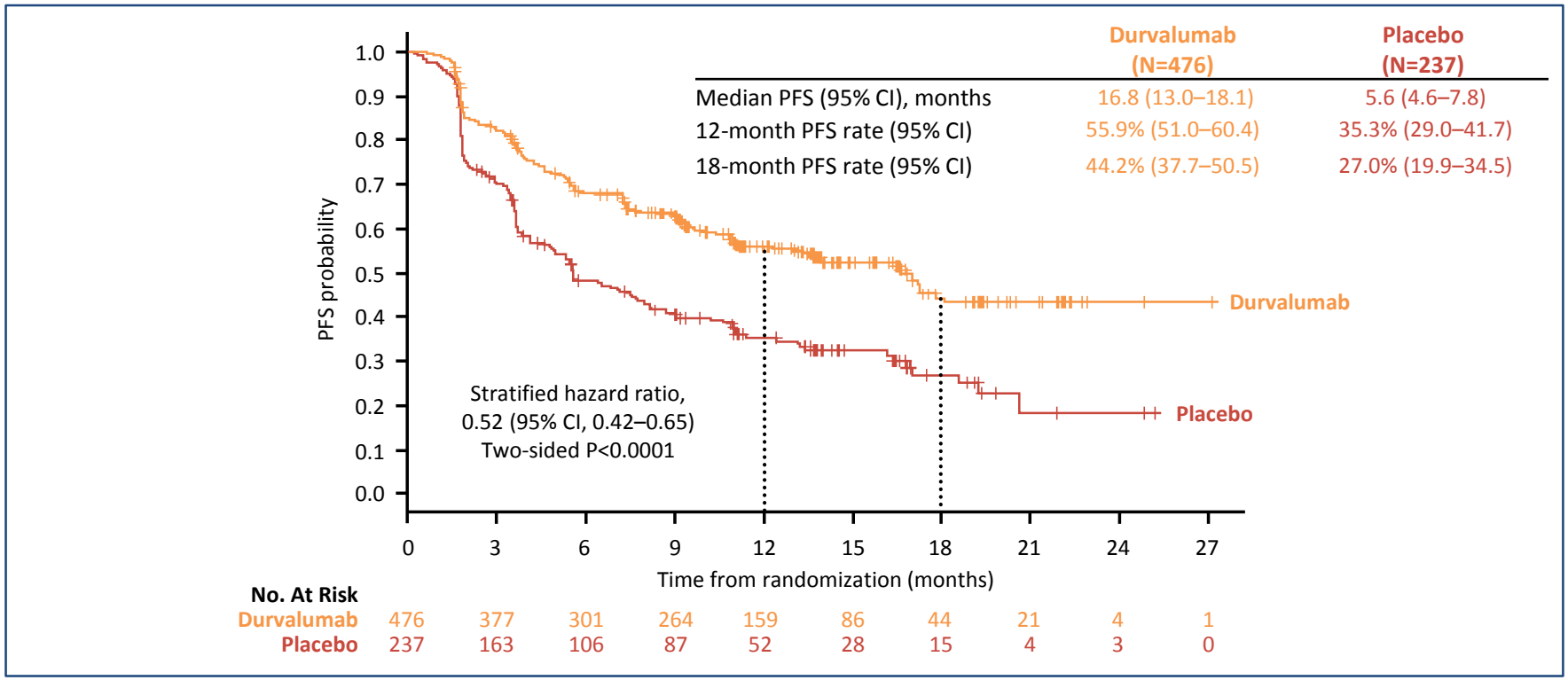
	Durvalumab (N=476)	Placebo (N=237)
Received treatment, n (%)	473 (99.4)	236 (99.6)
Treatment ongoing at data cutoff, n (%)	30 (6.3)	12 (5.1)
Completed 12 months of treatment, n (%)	202 (42.7)	71 (30.1)
Discontinued study treatment, n (%)	241 (51.0)	153 (64.8)
Subject decision	14 (3.0)	12 (5.1)
Adverse event	73 (15.4)	23 (9.7)
Severe non-compliance to protocol	1 (0.2)	1 (0.4)
Condition under investigation worsened	148 (31.3)	116 (49.2)
Development of study specific discontinuation criterion	1 (0.2)	1 (0.4)
Other	4 (0.8)	0
Ongoing in the study at data cutoff, n (%)	346 (73.2)	144 (61.0)
Discontinued study, n (%)	121 (25.6)	92 (39.0)
Received subsequent therapy after discontinuation, n (%)	145 (30.5)	102 (43.0)

Baseline Characteristics (ITT)

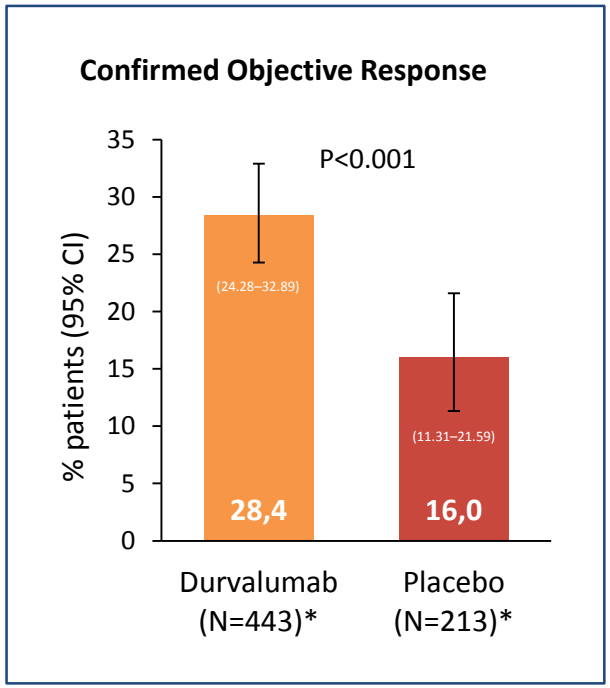
		Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
Age	Median (range), years	64 (31–84)	64 (23–90)	64 (23–90)
	≥65 years, %	45.2	45.1	45.2
Male, %		70.2	70.0	70.1
WHO performance status score, %*	0 / 1	49.2 / 50.4	48.1 / 51.5	48.8 / 50.8
Smoking status, %	Current / Former / Never	16.6 / 74.4 / 9.0	16.0 / 75.1 / 8.9	16.4 / 74.6 / 9.0
Disease stage, %†	IIIA / IIIB	52.9 / 44.5	52.7 / 45.1	52.9 / 44.7
Histology, %	Squamous / Non-squamous	47.1 / 52.9	43.0 / 57.0	45.7 / 54.3
PD-L1 status, %	Known: TC <25% / TC ≥25%	39.3 / 24.2	44.3 / 18.6	41.0 / 22.3
	Unknown‡	36.6	37.1	36.7
Prior chemotherapy, %	Adjuvant / Induction / Definitive cCRT	0.6 / 25.8 / 99.8	0.4 / 28.7 / 99.6	0.6 / 26.8 / 99.7
Prior radiotherapy, %*	<54 Gy	0.6	0	0.6
	54 to ≤66 Gy	92.9	91.6	92.4
	>66 to ≤74 Gy	6.3	8.0	6.9
	>74 Gy	0	0	0
Best response to prior cCRT, %¶	CR / PR / SD / PD	1.9 / 48.7 / 46.6 / 0.4	3.0 / 46.8 / 48.1 / 0	2.2 / 48.1 / 47.1 / 0.3

*Not reported or missing (durvalumab, placebo, total): WHO performance status (0.4% each), prior radiotherapy (0.2%, 0.4%, 0.3%).
†Other: durvalumab, 2.5%; placebo, 2.1%; total, 2.4%. ‡No sample collected or no valid test result. ¶Not evaluable/not applicable: durvalumab, 2.3%; placebo, 2.1%; total, 2.2%.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TC, tumor cell; TC ≥25%, ≥25% PD-L1 expression on tumor cells; TC <25%, <25% PD-L1 expression on tumor cells.

PFS by BICR (Primary Endpoint; ITT)



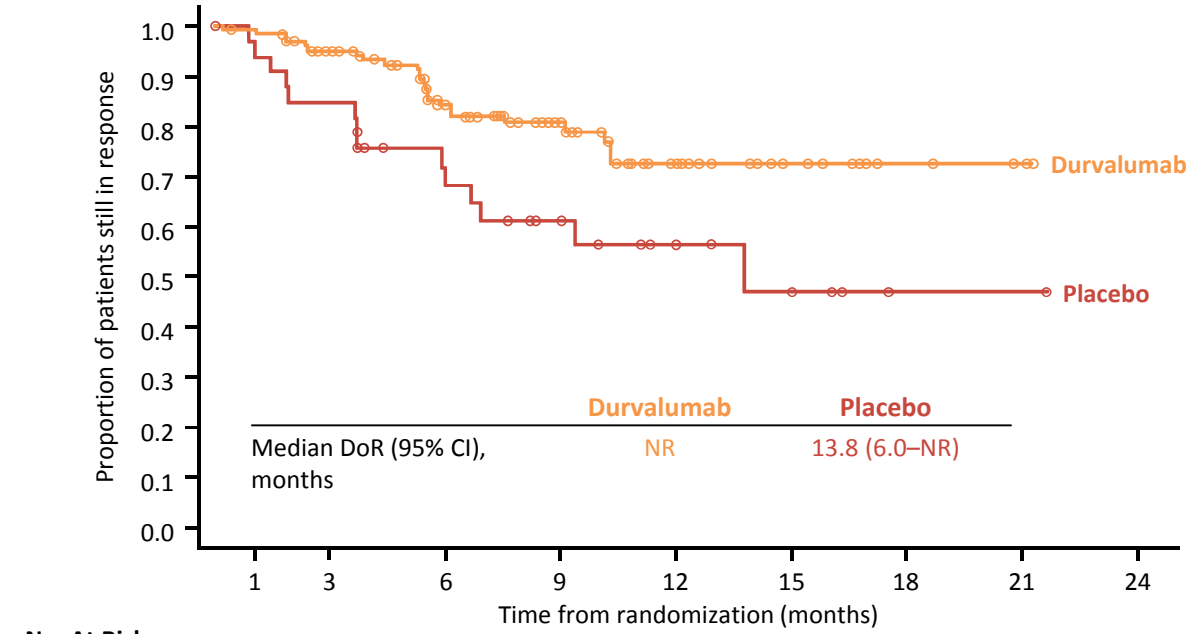
Antitumor Activity by BICR (ITT)



	Durvalumab (N=443)*	Placebo (N=213)*
Best overall response, n (%)		
Complete response	6 (1.4)	1 (0.5)
Partial response	120 (27.1)	33 (15.5)
Stable disease	233 (52.6)	119 (55.9)
Progressive disease	73 (16.5)	59 (27.7)
Non-evaluable	10 (2.3)	1 (0.5)
Duration of response, months		
Median (95% CI)	NR	13.8 (6.0–NR)
Ongoing response at data cutoff, %†		
At 12 months	72.8	56.1
At 18 months	72.8	46.8

*Patients with measurable disease at baseline. †Percentages calculated by Kaplan-Meier method.

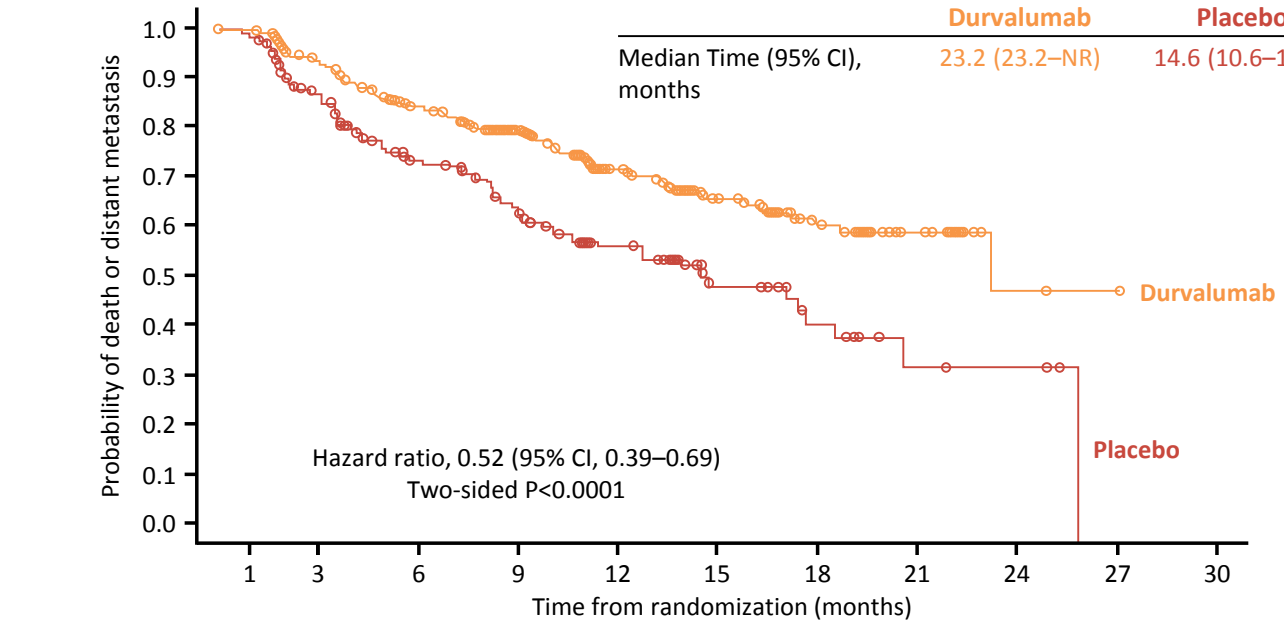
Duration of Response by BICR (ITT)



No. At Risk								
Durvalumab	126	109	77	49	24	12	4	2	0
Placebo	34	28	19	13	7	5	1	1	0

NR, not reached.

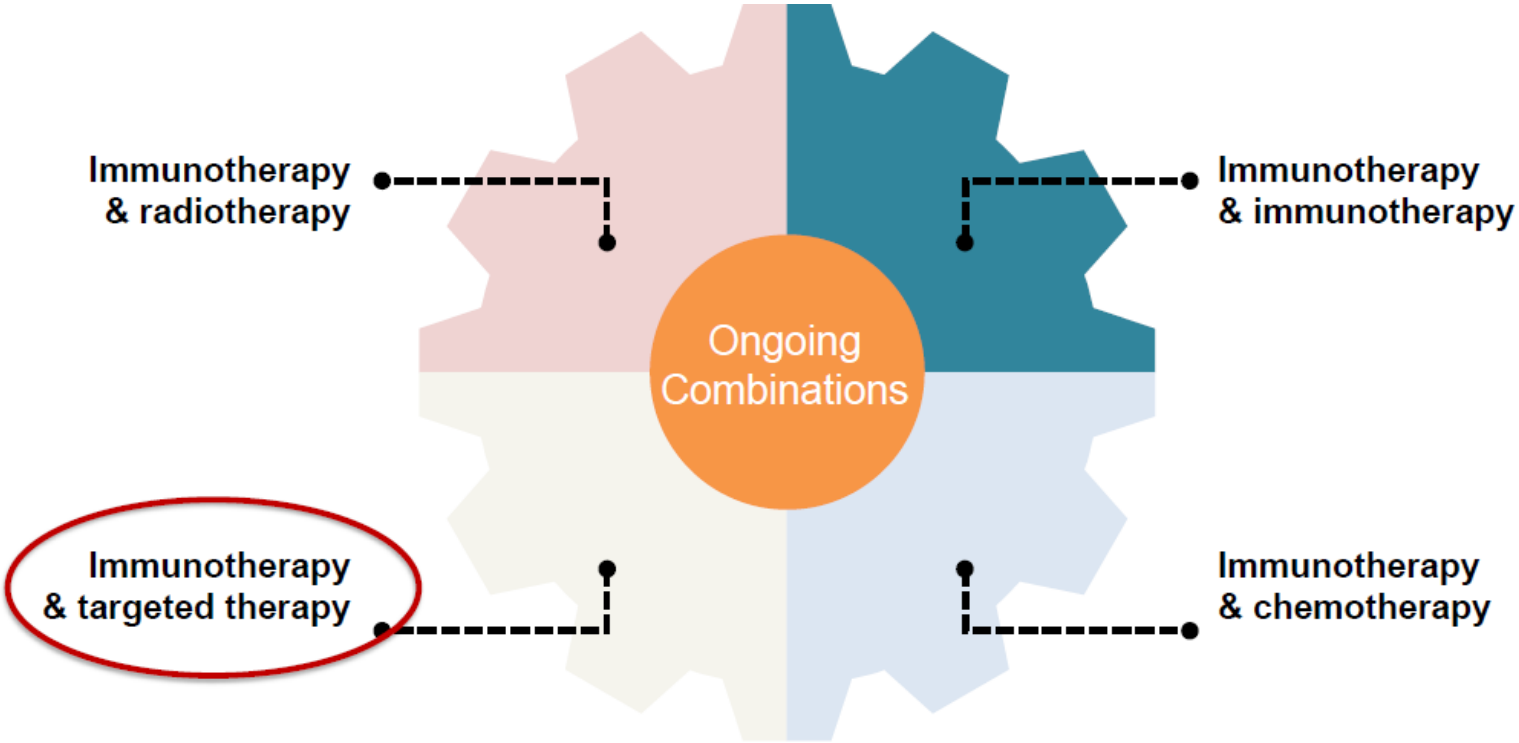
Time to Death or Distant Metastasis by BICR (ITT)



Summary

- Durvalumab demonstrated a statistically significant and robust improvement in PFS of >11 months versus placebo (HR 0.52; P<0.0001) at a planned interim analysis
  - The 12-month PFS rate was 55.9% with durvalumab and 35.3% with placebo, and the 18-month PFS rate was 44.2% and 27.0%, respectively
- PFS improvement with durvalumab was observed across all pre-specified subgroups, including patients who were unexpected to respond
  - e.g. non-smokers and patients with PD-L1 low/negative expression status
- Durvalumab demonstrated clinically meaningful improvement in ORR of 12% (P<0.001), with durable responses versus placebo (median DoR not reached vs 13.8 months)
- Patients receiving durvalumab had a lower incidence of new lesions, including new brain metastases, compared with patients receiving placebo
- Durvalumab was well tolerated with a manageable safety profile compared with placebo

Targeted therapies and I-O

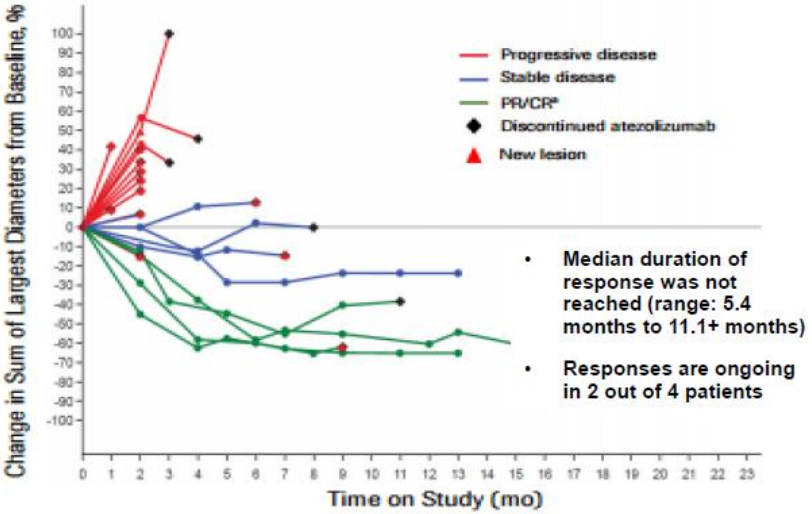


1. Lu H. *Front Immunol.* 2014;5:1-5. 2. Melero I, et al. *Nat Rev Cancer.* 2015;15(8):457-472. 3. Drake CG. *Ann Oncol.* 2012;23 Suppl 8:viii41-viii46, 4. Vanneman M, et al. *Nat Rev Cancer.* 2012;12(4):237-251. 5. Sznol M, et al. *Clin Cancer Res.* 2013;19(19):5542. 6. Formenti SC, et al. *J Natl Cancer Inst.* 2013;105(4):256-265. 7. Kang J, et al. *J ImmunoTher Cancer.* 2016;4:51.

Targeted therapies and I-O

Atezolizumab + Cobimetinib in KRAS^{mut} mCRC

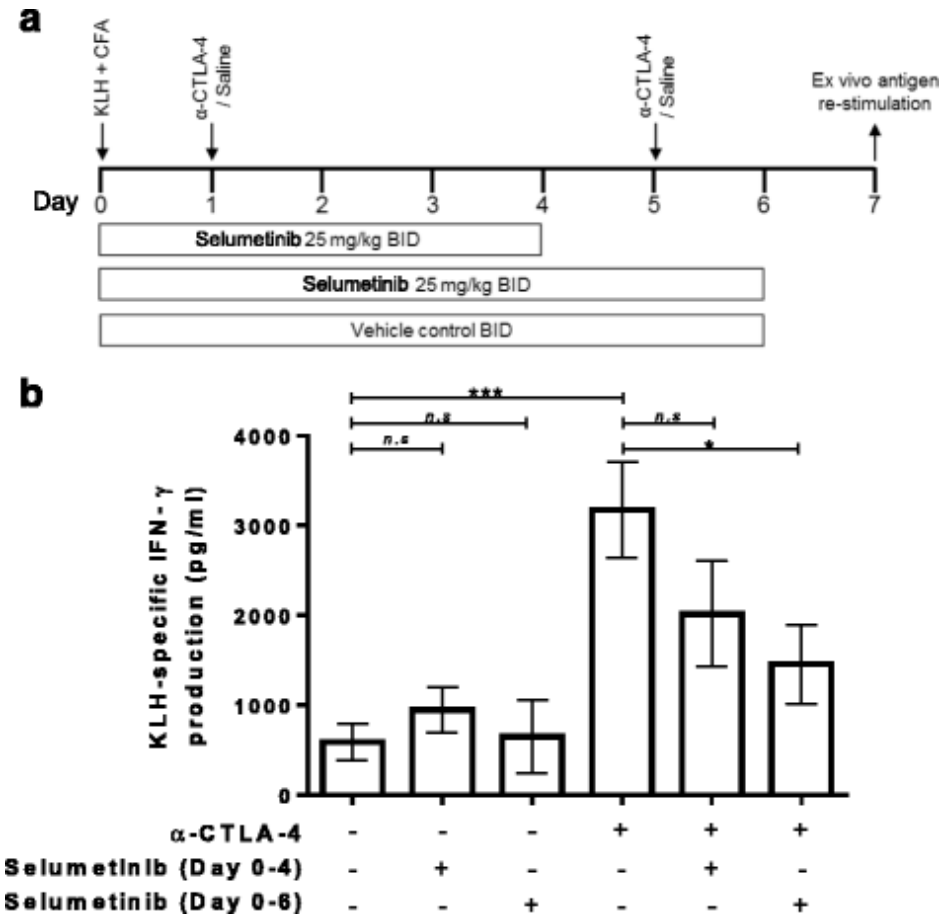
Confirmed Response per RECIST v1.1	*KRAS*-Mutant CRC (n = 20)	All CRC Patients (N = 23)
ORR	20%	17%
SD	20%	22%
PD	50%	52%
NE	10%	9%



Bendell JC, et al. *J Clin Oncol*. 2016;34(Suppl): Abstract 3502.

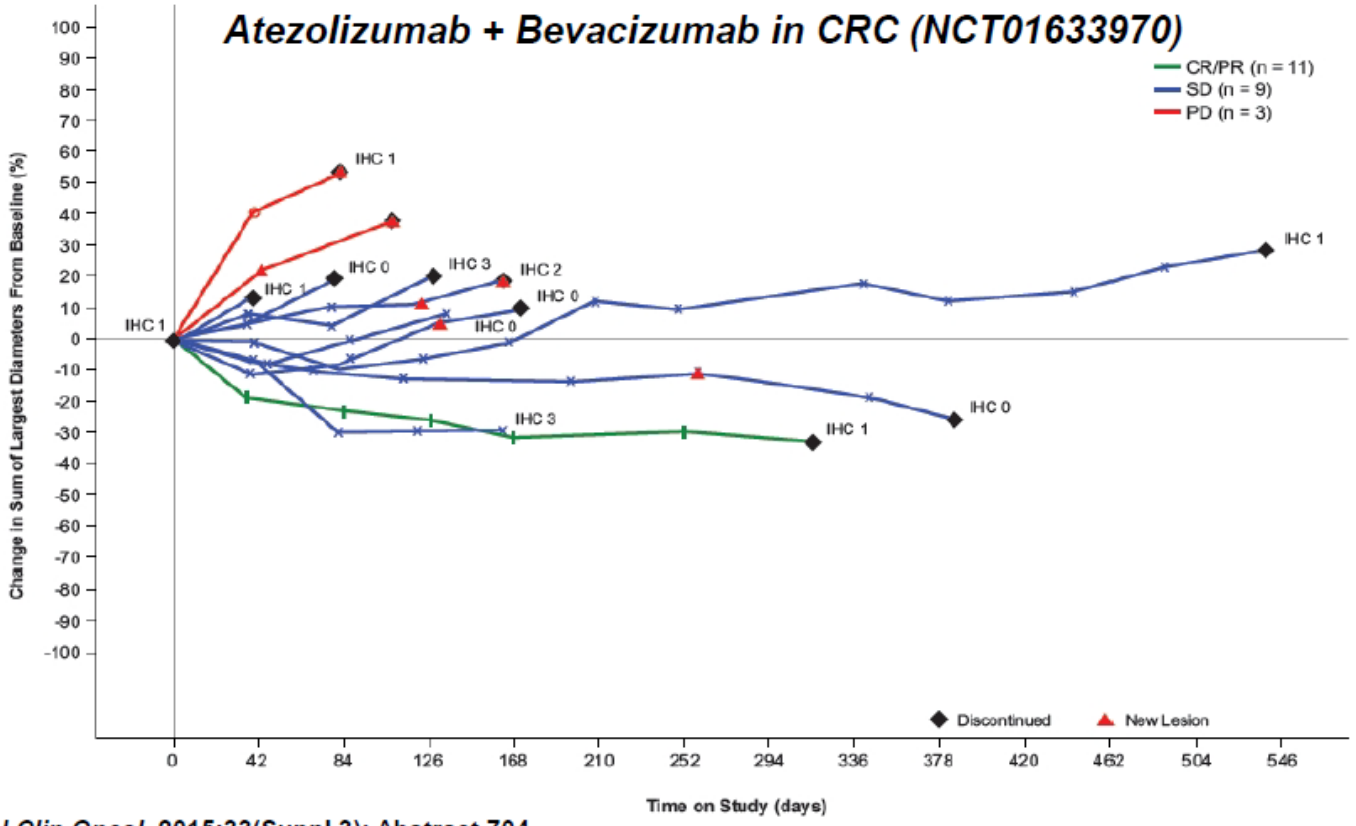
Targeted therapies and I-O

MEK inhibition triggers anti-tumour immunity



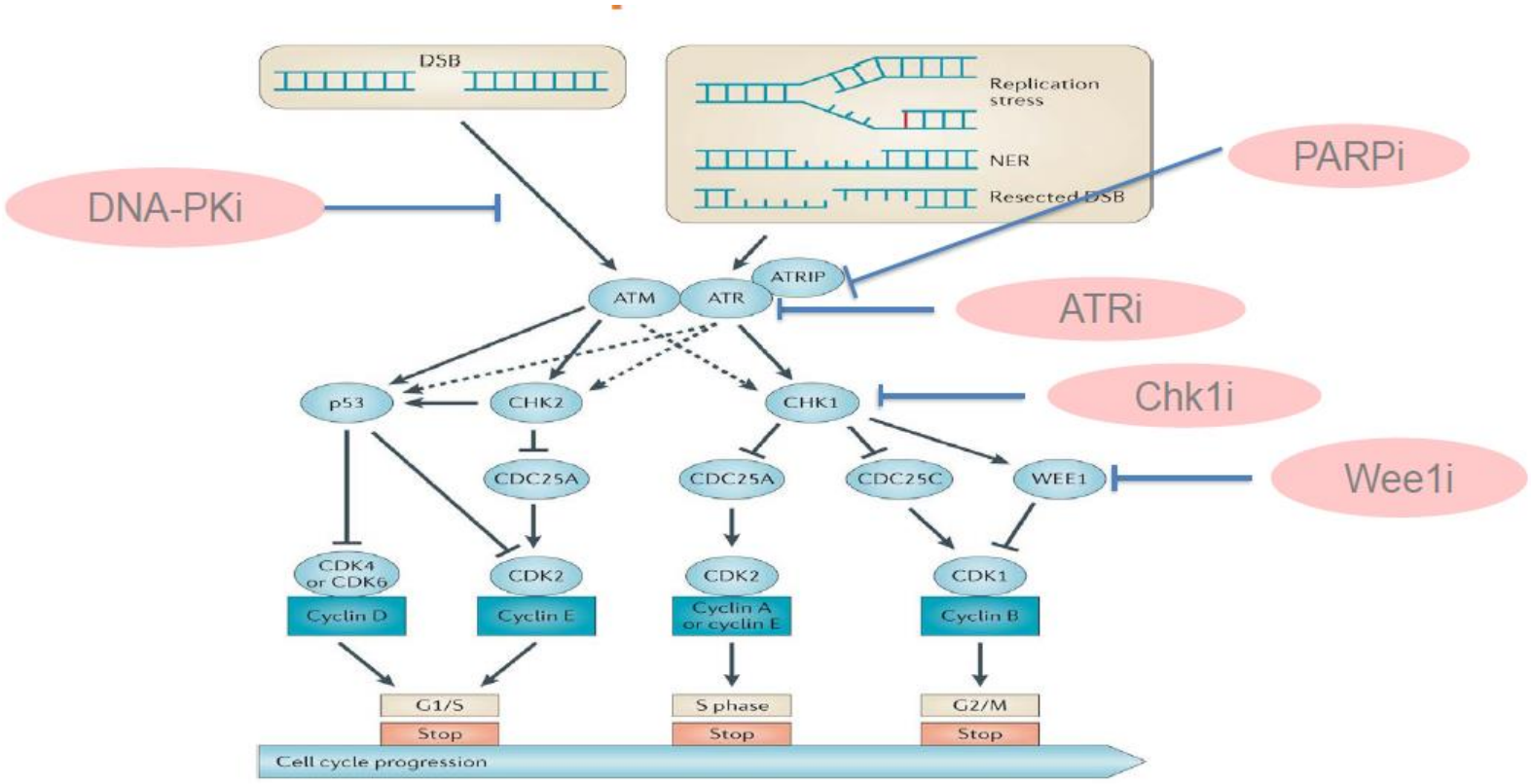
Poon E. Et al Journal for ImmunoTherapy of Cancer20175:63

Antiangiogenesis and I-O



Bendell JC, et al. *J Clin Oncol*. 2015;33(Suppl 3): Abstract 704.

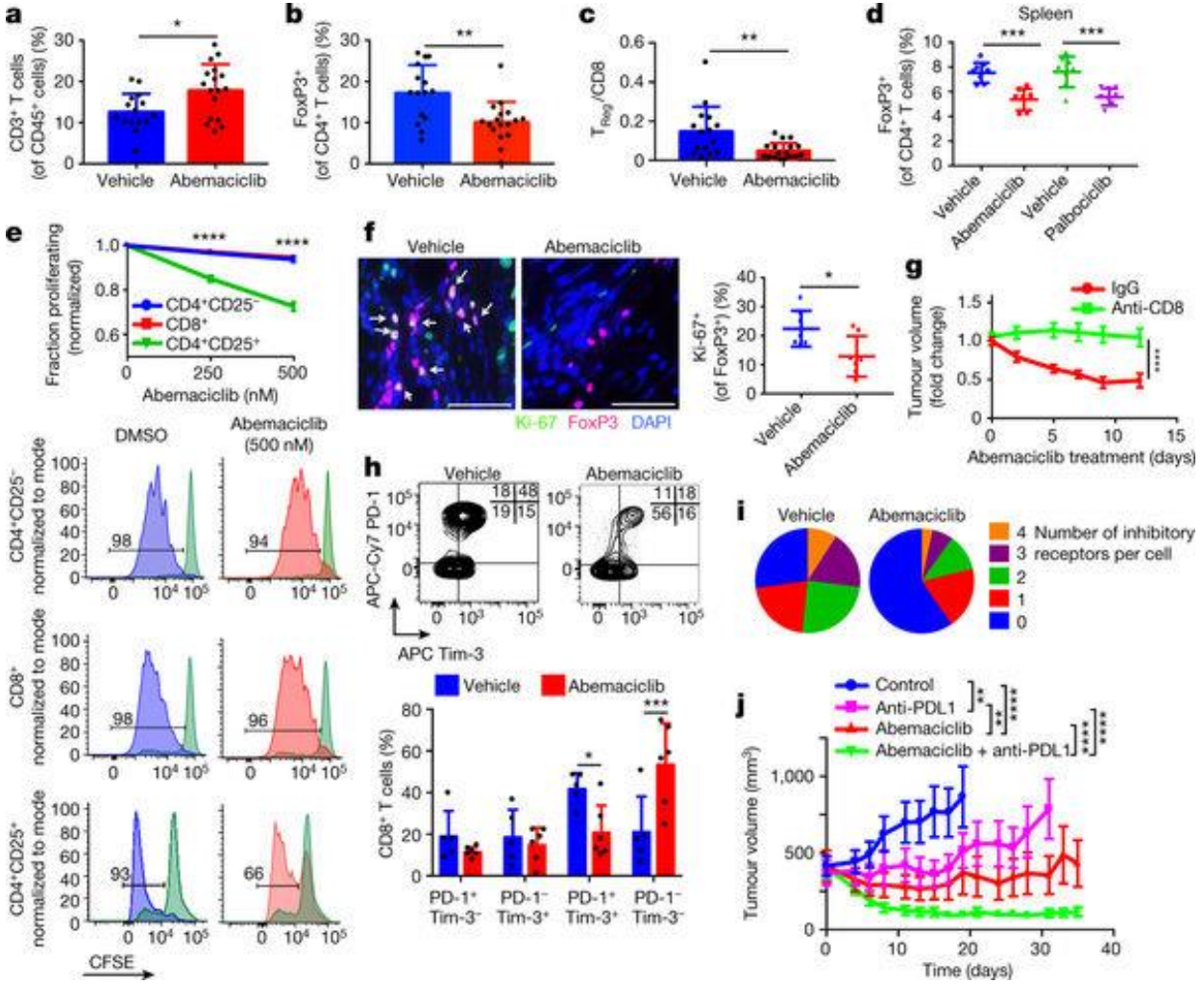
PARP inhibitors and I-O



Curtin NJ, et al. *Nat Rev Cancer.* 2012;12(12):801–817.

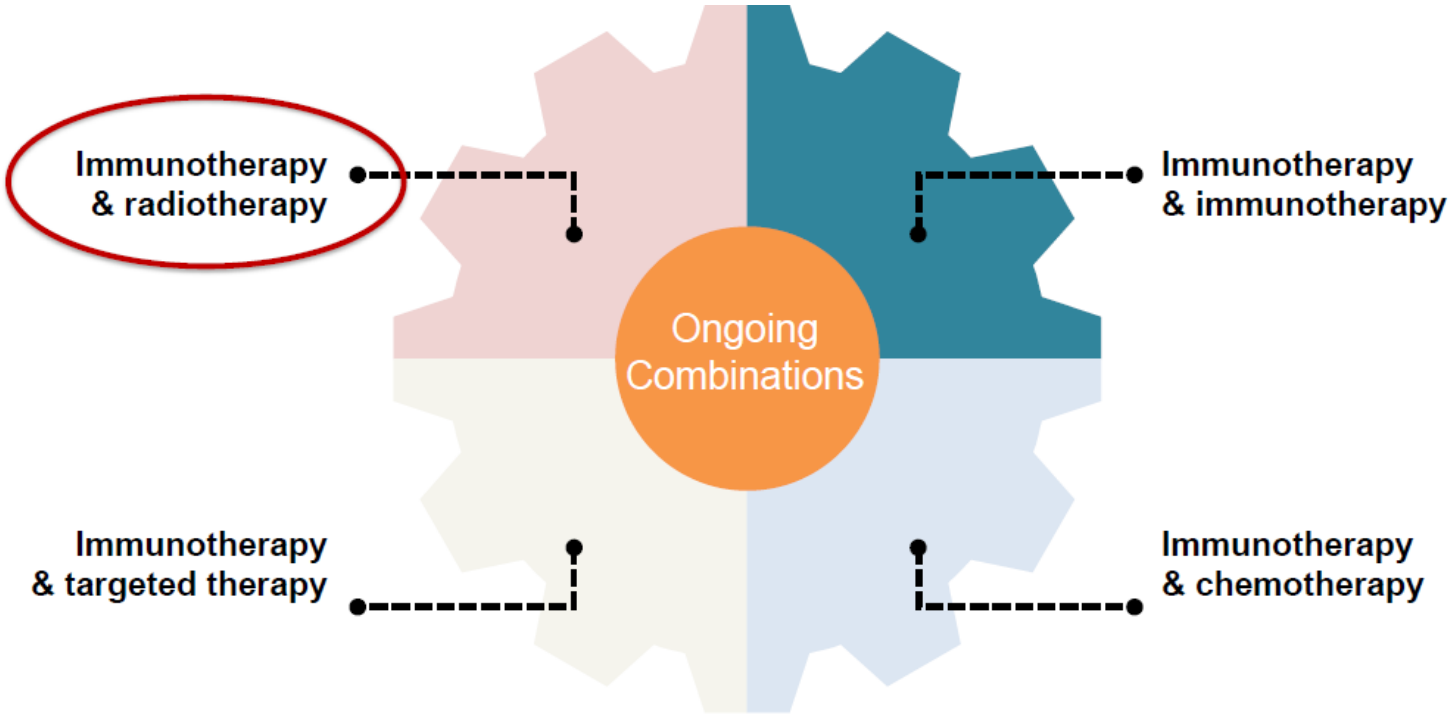
CDK 4-6 inhibitors and I-O

CDK4/6 inhibition triggers anti-tumour immunity



Goel S. Et al Nature 548, 471–475 (24 August 2017)

Radiotherapy and I-O



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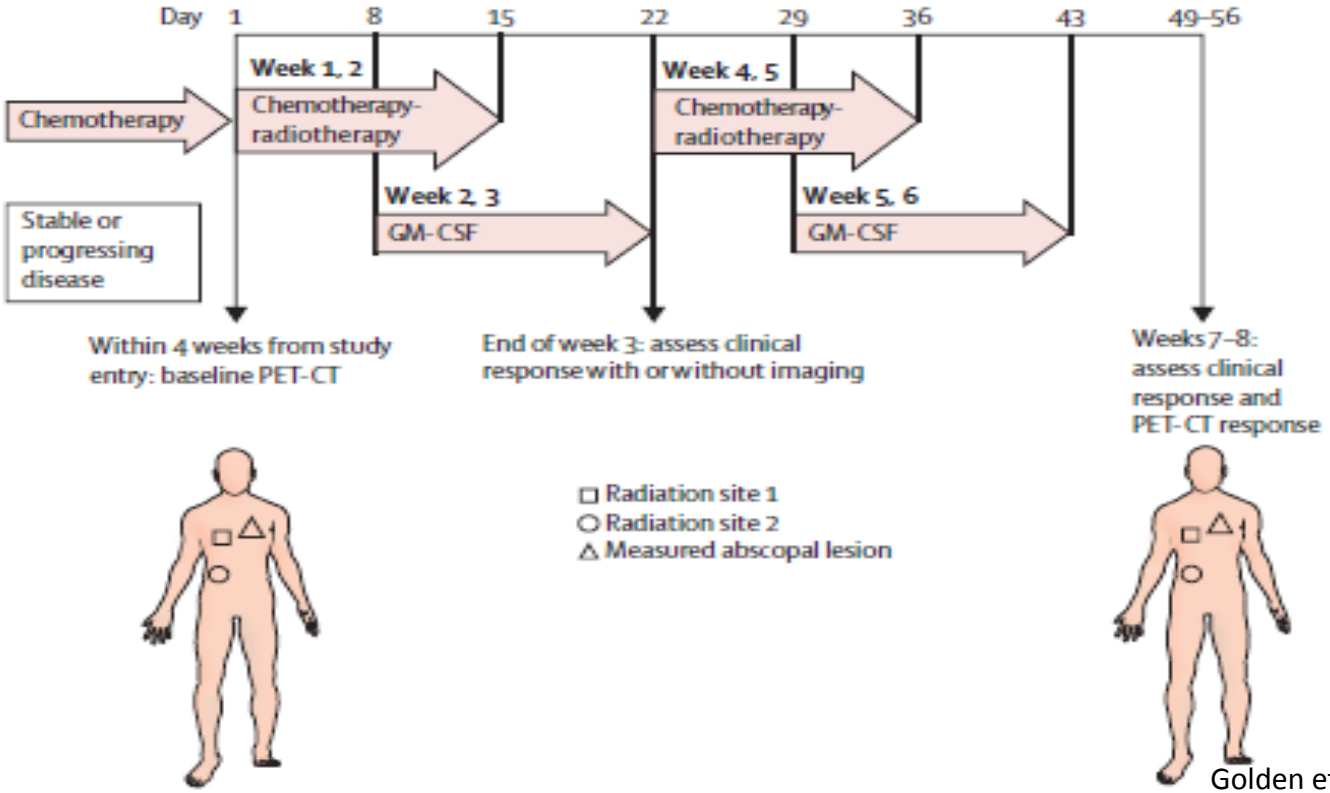
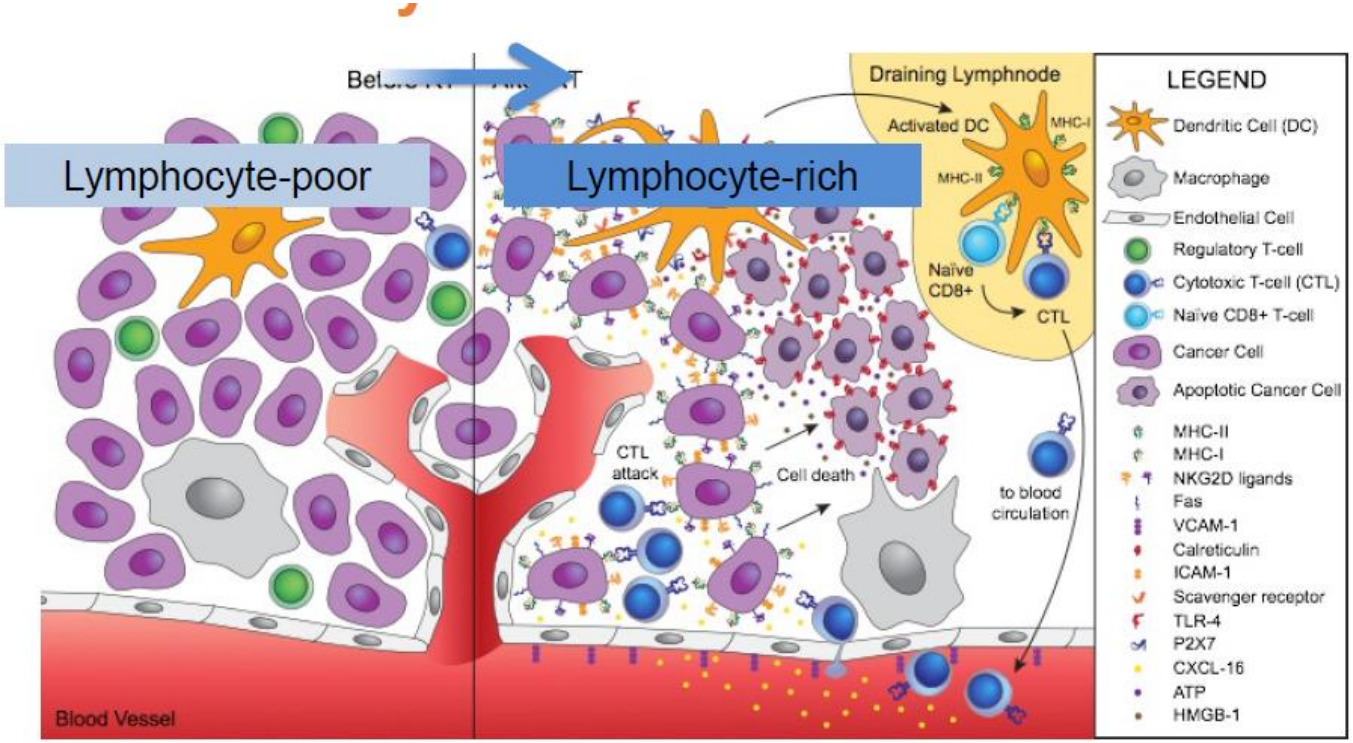
Abscopal effect

- Proof-of concept trial
- Included patients with stable or progressing metastatic solid tumours (≥3 measurable lesions) on single-agent chemotherapy or hormone therapy
- Simon two-stage design: ≥1 abscopal response in first 10 patients (stage 1)



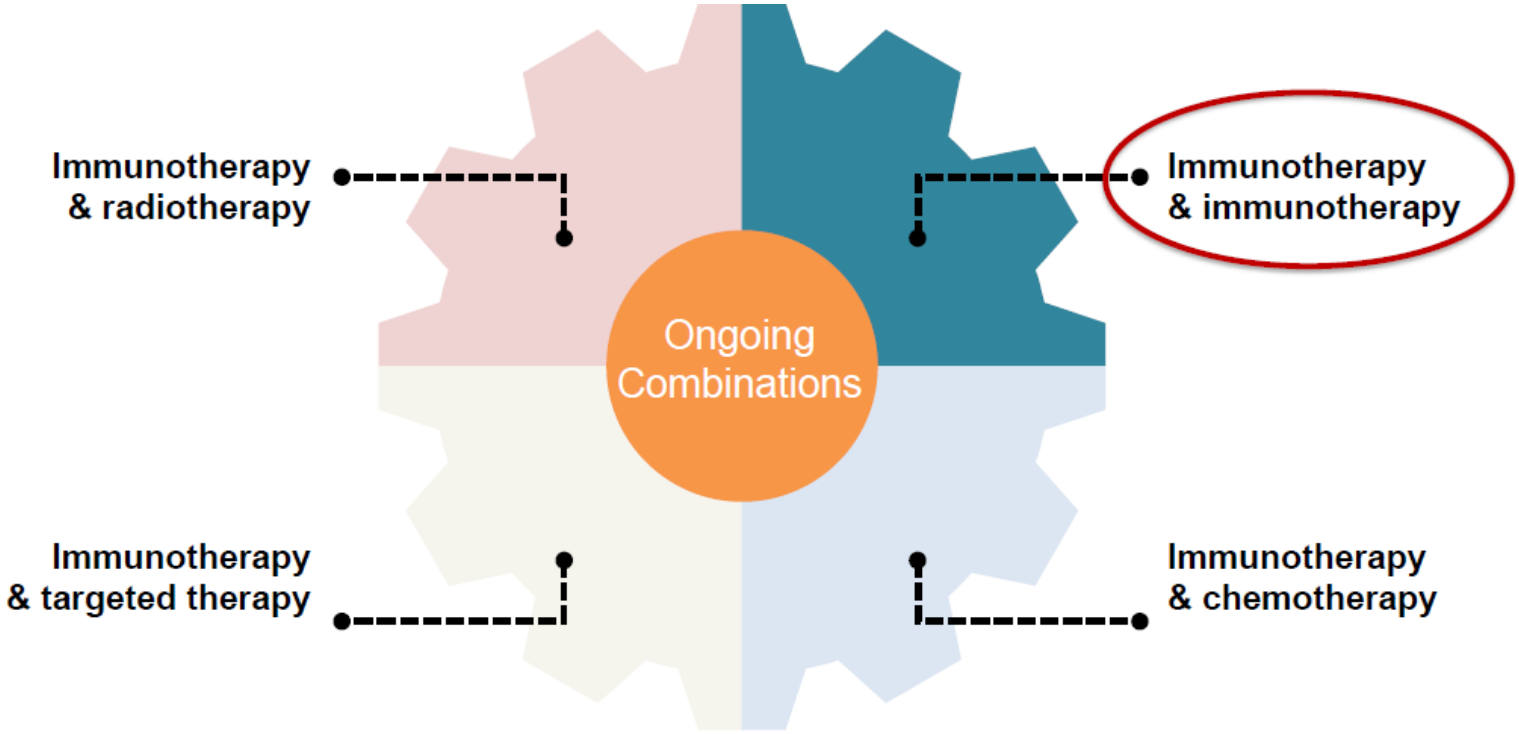
Golden et al. Lancet Oncol 2015;16:795–803

“Boosting” after “priming”



Demaria S, et al. *Front Oncol*. 2012;2:153.

I-O combination



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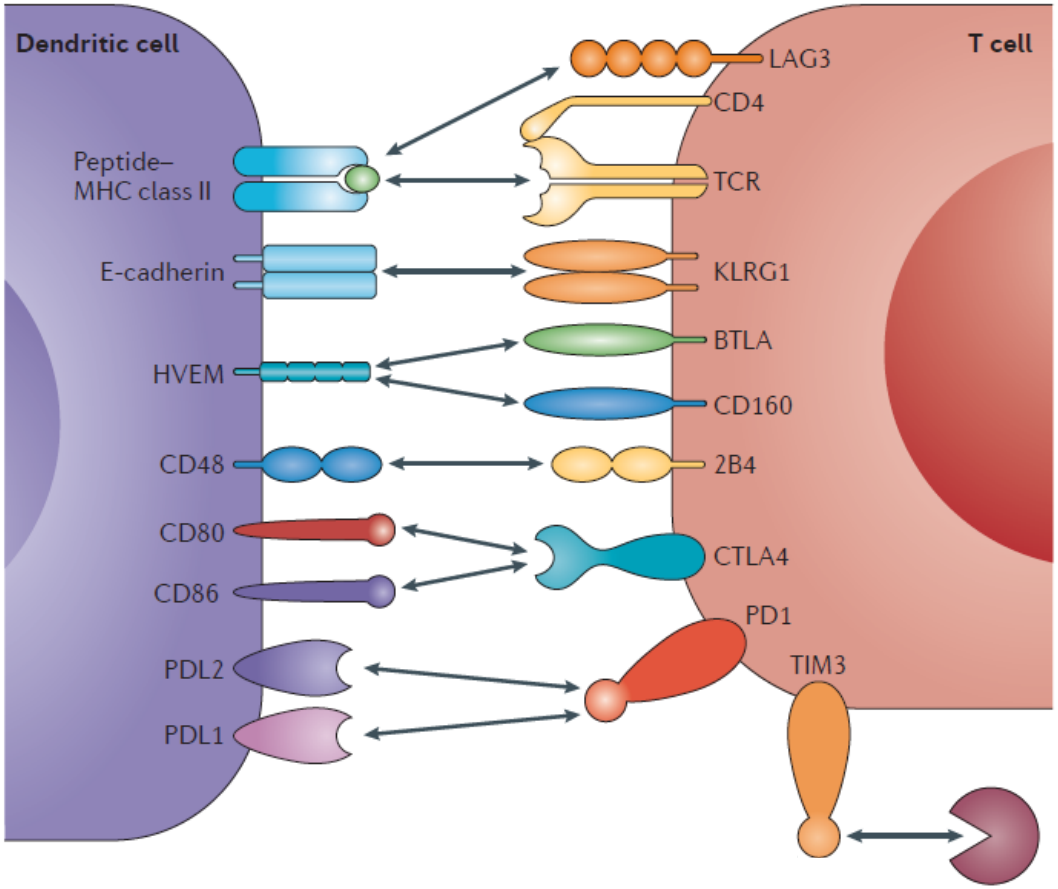
I-O combination

αPD-1/PD-L1 + αCTLA-4 Phase III Trials	Tumor Type
Nivolumab + ipilimumab	Neoadjuvant: NSCLC 1L: NSCLC, HNSCC,Urothelial cancers, RCC, Gastric, MPM 2L: ED-SCLC, NSCLC after progression on EGFR TKI (T790M-), GBM
Durvalumab + tremelimumab	1L: NSCLC, HNSCC, Urothelial cancers, ED-SCLC (+ chemo) 2L: HNSCC

LAG3: CD4 homologue, binding MHC II

Expression

- On exhausted T cells
- On TIL
- On T regs
- On NK



Function

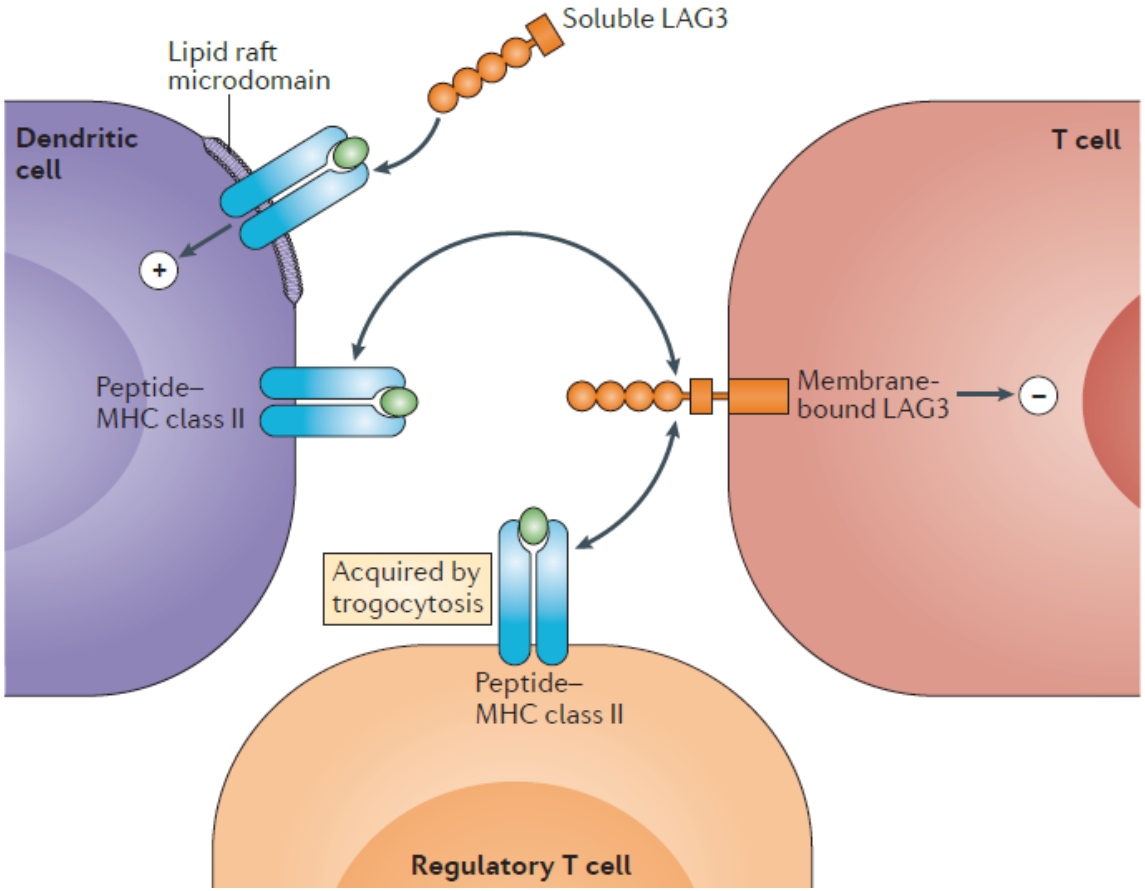
- Confers a Treg function on CD4 naïve T cells

LAG3 negatively regulates

- T-cell activation
- Proliferation
- Homeostatic expansion

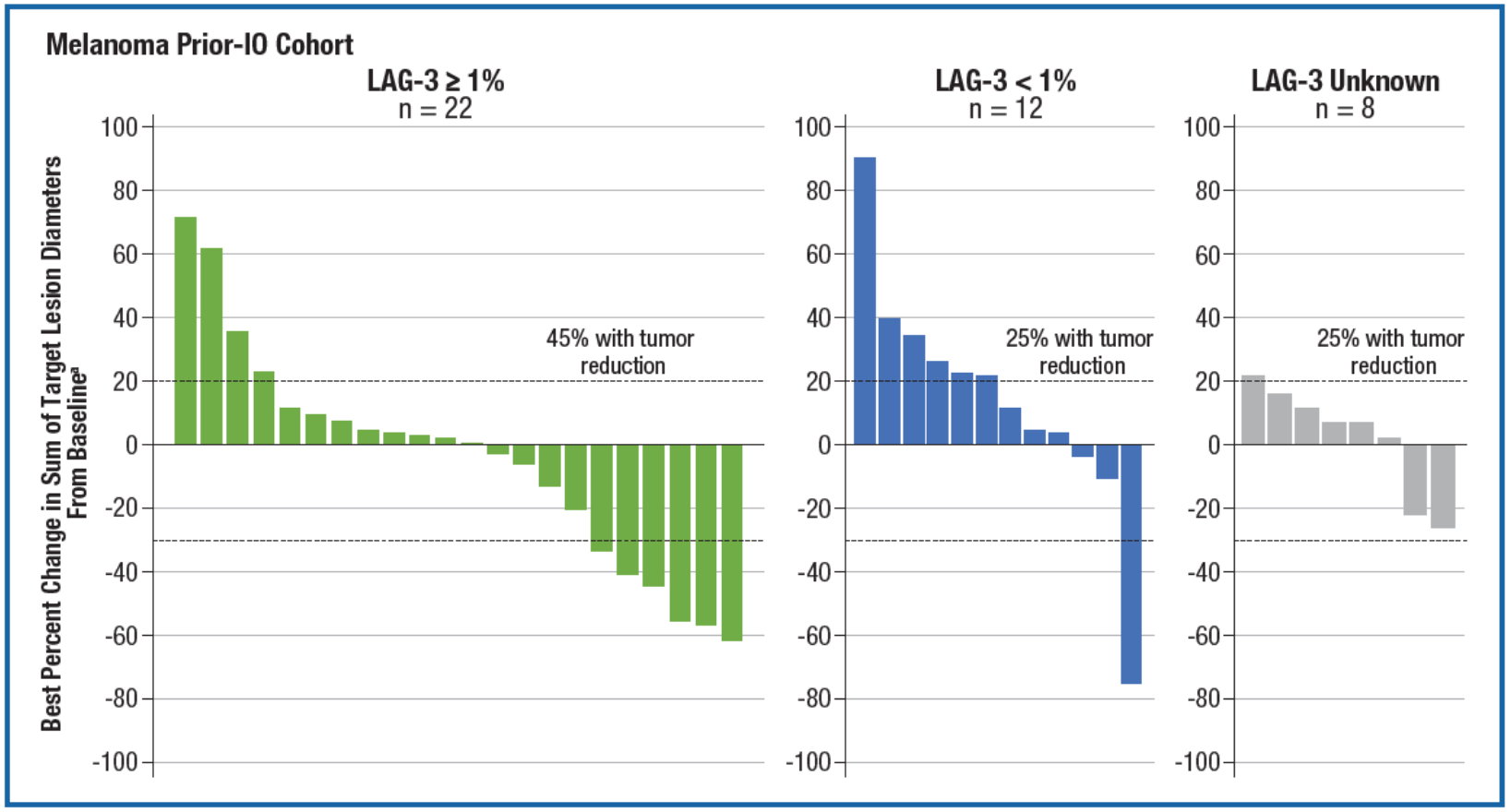
Adapted from Nature Reviews Immunology 15; 2015: 45-56

Soluble LAG3 is an immunoadjuvant



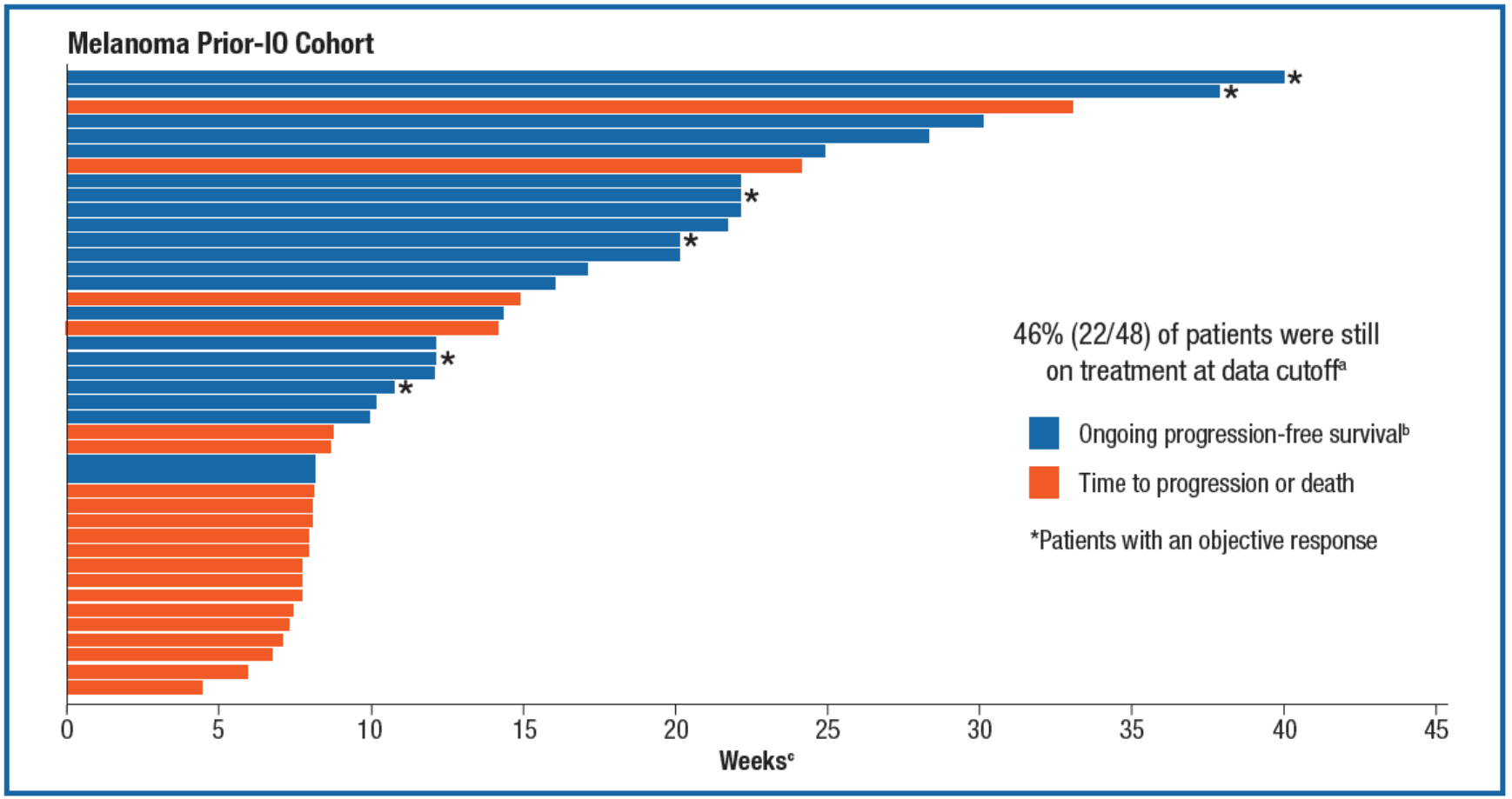
Adapted from Nature Reviews Immunology 15; 2015: 45-56

I-O combination



[a]Six patients had clinical progression prior to their first scan and are not included in the plot. One patient with best change from baseline > 30% had an unconfirmed best response of SD.

I-O combination



[a]Six patients had clinical progression prior to their first scan and are not included in the plot. [b]Censored on last visit. [c]Evaluations are planned for every 8 weeks.

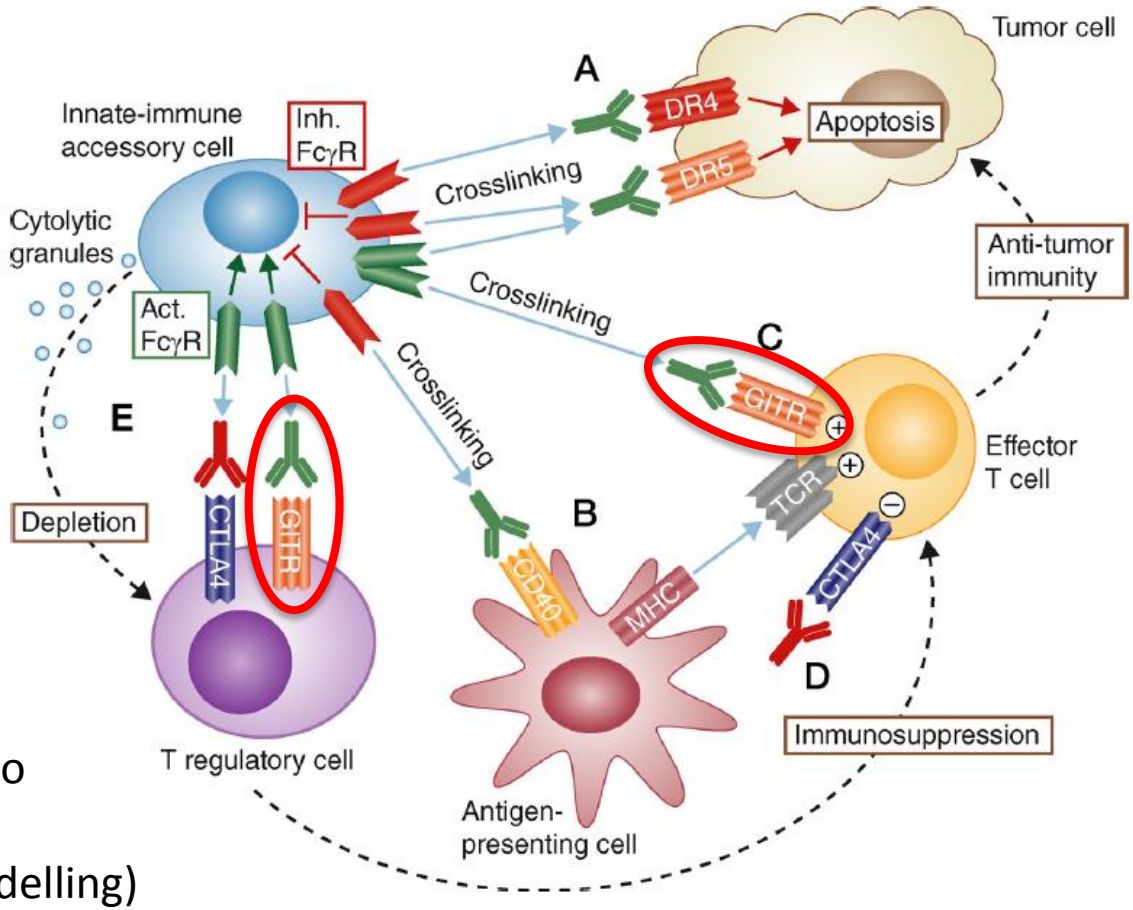
GITR

Expression of GITR

Cell type		
	Naïve	**Activated**
Regulatory T cells	High	Very high
T cells (CD4/CD8)	Intermediate	High
NK cells	Intermediate	High
Granulocytes	Intermediate	High
Mast cells	Intermediate	Intermediate
Eosinophils	Intermediate/low	
Basophils	Intermediate/low	
Monocytes	Low	Intermediate

GITR

Function:



On T regs:
Diverts the cells to Th9 phenotype (chromatin remodelling)

On T eff cells:
Increases survival (protection from activation-induced cell death (AICD) and function

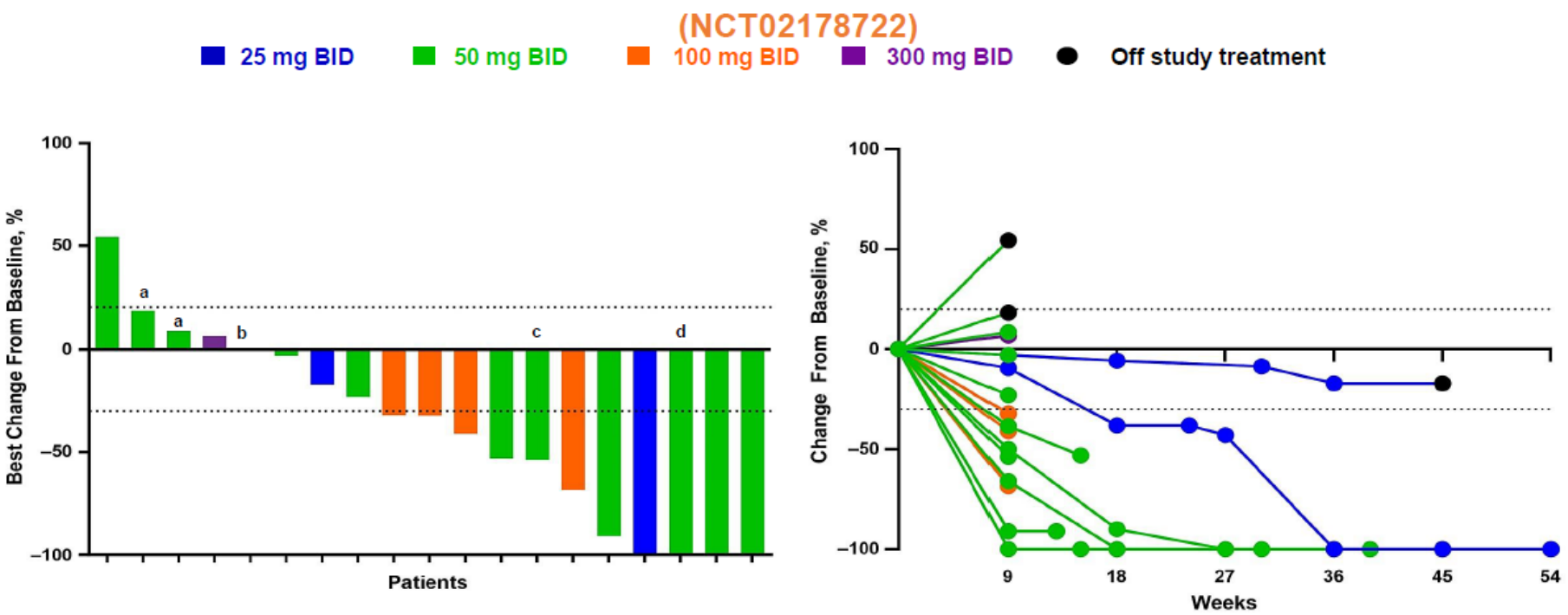
Boosts the effect of CD4 helpers

CA009-002: for solid tumors alone or in combination with Nivolumab

unclear role

J Ex Med; 210(9), 1695–1710

Anti IDO-1 and I-O



[a]Overall response is PD (SD for target lesions; PD for non-target lesions).
[b]Overall response is PD (target lesions not assessed; PD per new lesions).
[c]Overall response is PD (PR for target lesions; PD per new lesions).
[d]Overall response is PR (CR for target lesions; non CR/non PD for non-target lesions).

Gangadhar TC, et al. Presented at: 2015 SITC Annual Meeting; November 4-8, 2015; National Harbor, MD. Abstract O7.

Anti IDO-1 and I-O

Sunday June 4, Clinical Science Symposium; Hall D1 (9:45 AM to 11:15 AM)

Abstract 105: A phase Ib dose escalation study of combined inhibition of IDO1 (GDC-0919) and PD-L1 (atezolizumab) in patients (pts) with locally advanced or metastatic solid tumors

Presenter: Howard A Burris

Monday, June 5, GU (nonprostate); Arie Crown Theater (8:00 AM to 11:00 AM)

Abstract # 4503: Epacadostat + pembrolizumab in patients with advanced urothelial carcinoma: Preliminary phase I/II results of ECHO-202/KEYNOTE-037)

Presenter: David C Smith

Monday, June 5, Development Therapeutics; Hall D1 (1:15 PM to 4:15 PM)

Abstract #3003: Epacadostat + nivolumab in patients with advanced solid tumors: Preliminary phase I/II results of ECHO-204

Presenter: Raymond P Perez

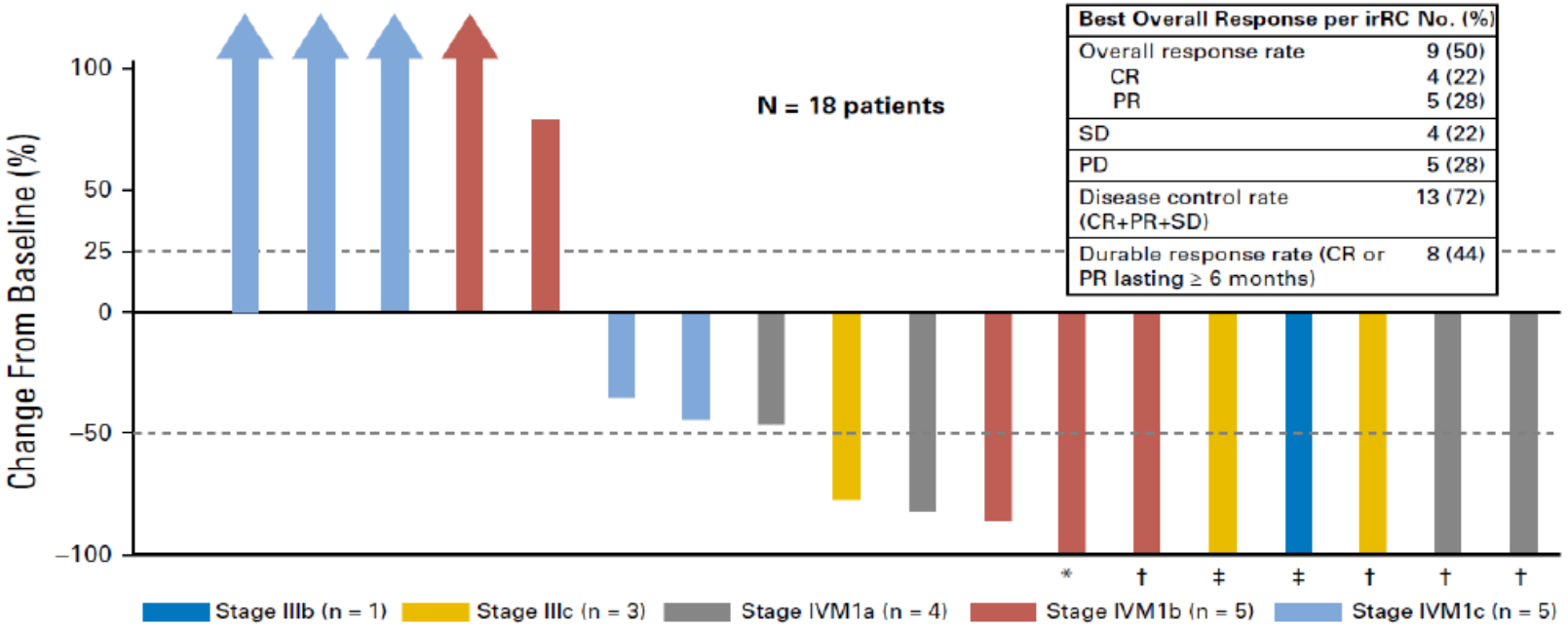
Tuesday, June 6, Clinical Science Symposium; S100a (8:00 AM to 9:30 AM)

Abstract 6010: Epacadostat + pembrolizumab in patients with SCCHN: Preliminary phase I/II results from ECHO-202/KEYNOTE-037.

Presenter: Omid Hamid

Oncolytic virus and I-O

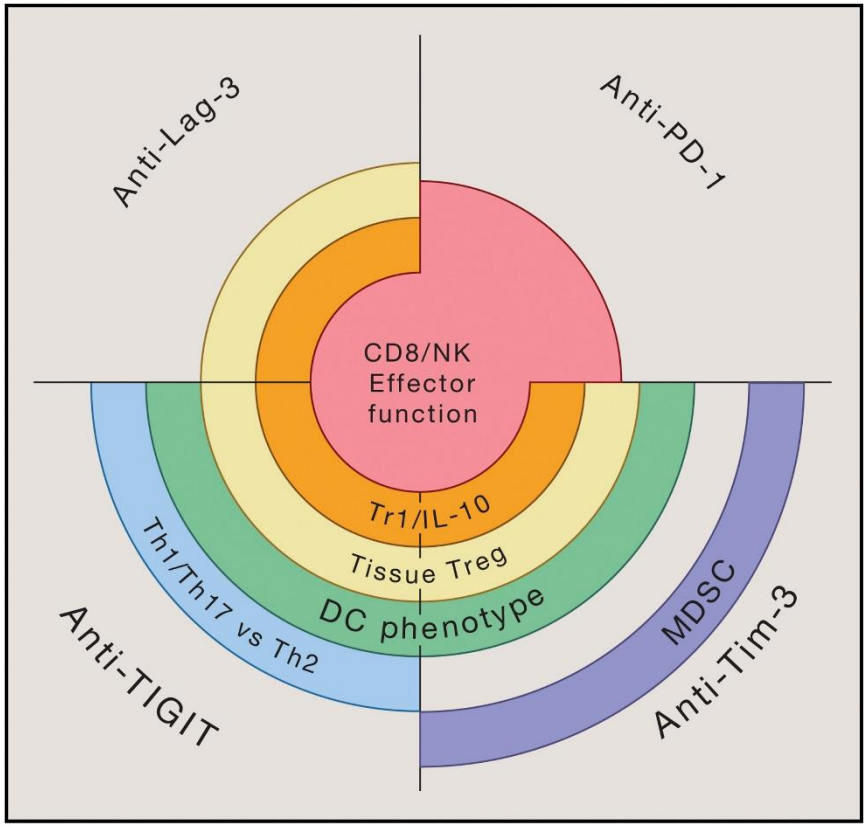
T-VEC (IT) + Ipilimumab (IV)



Puzanov I, et al. *J Clin Oncol*. 2016;34(22):2619-2626.

Other approaches for priming

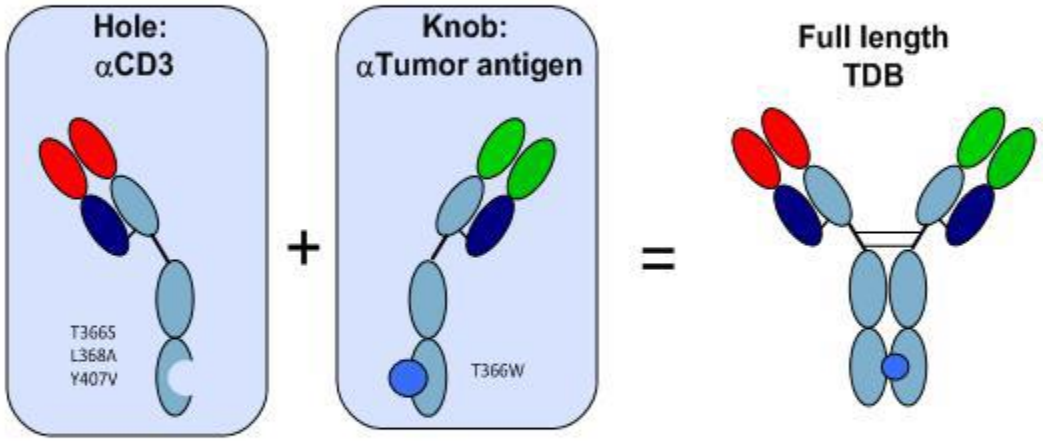
Combination of immune-checkpoints



Andreson Ac et al. Immunity 44, May 17, 2016

Next future

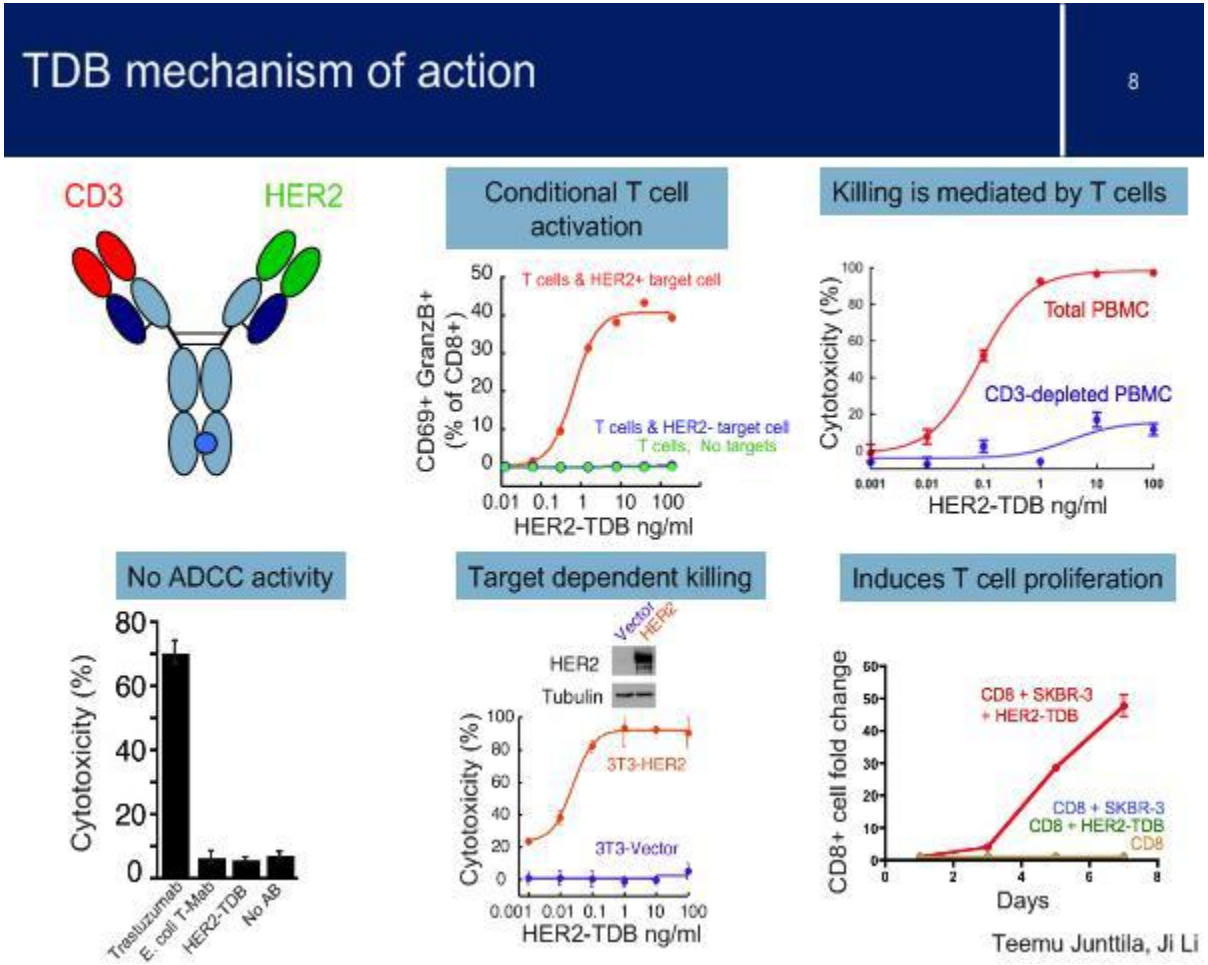
T cell dependent bispecific antibody (TDB) platform



- Produced using modular "knobs into holes" technology
- Effector functions removed (E. coli production / N297A)
- Minimal immunogenic potential
- PK is similar to conventional IgG1

Ridgeway...Carter. 1996 Prot. Engineering
Atwell...Carter. 1997 J. Mol Biol.

Next future


TDB mechanism of action
8
CD3
HER2
Conditional T cell activation
T cells & HER2+ target cell
T cells & HER2- target cell
T cells, No targets
CD69+ GranzB+ (% of CD8+)
HER2-TDB ng/ml
Killing is mediated by T cells
Total PBMC
CD3-depleted PBMC
Cytotoxicity (%)
HER2-TDB ng/ml
No ADCC activity
Cytotoxicity (%)
Trastuzumab
E. coli T-Mab
HER2-TDB
No AB
Target dependent killing
Vector
HER2
HER2
Tubulin
3T3-HER2
3T3-Vector
Cytotoxicity (%)
HER2-TDB ng/ml
Induces T cell proliferation
CD8 + SKBR-3 + HER2-TDB
CD8 + SKBR-3
CD8 + HER2-TDB
CD8
CD8+ cell fold change
Days
Teemu Junttila, Ji Li

Immunogram and immunogenicity

Tumor foreignness
Mutational load

Absence of inhibitory tumor metabolism
LDH, glucose utilization

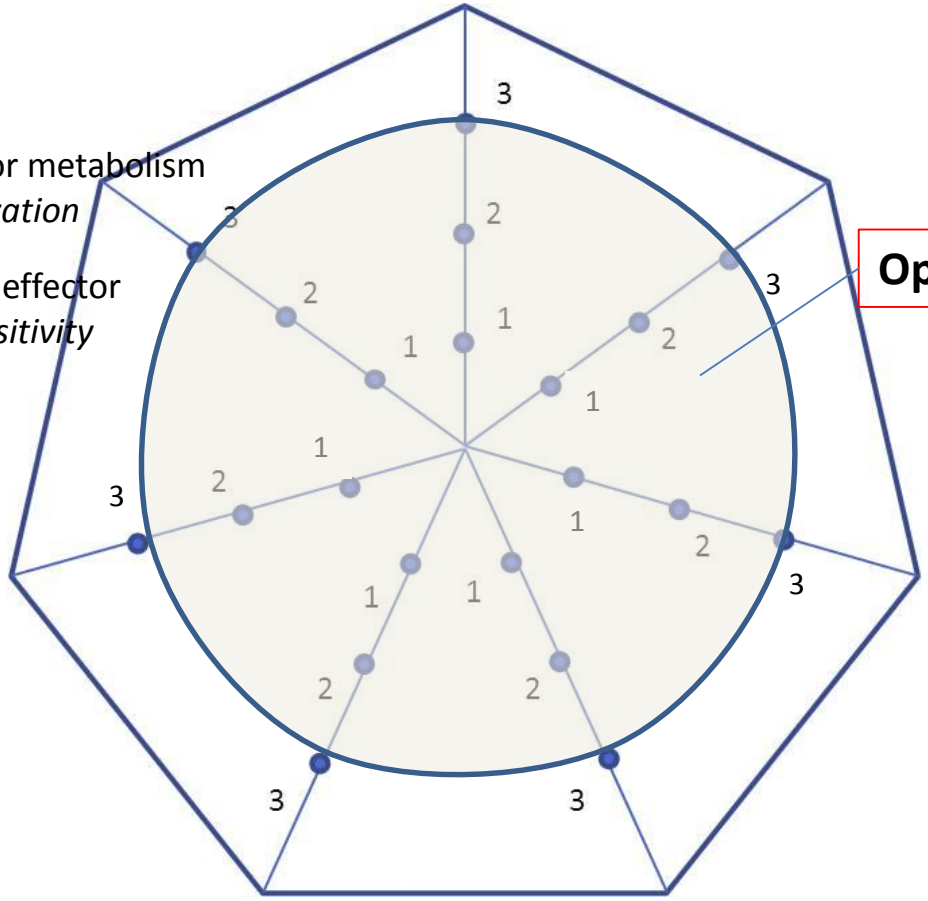
Tumor sensitivity to immune effector
MHC expression, IFN-γ sensitivity

Absence of soluble inhibitors
IL–6, CRP

General immune status
Lymphocyte count

Immune cell infiltration
Intratumoral T cells

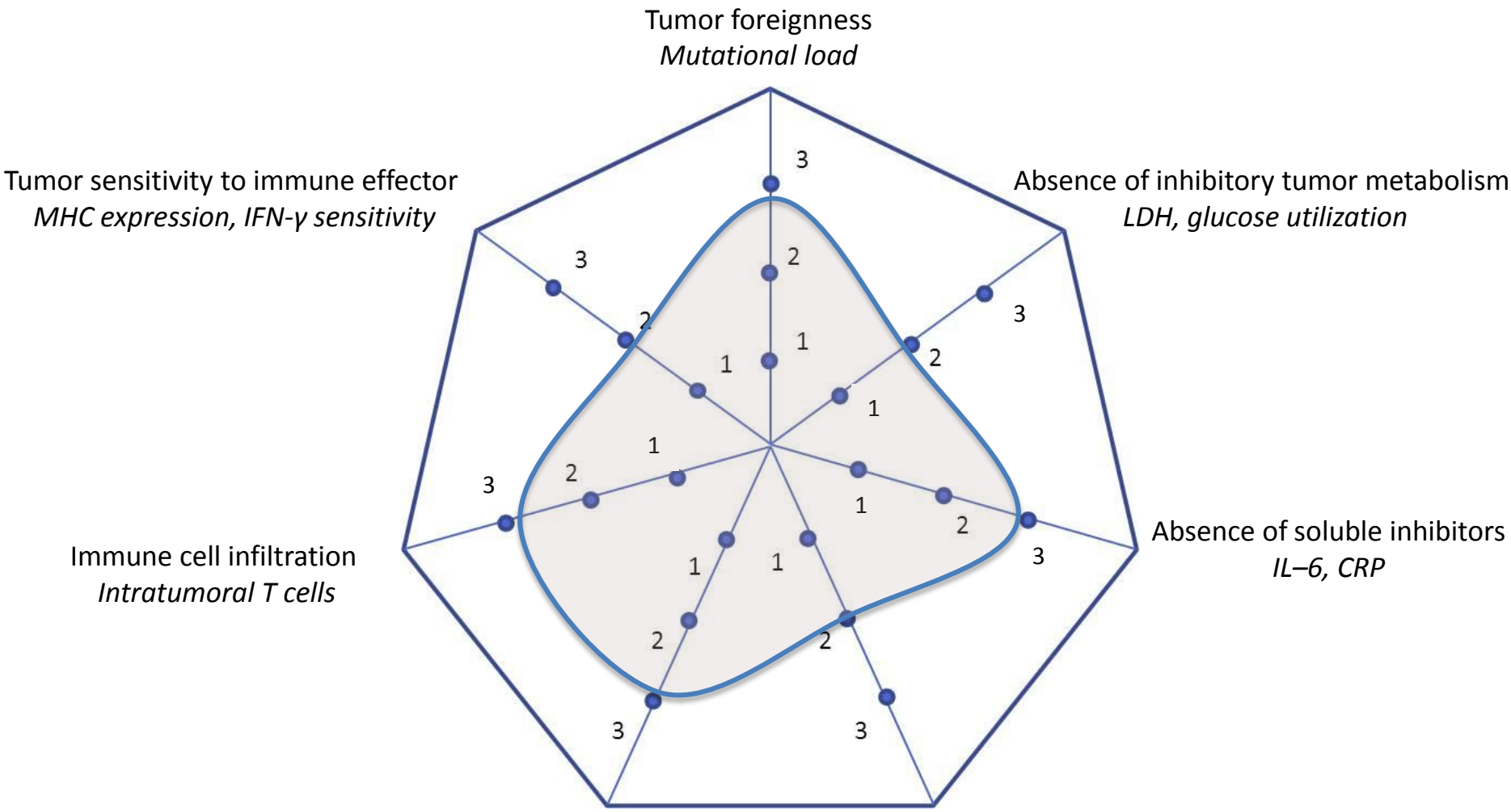
Absence of checkpoints
PD-L1



Optimal Immunogenicity

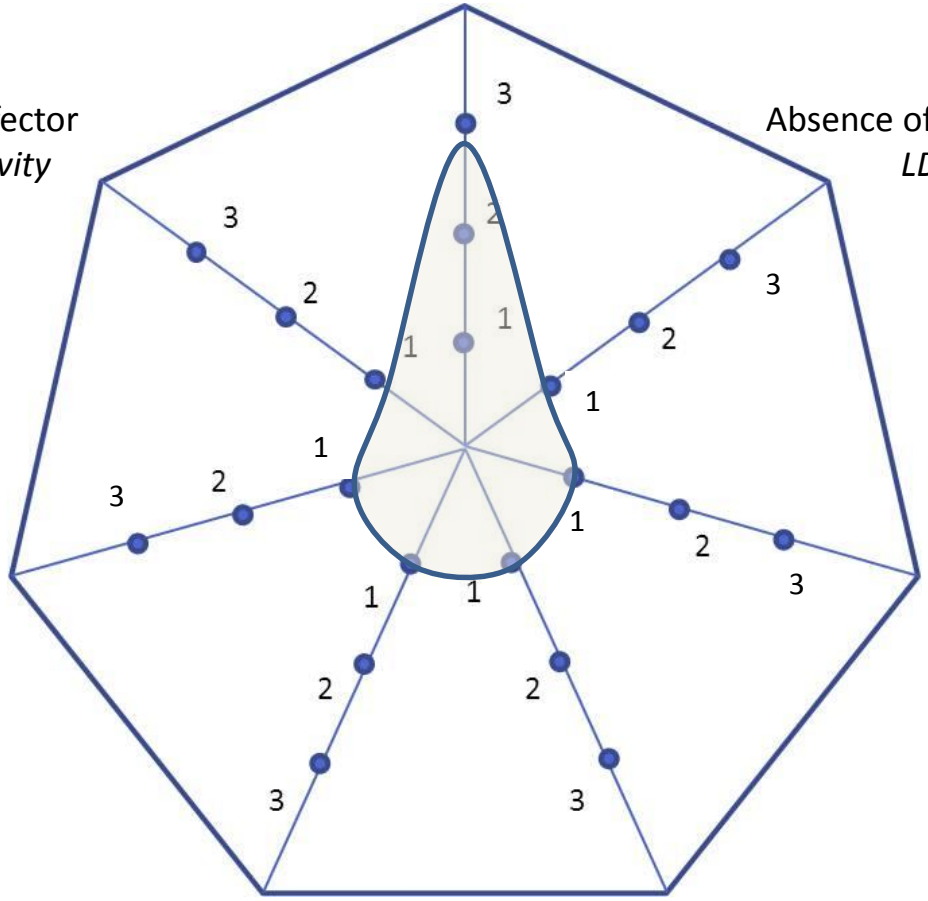
Science 352, 658 (2016)

Immunogram and immunogenicity



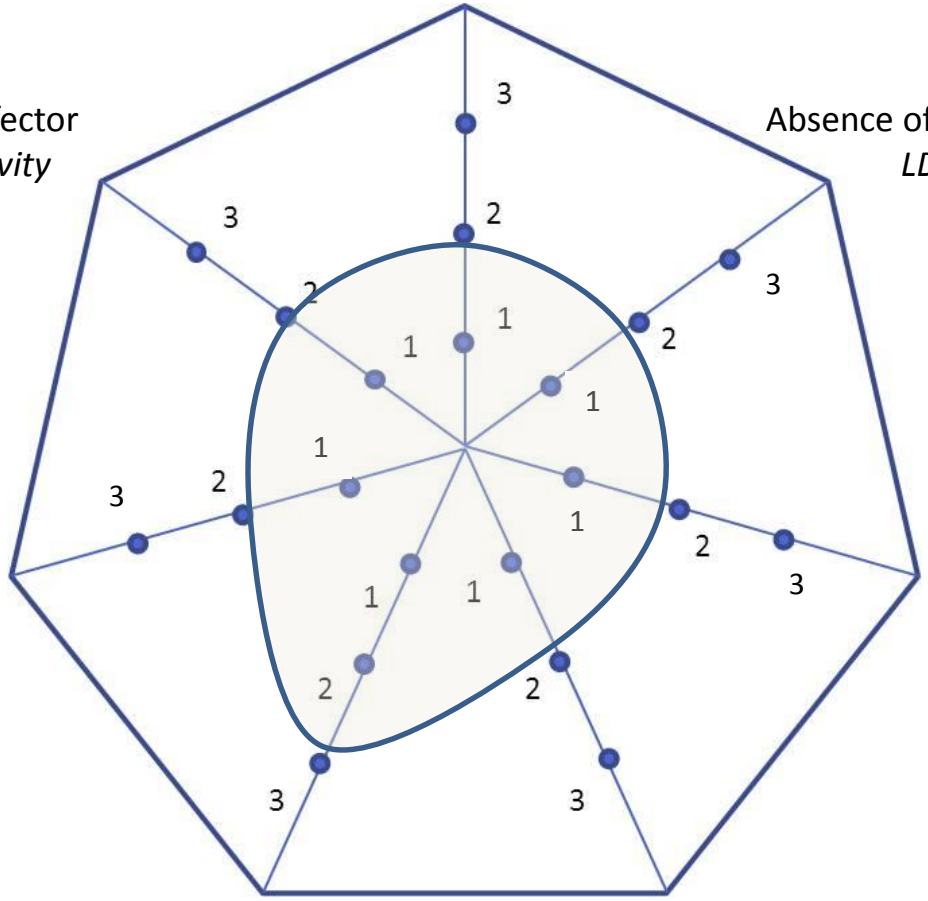
Science 352, 658 (2016)

Immunogram and immunogenicity



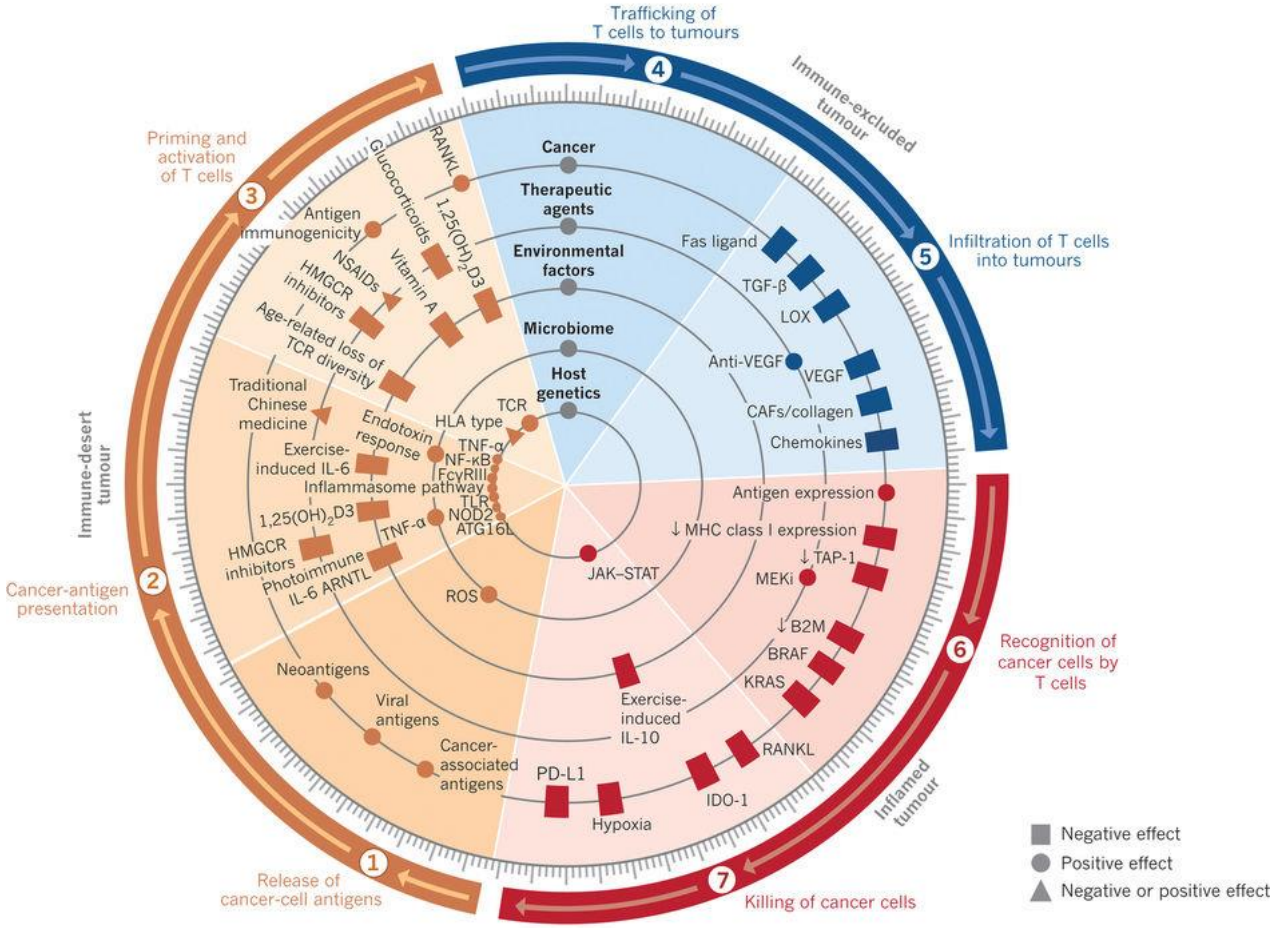
Science 352, 658 (2016)

Immunogram and immunogenicity



Science 352, 658 (2016)

From immunogram to cancer-immune set point



Chen D et al. Nature 541, 321–330 (2017)

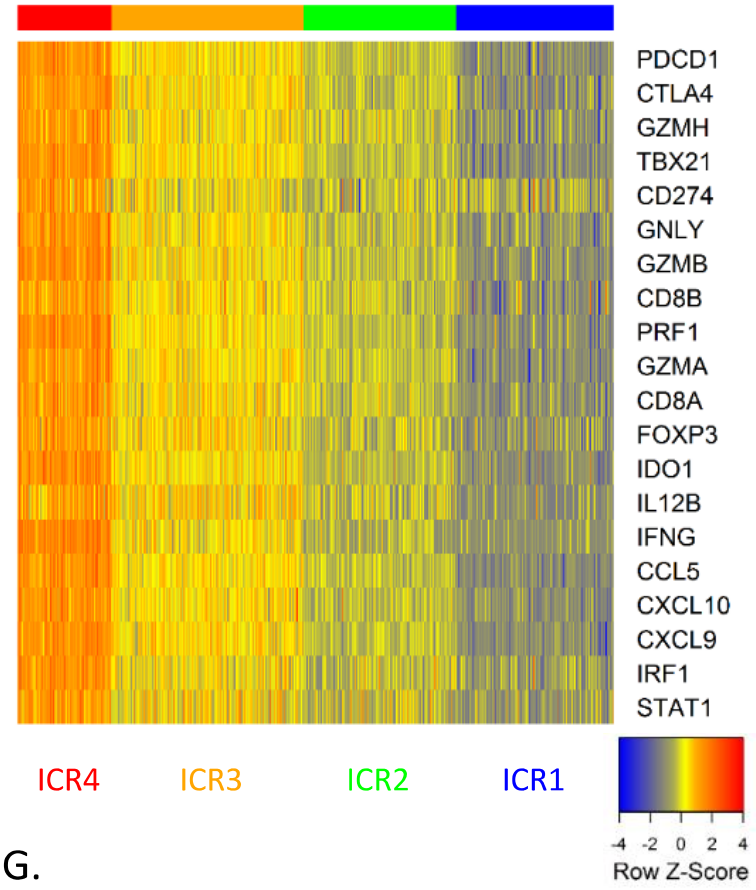
Cancer-Immune set point

The cancer-immune set point of a particular person is already determined by the time of clinical presentation, driven by the inherent immunogenicity of the tumour and by the responsiveness of the individual's immune system.

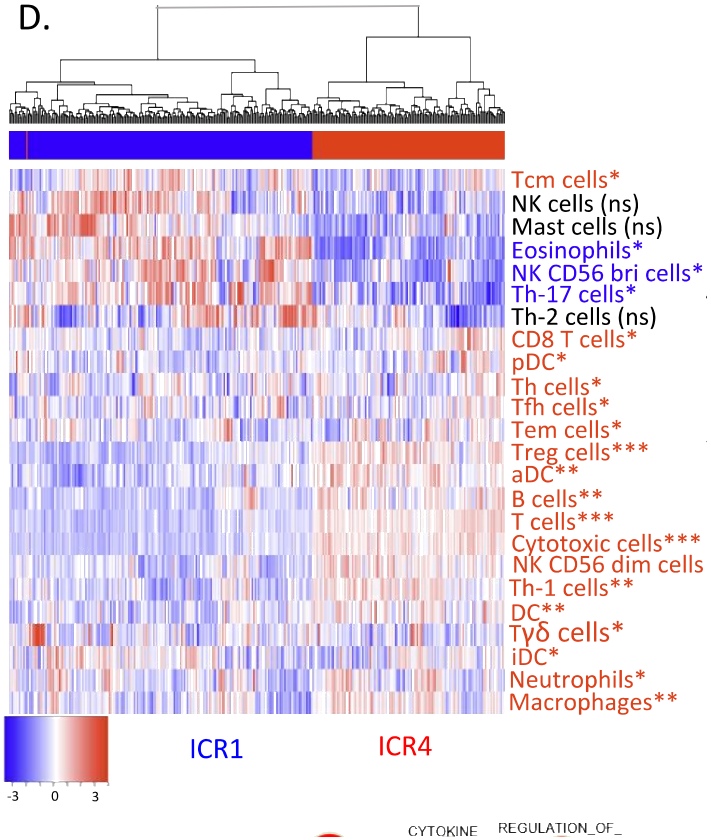
The features that determine the set point may therefore reflect genetic factors that are specific to a given tumour, the genetics of the person with cancer, or the extent to which antitumour immunity had developed initially.

Top 21 deferentially expressed pathways between ICR 1 and ICR 4

C.



D.



G.

CYTOKINE REGULATION_OF_

Hendrickx W et al. 2017, Oncoimmunology

Identification of genetic determinants of breast cancer immune phenotypes by integrative genome-scale analysis

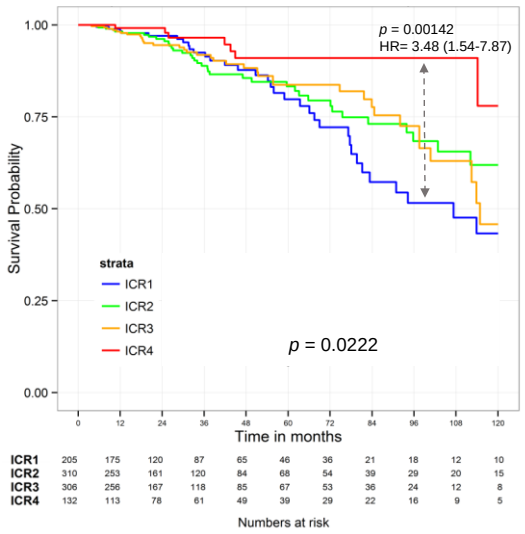
We validated these findings in a large meta-cohort of 1954 cancer gene expression data.

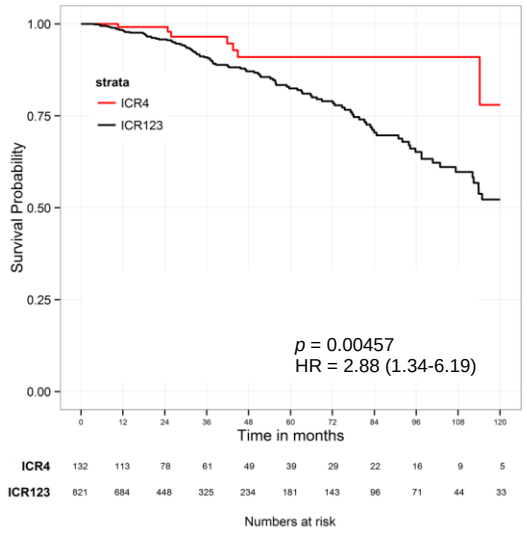
The ICR4 phenotype, which displays the upregulation of immune-regulatory transcripts such as PDL1, PD1, FOXP3, IDO1, and CTLA4, was associated with prolonged survival.

D. Bedognetti, … G Curigliano et al. 2016, In press

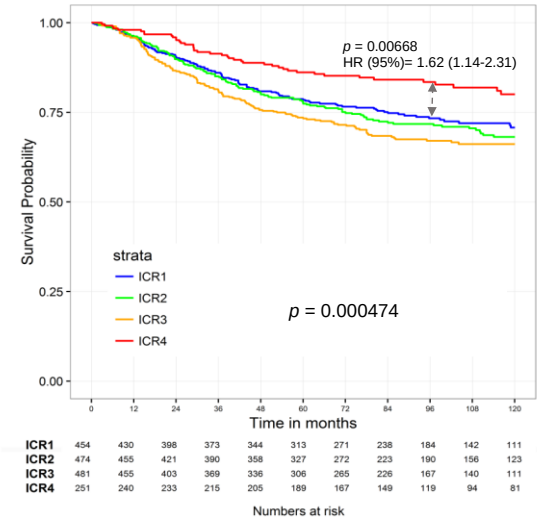
Survival and immune phenotypes

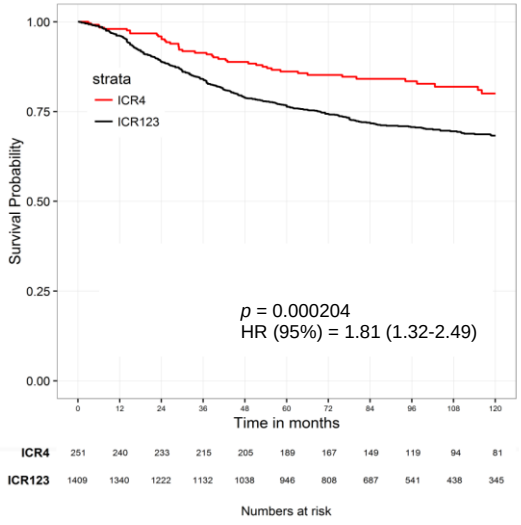
A.#





B.#





Identification of genetic determinants of breast cancer immune phenotypes by integrative genome-scale analysis

The number of non-silent or total mutations progressively decreased from ICR4 to ICR1, with a strong interaction with intrinsic molecular subtypes. No differences were observed among ICRs regarding the proportion of somatic mutations yielding predicted neoantigens.

TP53 mutations were enriched in the immune favorable phenotype (ICR4).

D. Bedognetti, … G Curigliano et al. 2016, In press

Specific somatic mutations and immunephenotypes according to intrinsic molecular subtypes

Cancer-Immune set point

Immunotherapy may work as a consequence of either its direct effect on F_{stim} and F_{inhib} (the cancer-immunity cycle) or its ability to alter the set point (enhancing the cancer-specific T-cell response).

The idea of a set point provides a frame-work to help organize the torrent of clinical and biomarker data that will emerge over the coming months and years.

Priorities

What are the priority / most rational IO-based combinations to explore?

How can we best balance efficacy with safety with IO-based combinations?

What influence does tumour type have on key considerations and priorities for IO-based combination therapy?

Thank you