Immuntherapie in der Onkologie

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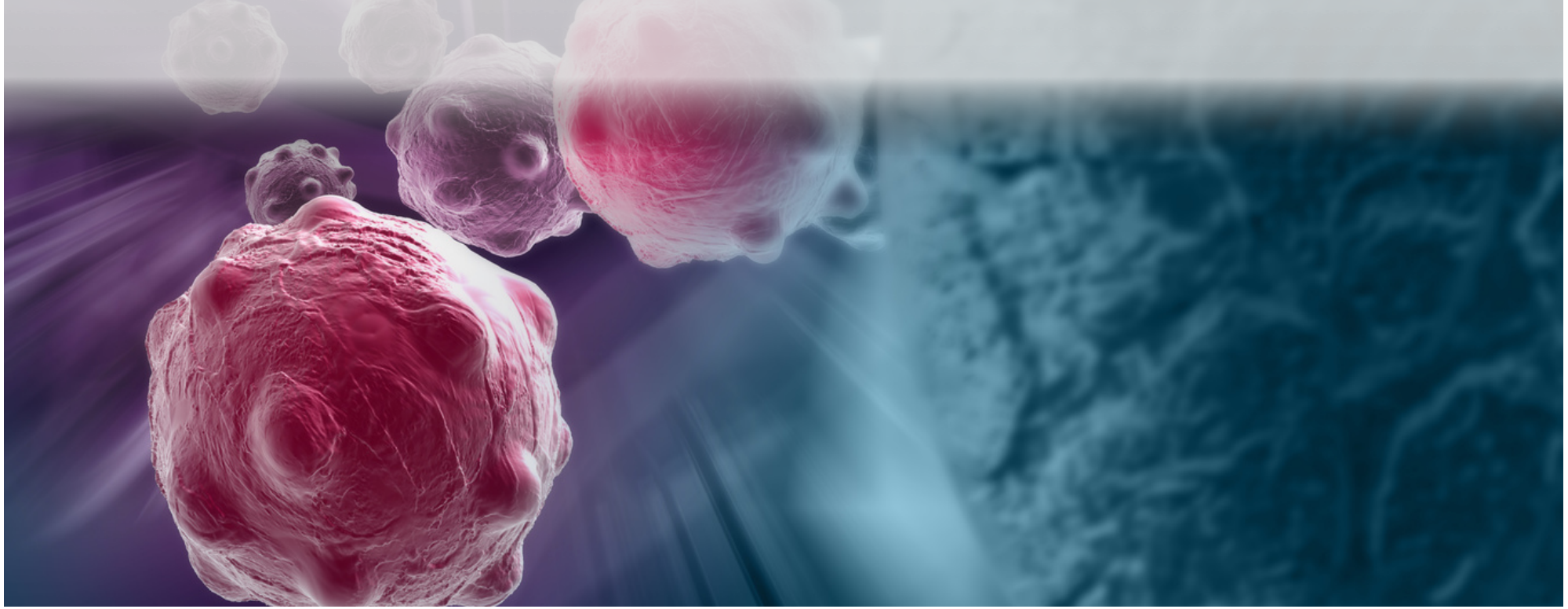

Krebs Immuntherapie

UNIVERSITÄTSmedizin.

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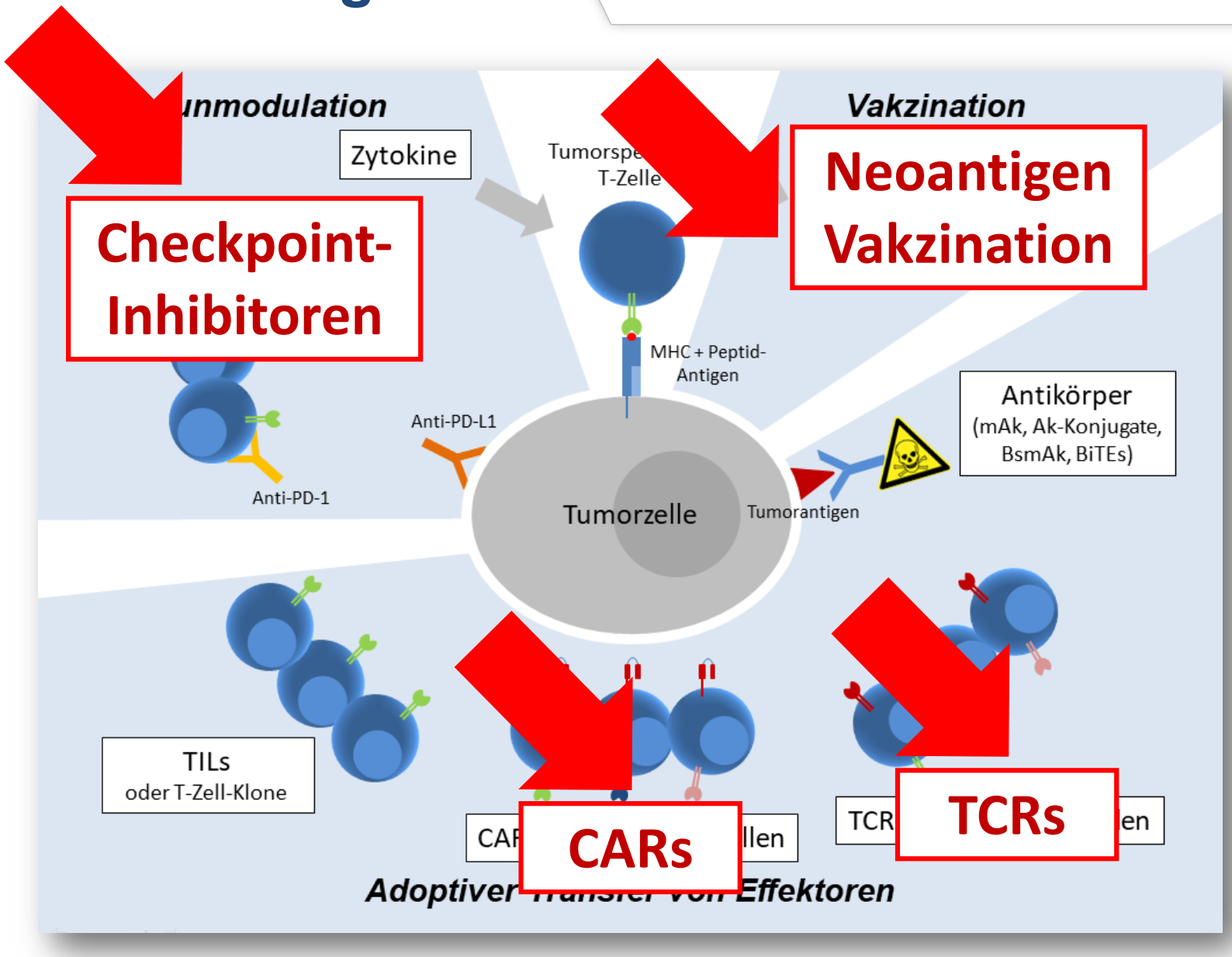
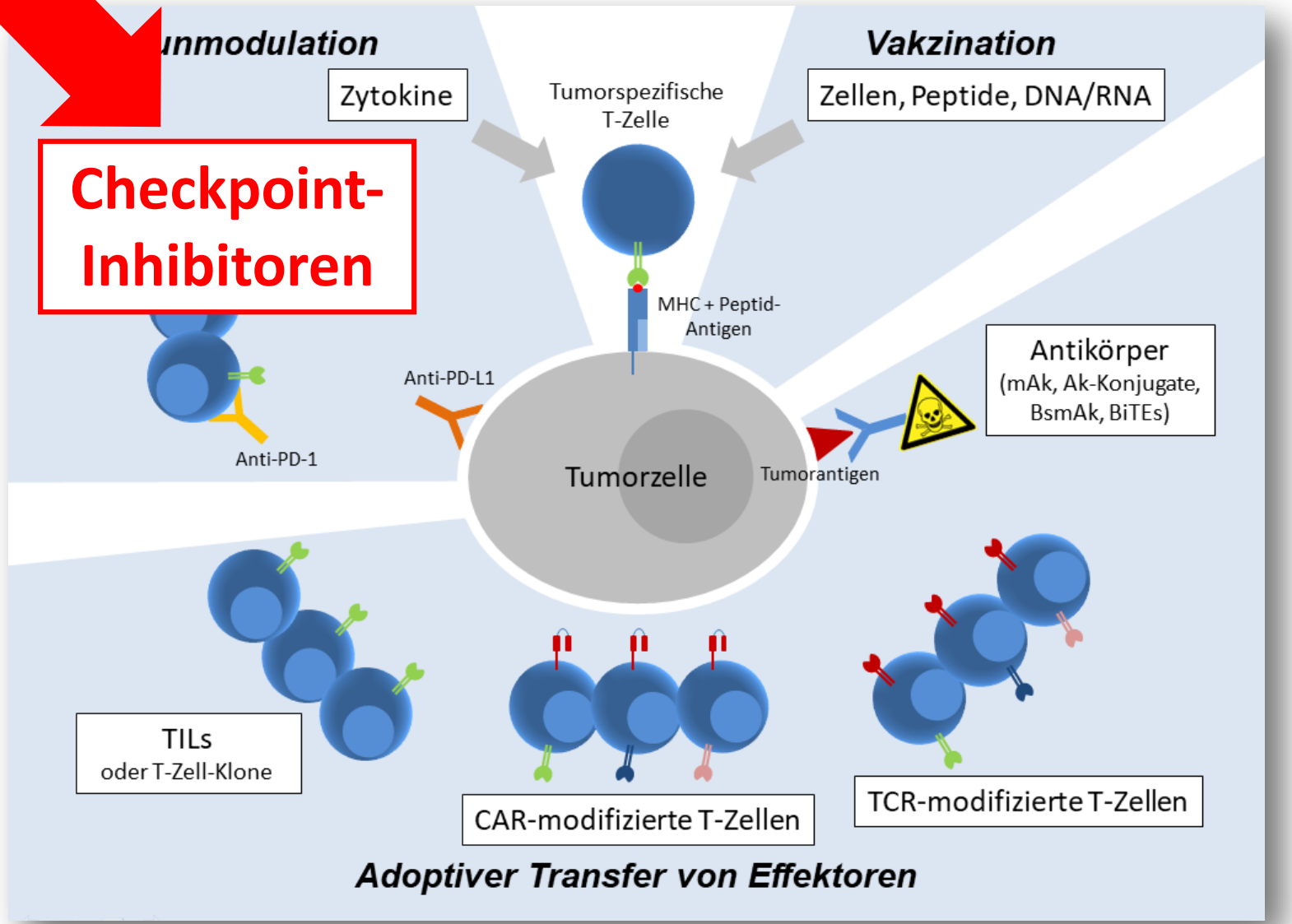
III. Medizinische Klinik und Poliklinik

Immunonkologie



Adaptiert nach Maus MV et al. Blood 2014;123:2625-35.

Immunonkologie



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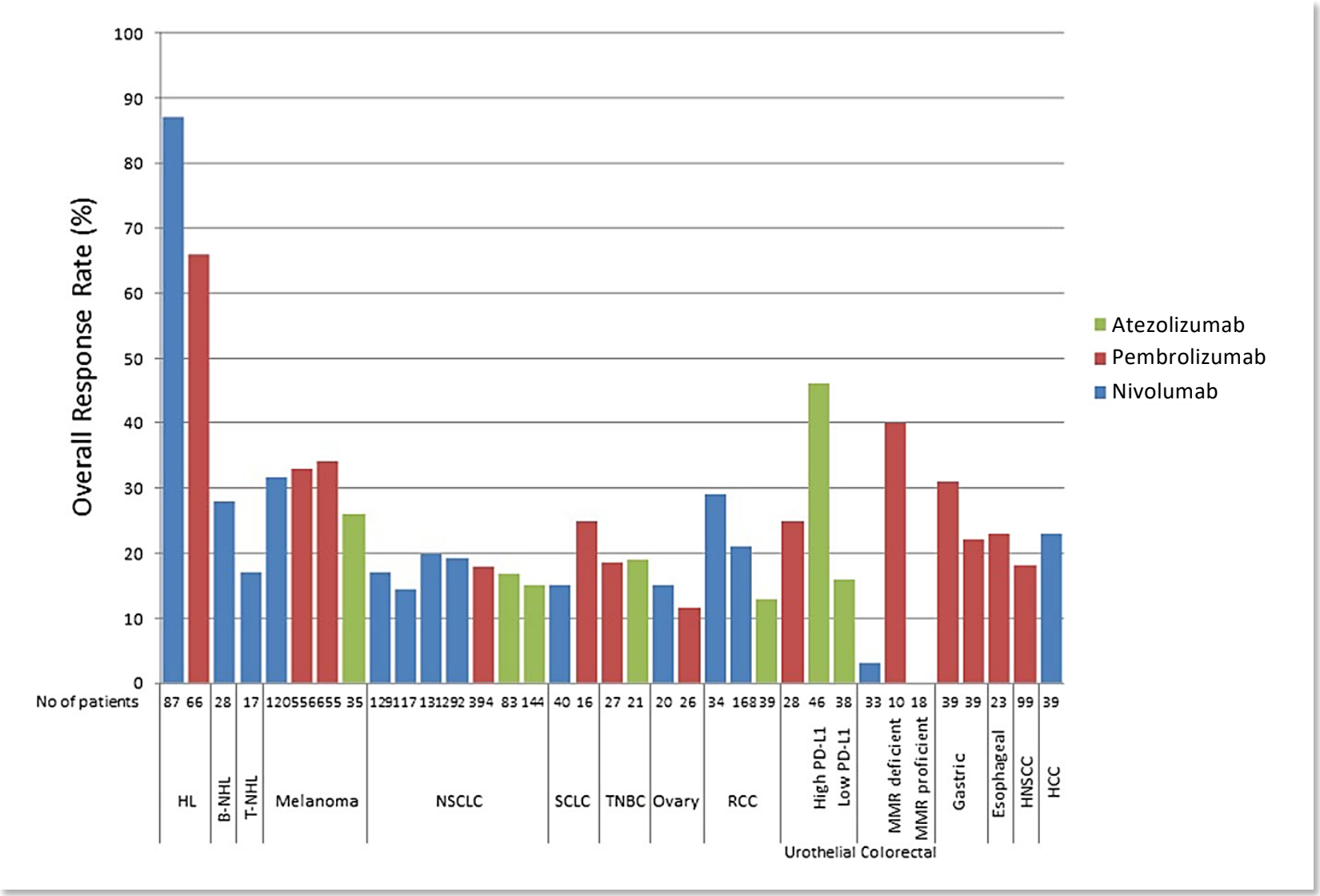
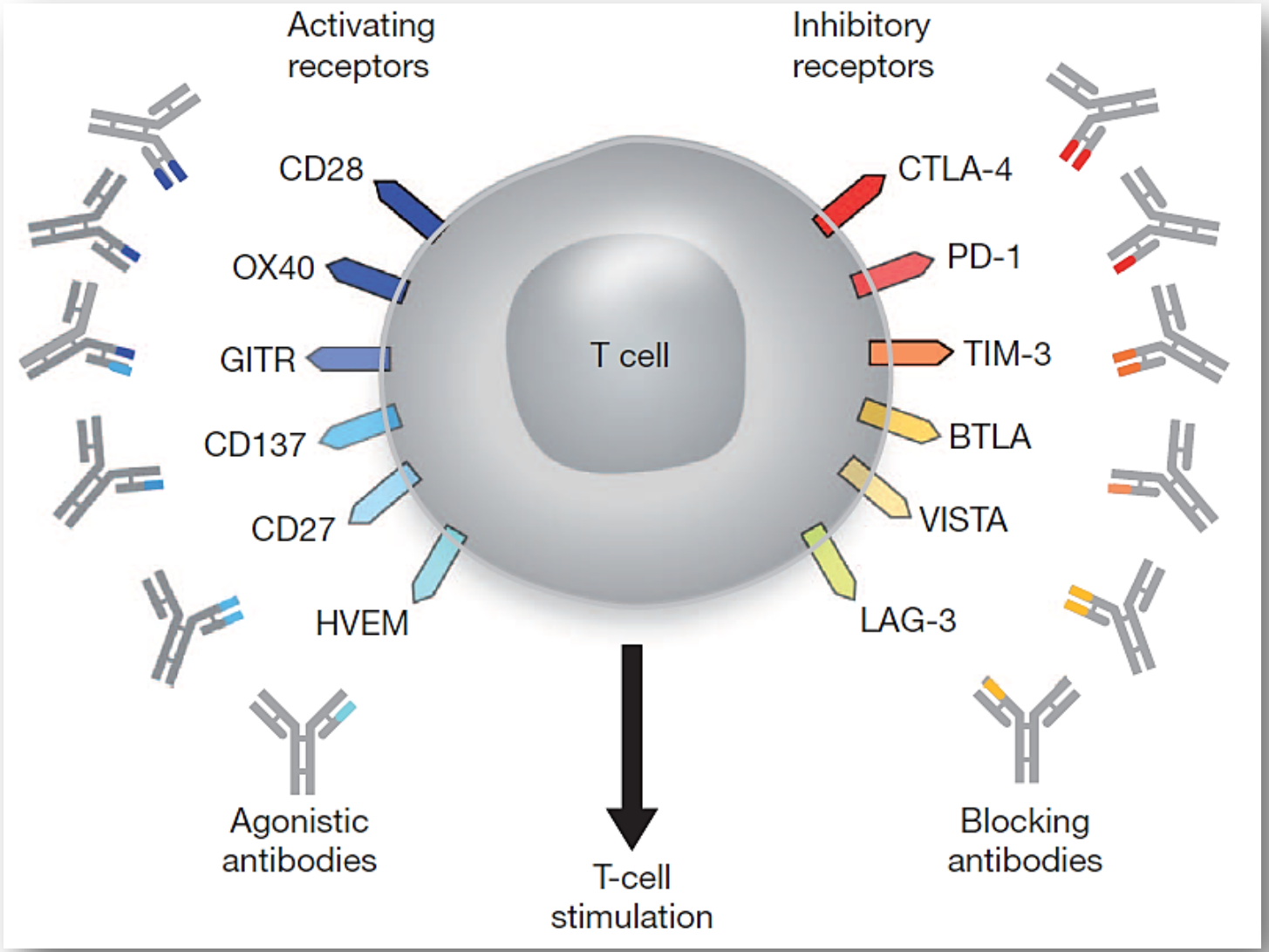
Ansprechen auf eine Blockade der PD-1/ PD-L1 Achse



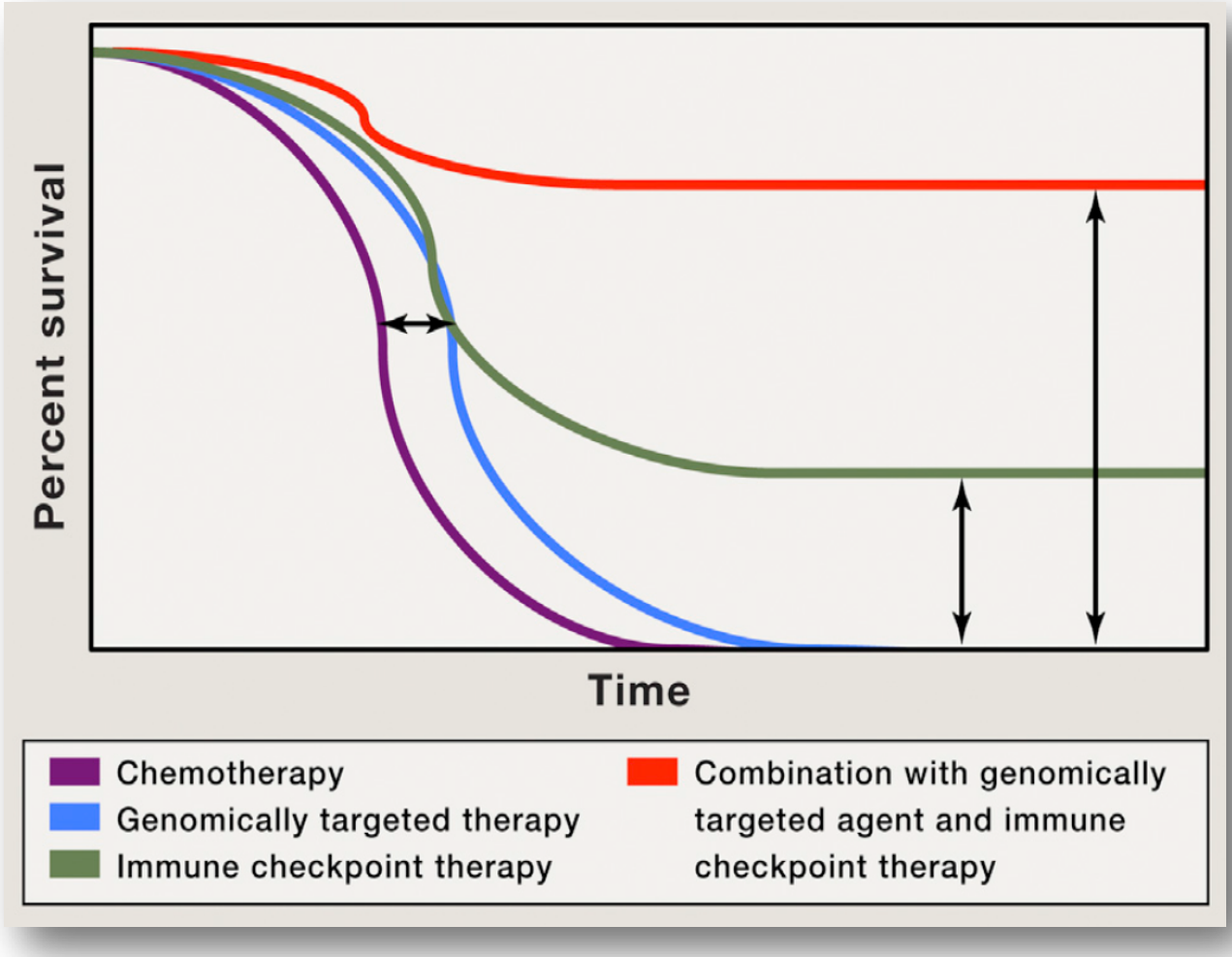
Matsuki E et al. Curr Treat Options in Oncol. 2016;17:31.

Ziele für Immunantikörper



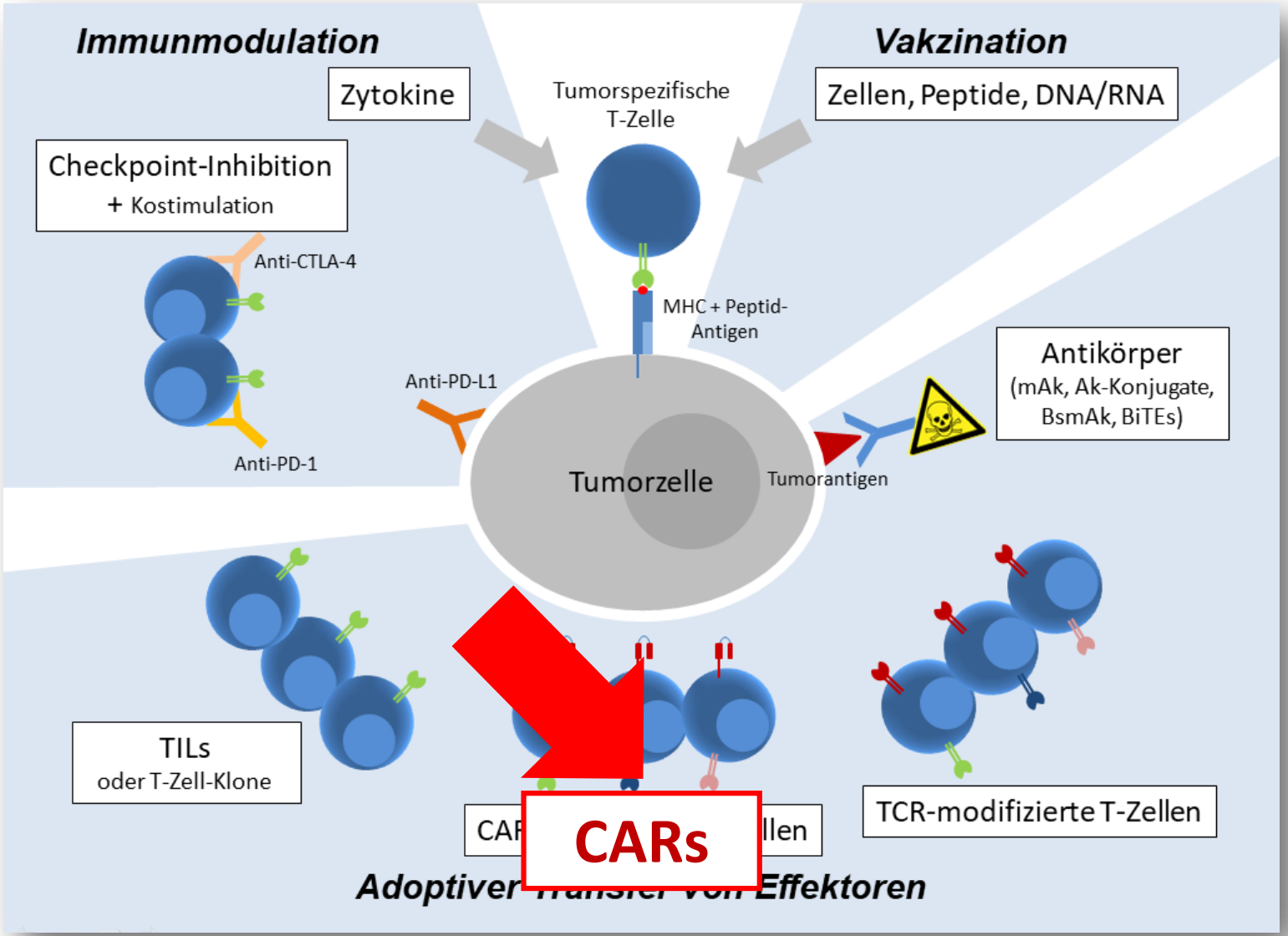
Mellmann I et al. Nature 2011;480(22):480-9.

Gegenwart und Zukunft der immunologischen Checkpoint Blockade



Padmanee S et al. Cell 2015;161:205-14

Immunonkologie



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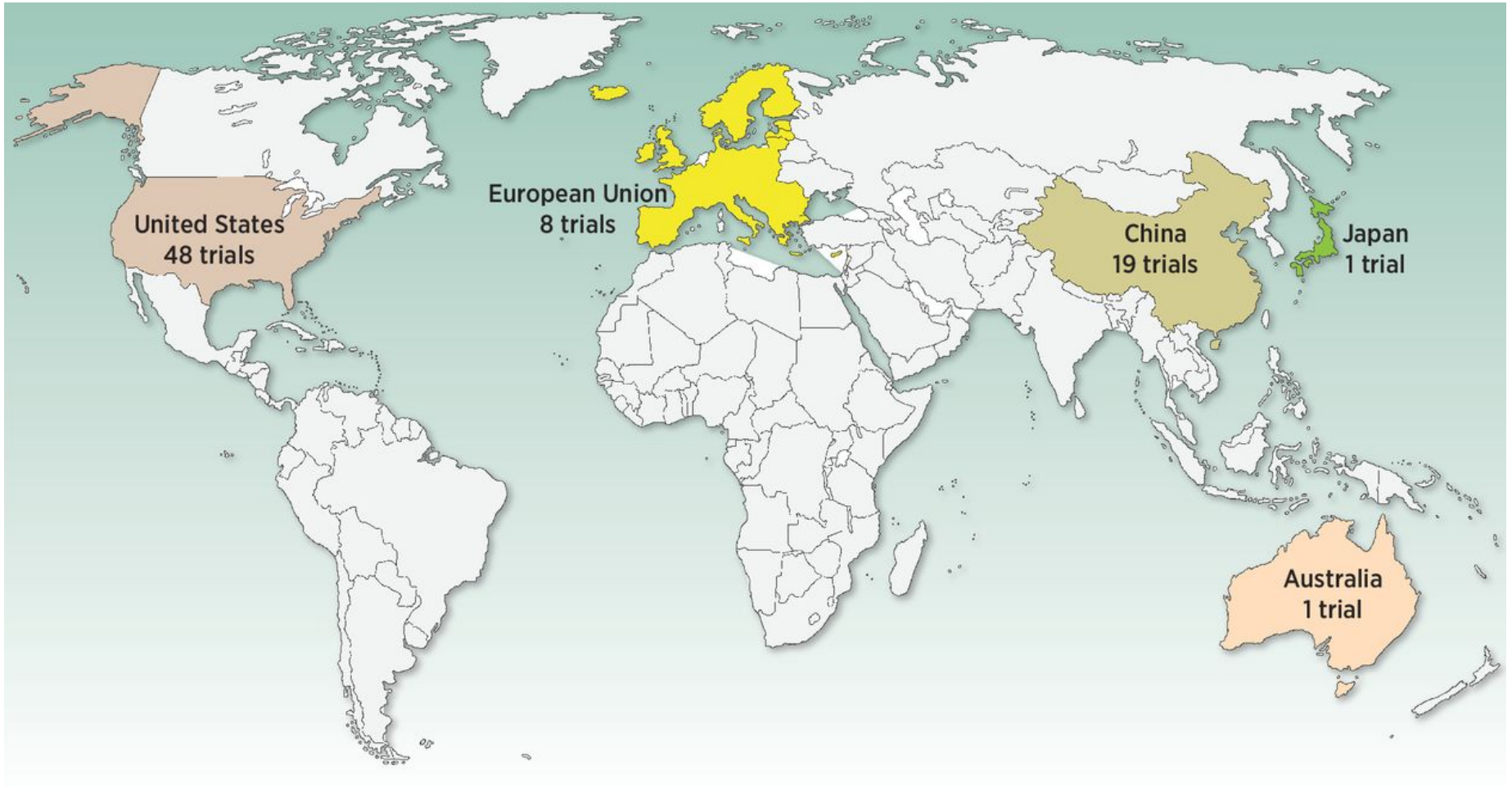
Heatmap indicating geographic locations (2016) **of ongoing or completed trials testing CAR T-cells**



Maus MV, June CH. Clin Cancer Res 2016;22:1875-84

CD19 CARs in DLBCL - Zulassungsstudien

	KYMRIAH (Novartis)	YESCARTA (Kite Pharma)	JCAR017 (Juno Therapeutics)
Wirksamkeit	**ORR 53,1%,** CR 39,5%, PR 13,6% 3 Monate: CR 32%, PR 6% 6 Monate: CR 30%, PR 7%	**ORR 82%,** CR 54% 15,4 Monate: RR 42%, CR 40% 18 Monate: OS 52%	ORR 75%, CR 56% 3 Monate: CR 40%, RR 49% 6 Monate: CR 37%, RR 40%

Schuster SJ et al. Blood 2017;130:577 / Neelapu SS et al. N Engl J Med. 2017;377:2531-44 / Abramson JS et al. Blood 2017;130:581.

CARs - Effizienz

- CD4s and polyfunctional T cells
- Bi / tri / quad - specific (= compound) CARs
- Epigenetic programming of CARs
- CRISPR/Cas9 targeting of CAR to TRAC locus (promoter) (AAV)
- Employing gamma (or epsilon) TCR signaling subunits – integration into the TCR complex
- In vivo transduction
- Steering CARs into solid tumors
- Combinations (…, checkpoint inhibition, trucks, homing receptors, …)

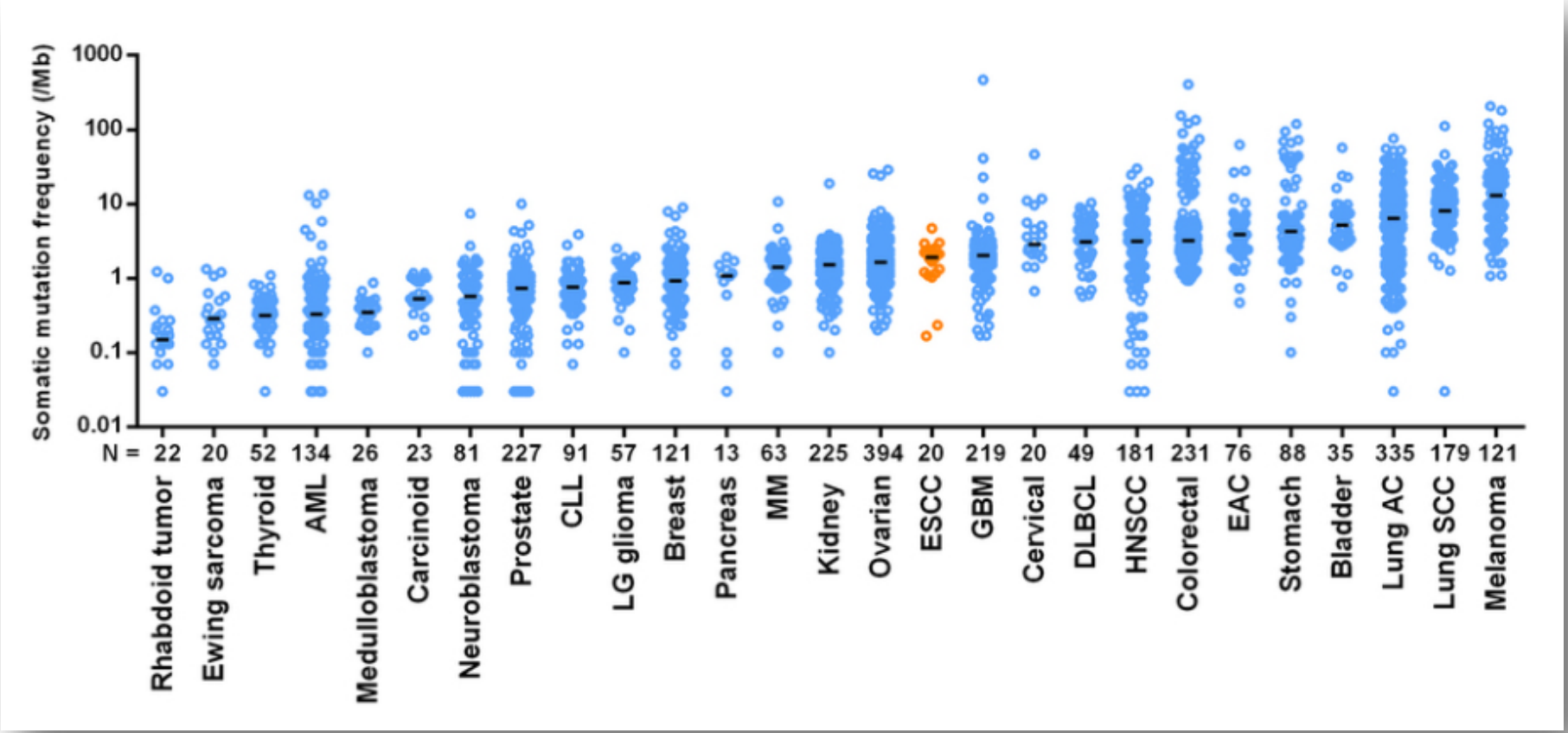
CARs - Sicherheit

CNS toxicity and CRS

B cell aplasia

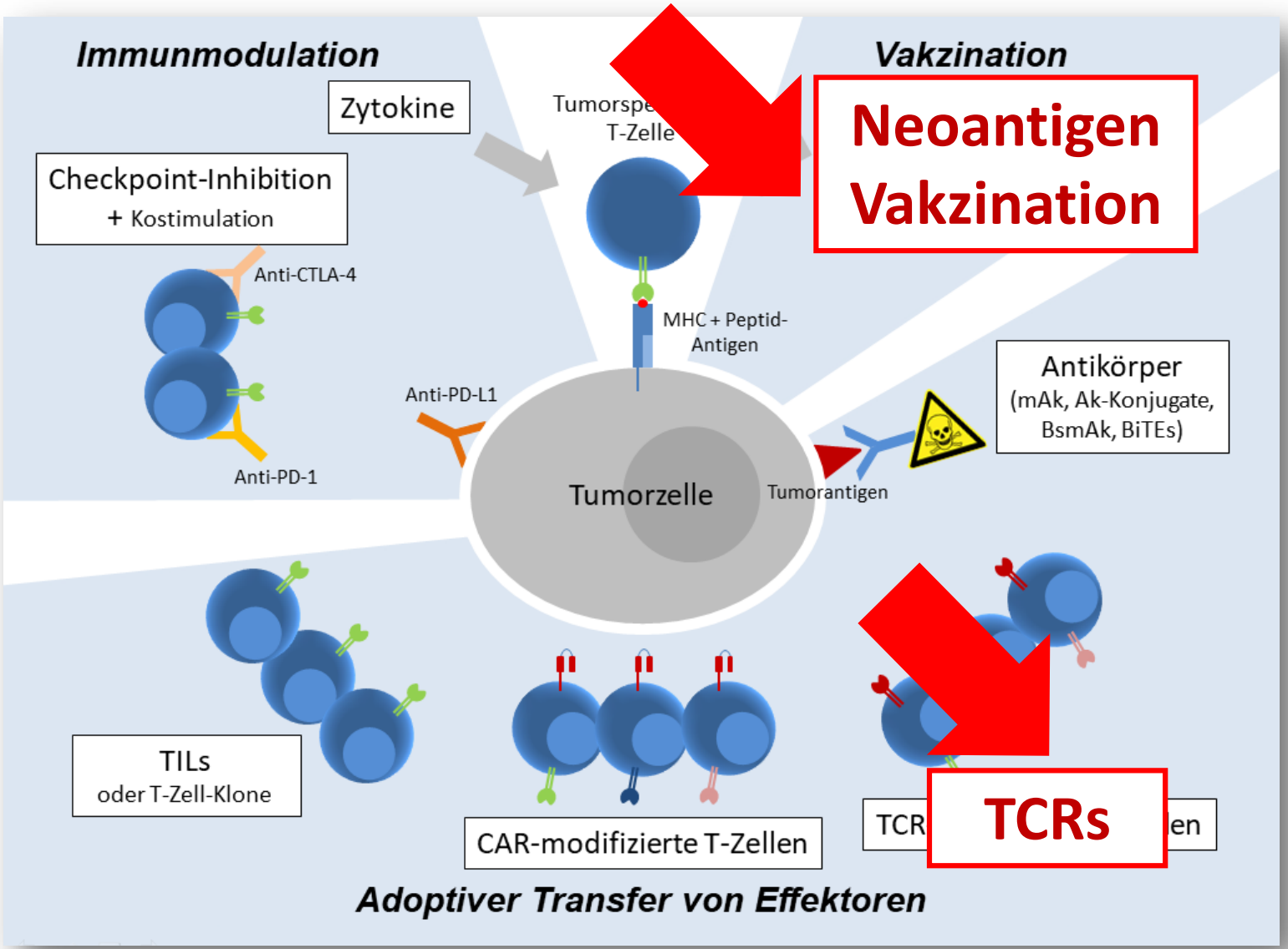
CRISPR/Cas9-mediated TCR replacement (?)

Erworbene Genmutationen bei Krebs



Nature Genetics. 2014;46:467–73. doi:10.1038/ng.2935

Immunonkologie



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Personalized RNA mutanome vaccines

… first-in-human application in melanoma

LETTER

doi:10.1038/nature23003

Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

Ugur Sahin[1,2,3], Evelyna Derhovanessian[1], Matthias Miller[1], Björn-Philipp Kloke[1], Petra Simon[1], Martin Löwer[2], Valesca Bukur[1,2], Arbel D. Tadmor[2], Ulrich Luxemburger[1], Barbara Schrörs[2], Tana Omokoko[1], Mathias Vormehr[1,3], Christian Albrecht[2], Anna Paruzynski[1], Andreas N. Kuhn[1], Janina Buck[1], Sandra Heesch[1], Katharina H. Schreeb[1], Felicitas Müller[1], Inga Ortseifer[1], Isabel Vogler[1], Eva Godehardt[1], Sebastian Attig[2,3], Richard Rae[2], Andrea Breitkreuz[1], Claudia Tolliver[1], Martin Suchan[2], Goran Martic[2], Alexander Hohberger[3], Patrick Sorn[2], Jan Diekmann[1], Janko Ciesla[4], Olga Waksmann[4], Alexandra-Kemmer Brück[1], Meike Witt[1], Martina Zillgen[1], Andree Rothermel[2], Barbara Kasemann[2], David Langer[1], Stefanie Bolte[1], Mustafa Diken[1,2], Sebastian Kreiter[1,2], Romina Nemecek[5], Christoffer Gebhardt[6,7], Stephan Grabbe[3], Christoph Höller[5], Jochen Utikal[6,7], Christoph Huber[1,2,3], Carmen Loquai[3]* & Özlem Türeci[8]*

T cells directed against mutant neo-epitopes drive cancer immunity. However, spontaneous immune recognition of mutations is inefficient. We recently introduced the concept of individualized mutanome vaccines and implemented an RNA-based poly-neo-epitope approach to mobilize immunity against a spectrum of cancer mutations[1,2]. Here we report the first-in-human application of this and RNA sequencing of routine tumour biopsies and healthy blood cells. Mutations were ranked according to: (1) predicted high-affinity binding to autologous HLA class II and high expression of the mutation-encoding RNA[2], and (2) predicted HLA class I binding. Ten selected mutations per patient (five for patient P09) were engineered into two synthetic RNAs, each encoding five linker-connected

Sahin U et al. Nature 2017;547(7662):222-6.

Immunonkologie

Erforderliche Maßnahmen

Checkpoint Inhibitoren

Klinische Studien und Reverse Translation

Masterplan CARs

Netzwerk ausgewiesener Spitzenzentren

Personalisierte Immunintervention

Förderung standortübergreifende Strukturen

Sequenzierung – Biobanking – Translation

Vielen Dank ☺