I. Witzel, Brustzentrum am UKE

Brustzentrum am UKE

Checkpoint-Inhibition beim Mammakarzinom

Universitätsklinikum Hamburg-Eppendorf

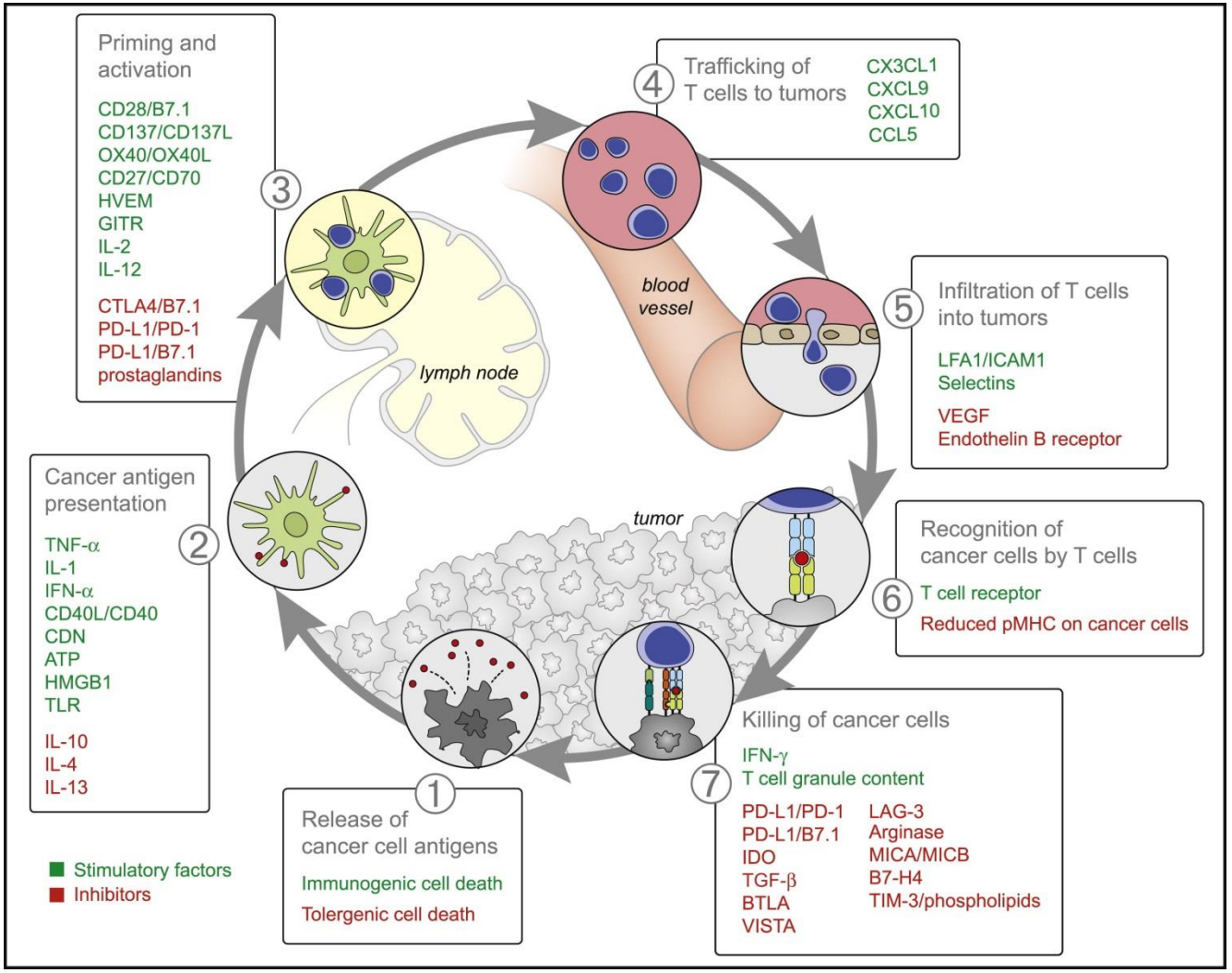
Überblick

- **Immunsystem und Krebs**
- **Einsatz beim Malignen Melanom**
- **Einsatz beim Mammakarzinom**
- **Herausforderungen**

„Immunsystem“ und Krebs

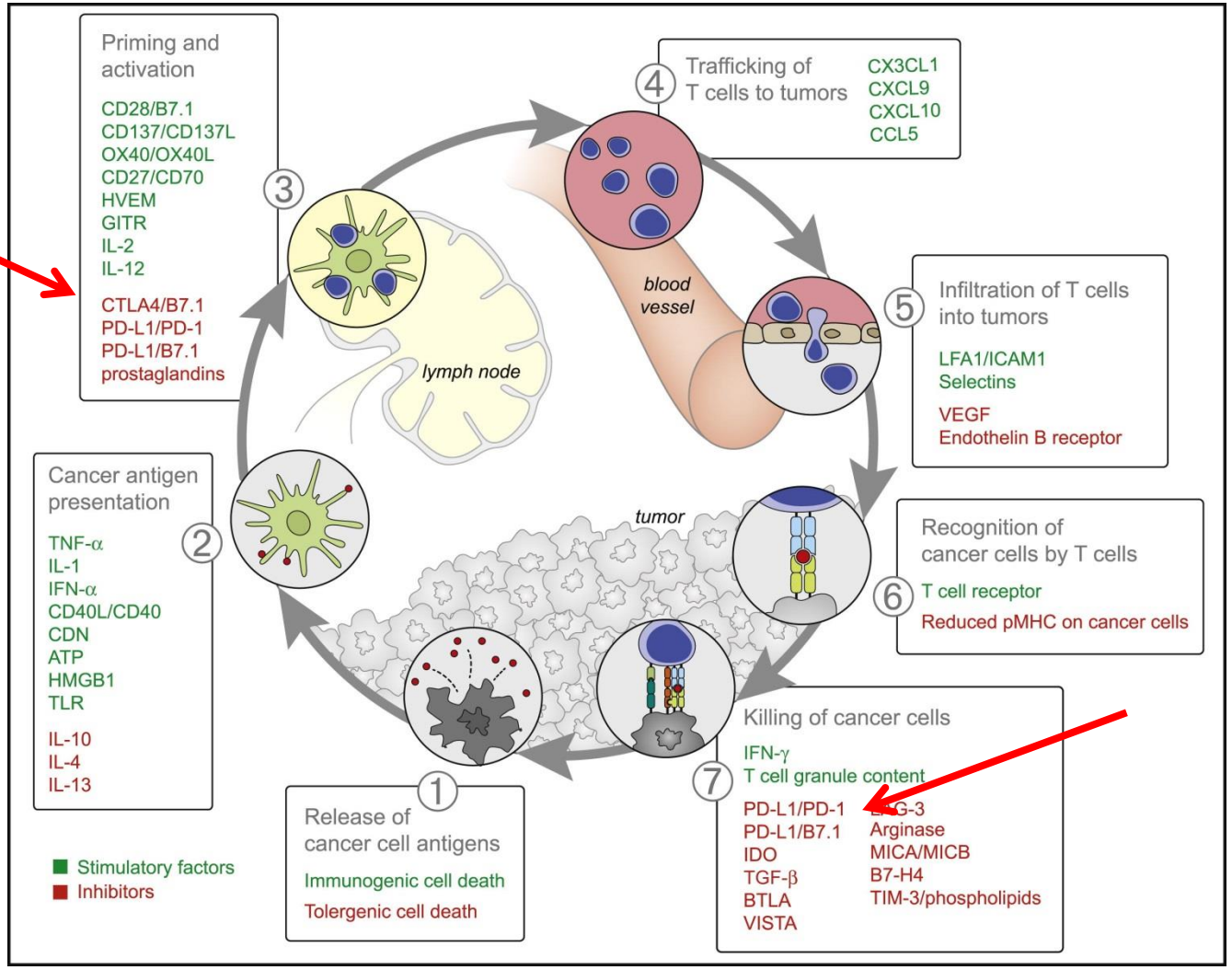
- **William Coley, amerikanischer Chirurg und Onkologe, injizierte ab 1890 Streptococcus pyogenes direkt in den Tumor und erreichte Ansprechraten von ca. 10%**
- **„ Vater der Krebsimmuntherapie“**

Es ist kompliziert…



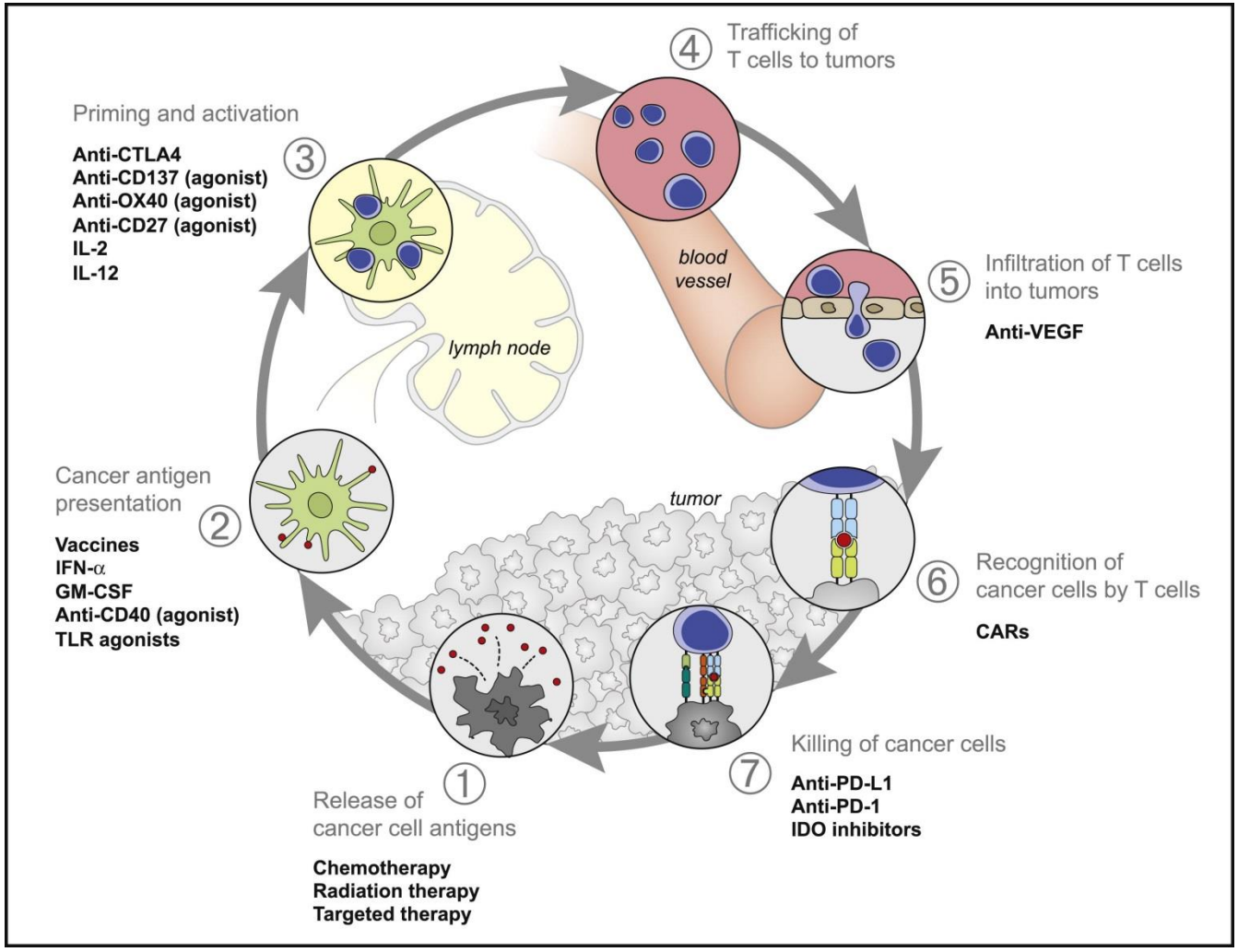
Chen et al., Immunity 2013 39, 1-10DImmunity. 2013 Jul 25;39(1):1-10. doi: 10.1016/j.immuni.2013.07.012OI: (10.1016/j.immuni.2013.07.012)

Es ist kompliziert…



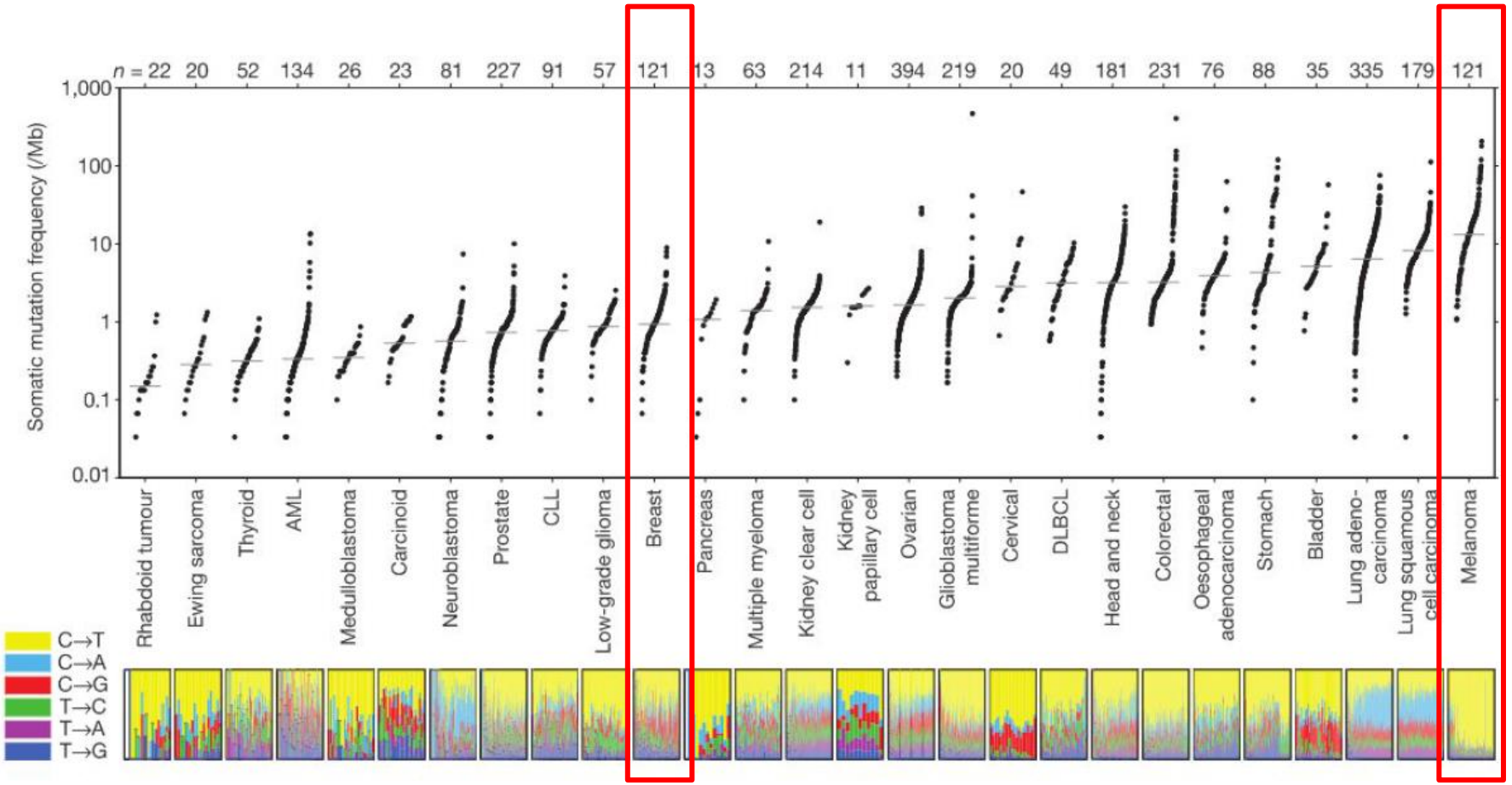
Chen et al., Immunity 2013 39, 1-10DImmunity. 2013 Jul 25;39(1):1-10. doi: 10.1016/j.immuni.2013.07.012OI: (10.1016/j.immuni.2013.07.012)

Viele Ansatzpunkte



Chen et al., Immunity 2013 39, 1-10DImmunity. 2013 Jul 25;39(1):1-10. doi: 10.1016/j.immuni.2013.07.012OI: (10.1016/j.immuni.2013.07.012)

Mutational Load



Lawrence et al., Nature 499, 214–218 (11 July 2013) doi:10.1038/nature12213 Received 14 June 2012 Accepted 22 April 2013 Published online 16 June 2013

EINSATZ BEIM MALIGNEN MELANOM

Studien zu Checkpoint-Inhibitoren in den zugelassenen Indikationen beim fortgeschrittenen malignen Melanom und nichtkleinzelligen Lungenkarzinom

Medikament	Phase	Publikationsjahr	Indikation	Endpunkt	Patientenzahl	medianes Gesamtüberleben		Referenz
						Prätherapiegruppe	Vergleichsgruppe	
Ipilimumab	III	2010	Zweitlinie, metastasiertes oder fortgeschrittenes Melanom	Gesamtüberleben	676	10 Monate (Ipilimumab + Vakzine)	6 Monate (Vakzine)	(5)
	III	2011	Erstlinie, metastasiertes oder fortgeschrittenes Melanom	Gesamtüberleben	502	11 Monate	9 Monate (DTIC)	(6)
Nivolumab	III	2015	metastasiertes Melanom ohne BRAF-Mutation	Gesamtüberleben	418	NE	14 Monate (DTIC)	(10)
	III	2015	Zweitlinie, fortgeschrittenes	Gesamt-	272	9 Monate	6 Monate	(20)
				PFS			(Ipilimumab, Nivolumab)	
	III	2015	metastasiertes oder lokal fortgeschrittenes Melanom	Gesamtansprechen	142	NE	NE PFS 4 Monate (Ipilimumab)	(17)
Pembrolizumab	I	2014	Ipilimumab-refraktäres Melanom	Sicherheit und Wirksamkeit	173	NB	keine	(9)
	I	2014	metastasiertes oder lokal fortgeschrittenes Melanom	Sicherheit und Wirksamkeit	411	NE	keine	*
	I	2015	Zweitlinie, fortgeschrittenes nichtkleinzelliges Lungenkarzinom	Sicherheit und Wirksamkeit	495	12 Monate	keine	(20)
	III	2015	metastasiertes oder lokal fortgeschrittenes Melanom	Gesamtüberleben und PFS	834	NE	NE (Ipilimumab)	(18)

1 Jahr Überleben von 35% vor 10 Jahren auf 95% heutzutage mit Checkpoint Inhibitoren beim Metastasierten Malignen Melanom

Kobold et al. 2013, Deutsches Ärztebatt

EINSATZ BEIM MAMMAKARZINOM

TILs beim Mammakarzinom

VOLUME 33 · NUMBER 9 · MARCH 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2–Positive and Triple-Negative Primary Breast Cancers

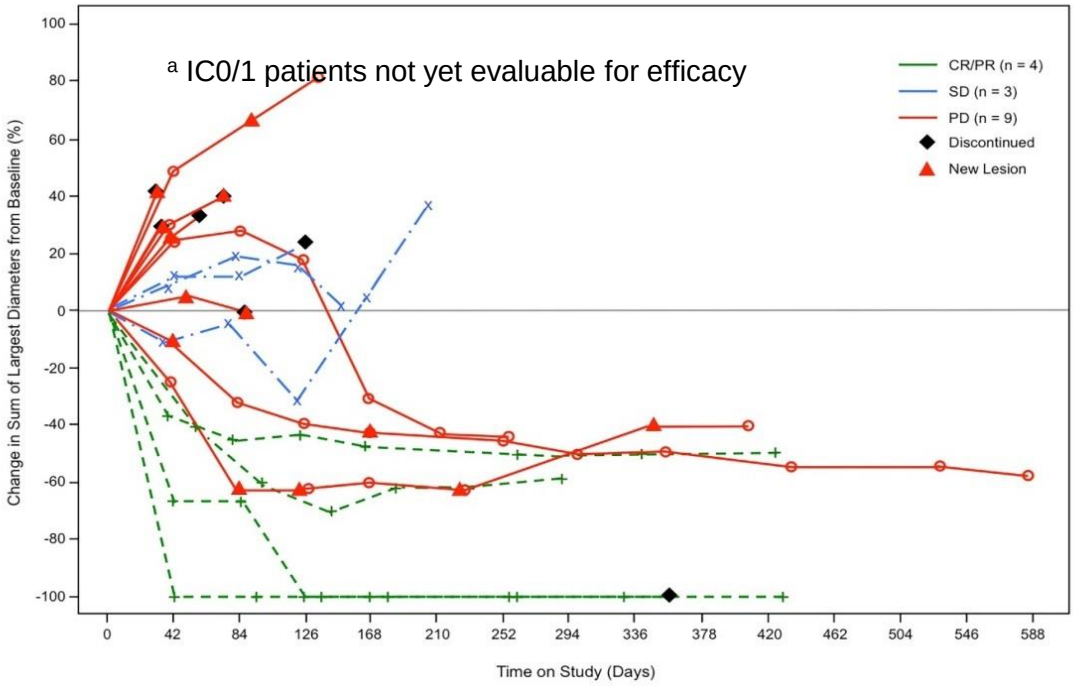
Carsten Denkert, Gunter von Minckwitz, Jan C. Brase, Bruno V. Sinn, Stephan Gade, Ralf Kronenwett, Berit M. Pfitzner, Christoph Salat, Sherene Loi, Wolfgang D. Schmitt, Christian Schem, Karin Fisch, Silvia Darb-Esfahani, Keyur Mehta, Christos Sotiriou, Stephan Wienert, Peter Klare, Fabrice André, Frederick Klauschen, Jens-Uwe Blohmer, Kristin Krappmann, Marcus Schmidt, Hans Tesch, Sherko Kümmel, Peter Sinn, Christian Jackisch, Manfred Dietel, Toralf Reimer, Michael Untch, and Sibylle Loibl

Brussels, Belgium; [9]German Breast Group, Neu-Isenburg; [10]Charité University Hospital, Institute of Pathology, Berlin, Germany; [11]Immunology in Cancer and Infection Laboratory, Queensland Institute of Medical Research (QIMR) Berghofer Medical Research Institute; School of Medicine, University of Queensland, Herston, Australia

Received 23 February 2014; accepted 25 February 2014

Phase I- Studie mit Atezolizumab (PDL1-AK) , TNBC metastasiert, viele Vortherapien (n=54)

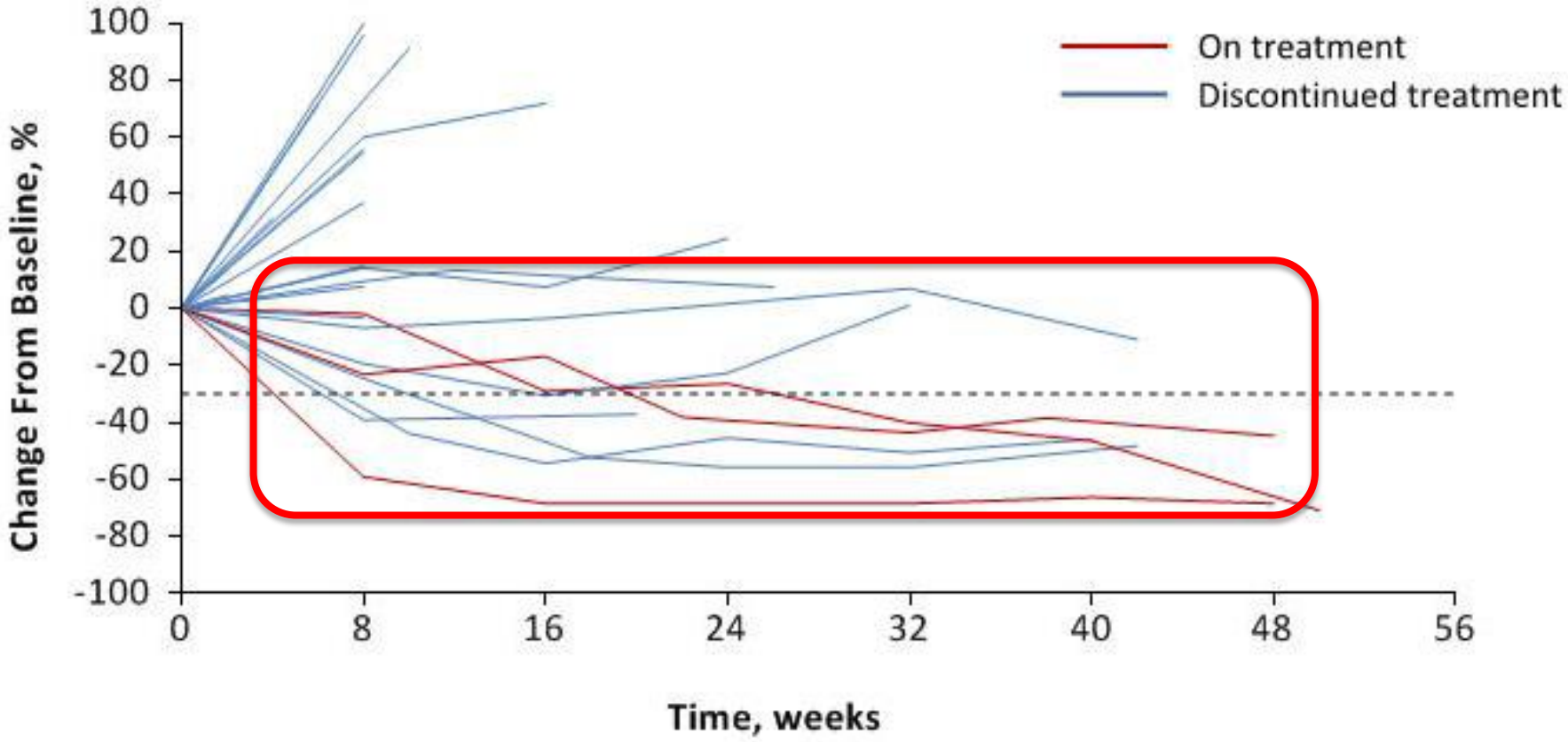
IC2/3 patients, n[a]	ORR (95% CI)	24-Week PFS (95% CI)
21	**19%** (5-42)	**27%** (7-47)



Emens LA, et al. AACR 2015

- Anti-PDL1 was generally well tolerated (n=54)
- Responses included
  - 2 CRs (1 IC3 and 1 IC2) and 2 PRs (IC2)
  - 3 of 4 responses ongoing
- In addition, three patients recorded as PD appeared to experience pseudoprogression, with durable shrinkage of target and new lesions
- Phase III study to start in H2 2015

Phase I – Studie mit Pembrolizumab (PD1-AK), TNBC metastasiert, Keynote – 012 (n=27)



Nanda R et al.; SABCS 2014 # S1-09

Phase Ib: Atezolizumab (PDL1-AK) + nab-Paclitaxel beim TNBC 1-3L (N=32)

DRAFT

Results

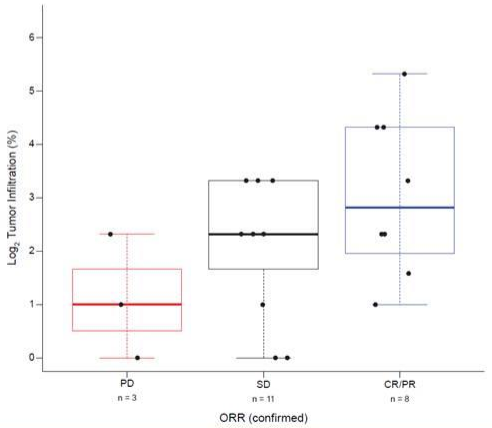
BOR per RECIST v1.1 by line of therapy

- 32 pts were evaluable for response
  - Median age (range): 55.5 y (32-84)
  - ECOG PS 1: 81%
  - Median no. (range) of prior systemic cancer therapies: 5 (1-10)
  - Prior taxane use: 88%

BOR	1L n = 13	2L n = 9[b]	3L+ n = 10
Confirmed ORR (95% CI)[a]	46% (19, 75)	22% (3, 60)	40% (12, 74)
CR	8%	0	0
PR	38%	22%	40%
SD	38%	67%	30%
PD	15%	0	30%

[a] Confirmed ORR defined as ≥ 2 consecutive assessments of CR or PR.
[b] One patient discontinued with clinical progression before first on-treatment tumor assessment.
Data cutoff date, Jan 14, 2016.

- Minimum efficacy follow up was ≥ 5 months
- Responses were seen in both patients with PD-L1–positive (IC1/2/3) and PD-L1–negative (IC0) tumors
- Baseline levels of tumor-infiltrating lymphocytes (TILs) showed a trend with increased ORR



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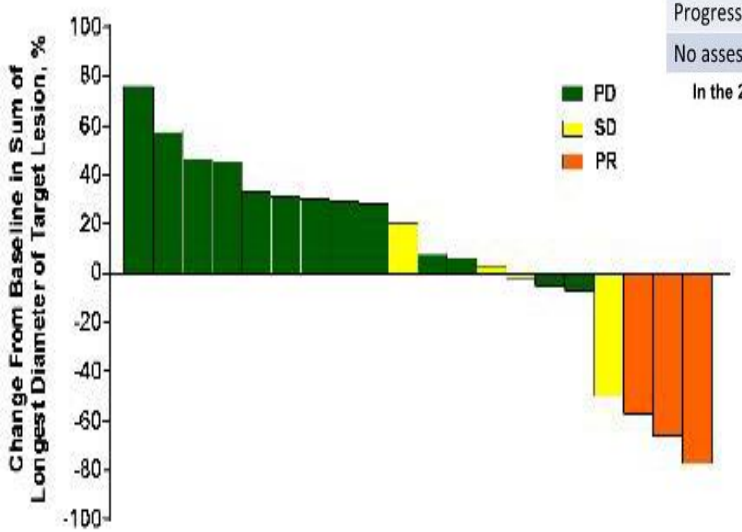
Adams S, et al. ASCO 2016 (abs 1009)

Phase Ib: Keynote-028 – Pembrolizumab (PD1-AK) beim hormonrezeptor-positiven metastasierten Mammakarzinom (n=25)

Ansprechrate 12%

	n (%)	95 % CI
Overall response rate	3 (12.0)	2.5-31.2
Complete response	0 (0.0)	0.0-13.7
Partial response[a]	3 (12.0)	2.5-31.2
Stable disease	4 (16.0)	4.5-36.1
Clinical benefit rate[b]	5 (20.0)	6.8-40.7
Progressive disease	15 (60.0)	38.7-78.9
No assessment[c]	3 (12.0)	2.5-31.2

In the 22 patients with at least one scan after baseline, ORR was 14% and CBR was 23%



Only patients with ≥1 evaluable postbaseline tumor assessment are included (n = 22). Data are presented for 20 patients; 2 patients were excluded due to non-evaluable postbaseline lesions.
Data cutoff date: July 1, 2015.

Rugo et al., SABCS 2015

Wirksamkeit von Avelumab (PDL1-AK) beim metastasierten Mammakarzinom – alle Subtypen

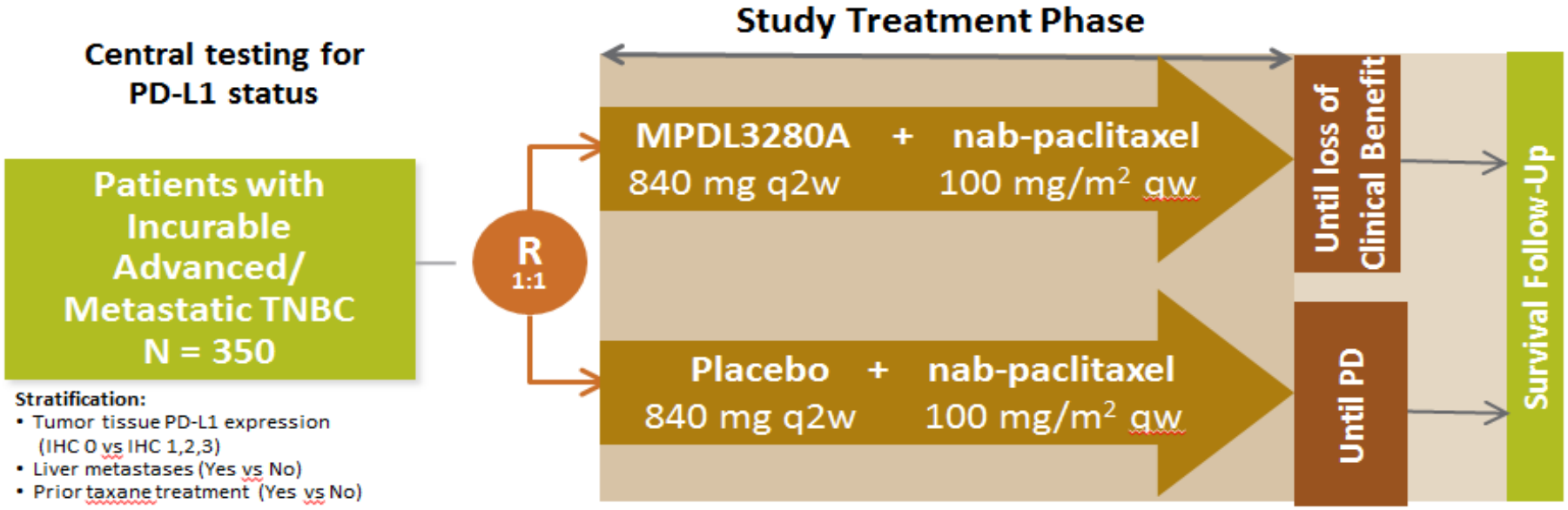
Best overall response*	Overall population (n=168)	Patients with TNBC (n=58)
CR, n (%)	1 (0.6)	0
PR, n (%)	7 (4.2)	5 (8.6)
SD†, n (%)	39 (23.2)	13 (22.4)
PD, n (%)	106 (63.1)	38 (65.5)
Non-evaluable‡, n (%)	15 (8.9)	2 (3.4)
ORR, % (95% CI)	4.8 (2.1, 9.2)	8.6 (2.9, 19.0)
DCR§, %	28.0	31.0

* Unconfirmed best overall response according to RECIST 1.1
† Stable disease at the first post-baseline tumor assessment after 6 weeks was required to qualify for a BOR of SD
‡ Non-evaluable includes 'missing' and 'not assessable'
§ DCR is defined as responses + SD

Dirix et al., SABCS 2015

Studie Impassion mit Atezolizumab (PDL-1 Antikörper) Erstlinientherapie bei TNBC

DESIGN: DOUBLE-BLIND | MULTICENTER | RANDOMIZED



OBJECTIVES:
MPDL3280A + nab-paclitaxel vs Placebo + nab-paclitaxel

PRIMARY ENDPOINT:
PFS
Co-primary in ITT and PD-L1 positive pts

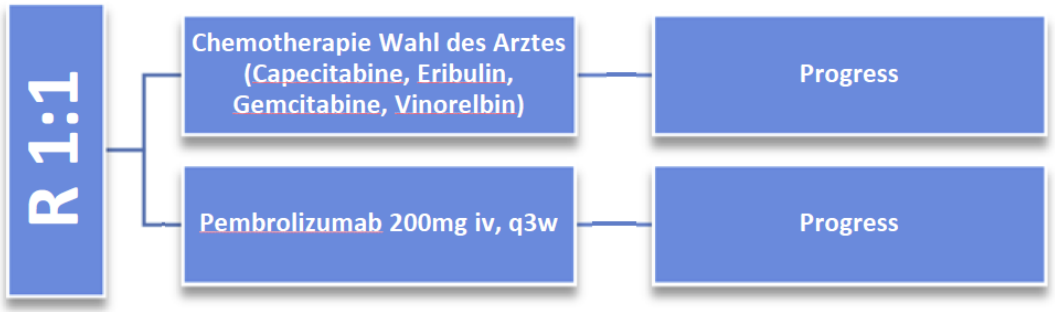
SECONDARY ENDPOINT:
- OS, ORR, and DOR per RECIST v1.1
- HRQoL

PD1-Antikörper Pembrolizumab ab Zweitlinie beim TNBC

MK-3475-119/KEYNOTE-119 (MSD) Pembrolizumab

2. & 3. Linientherapie für Patientinnen mit metastasiertem triple negativen Mammakarzinom.

This is a randomized, open-label trial of single agent pembrolizumab versus Treatment of Physician's Choice (TPC) monotherapy for patients with metastatic triple negative breast cancer (mTNBC) receiving second line (2L) or third line (3L) treatment in the metastatic setting

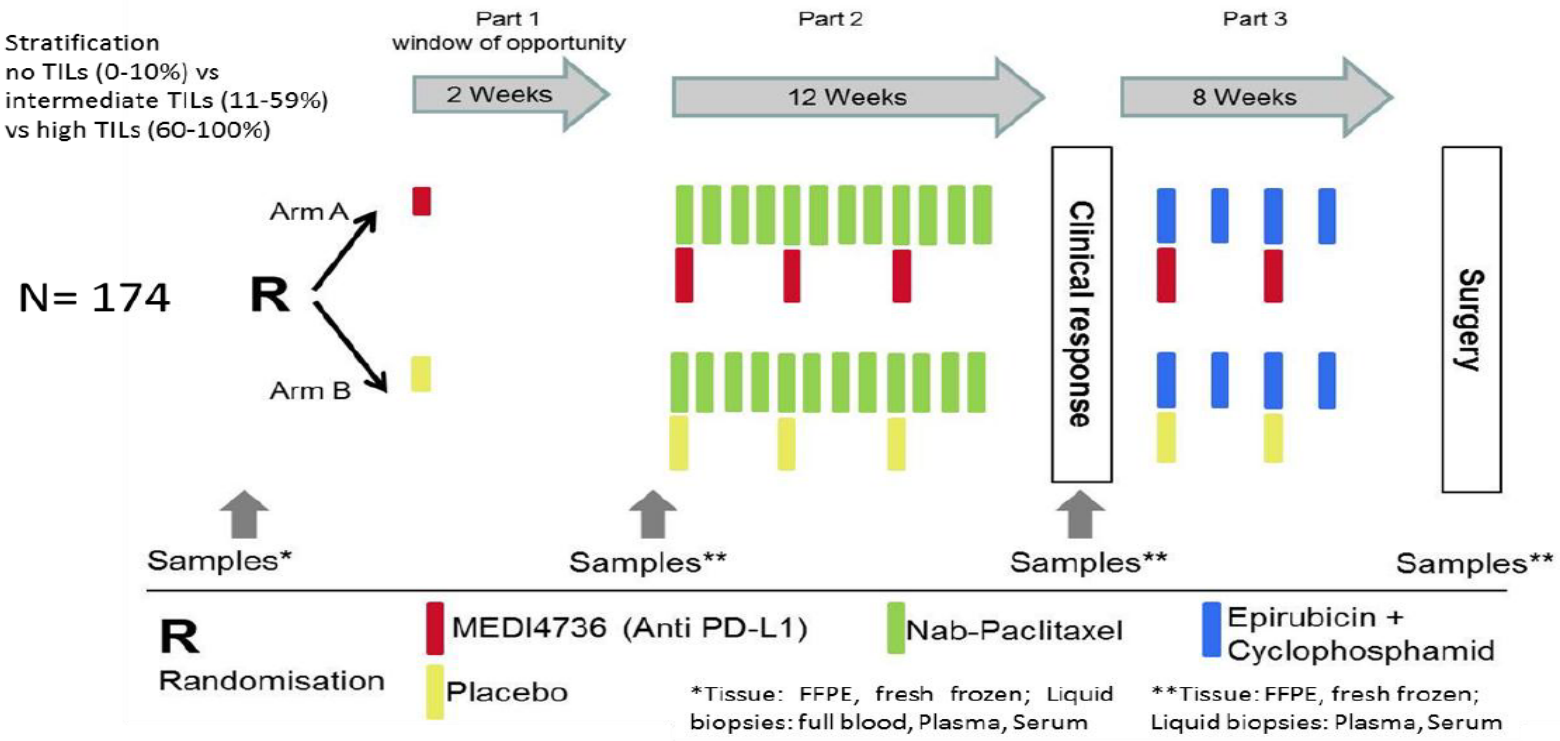


Einschlusskriterien

- Patients with incurable locally advanced or metastatic TNBC (per ASCO/CAP)
- Anthrazyklin- und/oder taxanhaltige Chemotherapie bereits erfolgt
- Have received either 1 or 2 prior systemic treatments for metastatic breast cancer and have documented disease progression on the most recent therapy

PDL1-Antikörper neoadjuvant in der GeparNuevo – GBG 89 beim TNBC

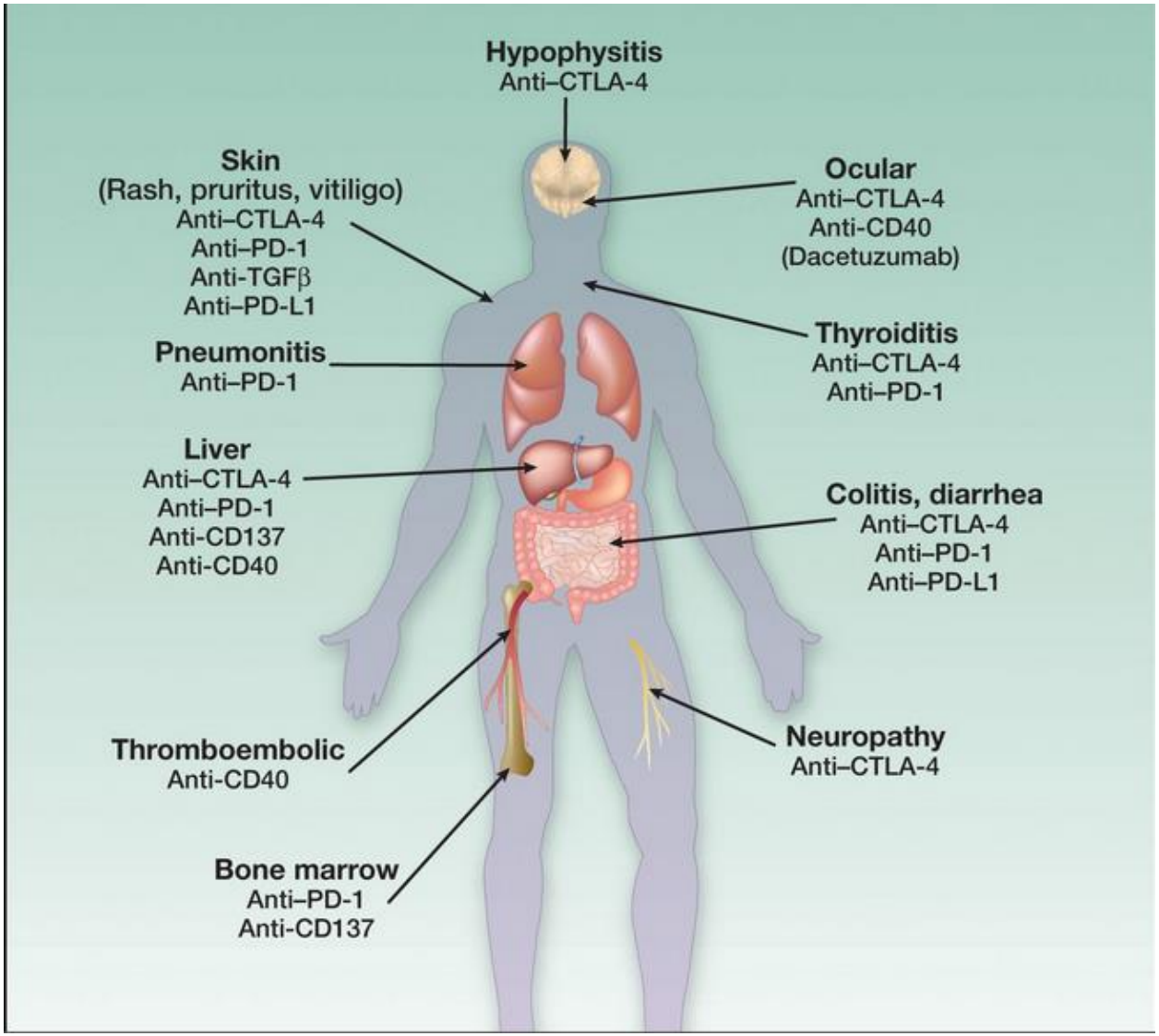
Randomisierte Phase II Studie zur Evaluierung des PDL1 Antikörpers MEDI4736 in Kombination mit einer Taxan-Anthrazyklin-haltigen Chemotherapie bei triplenegativem Brustkrebs (TNBC).



Überblick

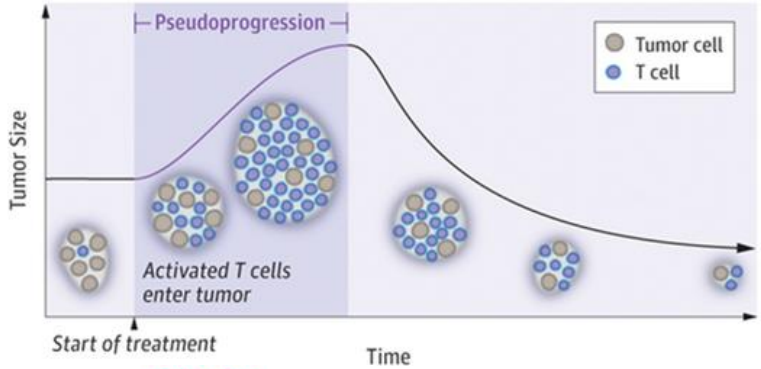
- **Immunsystem und Krebs**
- **Einsatz beim Malignen Melanom**
- **Einsatz beim Mammakarzinom**
- **Herausforderungen**

Nebenwirkungsspektrum



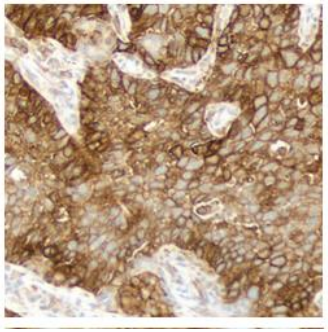
Melero I et al; Clin Cancer Res 2013;19:997-1008

Herausforderungen an die Checkpoint-Inhibitoren

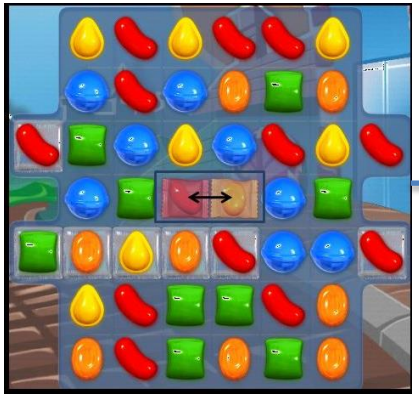


→ **Pseudoprogression**

PS ≥50%



→ **Biomarker ?**



→ **der richtige Kombinationspartner ?**

Fazit Immunmodulation

- **Phase II/III Studien laufen zu PD1- und PD-L1 Antikörper beim triple-negativen metastasierten Mammakarzinom**
- **Innovative Substanzen mit neuem Wirk- aber auch Nebenwirkungsspektrum**
- **Weitere Substanzen/Kombinationspartner in der Immunmodulationen werden untersucht**
- **Meilenstein in der Therapie steht noch aus**