

Wieso die kombinierte Checkpoint und Angiogenese Inhibition Sinn ergibt

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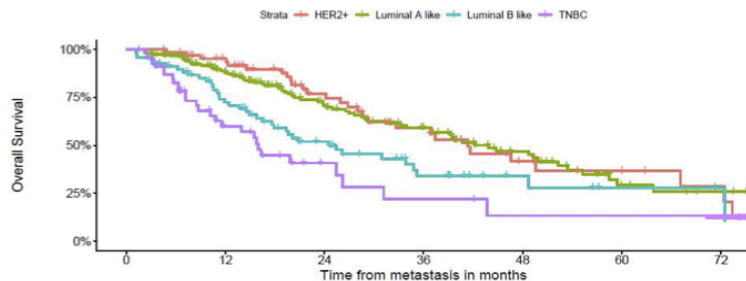
Disclosures	
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Stocks/Ownerships	None
Registered patents	None



Gesamtüberleben beim mTNBC in Deutschland



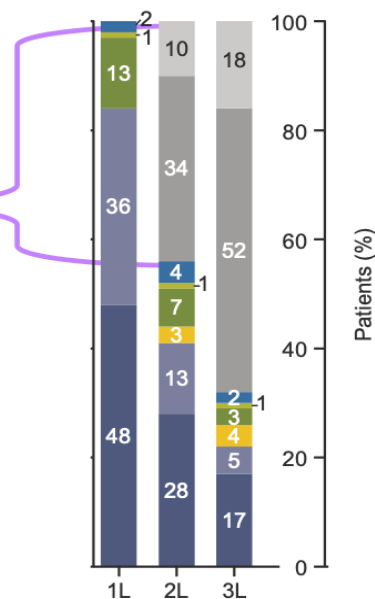
NCT Heidelberg (N=359) 2014-2022



) Estimated median survival per molecular type (total: n = 359, events = 160)

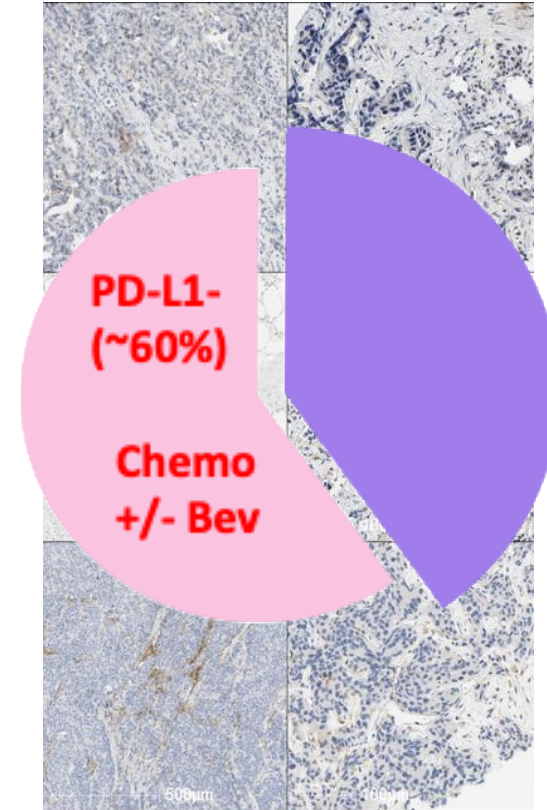
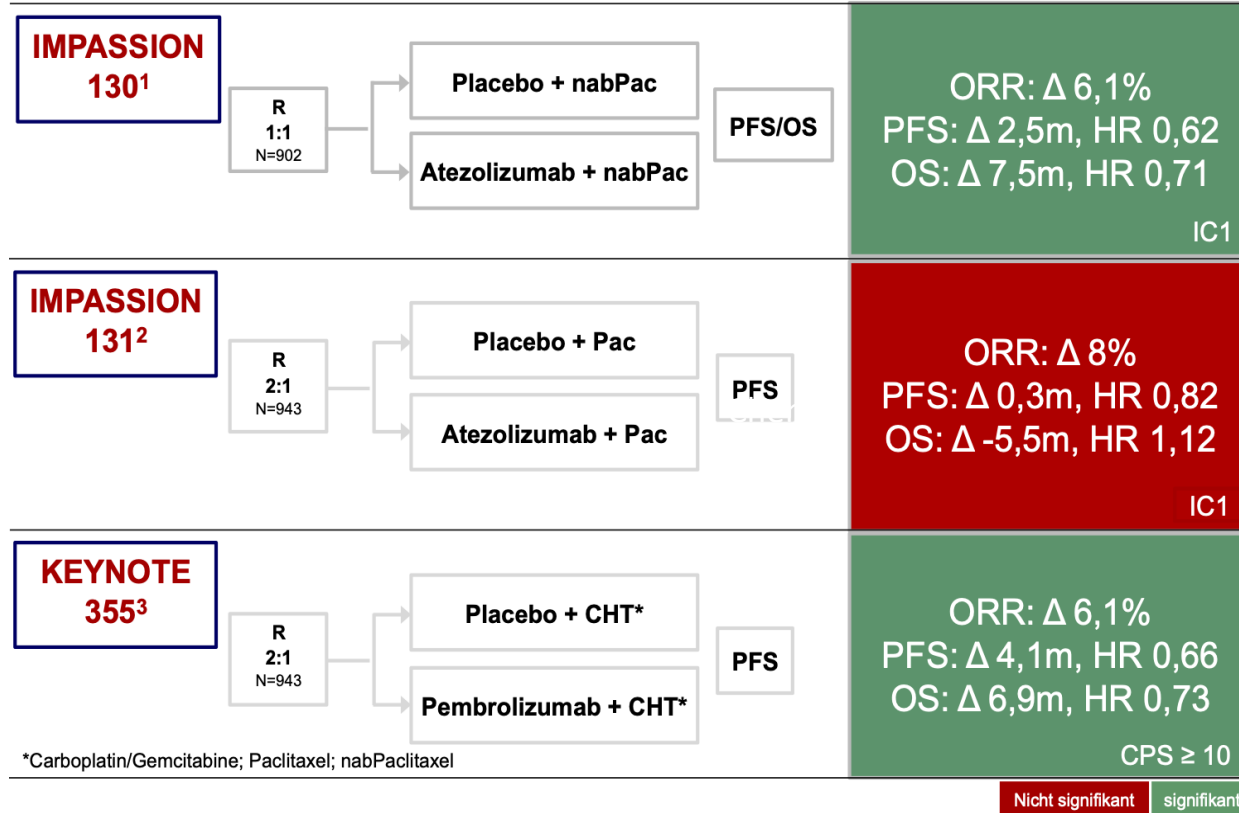
	records	events	median	0.95LCL	0.95UCL
TNBC	51	27	16	11	31
Luminal A like	172	67	44	37	55
Luminal B like	71	38	24	18	49
HER2+	65	28	41	29	73

Flatiron Health Data Base (US)
240 Zentren (TNBC n=2004) 2011-2022

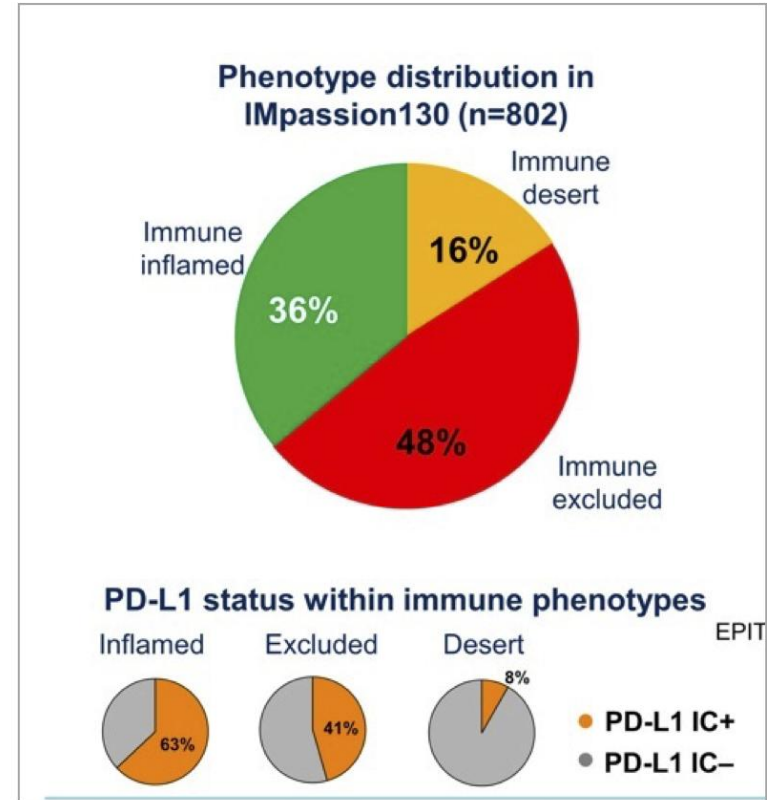
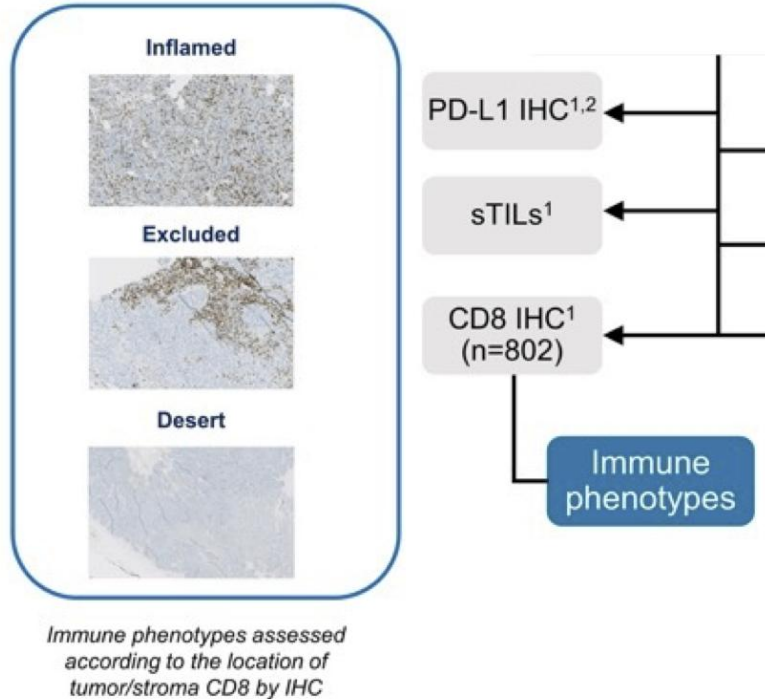


- 44% keine 2L
- 34% in 1L verstorben

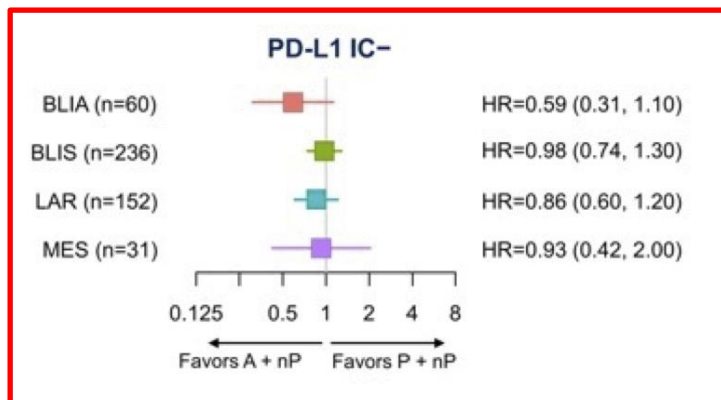
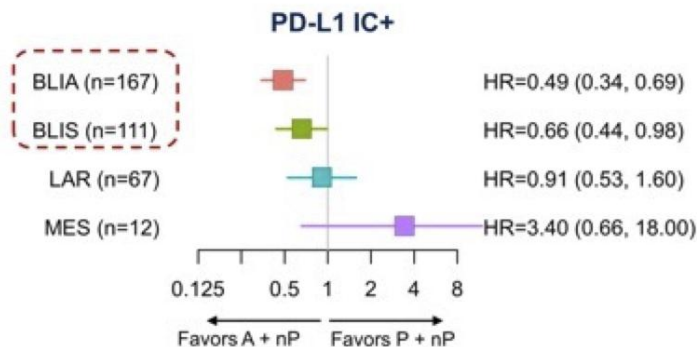
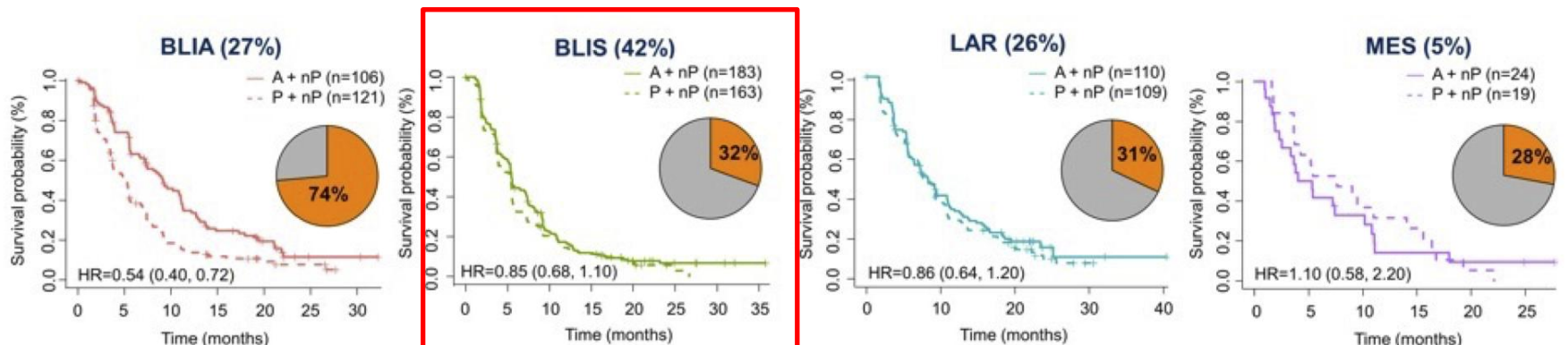
Pembrolizumab + CTx im Standard für 1L mTNBC PD-L1+



Exludierte und ignorante Muster bei PD-L1 Negativität



Exludierte und ignorante Muster bei PD-L1 Negativität



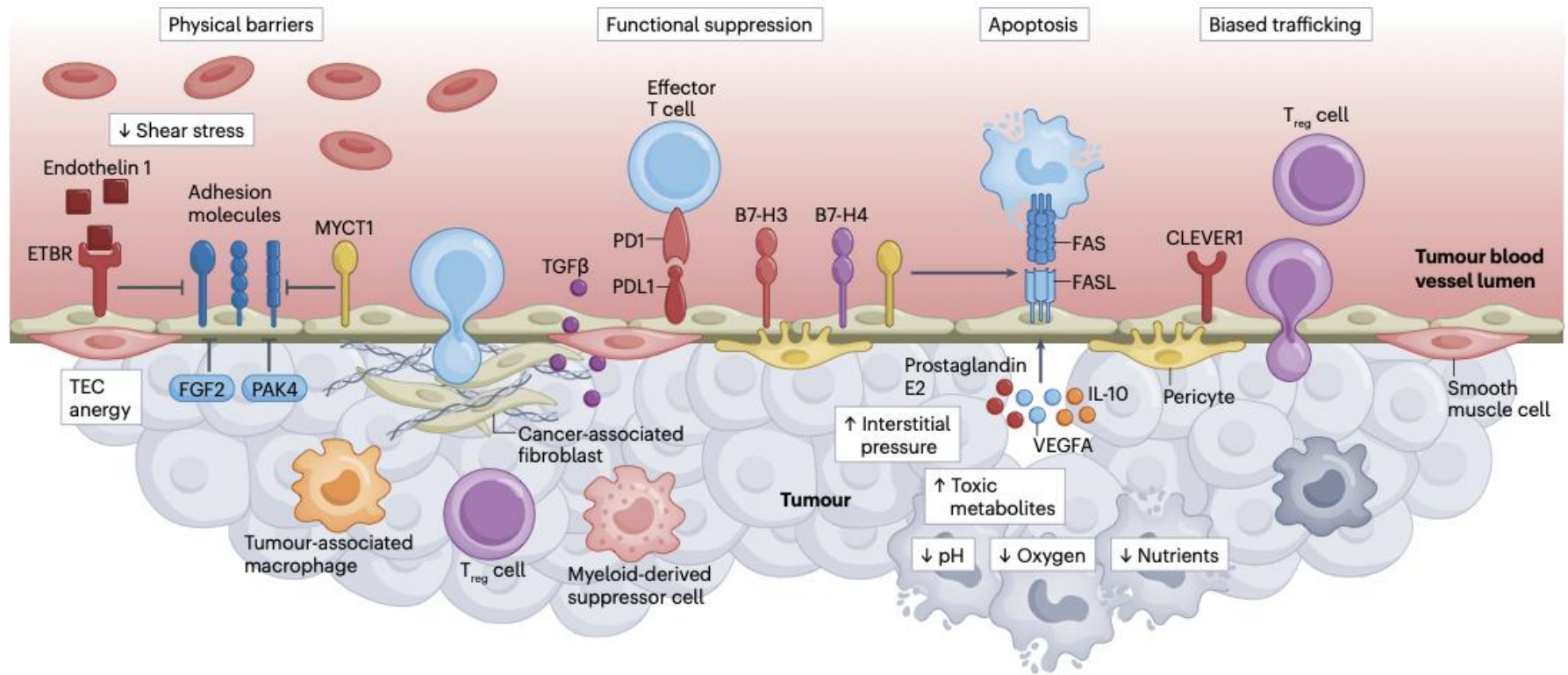
- PD-L1 IC+
- PD-L1 IC-

HRs adjusted for liver metastases and prior taxanes. *In the P + nP arm, BLIA and BLIS had poor PFS vs LAR subgroups.

Effekte der VEGF Blockade auf die Mikroumgebung

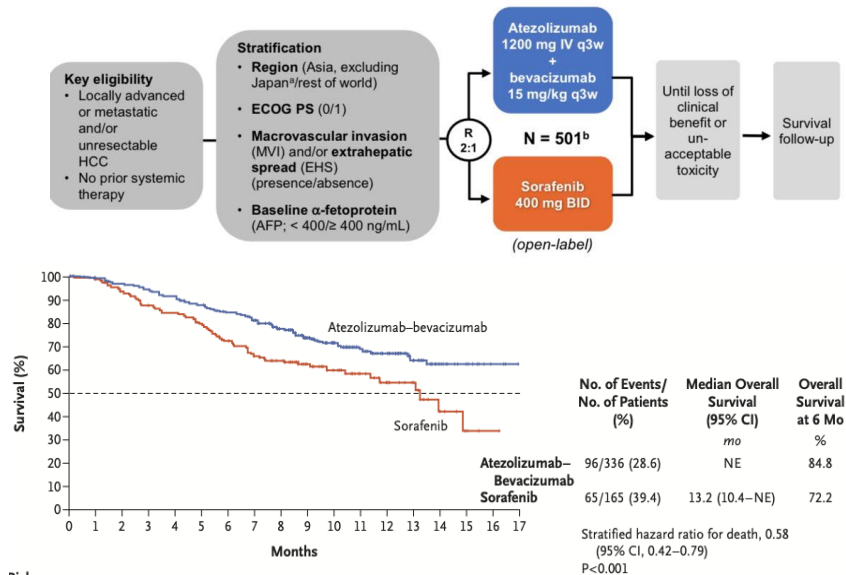
Targeted Immune Component	Effect of VEGF/VEGFR Blockade	Proposed Translational Mechanism	Key Literature Source(s)
Effector T Cells (CD8+)	Increased infiltration and activity	Upregulates endothelial adhesion molecules (ICAM-1, VCAM-1) to facilitate T-cell entry	Dirkx et al. (2003), Nowak-Sliwinska et al. (2018)
Regulatory T Cells (Tregs)	Reduced frequency and recruitment	Blocks direct VEGF-A/VEGFR2-mediated Treg proliferation	Terme et al.(2013), Facciabene et al.(2011)
MDSCs	Decreased accumulation	Inhibits differentiation and suppressive markers.	Gabrilovich et al.(1996) Huang et al. (2012)
Dendritic Cells (DCs)	Improved maturation and antigen presentation	Reverses VEGF-mediated inhibition of NF-B, allowing differentiation into mature antigen-presenting cells.	Gabrilovich et al.(1998) Oyama et al. (1998)
Tumor-Associated Macrophages (TAMs)	Reprogramming (M2 to M1-like)	Limits recruitment of suppressive M2-like macrophages and shifts polarization	Roland et al. (2009), De Palma et al. (2017)
Immune Checkpoints	Downregulation of PD-1, CTLA-4, TIM-3	Disrupts the VEGFR2-PLC-calcineurin-NFAT pathway that drives the T-cell exhaustion program.	Voron et al. (2015), Kim et al. (2019)
Tumor Vasculature	Vascular "Normalization"	Prunes leaky vessels to reduce hypoxia	Jain et al. (2005), Goel et al. (2011)

Effekte der VEGF Blockade auf die Mikroumgebung

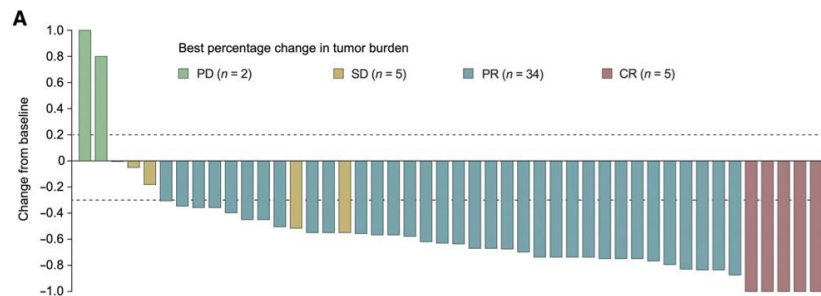
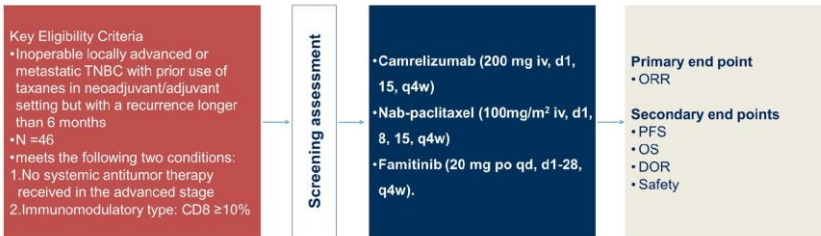


Rationale IO + anti-VEGF in metastatic TNBC

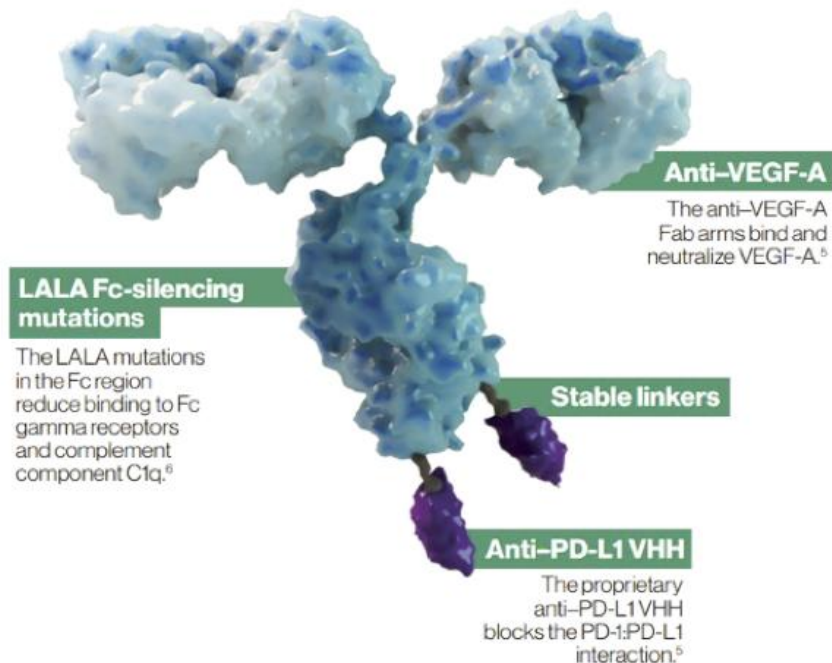
IMbrave150 study design



FUTURE-C-Plus Study Design (NCT04129996)



Rationale bispecific PD-L1/VEGF BNT327 (Pumitamig)



- Protein binding activity (K_D): PD-L1 5.5nM / VEGF < 0.4nM
- >1600 pts treated across 18 tumor types
- 8 pivotal trials ongoing
- Clinical activity as monotherapy and in combination

Phase Ib/II (n=42) PM8002/BNT327 + nabPaclitaxel in 1L mTNBC - Design

- Open-label Single-arm, Phase Ib/II Study of PM8002/BNT327 + nab-paclitaxel for 1L TNBC (NCT05918133)

Key Eligibility Criteria

- Patients with locally advanced or metastatic TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic advanced TNBC
- Age ≥ 18 years
- ECOG score 0-1
- Adequate organ function

PM8002/BNT327 20mg/kg Q2W
on Day 1, 15 of 28-day cycle
+
nab-paclitaxel 100mg/m²
on Day 1, 8, 15 of 28-day cycle

until disease progression/
unacceptable toxicity

- ✓ **Primary endpoints:** ORR (RECIST V1.1), safety (CTCAE 5.0)
- ✓ **Secondary endpoints:** PFS, DCR, OS

- As of July 05, 2024, 42 pts had been enrolled and received at least 1 dose of PM8002/BNT327 combined with nab-paclitaxel
- 11 pts remained on treatment
- Median follow-up time 16.3 months

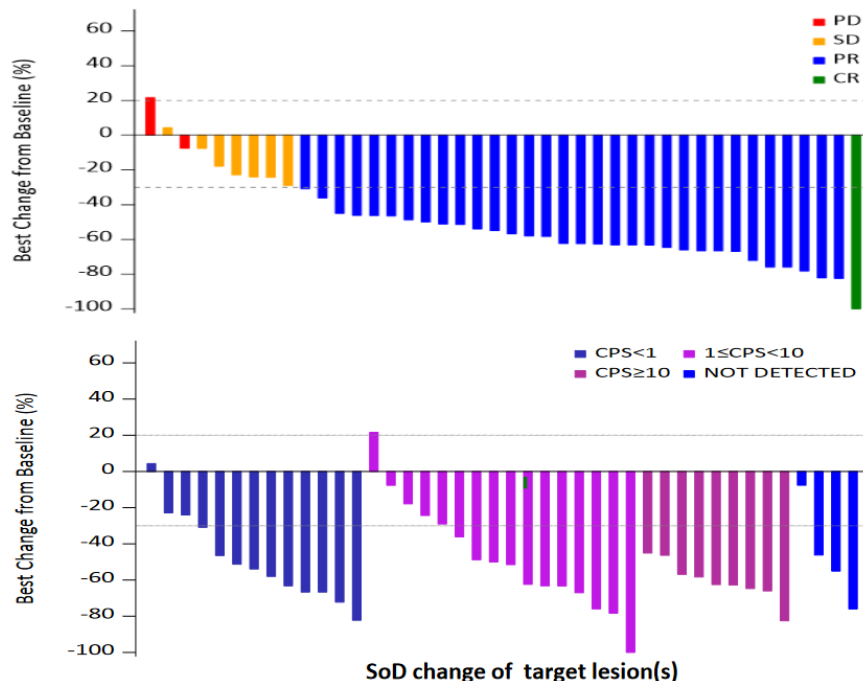
Patient Characteristics (n=42)

Median age, years (Q1, Q3)	53.5 (41.0, 60.0)
Number of metastatic sites, n (%)	
0-2	17 (40.5)
≥ 3	25 (59.5)
Liver metastasis, n (%)	
Yes	16 (38.1)
No	26 (61.9)
Brain metastasis, n (%)	
Yes	2 (4.8)
No	40 (95.2)
Neo/adjuvant Paclitaxel treatment, n (%)	
Yes	28 (66.7)
No	14 (33.3)

Phase Ib/II (n=42) PM8002/BNT327 + nabPaclitaxel in 1L mTNBC – Ansprechen

Variable	ITT	PD-L1 CPS<1	PD-L1 1≤CPS<10	PD-L1 CPS≥10	NOT DETECTED
Population (n)	42	13	16	9	4
CR	1 (2.4)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)
PR	32 (76.2)	10 (76.9)	10 (62.5)	9 (100.0)	3 (75.0)
SD	7 (16.7)	3 (23.1)	4 (25.0)	0 (0.0)	0 (0.0)
PD	2 (4.8)	0 (0.0)	1 (6.3)	0 (0.0)	1 (25.0)
ORR % (95% CI)	78.6 (63.2, 89.7)	76.9 (46.2, 95.0)	68.8 (41.3, 89.0)	100.0 (66.4, 100.0)	75.0 (19.4, 99.4)
cORR % (95% CI)	73.8 (58.0, 86.1)	76.9 (46.2, 95.0)	56.3 (29.9, 80.3)	100.0 (66.4, 100.0)	75.0 (19.4, 99.4)
DCR % (95% CI)	95.2 (83.8, 99.4)	100.0 (75.3, 100.0)	93.8 (69.8, 99.8)	100.0 (66.4, 100.0)	75.0 (19.4, 99.4)
mPFS (Mo), (95%CI)	13.5 (9.4, --)	NR (5.7, --)	14.0 (7.2, --)	10.8 (5.5, 13.5)	14.0 (1.8, --)

- For the ITT population, mTTR was 1.9 mo and mDoR 11.7 mo; mOS was not reached



CPS, combined positive score; CR, complete response; cORR, confirmed ORR; DCR, disease control rate; IHC, immunohistochemistry; mDoR, median duration of response; mPFS, median progress-free survival; mTTR, median time to response; Mo, month; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters

Phase Ib/II (n=42) PM8002/BNT327 + nabPaclitaxel in 1L mTNBC – Toxizität

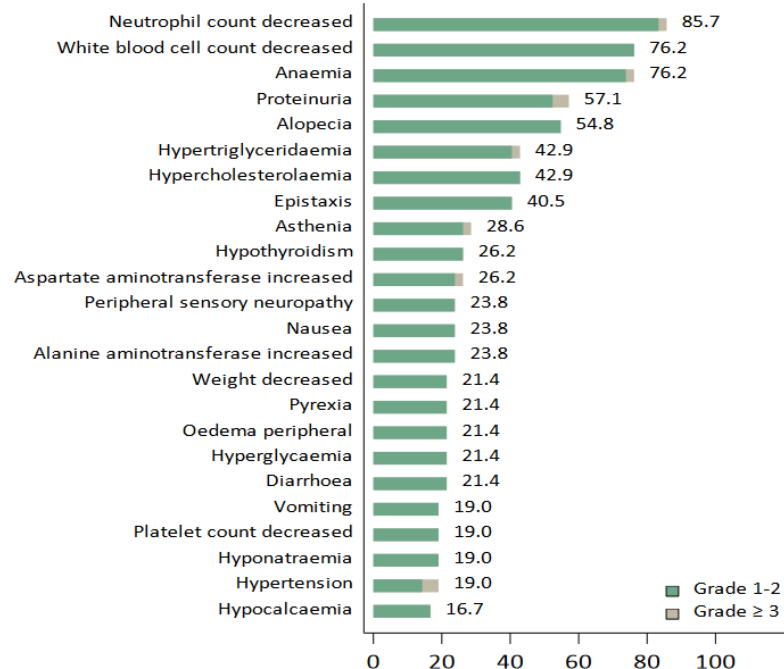
Safety

- Any-grade and grade ≥ 3 TRAEs of the combination regimen occurred in 100% and 59.5% pts, respectively. No Grade 5 TRAEs were observed
- TRAEs leading to treatment discontinuation occurred in 9.5% pts
- The most common immune-related adverse events (irAEs) included hyperthyroidism, hypothyroidism and rash
- The most common AEs typically associated with VEGF inhibition were hypertension and proteinuria, which were mostly Grade 1 or 2

Table 3. Overview of TRAEs of the combination regimen

Safety Overview	N=42 n (%)
All TRAEs	42 (100)
Grade 3-4 TRAEs	25 (59.5)
SAEs	10 (23.8)
TRAE leading to dose interruption	27 (64.3)
TRAE leading to dose reduction	6 (14.3)
TRAEs leading to treatment discontinuation	4 (9.5)
irAE	13 (31.0)
Grade 3-4 irAE	4 (9.5)

TRAE in $\geq 15\%$ of patients



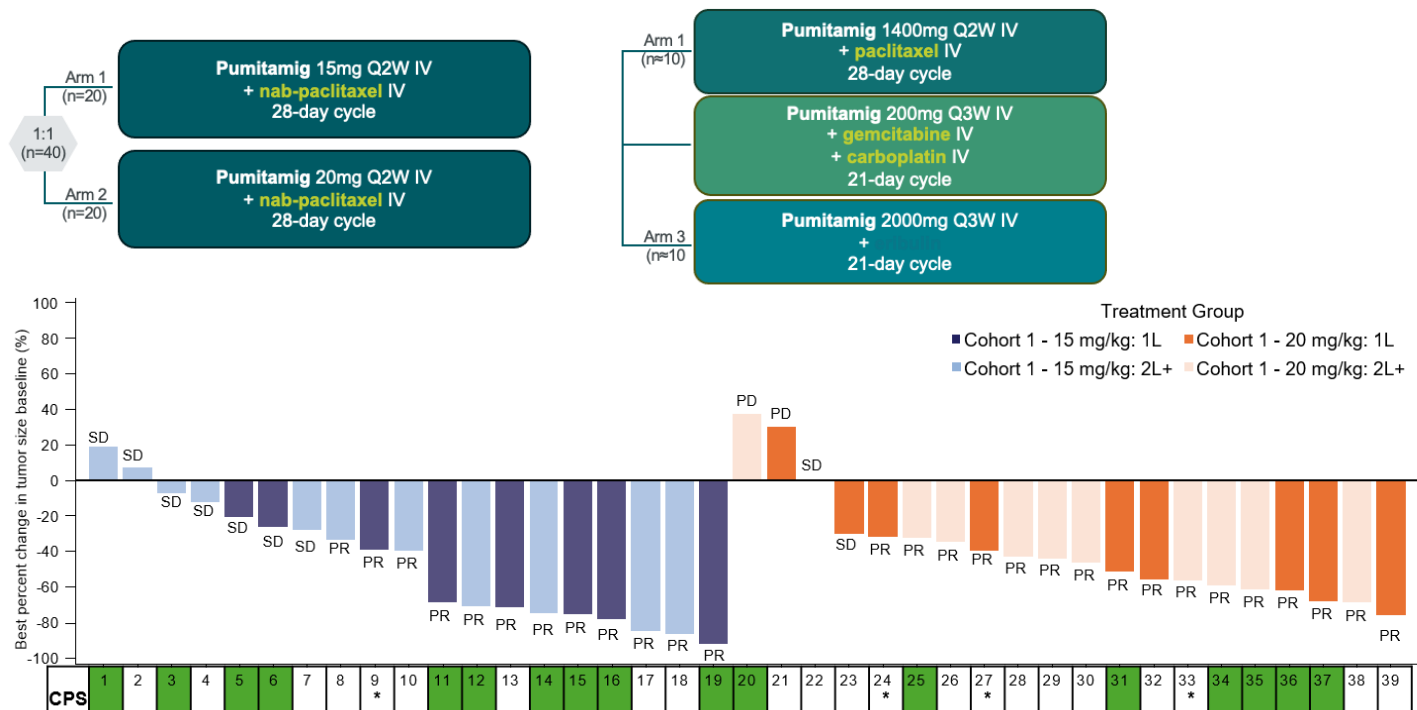
Phase II (n=42) BNT327-02: Global Phase 2, randomized, open-label Pumitamig + CTx in 1L/2L mTNBC (NCT06449222)

Key inclusion criteria:

- Age ≥18 years
- Histologically or cytologically confirmed locally advanced/metastatic TNBC
- 1L: no prior systemic treatment in the advanced setting (neo/adjuvant EOT from to recurrence ≥6 months)
- 2L: progression after 1L treatment with systemic chemotherapy or IO (≥2 doses of PD-(L)1 inhibitor)
- Measurable disease, per RECIST v1.1
- ECOG PS 0 or 1
- Adequate organ function
- Asymptomatic, stable brain metastases allowed

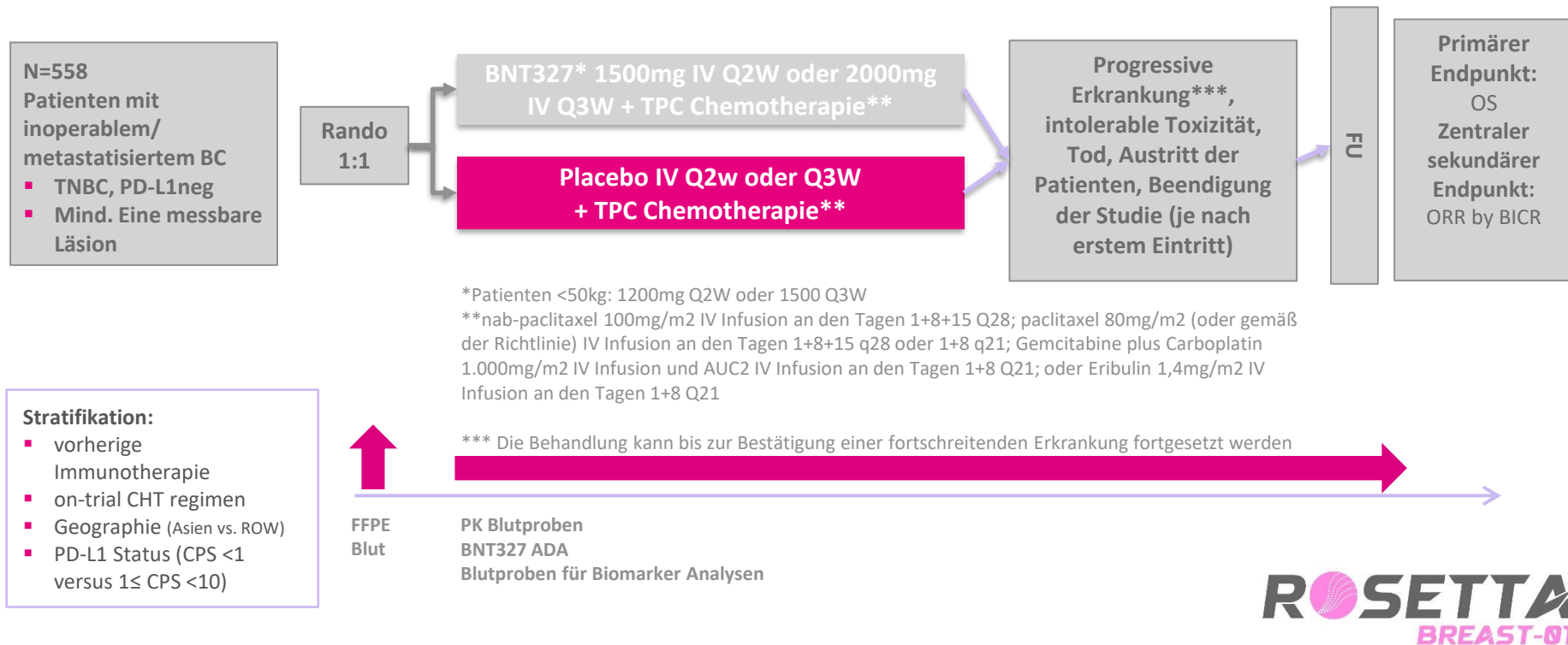
Exclusion criteria:

- Prior PD(L)-1/VEGF bsAb



ROSETTA Breast-01: multicentric, double-blind Phase III

Pumitamig (BNT327) + CTx (TPC) vs. Placebo + CTx (TPC) in 1L PD-L1 neg. mTNBC (n=558)



ROSETTA Breast-01: multicentric, double-blind Phase III

Pumitamig (BNT327) + CTx (TPC) vs. Placebo + CTx (TPC) in 1L PD-L1 neg. mTNBC (n=558)

Einschlusskriterien

- Metastasierter TNBC oder ER-low (ER1-9%) BC
- HER2neg gemäß ASCO CAP
- Nicht geeignet für eine PD(L)1-gerichtete Behandlung (CPS < 10 %)
- Bei ER-low: Nicht geeignet für eine endokrine Therapie
- Keine vorangegangene Behandlung im fortgeschrittenen Stadium
- Mindestens 6 Monate seit Abschluss einer kurativen Behandlung
- Ausreichende Organfunktion

Ausschlusskriterien

- systemische Antitumorthérapie für fortgeschrittene Erkrankung
- Behandlung mit einem PD(L)-1/VEGF-bispezifischen Antikörper
- Kürzliche Einnahme von systemischen Kortikosteroiden
- aktive Autoimmunerkrankung, die in den letzten 2 Jahren eine systemische Therapie erforderlich machte (mit Ausnahmen)
- Innerhalb der letzten 6 Monate: relevante kardiale Begleiterkrankung oder Bluthochdruck
- Mittleres QTcF >480 ms
- Kürzliche Impfung oder intravenöse Breitbandantibiotika oder größere Operation
- Schwere Gerinnungsstörungen oder therapeutische Antikoagulation oder Thrombozytenaggregationshemmung
- Vorgeschichte relevanter immunvermittelter Nebenwirkungen (irAEs), die zum Therapieabbruch führten
- Wundheilungsstörungen

Kontakt

- GBG Projektmanagement

Dr. Laura Steinmann

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und Partnerschaft – führend in der
Brustkrebs-Forschung

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