Engineered Anti-Cancer Antibodies with Enhanced Effector Functions

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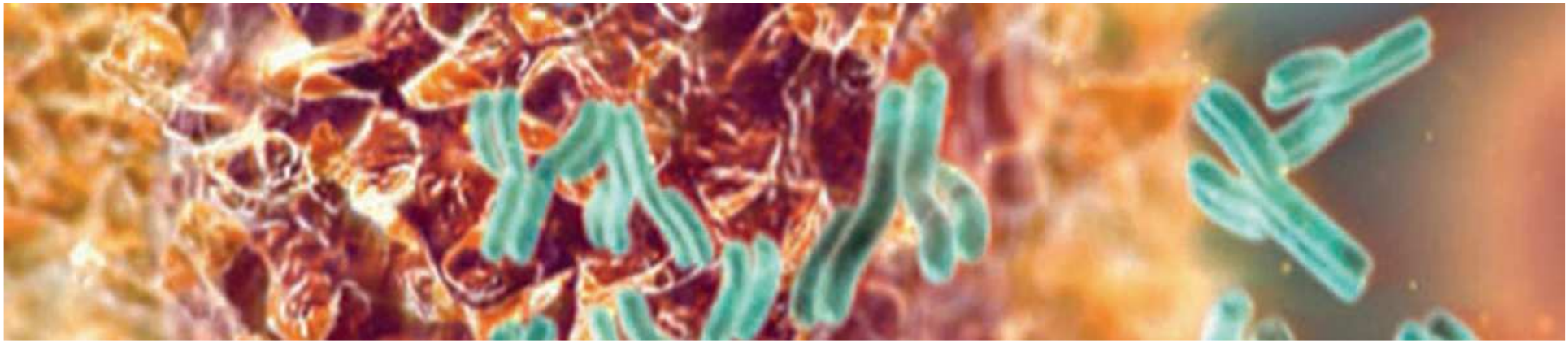
Roche Glycart

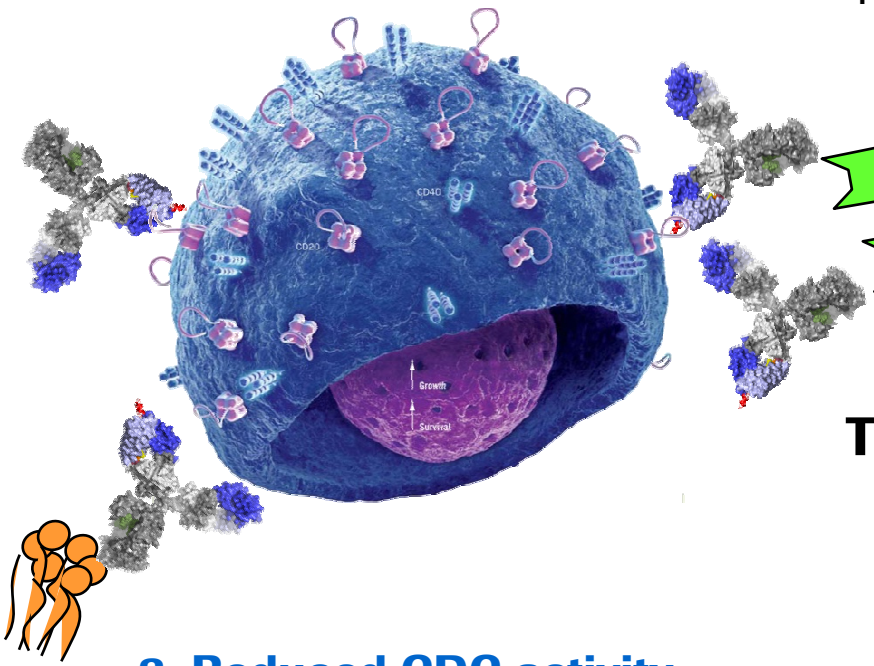
October 1, 2010



GA101: Mechanisms of action

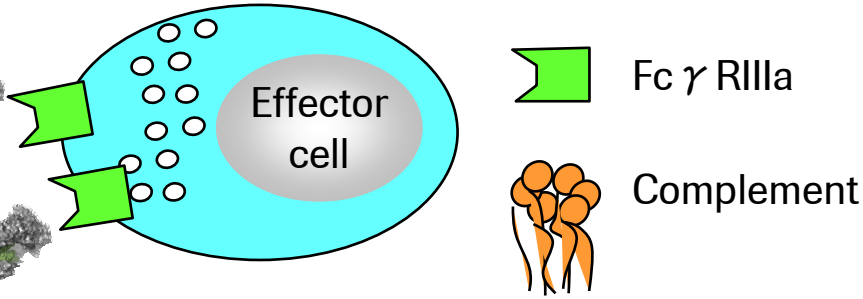
1. Increased direct cell death

Type II antibody & elbow-hinge modification



2. Increased ADCC

Higher affinity to the 'ADCC receptor'
Fc γ RIIIa (GlycoMab TM technology)



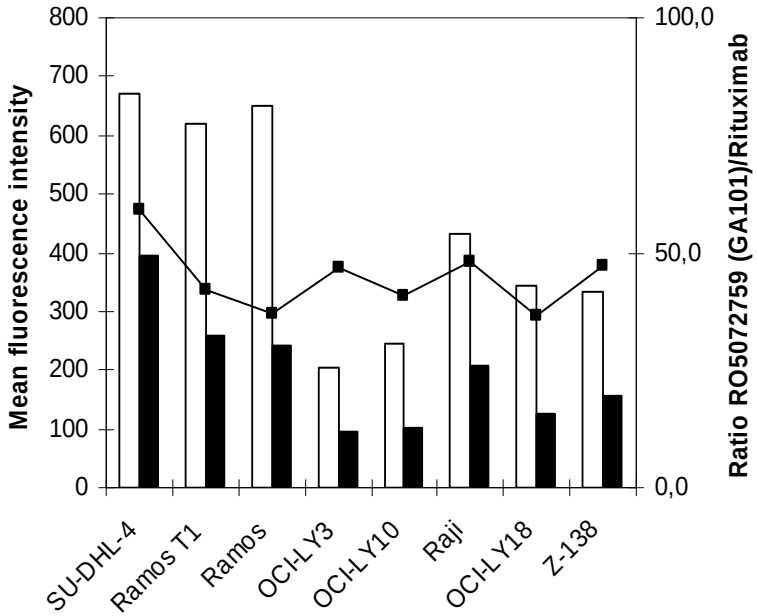
Type II CD20 antibody

3. Reduced CDC activity

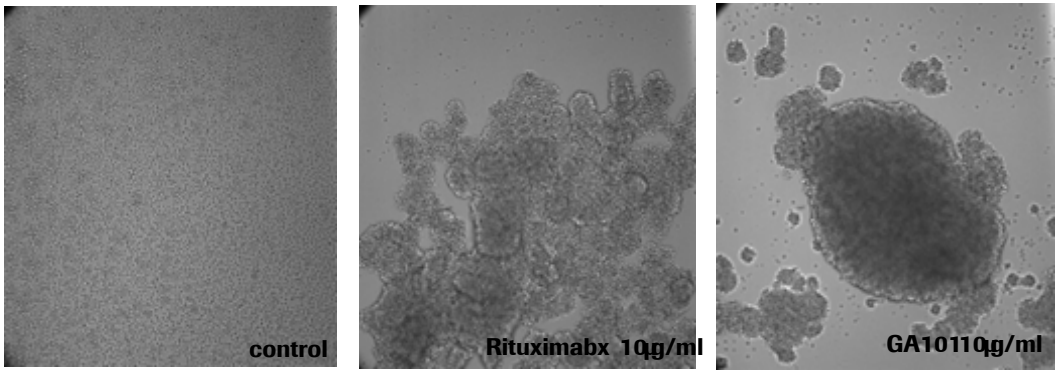
Type II antibody

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity

GA101: A typical type II CD20 antibody



Half-maximal binding of GA101

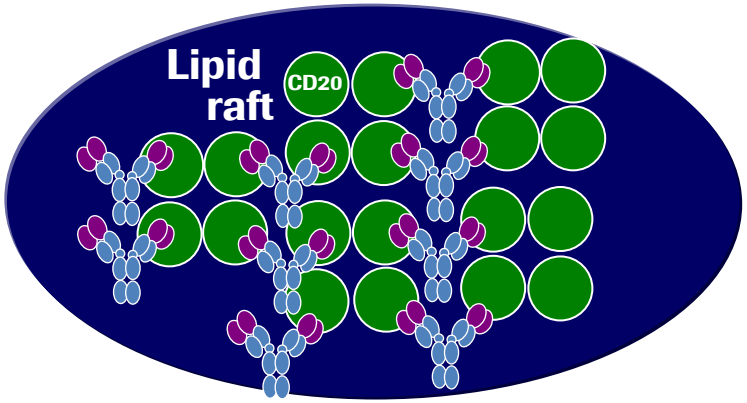


Induction of homotypic aggregation

Mössner E, et al. Blood 2010. 115(22): p. 4393-402

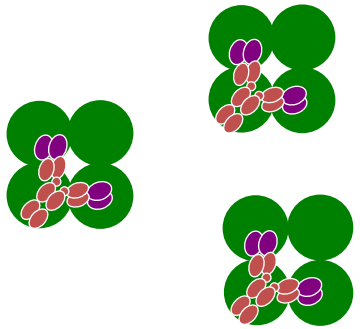
A model for Type I and type II CD20 binding?

Type I antibodies

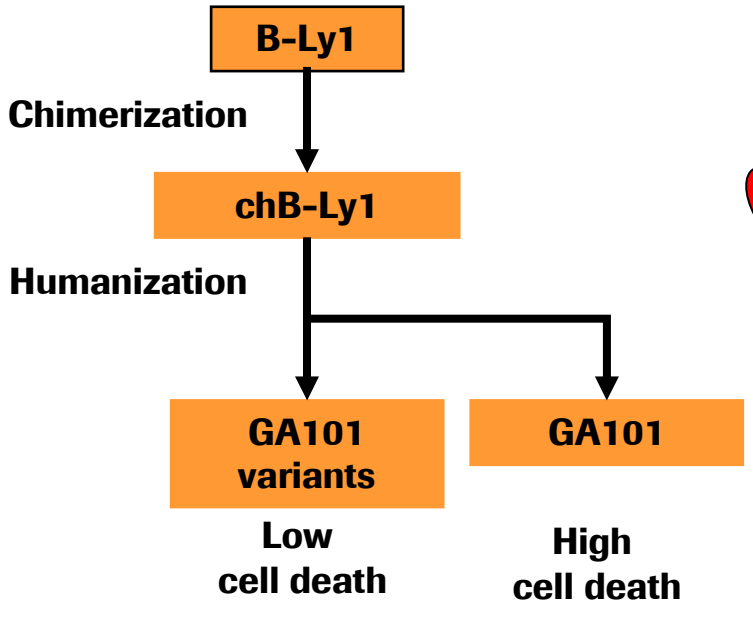


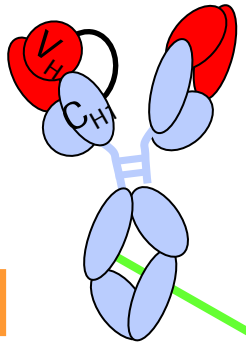
Type I:Type II
2:1

Type II antibodies

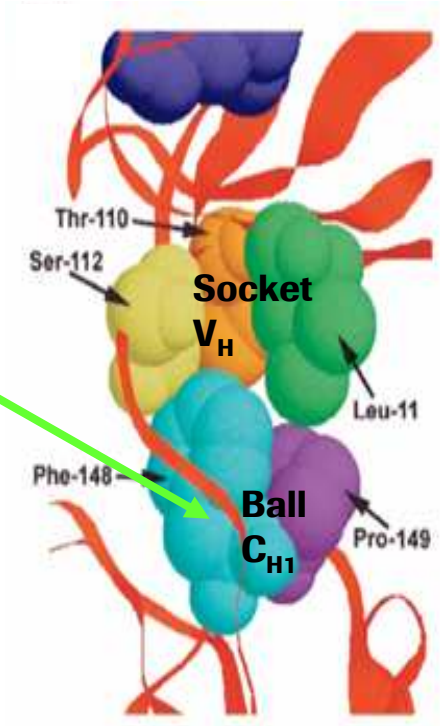


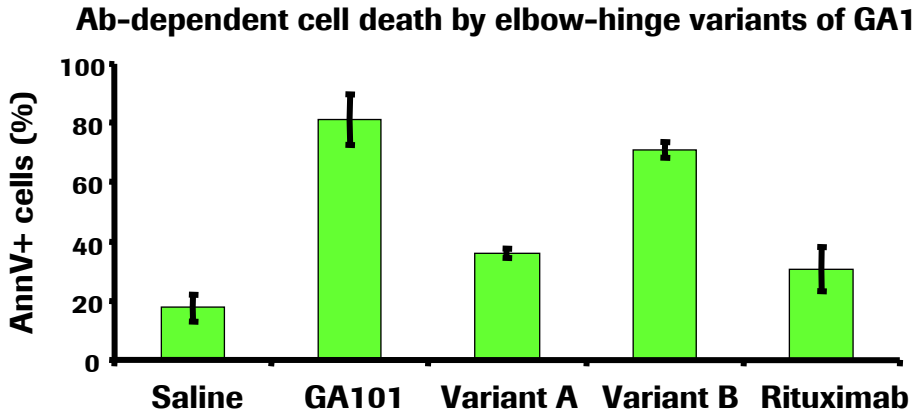
GA101: Elbow hinge amino acid exchanges can reduce the enhanced cell death induction





Elbow-hinge variants

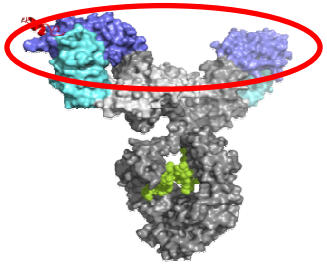




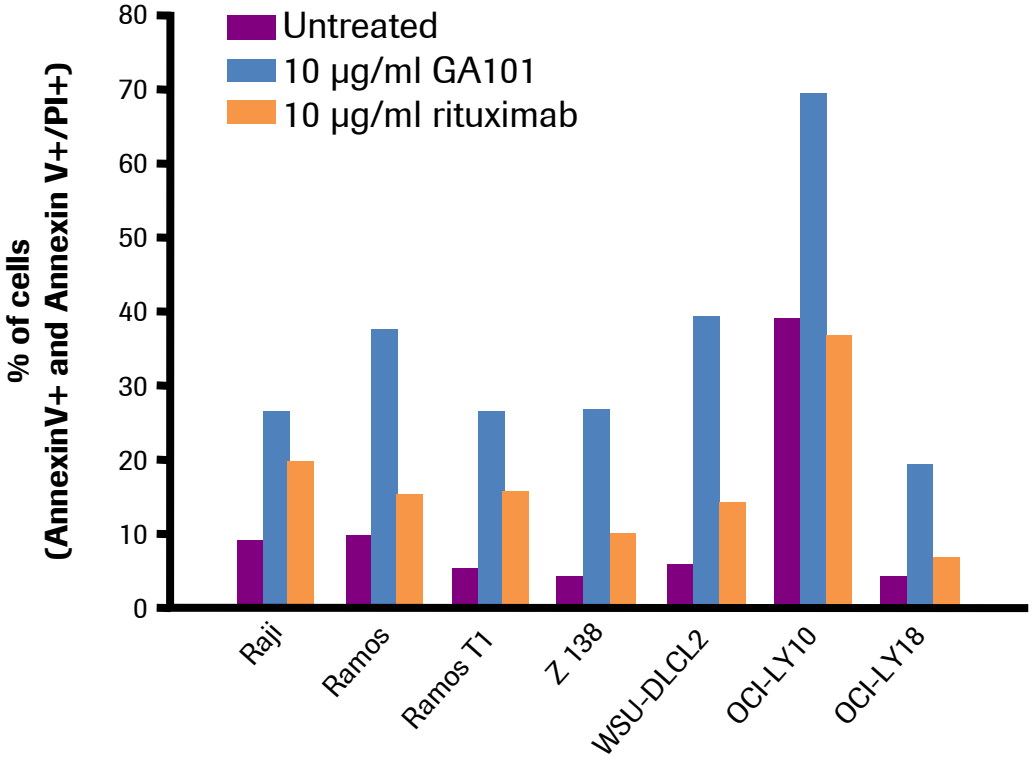
Data: E. Mössner

The type II mode of binding leads to increased direct cell death induction of tumour cells

Type II → ***Increased direct cell death***



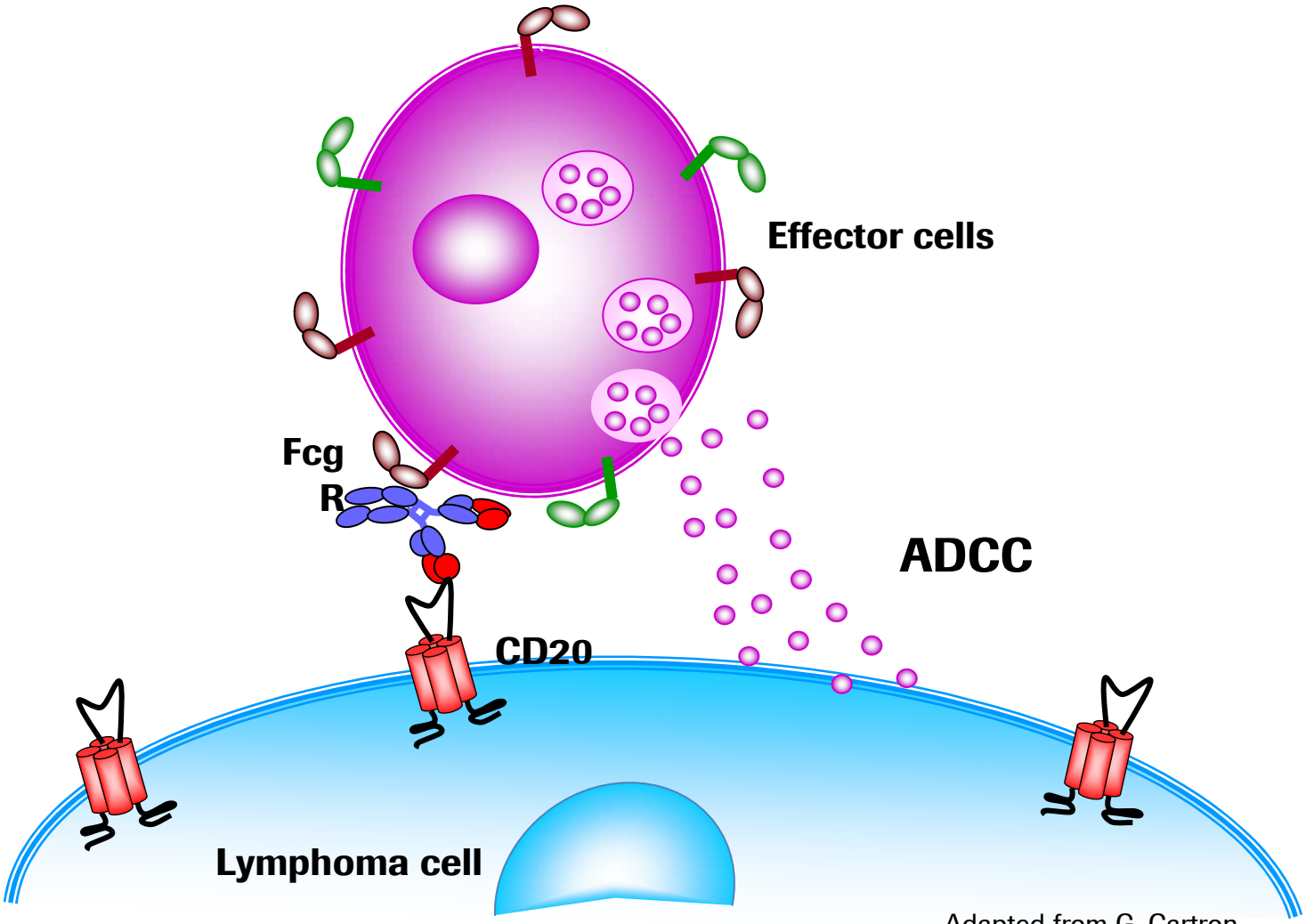
Direct cell death with GA101 vs rituximab



Type II mAbs (vs. Type I)
↑ Direct cell death
↓ CDC
ADCC activity
CD20 not localised to lipid rafts

Mössner E, et al. Blood 2010. 115(22): p. 4393-402

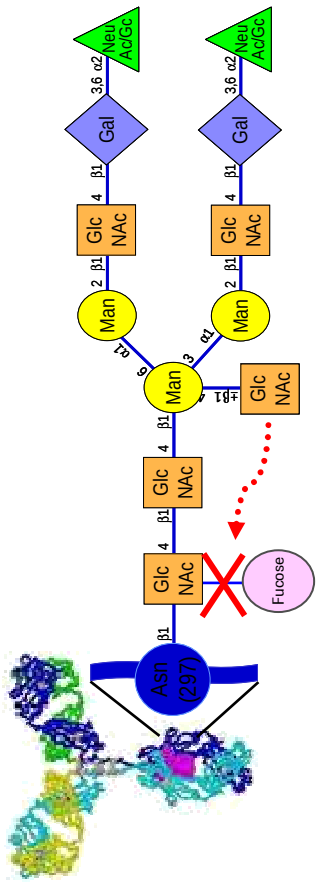
FcR related effector cell activities

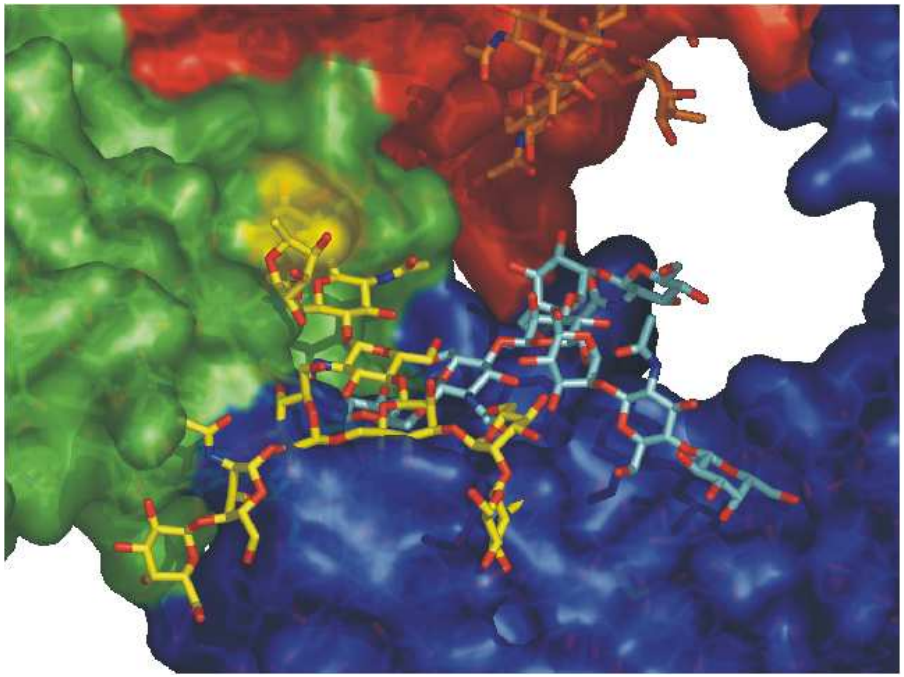


Adapted from G. Cartron

Enhancing ADCC via Fc-Glycoengineering

GlycoMAb™ technology: genetic engineering of CHO cell lines to produce antibody glycosylation variants with increased affinity to FcγRIIIa receptors and enhanced ADCC



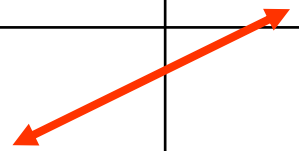


Increased affinity between antibody and FcγRIIIa receptor on killer cells by removal of core fucose

Ferrara C, et al. J Biol Chem. 2006;281:5032–36

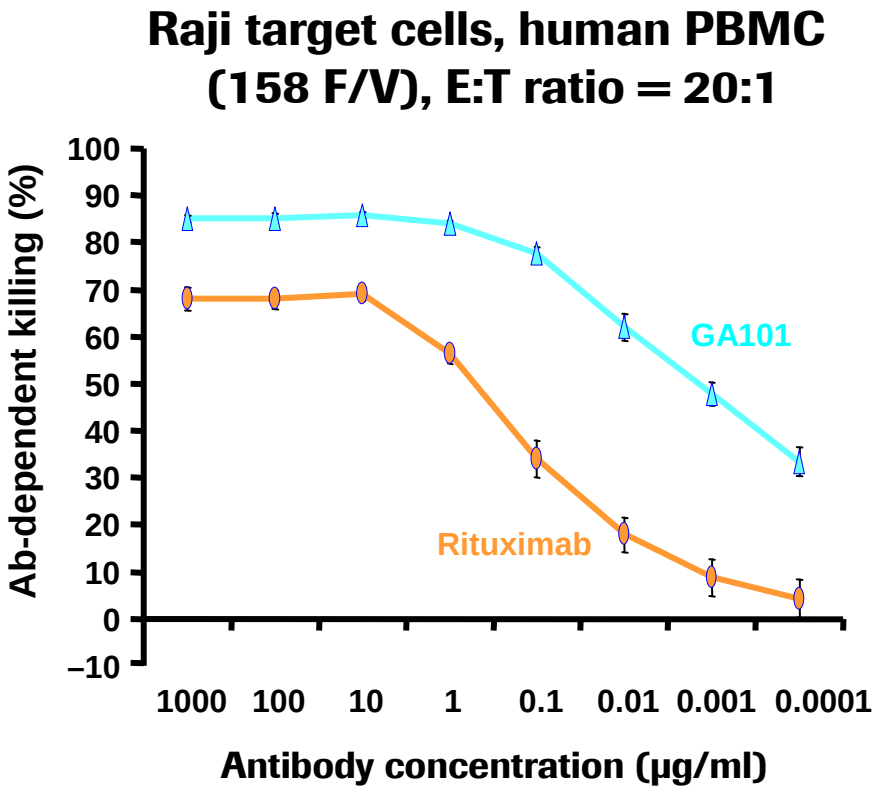
Glycoengineering brings Fc-FcγRIIIa binding to a high affinity range for the whole population

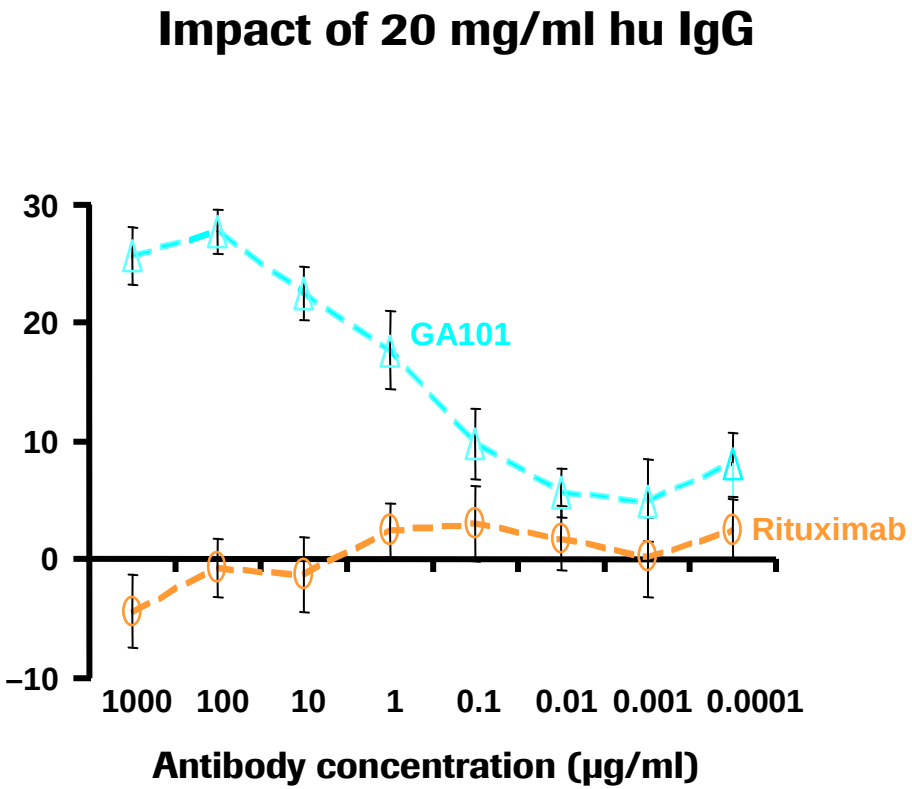
Binding Constants	Low Affinity (158F)	High Affinity (158V)
Unmodified AB	5000 nM	750 nM
Glycoengineered	150 nM	15 nM



Ferrara, C. *et al.* (2006), *J. Biol. Chem.* 281, 5032-6.

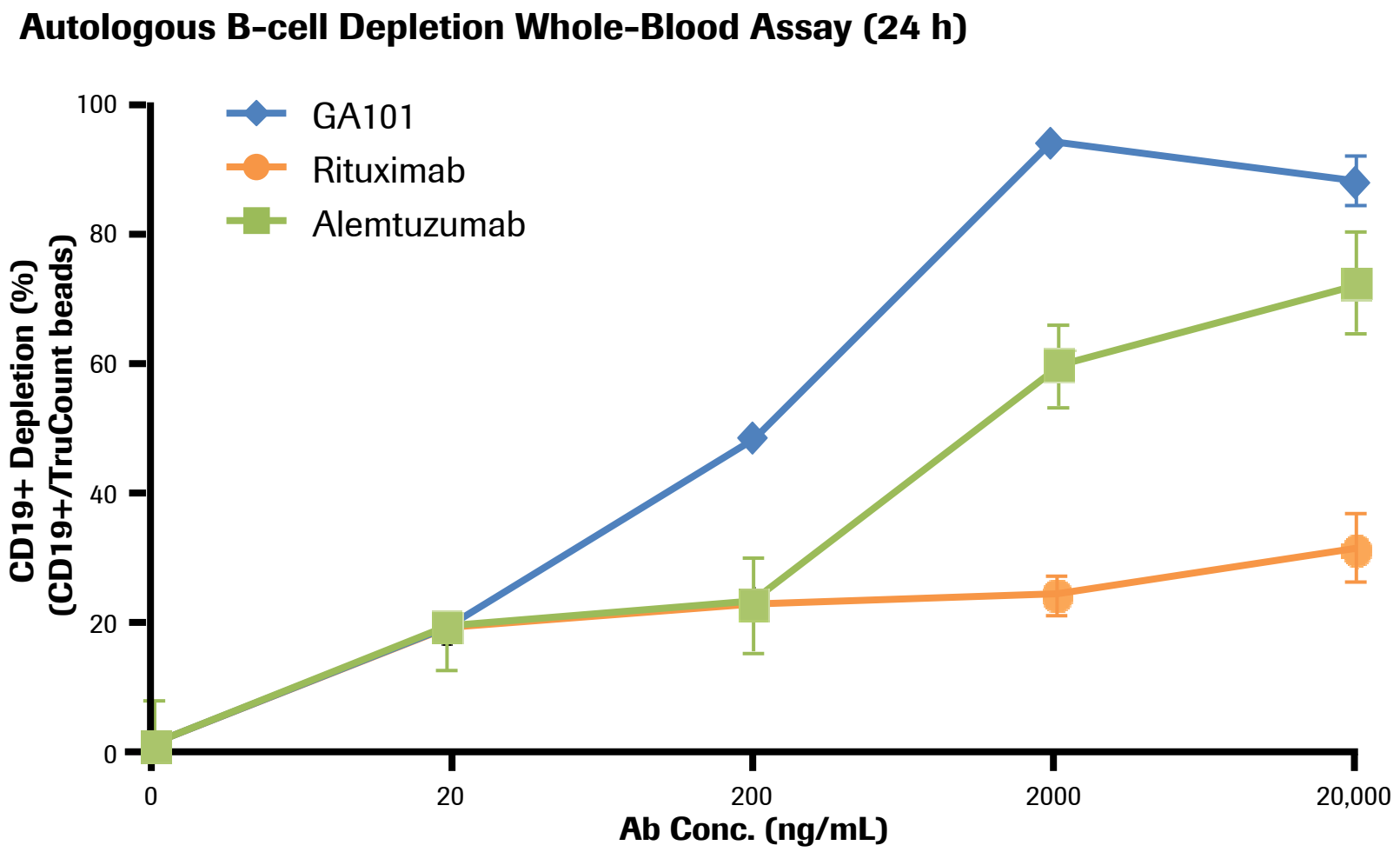
Glycoengineered GA101 shows enhanced ADCC vs rituximab





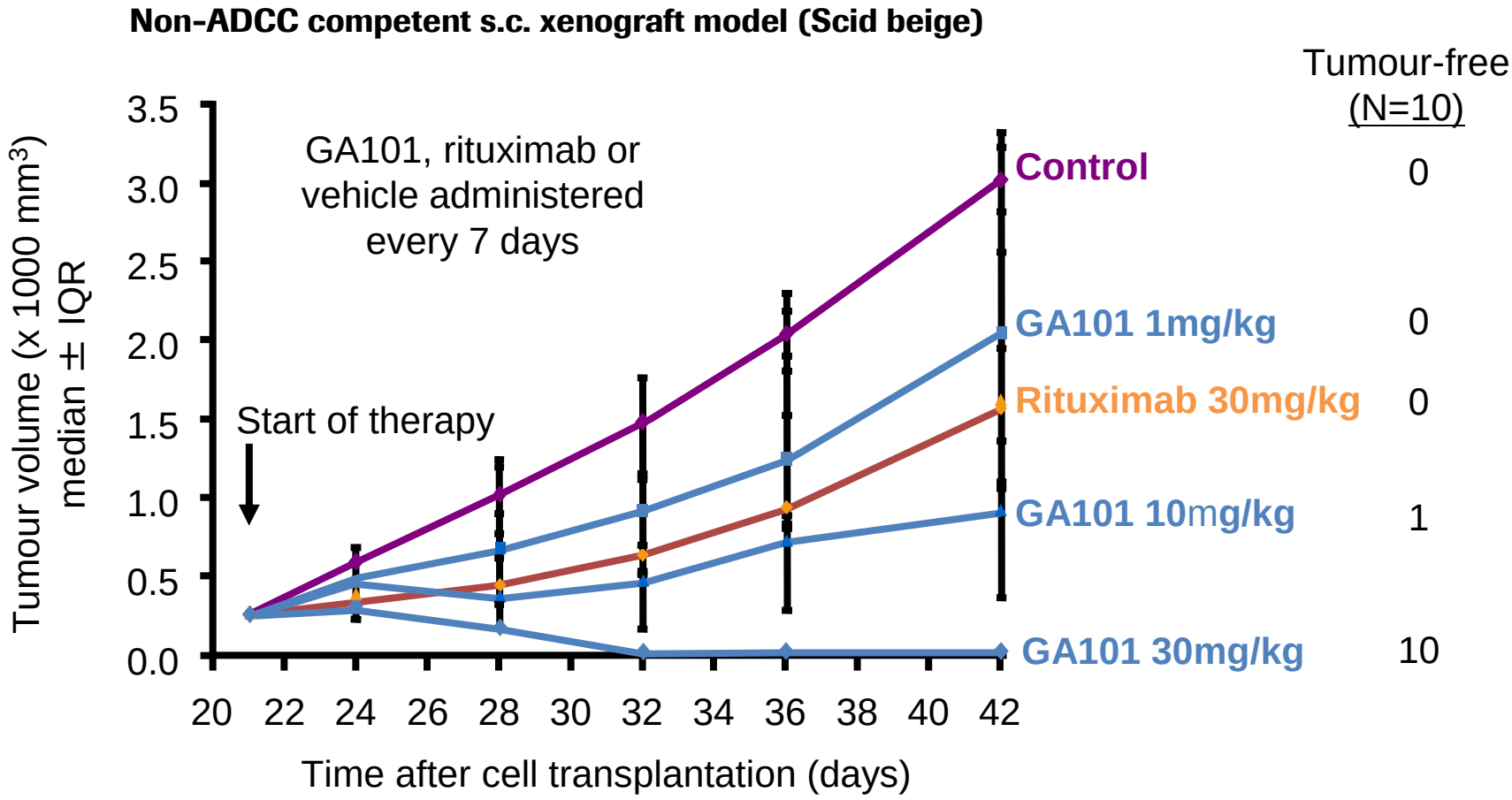
Data: R. Grau

Superior whole blood B-cell depletion by GA101 in blood from B-CLL patient



Mössner E, et al. Blood 2010. 115(22): p. 4393-402;

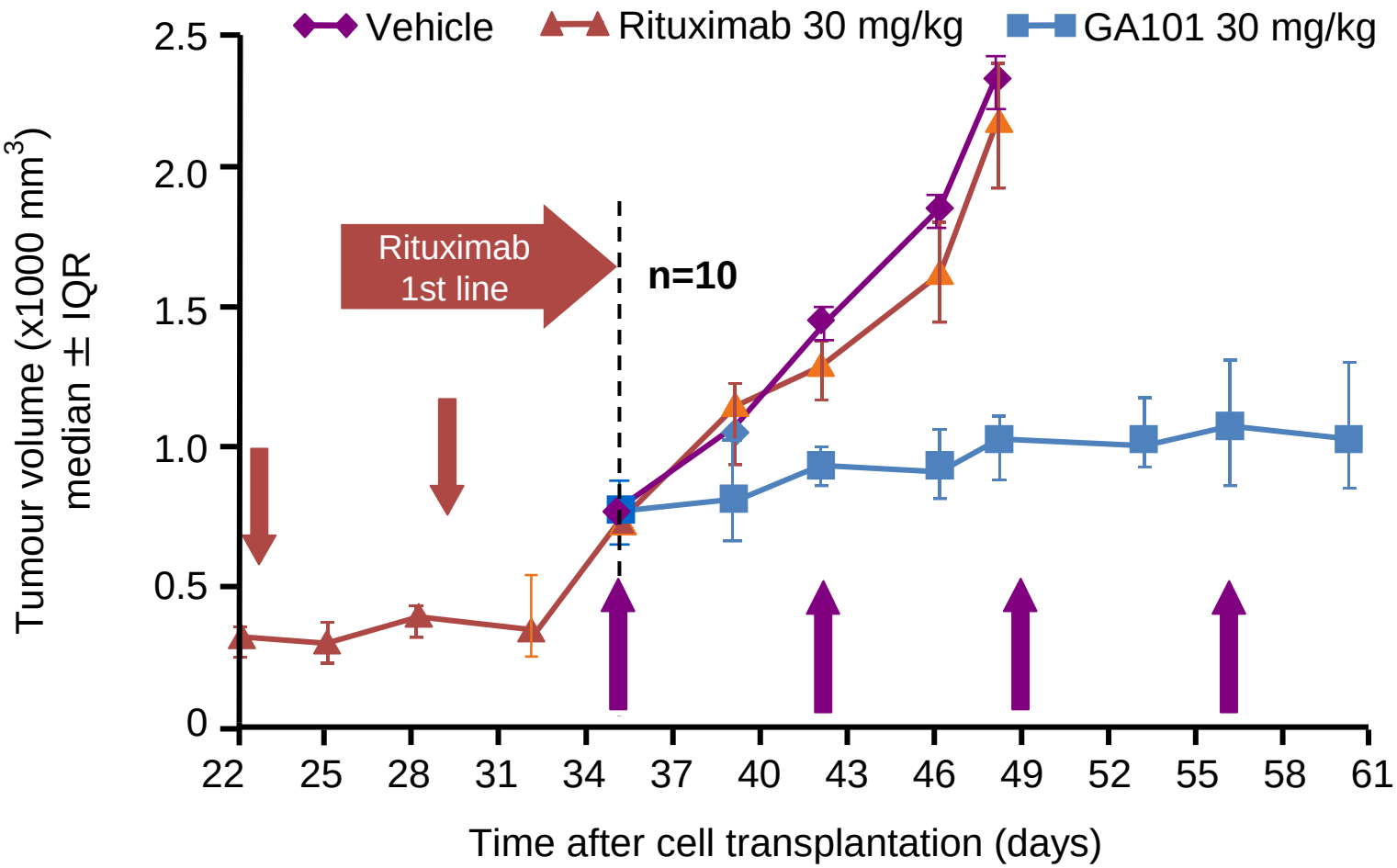
Superior GA101 efficacy & complete tumour remission in SU-DHL4 (DLBCL) xenograft



Mössner E, et al. Blood 2010. 115(22): p. 4393-402

DLBCL, diffuse large B-cell lymphoma; IQR, interquartile range

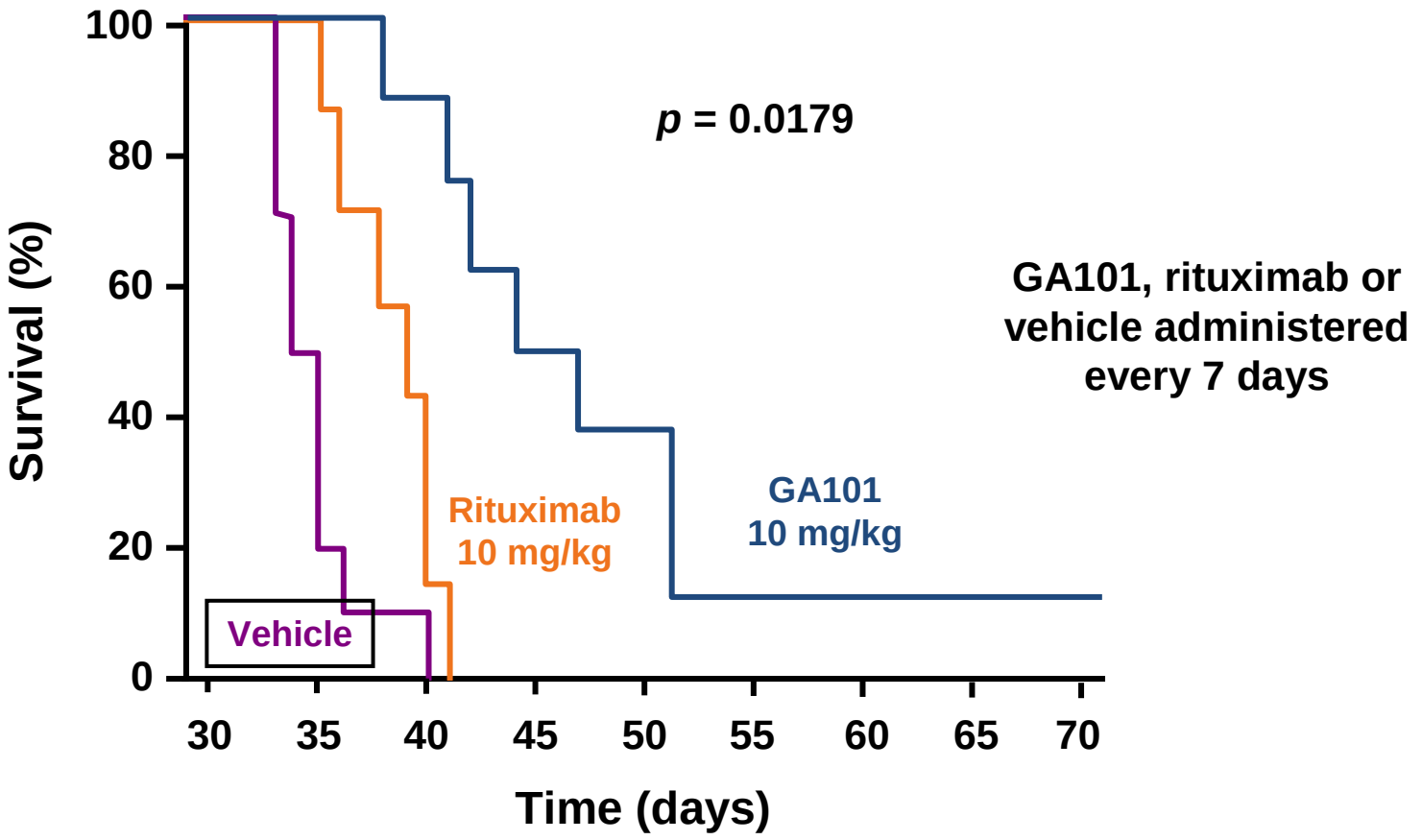
SU-DHL4 (DLBCL) xenograft progressing under rituximab responds to 2nd line treatment with GA101



Mössner E, et al. Blood 2010. 115(22): p. 4393-402

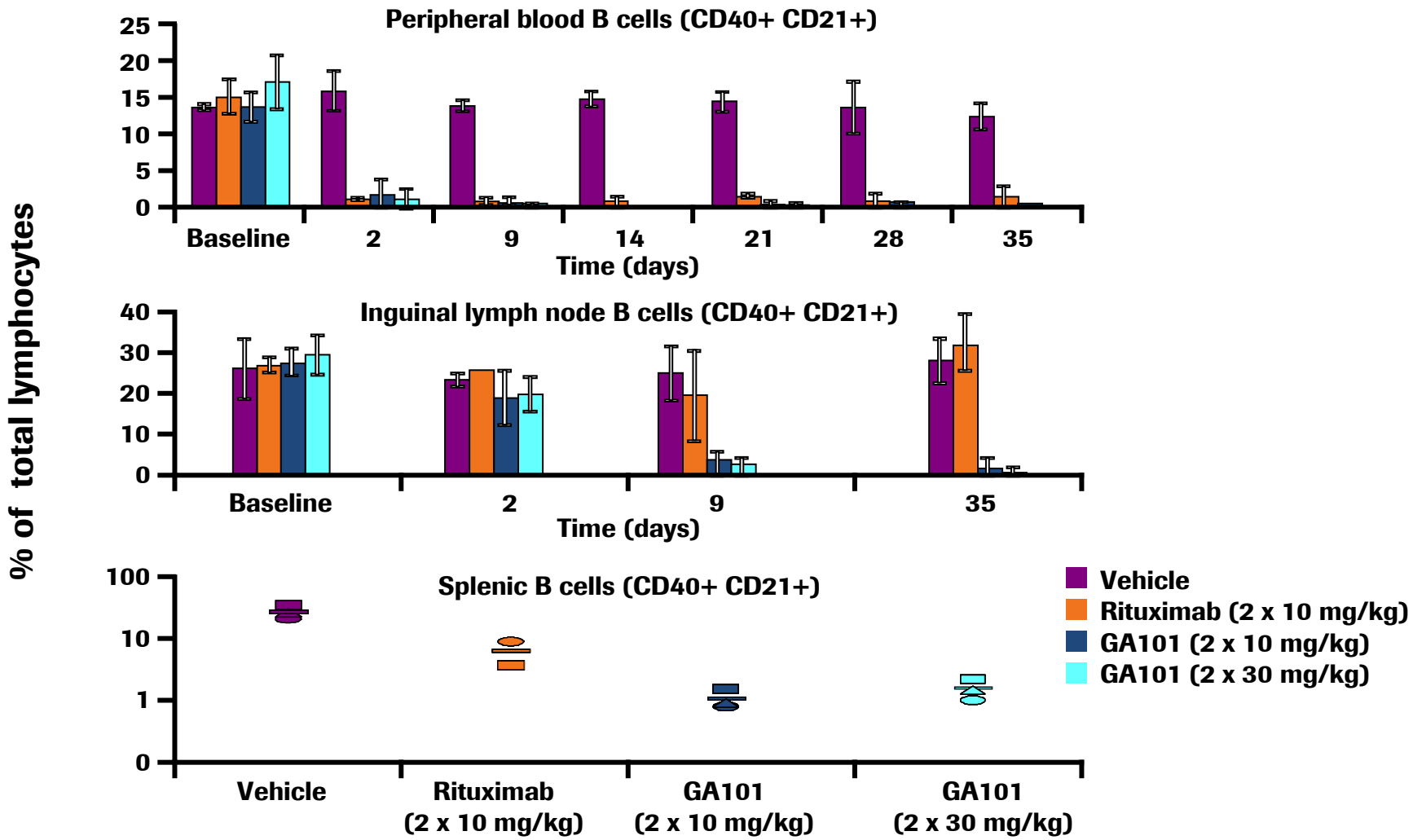
IQR, interquartile range

Increased median and overall survival in i.v. disseminated late stage Z138 (MCL) xenograft model



Mössner E, et al. Blood 2010. 115(22): p. 4393-402

GA101 shows superior tissue B-cell depletion versus type I CD20 antibodies in Cynomolgus



Mössner E, et al. Blood 2010. 115(22): p. 4393-402

GA101 (CD20): most advanced glycoengineered antibody in clinical development

Presented at EHA, June 2010

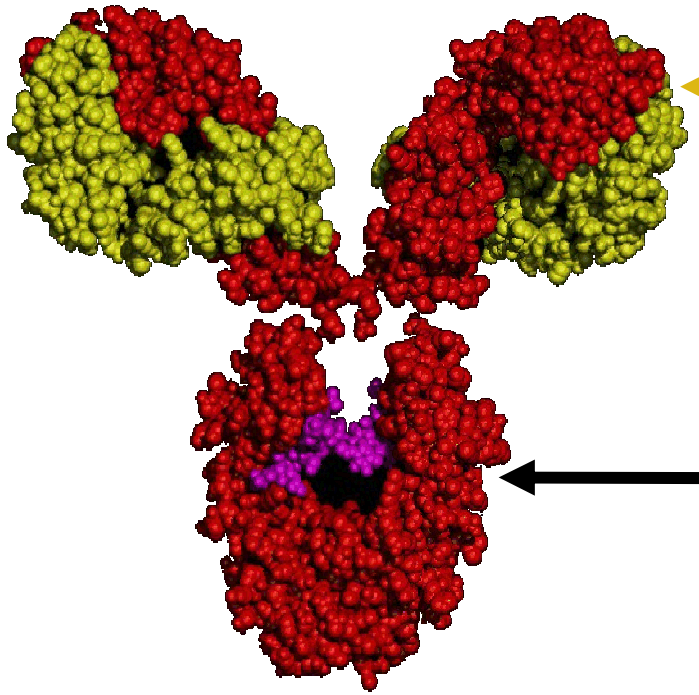
PROMISING EFFICACY WITH THE NEW ANTI-CD20 ANTIBODY GA101 IN HEAVILY PRE-TREATED PATIENTS – FIRST RESULTS FROM A PHASE II STUDY IN PATIENTS WITH RELAPSED/REFRACTORY INDOLENT NHL (INHL)

G Salles, MD, PhD1; F Morschhauser, MD, PhD2; C Thieblemont, MD, PhD3; P Solal-Celigny, MD4; T Lamy, MD, PhD5; H Tilly, MD6; P Feugier, MD7; S Le Gouill, MD, PhD8; E Gyan, MD PhD9; R Bouabdallah, MD10; M Wenger MD11; J Birkett, PhD12 and G Cartron, MD, PhD13

Conclusion: In this group of heavily pre-treated iNHL patients, single-agent GA101 was safe with a high response rate in HD cohort (55%), and responses also observed in rituximab-refractory patients (HD 55% [6/11]), supporting a possible dose-response relationship.

GA201

A glyco-engineered EGFR IgG1 Ab in clinical development



Humanized:

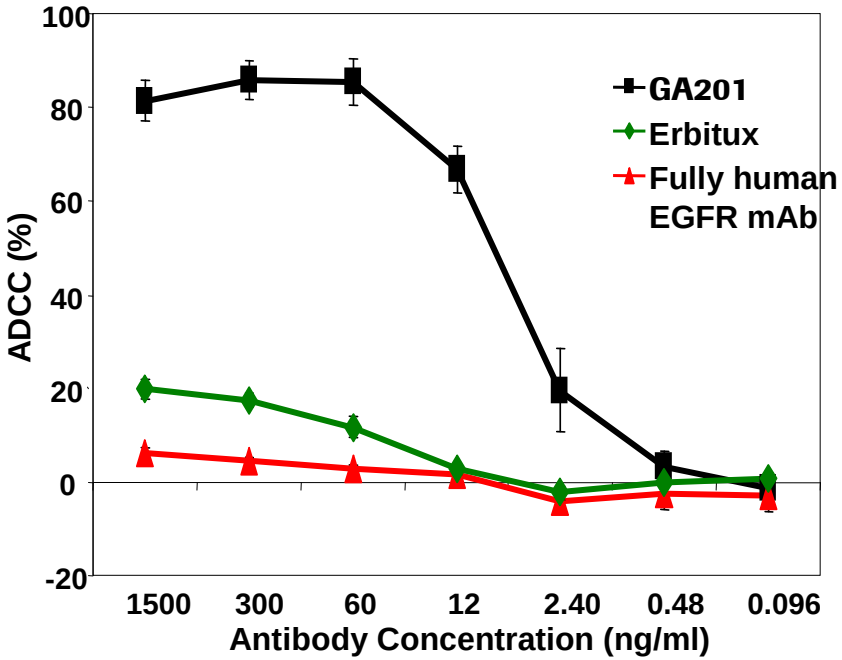
- Rodent VH & VL CDRs
- CDRs grafted on human VH & VL frameworks identical to human germline sequences

Glyco-engineered

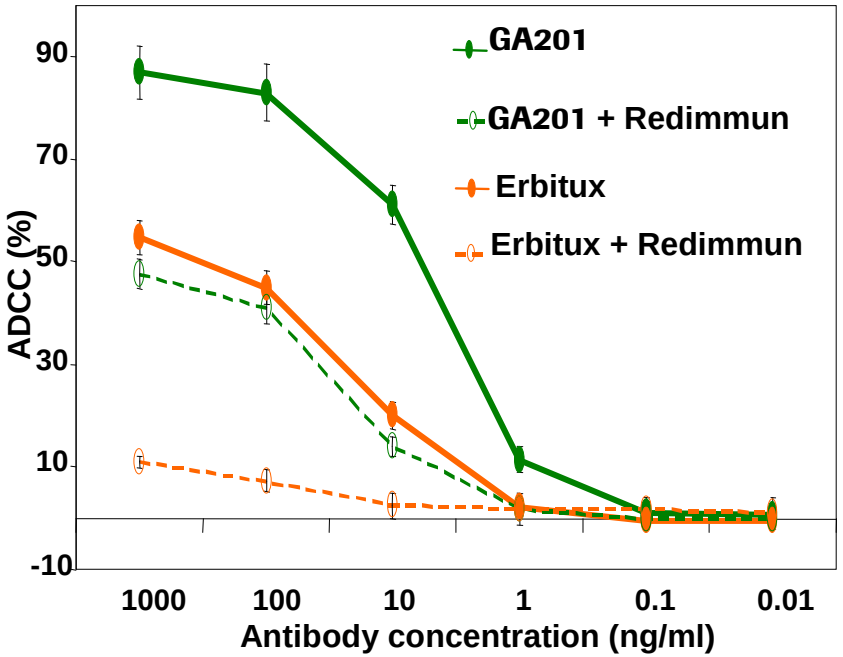
GA201: In vitro characteristics

ADCC activity against EGFR overexpressing A431 cells

GA201 vs. Other EGFR Abs
(NK92/FcγRIIIA-158F effector cells)



Effect of serum IgG
(NK92/FcγRIIIA-158V effector cells)



- **Superior *in vitro* ADCC activity of GA201 *vs.* Erbitux and fully human EGFR mAb against EGFR overexpressing A431 cells**
- **Advantage maintained or even more pronounced in the presence of Redimmun (hulg, containing a few percent afucosylated antibodies)**

Superior efficacy of GA201 in a lung tumor model in Scid-bg mice