Das tripelnegative Mammakarzinom

Neue Therapieansätze für eine Verlegenheitsdiagnose

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Conflict-of-interest-disclosure

Honoraria

Roche, Genomic Health, GlaxoSmithKline, AstraZeneca, Eisai, Celgene, Amgen, Gedeon Richter, Novartis, Pierre Fabre, Teva

Consulting or Advisory Role

Roche, Genomic Health, Teva, Pierre Fabre, Novartis

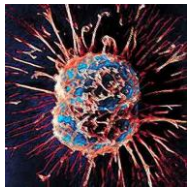
Research Funding

Eisai, Roche, Novartis, Boehringer Ingelheim

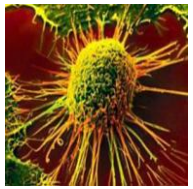
Travel, Accommodations, Expenses

Roche, Teva, PharmaMar, Celgene

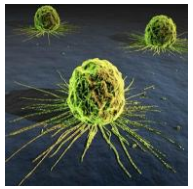
Überblick



Biologie des tripelnegativen Mammakarzinoms

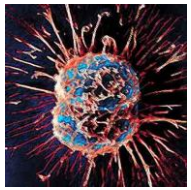


Chemotherapie des tripelnegativen Mammakarzinoms



Neue Substanzen für das tripelnegative Mammakarzinom

Überblick



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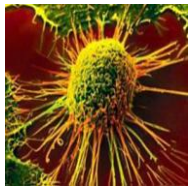

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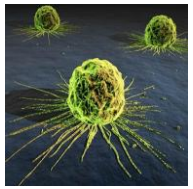
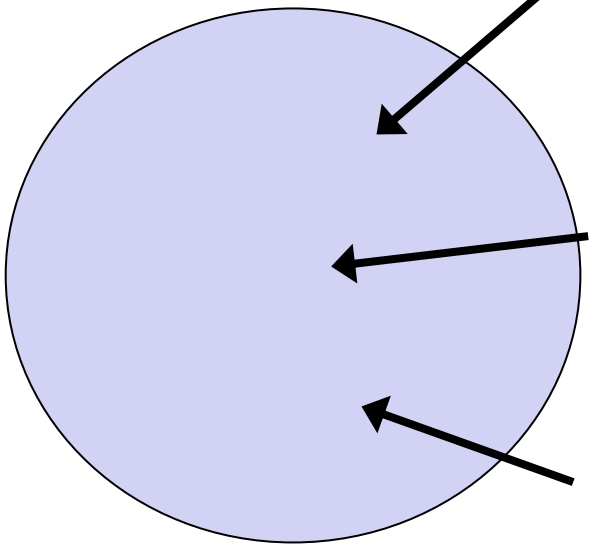


Neue Substanzen für das tripelnegative Mammakarzinom

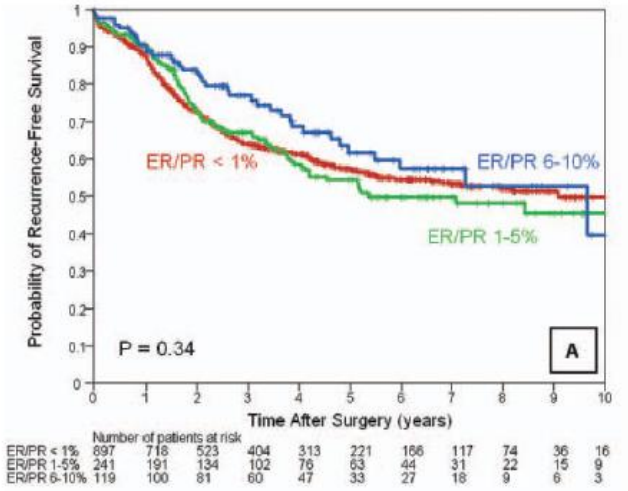
Definition des TNBC

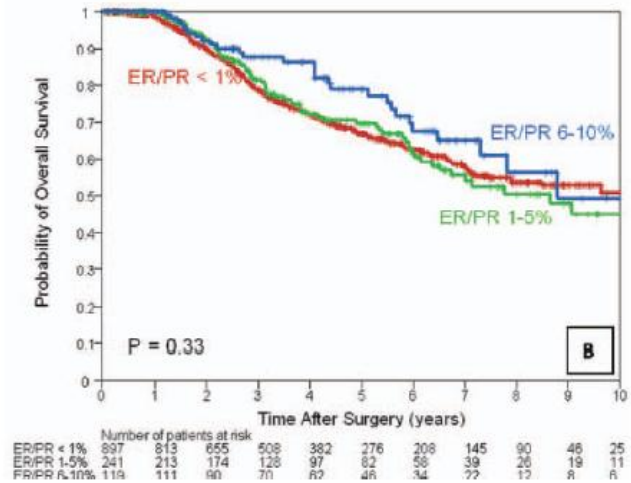


Fehlende Östrogen-rezeptorexpression
(ER negativ / <1%)

Fehlende Progesteron-rezeptorexpression
(PR negativ / <1%)

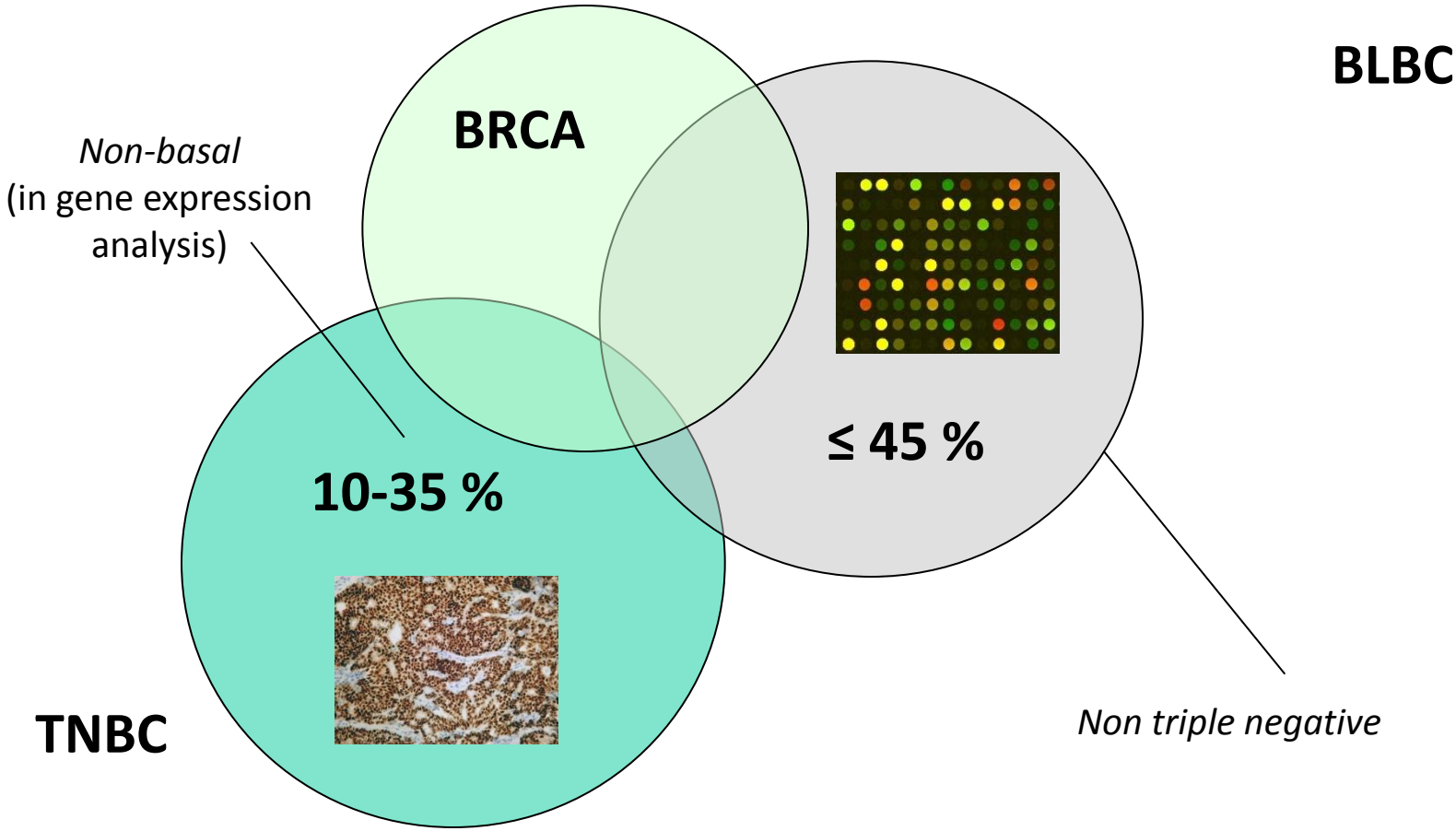
Fehlende Überexpression / -amplifikation von HER2/neu
(HER2 negativ)



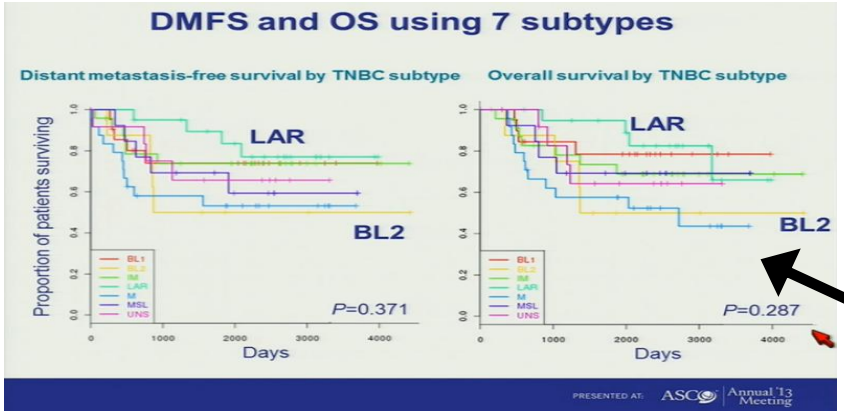


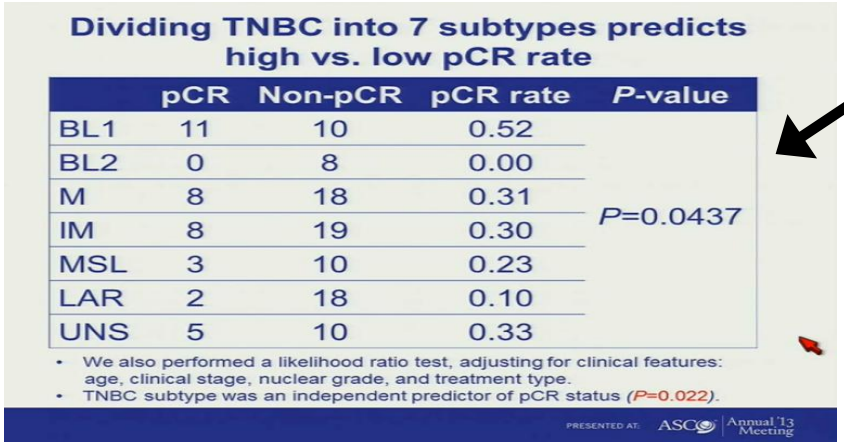
Gluz, Liedtke et al., Ann Onc 2009; Carey et al., Nat Rev Clin Oncol 2010; Foulkes et al., NEJM 2010; Raghav et al., Cancer 2012

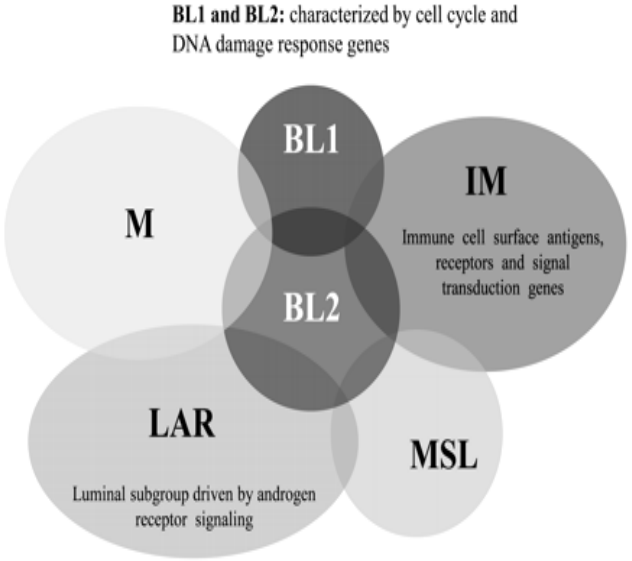
Zusammenhang zwischen TNBC, BLBC und BRCA



Prognostische Bedeutung der TNBC-Subtypen

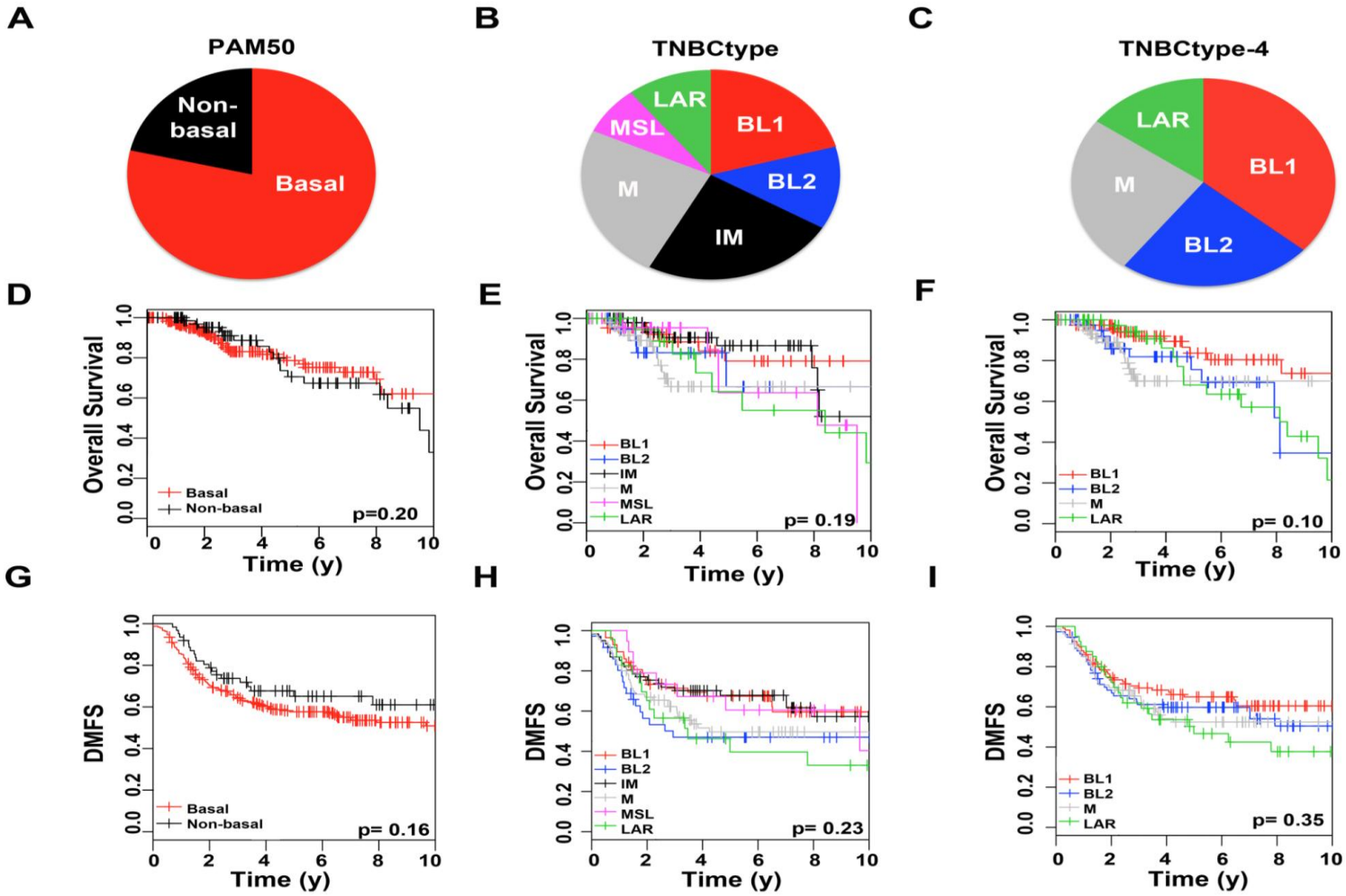






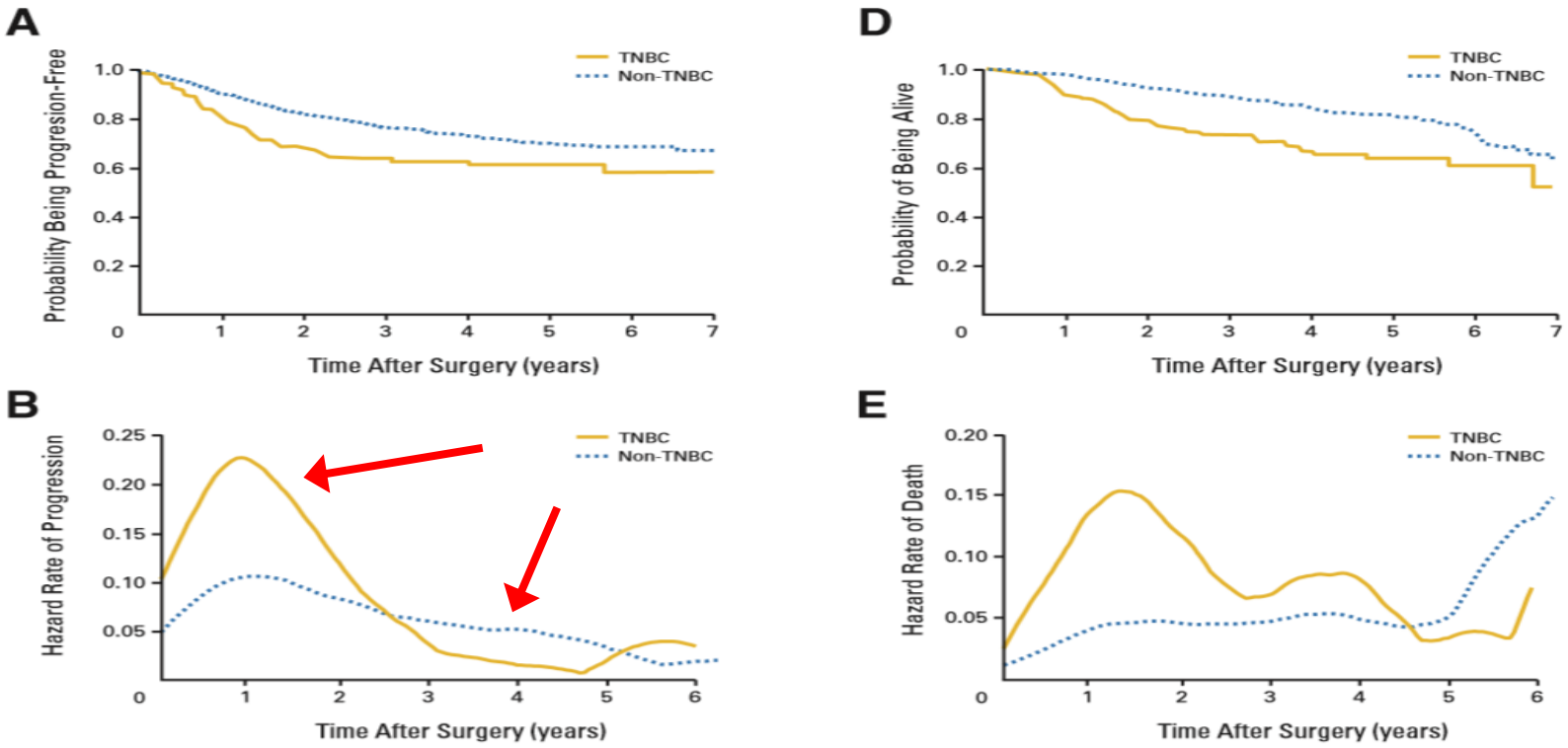
Lehmann et al., JCI 2011

Aktuelles Verständnis der TNBC-Subgruppen



Lehmann et al., PLoS One 2016

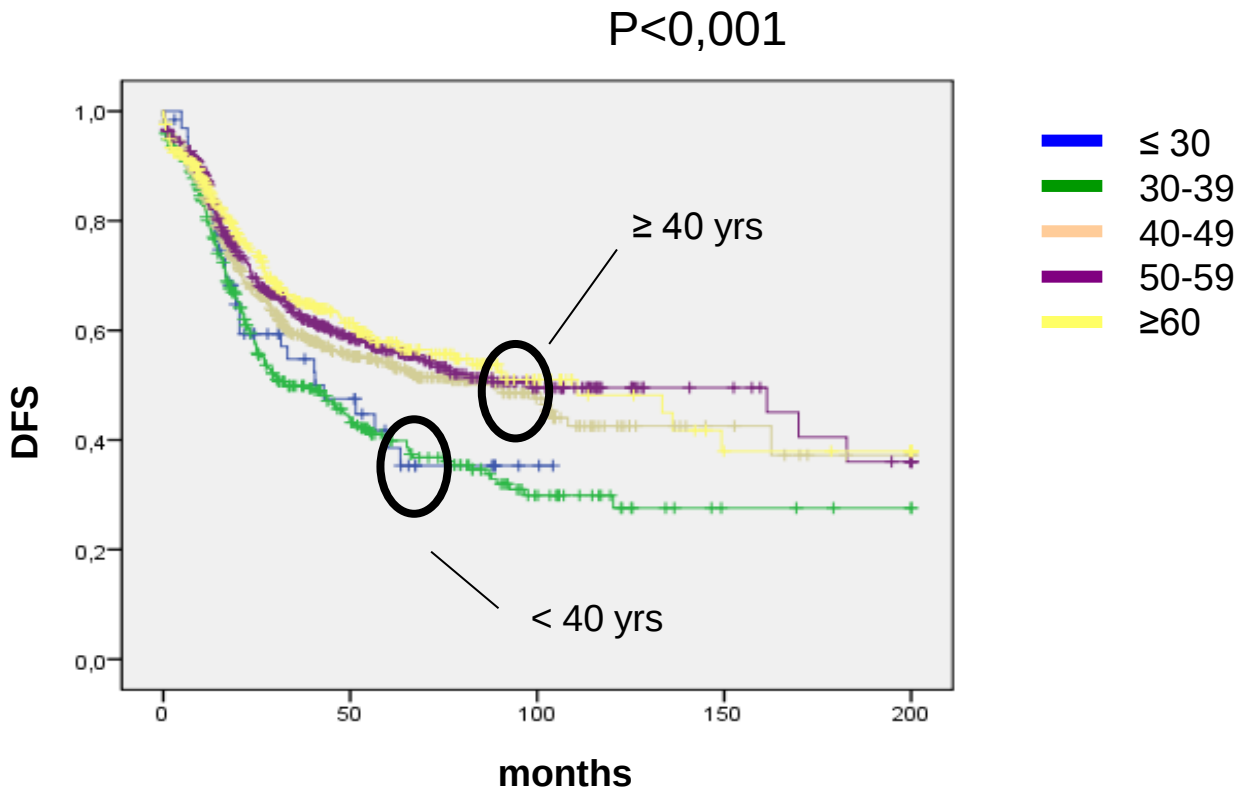
Prognose von Patientinnen mit TNBC



N=1118

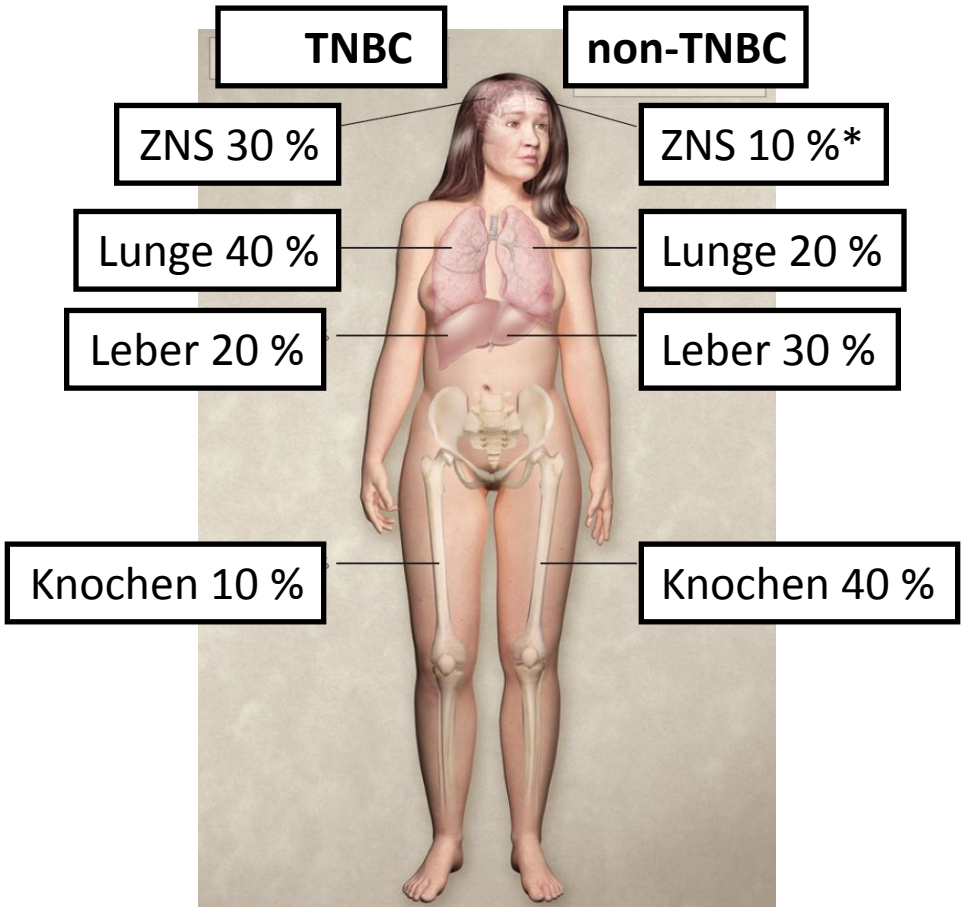
Liedtke et al., J Clin Oncol 2008
(Carey et al., CCR 2007; Dent et al., BCRT 2009; Nofech-Mozes et al., BCRT 2009)

Prognose von Patientinnen mit TNBC in Abhängigkeit des Alters



Liedtke et al., BCRT 2013

Metastasierungsmuster beim TNBC



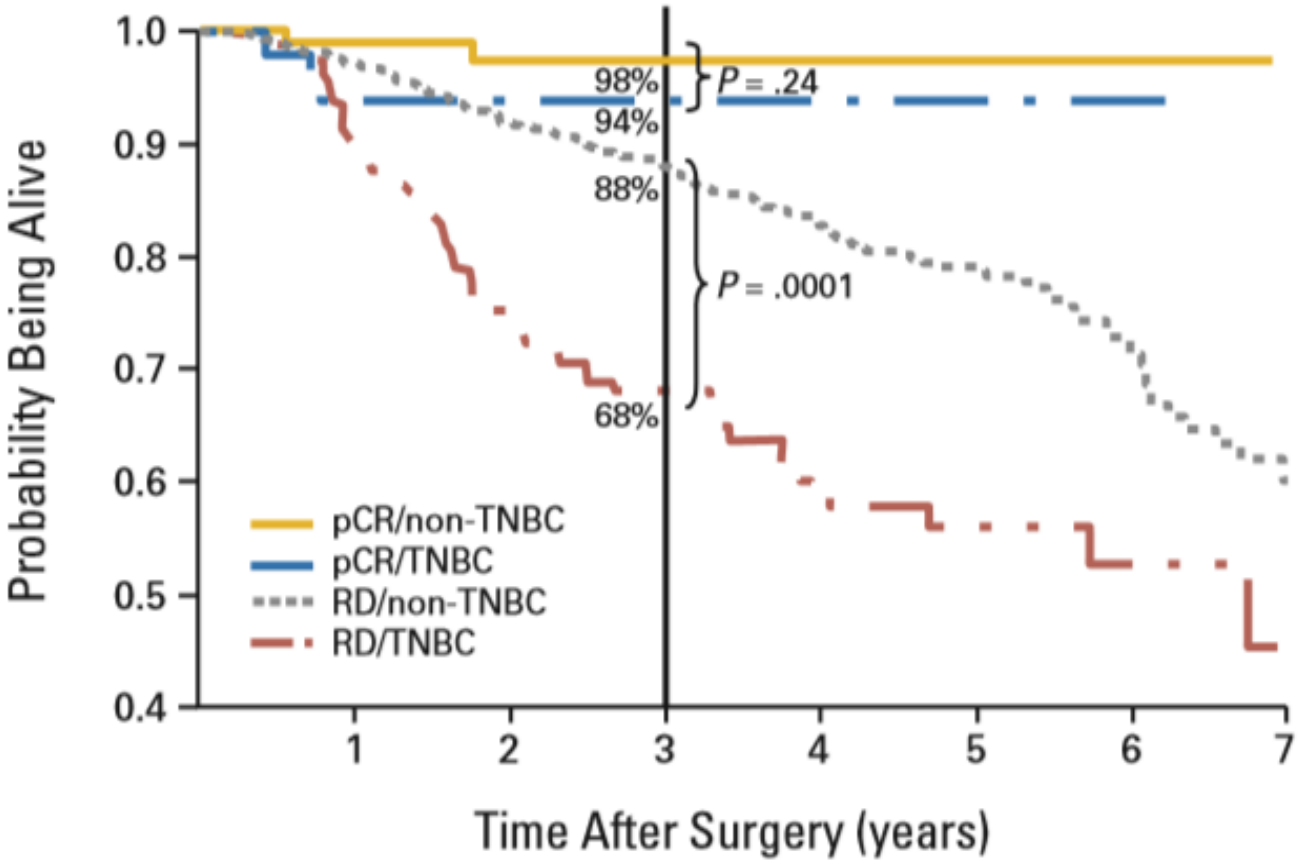
Foulkes et al., NEJM 2010

Chemotherapie-Sensitivität im neoadjuvanten Setting

		pCR-Rate	
	n	TNBC	andere
Liedtke et al.	**1118**	**22%**	**11%**
Bidard et al.	**293**	**17%**	**4%**
Fernadez-Morales et al.	**100**	**27%**	**11%**
Carey et al.	**107**	**27%**	**11%**
Kearn et al.	**145**	**17%**	**3%**
Rouzier et al.	**82**	**45%***	**18%***

* basal/non-basal in Genexpressionsanalysen

Zusammenhang zwischen Ansprechen auf Chemotherapie und Prognose

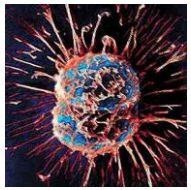


= CHEMO-SENSITIVE

= CHEMO-RESISTENT

Liedtke et al., J Clin Oncol 2008

Überblick



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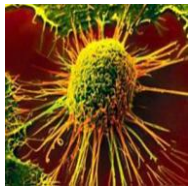
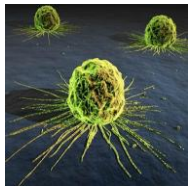
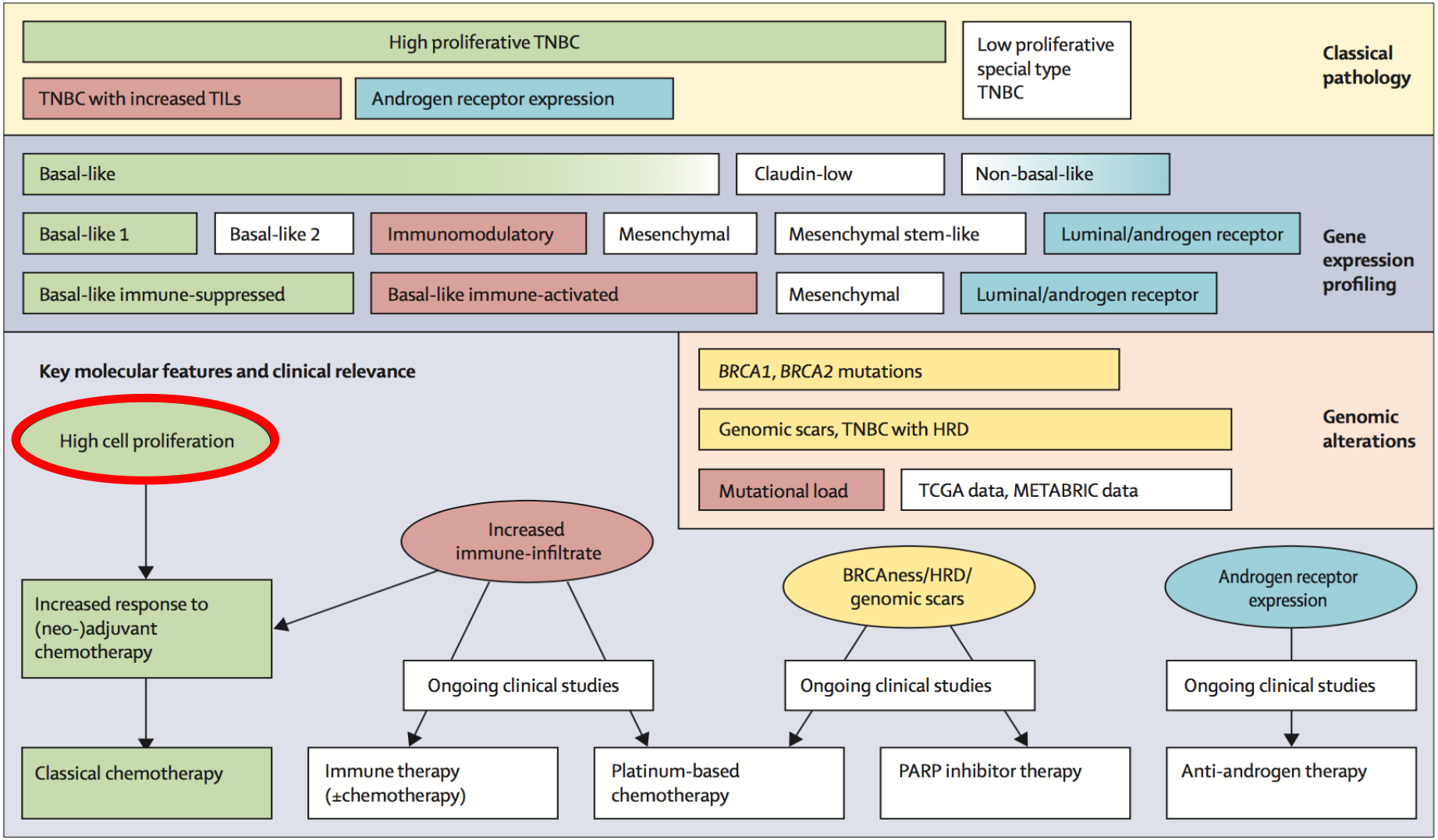


Chemotherapie des tripelnegativen Mammakarzinoms



Neue Substanzen für das tripelnegative Mammakarzinom

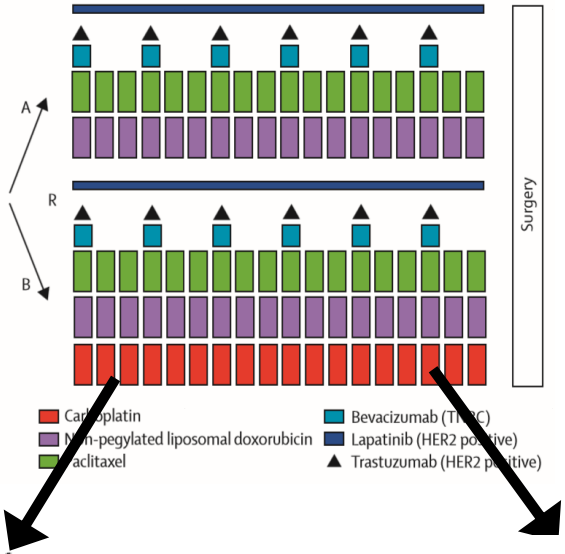
Molecular biology of TNBC

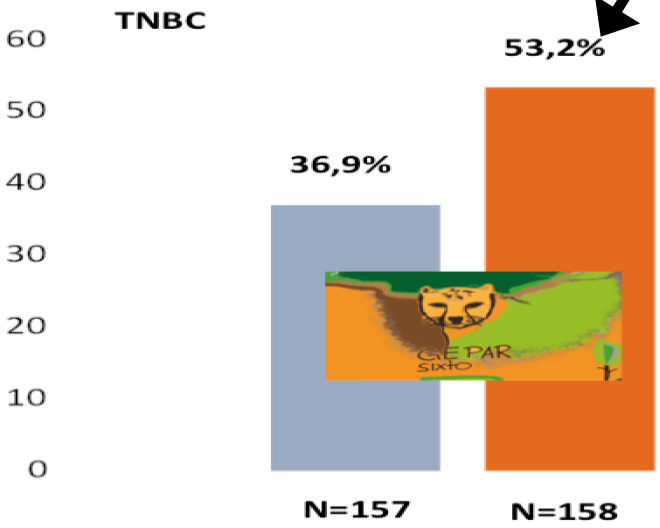


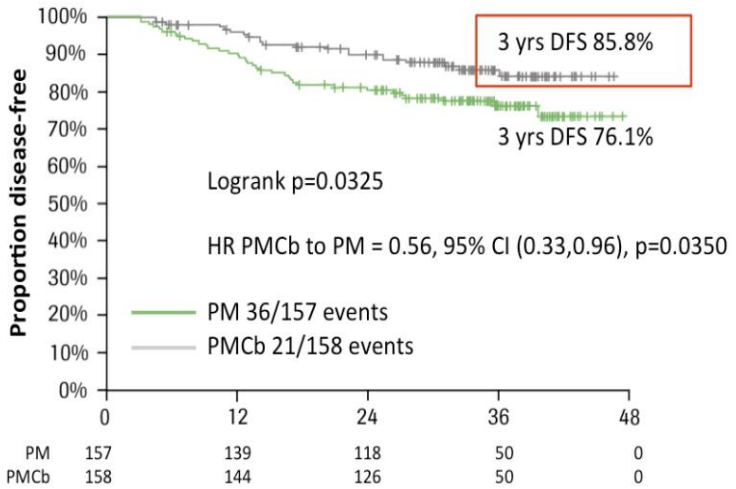
Denkert, Liedtke et al., Lancet 2016

Neoadjuvante Chemotherapie in TNBC (G6)

TNBC
+ HER2

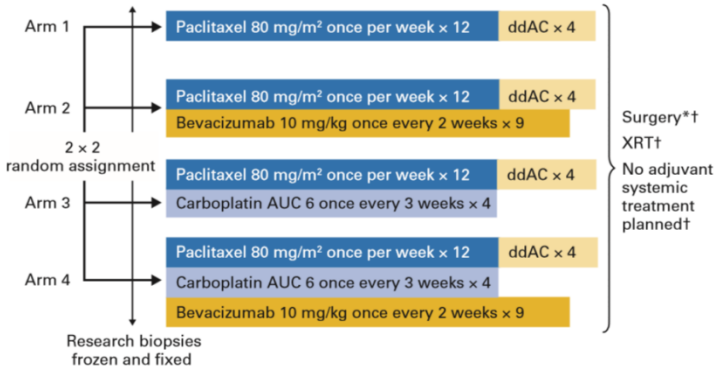


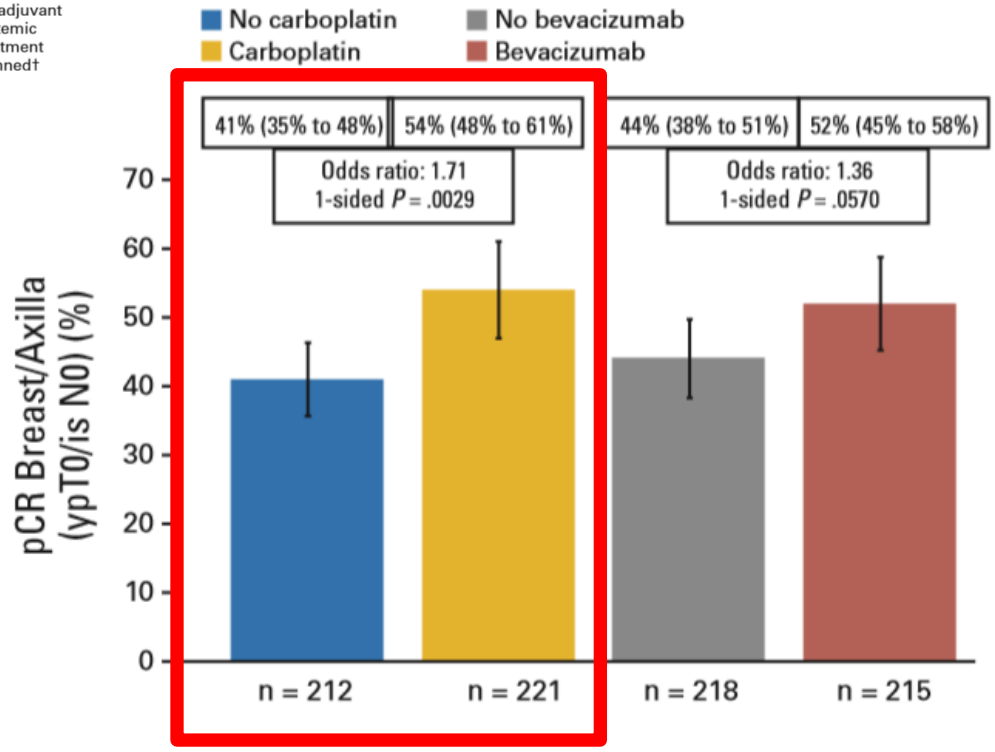




Von Minckwitz et al., Lancet Oncology 2014

Neoadjuvante Chemotherapie mit Carboplatin (CALGB 40603)

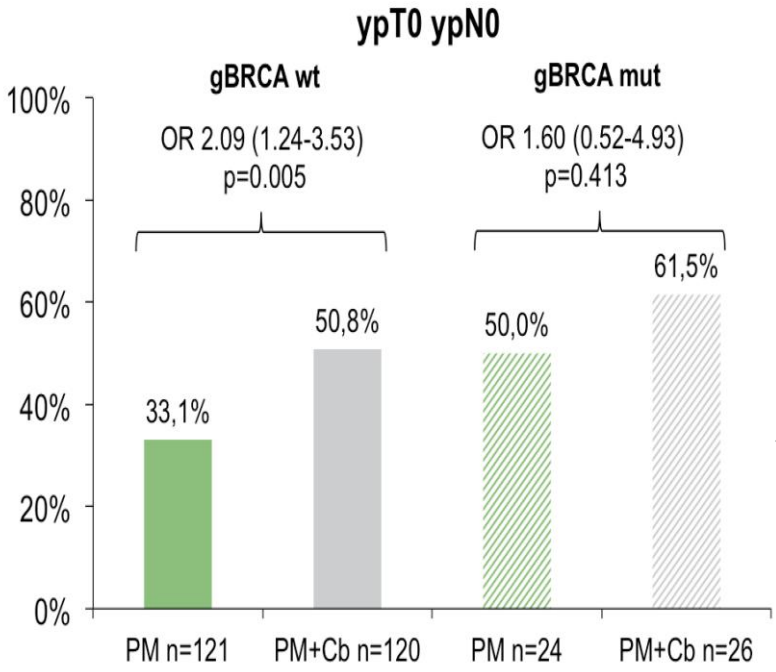


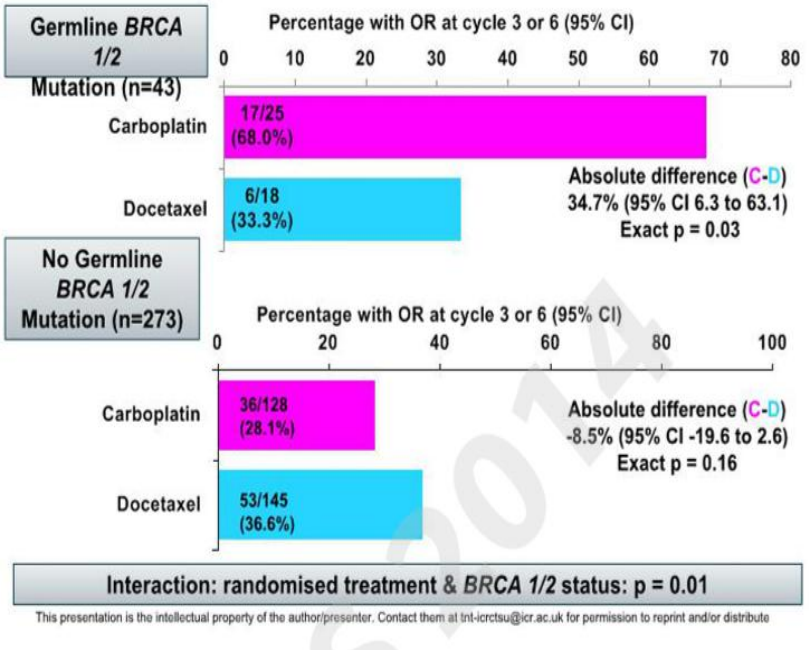


Sikov et al., JCO 2014

Sikov et al., JCO 2014

Ansprechraten nach BRCA-Status und Carboplatin beim TNBC





Von Minckwitz et al., SABCS 2015

Tutt et al., SABCS 2014

Empfehlungen zur platinhaltigen Chemotherapie

Triple-negatives metastasiertes Mammakarzinom

	Oxford / AGO LoE / GR		
Experimentelle Therapien innerhalb von Studien			++
Chemotherapie wie bei Patientinnen mit HR-pos / HER2-neg mBC			+
Carboplatin (vs. Docetaxel)	1b[a]	B	+/-
bei gBRCA Mutation	1b[a]	B	+
Gemcitabin/Cisplatin (vs. Gem/Pac)	1b	A	+
Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem)	2b[a]	B	+
Bevacizumab zusätzlich zur first-line Zytostatikatherapie	1b	B	+

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FORSCHEN LEHREN HEILEN

Subtyp-spezifische Strate… Systemtherapie

- Wenn die Indikation zur Chemotherapie aufgrund der Tumorbiologie gegeben ist, sollte eine neoadjuvante Therapie erwogen werden ++
- HR+/HER2- mit „niedrigem Risiko"
  - Endokrine Therapie ohne Chemotherapie ++
- HR+/HER2- mit „hohem Risiko"
  - Konventionell dosierte AT-basierte Chemotherapie ++
  - Dosisdichte, dosis-intensivierte Chemotherapie bei großer Tumorlast +
  - Anschließend endokrine Therapie ++
- HER2+
  - Trastuzumab (plus Pertuzumab neoadjuvant) plus ++
    - Sequenzielles A/T-basiertes Regime mit simultaner Gabe von T+H ++
    - Anthrazyklin-freie, Platin-haltige Therapie +
    - Anthrazyklin-freie, Taxan-haltige Therapie bei niedriger Tumorlast +
    - Dosisdichte, dosis-intensivierte Chemotherapie bei großer Tumorlast +
- Triple-negativ (TNBC)
  - Konventionell dosierte AT-basierte Chemotherapie ++
  - Dosisdichte, dosis-eskalierte Chemotherapie +
  - Neoadjuvant Platin-haltige Chemotherapie +

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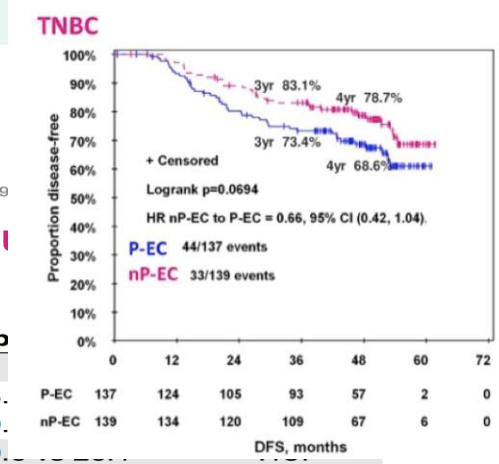
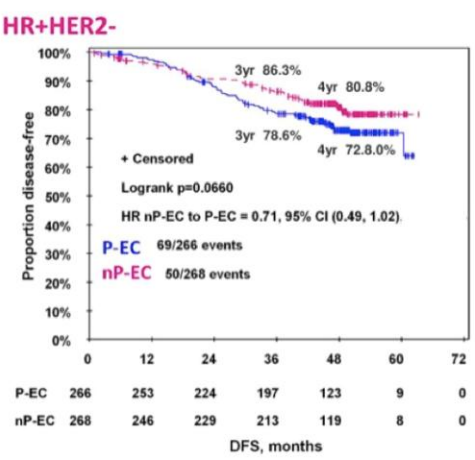
Liedtke et al. AGO Kommission Mamma. Breast Care 2017; www.ago-online.de

Bedeutung von Nab-Paclitaxel: G7 vs. ETNA

	Patients, n	Pac, % (95% CI)	Nab-pac, % (95% CI)	OR (95% CI)	p-value
Overall pCR	695	18.6 (14.7–23.1)	22.5 (18.2–27.3)	0.77 (0.52–1.13)	0.1858
Luminal B pCR	476	10.0	13.9	0.69 (0.39–1.21)	
TNBC pCR	219	37.3	41.3	0.85 (0.49–1.45)	
Objective clinical response	695	74.5 (69.6–79.0)	77.2 (72.4–81.5)	0.87 (0.61–1.23)	0.427

?





Gepar septo

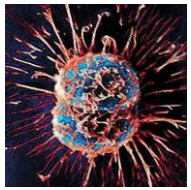
San Antonio Breast Cancer Symposium, December 9

pCR in Stratified Su

Parameter	Subgroup	p	
SPARC	SPARC negative	28.	
	SPARC positive	29.	
Ki67	Ki67<=20%	19.	
	Ki67>20%	**33.1 vs 44.0**	**.001**
Biological subtype	HER2-, HR+	12.0 vs 16.0	.183
	HER2-, HR-	**25.7 vs 48.2**	**<.001**
	HER2+, HR+	50.0 vs 56.4	.275
	HER2+, HR-	66.7 vs 74.6	.371
HER2	**HER2-**	**17.7 vs. 27.0**	**<.001**
	HER2+	**54.1 vs 61.8**	**.120**
HR-status	HR-	36.1 vs. 56.1	<.001
	HR+	25.6 vs. 29.9	.169

Gianni et al., ASCO 2016

Überblick



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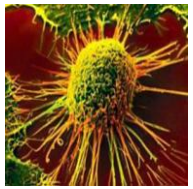

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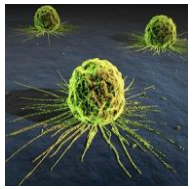
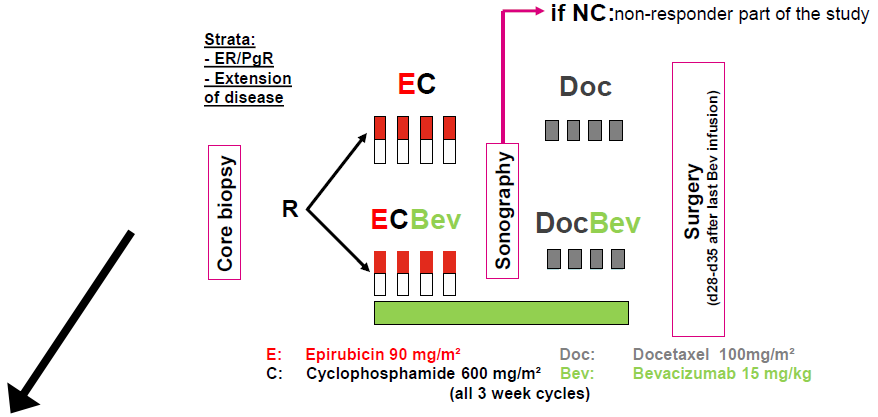
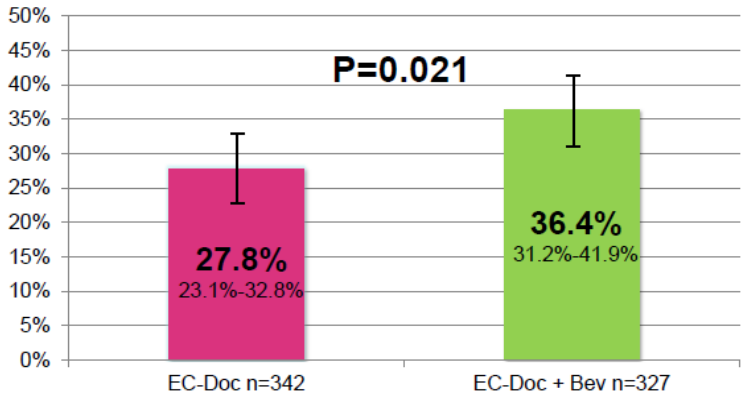


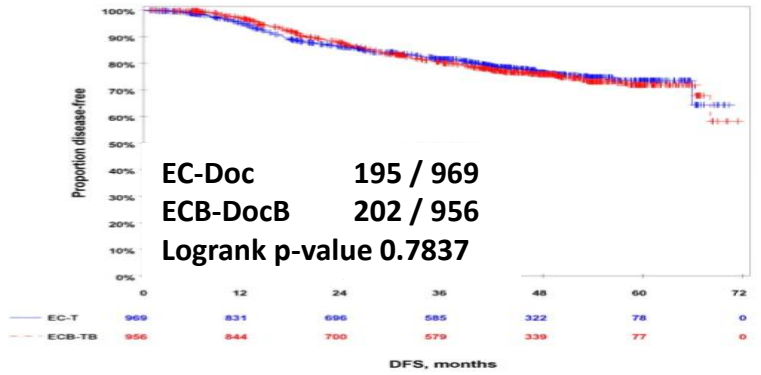
Neue Substanzen für das tripelnegative Mammakarzinom

Bevacizumab in der neoadjuvanten Therapie des TNBC



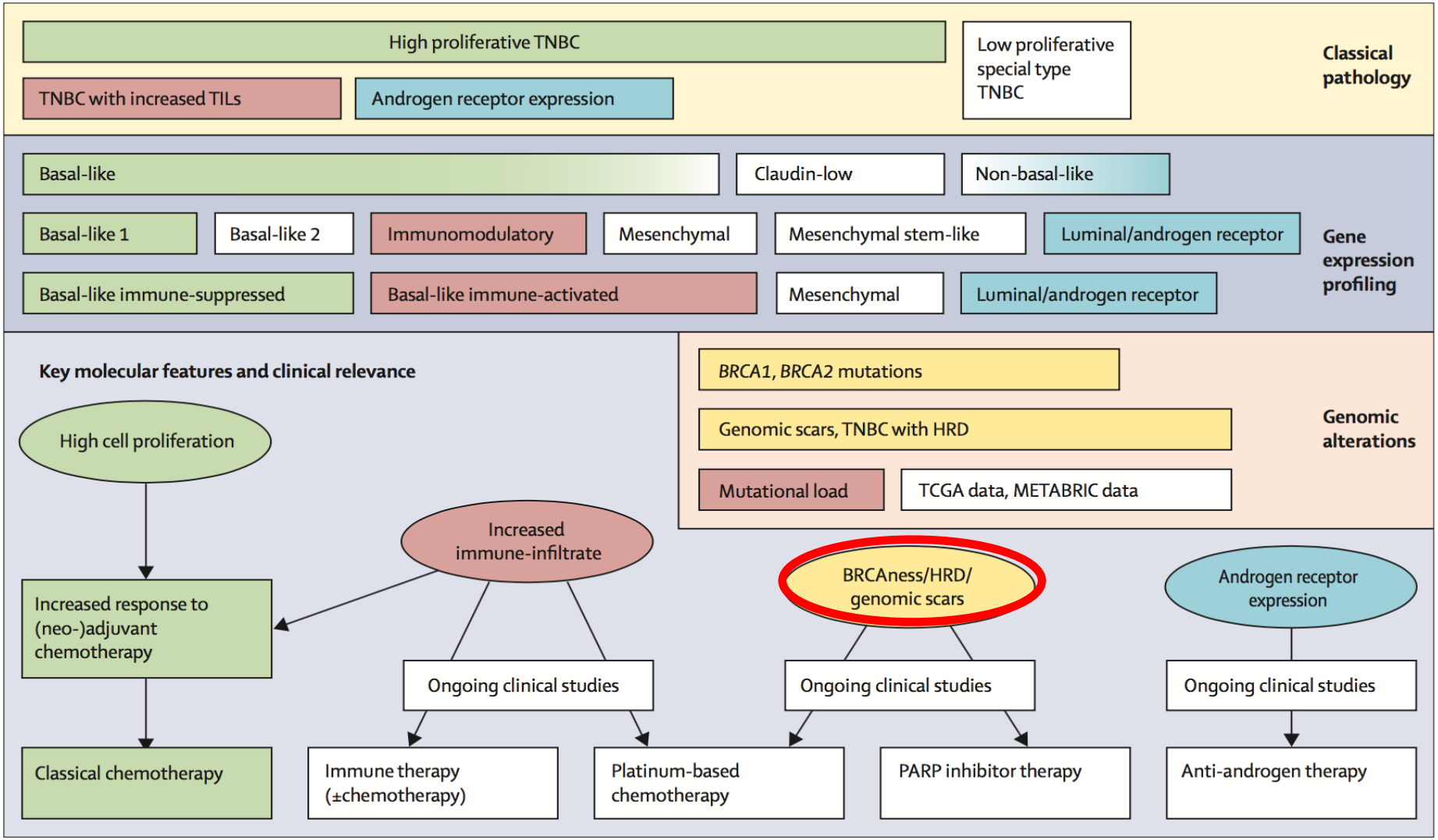


Huober et al., EJC 2013



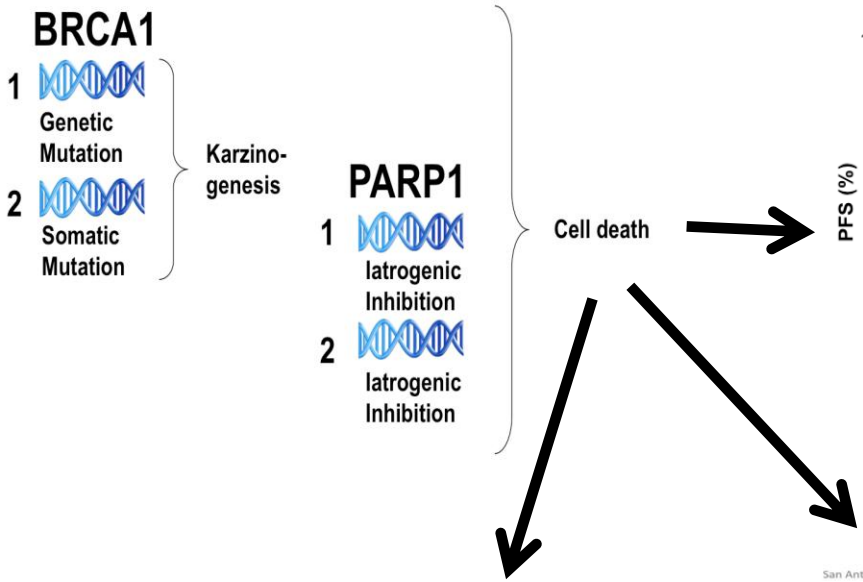
Von Minckwitz et al., NEJM 2012

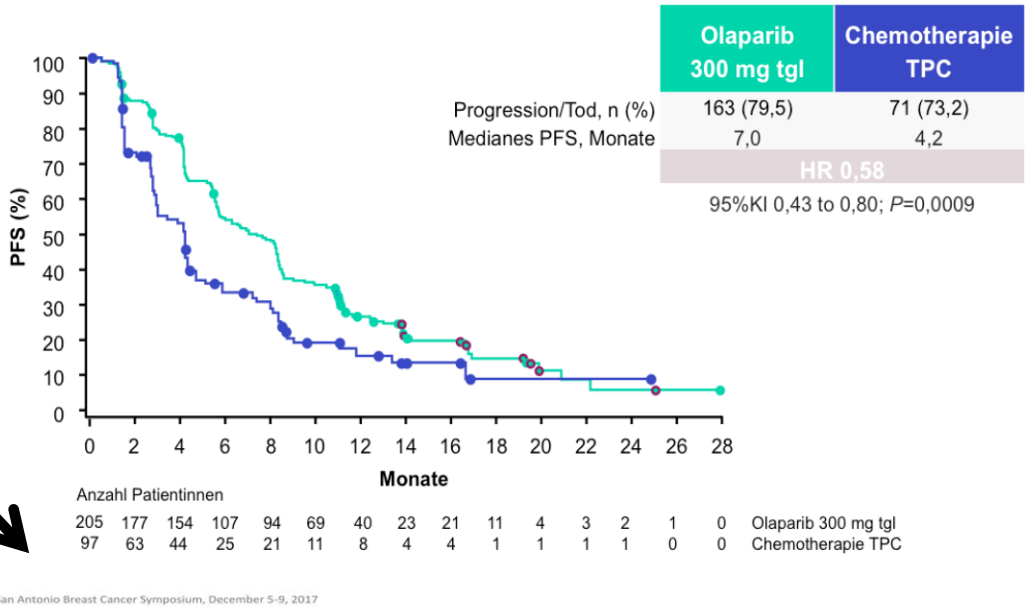
Molecular biology of TNBC



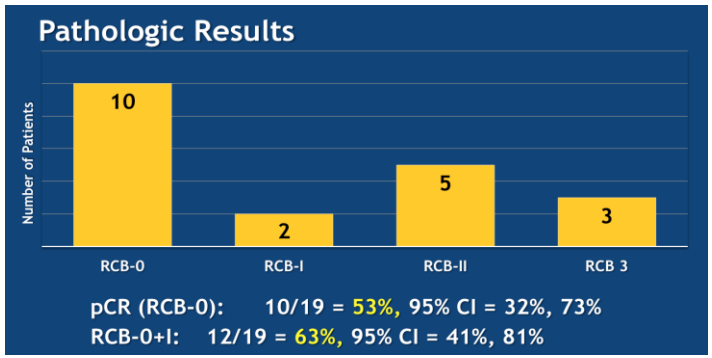
Denkert, Liedtke et al., Lancet 2016

PARP-Inhibitoren in Zusammenhang mit BRCA-Mutationen

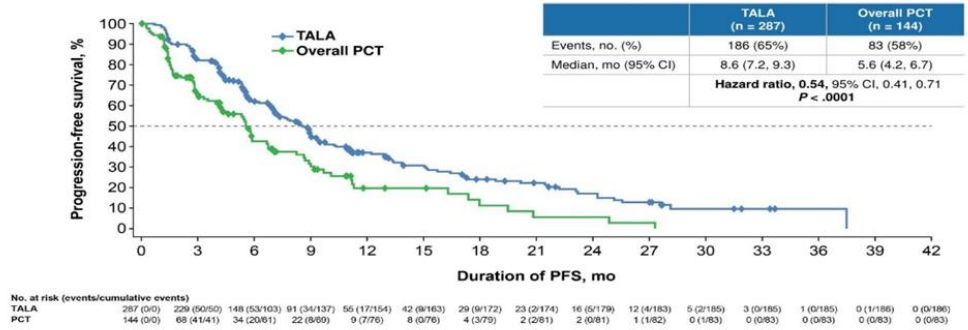




San Antonio Breast Cancer Symposium, December 5-9, 2017



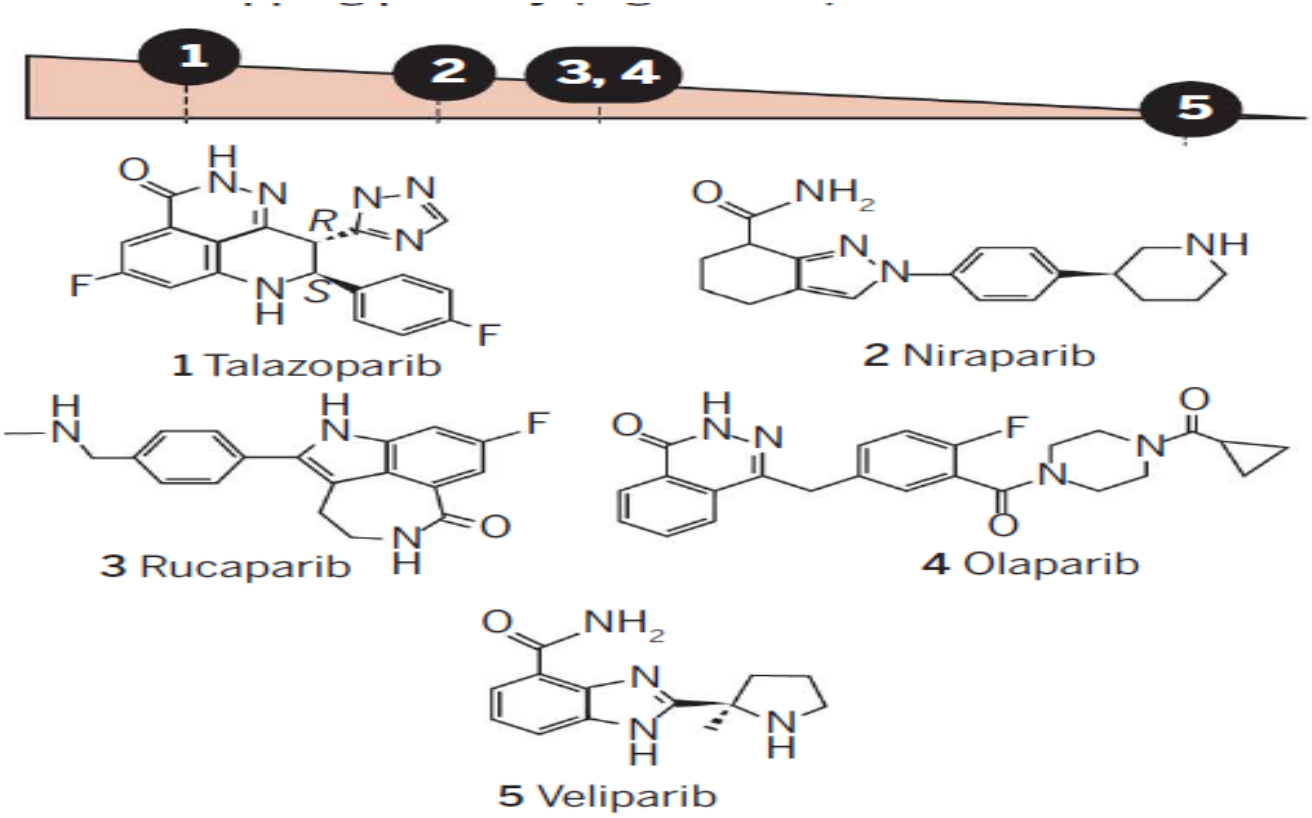
Primary Endpoint: PFS by Blinded Central Review



1-Year PFS 37 vs 20% Median follow-up time: 11.2 months

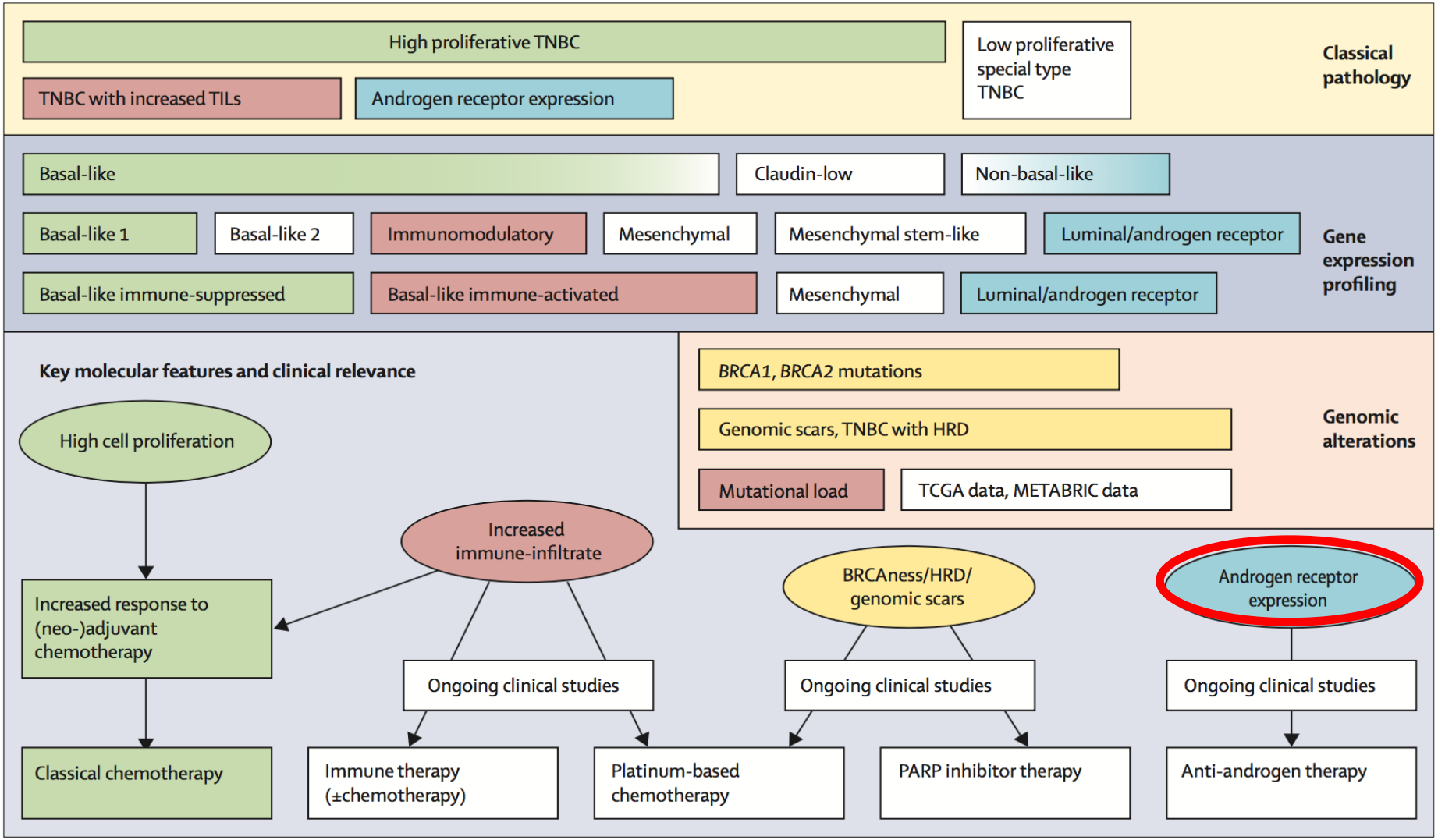
Litton et al., ASCO 2018 Robson et al., ASCO 2017

Trapping von PARP bei unterschiedlichen PARP-Inhibitoren



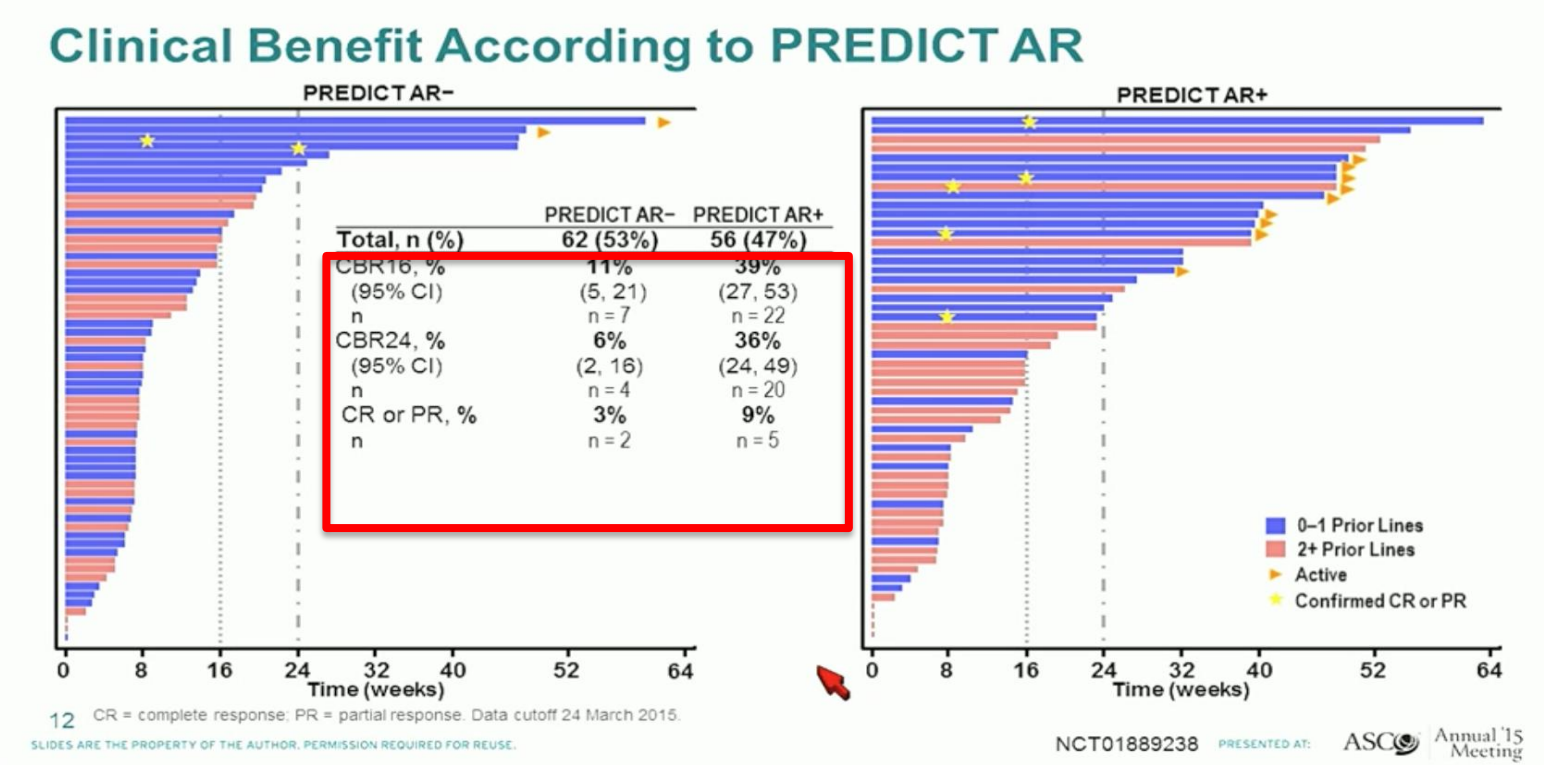
Lord et al., Science 2017

Molecular biology of TNBC



Denkert, Liedtke et al., Lancet 2016

Wirksamkeit der Antiandrogenen Therapie mit Enzalutamid beim TNBC



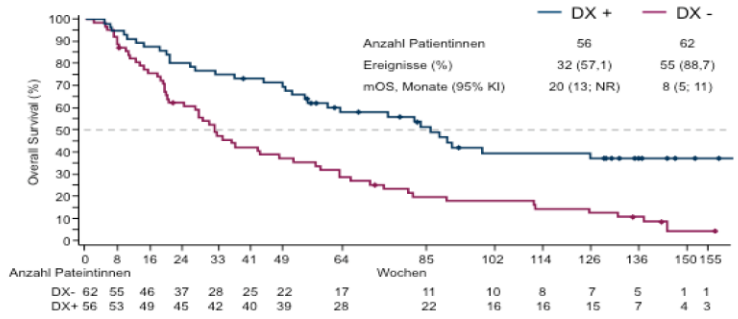
Predict AR = Gensignatur für „Androgenität“

Traina et al., ASCO 2015

Wirksamkeit der Antiandrogenen Therapie mit Enzalutamid beim TNBC

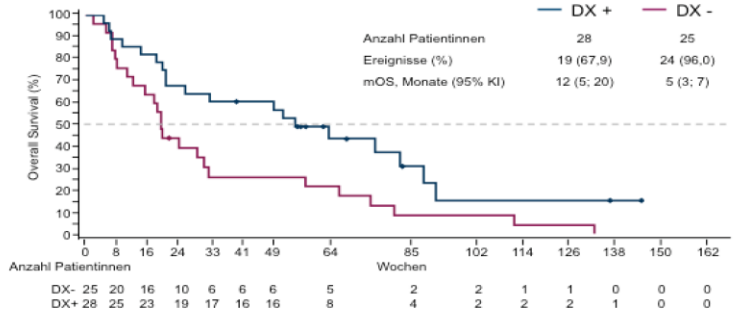
Overall Survival

Overall survival in der ITT Population, genom-basierter diagnostischer Status

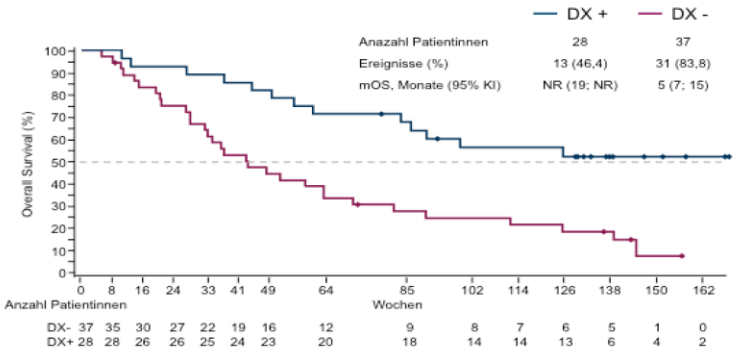


Abkürzungen: KI, Konfidenzintervall; DX+, diagnostisch positiv, DX-, diagnostisch negativ; ITT, intent-to-treat; mOS, medianes overall survival; NR, not reached.

Overall survival in Patientinnen mit ≥2 vorherigen Therapien in der ITT Population, genom-basierter diagnostischer Status

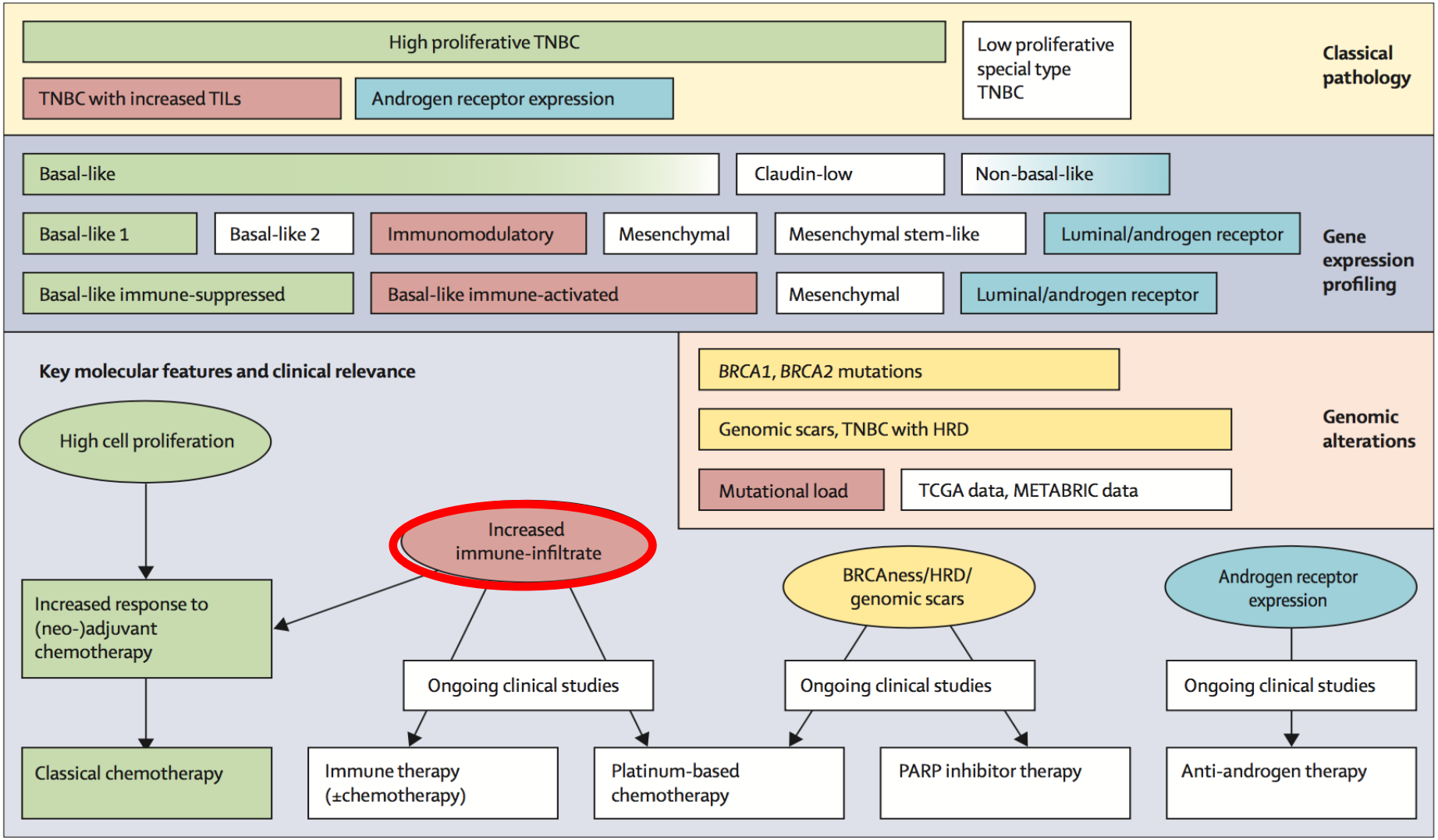


Overall survival in Patientinnen mit 0-1 vorherigen Therapien in der ITT Population, genom-basierter diagnostischer Status



Traina et al., ASCO 2017

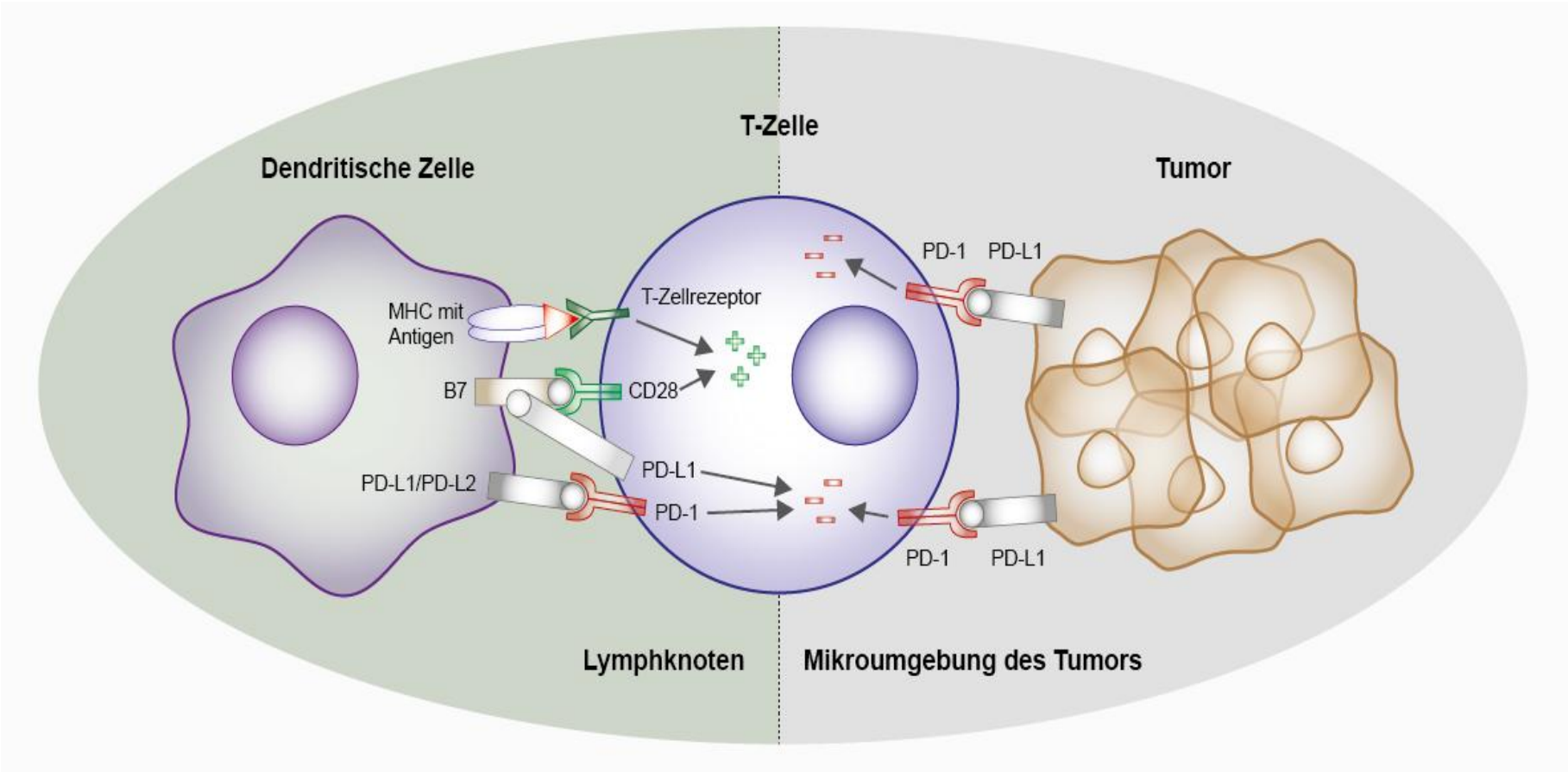
Molecular biology of TNBC



Denkert, Liedtke et al., Lancet 2016

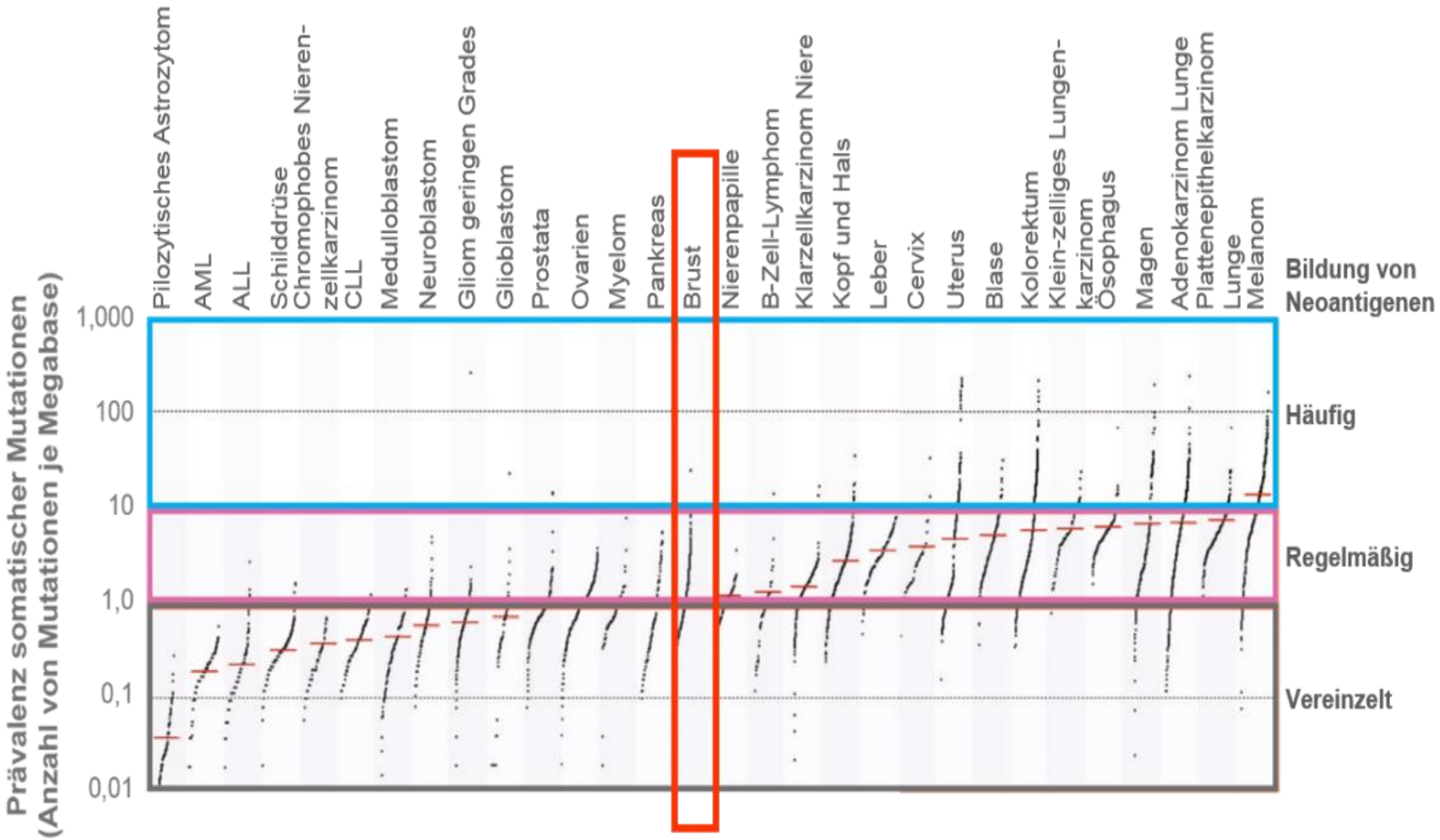
Interaktion zwischen Tumorzelle und Immunsystem

Interaktion zwischen Tumorzelle und Immunsystem



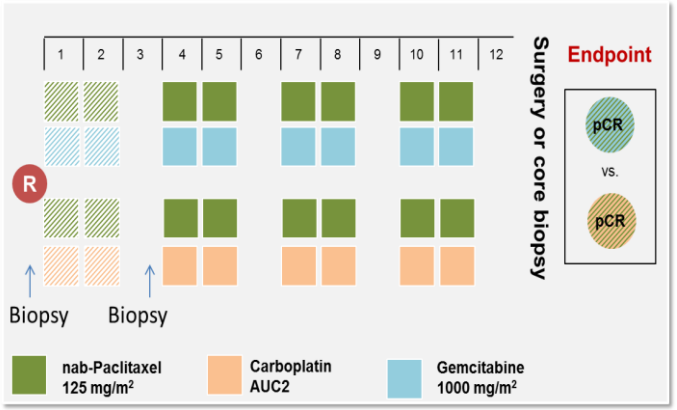
Ribas et al., NEJM 2012

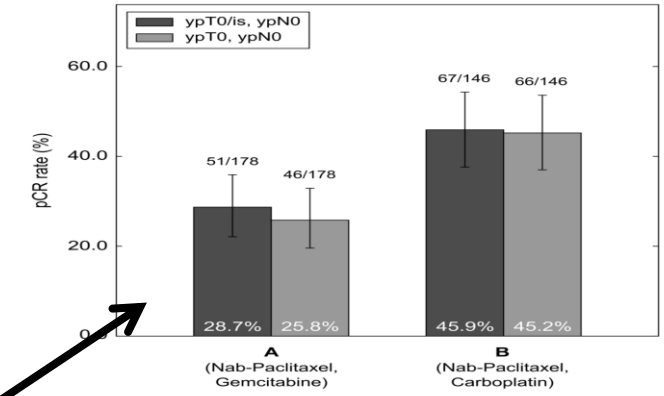
Häufigkeit von Neoantigenen in Malignomen

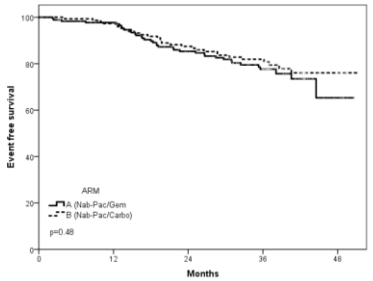


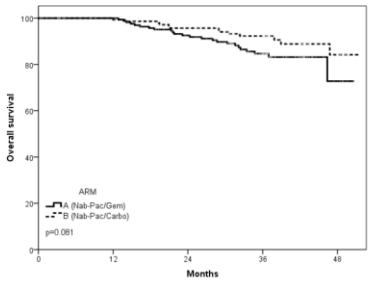
Schumacher, Schreiber. Science 2015

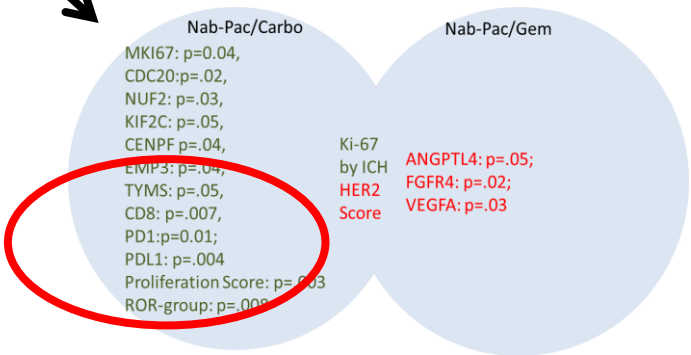
Ergebnisse der ADAPT-TN-Studie als Rationale für Immunonkologie





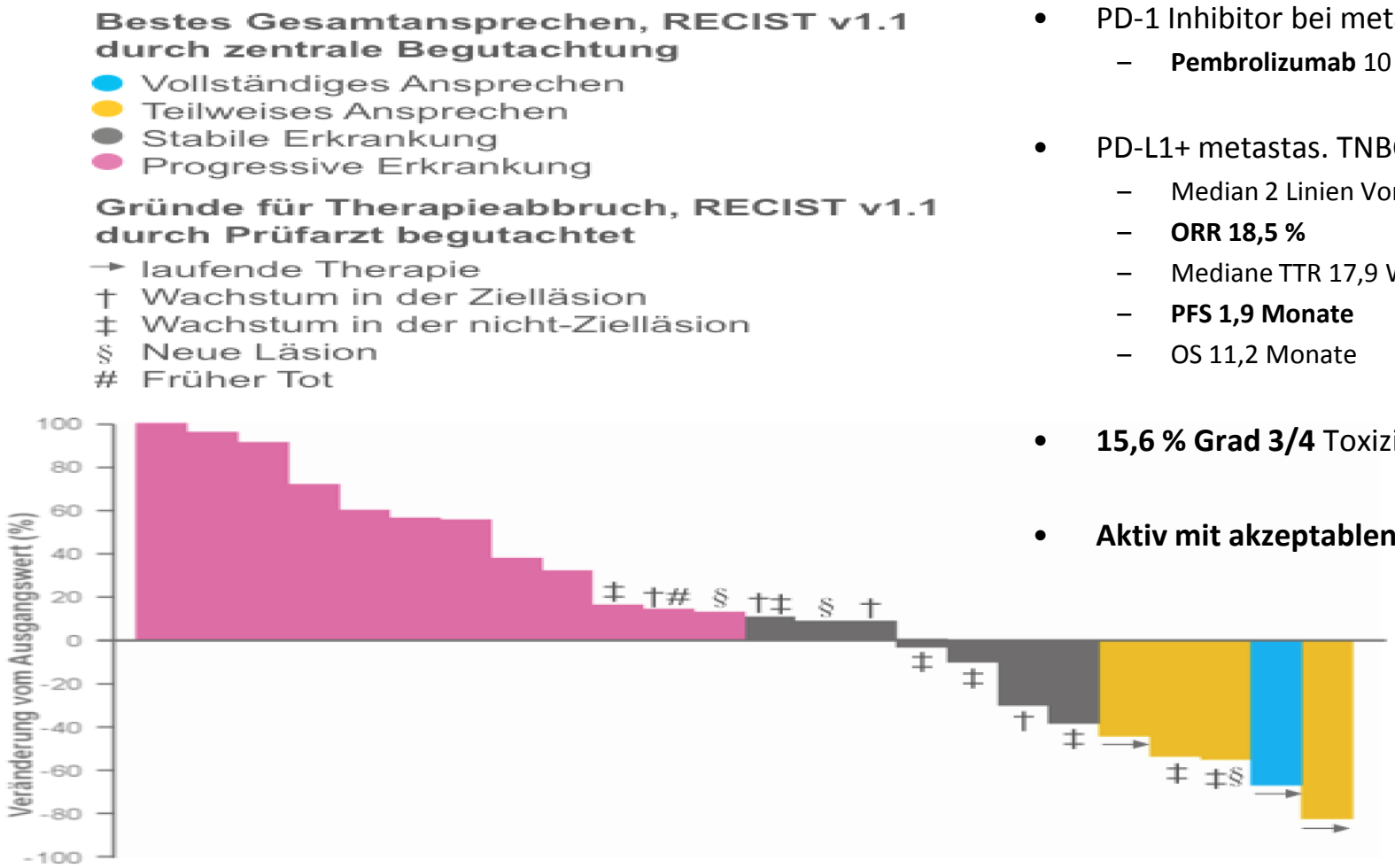






Gluz, Liedtke et al., JNCI (in print)

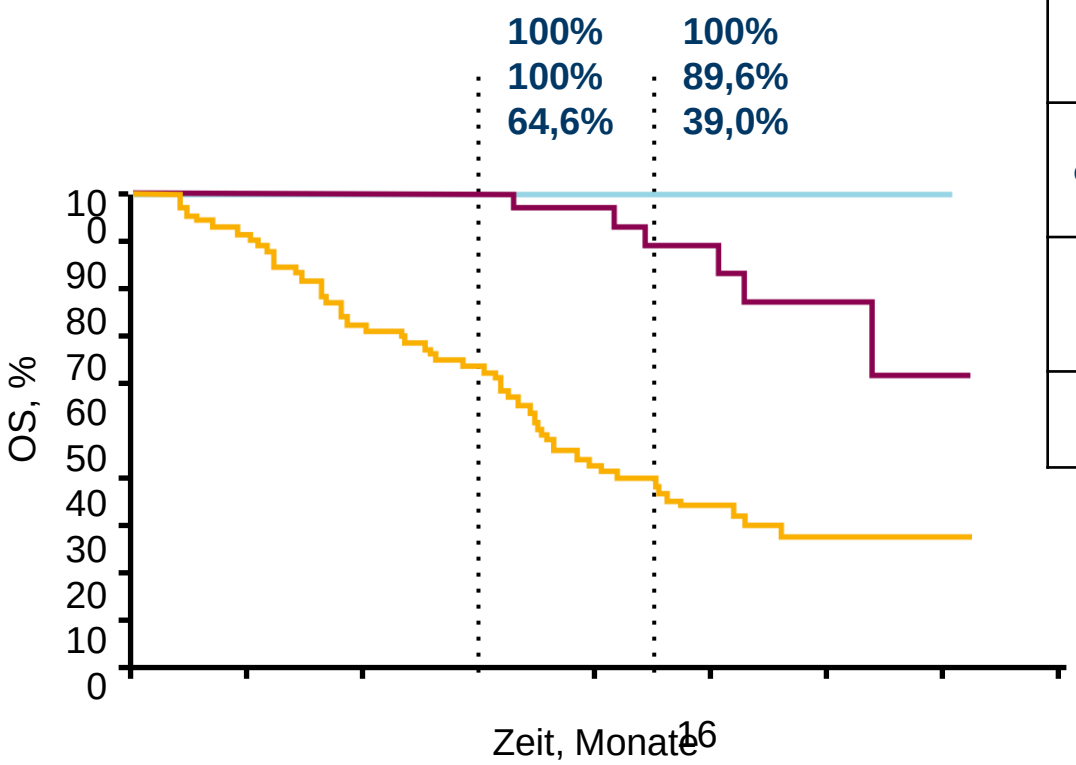
Pembrolizumab bei TNBC – KEYNOTE-012



- PD-1 Inhibitor bei metastas. TNBC
  - **Pembrolizumab** 10 mg/kg d1q2w
- PD-L1+ metastas. TNBC (n = 32)
  - Median 2 Linien Vorbehandlung
  - **ORR 18,5 %**
  - Mediane TTR 17,9 Wochen
  - **PFS 1,9 Monate**
  - OS 11,2 Monate
- **15,6 % Grad 3/4** Toxizitäten
- **Aktiv mit akzeptablen NW**

Nanda et al., J Clin Oncol 2016

KEYNOTE-086 (Phase II): Pembrolizumab-MONOtherapie beim mTNBC



	Ereignisse / Patientinnen n	Median (95%KI)
CR oder PR	0/8	Nicht erreicht (NR; NR)
SD	6/35	Nicht erreicht (12,7; NR)
PD	66/103	7,1 Monate (6,3; 8,8)

Adams S, et al. ASCO 2017

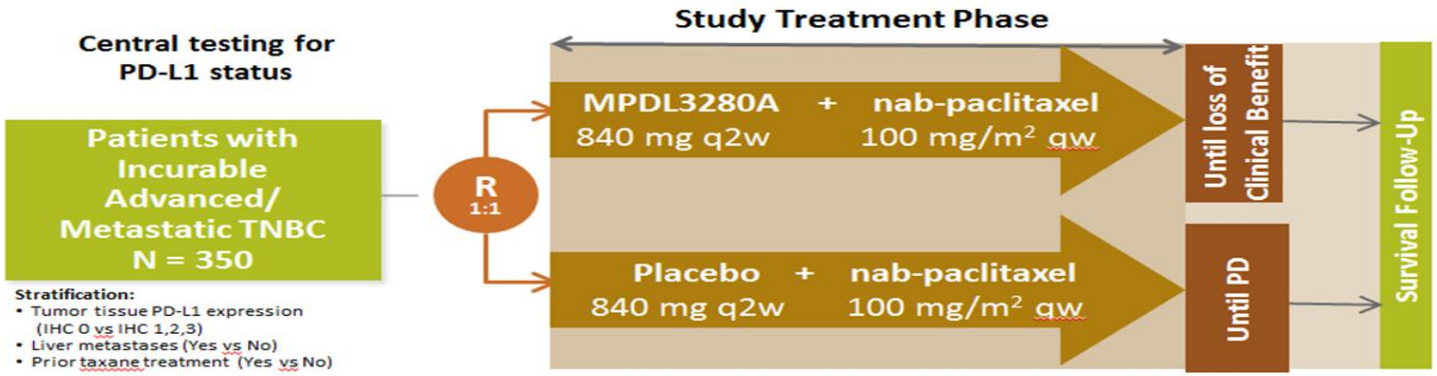
Design der IMpassion-Studie (Atezolizumab)

MUNICH 2018 ESMO congress

MUNICH GERMANY
19-23 OCTOBER 2018

Study Overview

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

Genentech
A Member of the Roche Group
Roche

anti PDL1
MPDL3280A

4

J Clin Oncol. 2018 Feb 14:JCO2017776385. doi: 10.1200/JCO.2017.77.6385. [Epub ahead of print]

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline.

Brahmer JR[1], Lacchetti C[1], Schneider BJ[1], Atkins MB[1], Brassil KJ[1], Caterino JM[1], Chau I[1], Ernstoff MS[1], Gardner JM[1], Ginex P[1], Hallmeyer S[1], Holter Chakrabarty J[1], Leighl NB[1], Mammen JS[1], McDermott DF[1], Naing A[1], Nastoupil LJ[1], Phillips T[1], Porter LD[1], Puzanov I[1], Reichner CA[1], Santomasso BD[1], Seigel C[1], Spira A[1], Suarez-Almazor ME[1], Wang Y[1], Weber JS[1], Wolchok JD[1], Thompson JA[1].

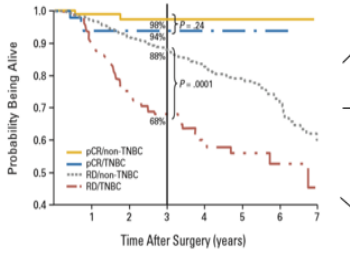
Author information

Abstract

Purpose To increase awareness, outline strategies, and offer guidance on the recommended management of immune-related adverse events in patients treated with immune checkpoint inhibitor (ICPi) therapy. Methods A multidisciplinary, multi-organizational panel of experts in medical oncology, dermatology, gastroenterology, rheumatology, pulmonology, endocrinology, urology, neurology, hematology, emergency medicine, nursing, trialist, and advocacy was convened to develop the clinical practice guideline. Guideline development involved a systematic review of the literature and an informal consensus process. The systematic review focused on guidelines, systematic reviews and meta-analyses, randomized controlled trials, and case series published from 2000 through 2017. Results The systematic review identified 204 eligible publications. Much of the evidence consisted of systematic reviews of observational data, consensus guidelines, case series, and case reports. Due to the paucity of high-quality evidence on management of immune-related adverse events, recommendations are based on expert consensus. Recommendations Recommendations for specific organ system-based toxicity diagnosis and management are presented. While management varies according to organ system affected, in general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities. ICPi therapy may be suspended for most grade 2 toxicities, with consideration of resuming when symptoms revert to grade 1 or less. Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of ICPis and the initiation of high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy. In general, permanent discontinuation of ICPis is recommended with grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement. Additional information is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki .

PMID: 29442540 DOI: 10.1200/JCO.2017.77.6385

Zusammenfassung: **Das tripelnegative Mammakarzinom**



Optimierung von Chemotherapie-Regimen

Entwicklung neuer zielgerichteter Substanzen

Identifikation von Patientinnen mit / ohne Ansprechen auf Chemotherapie

- Der Einsatz platinhaltiger Substanzen ist vielversprechend, und sollte neoadjuvant erfolgen.
- Neue potentielle Substanzen sind:
  - Immunmodulatoren (*Checkpoint-Inhibitoren*)
  - PARPi
  - Antiandrogene
- Vielversprechende Biomarker sind:
  - BRCA-Mutationen / BRCAness
  - Immunsignalling

Traina et al., ASCO 2017

10. International Charité-Mayo-Conference

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