Immuno-oncology in lung cancer

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Porto, 07 June 2014

Disclosure slide

I provided consultations or attended advisory boards for Astra-Zeneca, Eli Lilly Oncology, F. Hoffman-La Roche Ltd, Merck, Astellas and Pfizer, for which I received appropriate honoraria.

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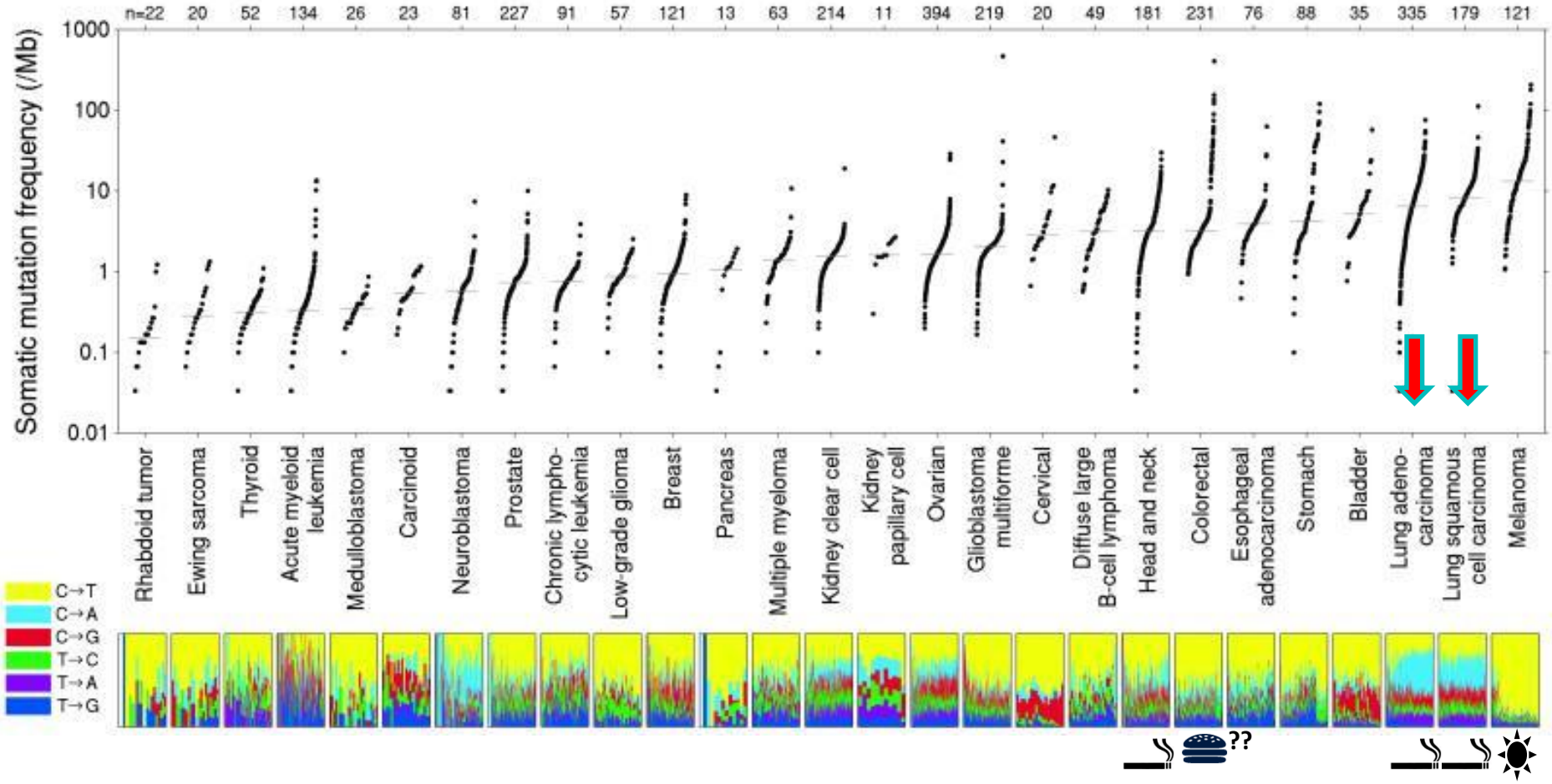
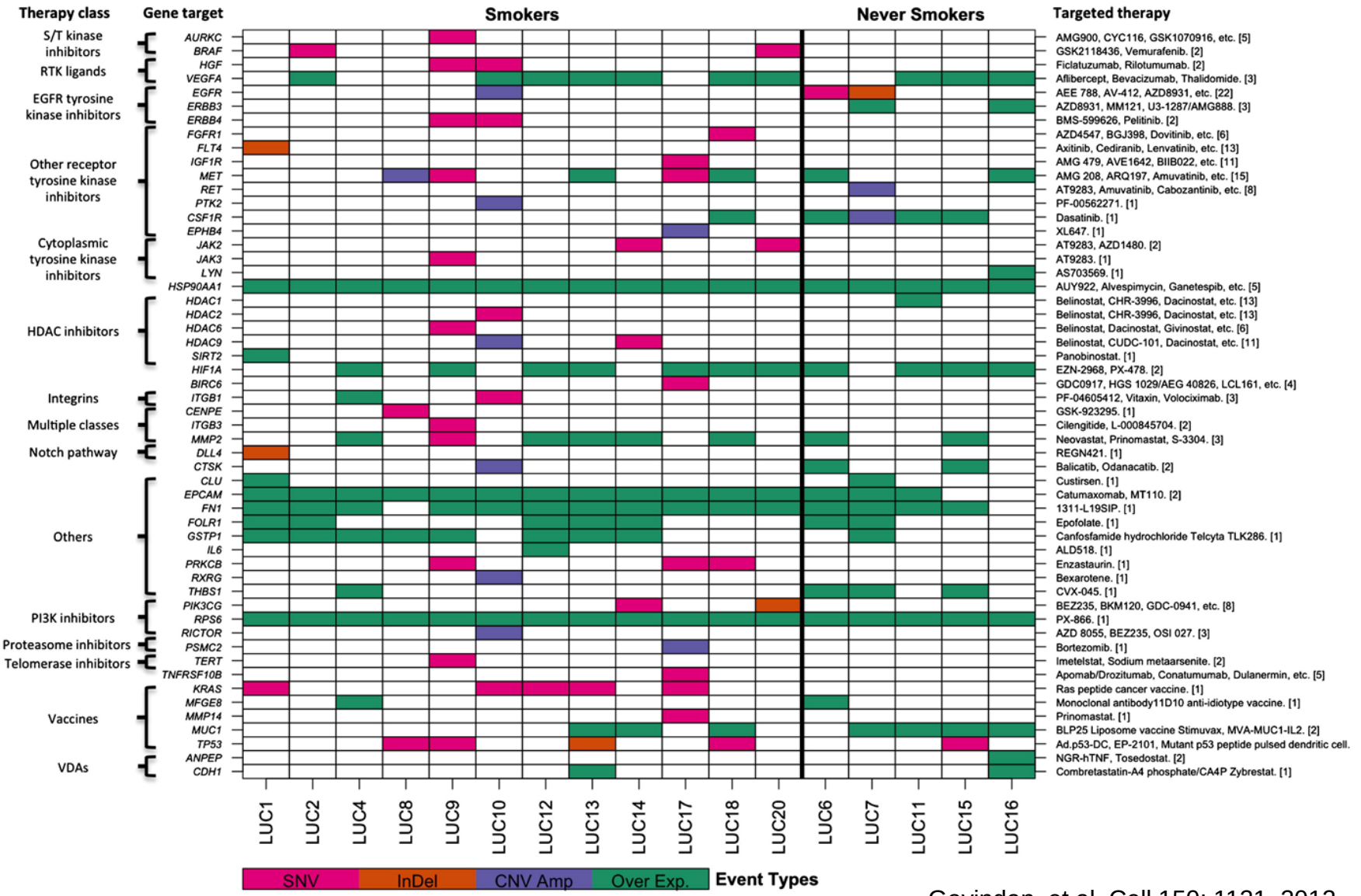
Rationale

Magnitude of genomic derangement



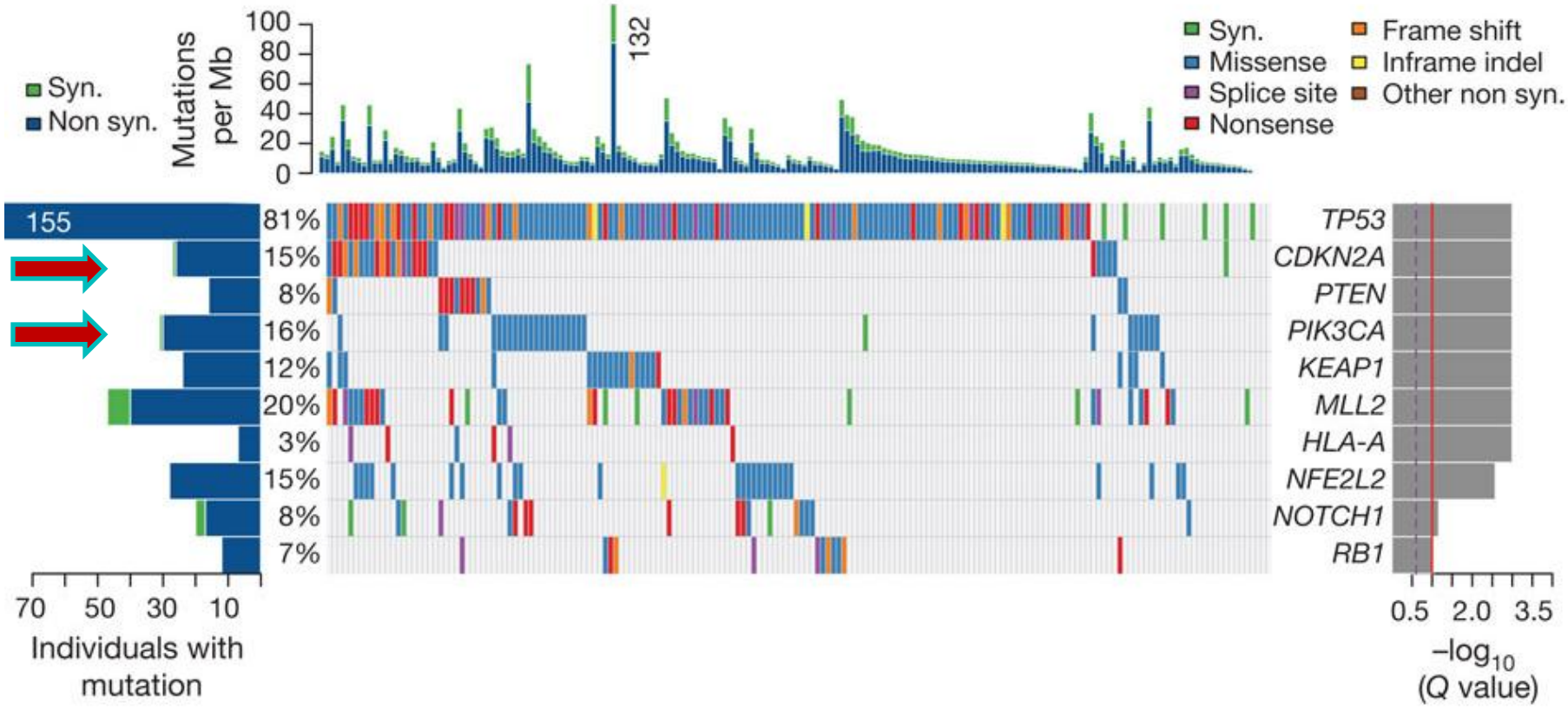
Lawrence MS, et al. Nature 499: 214-218, 2013

Drugable targets in smokers and never smokers



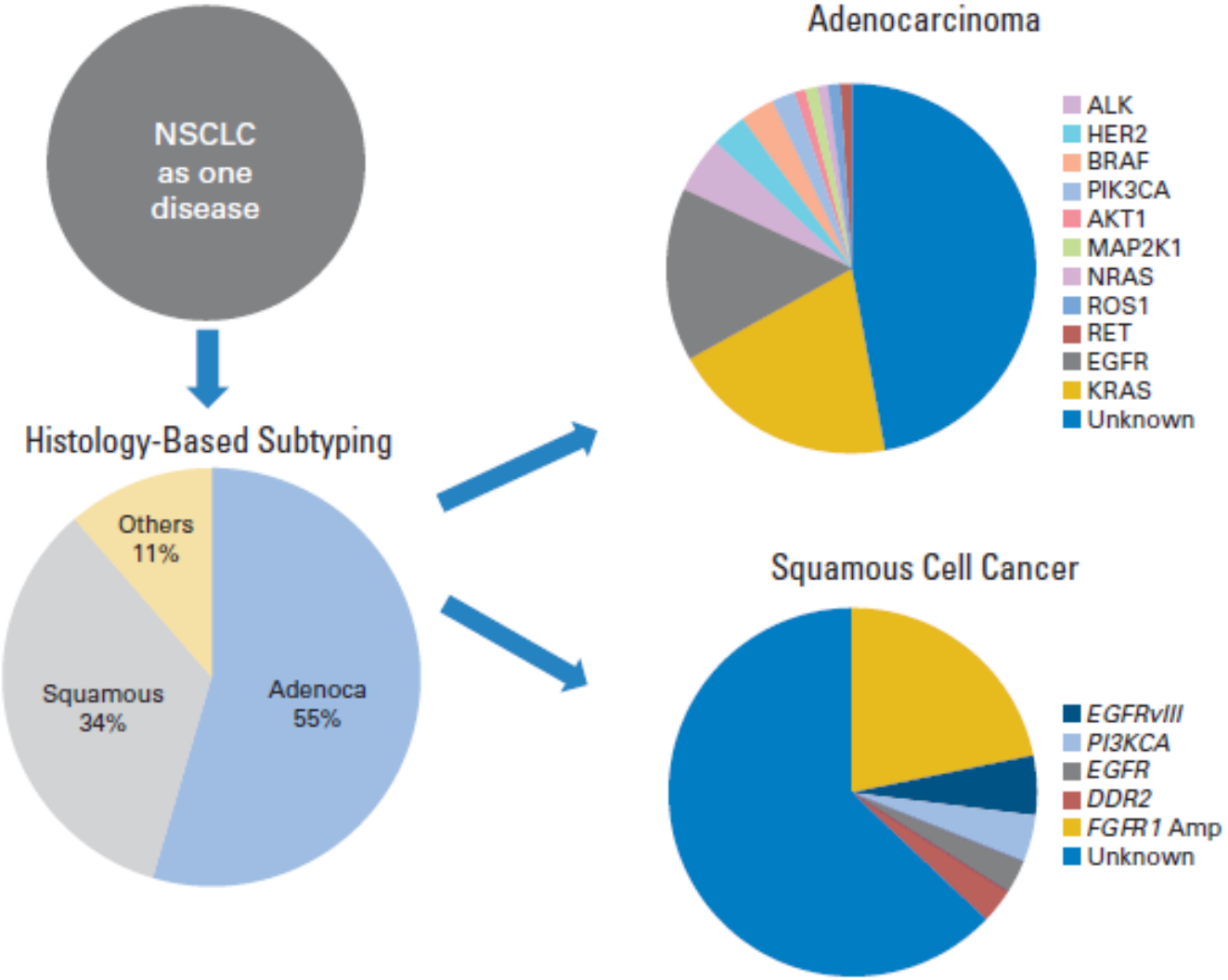
Govindan, et al. Cell 150: 1121, 2012

Significantly mutated genes in squamous NSCLC



Nature 489:519-525, 2012

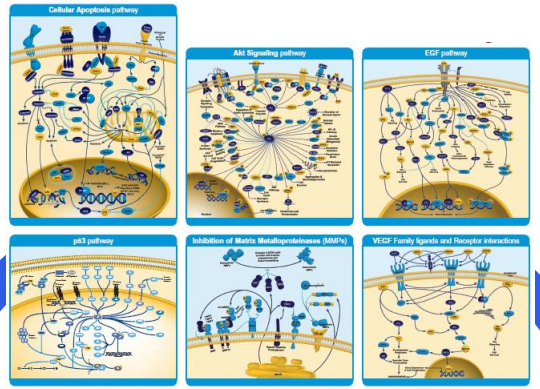
Evolution of NSCLC, from histology to molecular characteristics

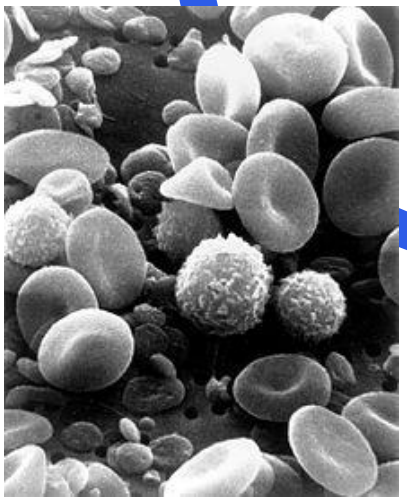


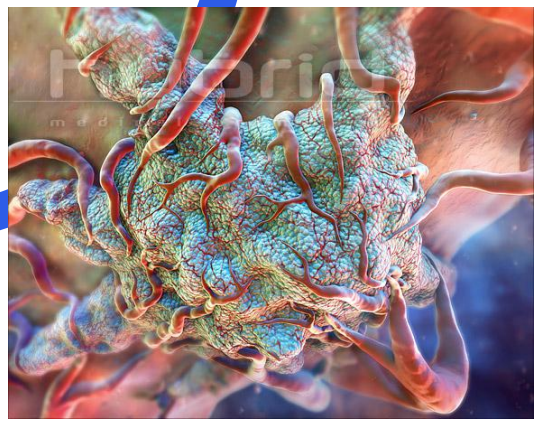
Li T, et al. JCO, 2013

Lung cancer

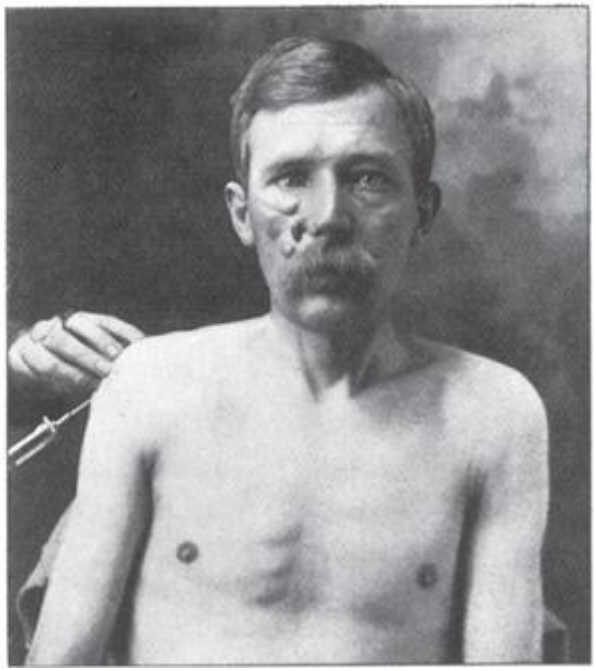

SCIENCE PHOTO LIBRARY


Cellular Apoptosis pathway
Akt Signaling pathway
EGF pathway
p53 pathway
Inhibition of Matrix Metalloproteinases (MMPs)
VEGF Family ligands and Receptor interactions





Willam Coley (1862 – 1936)



Role of the immune system in cancer and the process of immunoediting

Immunoediting describes the contrasting role of the immune system in protecting against tumour development and promoting tumour growth

Elimination

Cancer immunosurveillance

- Effective antigen processing/presentation
- Effective activation and function of effector cells
  - e.g., T-cell activation without co-inhibitory signals

Equilibrium

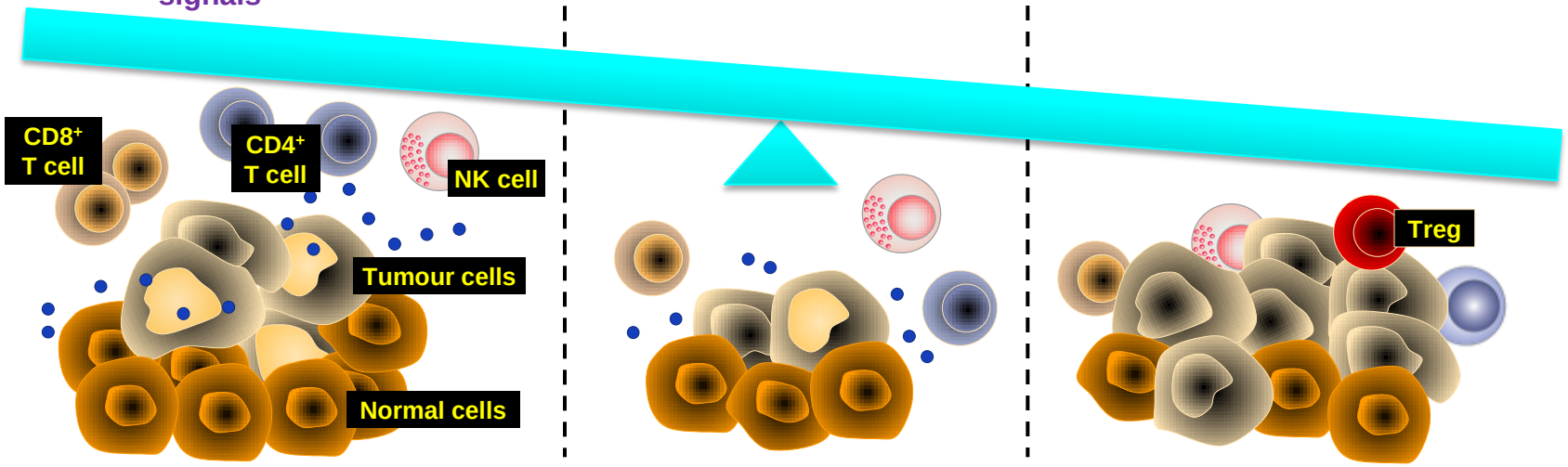
Cancer dormancy

- Genetic instability
- Tumour heterogeneity
- Immune selection

Escape

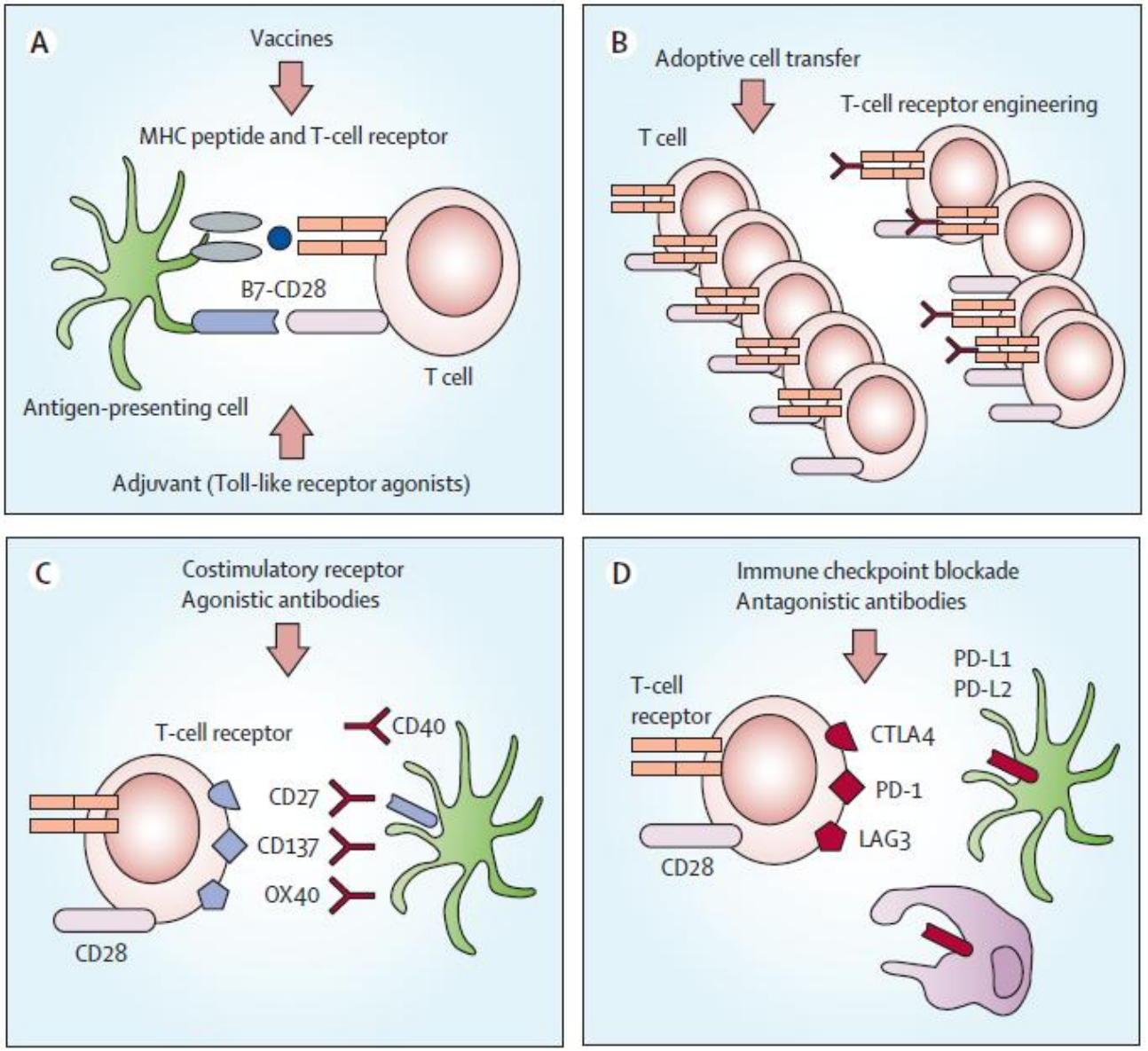
Cancer progression

- Tumours avoid elimination through the outgrowth of tumour cells that can suppress, disrupt, or 'escape' the immune system



Vesely MD, et al. Ann Rev Immunol 29:235-271, 2011

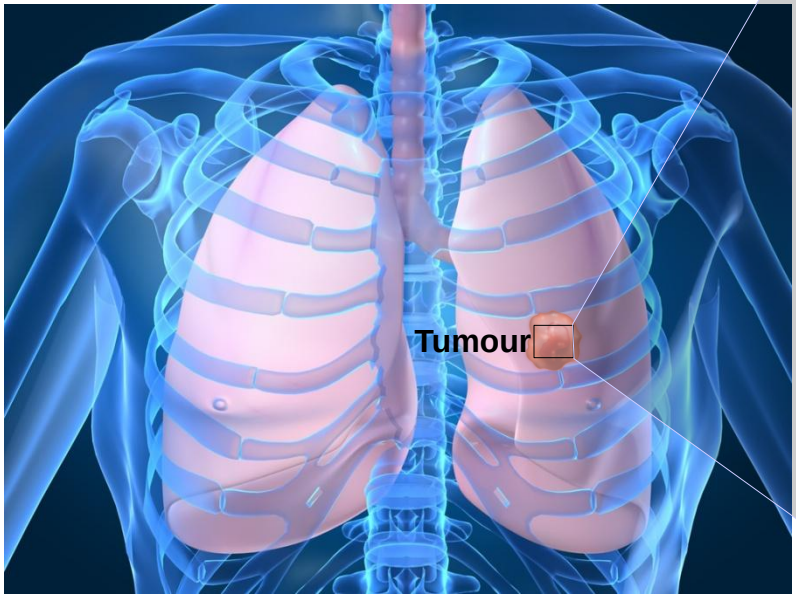
T-cell based immunomodulation

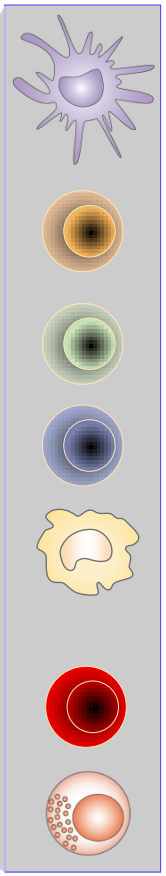


Tartour E, et al. Lancet Respir Med 1:551-563, 2013

Prognostic roles of immune cells in NSCLC

- Similar to melanoma and RCC, lung tumours are recognised by the immune system, and initiate an immune response
- Certain immune cells are associated with a better prognosis/improved outcome, while others suggest an unfavourable prognosis and disease outcome





Dendritic cells
Favourable prognosis[1]

CD3⁺ cells
Favourable prognosis[2–4]

CD8⁺ cells
Favourable prognosis[5–8]:

CD4⁺ cells
Favourable prognosis[6,9]:

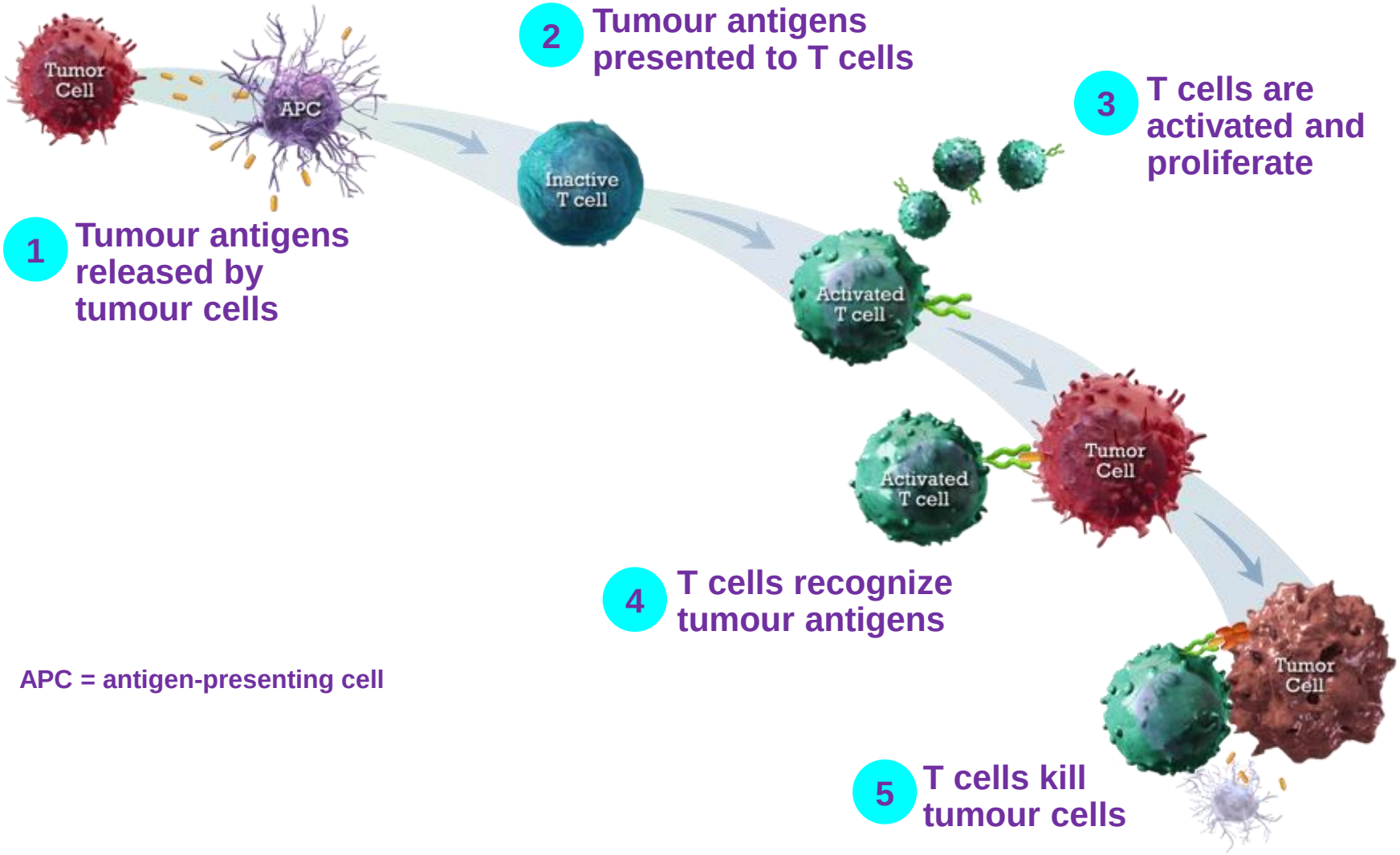
Macrophages
Favourable prognosis[7]:

Tregs
Unfavourable prognosis[10,11]:

NK cells
Unfavourable prognosis[12]:

1. Dieu-Nosjean MC, et al. *J Clin Oncol* 2008;26:4410–4117; 2. Petersen RP, et al. *Cancer* 2006;107:2866–2872; 3. Al-Shibli K, et al. *APMIS* 2010;118:371–382; 4. Ruffini E, et al. *Ann Thorac Surg* 2009;87:356–372; 5. Zhuang X, et al. *Appl Immunohistochem Mol Morphol* 2010;18:24–28; 6. Hiraoka K, et al. *Br J Cancer* 2006;94:275–280; 7. Kawai O, et al. *Cancer* 2008;113:1387–1395; 8. McCoy MJ, et al. *Br J Cancer* 2012;107:1107–1115; 9. Wakabayashi O, et al. *Cancer Sci* 2003;11:1003–1009; 10. Tao H, et al. *Lung Cancer* 2012;75:95–101; 11. Shimizu K, et al. *J Thorac Oncol* 2010;5:585–590; 12. Jin J, et al. *PLoS One* 2013;8:e61024

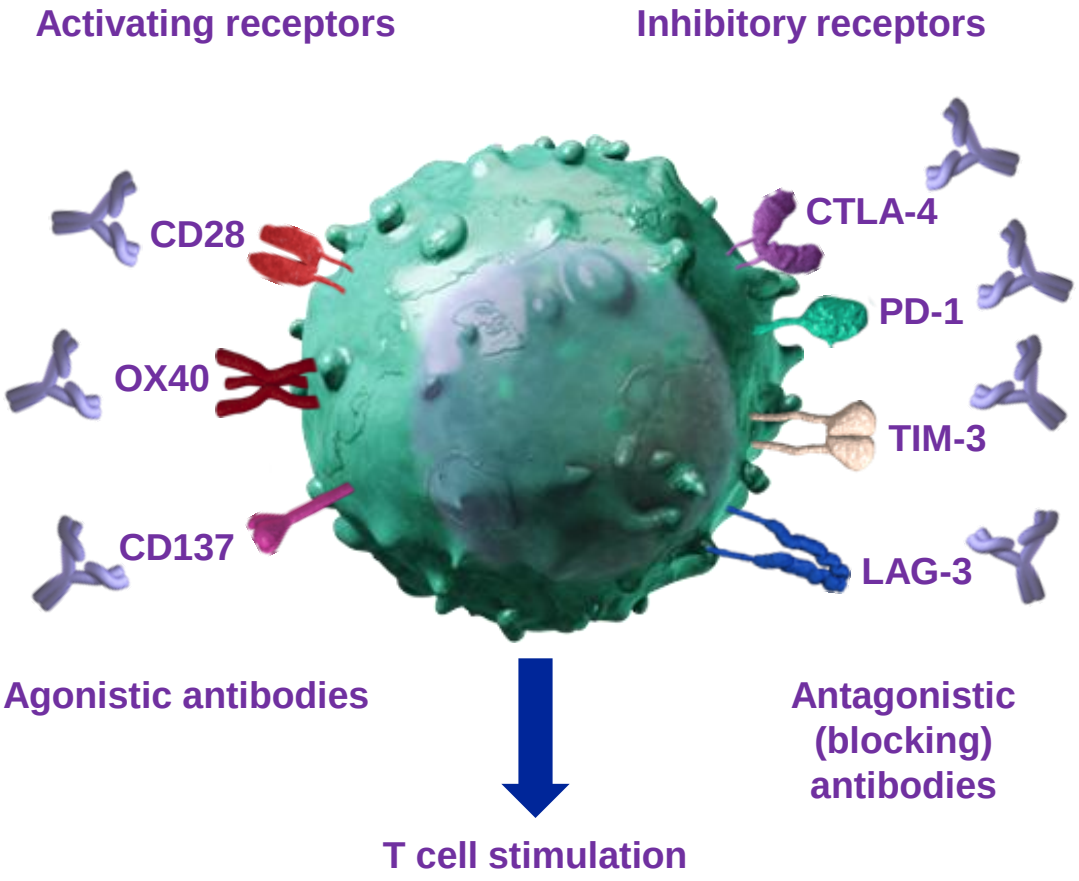
The T-cell antitumour response



APC = antigen-presenting cell

Andersen MH, et al. J Invest Dermatol 126:32–41, 2006; Pardoll DM. Nat Rev Cancer 11:252–264, 2012; Mellman I, et al. Nature 480:480–489, 2011; Heemskerk B, et al. EMBO J 32:194–203, 2013; Boudreau JE, et al. Mol Ther 19:841–853, 2011; Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

Regulating the T-cell immune response

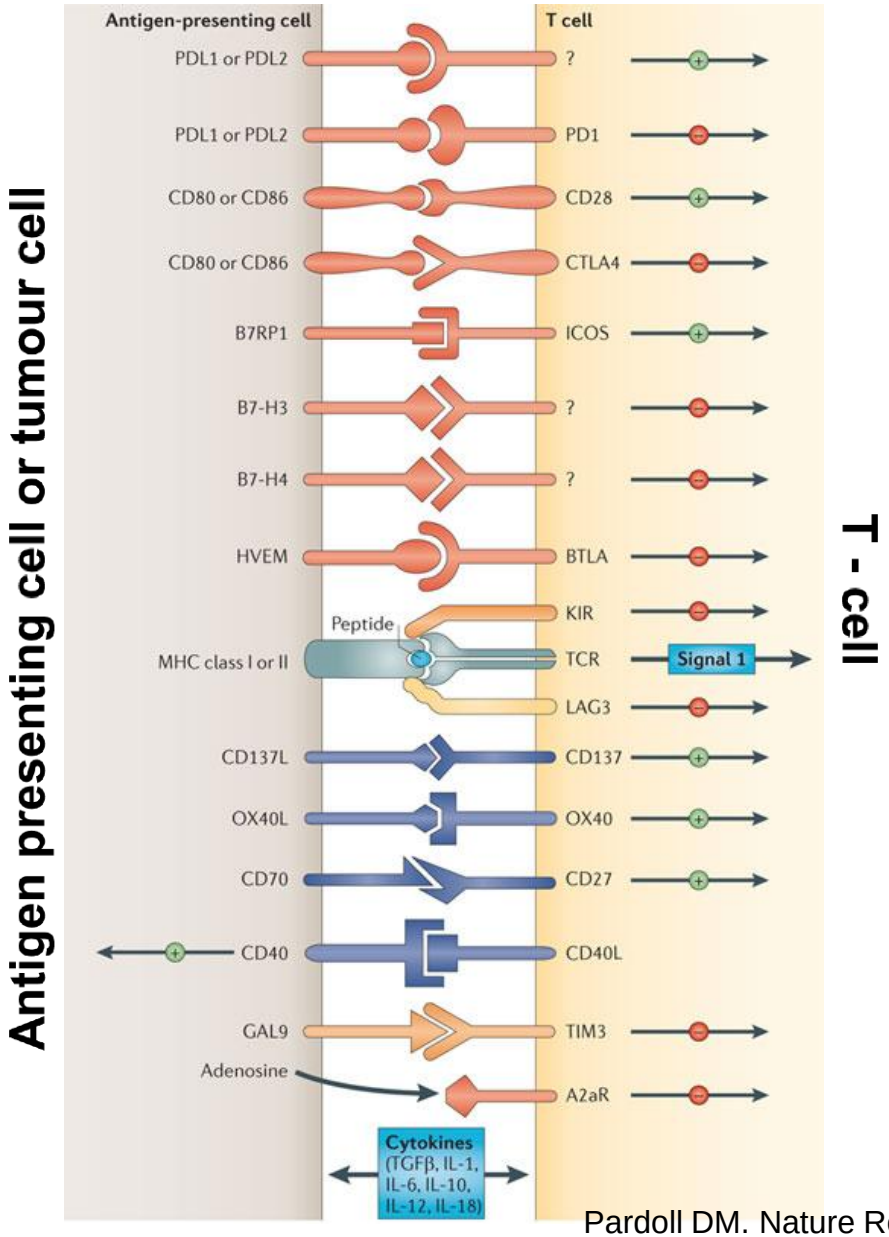


- T cell responses are regulated through a complex balance of inhibitory (‘checkpoint’) and activating signals
- Tumours can dysregulate checkpoint and activating pathways, and consequently the immune response
- Targeting checkpoint and activating pathways is an evolving approach to cancer therapy, designed to promote an immune response

[a]The image shows only a selection of the receptors/pathways involved
LAG-3 = lymphocyte-activation gene 3

Adapted from Mellman I, et al. Nature 480:481–489, 2011; Pardoll DM. Nat Rev Cancer 12:252–264, 2012

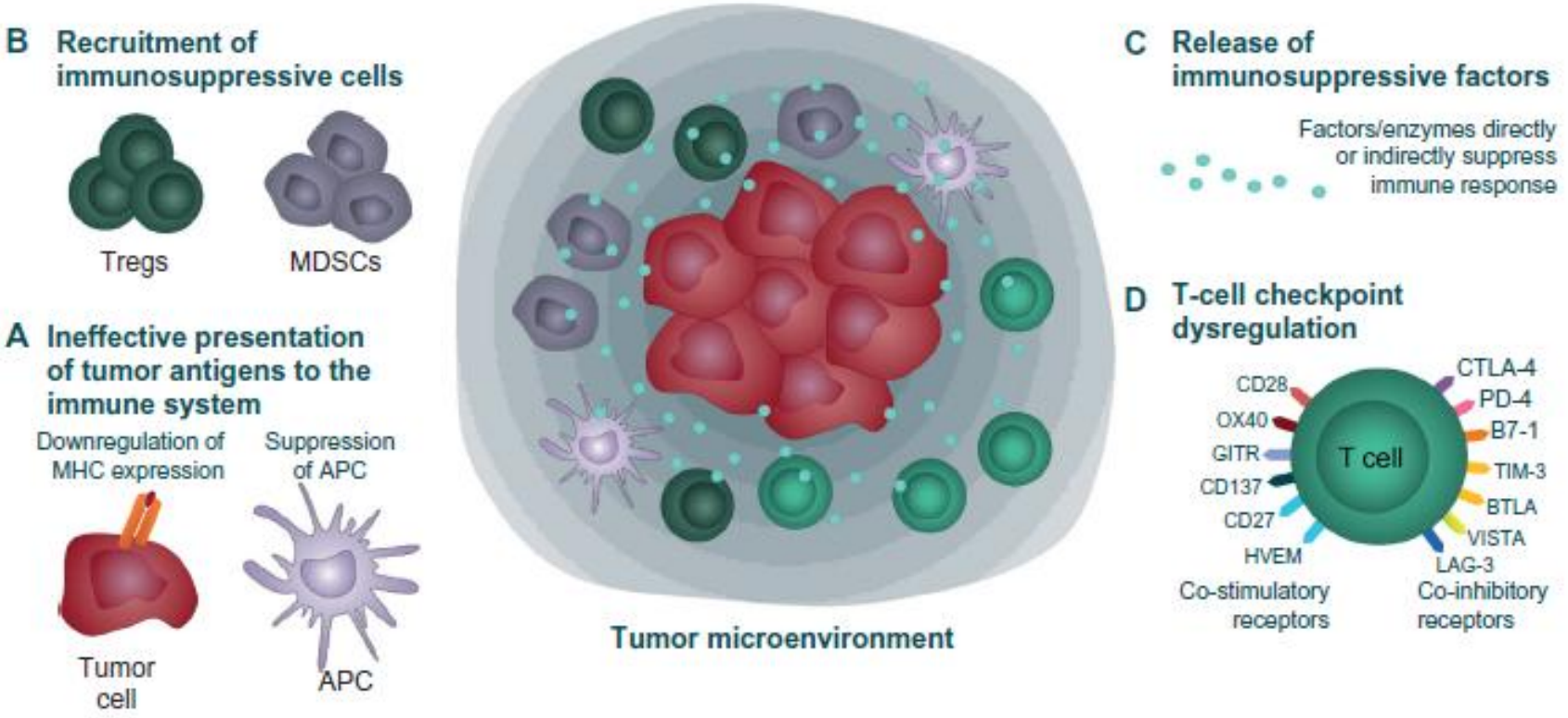
Multiple interactions regulate T-cell responses



Pardoll DM. Nature Rev Cancer 12:252-264, 2012

Tumours use various mechanisms to escape the immune system

Immune escape mechanisms are complex and frequently overlapping



Davies M, et al. Cancer Management and Research 6:63-75, 2014

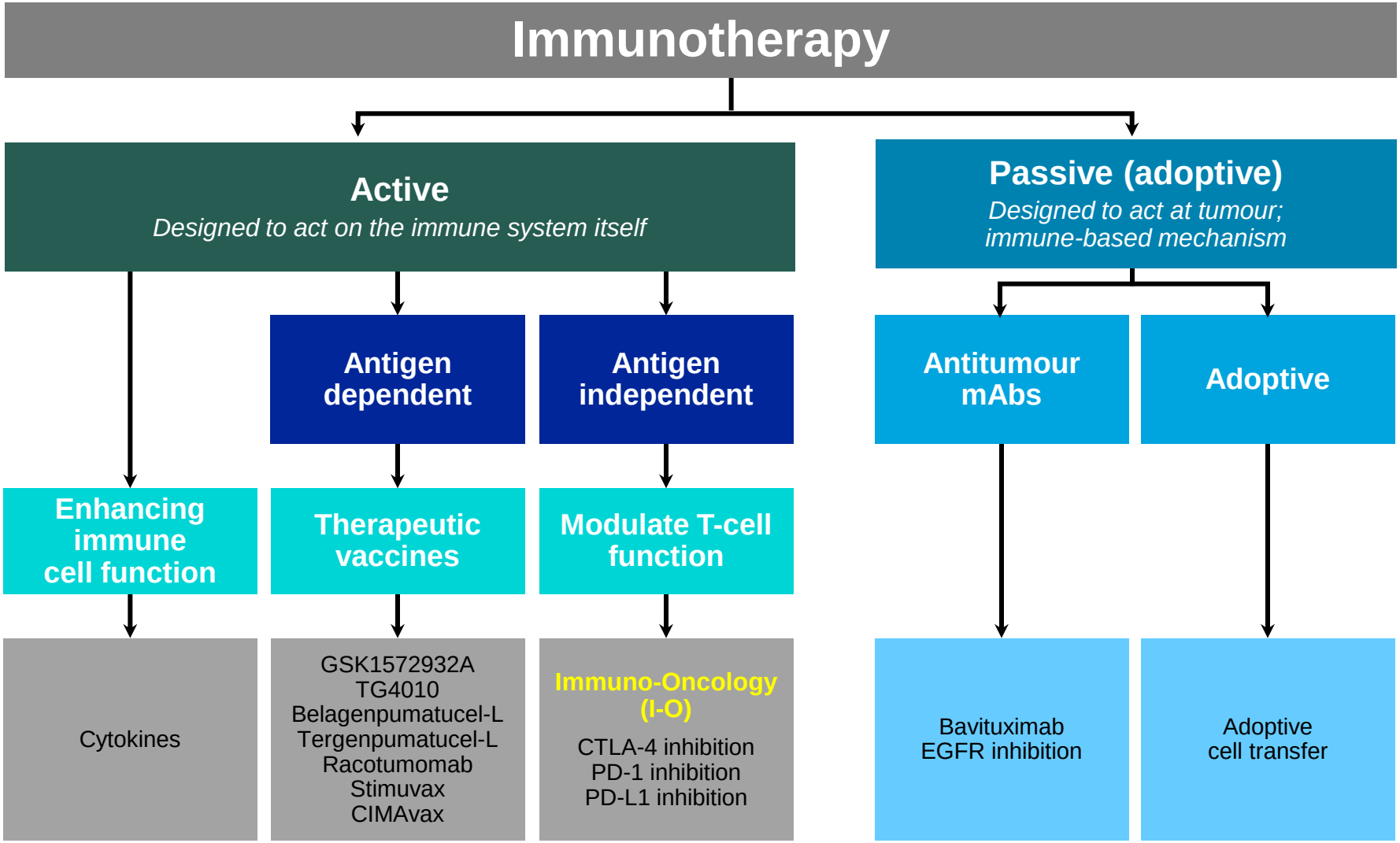
Data suggesting immune recognition and response in selected tumour types

Tumour type	Prognostic[a] tumour infiltrating lymphocytes[b]	Immune-related spontaneous tumour regression[c]
NSCLC	**Yes[1]**	**Yes[13] (rare)**
CRC	**Yes[2]**	**Yes[14]**
Breast	**Yes[3,4]**	**No**
Melanoma	**Yes[5,6]**	**Yes[15]**
Renal	**Yes[7,8]**	**Yes[16,17]**
Prostate	**Yes[9]**	**No**
Ovarian	**Yes[10]**	**No**
Head and neck	**Yes[11]**	**No**
Cervical	**Yes[12]**	**Evidence for cervical intraepithelial neoplasia 2/3[18,19]**

[a]Covers correlation with improved overall or progression-free survival, disease stage, or therapy outcome
[b]The type of lymphocyte dictates where there is a correlation with improved or worsened outcome
[c]Based on PubMed search conducted in October 2013 using the terms 'spontaneous regression' and the tumour type

1. Hiraoka K, et al. *Br J Cancer*. 2006;94:275–280; 2. Galon J, et al. *Science*. 2006;29:1960–1964; 3. Mahmoud SM, et al. *J Clin Oncol*. 2011;29:1949–1955; 4. Loi S, et al. *J Clin Oncol*. 2013;31:860–867; 5. Piras F, et al. *Cancer*. 2005;104:1246–1254; 6. Azimi F, et al. *J Clin Oncol*. 2012;30:2678–2683; 7. Siddiqui SA, et al. *Clin Cancer Res*. 2007;13:2075–2081; 8. Donskov F, et al. *Br J Cancer*. 2002;87:194–201; 9. Flammiger A, et al. *APMIS*. 2012;120:901–908; 10. Zhang L, et al. *N Engl J Med*. 2003;348:203–213; 11. Badoual C, et al. *Clin Cancer Res*. 2006;12:465–472; 12. Piersma SJ, et al. *Cancer Res*. 2007;67:354–361; 13. Nakamura Y, et al. *Lung Cancer*. 2009;65:119–122; 14. Bir AS, et al. *Anticancer Res*. 2009;29:465–468; 15. Kalialis LV, et al. *Melanoma Res*. 2009;19:275–282; 16. Kawai K, et al. *Int J Urol*. 2004;11:1130–1132; 17. Kumar T, et al. *Respir Med*. 2010;104:1543–1550; 18. Øvestad IT, et al. *Mod Pathol*. 2010;23:1231–1240; 19. Castle PE, et al. *Obstet Gynecol*. 2009;113:18–25

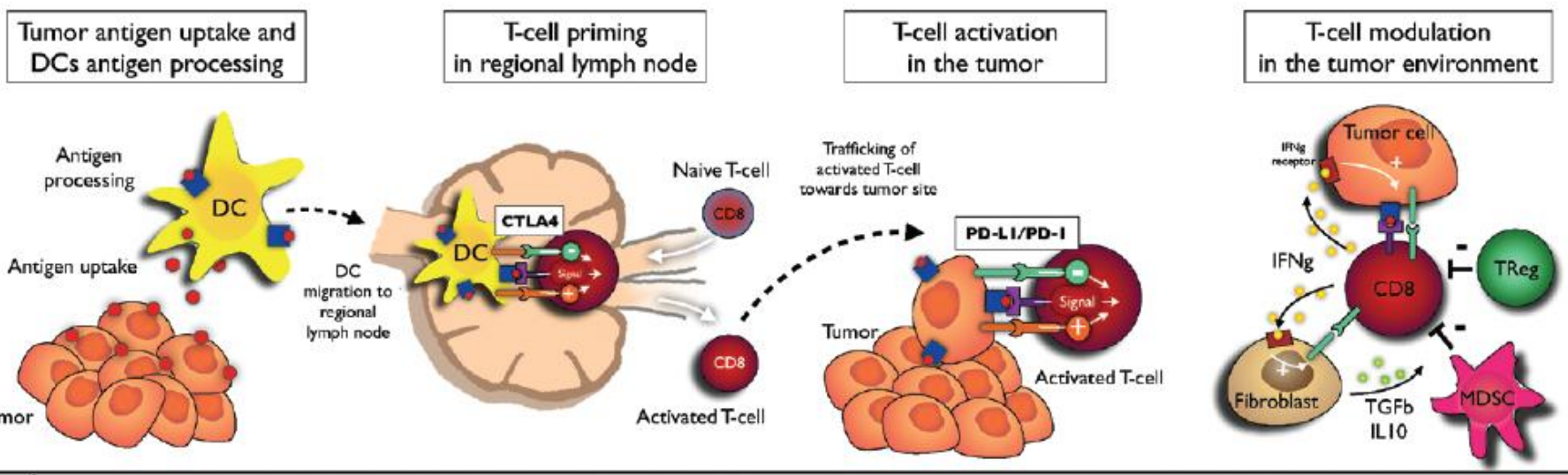
Potential investigational immunotherapeutic approaches as treatment options for lung cancer



CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1

www.clinicaltrials.gov accessed 26 March 2014; NCCN Guidelines®. NSCLC. V2.2013; Peters S, et al. *Ann Oncol*. 2012;23:vii56–vii64

NSCLC tumor immunology and modulation by conventional therapies



immune system modulation in NSCLC	> down-regulation of MHC-I	> up-regulation of PD-L1 through activation of PI3K/Akt ? MAPK ? Alk ?	> up-regulation of TRegs > up-regulation of MDSCs	> IL-10 and TGFß increased concentration by tumor environment > up-regulation of PD-L1 by IFNg secreted by activated T-cell
immuno modulation by NSCLC drugs	**immunogenic cell death** irradiation **vaccination strategies** MAGE-A3, MUC-1, rHU EGF	**up-regulation of MHC-I** paclitaxel, gemcitabine, erlotinib **DC maturation** paclitaxel, docetaxel, bevacizumab **anti-CTLA4** Ipilimumab, Tremelimumab	**anti-PD-1** MDX-1106, CT-011, MK-3475 **anti-PD-L1** MPDL-3280A, MDX-1105 **up-regulation of PD-L1** paclitaxel, etoposide	**TReg inhibition** cisplatin, paclitaxel, bevacizumab **MDSC inhibition** cisplatin, docetaxel, gemcitabine **down-regulation of PD-L1** by PI3Ki ? MEKi ? Crizotinib ?

Champiat S, et al. J Thorac Oncol 9:144-153, 2014

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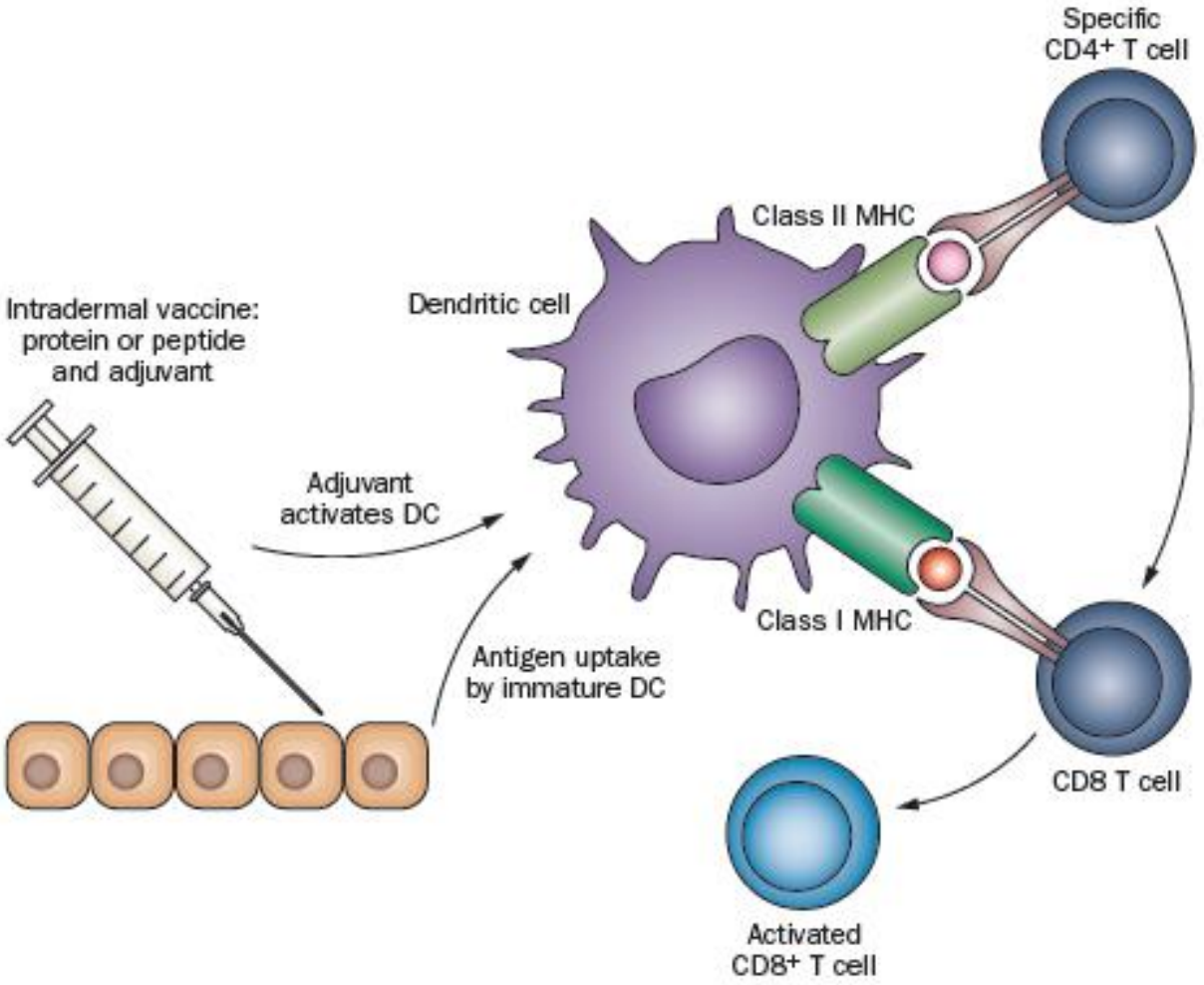
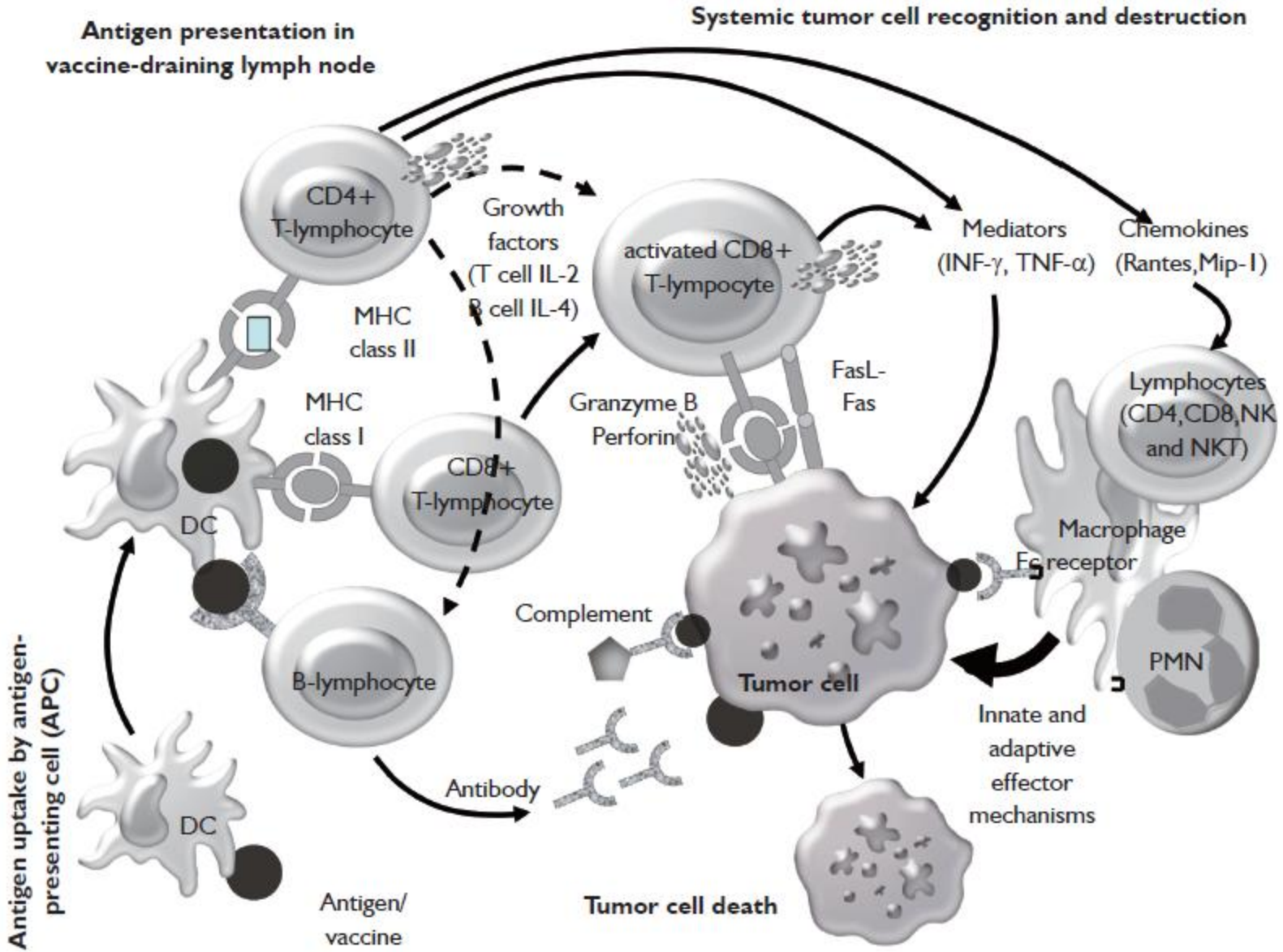
Vaccines

Mechanism of action of cancer vaccines



Drake GC, et al. Nat Rev Clin Oncol 11:24–37, 2014

Mechanism of action of cancer vaccines



Winter H, et al. J Thorac Dis 3:105–114, 2011

Monovalent vaccine clinical trials in NSCLC

Trial	Description	NSCLC stage	Patient (*n*)	Trial design	Endpoints	Secondary analysis/results
SCC TAA + CFA	CFA +/− SCC TAA vs. Control	Stage I-II SCC [1]	85	Phase III Randomized	Primary: • Survival (5-YS) • OS Secondary: • Adverse Effects	SCC TAA + CFA: 5-YS = 75%, MOS = 106 months CFA Alone: 5-YS = 53%, MOS = 71 months Control: 5-YS = 34%, MOS = 38 months
LUD99-010	Recombinant MAGE-A3 protein +/− AS02B	Stage I-II (MAGE-A3+)	17	Phase II Non-randomized	Primary: • Immune resp.	MAGE-A3 alone: (3/9) Abs to MAGE-A3 (1/9) HLA-A2 restricted CD8+ resp. MAGE-A3+ AS02B: (8/8) Abs to MAGE-A3 (4/8) HLA-DP4 restricted CD4 + resp. (1/8) HLA-A1 restricted CD8 + resp.
MAGE-A3 ASCI	Recombinant MAGE-A3 protein + AS15	Stage IB (122/182) Stage II (60/182) (MAGE-A3+)	182	Phase II Randomized (2:1) vax: placebo	Primary: • DFI Secondary: • Safety • DFS • OS	Hazard Ratio (favoring vax. arm): DFI = 0.74 DFS = 0.73 OS = 0.66 Relative improvement in DFI and DFS (27%)
MAGRIT	Recombinant MAGE-A3 protein + AS15	Stage IB-IIIA (MAGE-A3+)	2270 (expected)	Phase III Randomized (2:1) vax: placebo	Primary: • DFS Secondary: • Validation of gene signature predictive of response	Pending

Tucker ZC, et al. Cancer Treat Rev 38:650–661, 2012

Multivalent vaccine clinical trials in NSCLC

Trial	Description	NSCLC stage	Patient (n)	Trial design	Endpoints	Secondary analysis/results
GVAX	GM-CSF transduced, irradiated autologous tumor cells	Cohort A: IB–IIA (10/43) Cohort B: IIIA-IV (33/43)[2]	83	Phase I/II Non-randomized	Primary: • Safety • Feasibility • Immune resp. Secondary: • Tumor reg. • Disease prog. • Survival	• 80% vax. prod. success in cohort A • Immune resp. not associated with overall tumor reg. or surv. • Recurrences: 6/10 in cohort A
Autologous Dendritic Cell (ADC)	ADCs loaded with Her2/*neu*, CEA, WT1, MAGE-2, and survivin peptides	Stage IA–IIIA (13/16)[3] Stage IIIB (3/16)[4]	16	Phase II Non-randomized	Primary: • Immune resp. Secondary: • Clinical tolerability	• TAA specific response in (7/12) surgical pts. • No recurrence in (9/12) surgical pts. at mean post-vax F/U of 18 months. • Well tolerated

Tucker ZC, et al. Cancer Treat Rev 38:650–661, 2012

Phase II and III vaccine trials in NSCLC

Agent and trial	Phase	Design and description	*n*	Results and comments
MAGE-A3 vaccine with AS02 adjuvant[37]	II	Randomized trial of vaccine or placebo post resection of stage IB and II MAGE-A3+ NSCLC	182	Gene expression profile revealed a 43% reduction of recurrence in vaccine treated group (HR 0.57, 95% CI 0.36–1.2, *P*=0.99). Primary end point of disease-free interval was not significantly different between the two groups (HR 0.74, *P*=0.107)
Liposomal MUC-1 peptide vaccine (L-BLP-25)[64]	II	Randomized trial of L-BLP-25 vs BSC in patients with stage IIIB or IV NSCLC with stable or responsive disease post chemotherapy or chemoradiation	171	Primary end point of median OS 17.2 months L-BLP-25 vs 13 months BSC (*P*=0.066); subgroup analysis: stage IIIB patients OS 30.6 months vs 13.3 months in BSC arm
Vacccinia/MUC-1 vaccine (TG4010)[69]	II	Randomized trial of cisplatin and vinorlbine with TG4010 vs TG4010 as a single agent until disease progression followed by addition of vinorelbine and cisplatin in patients with MUC-1-positive advanced NSCLC	65	Primary end point of response was met only for the concurrent TG4010 and chemotherapy arm; response rate 29.5%
Vacccinia/MUC-1 vaccine (TG4010)[70]	IIB	Randomized trial of gemcitabine and cisplatin vs the same combination with TG4010 in patients with stage 4 NSCLC	108	Patients with normal level of activated NK cells at baseline had an improvement in 6-month PFS and OS. Patients with high levels of active NK cells had increased toxic effects. Primary end point of 6-month PFS met only for the concurrent TG4010 arm (43%), but not significantly different from chemotherapy alone (35%)
Allogeneic whole cell NSCLC line vaccine with anti-sense TGF-β (Belagenpumatucel-L)[49]	II	Randomized multi-dose trial in NSCLC with low volume stage II, IIIA, IIIB, IV disease	75	Response rate 15%; OS, 441 days in advanced-stage disease setting
MAGE-A3 NCT00480025	III	Randomized phase III trial of patients with resected stage IB–IIIA MAGE-A3+ NSCLC post resection or adjuvant chemotherapy	2,289	Primary end point: DFS
L-BLP-25 NCT00409188	III	Randomized trial comparing vaccine vs placebo in patients with unresectable stage III with stable or responding disease after chemoradiotherapy	1,464	Primary end point: OS not met
L-BLP-25 NCT01015443*	III	Randomized trial comparing vaccine vs placebo in patients with unresectable stage III with stable or responding disease after chemoradiotherapy	420	Primary end point: OS
L-BLP-25 NCT00828009‡	II	BLP25 vaccine and bevacizumab after chemoradiotherapy for patients with unresectable stage IIIA/B NSCLC	55	Primary end point: safety
TG4010 NCT01383148	IIB/III	Randomized trial comparing platinum combination chemotherapy with or without vaccine in patients with stage IV NSCLC	1,000	Primary end point: OS
Belagenpumatucel-L NCT00676507	III	Randomized trial of vaccine or placebo in patients with stage IIIA, IIIB or IV NSCLC with stable or responding disease after initial chemotherapy	506	Primary endpoint: OS

Drake GC, et al. Nat Rev Clin Oncol 11:24–37, 2014

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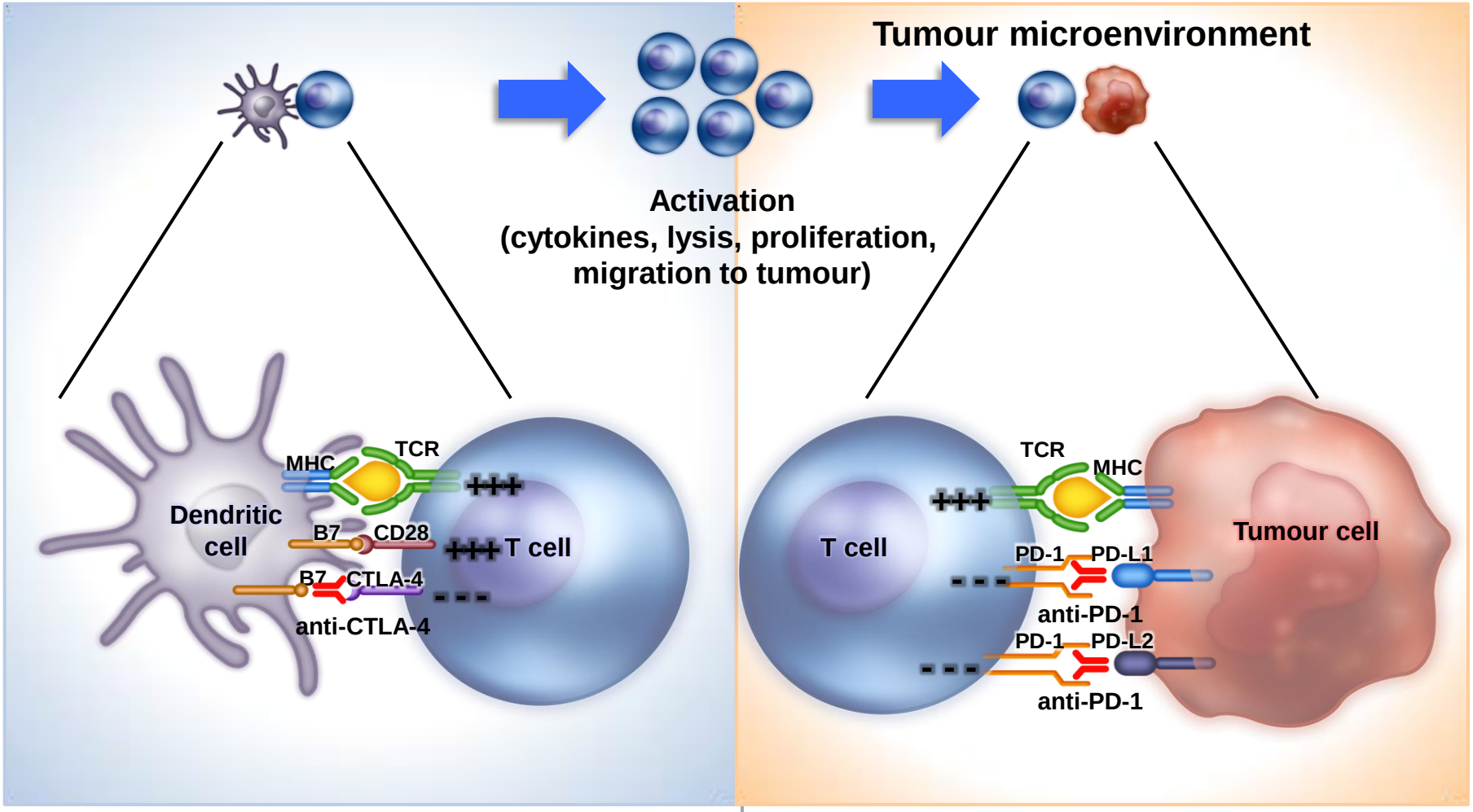
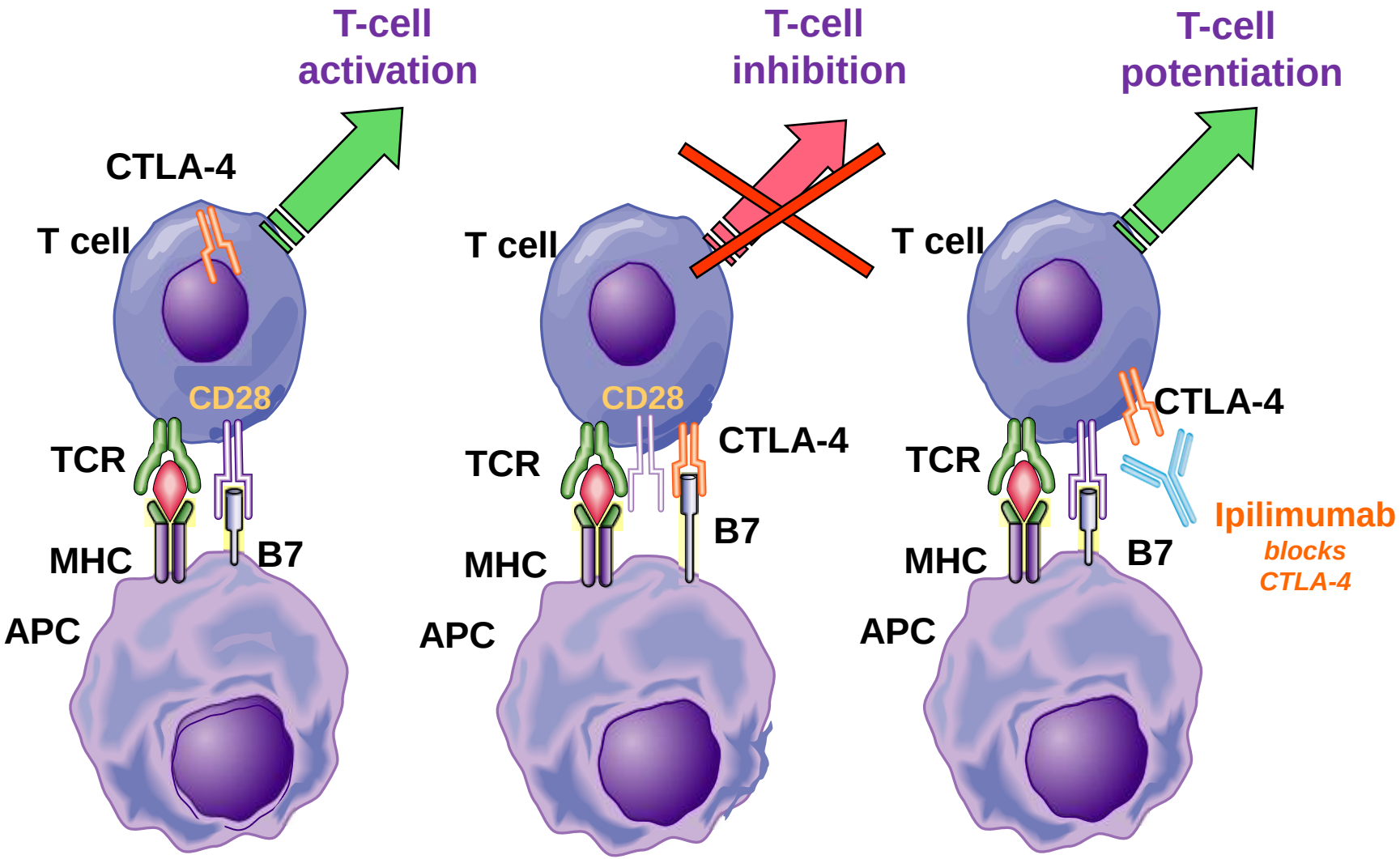
CTLA-4

Differences in CTLA-4 and PD-1 blockade



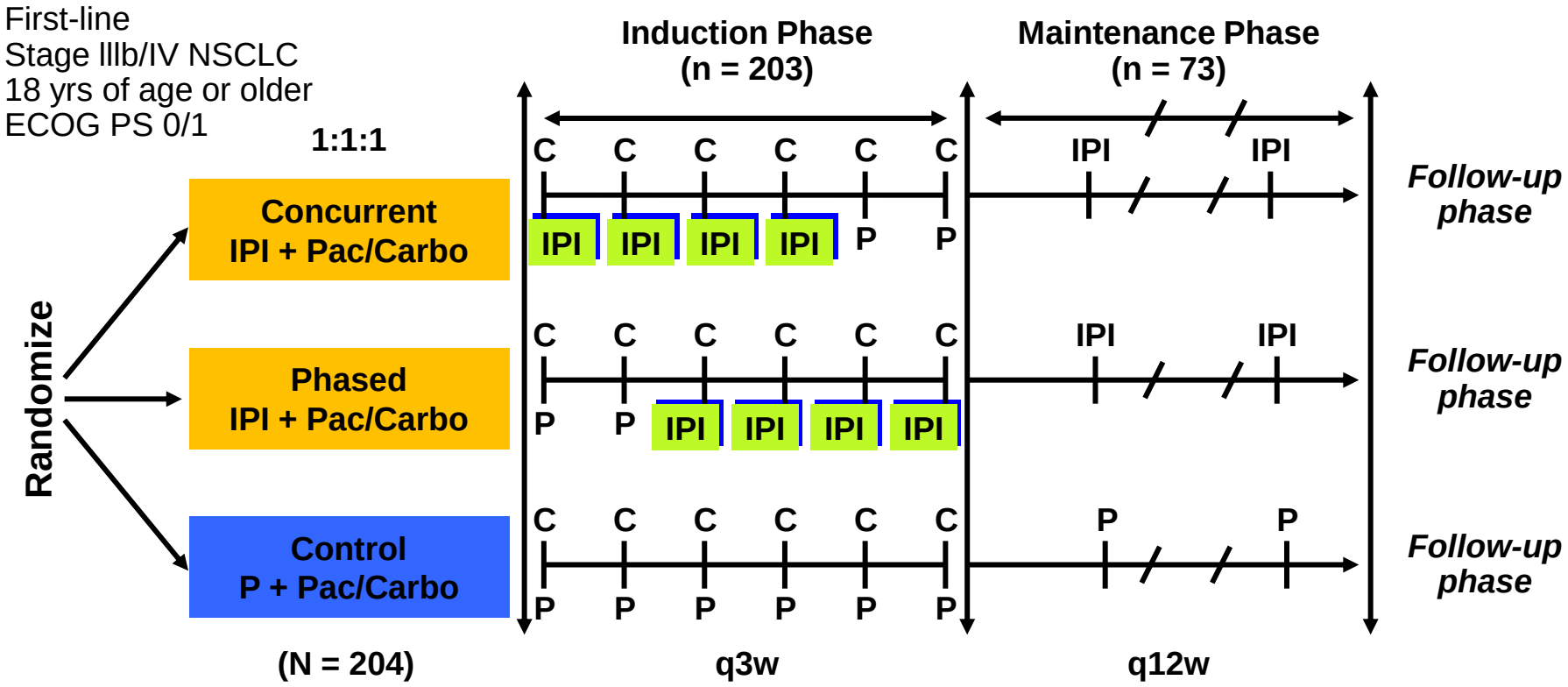
Ribas A, et al. N Engl J Med 366:2517–2519, 2012

Ipilimumab blocks CTLA-4 and augments T-cell activation



Adapted from Weber J. Cancer Immunol Immunother 58:823, 2009

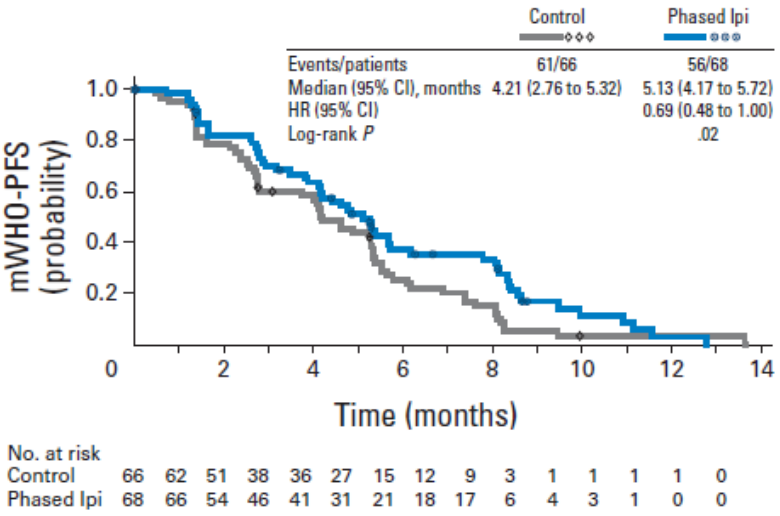
Randomized phase II study of Ipilimumab and CT in advanced NSCLC

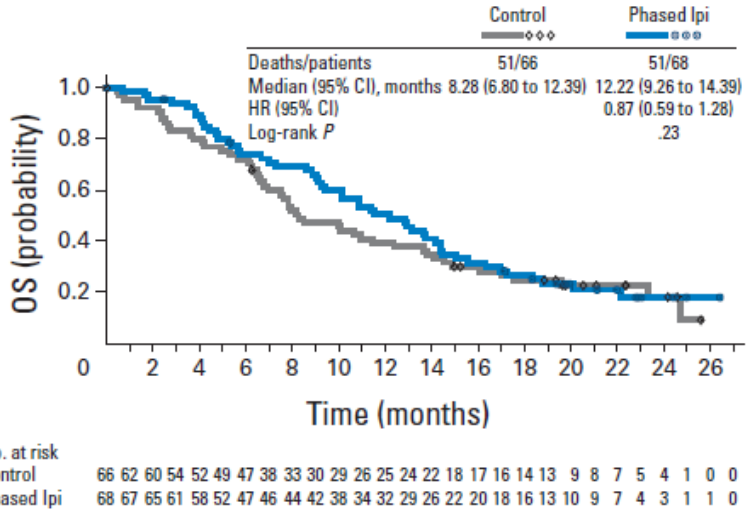


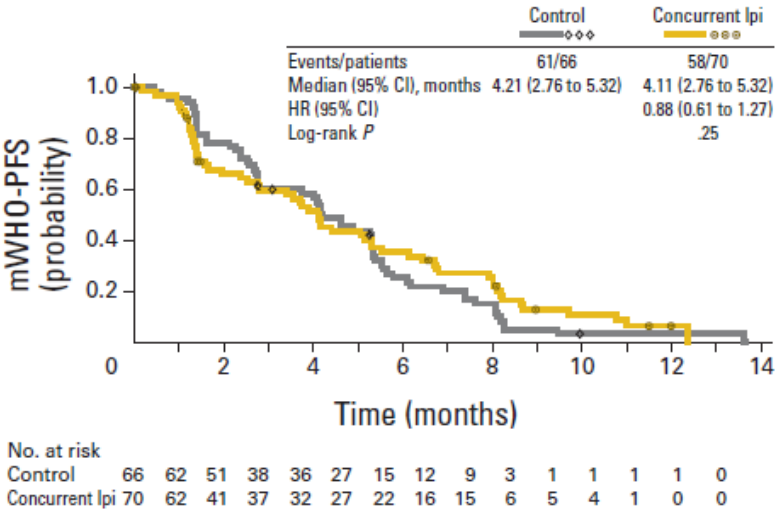
- Primary endpoint: irPFS
- Cx regimen: Pac 175 mg/m^2/carbo AUC 6 prior to start of ipilimumab (10 mg/kg)

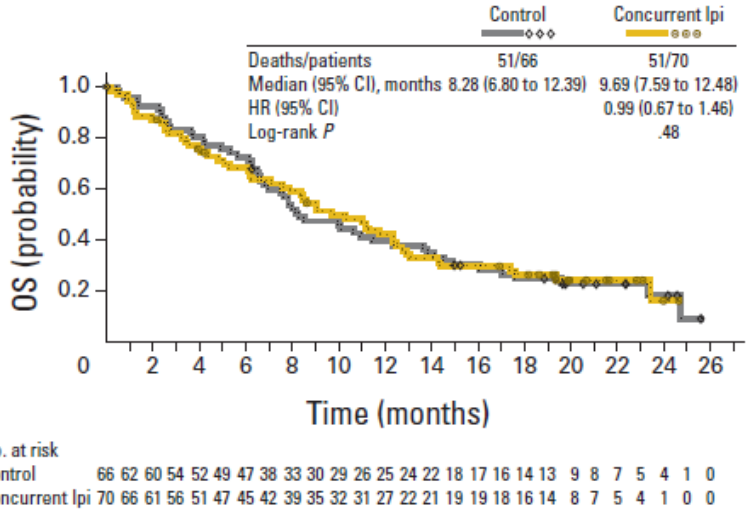
Lynch TJ ,et al. J Clin Oncol 30:2046-2054, 2012

Randomized phase II study of Ipilimumab and CT in advanced NSCLC









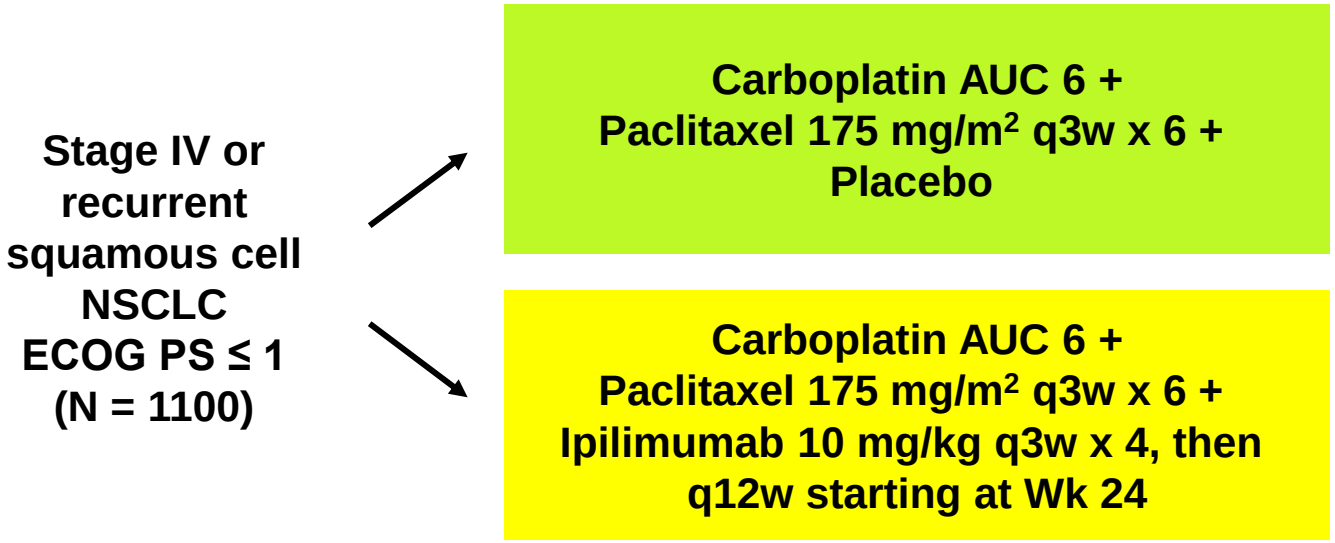
Lynch TJ, et al. J Clin Oncol 30:2046-2054, 2012

Randomized phase II study of Ipilimumab and CT in advanced NSCLC

Event	Control (n = 65)			Concurrent Ipilimumab (n = 71)			Phased Ipilimumab (n = 67)		
	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4
Any adverse event, %	31	29	11	16	30	27	19	42	12
Any treatment-related adverse event, %	43	29	8	35	24	17	43	31	8
Treatment-related non-hematologic adverse events, %									
Fatigue	22	5	0	20	7	1	19	5	0
Alopecia	46	NA	NA	34	NA	NA	45	NA	NA
Rash	8	2	0	25	3	0	10	3	0
Pruritus	5	2	0	17	0	0	8	0	0
Arthralgia	11	0	0	16	0	0	12	2	0
Asthenia	3	2	0	4	3	0	16	2	0
Diarrhea	14	3	0	23	7	0	18	5	0
Nausea	31	2	0	25	1	0	31	2	0
Vomiting	15	2	0	17	1	0	16	2	0
Peripheral neuropathy*	23	2	0	13	1	0	10	0	0
Peripheral sensory neuropathy*	11	2	0	8	0	0	16	3	0
Hematologic abnormalities, %†									
Thrombocytopenia	35	8	2	39	2	0	40	3	0
Neutropenia	32	8	2	26	5	3	34	2	0
Anemia	89	6	0	80	8	3	92	6	0
Liver-function enzymes, %†									
ALT	35	2	0	40	2	0	29	2	0
AST	32	2	0	25	2	0	31	2	0

Lynch TJ, et al. J Clin Oncol 30:2046-2054, 2012

Ongoing phase III: Ipilimumab in squamous NSCLC



- Double-blind study
- Primary endpoint: OS
- Secondary endpoints: OS in patients who receive 1 dose of ipilimumab/ placebo, PFS, RR

ClinicalTrials.gov. NCT01285609

Immuno-oncology in lung cancer

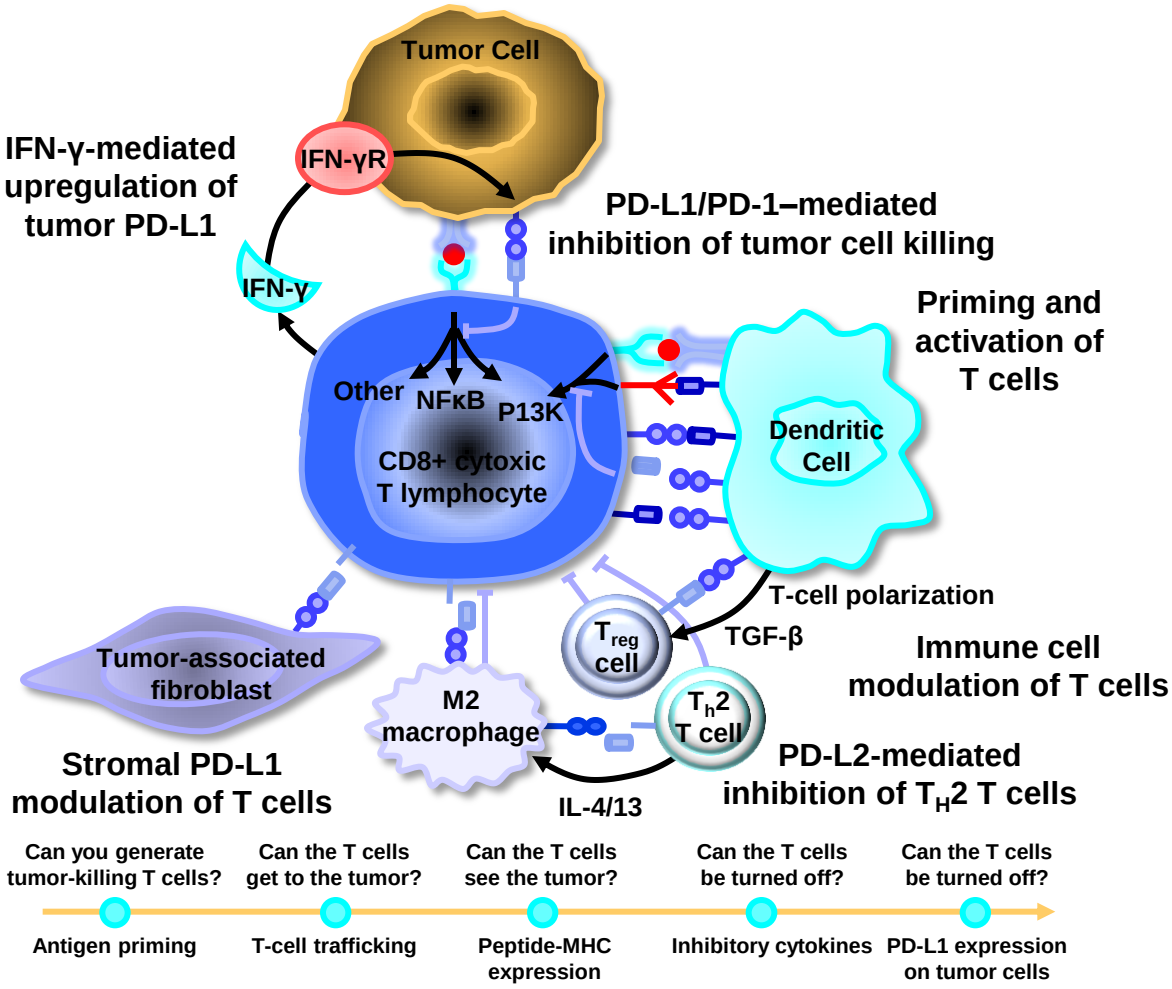
centro hospitalar do Porto

U.PORTO

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

PD-1 & PD-L1

Blockade of PD-1 binding to PDL1 (B7-H1) and PDL-2 (B7-DC) revives T cells



- PD-L1 expression on tumor cells is induced by γ-interferon
- In other words, activated T cells that could kill tumors are specifically disabled by those tumors

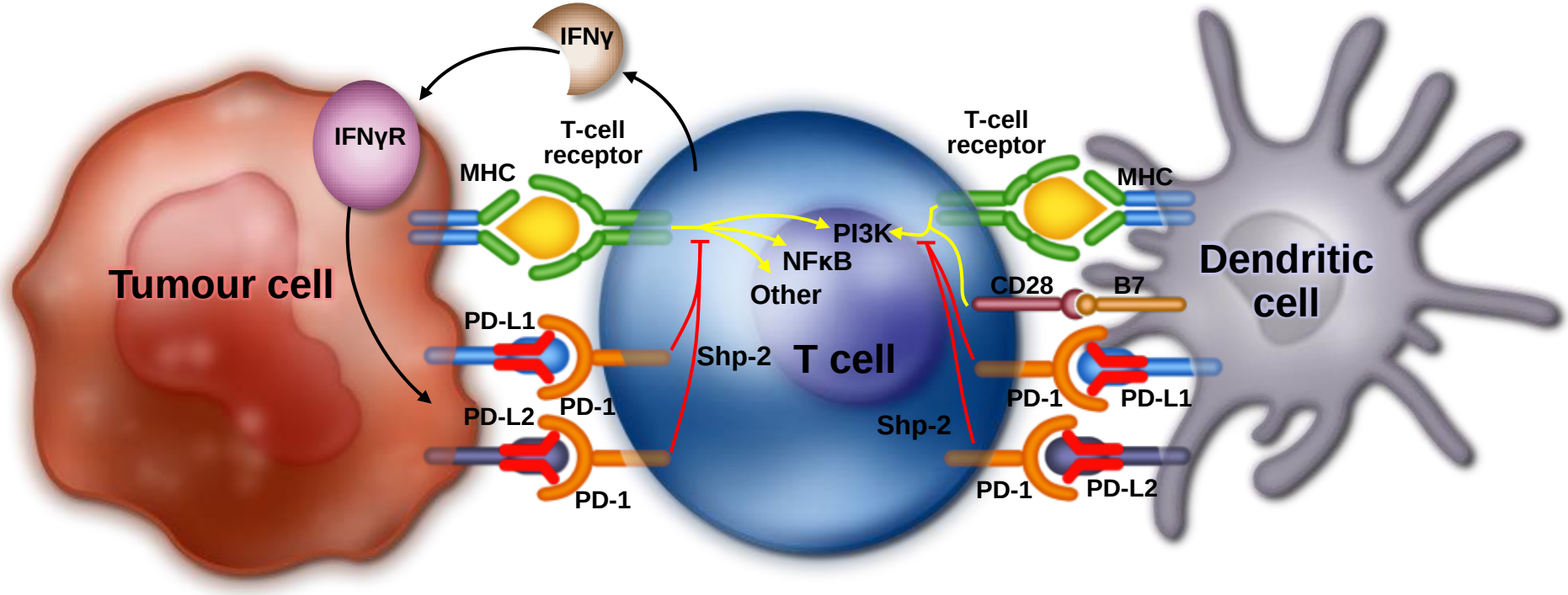
- PD-1
- PD-L1
- PD-L2
- T-cell receptor
- MHC-1
- CD28
- Shp-2
- B7.1

Sznol M, et al. Clin Cancer Res. 19:1021-1034, 2013

Role of PD-1 pathway in suppressing antitumour immunity

Recognition of tumour by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 upregulation on tumour

Priming and activation of T cells through MHC/antigen and CD28/B7 interactions with antigen-presenting cells



Nivolumab is a PD-1 receptor blocking antibody

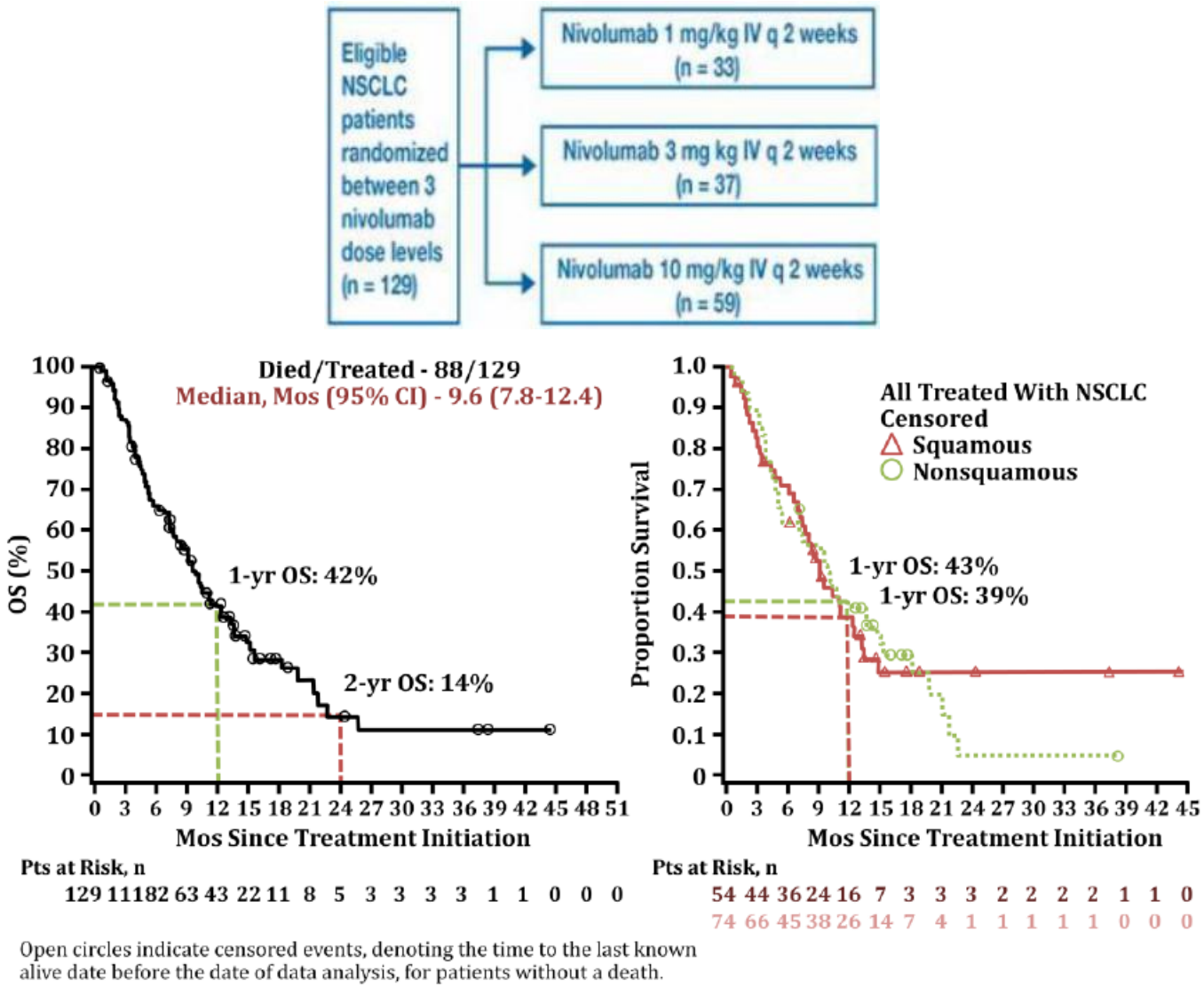
Ribas A, et al. N Engl J Med 366:2517–2519, 2012

Somme immune checkpoint inhibitors in NSCLC

Compound	Company	Target	Development Stage in NSCLC
Ipilimumab	Bristol-Myers Squibb	CTLA4	Phase III
Tremelimumab	MedImmune	CTLA4	Phase I
Nivolumab (BMS-936558)	Bristol-Myers Squibb	PD-1	Phase III
Lambrolizumab (MK-3475)	Merck	PD-1	Phase III
BMS-936559	Bristol-Myers Squibb	PD-L1	Phase I
Medi-4736	MedImmune	PD-L1	Phase I
MPDL-3280A	Genentech	PD-L1	Phase III

Champiat S, et al. J Thorac Oncol 9:144-153, 2014

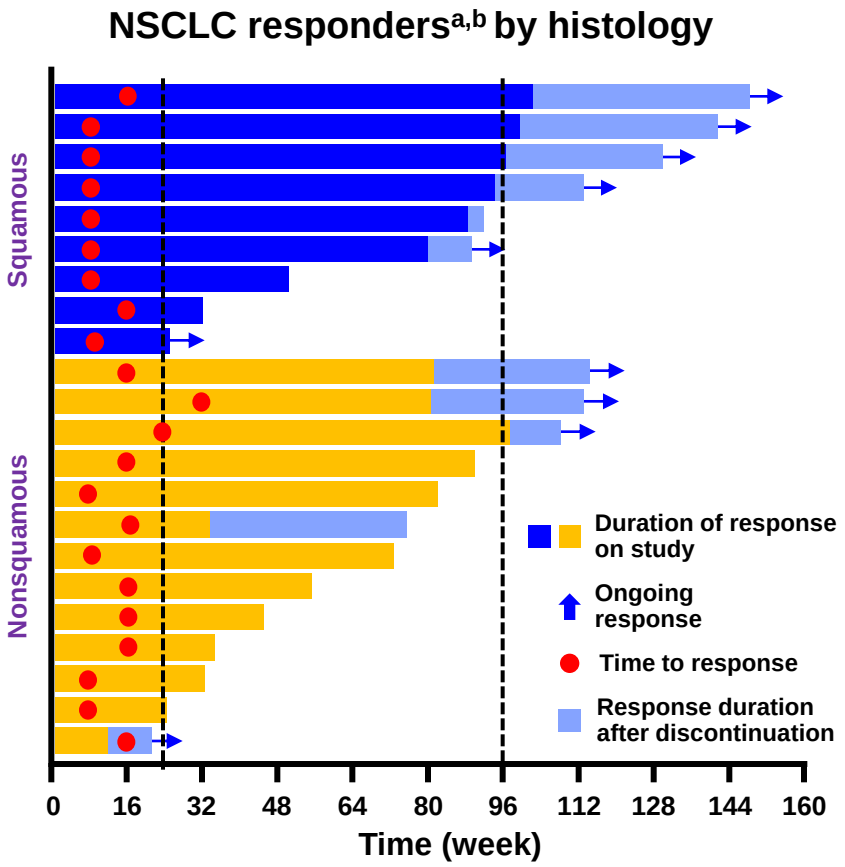
Nivolumab phase I trial in squamous/nonsquamous NSCLC

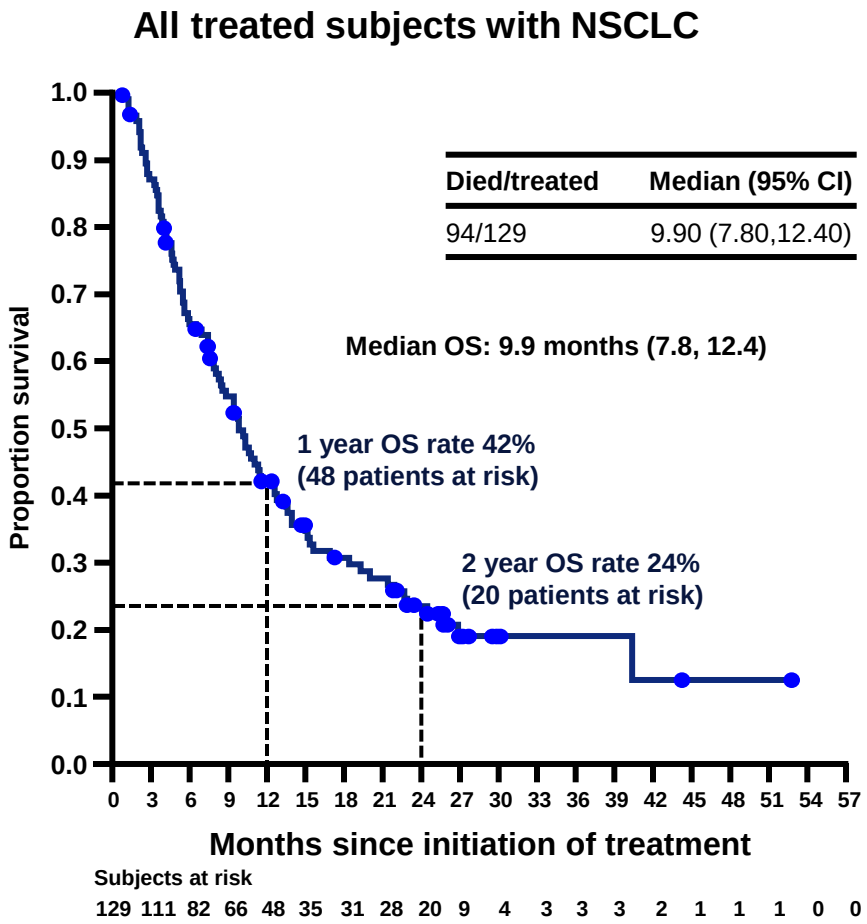


Open circles indicate censored events, denoting the time to the last known alive date before the date of data analysis, for patients without a death.

Brahmer JR, et al. ASCO 2013. Abstract 8030

Duration of response and overall survival with nivolumab monotherapy in NSCLC





Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

[a]Responses were assessed by modified RECIST v1.0

[b]All efficacy analyses based on data collected as of September 2013

Adapted from Brahmer JR, et al. Mini-Oral presentation at WCLC 2013. *J Thorac Oncol.* 2013;8(suppl 2):abstract: MO18.03

Nivolumab: activity across NSCLC histology

NSCLC histology	Dose (mg/kg)	ORR % (n/N)	Stable disease rate ≥24 week, % (n/N)
Squamous	All doses	16.7 (9/54)	14.8 (8/54)
	1	0 (0/18)	26.7 (4/15)
	3	22.2 (4/18)	5.6 (1/18)
	10	23.8 (5/21)	14.3 (3/21)
Nonsquamous	All doses	17.6 (13/74)	6.8 (5/74)
	1	5.6 (1/18)	5.6 (1/18)
	3	26.3 (5/19)	10.5 (2/19)
	10	18.9 (7/37)	5.4 (2/37)

Brahmer JR, et al. ASCO 2013. Abstract 8030

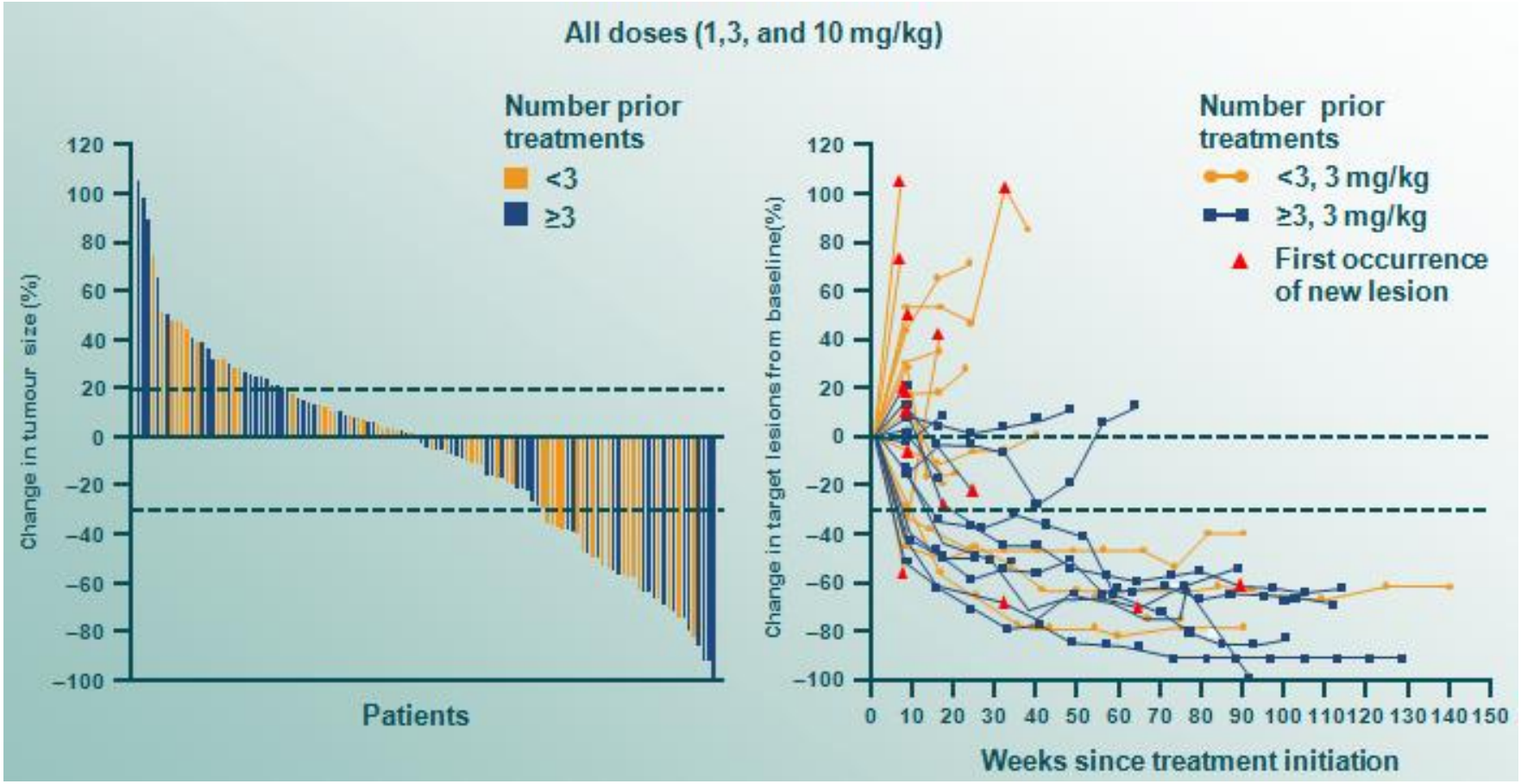
Selected adverse events (≥1%) in patients with NSCLC treated with nivolumab

- Select adverse event defined as an event with potential immunological aetiologies that require more frequent monitoring and/or unique intervention
- All patients have ≥1 year of follow-up
- Drug-related pneumonitis (any grade) occurred in 8 NSCLC patients (6%); 3 patients (2%) had grade 3-4 pneumonitis of which 2 cases were fatal

	Patients, n (%) N=129	
	Any grade	Grade 3/4
Any treatment-related select adverse event	**41 (53)**	**5 (6)**
Skin	**16 (20)**	**0**
Gastrointestinal	**12 (15)**	**1 (1)**
Pulmonary	**7 (9)**	**2 (3)**
Endocrinopathies	**6 (8)**	**0**
Hepatic	**5 (6)**	**1 (1)**
Infusion reaction	**4 (5)**	**1 (1)**
Renal	**3 (4)**	**0**

Adapted from Brahmer JR, et al. Mini-Oral presentation at WCLC 2013. *J Thorac Oncol.* 2013;8(suppl 2):abstract: MO18.03

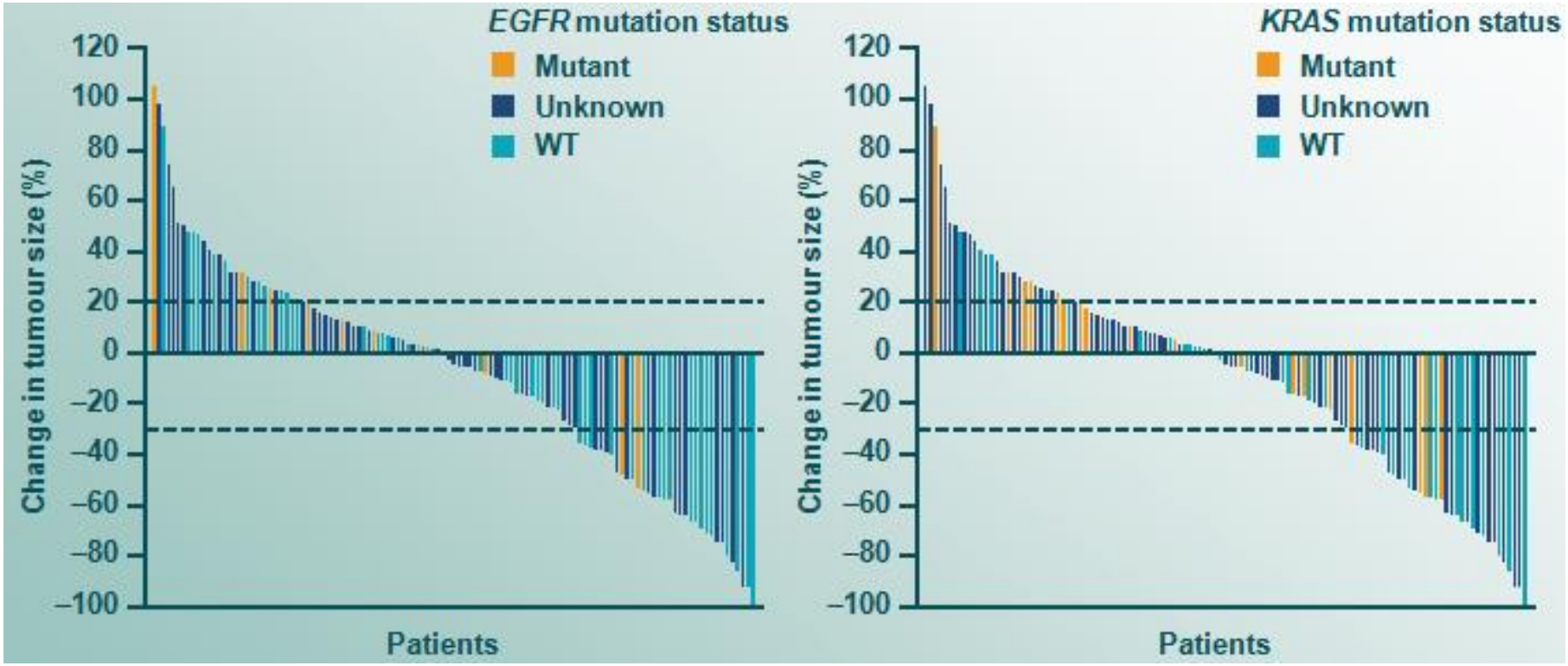
Nivolumab: change in tumour burden and response kinetics by number of prior therapies



Dashed horizontal lines denote 30% decrease for PR (in the absence of new lesions) and 20% increase for PD per RECIST v1.0

Adapted from Gettinger S, et al. Poster presentation at WCLC 2013. *J Thorac Oncol.* 2013;8(suppl 2):abstract: P2.11-038

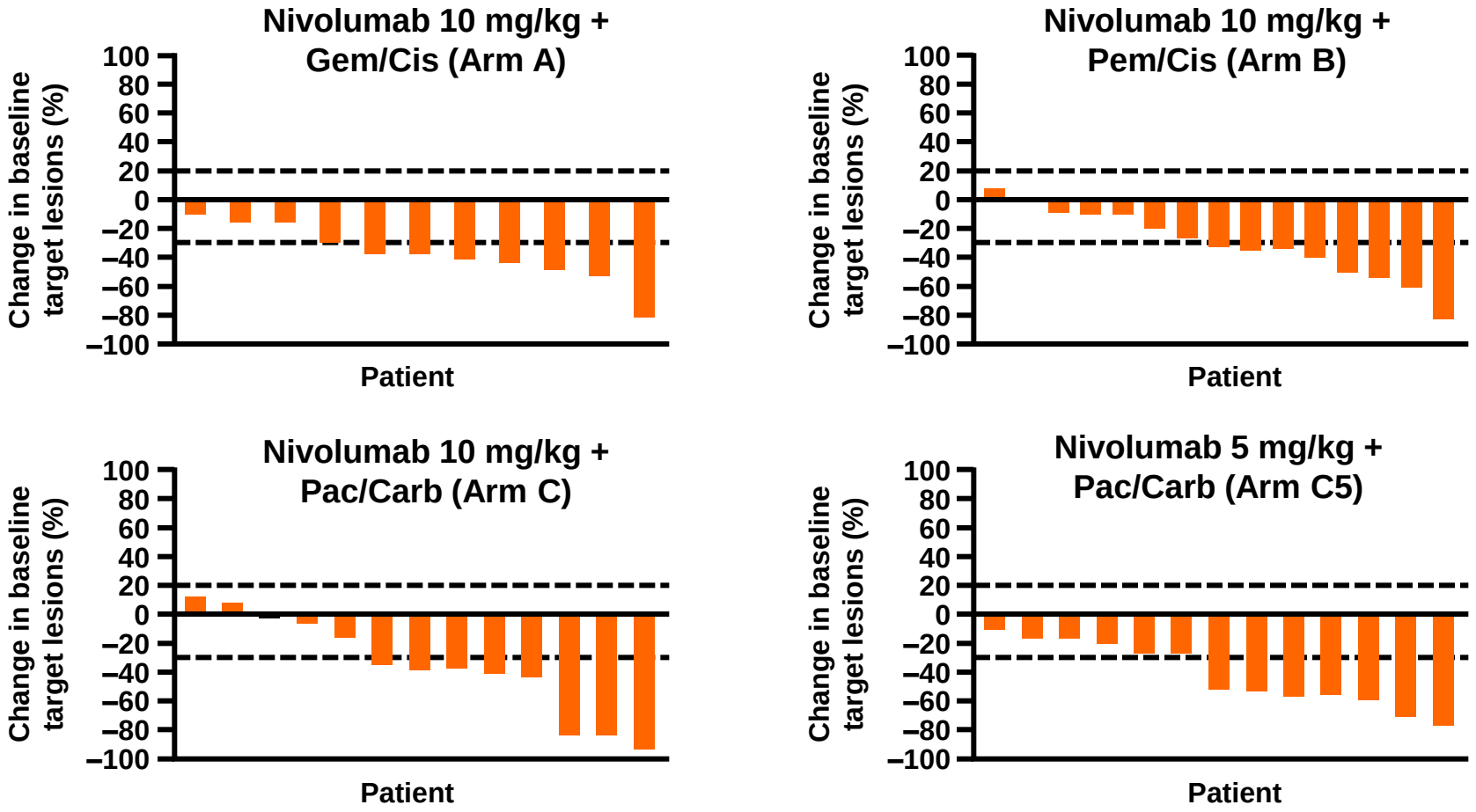
Nivolumab: change in tumour burden according to *EGFR* and *KRAS* mutation status



Dashed horizontal lines denote 30% decrease for PR (in the absence of new lesions) and 20% increase for PD per RECIST v1.0

Adapted from Gettinger S, et al. Poster presentation at WCLC 2013. *J Thorac Oncol.* 2013;8(suppl 2):abstract: P2.11-038

Nivolumab plus CT: change in tumour burden



Baseline tumour measurements are standardised to zero; tumour burden is measured as the sum of the longest diameters of target lesions

Horizontal lines denote 30% decrease for PR and 20% increase for PD per RECIST 1.1 Only patients with both baseline and on-study target lesion measurements are included

Rizvi NA, et al. ASCO 2013. Abstract 8072

Nivolumab plus CT: duration of response

	Nivolumab (10 mg/kg)			Nivolumab (5 mg/kg)
	Gem/Cis n=12 (Arm A)	**Pem/Cis n=15 (Arm B)**	**Pac/Carb n=15 (Arm C)**	**Pac/Carb n=14 (Arm C5)[a]**
Number of responders, n	4	7	7	7
Ongoing responders, n (%)	2 (50)	2 (29)	2 (29)	5 (71)
Estimated median duration of response,[b,c] weeks	NR	25	26	22
Response duration[d]	12/18/ 33+/36+	13/14+/ 18+/18/ 25/32/38	11+/12/14/ 24/27/29/ 39+	11/12+/16+/17+/ 22+/22/24+

Carb = carboplatin; Cis = cisplatin; Gem = gemcitabine; Pac = paclitaxel; Pem = pemetrexed
[a]Protocol was amended to include an extra arm for this combination;
[b]Time from first response to documented progression, death, or last tumour assessment;
[c]Estimated mean duration determined by Kaplan-Meier curves;
[d]+indicates ongoing response

Rizvi NA, et al. ASCO 2013. Abstract 8072

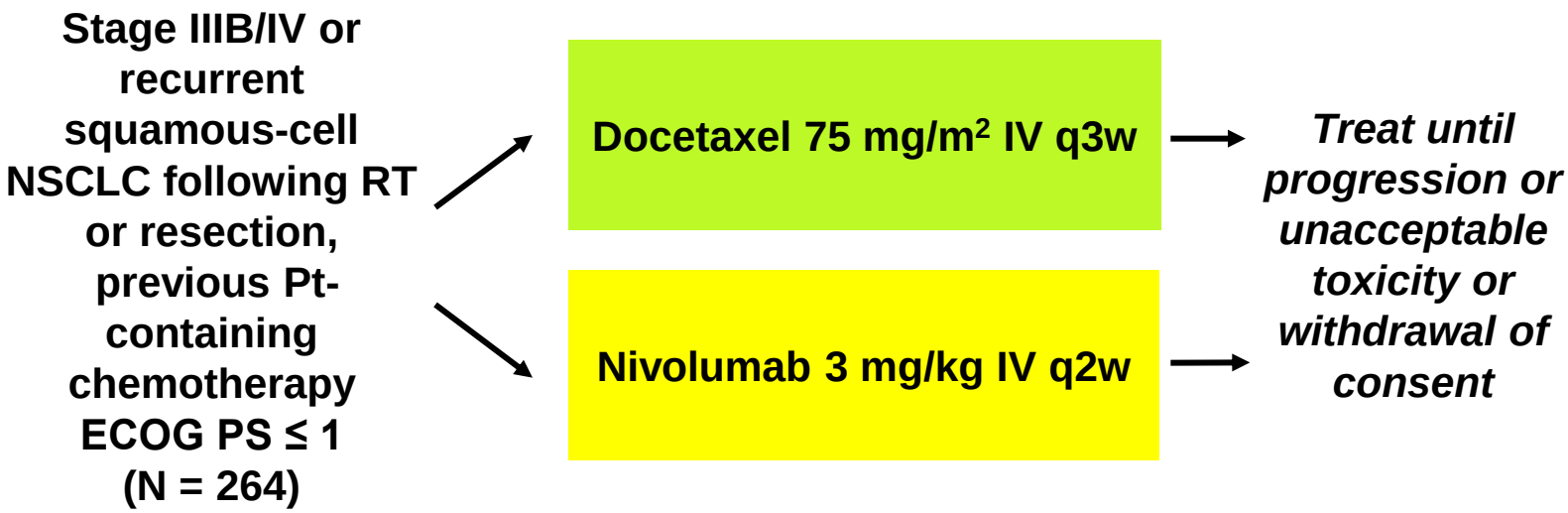
Nivolumab plus CT: duration of response

	Nivolumab (10 mg/kg)			Nivolumab (5 mg/kg)	
Treatment-related AE, n (%)	Gem/Cis n=12 (Arm A)	Pem/Cis n=15 (Arm B)	Pac/Carb n=15 (Arm C)	Pac/Carb n=14 (Arm C5)[a]	Total N=56
Any AE	0	5 (33)	3 (20)	4 (29)	12 (21)
Pneumonitis	0	2 (13)	0	2 (14)	4 (7)
Acute renal failure	0	1 (7)	0	2 (14)	3 (5)
Hypersensitivity	0	1 (7)	2 (13)	0	3 (5)
Colitis	0	1 (7)	1 (7)	0	2 (4)

Carb = carboplatin; Cis = cisplatin; Gem = gemcitabine; Pac = paclitaxel; Pem = pemetrexed
[a]Protocol was amended to include an extra arm for this combination

Rizvi NA, et al. ASCO 2013. Abstract 8072

Ongoing phase III: Nivolumab in squamous NSCLC



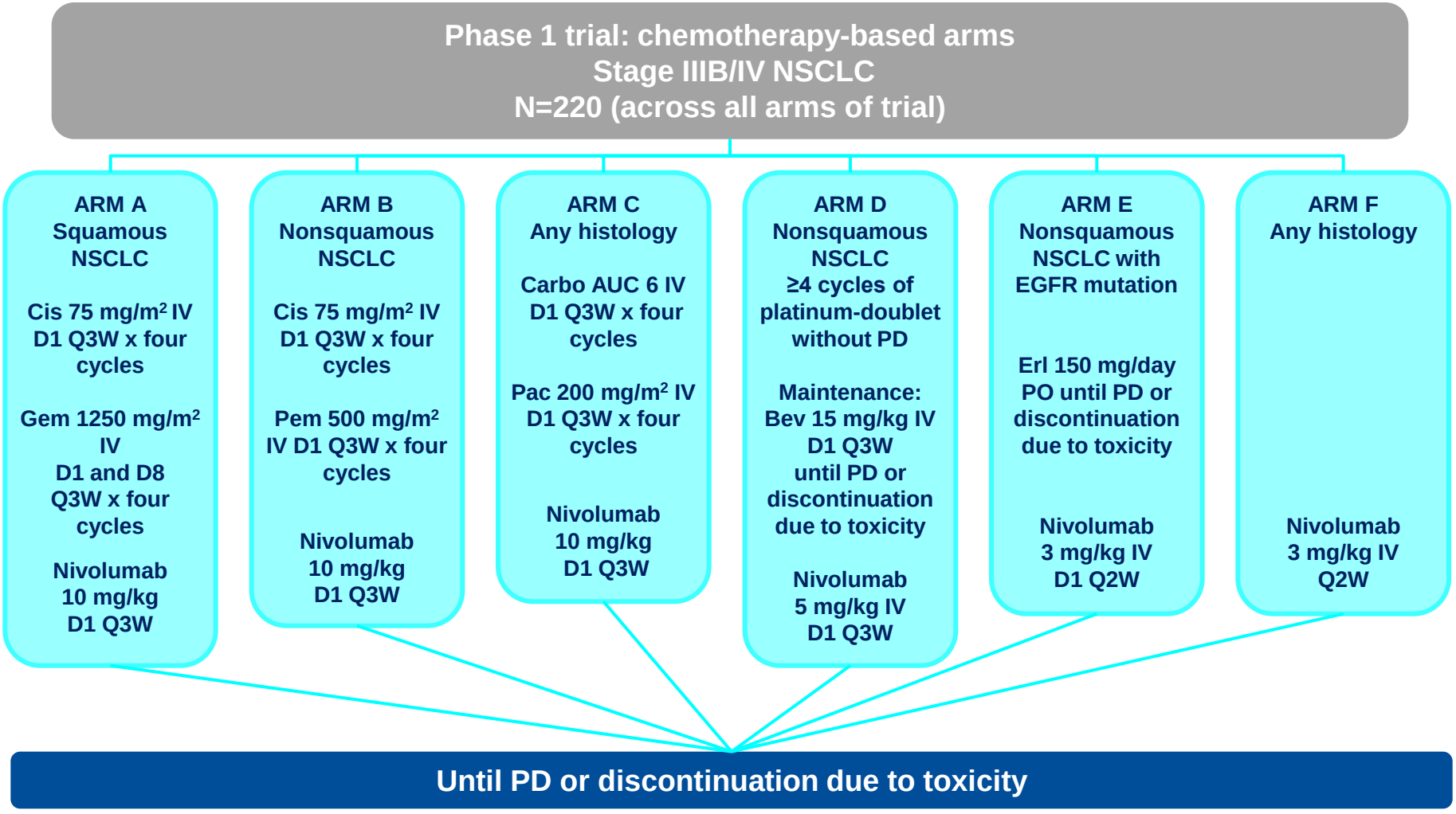
- Primary endpoints: ORR, OS
- Secondary endpoints: PFS, ORR, and OS in PD-L1–positive vs PD-L1–negative subgroups, duration of OR, time to OR, proportion of patients exhibiting disease-related symptom progression as per Lung Cancer Symptom Scale

ClinicalTrials.gov. NCT01642004

Nivolumab development in NSCLC

Setting	Population	Study	Design	Endpoint	Status
1st-line	Treatment-naïve	CA209-012 (phase 1)	Nivolumab monotherapy; nivolumab combined with platinum doublets; erlotinib; bevacizumab or ipilimumab	Safety; antitumour activity	Ongoing
	Treatment-naïve	CA209-026 (phase 3)	Nivolumab vs investigator's choice of chemotherapy	PFS in high PD-L1 expression tumours	Not yet recruiting
2nd-line	Prior platinum, squamous histology	CA209-017 (phase 3)	Nivolumab vs docetaxel	ORR/OS	Ongoing/ Accrual complete
	Prior platinum, nonsquamous histology	CA209-057 (phase 3)	Nivolumab vs docetaxel	OS	Ongoing/ Accrual complete
3rd-line and beyond	Squamous histology, ≥2 prior treatments	CA209-063 (phase 2)	Nivolumab monotherapy	ORR	Ongoing/ Accrual complete

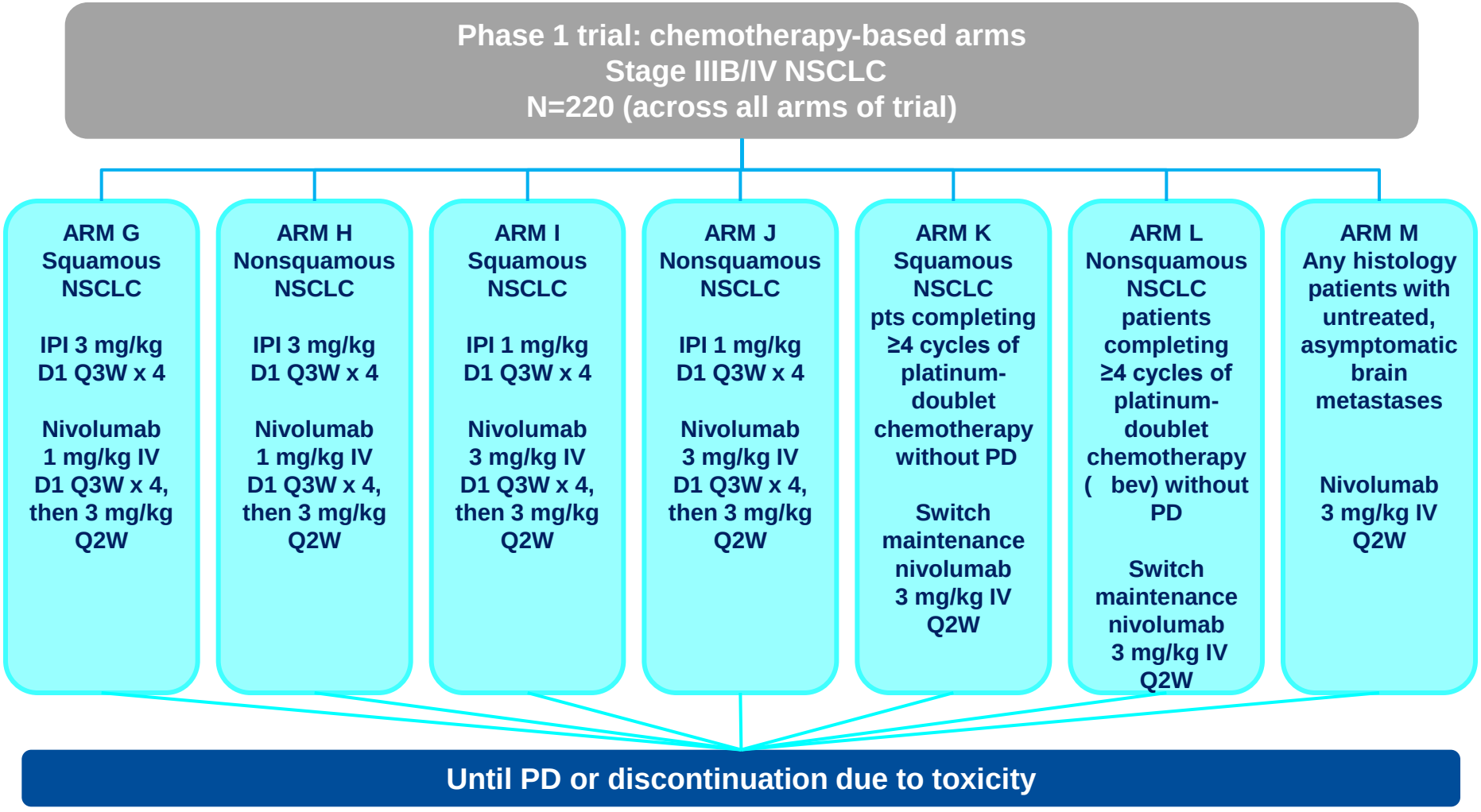
CA209-012/NCT01454102: ARMS A-F



Protocol was amended to include Arm C5 to obtain further information regarding clinical safety and activity of nivolumab at 5 mg/kg in combination with paclitaxel and carboplatin.

www.clinicaltrials.gov

CA209-012/NCT01454102: ARMS G-M



www.clinicaltrials.gov

Lambrolizumab (MK-3475) in 2nd line for NSCLC

Objectives of Protocol:

- Assess safety and efficacy in patients with previously treated NSCLC

Eligibility Criteria for Protocol:

- 2 prior systemic therapies
- ≥1 measurable lesion
- ECOG PS of 0-1
- Submission of a new tumor specimen for PD-L1 analysis

Treatment: 10 mg/kg IV Q3W until progression by irRC, intolerable toxicity, or consent withdrawal

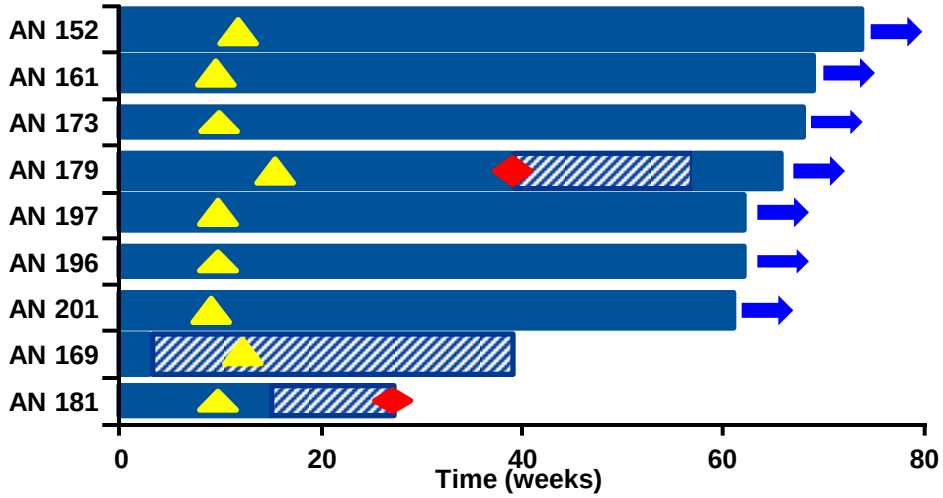
Patients: N = 38: 42% male, 45% aged ≥65 years, 58% with ECOG PS 1, 66% former/current smokers, 16% squamous, 11% treated brain metastases

PD-L1 Status: Assessed with a Merck proprietary IHC clinical trial assay; 61% positive (>0), 26% negative, 13% not evaluable; potential cut point determined by the Youden Index from a receiver operator characteristics curve

IASLC, 15th WCLC, abst 2416, 2013

Lambrolizumab (MK-3475) in 2nd line for NSCLC

Subgroup	irRC, Investigator Review			RECIST v1.1, Independent Review			
	N	ORR, n (%) [95% CI]	Median PFS, wk (95% CI)	N	ORR,* (%), [95% CI]	Median PFS, wk (95% CI)	Median OS, wk (95% CI)
All	38	9 (24%) [11%, 40%]	9.1 (8.3, 17.4)	33	7 (21%) [9%, 39%]	9.7 (7.6, 17)	51 (14, NR)
Non-squamous	31	7 (23%) [10%, 41%]	9.1 (8.3, 17.0)	26	4 (16%) [4%, 35%]	10.3 (7.6, 17)	35 (14, NR)
Squamous	6	2 (33%) [4%, 78%]	23.5 (2.7, NR)	6	2 (33%) [4%, 78%]	15.2 (1.4, NR)	NR (2.7, NR)
Patients with measurable disease on baseline imaging and an evaluable tumor specimen for PD-L1							
Score ≥ potential cut point	9	6 (67%) [30%, 93%]	—	7	4 (57%) [18%, 90%]	—	—
Score < potential cut point	24	1 (4%) [0%, 21%]	—	22	2 (9%) [1%, 29%]	—	—



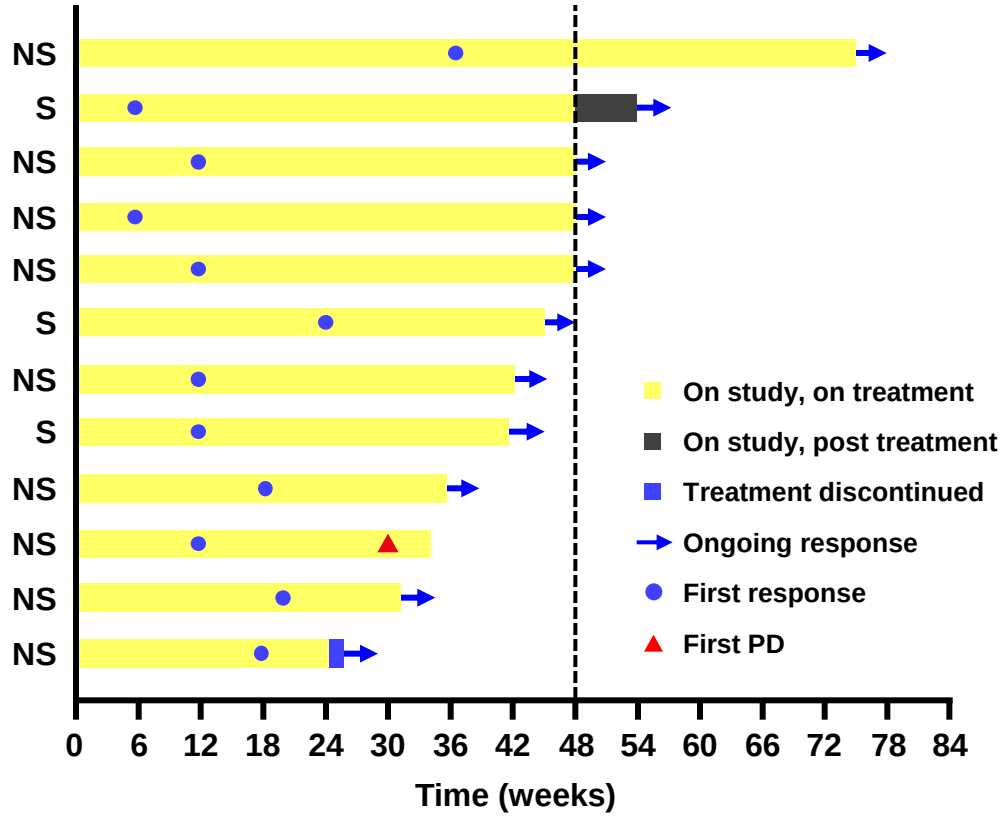
MK-3475 Responders Have Prolonged Duration of Response

On therapy
Confirmed response
Off therapy
Progression
Therapy continuing

IASLC, 15th WCLC, abst 2416, 2013

MPDL3280A in monotherapy in NSCLC: phase I trial

- Response in 12/53 patients (ORR: 23%)
  - 3 squamous
  - 9 nonsquamous
- PD rate: 40% (21/53)
- Rapid and durable responses

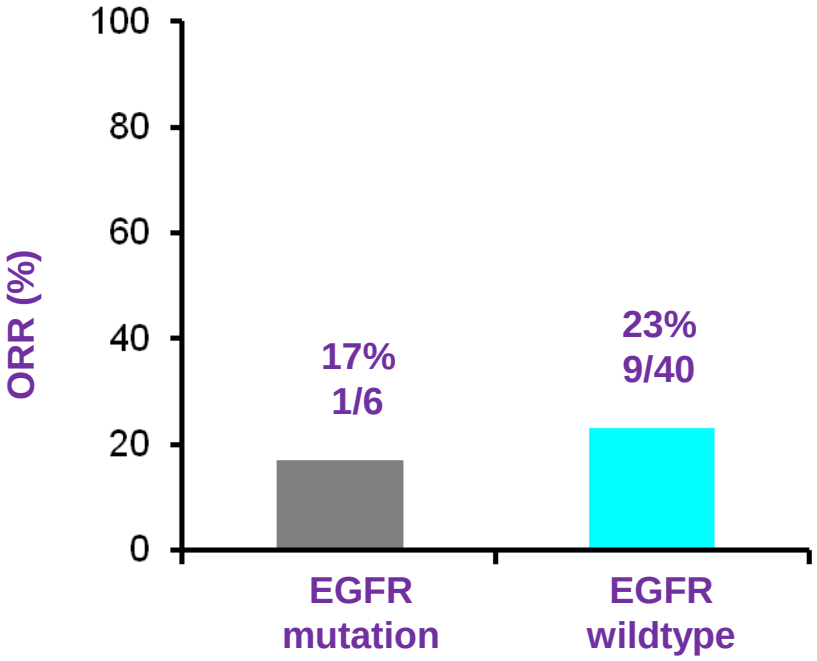


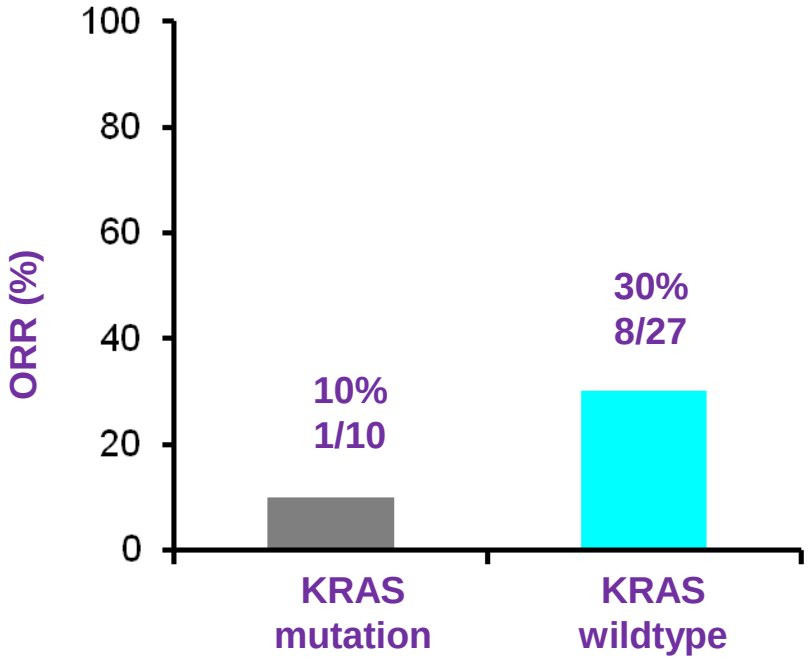
PD = progressive disease; ORR = objective response rate; NS = nopnsquamous; S = squamous
[a]ORR includes investigator assessed unconfirmed and confirmed partial responses per RECIST v1.1
[b]patients experiencing ongoing benefit per investigator
Patients first dosed at 1-20 mg.kg by Oct 1 2012. Data cut off April 30 2013

Horn L, et al. Mini-Oral presentation at WCLC 2013. *J Thorac Oncol.* 2013;8(suppl 2):abstract: MO18.01

MPDL3280A: activity across NSCLC patient subgroups

- EGFR status (n=53)
  - EGFR mutation positive: 11%; EGFR wildtype: 76%; Unknown: 13%
- KRAS status (n=53)
  - KRAS mutation positive: 19%; KRAS wildtype: 51%; Unknown: 30%





Horn L, et al. Mini-Oral presentation at WCLC 2013. *J Thorac Oncol.* 2013;8(suppl 2):abstract: MO18.01

Efficacy ?

Anti-PD-1 **Nivolumab**

- 129 NSCLC pts[1] – ORR 17,1%, (21,7%)*
  - *50% responded in 8 weeks*
  - *Median OS 9,9 months*

Anti-PD-1 **MK-3475**

- 38 NSCLC pts[2] – ORR 21%, (24%)*
- 221 NSCLC pts (80% PD-L1+)[3] – ORR 15%, (21%)*

Anti-PD-L1 **MPDL3280A**

- 175 pts[5] (85 NSCLC – 53 evaluable – 85% PD-L1+) – ORR 23%

Anti-PD-L1 **BMS 936559**

- 207 pts[4] (75 NSCLC – 49 evaluable) – ORR 10%

Anti-PD-L1 **MEDI4736**

- 26 pts[6] (13 NSCLC) – ORR 15%

*including immune responders, irRECIST

[1]Brahmer, et al. IASLC WCLC, 2013 [2]Garon E, et al. IASLC WCLC, 2013 [3] Garon E, et al. ASCO 2014 abstr 8020
[4]Brahmer, et al. NEJM 2012 [5]Horn L, et al. IASLC WCLC ,2013 abstr MO18.01
[6]Soria JC, et al. European Cancer Congress 2013 abstr 3408

Toxicity ?

Anti-PD-1 **Nivolumab -** 129 NSCLC pts[1]

- 53% related AEs, 5% Gr 3-4
- Pneumonitis – 6%, Gr 3-4 3 pts (2%) – 2 deaths

Anti-PD-1 **MK-3475 -** 221 NSCLC pts[2]

- 48% related AEs - fatigue, 6% Gr 3-4
- Pneumonitis – Gr 3-4 3 pts (1%)

Anti-PD-L1 **MPDL3280A -** 85 NSCLC pts[4]

- 66% related AEs, 11% Gr 3-4 - fatigue
- No Gr 3-5 pneumonitis

Anti-PD-L1 **BMS 936559 -** 207 pts[4]

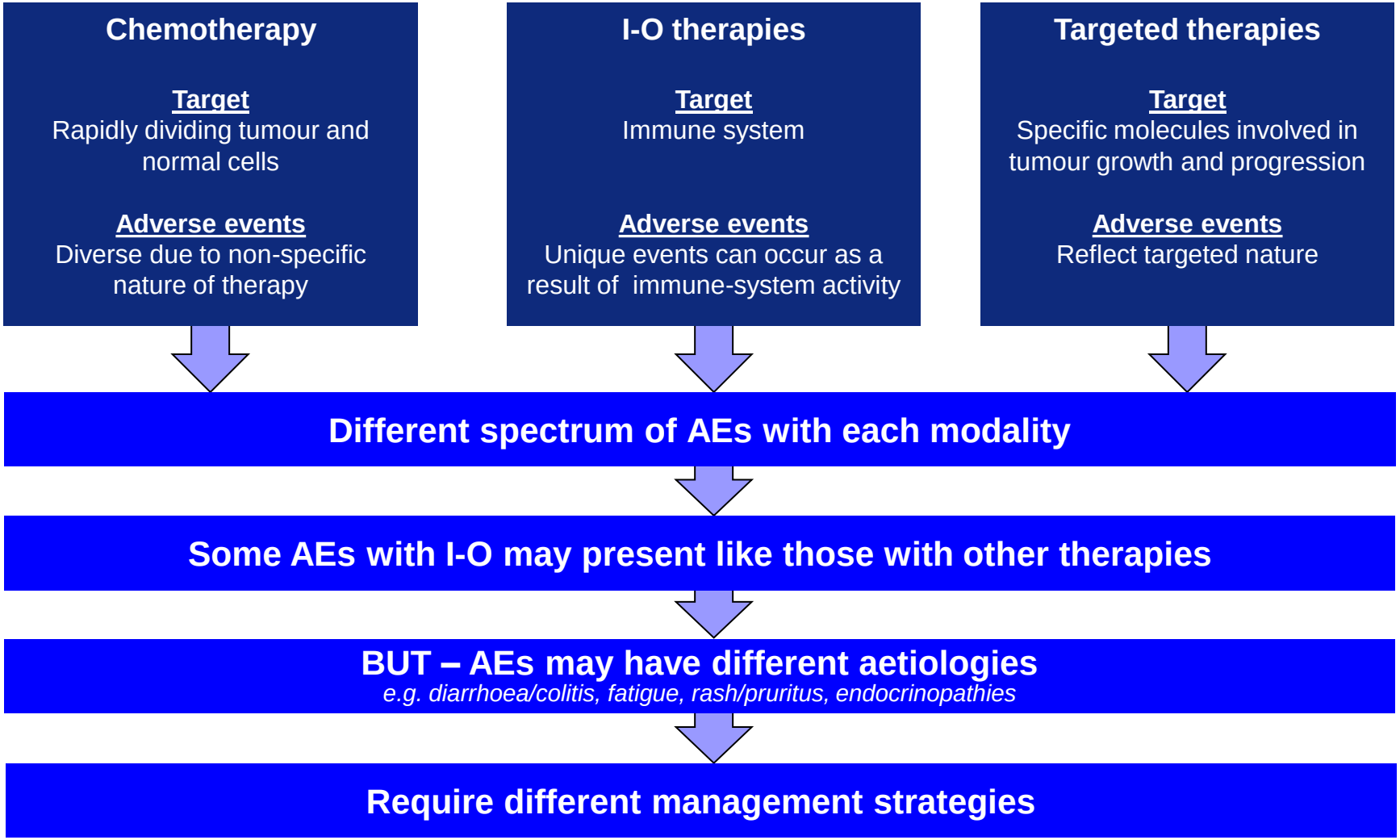
- 61% related AEs, 9% Gr 3-4
- No pneumonitis

Anti-PD-L1 **MEDI4736 -** 26 pts[5] (13 NSCLC)

- 34% related AEs, no Gr 3-4
- No pneumonitis, no colitis

[1]Brahmer, et al. IASLC WCLC, 2013 [2]Garon E, et al. IASLC WCLC, 2013 [3]Brahmer, et al. NEJM 2012
[4]Horn L, et al. IASLC WCLC ,2013 abstr MO18.01 [5]Soria JC, et al. European Cancer Congress 2013 abstr 3408

Tolerability of oncology therapies



American Cancer Society. *Treatment types* http://www.cancer.org/; Topalian SL, et al. *N Eng J Med* 2012;366(26):2443–2454 and oral presentation at ASCO 2013: *J Clin Oncol* 2013;31(15 suppl):abstract 3002; Hamid O, et al. *N Eng J Med* 2013;369:134–144; Dendreon. PROVENGE® Prescribing Information updated June 2011; Bristol-Myers Squibb. YERVOY (ipilimumab) REMS and Prescribing Information available at http://www.yervoy.com accessed November 26, 2013

Predicting / Enriching for response ?

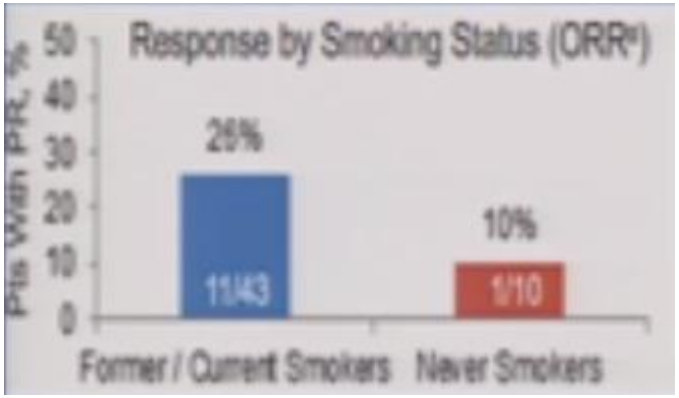
ORR : 17,1 – 24 %

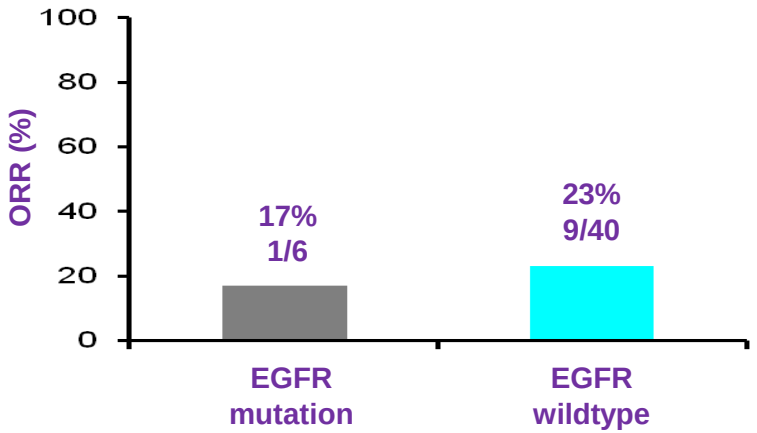
- Tissue:
  - IHC for T cells and PD-L1
  - Gene signature for immune responsiveness, immunoscore
- Blood markers, imaging
- Clinical factors

Clinical factors for response ?

- **Histology?** – SCLC more likely to respond?
  - Nivolumab 14/76 RR - 33% SCLC, 12% non-SCLC [1]
  - MK-3475 9/38 RR – 33% SCC, 23 non-SCLC [2]

- **Smoking? Mutation status?**
  - 85 pts, with MPDL3280A [3, 4]





[1]Brahmer, et al. IASLC WCLC, 2013 [2]Garon E, et al. IASLC WCLC, 2013
[3]Horn L, et al. IASLC WCLC ,2013 abstr MO18.01 [4]Soria JC, et al. European Cancer Congress 2013 abstr 3408

Planned and ongoing lung cancer trials

Phase	Treatment	Patient population	Status
Nivolumab			
1	Plus various (including ipilimumab)	NSCLC	Recruiting
1B	Monotherapy	Advanced or recurrent NSCLC	Ongoing*
2	Monotherapy	Advanced or metastatic NSCLC	Ongoing*
3	Monotherapy	Squamous NSCLC	Ongoing*
3	Monotherapy	Stage IV first line or PDL-1+ NSCLC	Not yet open
3	Monotherapy	Following platinum failure	Ongoing*
3	Monotherapy	Advanced or metastatic NSCLC	Not yet open
Pembrolizumab			
1	Monotherapy and plus chemotherapy	NSCLC	Recruiting
1	Monotherapy	PDL-1+ NSCLC	Recruiting
1	Monotherapy	Locally advanced NSCLC	Recruiting
1/2	Combination	Advanced or metastatic NSCLC	Recruiting
2	Monotherapy	NSCLC and brain metastases	Not yet open
2/3	Monotherapy	Prior-treated NSCLC	Recruiting

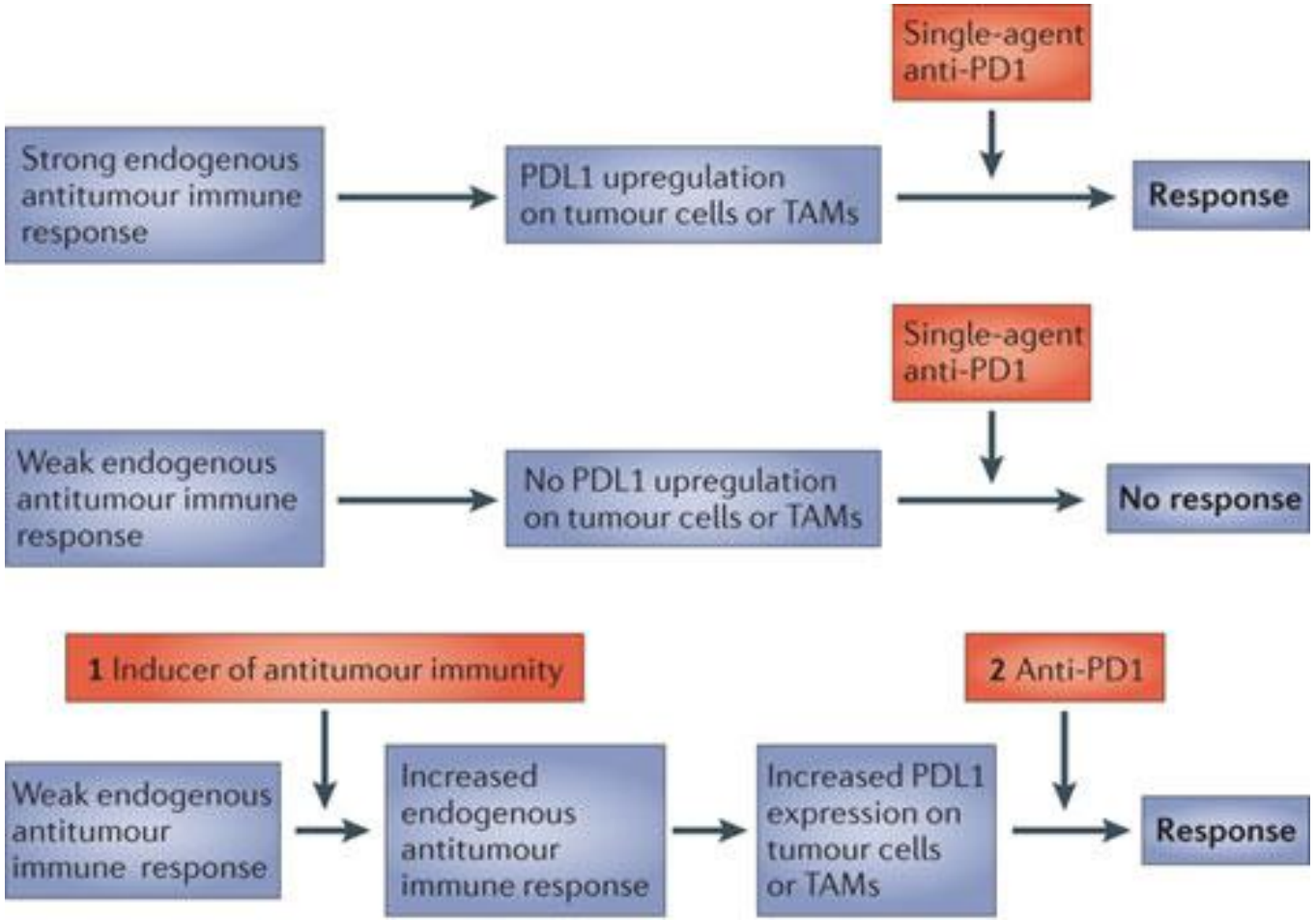
Phase	Treatment	Patient population	Status
Ipilimumab			
1	Plus erlotinib or crizotinib	Extensive disease SCLC	Not yet open
1	Plus chemotherapy	Neoadjuvant NSCLC	Recruiting
1	Plus pembrolizumab	Locally advance or metastatic NSCLC	Recruiting
2	Monotherapy	Limited disease SCLC	Not yet open
2	Plus carboplatin and etoposide	Extensive disease SCLC	Recruiting
3	Plus etoposide and platinum therapy	Newly diagnosed extensive disease SCLC	Recruiting
3	Plus paclitaxel and carboplatin	Squamous NSCLC	Recruiting
MPDL3280A1			
1b	Plus Tarceva	NSCLC	Not yet open
2	Monotherapy	PDL-1+ locally advanced NSCLC	Recruiting
2	Plus docetaxel	Locally/advanced disease post-platinum NSCLC	Recruiting
3	Monotherapy	Locally/advanced disease post-platinum NSCLC	Recruiting
Tremelimumab			
1	Plus gefitinib	NSCLC	Recruiting
1b	Plus MED14763	Advanced NSCLC	Recruiting

www.clinicaltrials.gov, accessed 26 March 2014

*** And not recruiting**

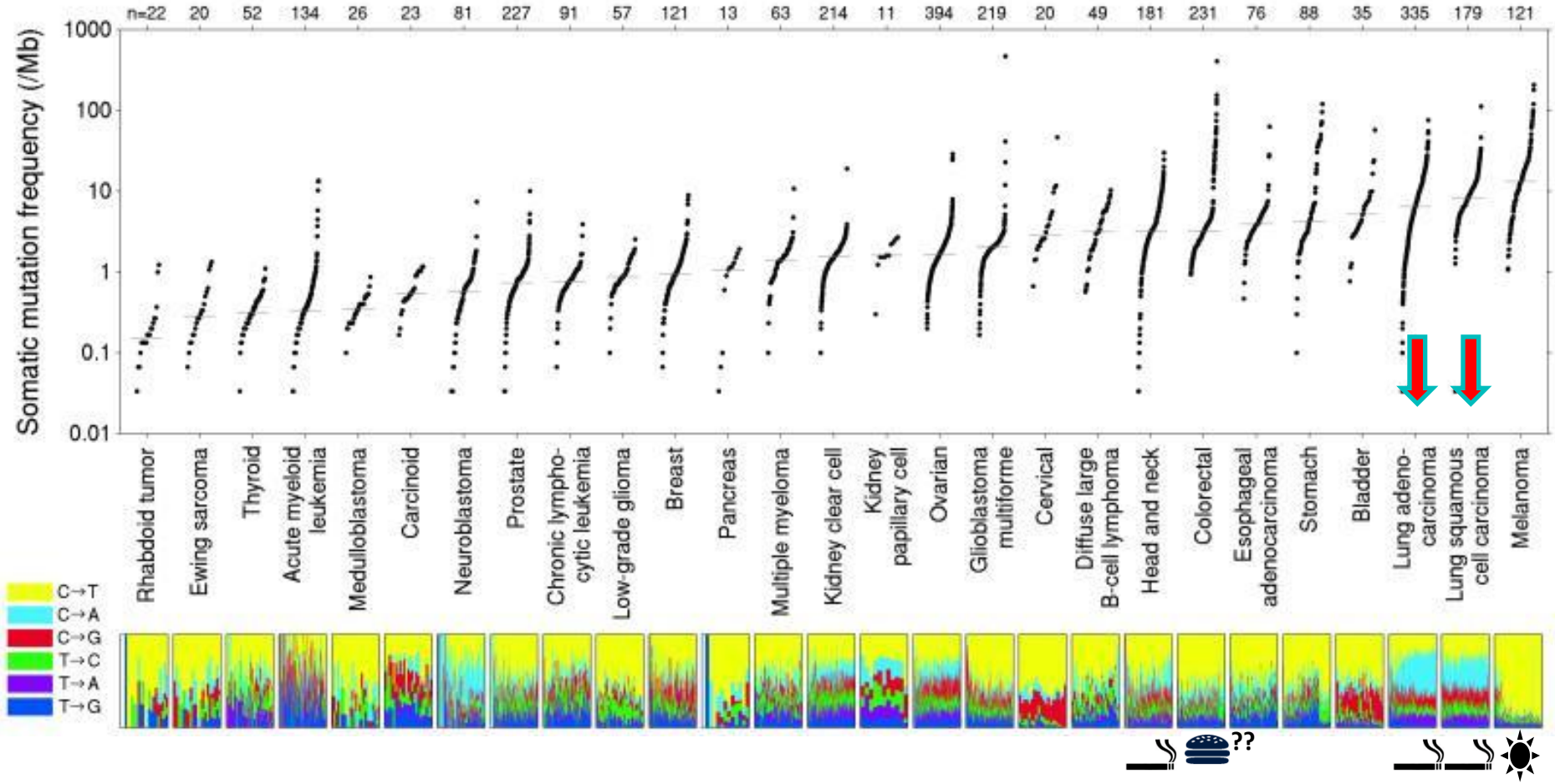
Implications of the adaptive immune resistane mechanism for combinatorial immunotherapy of cancer

Will immunotherapy obsolete CT/targeted therapy?
No – CT/targeted therapy primes tumour immunity



Pardoll DM. Nature Rev Cancer 12:252-264, 2012

Magnitude of genomic derangement



Tumours with increased mutations are more likely to have increased T cells

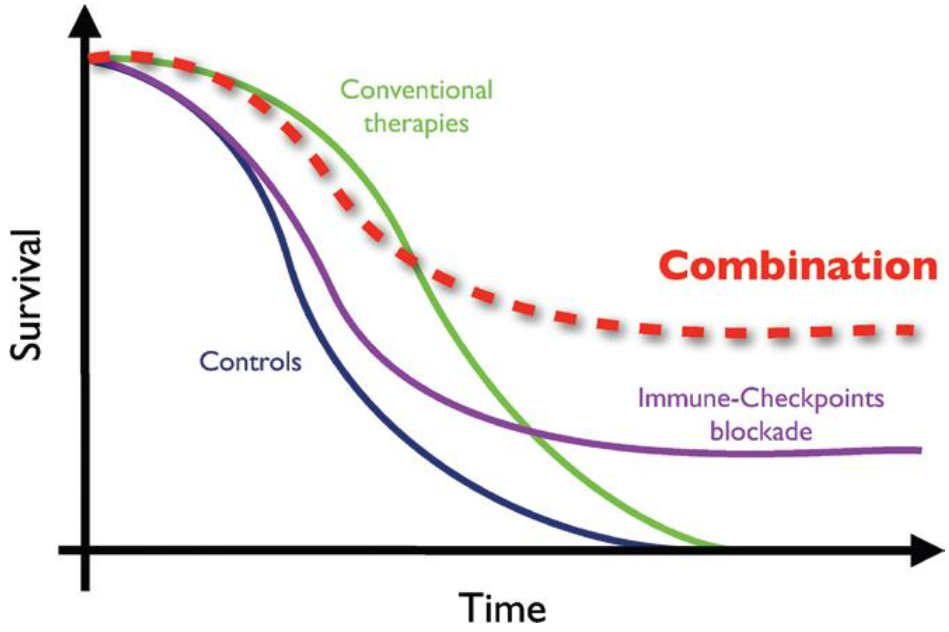
Lawrence MS, et al. Nature 499: 214-218, 2013

Immunotherapy – The beginning of the end for cancer

Transforming cancer into chronic disease

“Immunotherapies wil likely become the treatment backbone in up 60% of cancers over the next 10 years compared with < 3% today.”

Andrew Baum, MD



Champiat S, et al. J Thorac Oncol 9:144-153, 2014

Open questions

→ Anti-PD1 vs anti-PD-L1 (schedule)

→ Augment the efficacy (combination therapy, sequencing, maintenance)

→ Combination therapy (CT, targeted agents, immunotherapy)

→ Duration of therapy (1 year, 2 years, indefinitely)

→ Toxicity (pneumonitis)

→ Treat beyond progression

→ What to do after acquired resistance

→ PD-L1 as a predictive biomarker or other biomarkers

Summary

→ Anti-tumour immune response through vaccination is appealing, but achieving objective response is quite rare.

- *Nevertheless cancer vaccines remain a valid treatment that need further development*
- *New formulations/vaccine vectors, new antigens and application together with checkpoint blockade will likely rejuvenate cancer vaccine strategies*

→ Immune-checkpoint blockade (CTLA-4, PD-1, PG-L1 antibodies) has demonstrated clear evidence of objective responses and survival.

- *Probably and like several trials are seeking, we will need to combine conventional therapy with immune checkpoint blockade*
- *Unanswered safety and efficacy questions*

→ Immunotherapies and combination immunotherapies will be the wave of the future.

- *Key: improve responses*

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