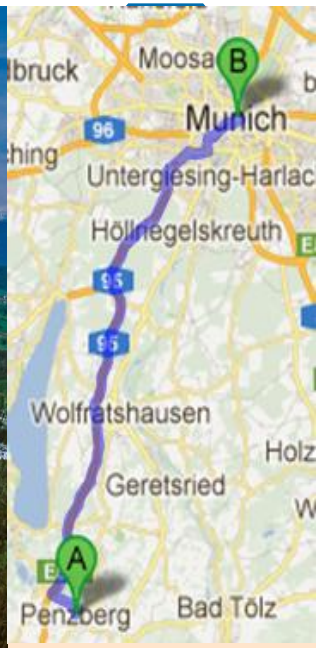
NCT Conference, Heidelberg, Germany, September 24, 2013

Roche Penzberg: A fully integrated Oncology R & D site with all key functions



Roche Penzberg, 30 km South of Munich and 25 km North of Garmisch. (A 6 minutes drive with your 911) With 5000 employees probably the largest R+D site in Europe

Manipulation of the Tumor Micro Environment by Depletion of Tumor Associated Macrophages

Klaus Bosslet, Head Discovery Oncology Penzberg, Pharma Research and early Development (pRED), Roche Diagnostics GmbH;

pRED Oncology
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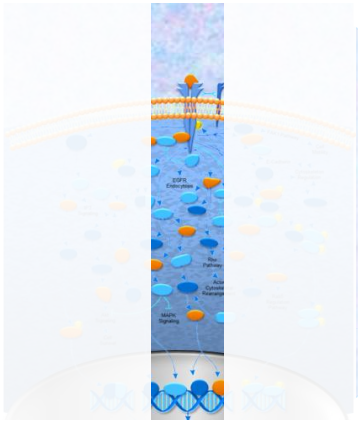
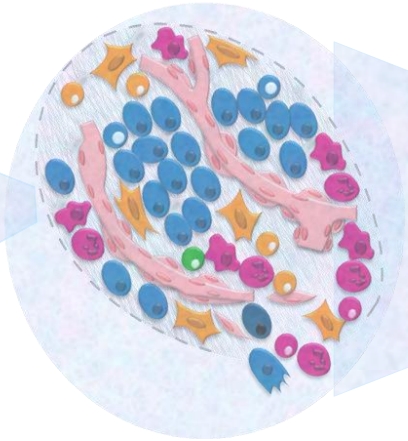
Vision – where the science is driving us

Understand patients and their disease to achieve CURE

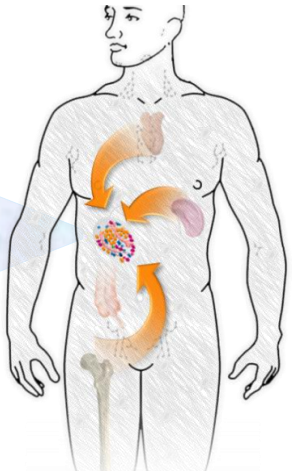
Dysregulated cell signaling



Tumor-Micro-Environment (TME)



Cancer Immunotherapy



Cancer cell-directed targets

- Signalling inhibition (e.g. ALK; HER3)
- Apoptosis induction (e.g. targeted IT)
- Tumor Suppression (e.g. MDM2)

Modulate immuno suppressive TME

- Elimination and switching of M2 macrophages (e.g. CSF1R Mab, AICs)
- Anti-Angiogenesis (e.g. Ang2/VEGF Mab)

Engage host immune response via

Systemic modulation of immunity

Tumor targeted immune modulation

- Glyco-enhanced Abs
- Cytokine Ab fusions
- T-cell bispecific Abs

Individually necessary but not sufficient. CURE requires a multi-paradigm approach.

Modulation of the Tumor Micro Environment

Cancer drugs with „step change potential“ have to overcome these Treatment Barriers

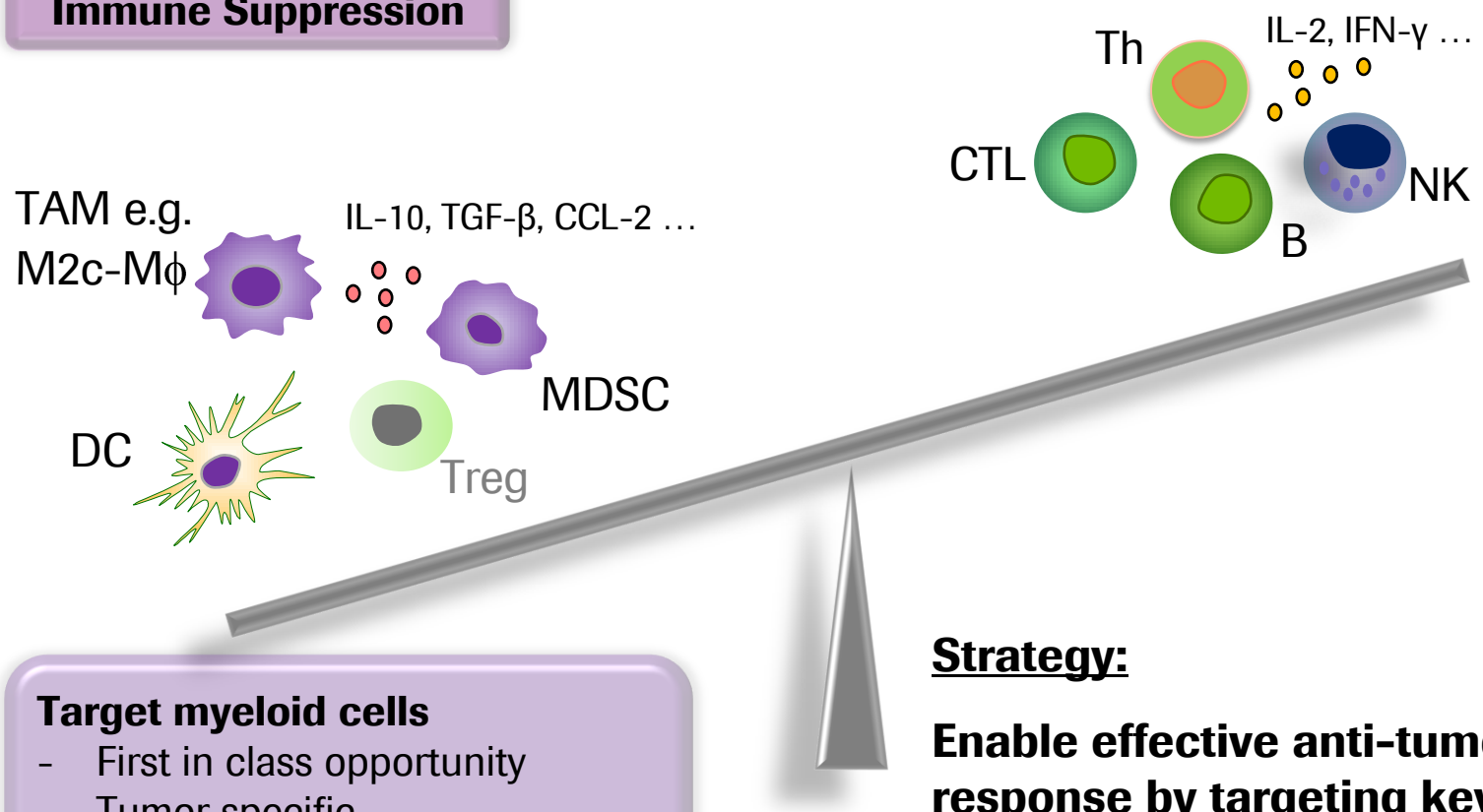
Treatment Barriers in Tumor Micro Environment

- **Tumor heterogeneity:**
  Molecular and cellular heterogeneity of tumor cell population => limits efficacy of targeted signal transducing and apoptosis inducing drugs
- **Cancer initiating cells:**
  A quiescent cell within the tumor micro environment with the potential to generate a new tumor being vastly resistant towards anti proliferative drug therapy
- **Tumor supportive ECM:**
  Connective tissue and CAFs generate a pro-tumorigenic milieu, produce growth factors contributing to resistance towards targeted drugs
- **Aberrant vascular network:**
  Limits accessibility for both low molecular as well as high molecular weight drugs
- **Immuno suppressive phenotype:**
  Accumulation of anergic immune and inflammatory cells within the tumor mass (T-reg and M2 MΦ accumulation)
  => T-cells activated by peripheral immunisation show limited efficacy in the established tumor micro environment

Tumors escape host immune response by inducing an immuno- suppressive Tumor Microenvironment (iTME) by recruitment of myeloid cells

Tumor Immunity

Immune Suppression



Target myeloid cells

- First in class opportunity
- Tumor specific
- Low risk for autoimmunity

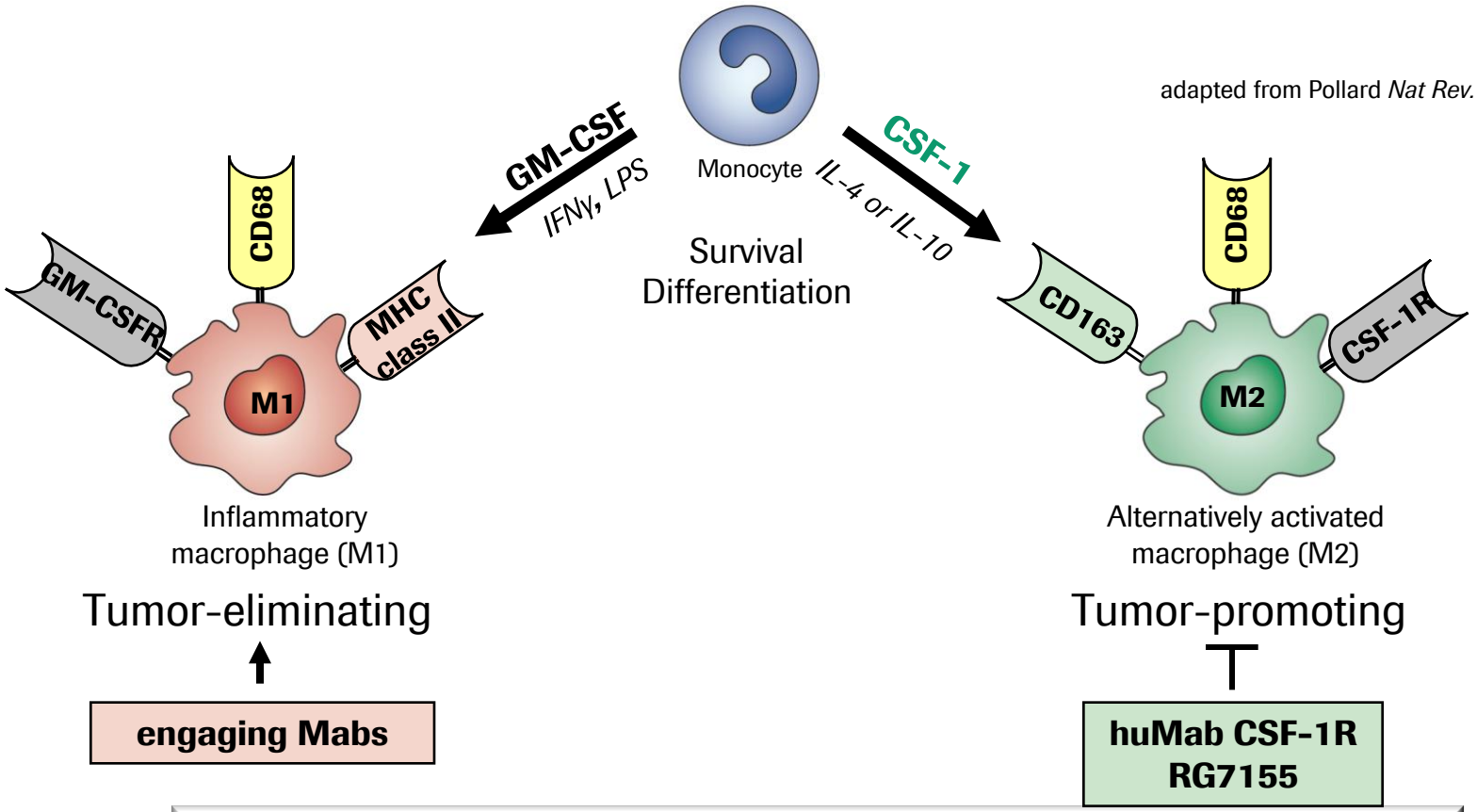
Strategy:

Enable effective anti-tumor immune response by targeting key immunosuppressive myeloid cells

CSF-1R as Survival and Differentiation Factor for TAMs

Tumor associated macrophages are alternatively activated M2 -Mφ

M2-Mφ can be discriminated from M1-Mφ by differential expression of scavenger receptor CD163



Depletion of M2-Mφ by anti-CSF-1R therapy offers opportunity

- to inhibit various signaling and effector molecules at the same time
- to target genetically stable cells in contrast to genetically instable tumor cells

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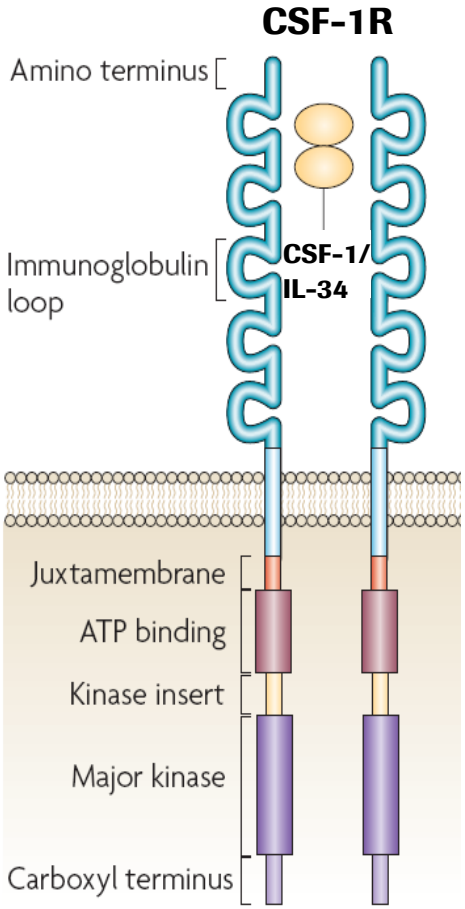
Colony-Stimulating Factor-1 Receptor structure

Binding of CSF-1 or IL-34 induce homodimerization



Adapted from Hamilton J *Nature Rev Immunol* . 2008; 8(7):533-544

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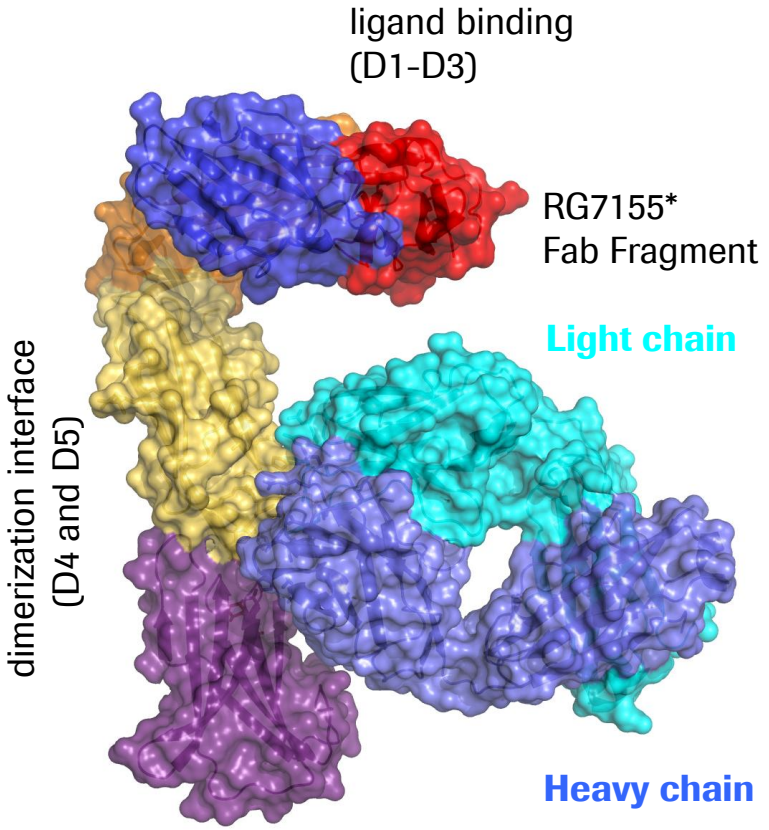
RG7155, a novel humanized FIC anti-CSF-1R mAb

Highly potent, specific and purely antagonistic CSF-1R inhibitor



Summary of key data for RG7155

Isotype:	IgG1
Binding to domain in CSF-1R ECD:	domain D4/D5
Affinity to human CSF-1R (Biacore):	<1nM
Affinity to Cynomolgus CSF-1R (Biacore):	<1nM
Inhibition of pCSF-1R*:	<2 nM
Inhibition of CSF-1/CSF-1R complex formation IC_{50}:*	<1 nM
Monocyte survival assay IC_{50}:	<1 nM
Osteoclast differentiation assay IC_{50}:	<3 nM
Activation of monocytes:	none
NIH3T3 CSF-1R (L301S,Y969F) viability IC_{50}:	<100nM

* Chimeric antibody variant

Data: Kaluza, Scheiblich, Lanzendörfer, Fertig/Runza and Dimoudis labs,
Crystal structure: J. Benz and I. Gorr and team pRED Basel and Penzberg

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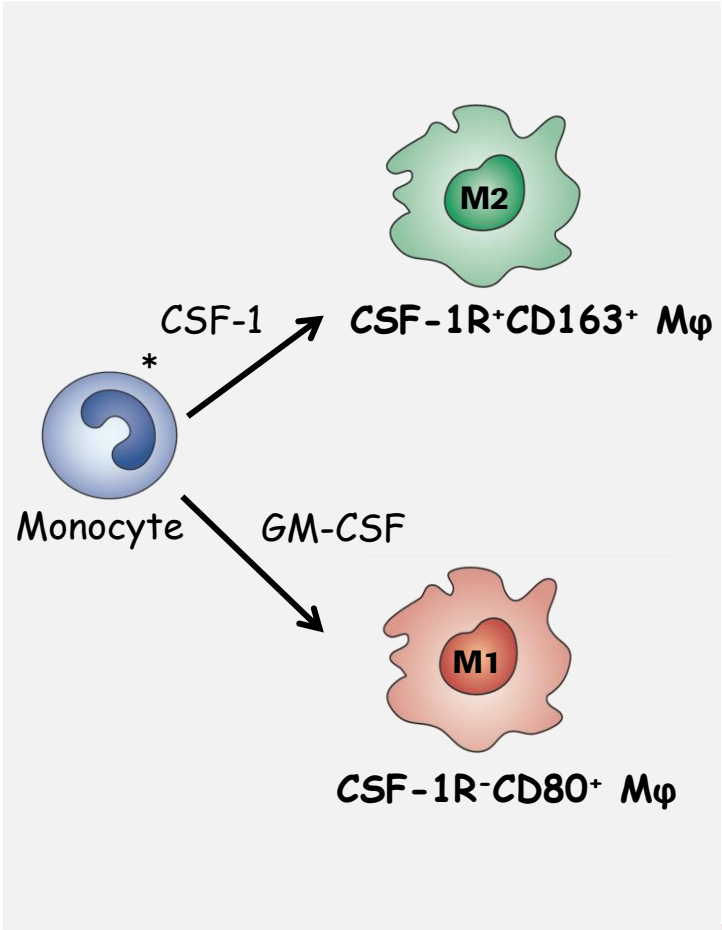
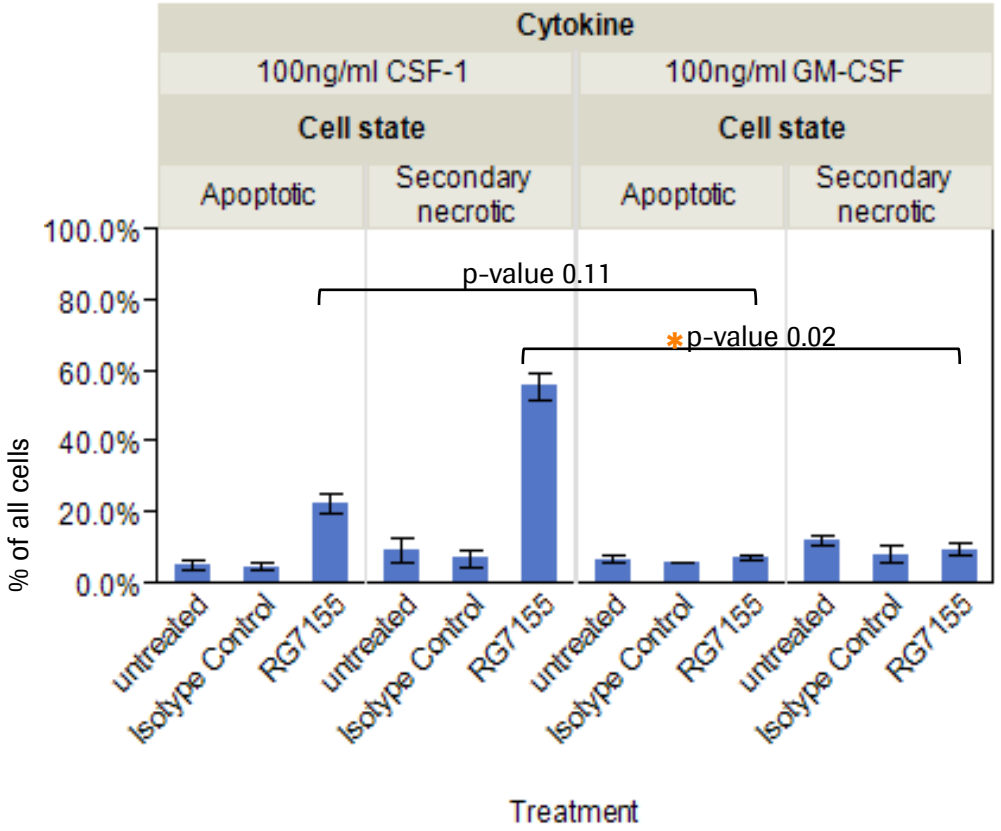
RG7155 targets essential Mφ pathway

RG7155 induces cell death of M2-like CSF-1R^{+}CD163^{+} Mφ





*adapted from J. Pollard *Nat Rev Immunol.* 2009; 9(4):259-270

Data: Valeria Runza lab pRED Penzberg

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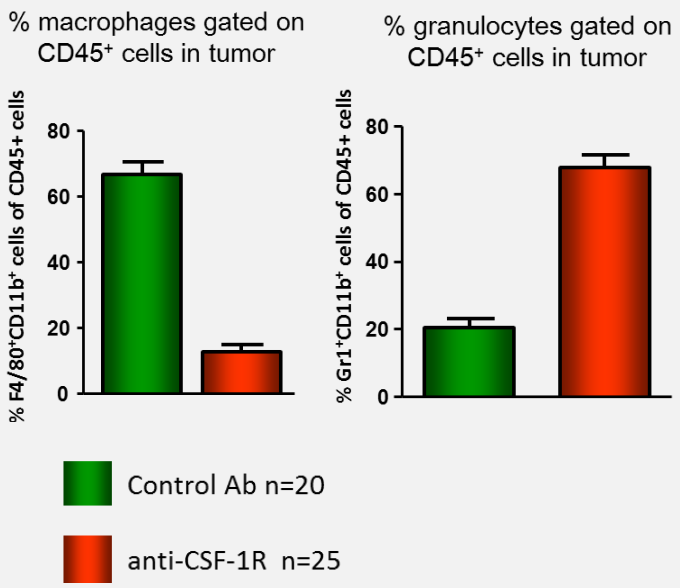
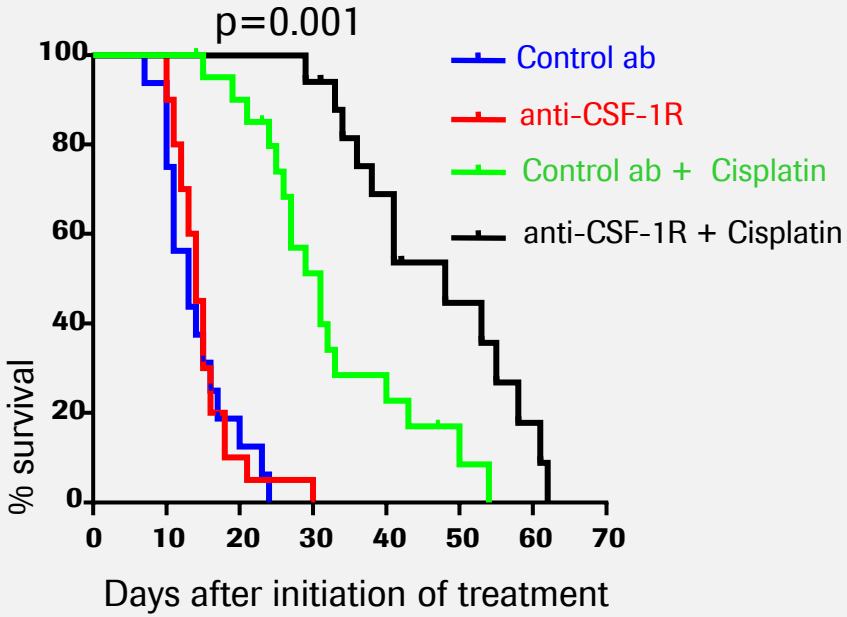
Anti–CSF-1R mAb in transgenic BC model

Targeting mouse CSF-1R enhances efficacy of chemotherapy





Karin deVisser lab Netherlands Cancer Institute, Amsterdam

Oral Presentation Metamia Ciampricotti, Keystone Symposium Dublin 2012

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