Targeting the host in triple negative breast cancer

Giuseppe Curigliano M.D. Ph.D.
Division of Medical Oncology
European Institute of Oncology
Milano, Italia

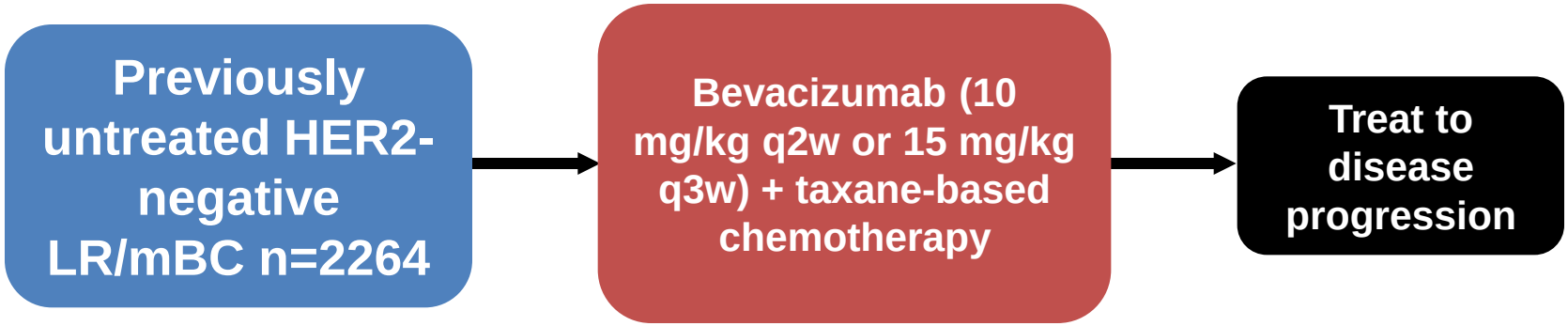
The Host

- Angiogenic vascular cells
- Infiltrating immune cells
- Cancer associated fibroblastic cells and adipocytes

Angiogenic vascular cells

- *Sustaining proliferative signaling:* angiogenic switch and increased rates of cancer cell proliferation
- *Resisting cell death*: Abnormal vasculature fuels tumor progression and treatment resistance
- *Activation of invasion and metastasis*: Tumor vasculature hyper-stimulated by VEGF reduces pericyte coverage.

Bevacizumab



- Primary endpoint: safety
  - Secondary endpoints: time to progression, OS, safety in patients with CNS metastases

ATHENA included 585 patients with TNBC (26%)

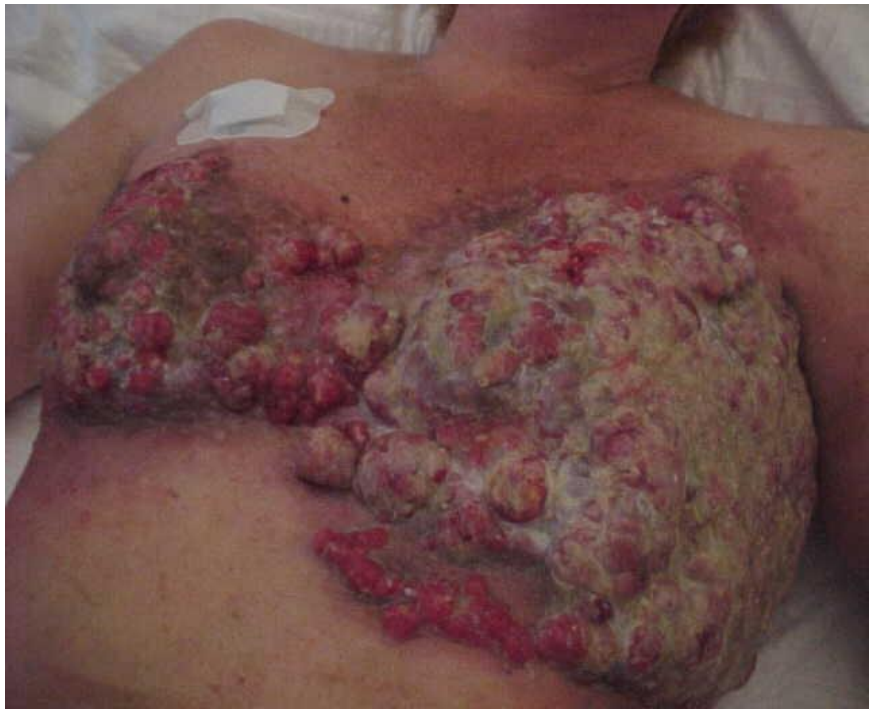
Thomssen C et al. Oncology 2012; 82:218-227

Bevacizumab in TNBC

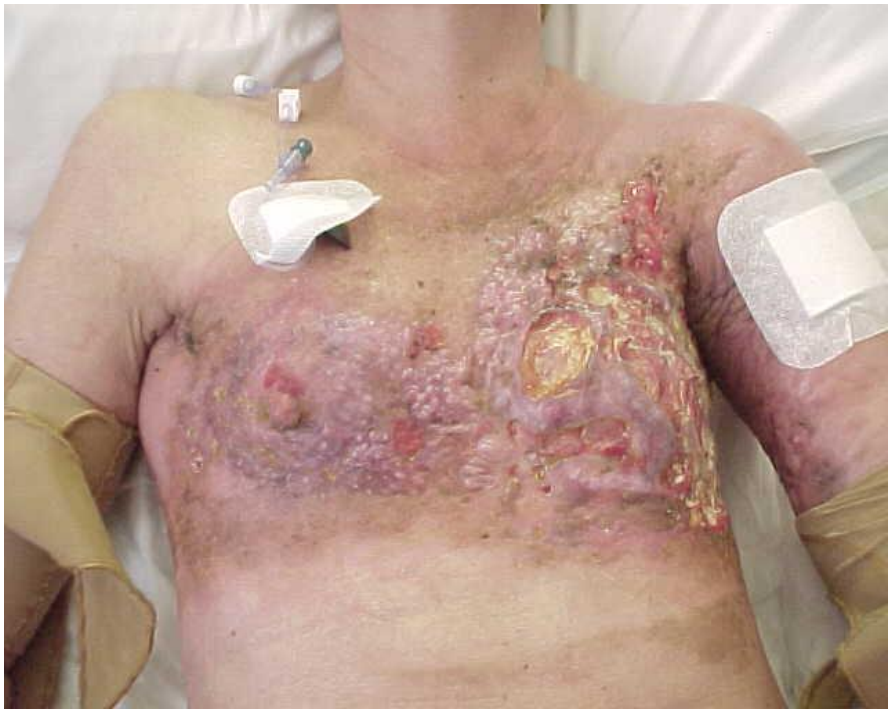
Outcome	TNBC (n=585)	Non-TNBC (n=1616)
Time to progression		
•Events, n (%)	439 (75)	1158 (72)
•Median, months (95% CI)	7.2 (6.6–7.8)	10.6 (10.0–11.0)
Overall survival		
•Events, n (%)	362 (62)	816 (51)
•Median OS, months (95% CI)	18.3 (16.4–19.7)	27.3 (26.3–29.3)
Overall response rate, %	49	51

Thomssen C et al. Oncology 2012; 82:218-227

Bevacizumab in TNBC



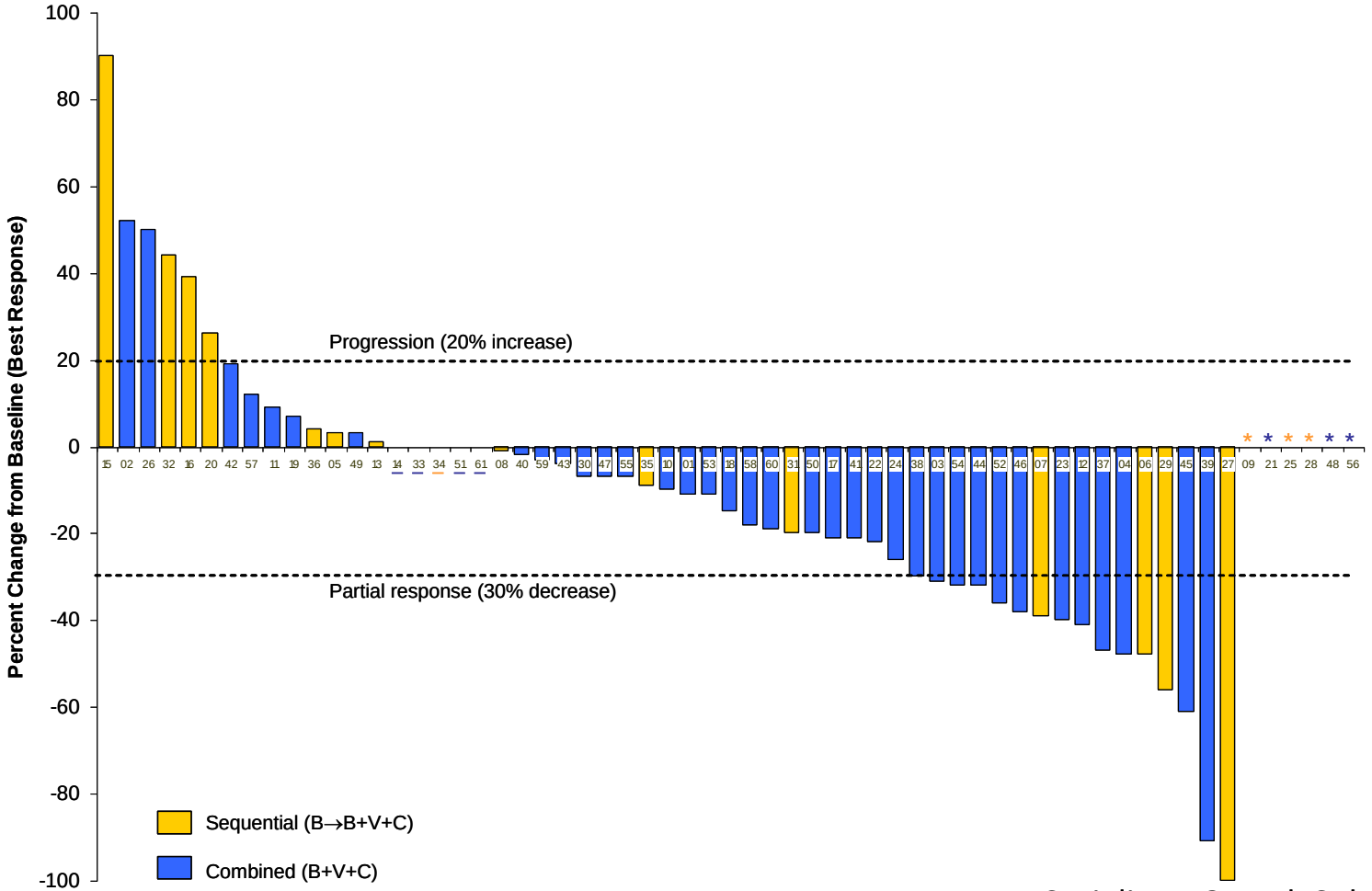
19.07.2007



18.10.2007

Curigliano G et al. Submitted

Bevacizumab in TNBC

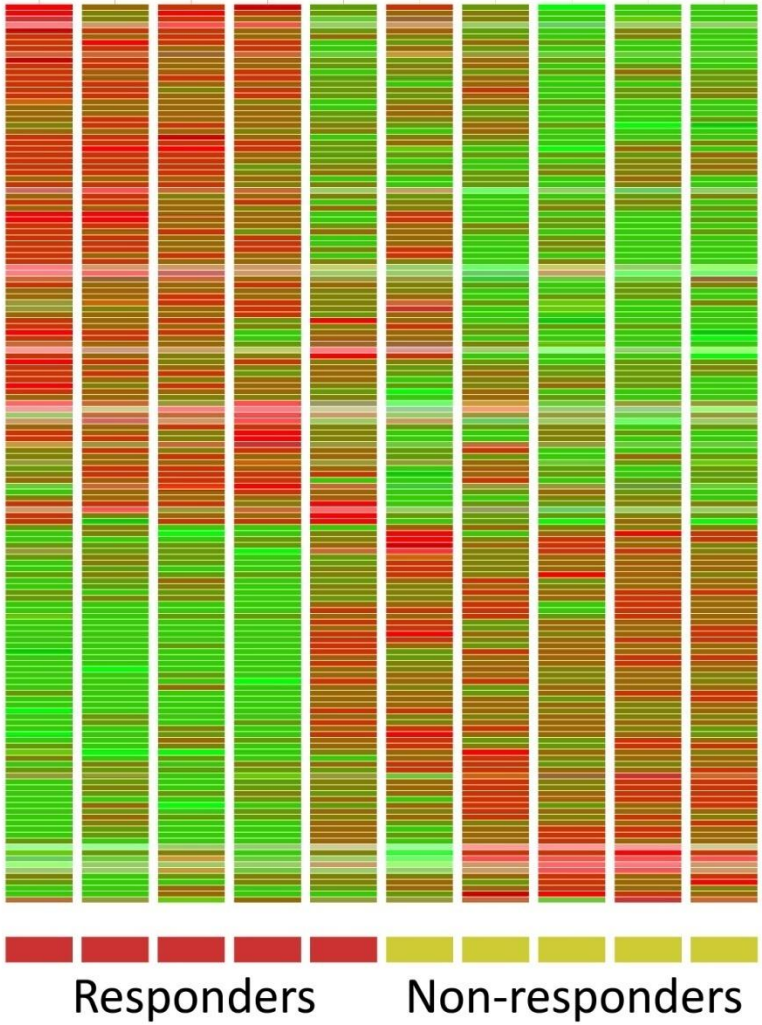


Curigliano G et al. Submitted

* target lesions not evaluable

Bevacizumab in TNBC

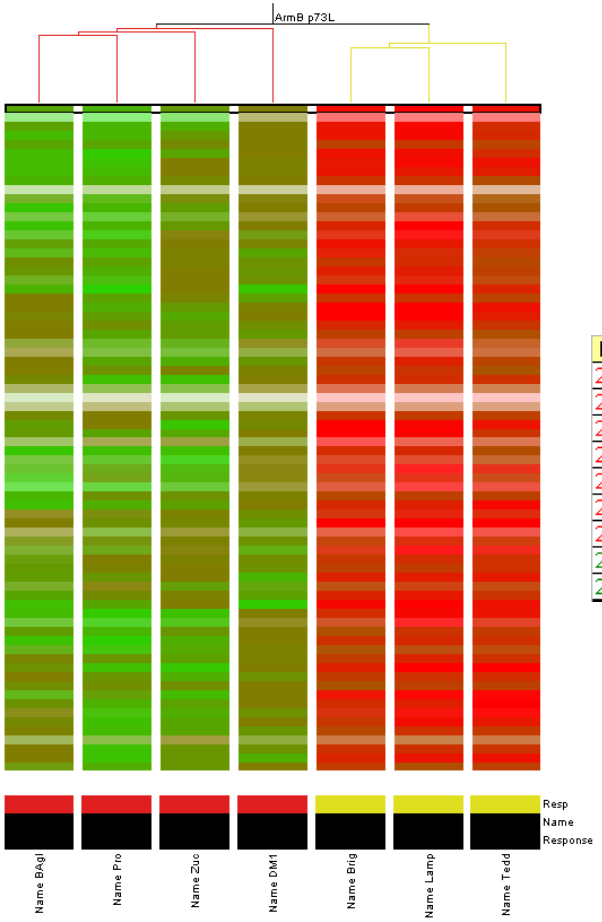
Expression pattern of approximately 160 genes correlates with response to bevacizumab



Curigliano G et al. Submitted

Bevacizumab in TNBC

Supervised clustering of samples: responders vs progressive

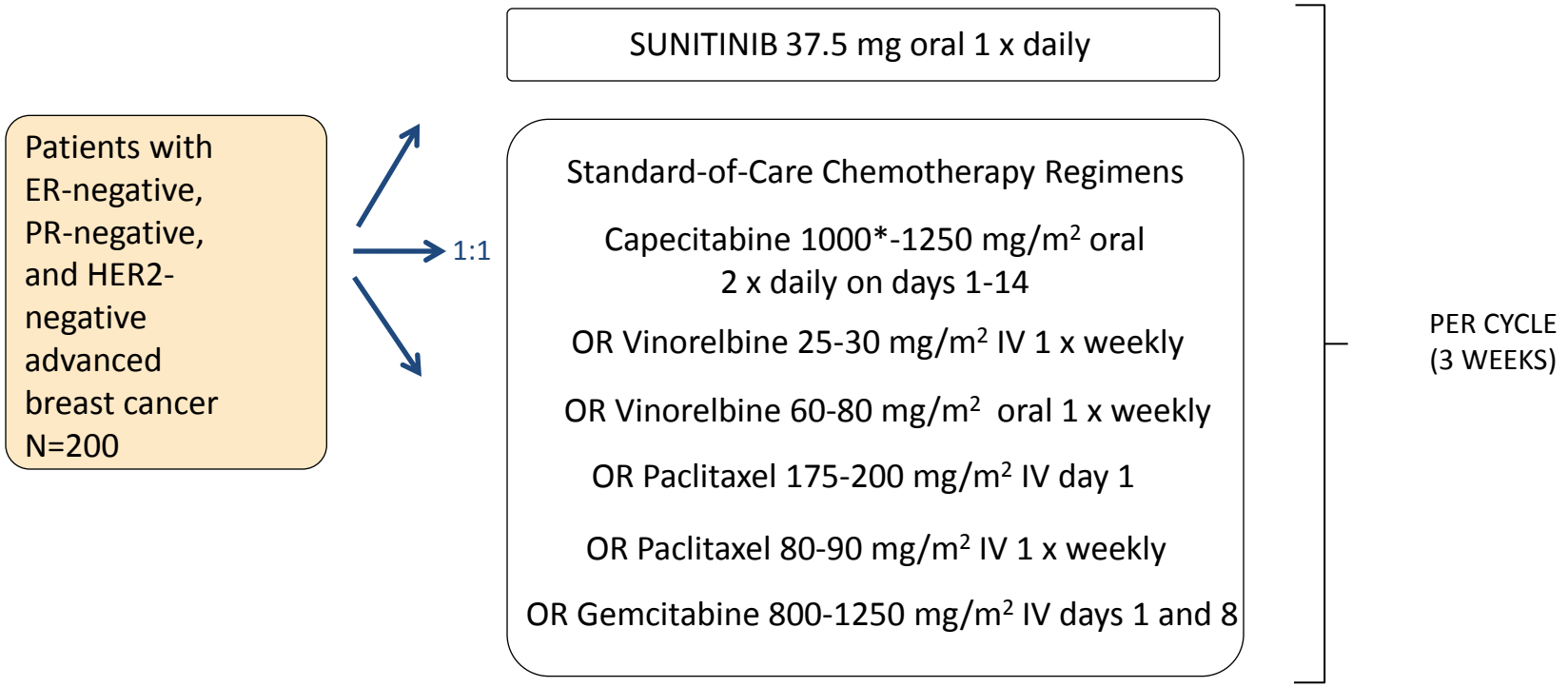


75 gene signature

Probeset ID	Symbol	Reg	AvgT/N	Partek T/N	Location	Type	Drugs
204475_at	MMP1	U	555.7	216.8	Extracellular Space	peptidase	
207039_at	CDKN2A	U	13.6	16.6	Nucleus	transcription regulator	
219493_at	SHCBP1	U	18.8	14.7	Unknown	other	
209642_at	BUB1	U	24.6	14.5	Nucleus	kinase	
212464_s_at	FN1	U	7.4	6.9	Plasma Membrane	enzyme	
205479_s_at	PLAU	U	5.4	4.8	Extracellular Space	peptidase	
203214_x_at	CDC2	U	7.1	3.7	Nucleus	kinase	flavopiridol
203685_at	BCL2	D	-5.2	-5.3	Cytoplasm	other	oblimersen, (-)-gossypol
227550_at	GFRA1	D	-17.6	-7.3	Plasma Membrane	transmembrane receptor	

Curigliano G et al. Submitted

Sunitinib



Trial design	Endpoints	Study sites	Indication	FPFV
Multinational, multi-center, randomized, open label	**Primary:** PFS **Secondary:** safety, ORR, OS, QoL, PK, biomarker	US, EU	2nd line (Triple -)	Enrolling

Curigliano G et al. Submitted

Variable	Sunitinib (n = 113)	SOC (n = 104)
Progression-free survival		
Events, %	82	76
Median, months	2.0	2.7
95% CI	1.5–2.8	1.7–2.8
P	0.888	
Overall survival		
Events, %	85	84
Median, months	9.4	10.5
95% CI	5.8–11.2	8.5–13.8
P	0.839	
Objective response %		
	3	7
95% exact CI	1–8	3–13
P	0.962	

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Bevacizumab

Drug	Dose	Day
		1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
CTX	50 mg daily	
Capecitabine	1500 thrice daily	
Bev	10mg/kg q2w	

40 pts assessable for CB

Overall CB rate (1CR + 18 PRs + 8 SDs ≥ 24 weeks) of 68% (95% CI, 51% to 81%)]

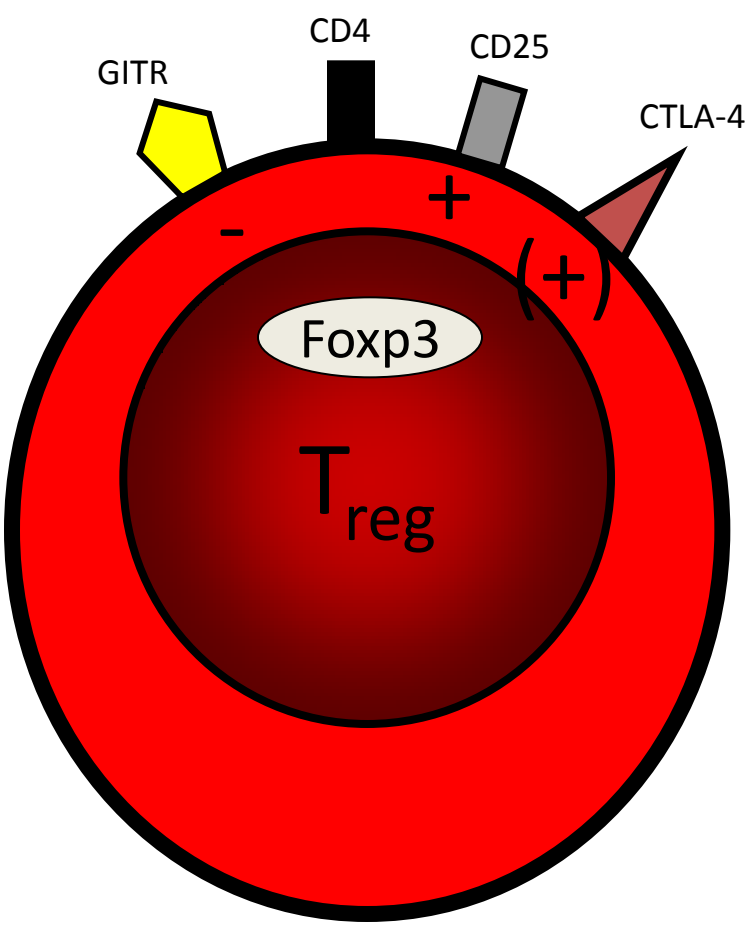
Median TTP = 42 weeks (95%CI,26 to 72ws)

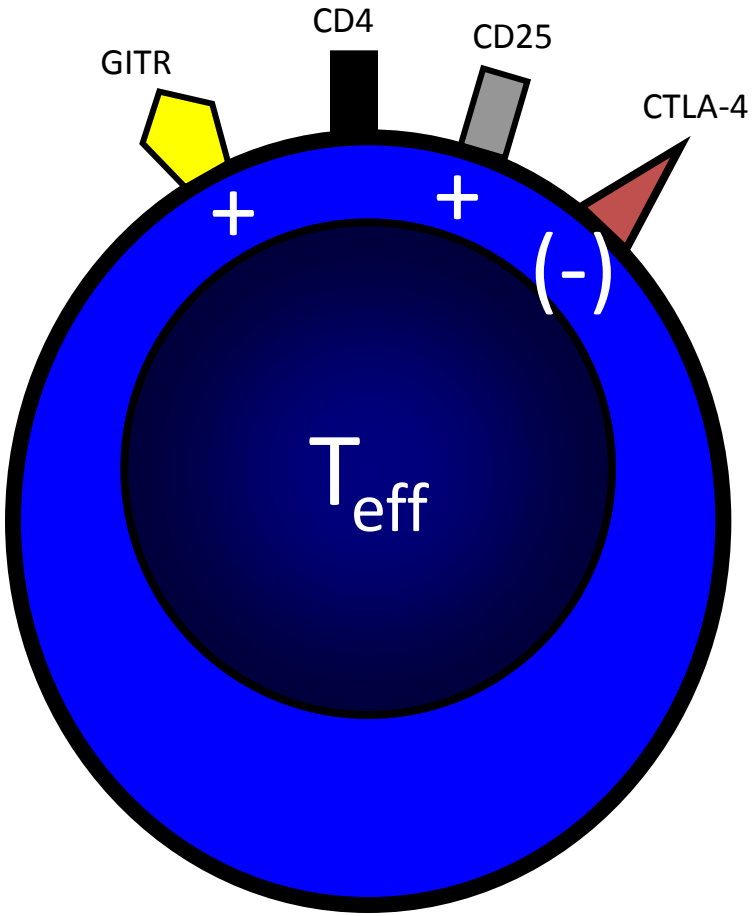
S. Della Pasqua et al JCO 2008

Infiltrating Immune Cells

- *Sustaining proliferative signalling:* Inflammation and cancer, release of mitogenic growth mediators
- *Resisting cell death*: tumor-associated macrophages promote survival in metastatic breast cancer cells.
- *Activation of invasion and metastasis*: Tumor associated macrophages through CSF1R signalling increase metastatic potential.

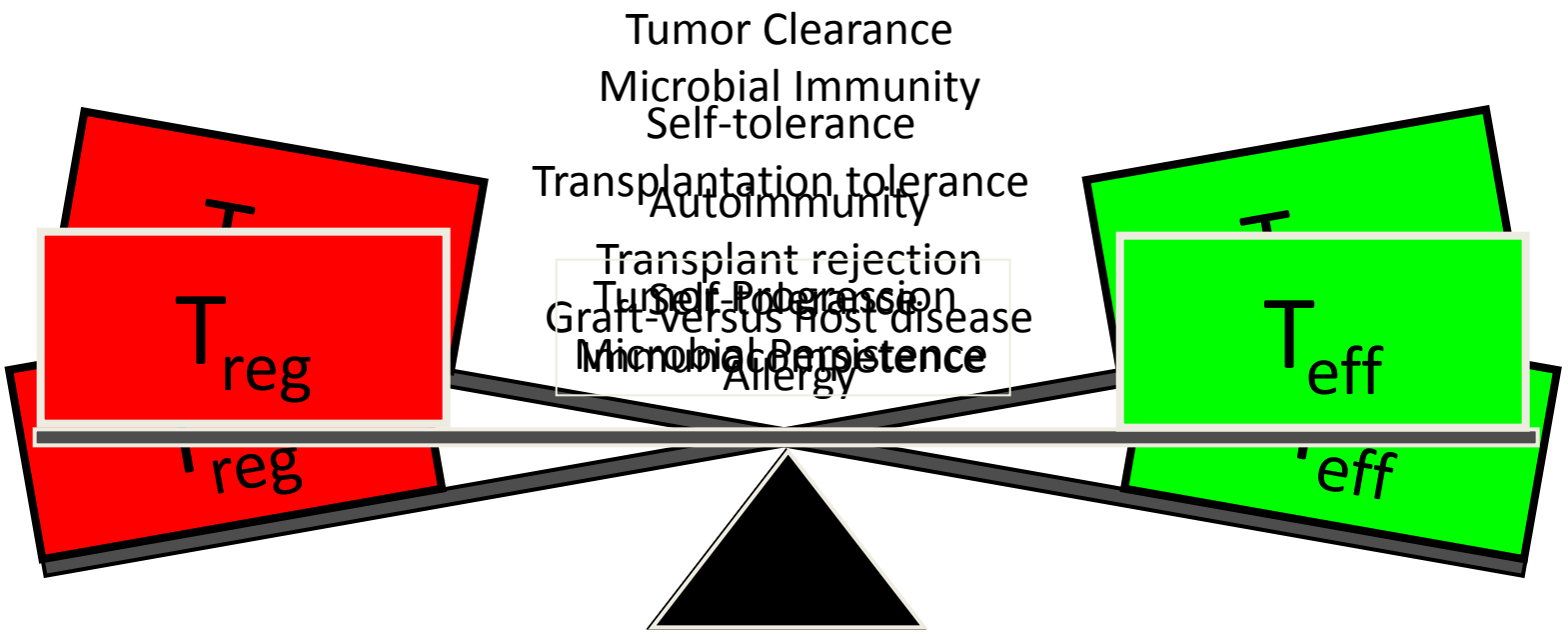
T_{Reg} vs T_{Eff} immunophenotype



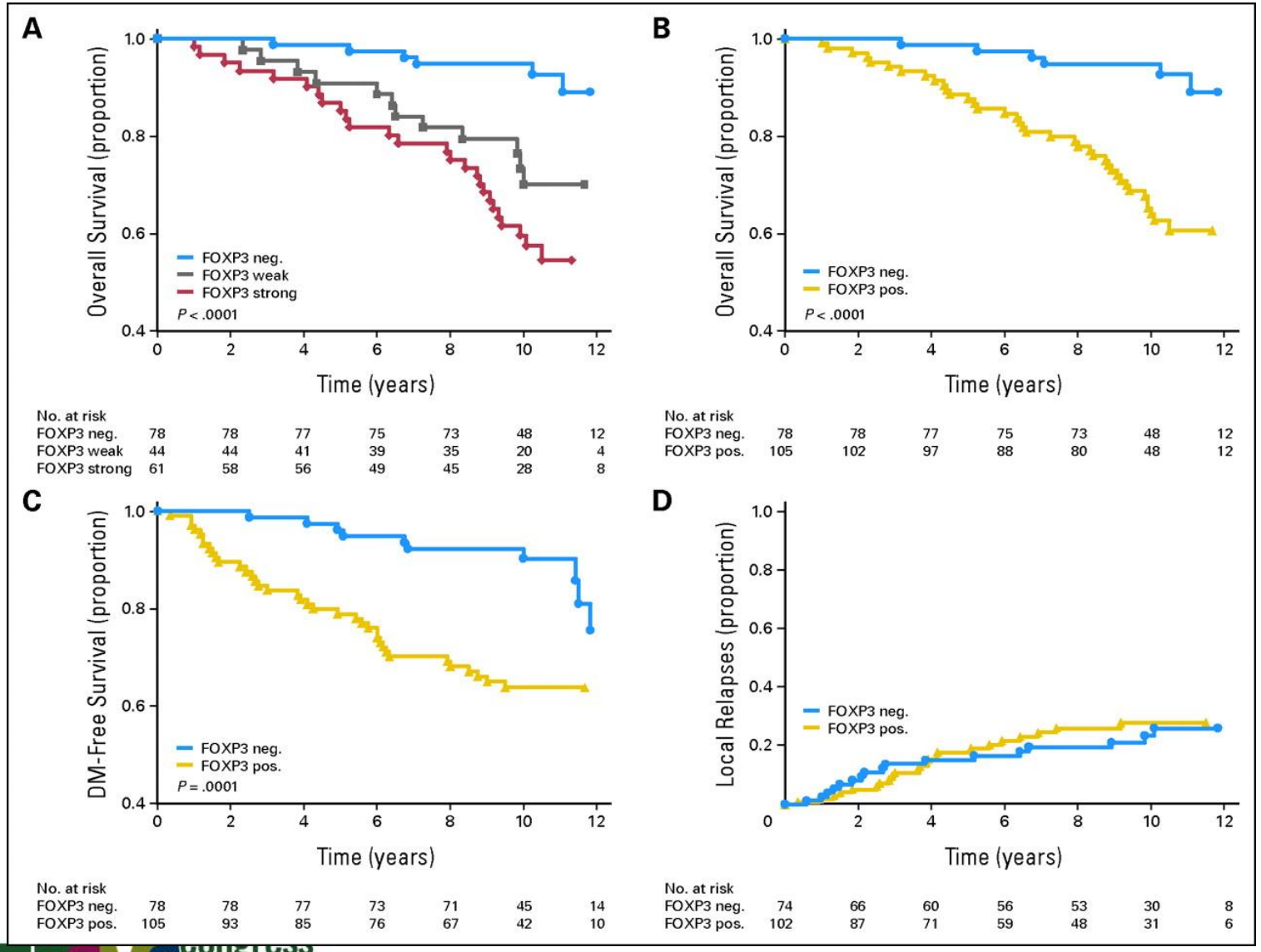


T_{reg} cells express high amounts of Foxp3 mRNA, protein

Modulation of immune responses by T_{reg} cells

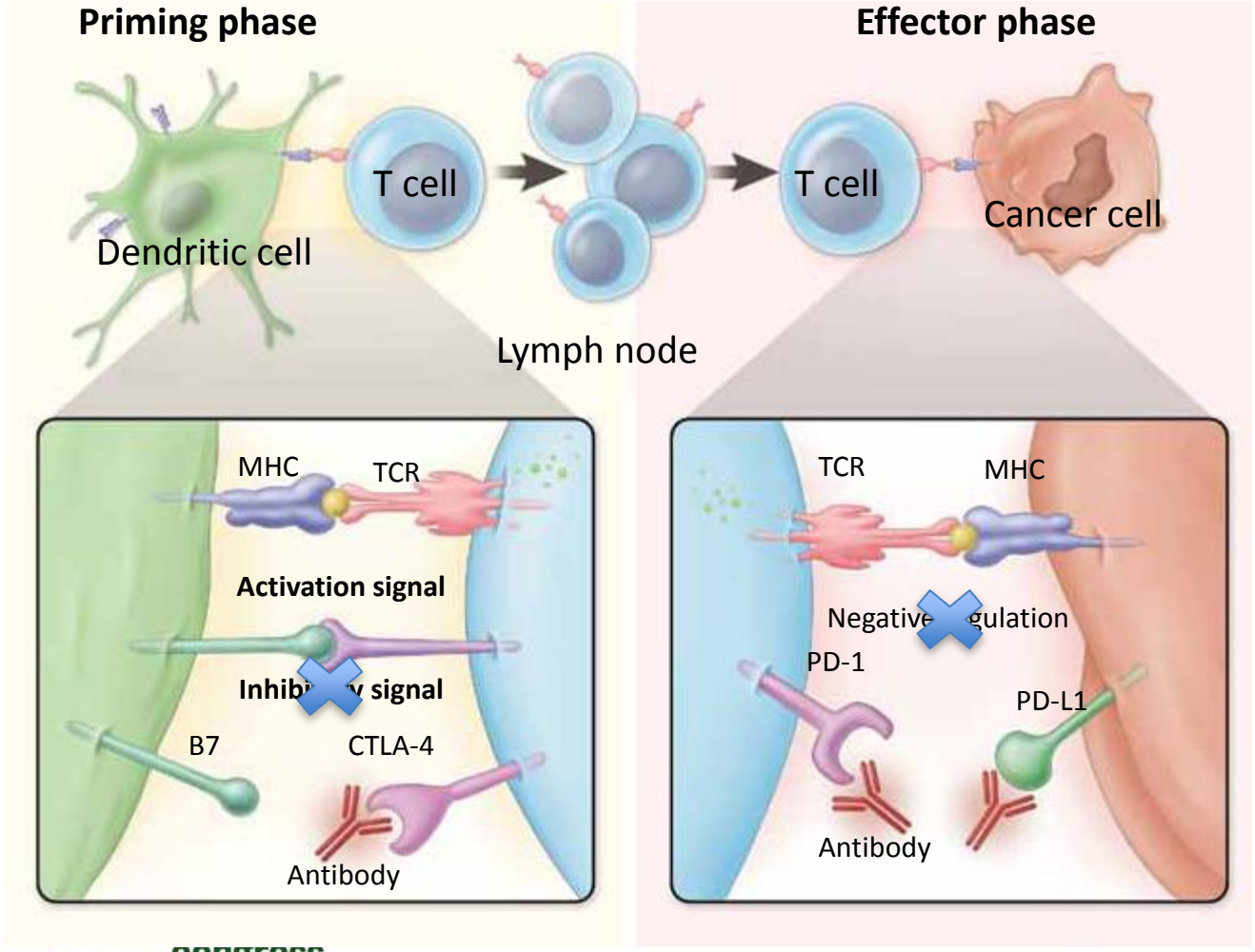


T_{reg} and breast cancer



Merlo A et al. JCO 2009;27:1746-1752

Targets for antibody therapy

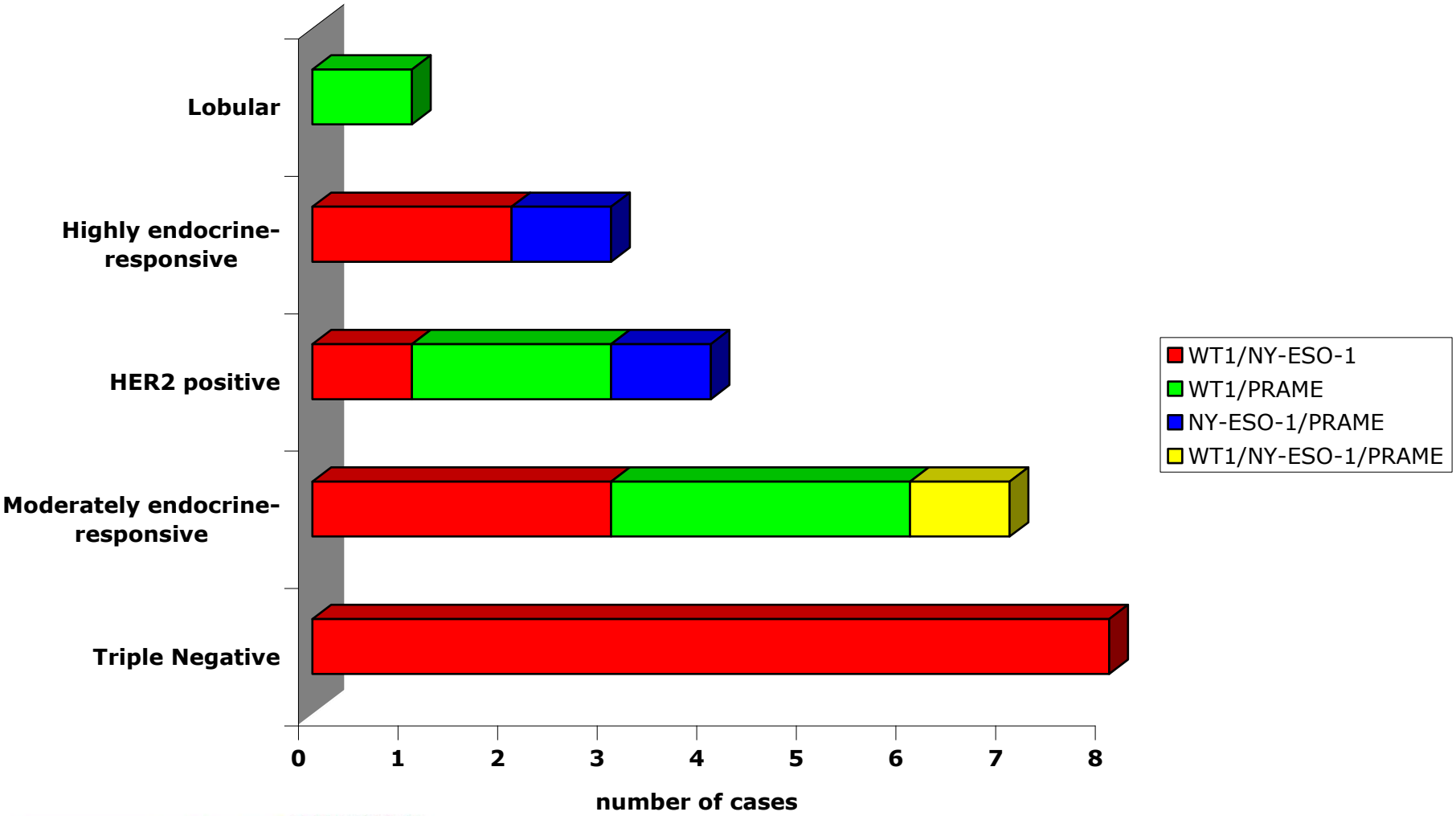


Anti–PD-1 Antibody in Breast Cancer

- PD-L1 but is highly expressed on the cell surface of breast cancer cells but not on normal breast epithelium.
- PD-Ligand blockade enhances CD8+ T cell proliferation and cell number in alloreaction with the MDA231 breast cancer cell line.
- Blockade of PD-L:PD-1 pathway enhances IFN-γ production in CD8 T cells in allo-reaction with the MDA231 breast cancer cell line.

Brown J, J Immunol. 2003 Feb 1;170(3):1257-66

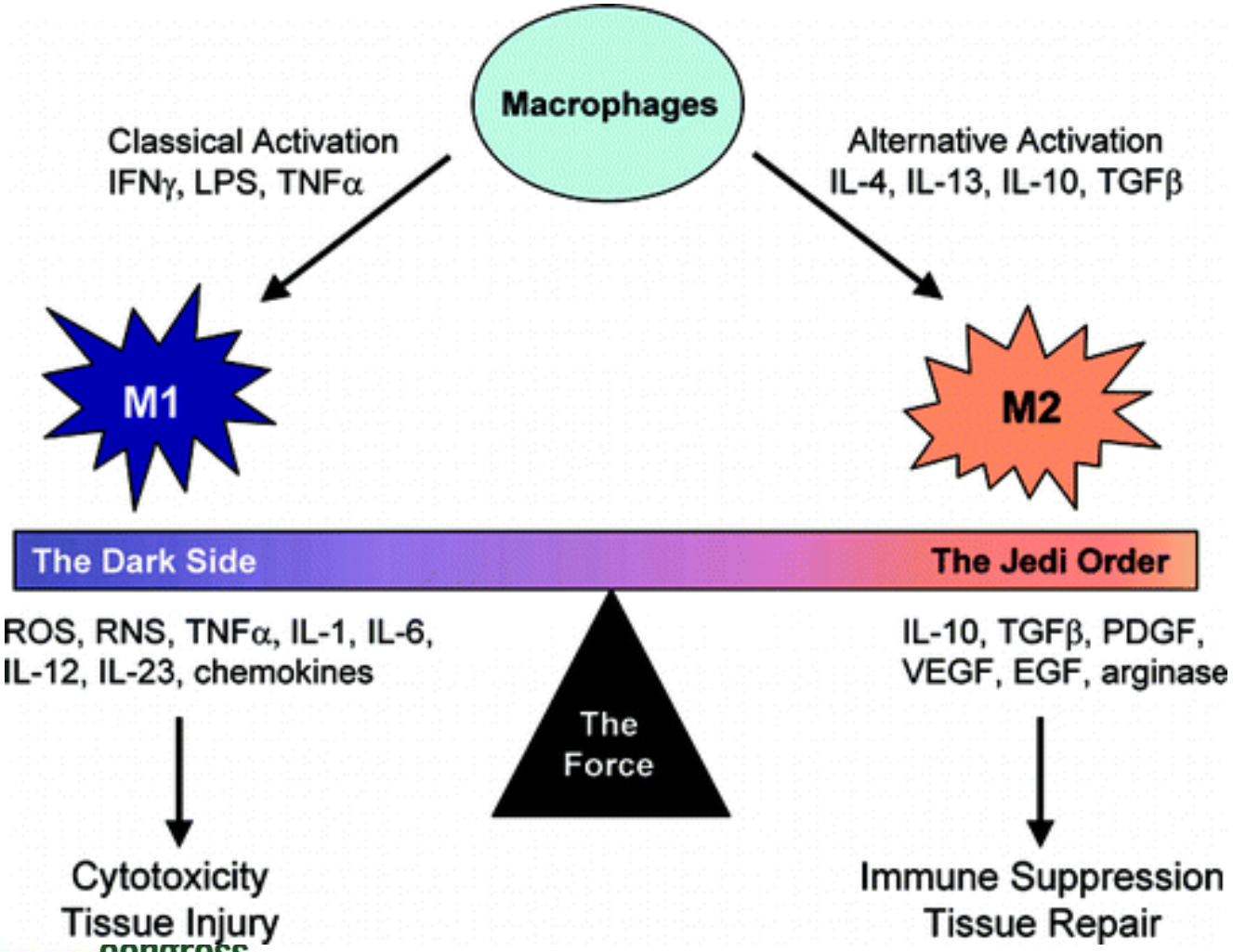
Antigens in breast cancer



Curigliano G and G. Viale, Data unsubmitted

Macrophage polarization

Central role in orchestrating the inflammatory response

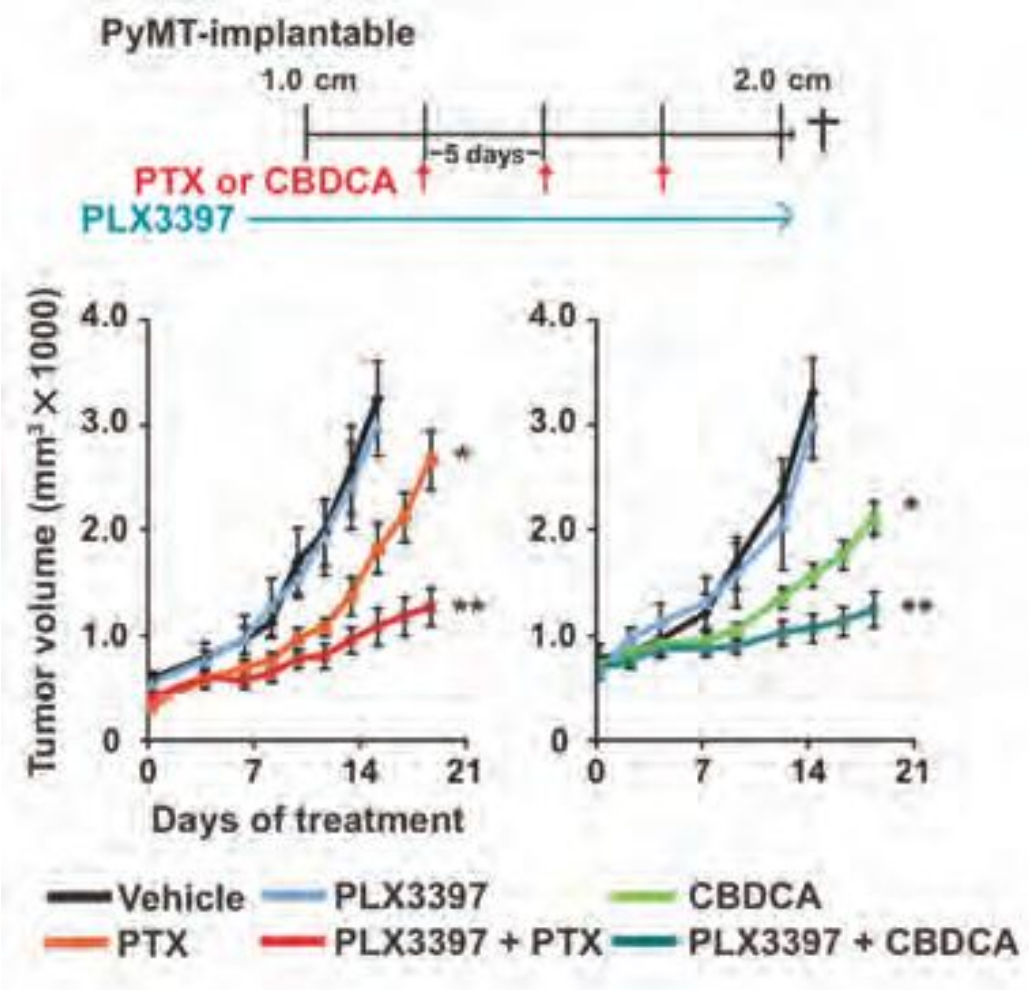


Targeting TAM to treat breast cancer?

- Cytotoxic therapies induce mammary epithelial cells to produce macrophage recruitment factors, including colony stimulating factor 1 (CSF1) and interleukin, which together enhance CSF1 receptor (CSF1R)–dependent macrophage infiltration
- Blockade of macrophage recruitment with CSF1R-signaling antagonists, in combination with paclitaxel, improved survival of mammary tumor–bearing mice by slowing primary tumor development and reducing pulmonary metastasis.

Denardo DG et al. Cancer Discov. 2011 Jun;1(1):54-67.

Targeting TAM to treat breast cancer?



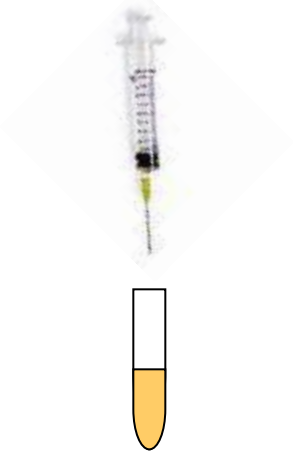
Denardo DG et al. Cancer Discov. 2011 Jun;1(1):54-67.

Tumor microenvironment

- *Sustaining proliferative signalling:* fibroblasts proximal to tumor are “educated”, differentiated into other cells
- *Resisting cell death*: CAFs can orchestrate functional attributes associated with epithelial-to-mesenchymal transition (EMT)
- *Activation of invasion and metastasis*: CAF-derived effector is the c-Met ligand HGF, which stimulates both invasiveness and proliferation

Adipocytes

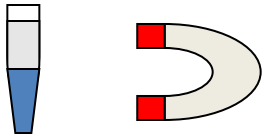
Abdominal or thigh Human white adipose tissue (WAT)



>150 samples

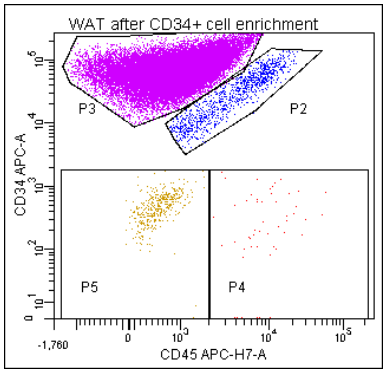
Enzymatic digestion

Stromal vascular fraction



Immunomagnetic separation

Purified CD34+ WAT-derived cells



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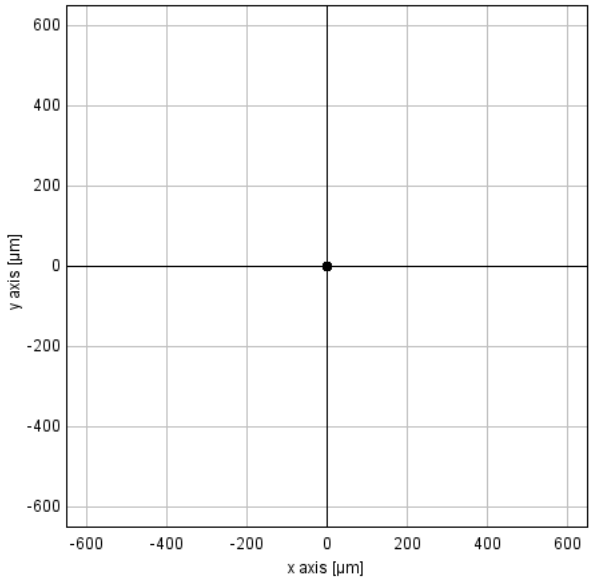
Courtesy dr Bertolini F.

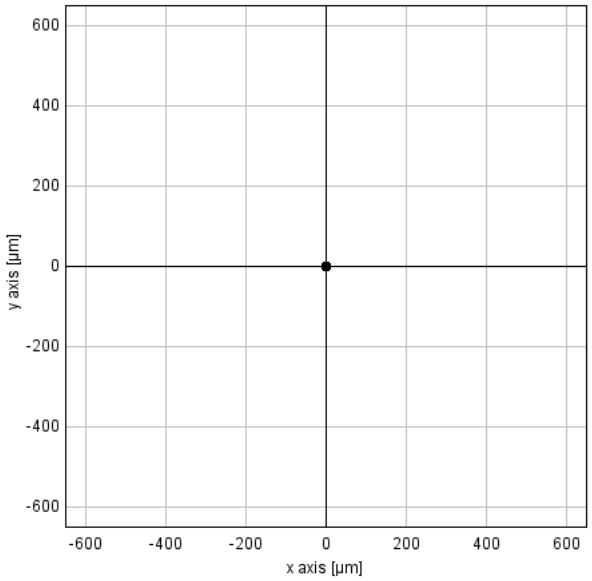
www.esmo2012.org

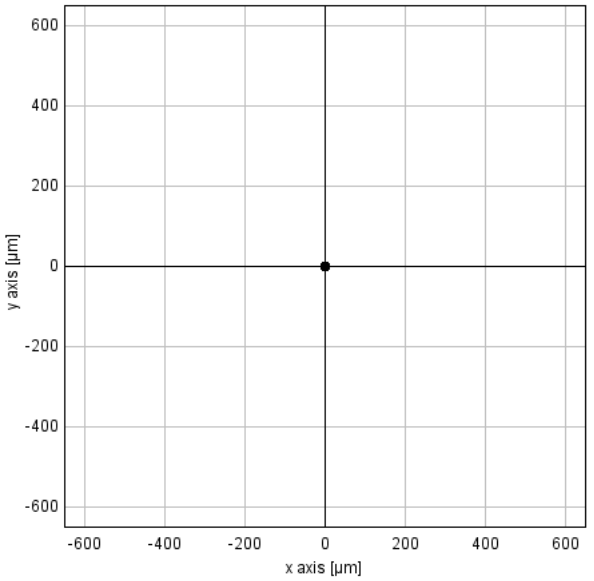
WAT cells increase tumor cell invasion *in vitro*

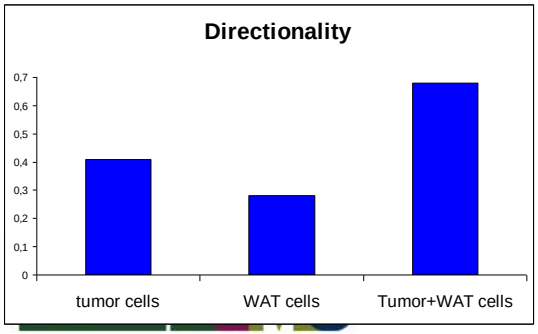
48h time lapse microscopy through a 3D collagen gel + EGF, HFG, PDGF and Insulin

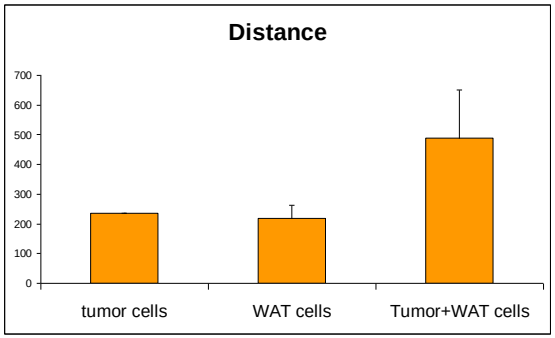
Breast cancer cells | **WAT** | **Cancer cells +WAT**

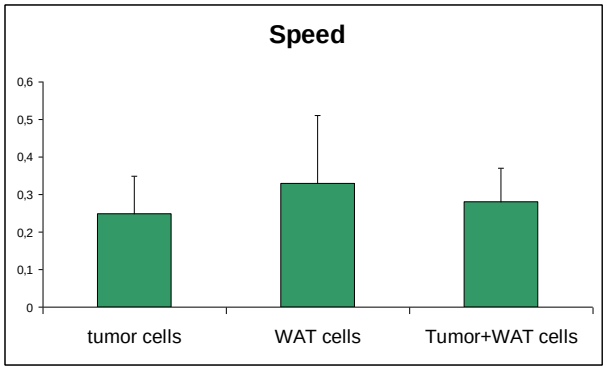






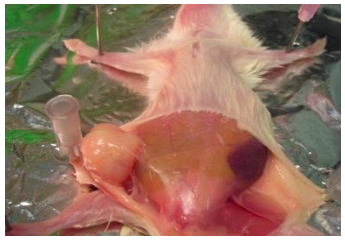




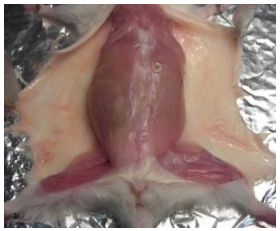


Courtesy dr Bertolini F.

WAT-derived cells increase lung metastases

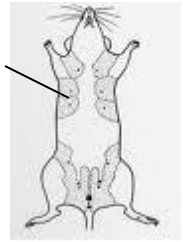


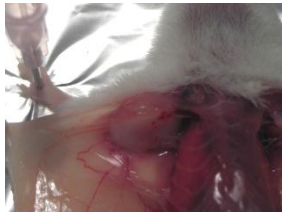
primary tumor



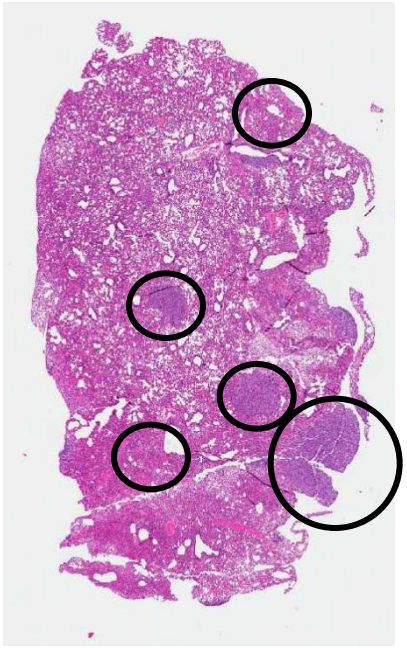
mastectomy

WAT cells

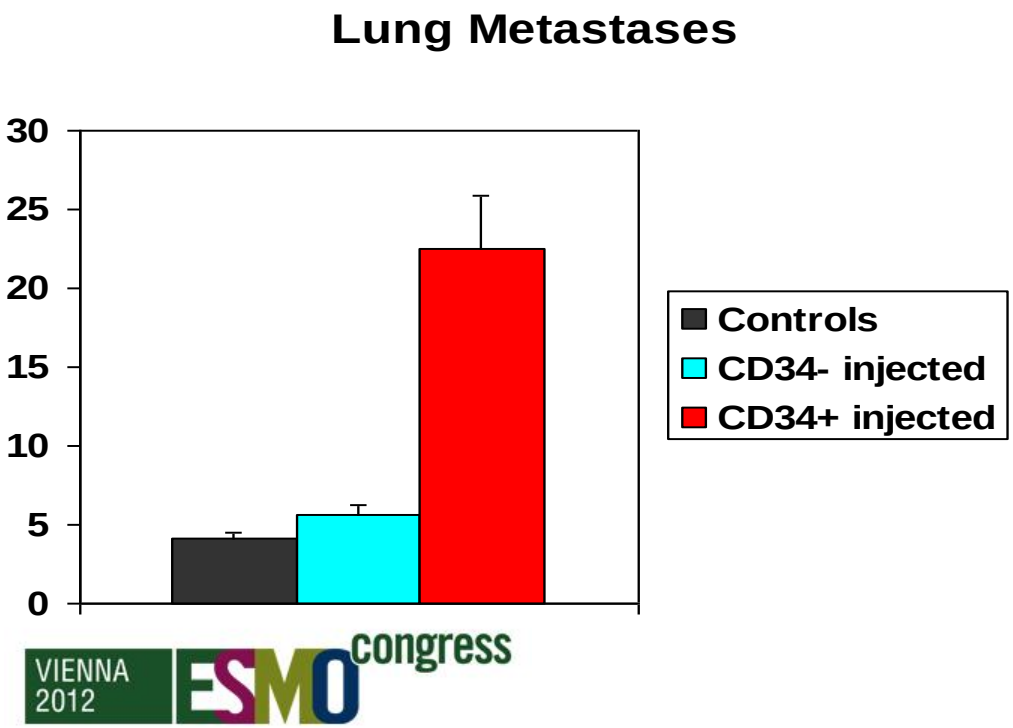




axillary lympho node metastases



lung metastases



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Courtesy dr Bertolini F.

Targeting the host in TNBC

- **Angiogenic vascular cells**: Explore new clinical setting and new combination schedules
- **Infiltrating immune cells**: Manipulate the immune system using available immune strategies: overcome tolerance and activate immune system
- **Tumor microenvironment**: Target pathways of communication between stromal and tumors cells

Thank you