Hvilke medisinske behov har vi løst om 10 år?

IMMUNTERAPI MOT KREFT

Farmasidagene 2015

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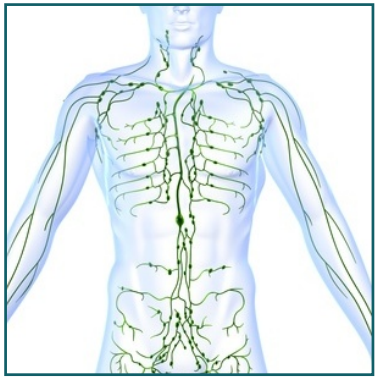
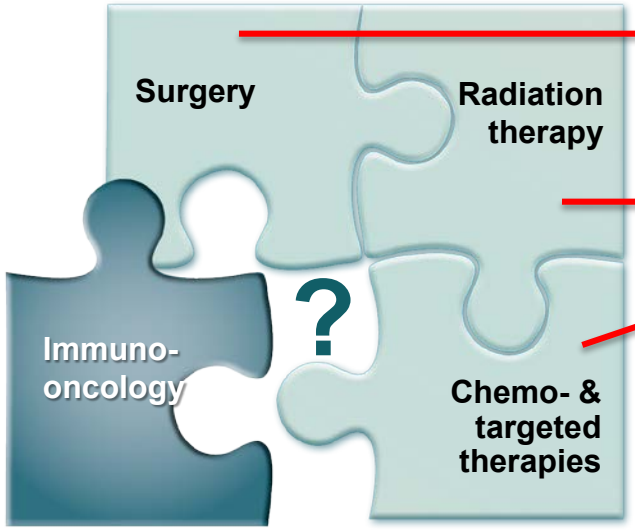
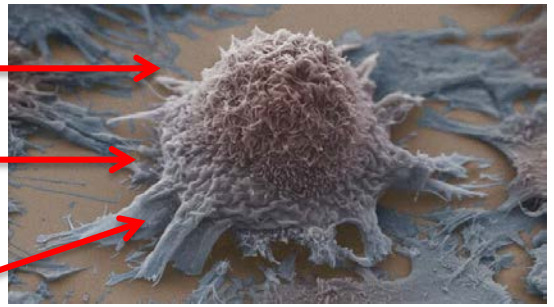
Immuno-oncology as a new therapeutic treatment concept[1]

- Conventional oncological approaches directly target the tumor.[2]
- In immuno-oncology, the natural ability of the body's own immune system is used to fight the cancer.[2]



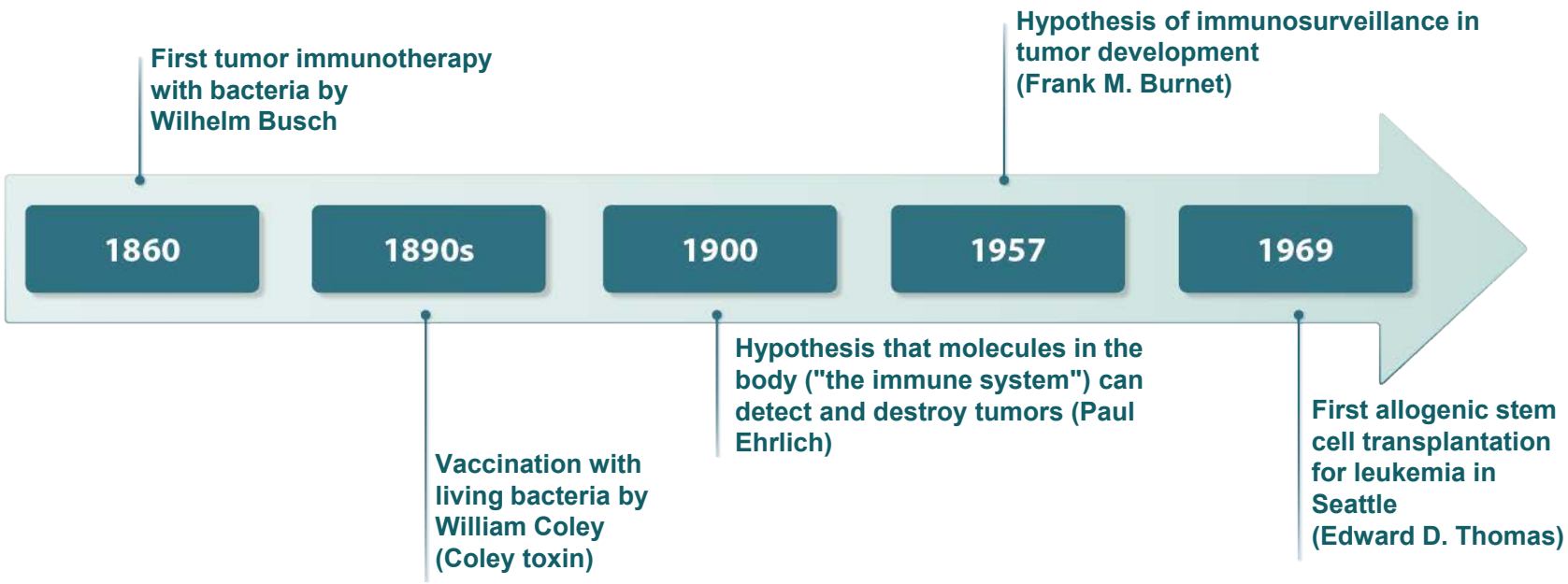




1. DeVita and Rosenberg, N Eng J Med 2012, 366: 2207; 2. Borghaei et al, Eur J Pharmacol 2009, 625: 41.

Immuno-Oncology

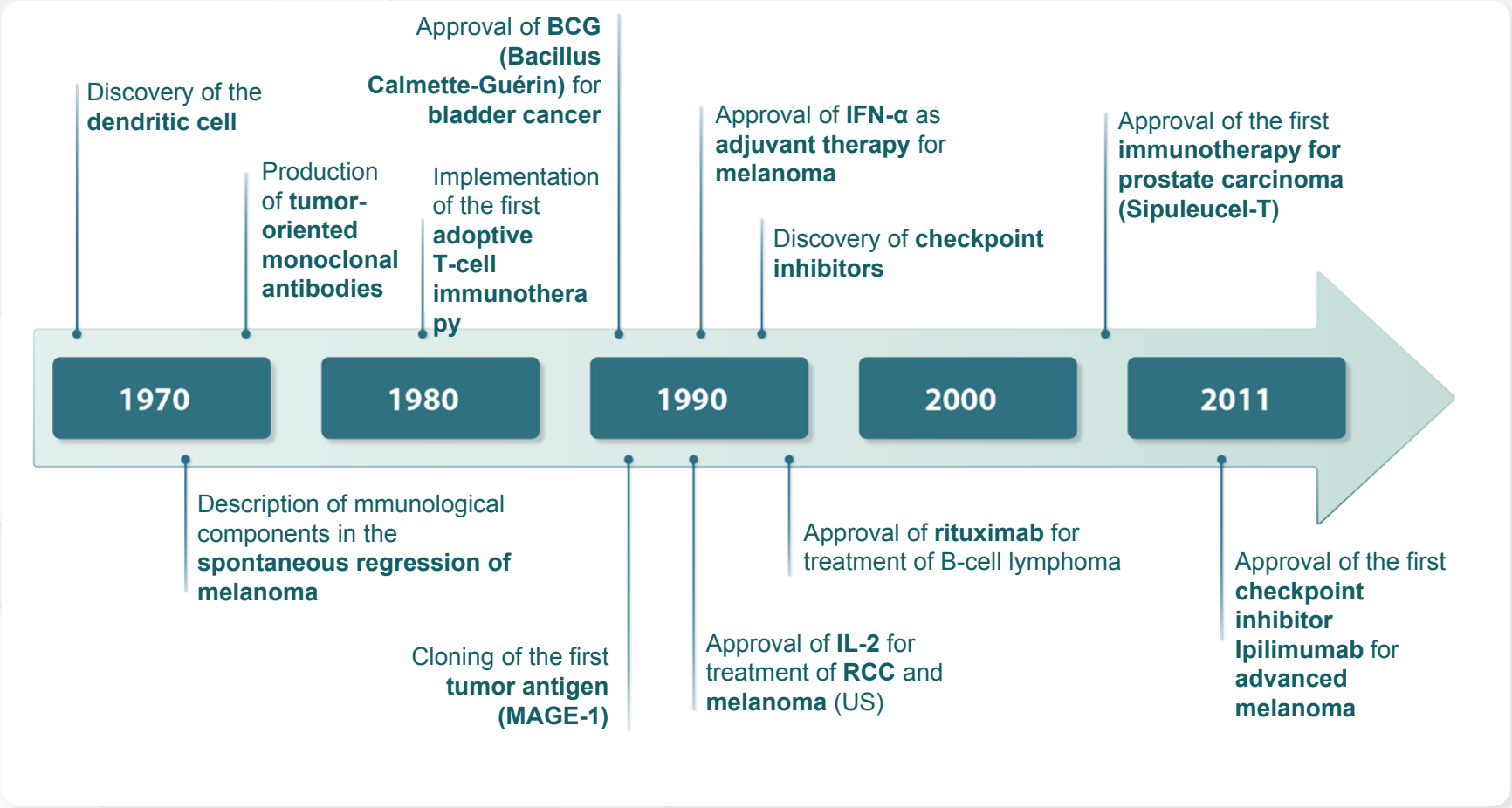
Immunotherapeutic approaches in cancer – Milestones of the 19th and 20th century



Kim et al, Cancer Control 2002; 9(1): 22; Waldmann TA, Nat Med 2003, 9(3): 269; Burnet FM, BMJ 1957, 1: 779 & 841; Thomas ED, Nature 2012, Nov 15: 491(7424): 334.

Immuno-Oncology

Immunotherapeutic approaches in cancer – Milestones of the 20th and 21st century



Adapted from Kirkwood et al, CA Cancer J Clin 2012, 62: 309; George et al, JNCCN 2011, 9: 1011; Garbe et al, The Oncologist 2011, 16: 2; Rosenberg, Sci Transl Med 2012, 4: 127ps8; Cheeve et al, Clin Cancer Res 2011, 17: 3520; Kantoff et al, N Engl J Med 2010, 363; Mansh and Yale, Biol Med 2011, 84: 381; Hodi et al, N Engl J Med 2010, 363: 711

Immuno-Oncology

Breakthrough of the Year 2013

Immuno-Oncology

Important mediators of immune response

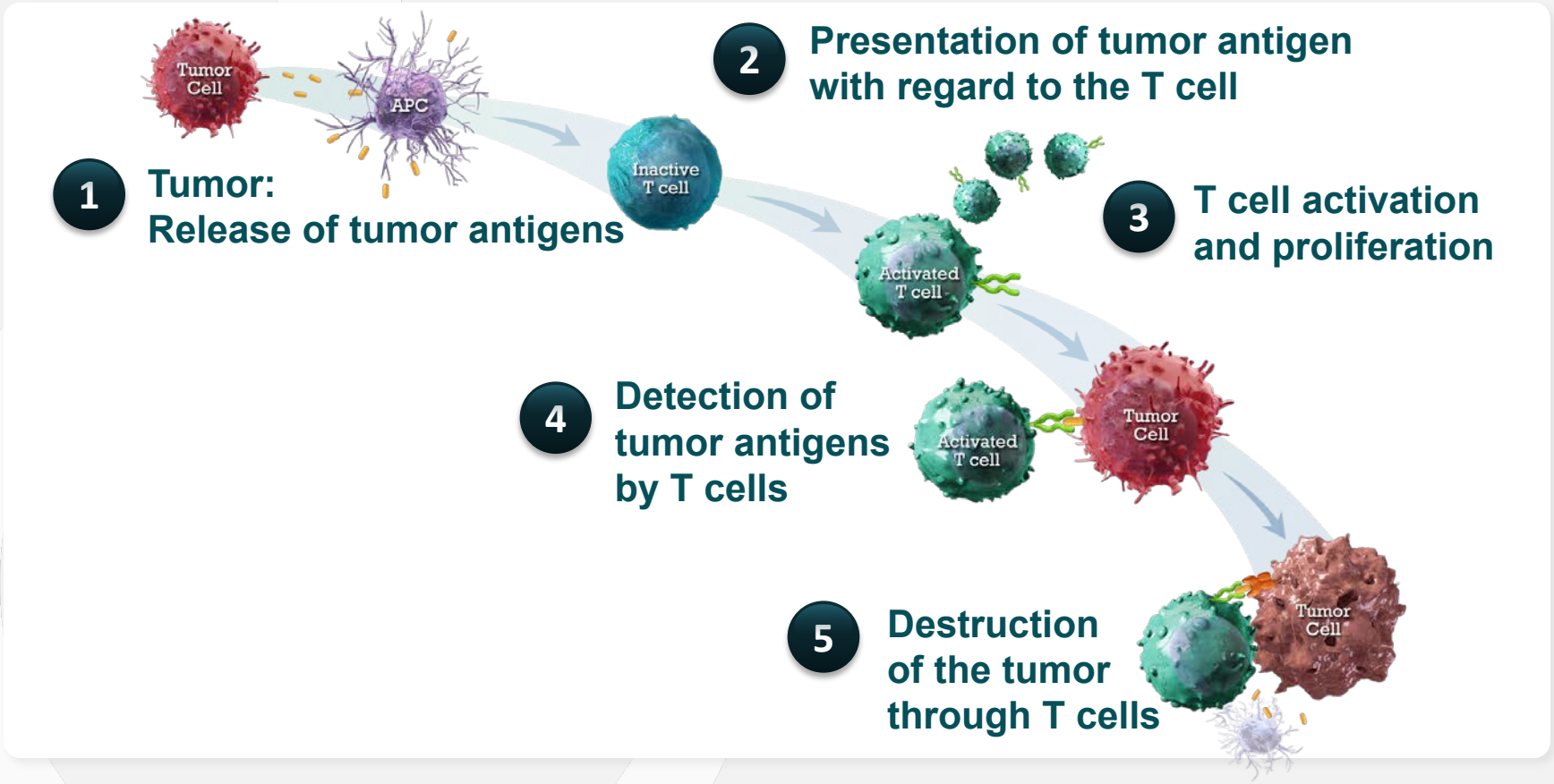
Innate
Antigen-independent

Adaptive
Antigen-dependent

Adapted according to Woelfel et al, 2014

Immuno-Oncology

The T-cell-mediated antitumor immune response

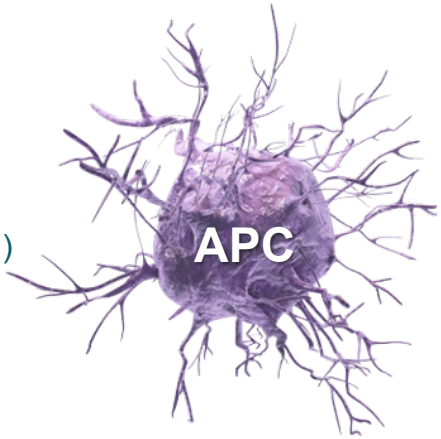


Andersen et al, J Invest Dermatol 2006, 126: 32; Pardoll DM, Nat Rev Cancer 2012, 11: 252; Mellman et al, Nature 2011, 480: 480; Heemskerk et al, EMBO J 2013, 32: 194; Boudreau et al, Mol Ther 2011, 19: 841; Janeway et al, Immunobiology: The Immune System in Health and Disease. 6th ed, 2004.

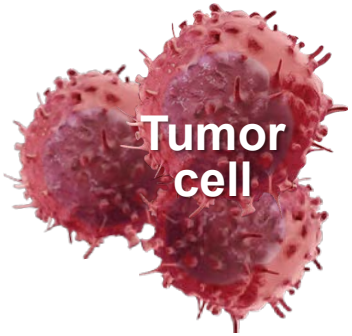
Immuno-Oncology

Tumors use complex mechanisms to escape the immune system and suppress it

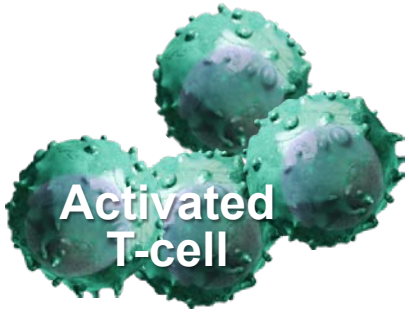
1 Inhibition of the tumor antigen presentation
(e.g. down-regulation of MHC I)



2 Secretion of immunosuppressive factors
(e.g. TGF-B)



3 Inhibition of the attack through immune cells
(e.g. interruption of T-cell checkpoint signal pathways)

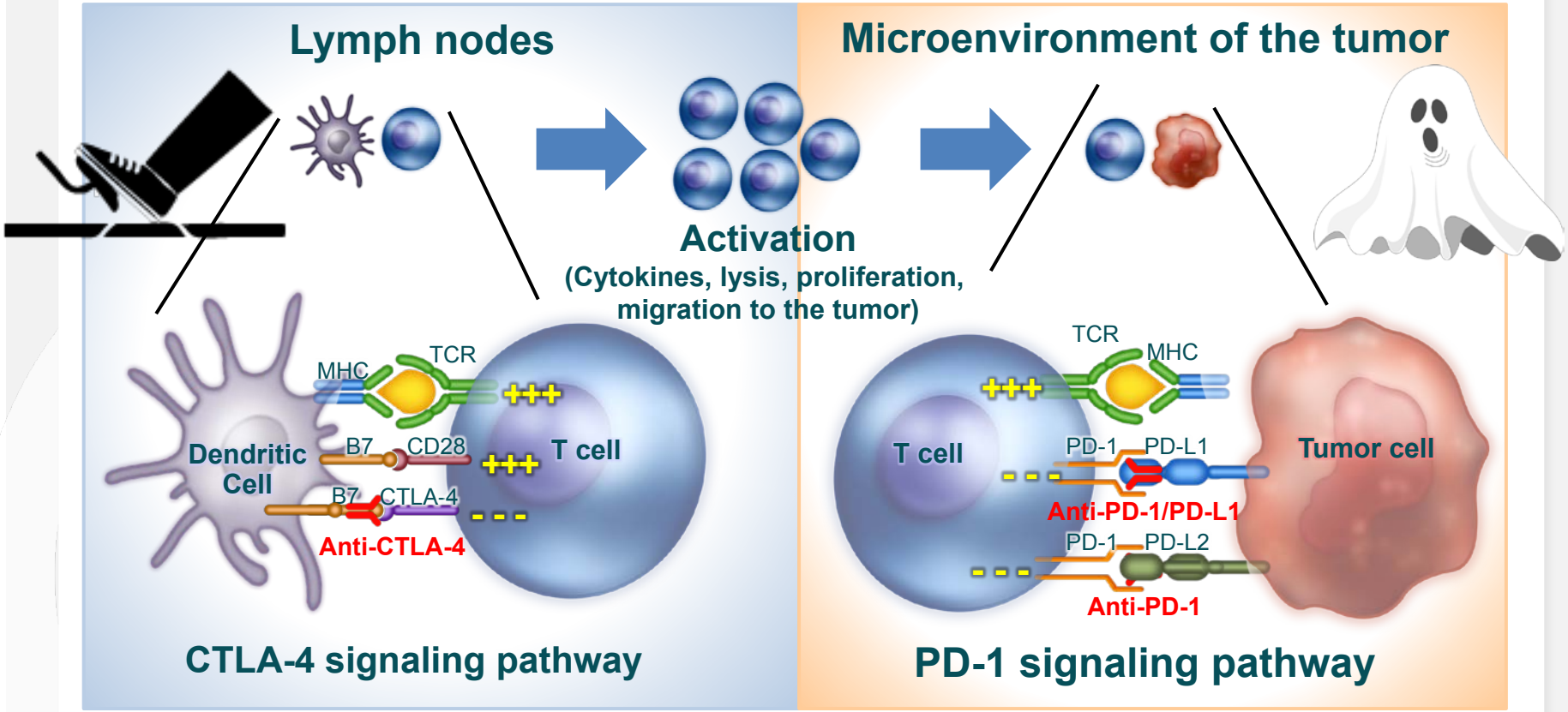


4 Recruitment of immunosuppressive cell types
(e.g. regulatory T-cells)

Drake et al, Adv Immunol 2006, 90: 51; Vesely et al, Annu Rev Immunol 2011, 29: 235

Immuno-Oncology

Blockade of the CTLA-4 and PD-1 signaling pathways



CTLA-4 regulates the **amplitude of the earlier activation** of naive and memory T cells.

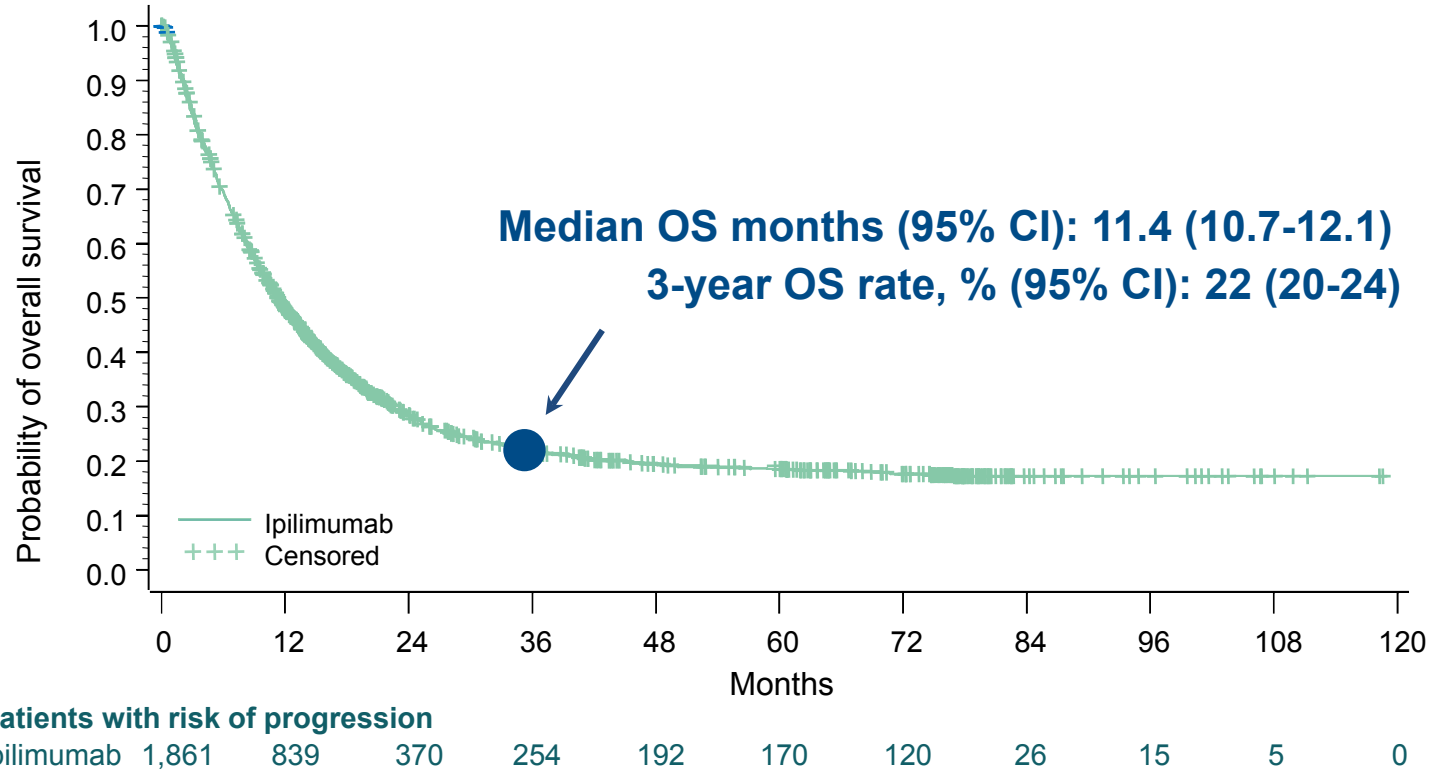
PD-1 limits the **T-cell activation** in the **periphery** during an inflammatory reaction.

Wolchock et al, J Clin Oncol 2013 ASCO Annual Meeting Abstracts 31:15_suppl

Immuno-Oncology

Immuno-oncology: Proof of Concept

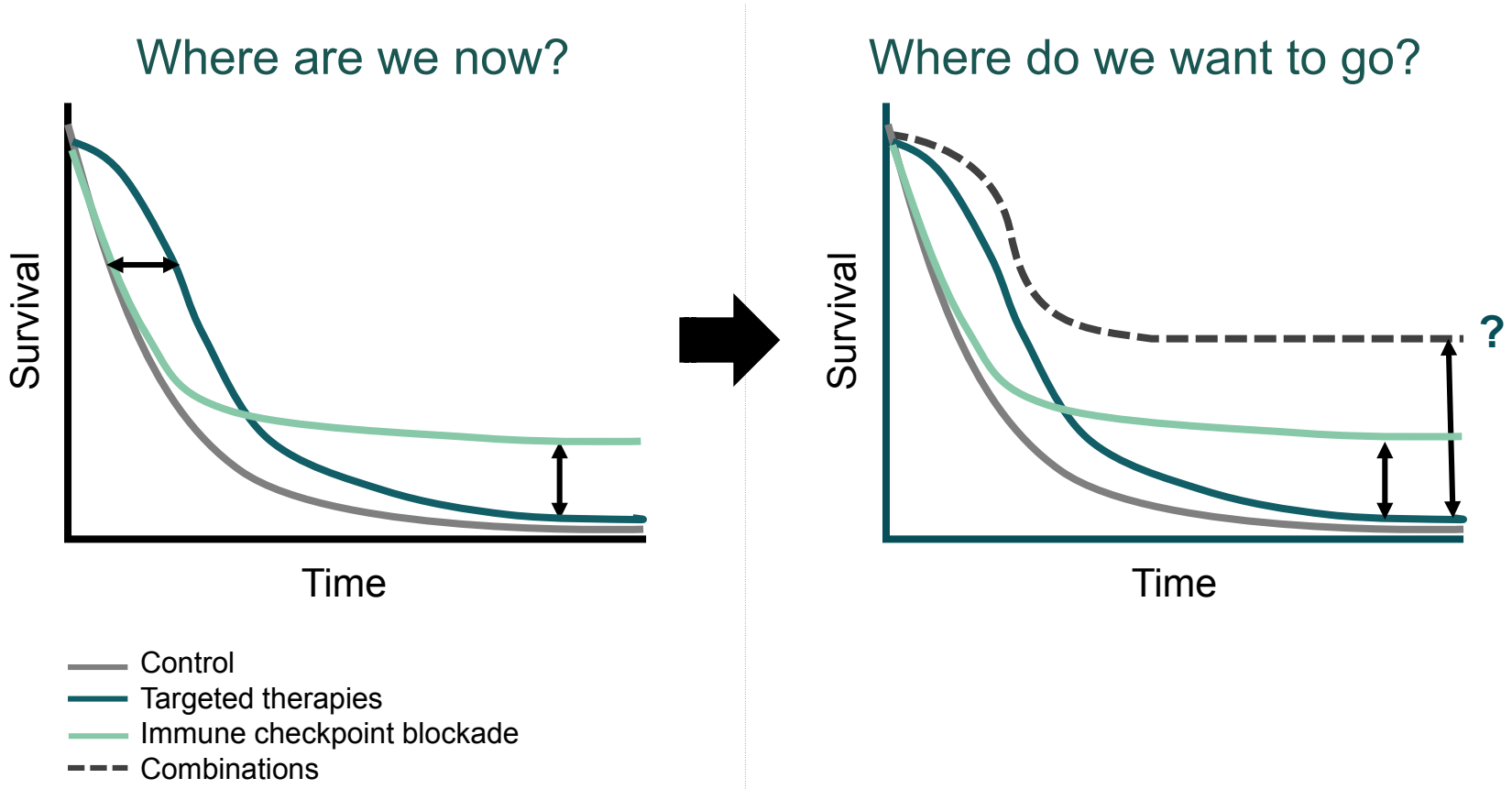
- Long-term data of ipilimumab of 1861 melanoma patients (8 Ph. II, 2 Ph. III, 2 Ph. IV studies)



Schadendorf et al, annual presentation at ECCO/ESMO 2013, abstract # 24LBA

Immuno-Oncology

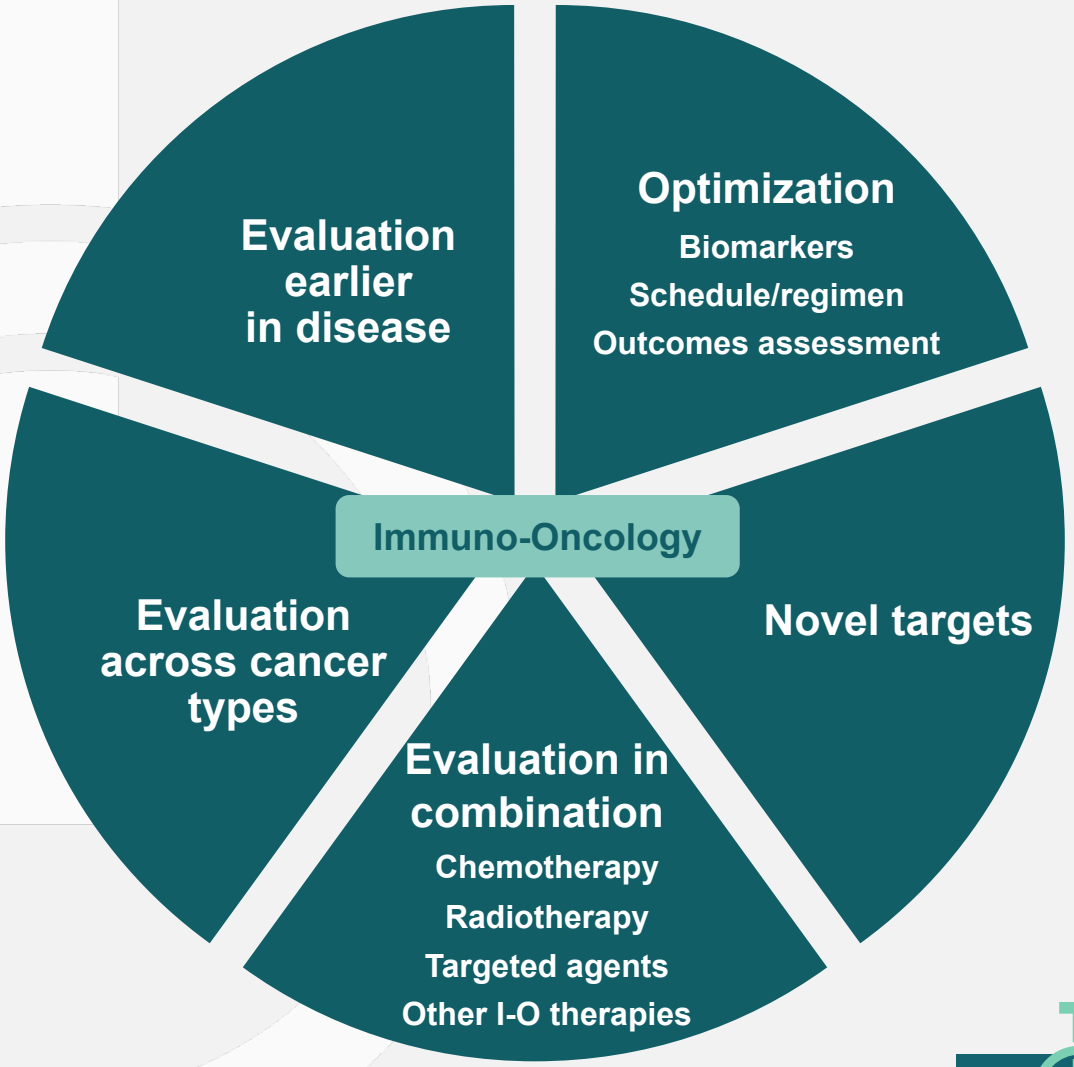
Future prospects



Adapted from Ribas A, presented at WCM, 2013; Ribas et al, Clin Cancer Res. 2012; 18: 336; Drake CG, Ann Oncol. 2012; 23(suppl 8): viii41.

Immuno-Oncology

What may the Future Hold?[1–4]



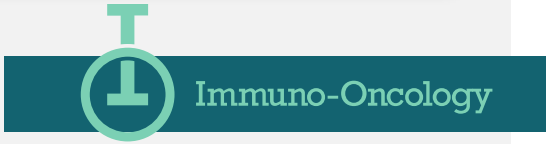
1. Drake CG. *Ann Oncol*. 2012;23(suppl 8):viii41–viii46; 2. Eggermont AM. *Ann Oncol*. 2012;23(suppl 8):viii53–viii57; 3. Eggermont AM, et al. *Eur J Cancer*. 2013;49:2965–2967; 4. Mellman I, et al. *Nature*. 2011;480:480–489.

Immuno-Oncology

Selected I-O combination approaches across multiple tumor types

I-O + Chemotherapy	I-O + Radiotherapy	I-O + targeted therapies
Ipilimumab + etoposide/platinum (SCLC)	Ipilimumab + radiotherapy (melanoma, NHL, colon, rectal)	Ipilimumab + trametinib + dabrafenib (melanoma)
Ipilimumab + paclitaxel/carboplatin (lung cancer and melanoma)	Poxviral vaccine + radiotherapy (prostate cancer)	Ipilimumab + rituximab (B-cell lymphoma)
Ipilimumab + fotemustine (melanoma)	LC9018 (vaccine) + radiotherapy (carcinoma of the uterine cervix)	Ipilimumab then vemurafenib (melanoma)
Ipilimumab + temozolomide (melanoma)	Adoptive dendritic cell immunotherapy + radiotherapy (heptoma)	Ipilimumab + dasatinib (GIST)
Nivolumab + chemotherapy (NSCLC)	CpG + radiotherapy (B-cell lymphoma)	Ipilimumab + bevacizumab (melanoma)
IMP321 (LAG-3) + paclitaxel (breast cancer)	Sipuleucel-T + radiation therapy (CRPC)	Nivolumab + everolimus (RCC)
Pembrolizumab + paclitaxel or carboplatin (NSCLC)		Nivolumab + erlotinib (NSCLC)
		Nivolumab + Ipilimumab or bevacizumab (NSCLC)
		Nivolumab + sunitinib, or pazopanib (RCC)
		Pidilizumab + rituximab (follicular lymphoma)
		Urelumab + rituximab (B-cell NHL or CLL)
		Pembrolizumab + bevacizumab or pemetrexed or ipilimumab or erlotinib or gefitinib (NSCLC)
		Tremelimumab plus MEDI4763 (advanced solid tumors)
		MPDL3280A + avastin (RCC)

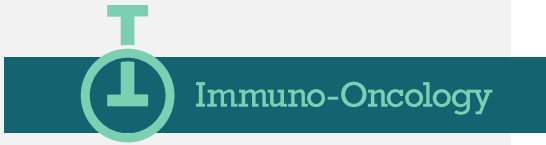
www.clinicaltrials.gov accessed 26 March 2014;; Formennti et al, J Natl Cancer Inst 2013; 105(4): 256; Ferrara et al, Curr Opin Mol Ther 2009; 11: 37



The Bristol-Myers Squibb I-O portfolio covers a large range of target structures and combination approaches in multiple tumor types

GASTROINTESTINAL	GENITOURINARY	LUNG	MELANOMA	HEMATOLOGIC	OTHER
Ipilimumab **Anti-CTLA-4** Advanced Gastric – Phase II	**Nivolumab[a]** **Anti-PD-1** 2nd/3rd line Advanced RCC – Phase III	**Nivolumab[a]** **Anti-PD-1** 2nd line – Phase III Advanced NSCLC (nonsquamous)	**Nivolumab[a]** **Anti-PD-1** 1st line Advanced Melanoma – Phase III	**Nivolumab[a]** **Anti-PD-1** Hematologic Malignancies – Phase I	**Lirilumab/nivolumab[a]** **Anti-KIR/Anti-PD-1** Solid tumors – Phase I
Nivolumab[a] **Anti-PD-1** Advanced HCC – Phase I	**Ipilimumab** **Anti-CTLA-4** Prostate – Phase III (post hormonal therapy)	**Nivolumab[a]** **Anti-PD-1** 2nd line – Phase III Advanced NSCLC (squamous)	**Nivolumab[a]** **Anti-PD-1** 2nd/3rd line Advanced Melanoma – Phase III	**Nivolumab[a,b]** **Anti-PD-1** NHL (FL and DLBCL) – Phase II	**Denenicokin/** **Nivolumaba** **IL-21/Anti-PD-1** Solid tumors – Phase I
	Ipilimumab **Anti-CTLA-4** Ovarian – Phase II	**Nivolumaba,b** **Anti-PD-1** 1st line – Phase III PD-L1[+] NSCLC	**Ipilimumab** **Anti-CTLA-4** Dose optimization Metastatic Melanoma – Phase III	**Nivolumab[a]/Dasatinib** CML – Phase I	**Lirilumab[a]/Ipilimumab** **Anti-KIR/Anti-CTLA-4** Solid tumors – Phase I
	Nivolumab[a] **Anti-PD-1** Advanced RCC – TKI or mAb combination Phase I	**Nivolumaba** **Anti-PD-1** 3rd line – Phase III Advanced NSCLC (squamous)	**Ipilimumab** **Anti-CTLA-4** Adjuvant Melanoma – Phase III		**Urelumab** **Anti-CD137** Phase I
	Nivolumab[a]/Ipilimumab **Anti-PD-1/Anti-CTLA-4** RCC – Phase I	**Ipilimumab** **Anti-CTLA-4** 1st line – Phase III Advanced NSCLC (squamous)	**Ipilimumab** **Anti-CTLA-4** Adolescent Melanoma – Phase II		**Nivolumab[a]** **Anti-PD-1** Solid tumors – Phase I
		Ipilimumab **Anti-CTLA-4** ED-SCLC – Phase III	**Nivolumab[a]/Ipilimumab** **Anti-PD-1/Anti-CTLA-4** 1st line Advanced Melanoma – Phase III		**Nivolumab[a]/** **Ipilimumab** **Anti-PD-1/Anti-CTLA-4** Solid tumors – Phase I
		Nivolumab[a]/Ipilimumab **Anti-PD-1/Anti-CTLA-4** NSCLC – Phase I			**Nivolumab[a]/** **Ipilimumab[b]** **Anti-PD-1/Anti-CTLA-4** GBM – Phase II

a Development partnership: nivolumab, ONO Pharmaceuticals; lirilumab, Innate Pharmaceuticals; b Published on www.clinicaltrials.gov, not yet recruiting; CML = chronic myeloid leukemia; DLBCL = diffuse large B-cell lymphoma; ED-SCLC = extensive-stage disease small cell lung cancer; TKI = tyrosine kinase inhibitor. www.clinicaltrials.gov accessed 1 February 2014.

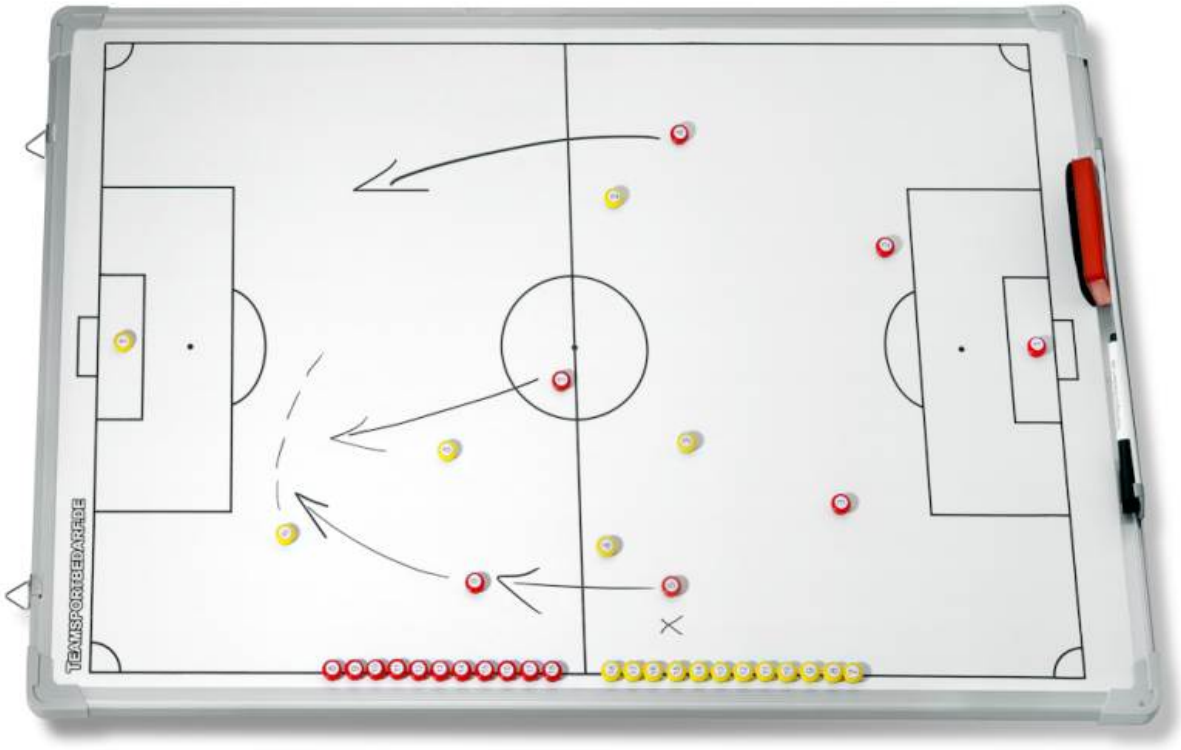


Tolerability Considerations With I-O Therapy

- Therapies designed to enhance the patient's immune response against the tumor can result in a novel spectrum of AEs arising from the activation of the immune system[1]
  - Termed immune-mediated adverse reactions
- Immune-mediated adverse reactions may be unfamiliar to clinicians[1,2]
- Immune-mediated adverse reactions can be serious and potentially fatal[1,2]
- Require prompt recognition and treatment[1]
- Require education of the patient and healthcare team[3]

1. Postow M, et al. *Cancer J.* 2012;18:152–159; 2. Amos SM, et al. *Blood.* 2011;118:499–509; 3. Ledezma B, et al. *Cancer Manag Res*. 2014;6:5–14.

Teamwork as the key to success



Immuno-Oncology

Takk for oppmerksomheten!

Les mer på www.immunonkologi.no

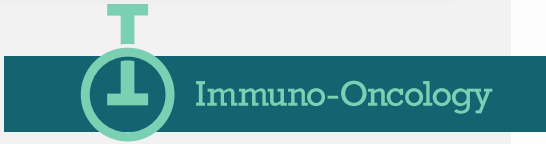
Immuno-Oncology

BACKUP

Therapies in clinical development: Immune checkpoint inhibitors

Target pathway	Molecule	Setting(s)	Company
CTLA-4	Ipilimumab	Advanced melanoma	BMS
		Adjuvant melanoma, NSCLC/SCLC, CRPC	
		Hematologic malignancies and other solid tumors	
	Tremelimumab	NSCLC, CRC, HCC, PC, mesothelioma	MedImmune / AZ; Pfizer
		RCC, PC, BC, pancreatic cancer	
PD-1	Nivolumab (BMS-936558)	Melanoma, NSCLC, RCC	BMS
		Various solid tumors and treatment combinations	
	Pembrolizumab (MK-3475)	Advanced melanoma, bladder, breast, head and neck and other solid tumors	Merck
	Pidilizumab (CT-011)	Metastatic melanoma, NHL, AML, CRC, prostate, pancreatic and hepatocellular	CureTech
	MPDL3280A (RG7446)	Locally advanced/metastatic melanoma, RCC, NSCLC, SCCHN and other solid tumors	Roche
	MEDI4736	Various solid tumors	AstraZeneca
	AMP-224	Lymphoma and solid tumors	Amplimmune / GSK and NCI
	rHIgM12B7	Melanoma	Mayo Clinic
LAG-3	BMS-986016 (MDX-1408)	Solid tumors (as of September 2013)	BMS
	IMP701	Preclinical	Immutep SA

AML = acute myelogenous leukemia; BC = breast cancer; CRC = colorectal cancer; GIST = gastrointestinal stromal tumor; HCC = hepatocellular carcinoma; MBC = metastatic breast cancer; NHL = non-Hodgkin's lymphoma; PC = prostate cancer; SCCHN = small-cell carcinoma of head and neck; SCLC = small cell lung cancer
www.clinicaltrials.gov, status: November 2013; Representation not complete



Therapies in clinical development: T-cell checkpoint stimulators

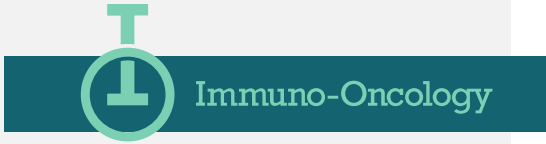
Target pathway	Molecule	Setting(s)	Company
CD137 (4-1BB)	Urelumab (BMS-663513)	B-cell NHL/CLL, melanoma and advanced solid tumors	BMS
	PF-05082566	NHL and solid tumors	Pfizer
OX-40 (CD134)	Anti-OX-40	Melanoma, breast, and prostate cancer	AgonOx
GITR	TRX518	Melanoma and solid tumors	GITR Inc.
CD27	CDX-1127	CD27-expressing hematologic malignancies and solid tumors	Celldex Therapeutics
CD40	CP-870, 893	Various advanced tumors; pancreatic cancer	Pfizer
	ISF35	CLL and NHL	Memgen LLC
	Chi Lob 7/4	Advanced treatment-refractory CD40+ solid tumors and DLBCL	CRUK
	Lucatumumab (HCD122)	CLL and MM; in rituximab-refractory follicular lymphoma	Novartis
	Dacetuzumab (SGN-40)	NHL/MM, diffuse large B-cell lymphoma	Seattle Genetics Inc.

CLL = chronic lymphocytic leukemia; GITR = glucocorticoid-induced tumor necrosis factor receptor related gene
www.clinicaltrials.gov, status: November 2013
Representation not complete

Therapies in clinical development: Expanding functional immune cells

Target pathway	Molecule	Setting(s)	Company
IDO	INCB024360	Gynecologic cancers and MDS	Incyte
		Unresectable/metastatic melanoma	
		Advanced solid tumors	
	Indoximod	MBC, CRPC	NewLink Genetics Corp.
		Metastatic solid tumors	
IL-21	Denenicokin (BMS-982470)	Metastatic melanoma, mRCC	BMS
		Metastatic melanoma and mRCC advanced/metastatic solid tumors mRCC, NHL	
IL-15	rhIL-15	Phase I/advanced malignancies	National Cancer Institute

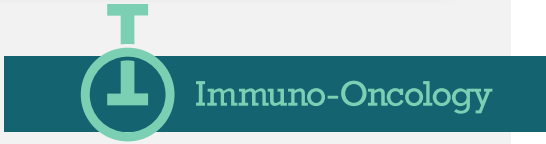
IDO = indolamine-2,3-dioxygenase; MDS = myelodysplastic syndrome; mRCC = metastatic renal cell carcinoma
www.clinicaltrials.gov, Stand November 2013
Representation not complete



Therapies in clinical development: Expanding functional immune cells

Target pathway	Molecule	Setting(s)	Company
KIR	Lirilumab (BMS-986015; IPH2102)	AML, MM, lymphoma and solid tumors	Innate Pharma/BMS
CD137 (4-1BB)[a]	Urelumab (BMS-663513)	B-cell NHL/CLL melanoma and advanced solid tumors	BMS
	PF-05082566	NHL, B-cell lymphoma and other solid tumors	Pfizer

a Dual action on T cells and NK cells
www.clinicaltrials.gov, Stand November 2013
Representation not complete



Therapies in clinical development: Cancer vaccine in phase III for solid tumors[a]

Name	Setting	Company
Autologous (patient-specific)		
DCVax™-L	Newly diagnosed GBM (+SOC)	Northwest Biotherapeutics Inc.
CVac™	Epithelial ovarian cancer in complete remission	Prima BioMed Ltd
Antigen-specific ("Off-the-shelf")		
GSK 2132231A	Melanoma (adjuvant setting),[b] NSCLC (adjuvant setting) [c]	GlaxoSmithKline plc
L-BLP25 (Stimuvax™)	NSCLC	Merck
PSA-TRICOM (Prostvac™)	Prostate cancer	Bavarian Nordic A/S
Algenpantucel-L (HyperActute™ Pancreas Immunotherapy)	Borderline resectable or locally advanced pancreatic cancer	NewLink Genetics Corp.
Tergenpumatucel-L (HyperActute™ Lung Immunotherapy)	Progressive or relapsed NSCLC	NewLink Genetics Corp.
IMA901	Advanced RCC	Immatics Biotechnologies
Talimogene laherparepvec (OncoVex GM-CSF)	Melanoma	Amgen
Belagenpumatucel-L (Lucanix™)	NSCLC[c]	NovaRx

GBM = glioblastoma multiforme; ICAM-1 = intercellular adhesion molecule 1; LFA-3 = lymphocyte function associated antigen-3; PSA = prostate-specific antigen; SOC = standard of care a Only vaccine from ongoing phase III studies were taken into account here (status: November 2013)); b Study has not reached a primary endpoint (GSK Press Release Sept 5, 2013); c Study has not reached the primary endpoint (improved OS) (Giaccone G, et al. ECC Congress. 2013 Abs LBA2).