

Concept of Immuno-Oncology/therapy

Interest on lung cancer brain metastases?

4th Annual Brain Metastases Research and Emerging Therapy Conference
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Fabrice Barlesi, MD, PhD

*Multidisciplinary Oncology
& Therapeutic Innovations Dept
INSERM U911
Marseille - France*



**Assistance Publique
Hôpitaux de Marseille**



Disclosure slide

I provided consultations and attended advisory boards for Astra-Zeneca, Bristol-Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Glaxo-Smithkline, Novartis, and Pfizer, for which I received appropriate honoraria.

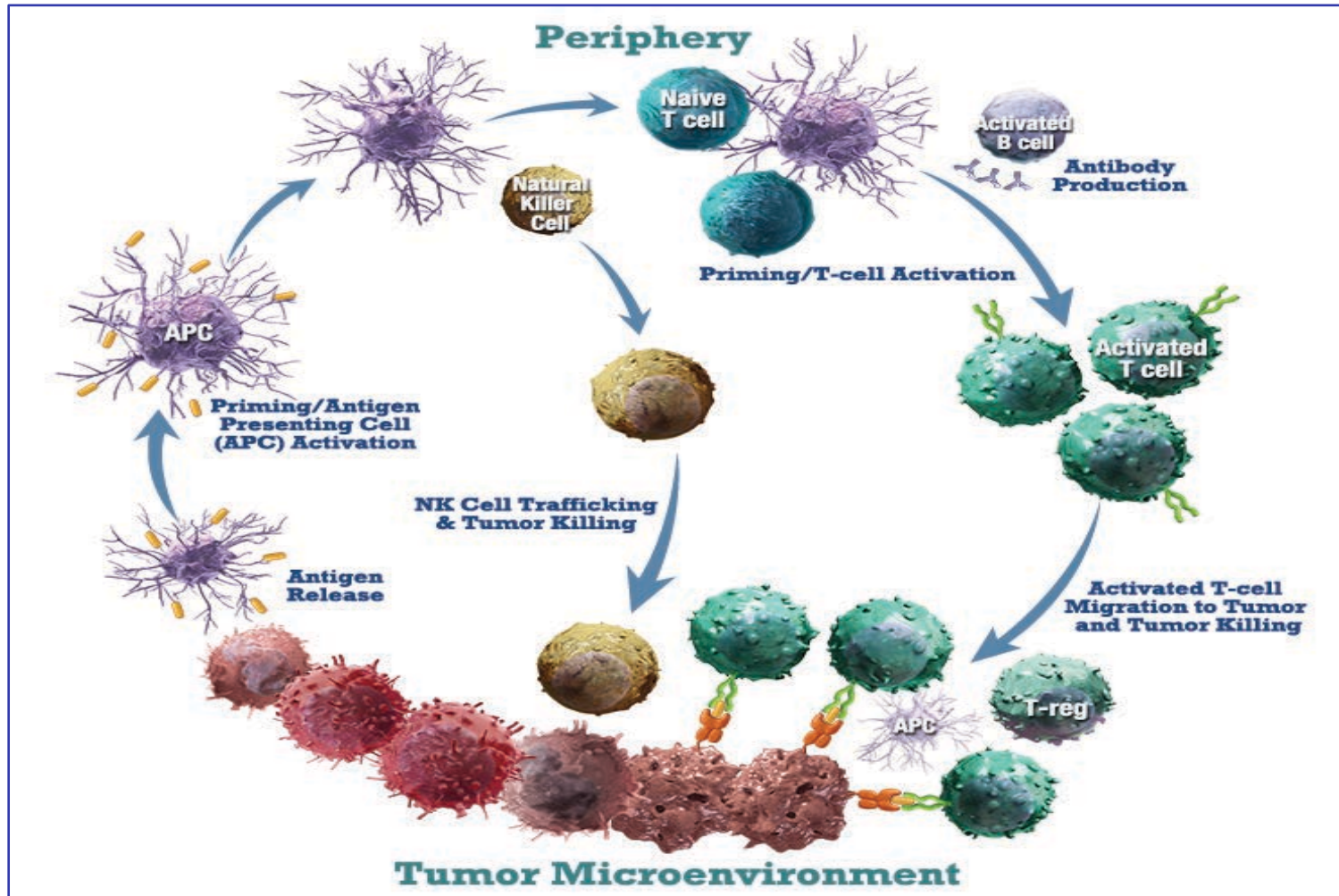
Agenda

- **Concept of immuno-oncology**
- **Main compounds and registrations**
- **Focus on lung cancer results**
- **Interest in lung cancer brain mets treatment**

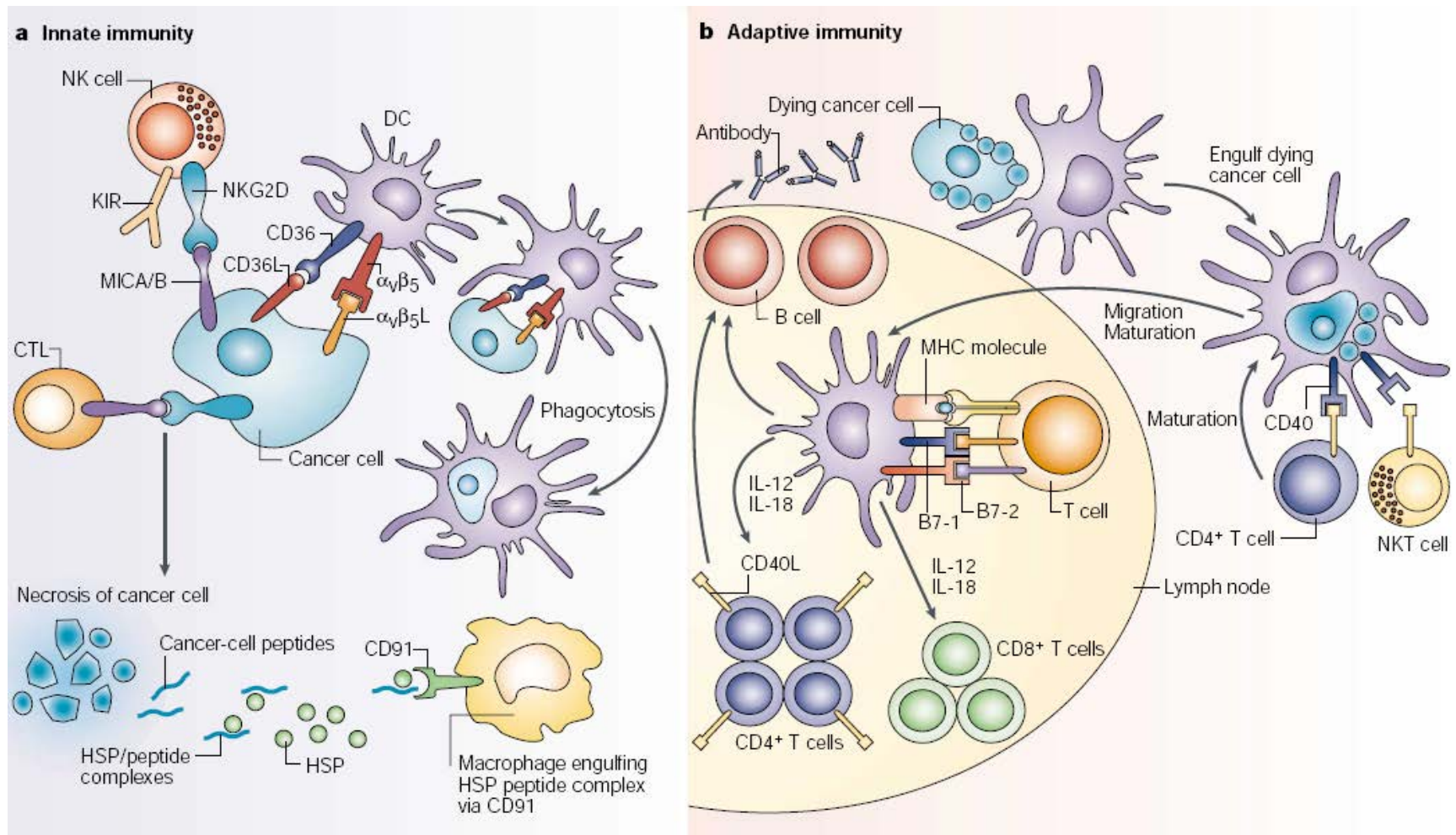
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Multiple and complex mechanisms

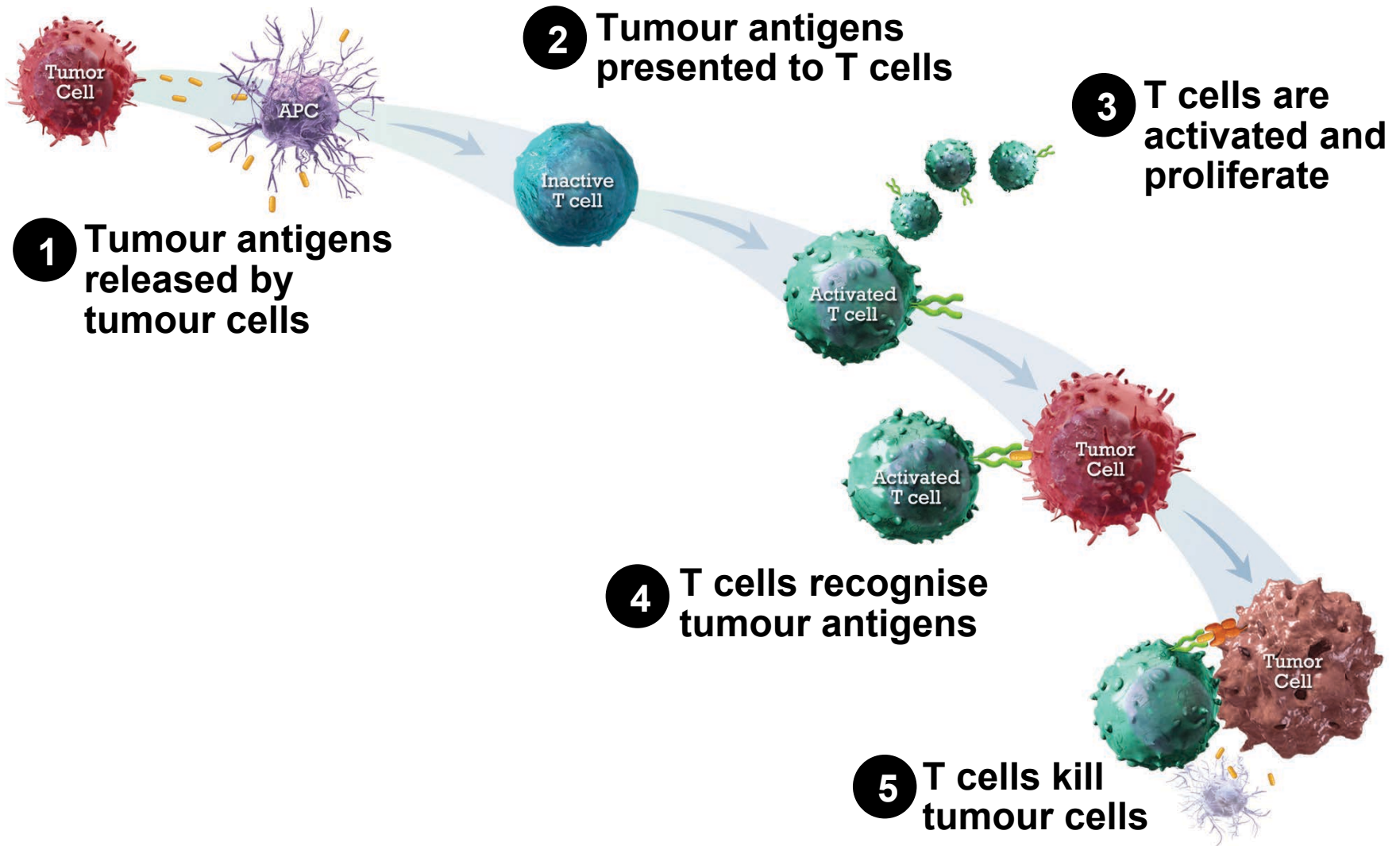


Innate and adaptative components



Dranoff G, Nat Rev Cancer 2004

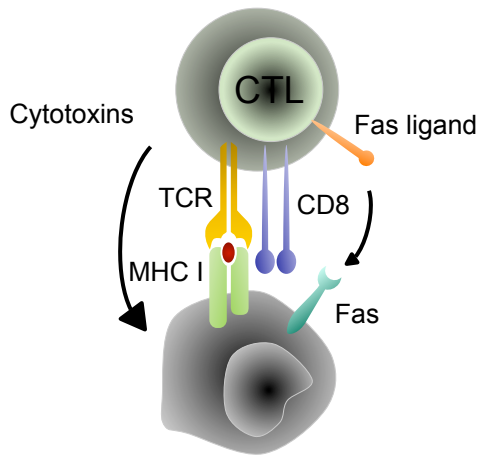
T-cell anti-tumor response



Other key effector cells

CD8⁺ Effector T cells

Destroy tumour cells

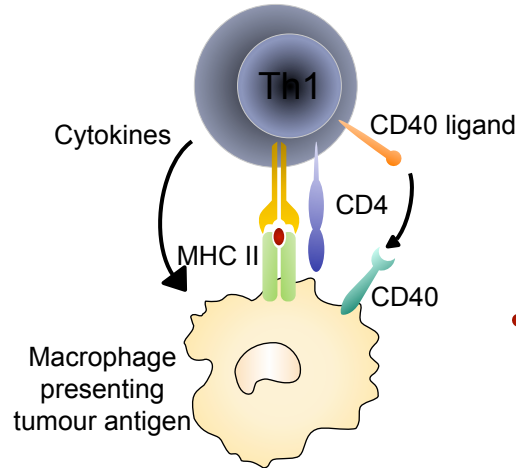


Key cytotoxic effector molecules

Perforin
Granzymes
Granulysin
Fas ligand

Th1 CD4⁺ Helper T cells

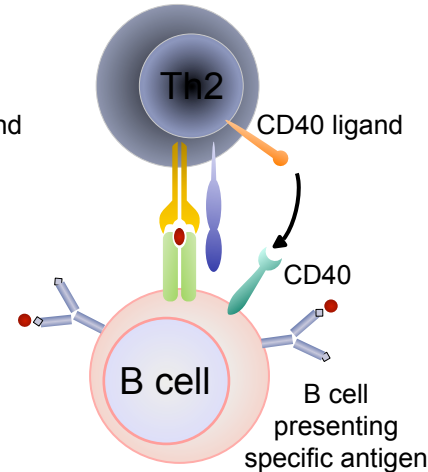
Produce cytokines that mediate inflammatory and effector responses; modulate CTLs



Key effector molecules

IFN- γ
GM-CSF
TNF- α
CD40 ligand
Fas ligand

Help B cells make antibody; modulate CTLs

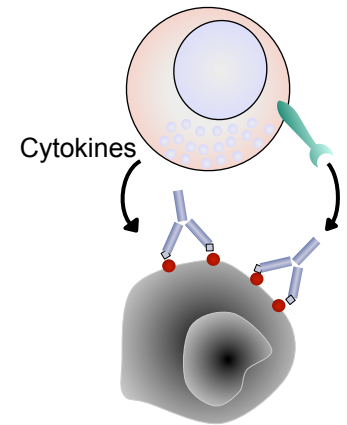


Key effector molecules

IL-4
IL-5
IL-15
CD40 ligand

Natural Killer cells

Destroy antibody-coated tumour cells or tumour cells lacking MHC I

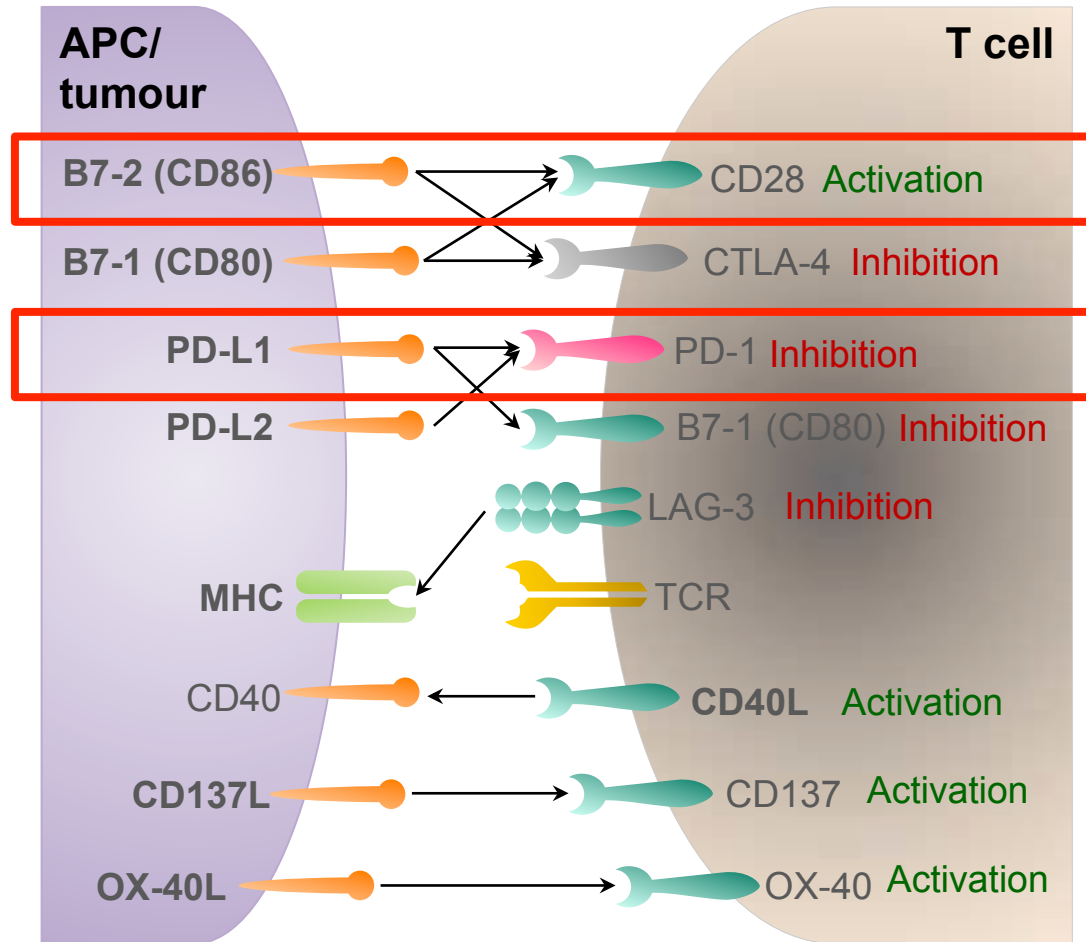


Key effector molecules

IFN- γ
TNF- α

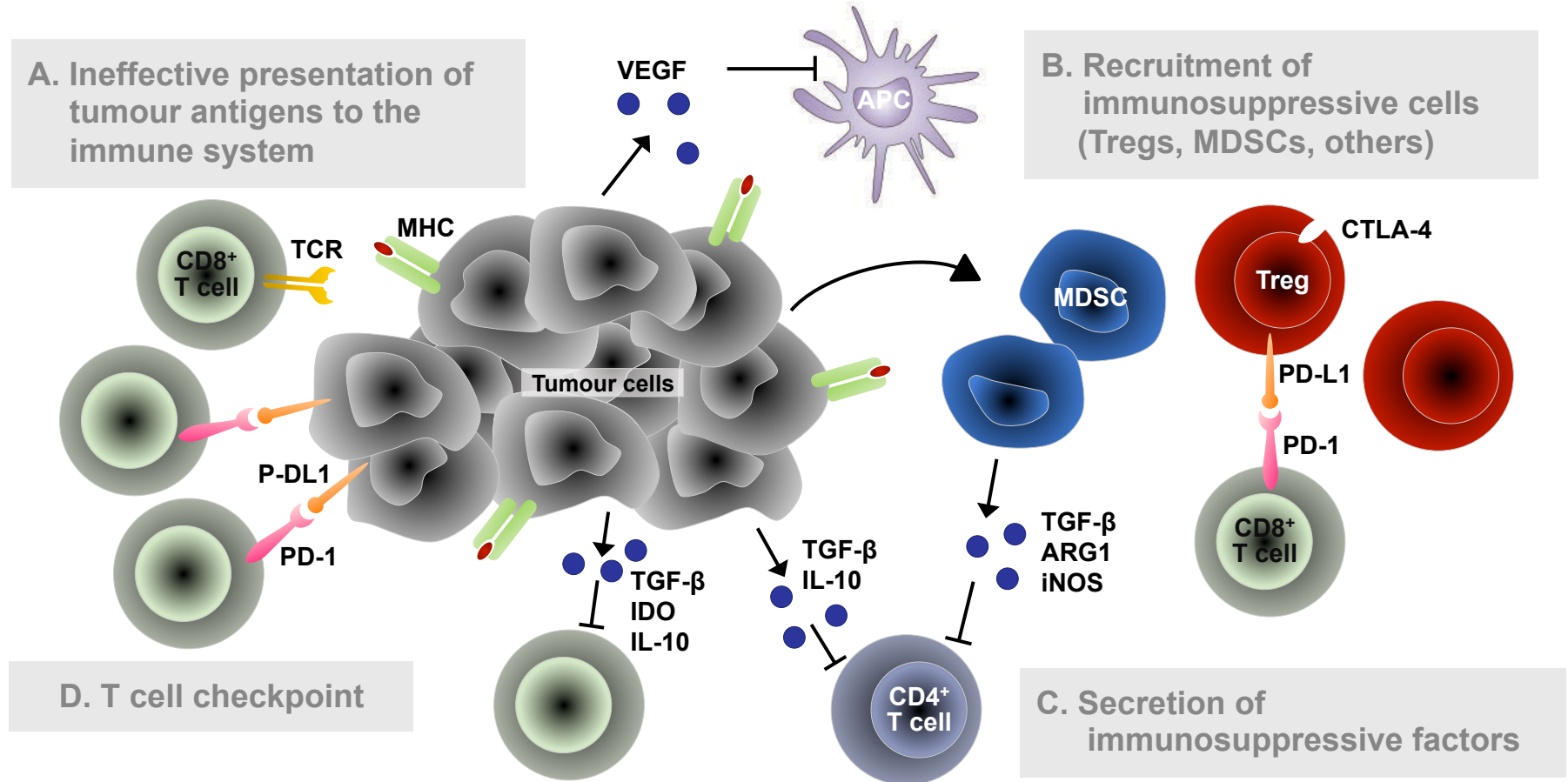
Gettinger et al, ASCO 2014 (Abs#8024)

Immune checkpoints limit immune response



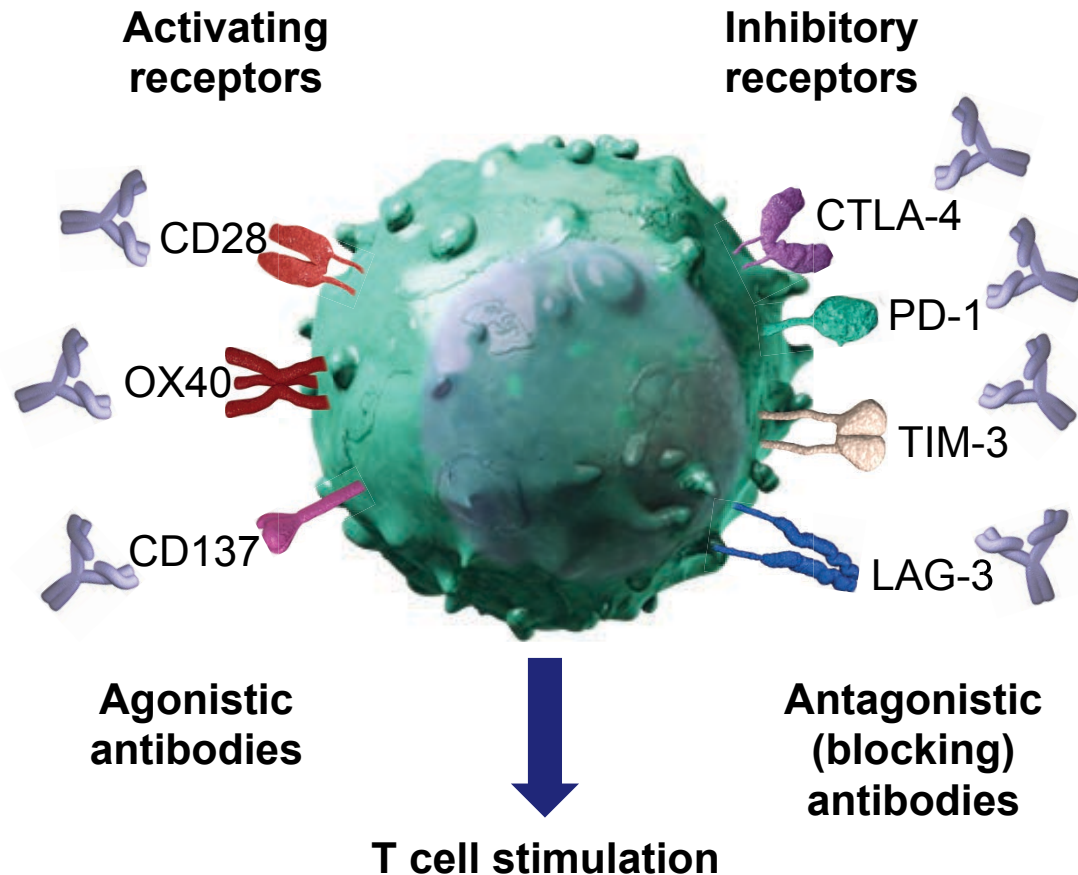
Pardoll DM, Nat Rev Cancer 2012

Mechanisms to escape the immune system

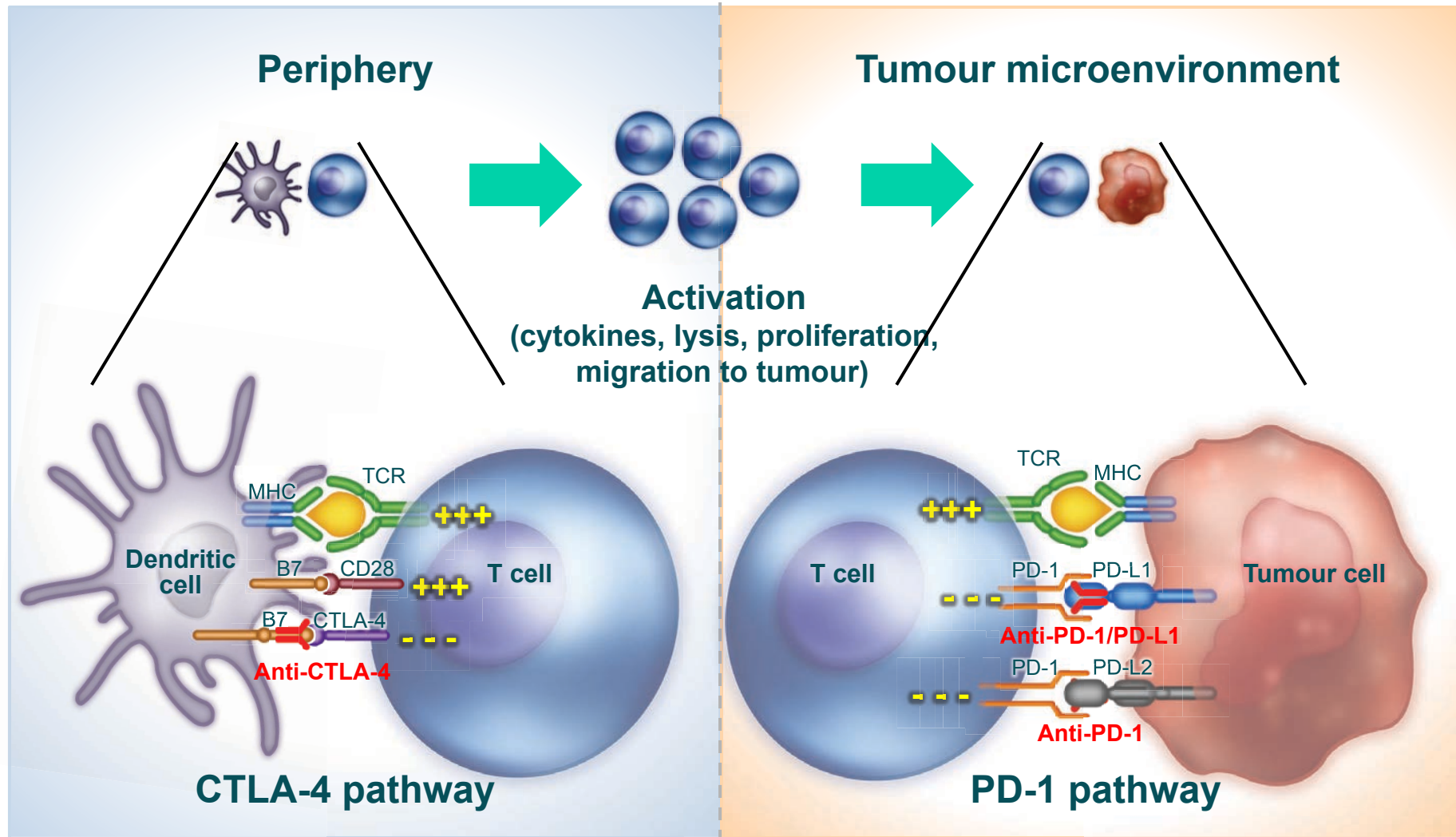


Vesely MD et al, *Ann Rev Immunol* 2011

Strategies to overcome evasion mechanisms



Strategies to overcome evasion mechanisms



Vesely MD et al, Ann Rev Immunol 2011

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Currently explored strategies

Immune Pathways

Inhibition of T cell checkpoint pathways

- CTLA-4^a
- PD-1 pathway^a
- LAG-3

Promotion of T cell activation pathways

- CD137 signaling
- OX-40 signaling
- CD40 activation
- Recombinant IL-21 administration (cytolytic activity of NK and CD8⁺ T cells)

Potentiation of immune effector function

- IDO inhibition
- Systemic recombinant IL-21 administration
- Systemic IL-2 or IFN- α administration^a
- Arginase inhibitors

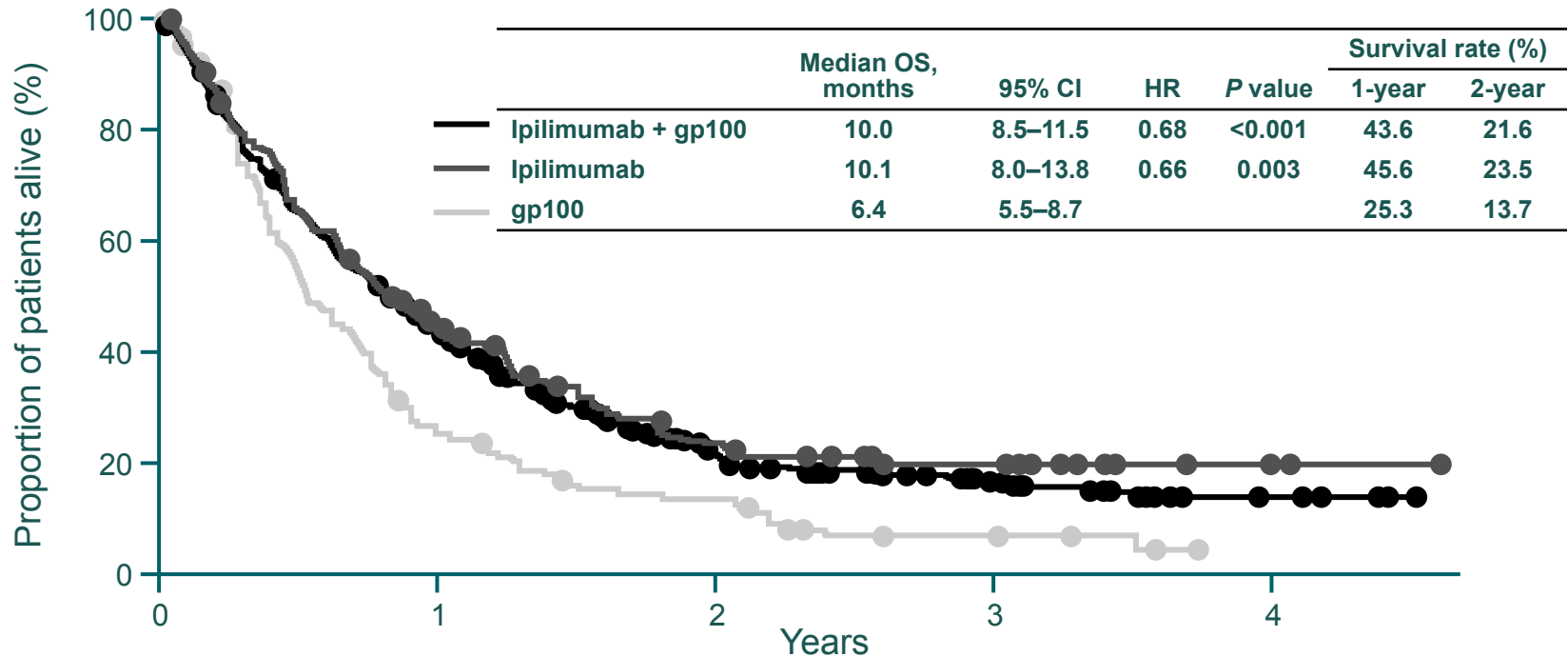
Enhancing innate immune function

- Activation of NK-cell inhibitory receptors (KIRs)
- Stimulating NK cells to increase ADCC against antibody coated tumour cell

Potential as monotherapy and in combination

Melanoma, lung cancer, kidney cancer, prostate cancer, NHL, sézary syndrome, neuroblastoma, GIST, glioblastoma, pancreatic cancer, head and neck cancer, breast cancer, CML, CLL...

‘First in class’: Ipilimumab for adv. melanoma



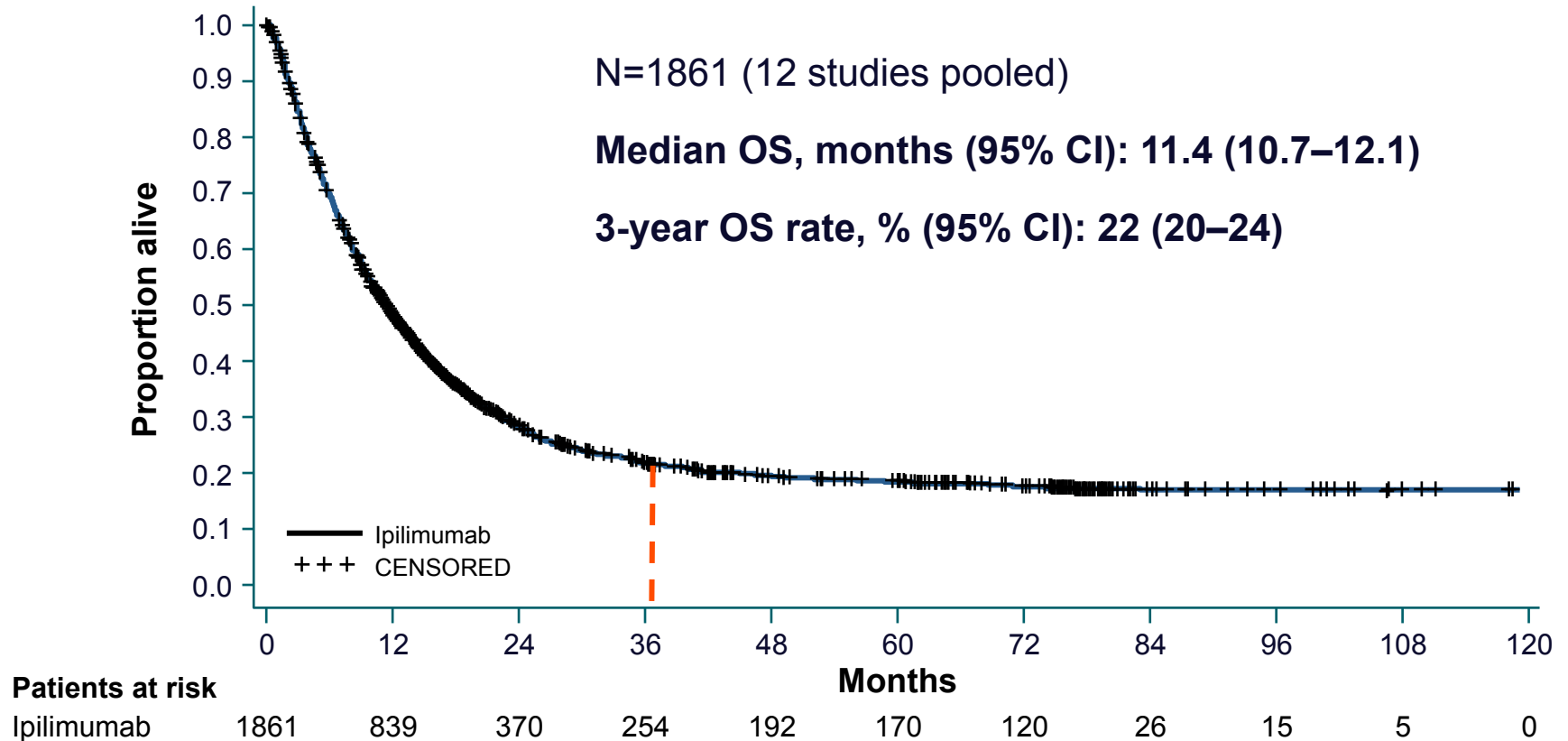
- The most frequently reported immune-related adverse events associated with ipilimumab monotherapy ($\geq 10\%$, all grades) in a phase 3 trial were: diarrhea (28%), pruritus (24%), and rash (19%)

Hodi FS et al, N Engl J Med 2010

Registered drugs

Compounds	MoA	Registration	Indication
Ipilimumab (BMS)	CTLA4 inhibitor	2011	Adv. Melanoma 2L
Nivolumab (BMS)	PD1 inhibitor	2014 Japan (Q4 FDA?)	Adv. Melanoma
Pembrolizumab (MSD)	PD1 inhibitor	Sept. 2014 (acc. FDA approval)	Adv. Melanoma after ipilimumab

Survival plateau

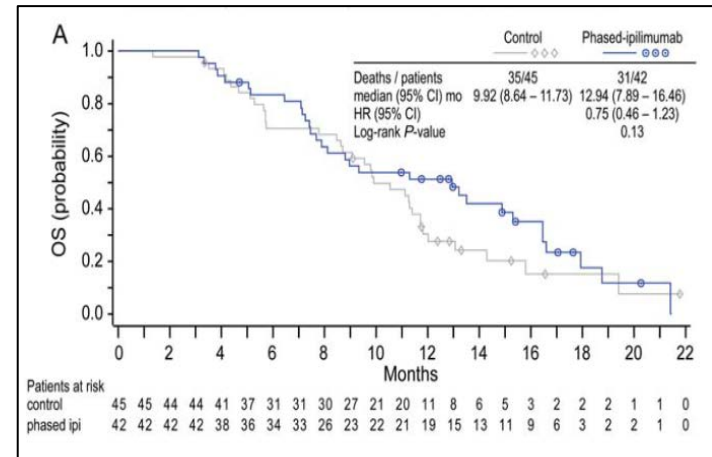
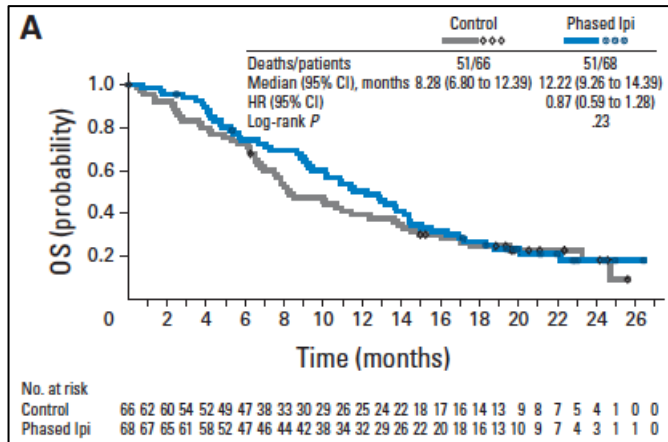
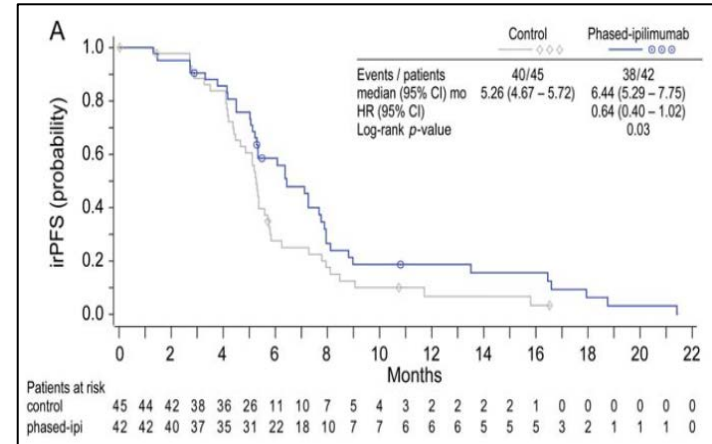
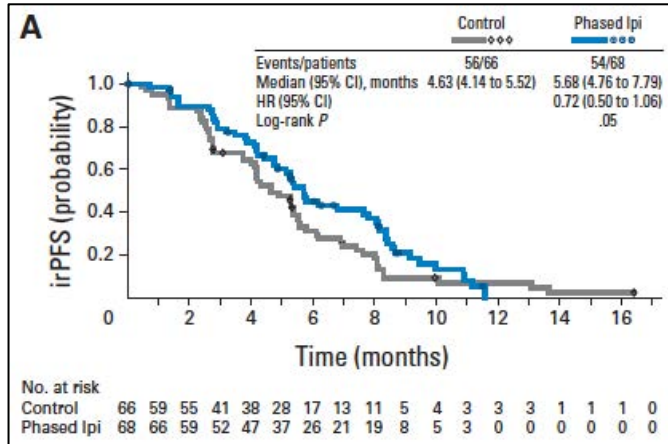


Schadendorf D et al, ECC Congress 2013 Abs 124LBA

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CTLA4 inhibitor: Ipilimumab



Lynch T et al, J Clin Oncol 2012; Reck M et al, Ann Oncol 2013

A

Baseline

B

After 6 cycles
Cx/Ipilimumab

C

After Ipilimumab
maintenance

D

6 years from diagnostic
4 years on BSC only

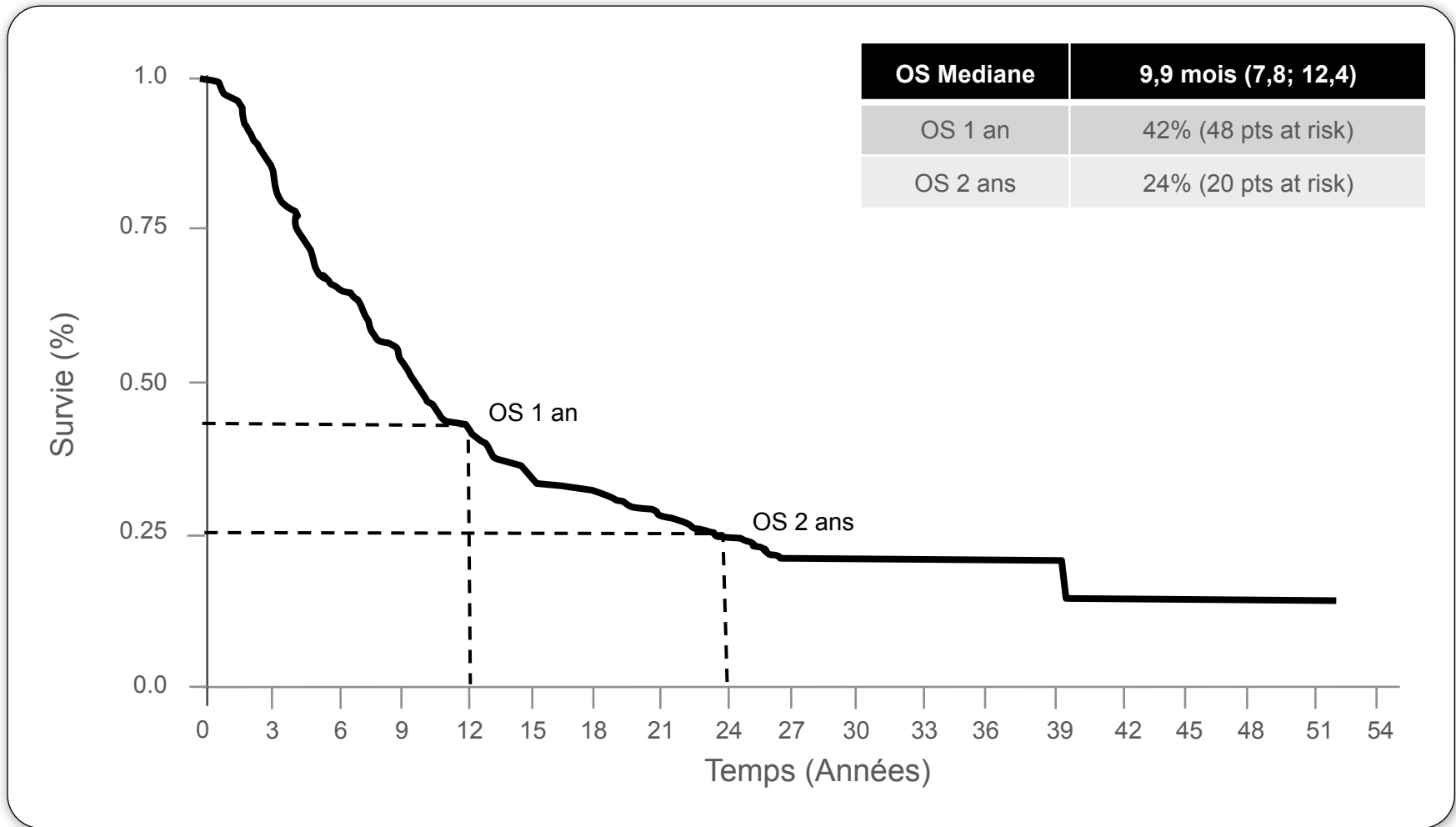
PD1 inhibitor: Nivolumab

Table 2. Clinical Activity of Anti-PD-1 Antibody in the Efficacy Population.*

Dose of Anti-PD-1 Antibody	Objective Response [†] no. of patients/ total no. of patients	Objective-Response Rate [‡] % (95% CI)	Duration of Response [§] mo	Stable Disease ≥24 wk no. of patients/ total no. of patients	% (95% CI)	Progression-free Survival Rate at 24 wk % (95% CI)
Non-small-cell lung cancer						
Squamous						
1.0 mg/kg	0/5	0		0/5	0	0
3.0 mg/kg	3/6	50 (12–88)	ND	0/6	0	50 (10–90)
10.0 mg/kg	3/7	43 (10–82)	ND	0/7	0	43 (6–80)
All doses	6/18	33 (13–59)	ND	0/18	0	33 (12–55)
Nonsquamous						
1.0 mg/kg	0/12	0		1/12	8 (0.2–39)	14 (0–37)
3.0 mg/kg	3/13	23 (5–54)	ND	2/13	15 (2–45)	37 (10–64)
10.0 mg/kg	4/31	13 (4–30)	ND	2/31	6 (0.8–21)	21 (6–36)
All doses	7/56	12 (5–24)	ND	5/56	9 (3–20)	22 (11–34)
Unknown type						
1.0 mg/kg	1/1	NA	ND	0/1	0	NA
10.0 mg/kg	0/1	0		0/1	0	0
All types						
1.0 mg/kg	1/18	6 (0.1–27)	9.2+	1/18	6 (0.1–27)	16 (0–34)
3.0 mg/kg	6/19	32 (13–57)	30.8+, 7.6+, 5.5+, 3.7+, 1.9+, NA**	2/19	11 (1–33)	41 (18–64)
10.0 mg/kg	7/39	18 (8–34)	14.8+, 7.6+, 7.3+, 6.7, 4.2, 3.7+, 3.7	2/39	5 (0.6–17)	24 (11–38)
All doses	14/76	18 (11–29)		5/76	7 (2–15)	26 (16–36)

Topalian et al, N Engl J Med 2012

PD1 inhibitor: Nivolumab



Brahmer et al, WCLC 2013

PD1 inhibitor: Pembrolizumab*

Key patient inclusion criteria

- Stage IV NSCLC
 - No prior systemic therapy
 - PD-L1 expressing tumours
 - ECOG PS 0–1
 - *EGFR/ALK* negative
- (n=84)

R

MK-3475 10 mg/kg q3w
(n=23)

PD

MK-3475 2 mg/kg q3w
(n=6)

PD

MK-3475 10 mg/kg q2w
(n=16)

PD

Primary endpoint

- Tumour response

Secondary endpoint

- Immune-related response criteria

**Lambrolizumab*, MK3475

Rizvi et al, ASCO 2014



PD1 inhibitor: Pembrolizumab*

- **Key results**

- MK-3475 showed ORR of 26% by independent central review and 47% by investigator assessment (table)

	RECIST v1.1 per independent central review	Immune-related response criteria per investigator assessment
ORR (95% CI), %	26 (14, 42)	47 (32, 62)
Interim median PFS (95% CI), weeks	27.0 (13.6, 45.0)	37.0 (27.0, NR)
Responses ongoing, n/N (%)	11/11 (100)	19/21 (90)
Responders remaining on treatment, n/N (%)	7/11 (64)	18/21 (86)

- Treatment-related AEs (any grade) occurring in >5% of patients were: fatigue (22%), pruritus (13%), hypothyroidism (9%), dermatitis acneiform (7%), diarrhoea (7%), dyspnoea (7%) and rash (7%)

**Lambrolizumab, MK3475*

Rizvi et al, ASCO 2014

PDL1 inhibitor: BMS compound (stopped?)

Table 2. Clinical Activity of Anti-PD-L1 Antibody in the Efficacy Population.*

Tumor Type and Dose	No. of Patients	Objective Response†		Duration of Response‡	Stable Disease ≥24 Weeks		Rate of Progression-free Survival at 24 Weeks§
		no. of patients	% (95% CI)		no. of patients	% (95% CI)	
Non-small-cell lung cancer							
All patients, 1 mg/kg	11	0	0 (0–29)	NA	0	0 (0–29)	NA
All patients, 3 mg/kg	13	1	8 (0–36)	2.3+	1	8 (0–36)	34 (7–60)
Squamous subtype	4	0	0 (0–60)	NA	1	25 (0–81)	50 (1–99)
Nonsquamous subtype	9	1	11 (0–48)	ND	0	0 (0–34)	25 (0–55)
All patients, 10 mg/kg	25	4	16 (5–36)	16.6+, 12.6+, 9.8, 3.5	5	20 (7–41)	46 (25–67)
Squamous subtype	8	1	13 (0–53)	ND	2	25 (3–65)	47 (10–83)
Nonsquamous subtype	17	3	18 (4–43)	ND	3	18 (4–43)	46 (20–72)
All patients, all doses	49	5	10 (3–22)		6	12 (5–25)	31 (17–45)
Squamous subtype	13	1	8 (0–36)	ND	3	23 (5–54)	43 (15–71)
Nonsquamous subtype	36	4	11 (3–26)	ND	3	8 (2–23)	26 (10–42)
Ovarian cancer	1	0	0 (0–98)	NA	0	0 (0–98)	NA
3 mg/kg	1	0	0 (0–98)	NA	0	0 (0–98)	NA
10 mg/kg	16	1	6 (0–30)	1.3+	3	19 (4–46)	25 (4–46)
All doses	17	1	6 (0–29)		3	18 (4–43)	22 (2–43)
Renal-cell cancer, 10 mg/kg	17	2	12 (2–36)	17, 4	7	41 (18–67)	53 (29–77)

Brahmer et al, N Engl J Med 2012

PDL1 inhibitor: MPDL3280A

- **Key results**

- Grade 3-4 treatment-related AEs occurred in 11% of patients
- Objective response rate was 23% (21% in the global cohort)
- Survival outcomes among all patients are shown in the table

	SD of 24wks or longer %	24-wks PFS rate %
Overall population (n=175)	19	42
NSCLC (n=53)	17	45
Non-squamous (n=42)	17	44
Squamous (n=11)	18	46

NSCLC population	ORR	PD rate
IHC 3	83 % (5/6)	17 % (1/6)
IHC 2 et 3	46 % (6/13)	23 % (3/13)
IHC 1/2/3	31 % (8/26)	38 % (10/26)

Soria JC et al, ESMO 2013

PDL1 inhibitor: MEDI4736

- **Study design**

- Ongoing phase I study of patients with NSCLC who are receiving MEDI4736 IV q2w or q3w using 3+3 dose-escalation followed by expansion cohorts

- **Key results**

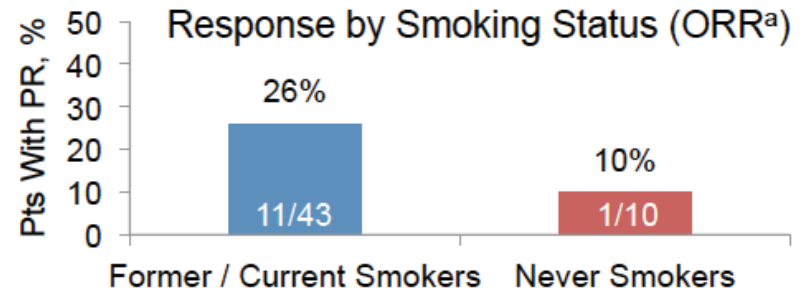
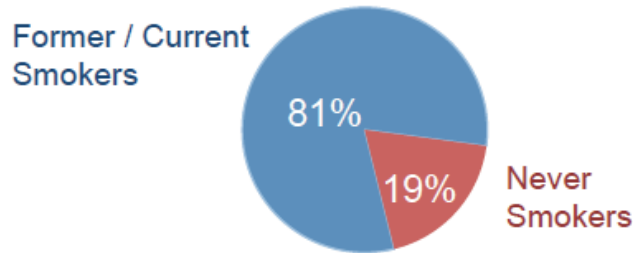
- As of May 2014, 155 patients with NSCLC have been treated in the dose-escalation and expansion cohorts, 143 patients were dosed at 10 mg/kg q2w (median duration of 6 weeks)
- Grade 3/4 treatment-related AEs were seen in 3% of all patients; the most common grade ≥ 3 AE was arthralgia (1%)
- Efficacy of MEDI4736 10 mg/kg q2w was higher in patients with PD-L1 expression

NSCLC population	ORR (CR+PR) %	DCR %
Overall	13	30
PD-L1 IHC +	39	54
PD-L1 IHC -	5	32

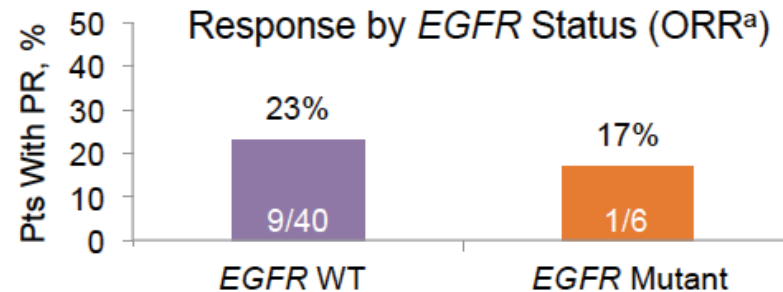
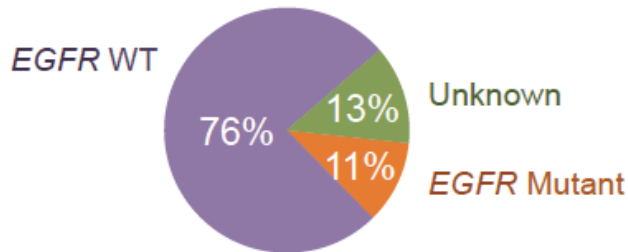
Brahmer et al, ASCO 2014

Predictive factors?

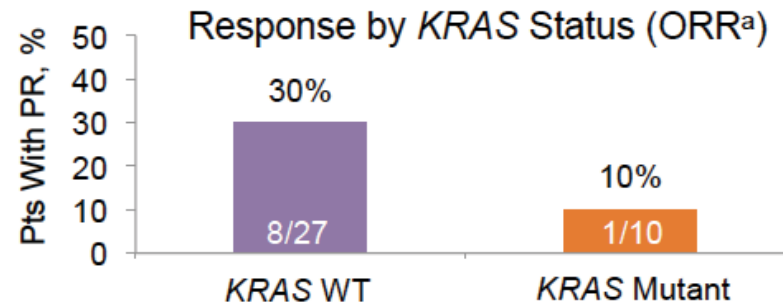
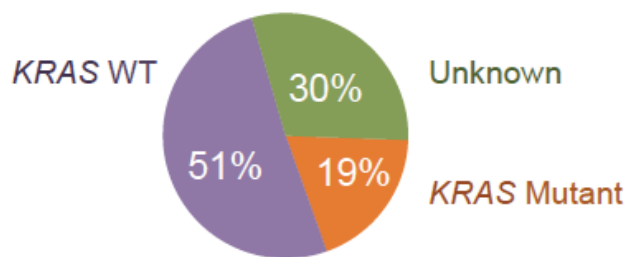
Smoking Status (NSCLC; n = 53)



EGFR Status (NSCLC; n = 53)



KRAS Status (NSCLC; n = 53)



ORR for the PDL1 inhibitor MPDL3280A

Horn et al, WCLC2013

CTLA4/PDL1 expression (resected NSCLC)

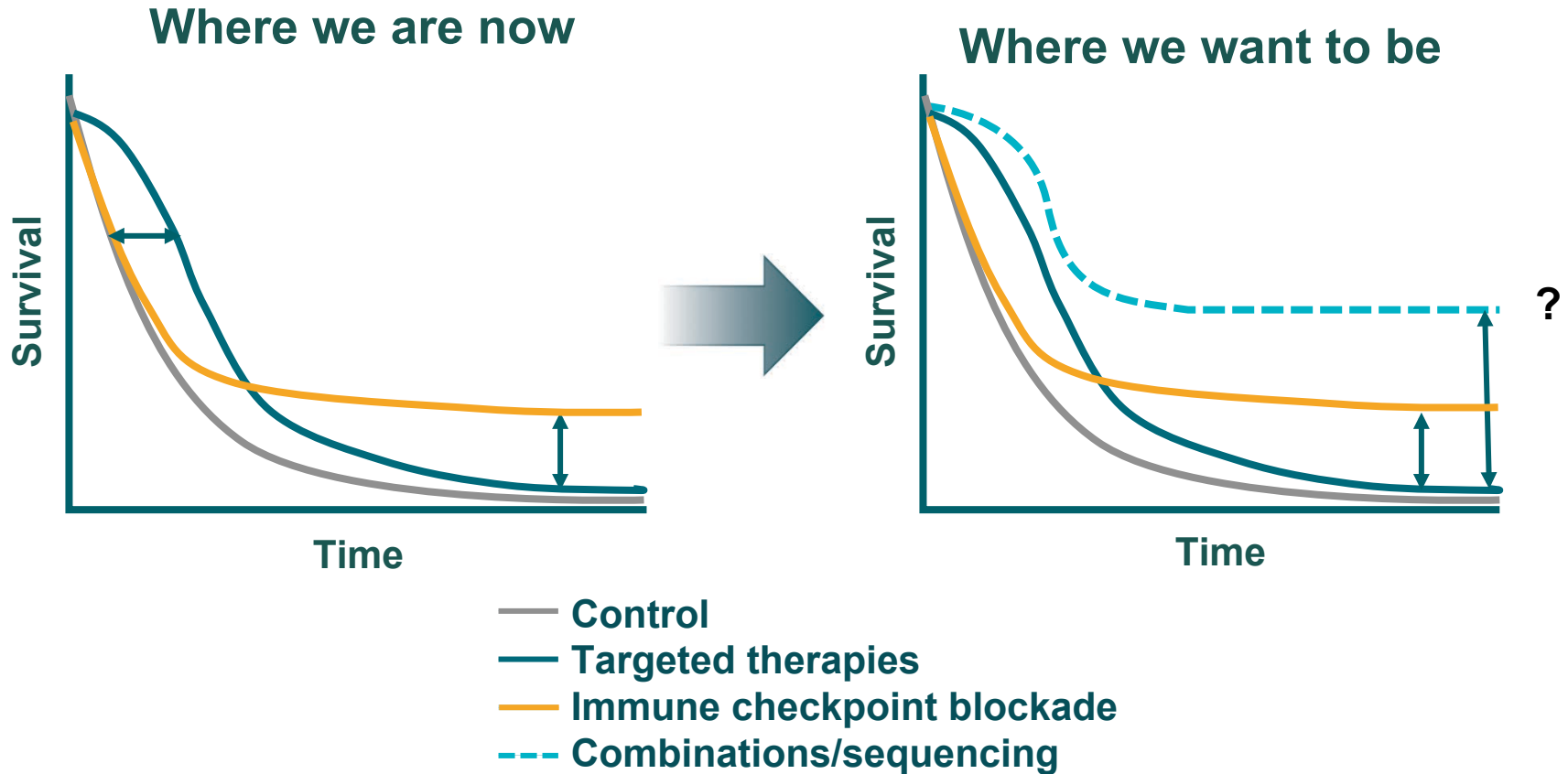
Tumor expression of CTLA-4, PD-L1 in resected NSCLC.

Author	N	Histologic subtype	Pathologic stage	Detection method/Ab clone	Cellular localization	% PD-L1 + ve	Clinpathological association	Association with immune cells/TILs	Prognosis
CTLA-4									
Salvi [34]	81	Mixed	I-III	IHC anti CTLA-4/14D3	Cell surface, cytoplasm	50.6	Non-squamous	Not reported	OS: neutral 5 year survival 64.8 vs. 45.9%
Zheng [35]	89	Mixed	I-IV	IHC anti-CTLA-4	Not reported	86.5	Older age, poorer differentiation	Not reported	Not reported
PD-L1									
Yang [45]	163	ADC	I	IHC anti-PD-L1/Proteintech Group Chicago, IL	Membrane	39.9	Vascular invasion, higher grade differentiation	No association with TILs	RFS: improved, OS: neutral
Velcheti [46]	204 (US)	Mixed	I-IV	QIF/5H1	Membrane	36.1	None	Increased inflammatory infiltrate	OS: improved 60 v 27 months
	340 (Greece)	Mixed	I-IV	QIF/5H1	Membrane	24.8	Lower stage	Increased inflammatory infiltrate	OS: improved NR v 31 months
	173 (US)	Mixed	I-IV	mRNA	Not applicable	50.8	None	Increased inflammatory infiltrate	OS: improved
	314 (Greece)	Mixed	I-IV	mRNA	Not applicable	53.2	None	Increased inflammatory infiltrate	OS: improved
Chen [47]	208	Mixed	I-IV	IHC anti-PD-L1	Cytoplasm, membrane	65.3	Non-smokers, less LN metastasis	Increased macrophages	Not reported
Velcheti [52]	445	Mixed	I-IV	QIF/5H1	Not reported	27.4	Not reported	Not reported	Not reported
	13	Sarcomatoid	I-IV	QIF/5H1	Not reported	69.2	Not reported	Not reported	Not reported
Chen [48]	120	Mixed	I-III	IHC anti-PD-L1/236A/E7	Cytoplasm, membrane	57.5	Not reported	Not reported	OS: reduced
Boland [49]	214	SCC	I-IV	IHC anti PD-L1/5H1	Membrane	19.6	Not reported	No association with TILs	OS: neutral
Mu [50]	109	Mixed	I-III	IHC anti-PD-L1/not reported	Cytoplasm, membrane	53.2	ADC	Increased dendritic cells	OS: reduced PD-L1 + <3 year survival 46%, >3Y survival 12%
Konishi [51]	52	Mixed	I-IV	IHC anti-PD-L1/M1H1	Cytoplasm, membrane	27.2	None	Reduced TILs	OS: neutral 5 year survival 59% v 48%

Ab: antibody; ADC: adenocarcinoma; IHC: immunohistochemistry; LN: lymph node; NR: not reached; OS: overall survival; PD-L1: programmed death-1 ligand; QIF: quantitative fluorescence; RFS: relapsed free survival; SCC: squamous cell carcinoma; TILs: tumor infiltrating lymphocytes.

Sundar R et al, Lung Cancer 2014

Synergy of combination strategies?



EGFR-TKI + PD1 inhibitor

Key patient inclusion criteria

- Stage IIIB/IV NSCLC
 - Non-squamous
 - EGFR+
 - CT naïve
- (n=21)

Nivolumab 3 mg/kg q2w
+ erlotinib 150 mg/day

PD

Primary endpoint

- Safety and tolerability

Secondary endpoints

- Objective response rate and PFS at 24 weeks

Rizvi et al, ASCO 2014

EGFR-TKI + PD1 inhibitor

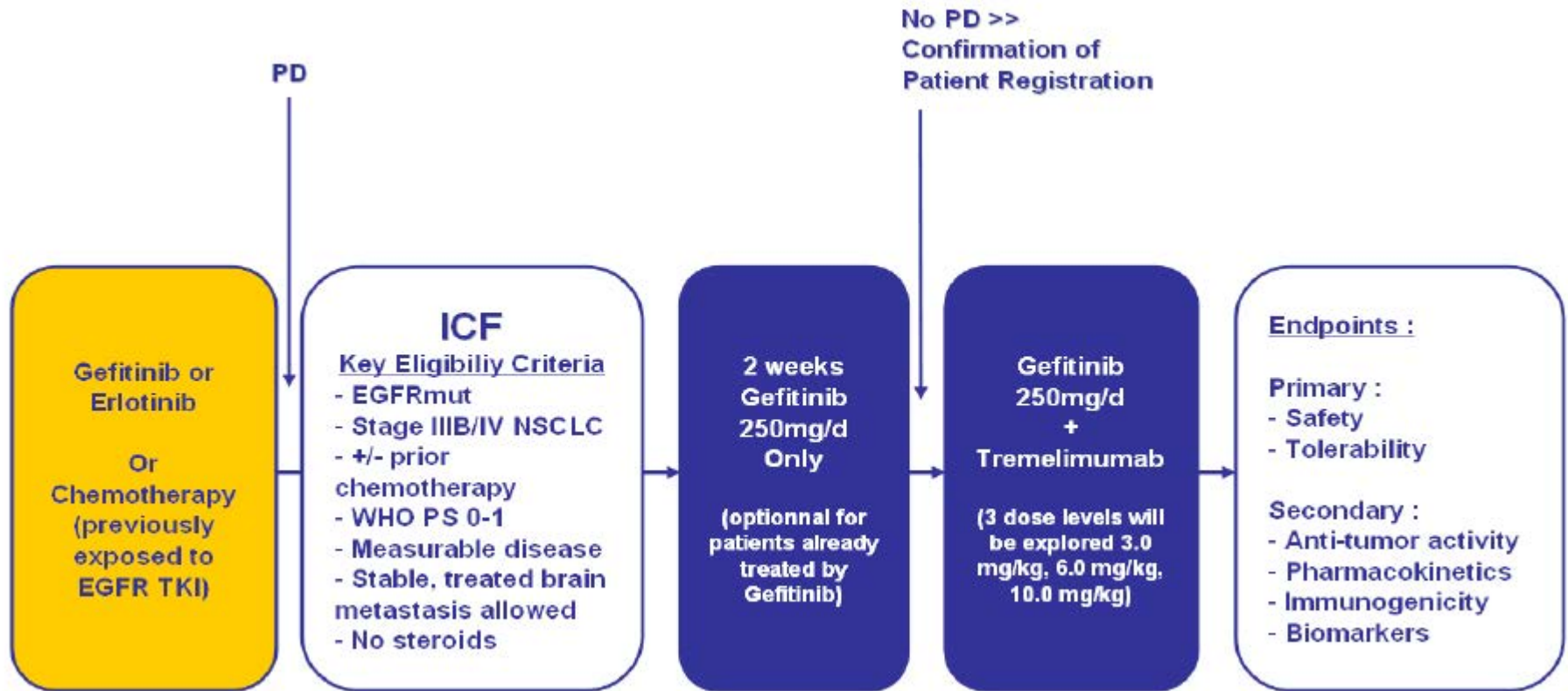
- **Key results**

- Grade 3 treatment-related AEs occurred in 24% of patients (no grade 4 reported)
- Objective response rate was 19% (PR in 3 of 20 patients treated previously with erlotinib and 1 of 1 patient with no prior erlotinib)
- Survival outcomes among all patients are shown in the table

Nivolumab+erlotinib (n=21)	
PFS	
PFS rate (95% CI) at 24 weeks, %	51 (28, 70)
Median (range) PFS, weeks	29.4 (4.6, 81.7+)
OS	
1-year OS rate (95% CI), %	73 (46, 88)
Median (range) OS, weeks	NR (10.7+, 86.9+)

Rizvi et al, ASCO 2014

EGFR-TKI + CTLA4 inhibitor



Selected ongoing studies of immune checkpoint mediators.

Phase	Patient population	N	Regimen	Control	Primary endpoint	Clinical trials.gov
CTLA-4						
I	ALK/EGFR mutant NSCLC 1st line	46	Ipilimumab + erlotinib	None	Toxicity	NCT01998126
II	NSCLC 1st line	204	Ipilimumab + crizotinib Ipilimumab + Carboplatin/paclitaxel Concurrent vs sequential	Carboplatin/paclitaxel	irPFS	NCT00527735
III	Squamous NSCLC 1st line	920	Ipilimumab + Carboplatin/paclitaxel	Carboplatin/paclitaxel	OS	NCT01285609
I	EGFR mutant NSCLC 1st line	24	Tremelimumab + Gefitinib	None	Toxicity	NCT02040064
II	NSCLC after 1st line, maintenance	87	Tremelimumab	BSC	PFS	NCT00312975
PD-1						
I	EGFR mutant NSCLC 1st line	24	Tremelimumab + Gefitinib	None	Safety, RP2D	NCT02040064
I	1st line, Squamous, non-squamous NSCLC	250	Nivolumab in combination with platinum doublet, bevacizumab maintenance, erlotinib, ipilimumab, or nivolumab alone	None	Toxicity	NCT01454102
II	Squamous NSCLC, 3rd or more line	100	Nivolumab	None	ORR	NCT01721759
III	Nonsquamous NSCLC, 2nd line	574	Nivolumab	Docetaxel	OS	NCT01673867
III	Squamous NSCLC, 2nd line	264	Nivolumab	Docetaxel	ORR	NCT01642004
I	NSCLC 1st line	30	Lambrolizumab (MK-3475) monotherapy or in combination with platinum doublet	None	Toxicity	NCT01840579
I	Pre-treated NSCLC, PD-L1+	24	Lambrolizumab	None	ORR	NCT02007070
I	Advanced stage melanoma/NSCLC	1137	Various doses of Lambrolizumab	None	Toxicity	NCT01295827
I/II	NSCLC, any line	320	In combination with platinum doublet ± bevacizumab, erlotinib, gefitinib, or ipilimumab	None	PFS/ORR	NCT02039674
II/III	NSCLC 2nd line after platinum doublet	920	Lambrolizumab low dose/high dose	Docetaxel	OS	NCT01905657
PD-L1						
I	Advanced stage solid tumors	20	MSB0010718C	None	DLT	NCT01943461
I	Advanced stage selected solid tumors	590	MSB0010718C	None	DLT	NCT01772004
IB	EGFR mutant NSCLC 1st line	32	MPDL3280A + Erlotinib	None	DLT	NCT02013219
II	PD-L1 + NSCLC, any line	130	MPDL3280A	None	ORR	NCT01846416
II	PD-L1 + NSCLC, any line	300	MPDL3280A	None	ORR	NCT02031458
II	NSCLC, 2nd line after platinum doublet	300	MPDL3280A	Docetaxel	OS	NCT01903993
III	NSCLC, 2nd line after platinum doublet	850	MPDL3280A	Docetaxel	OS	NCT02008227
IB	NSCLC, any line	208	MEDI4736 + tremelimumab	None	DLT, MTD	NCT02000947
LAG3						
I	Advanced stage solid tumors		BMS-986016 ± nivolumab	None	Safety, DLT	NCT01968109
KIR						
I	Advanced stage solid tumors	150	Lirilumab + nivolumab	None	DLT, MTD	NCT01714739
I	Advanced stage solid tumors	125	Lirilumab + ipilimumab	None	DLT, MTD	NCT01750580
CD27						
I	Advanced solid tumors	170	CDX-1127	None	Toxicity	NCT01460134

ALK: anaplastic lymphoma kinase; BSC: best supportive care; DLT: dose limiting toxicity; EGFR: epidermal growth factor receptor; irPFS: immune related progression free survival; MTD: maximally tolerated dose; NSCLC: non-small cell lung cancer, ORR: overall response rate; OS: overall survival; PFS: progression free survival; RP2D: recommended phase II dose.

*Sundar R et al,
Lung Cancer 2014*

Agenda

- Concept of immuno-oncology
- Main compounds and registrations
- Focus on lung cancer results
- **Interest in lung cancer brain mets treatment**

PK data

- No published data for check-point inhibitors / lung cancer
- Antibodies: bevacizumab
- Proof of concept in melanoma patients

Clinical data

- No published data (even case reports)
- Brain mets usually excluded from clinical trials

Clinical data

Compounds	Histology	Combo	N	Brain PRG only
Anti-CTLA4	NSCLC/SCLC	CBDCA/TXL	12 (vs PCB)	1
Anti-CTLA4	NSCLC	CBDCA doublet	11 (vs PCB)	0
Anti-CTLA4	EGFRm	EGFR-TKI	8	0
PD1 inhibitor	nsqNSCLC	No	7	2
PD1 inhibitor	sqNSCLC	No	2	1
PD1 inhibitor	NSCLC	No	7	0
PDL1 inhibitor	NSCLC	No	3 (vs PCB)	0

Personal unpublished data

Ongoing trial (USA/Canada)

Key patient inclusion criteria

- Stage IIIB/IV NSCLC
- Any histology
- < 4 asymptomatic brain mets, w/o edema
- 1 prior regimen at least
- No WBRT, SRS, surgery (Arm M)

Nivolumab 3 mg/kg q2w

PD

Primary endpoint

- Safety and tolerability

Secondary endpoints

- Objective response rate and PFS

ClinicalTrials.gov Identifier: NCT01454102

Conclusions

- **Immunotherapy is now a key player in oncology**
- **Predictive factors are needed**
- **Impact on brain mets management has to be assessed in specific clinical trials**