Phase I studies of MoAbs in Oncology

A clinician point of view

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Lymphoma: a challenge for clinical research and new drug developments

- 6th cancer by incidence in the world
- Nb of new cases: + 100% in 25 years.
- About 25 different pathological entities:
  - sharing however common Ag / critical pathways
- Some are curable with chemotherapy (dose/schemes)
- Others have a chronic disease history
  - The immune system may play a crucial role in disease control
  - Patients are optimal candidates for new agents

Lymphoma : progress made in recent years

Significant increase in survival rates

Introduction of new agents
- anti-CD20 moAB

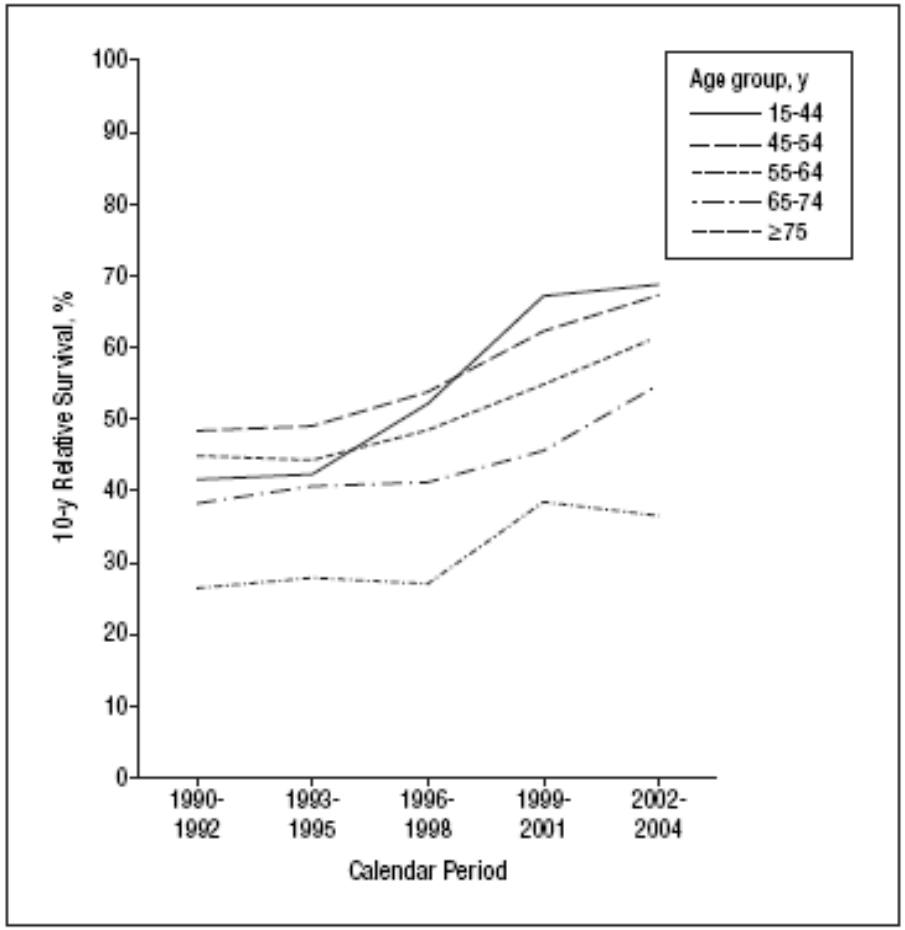
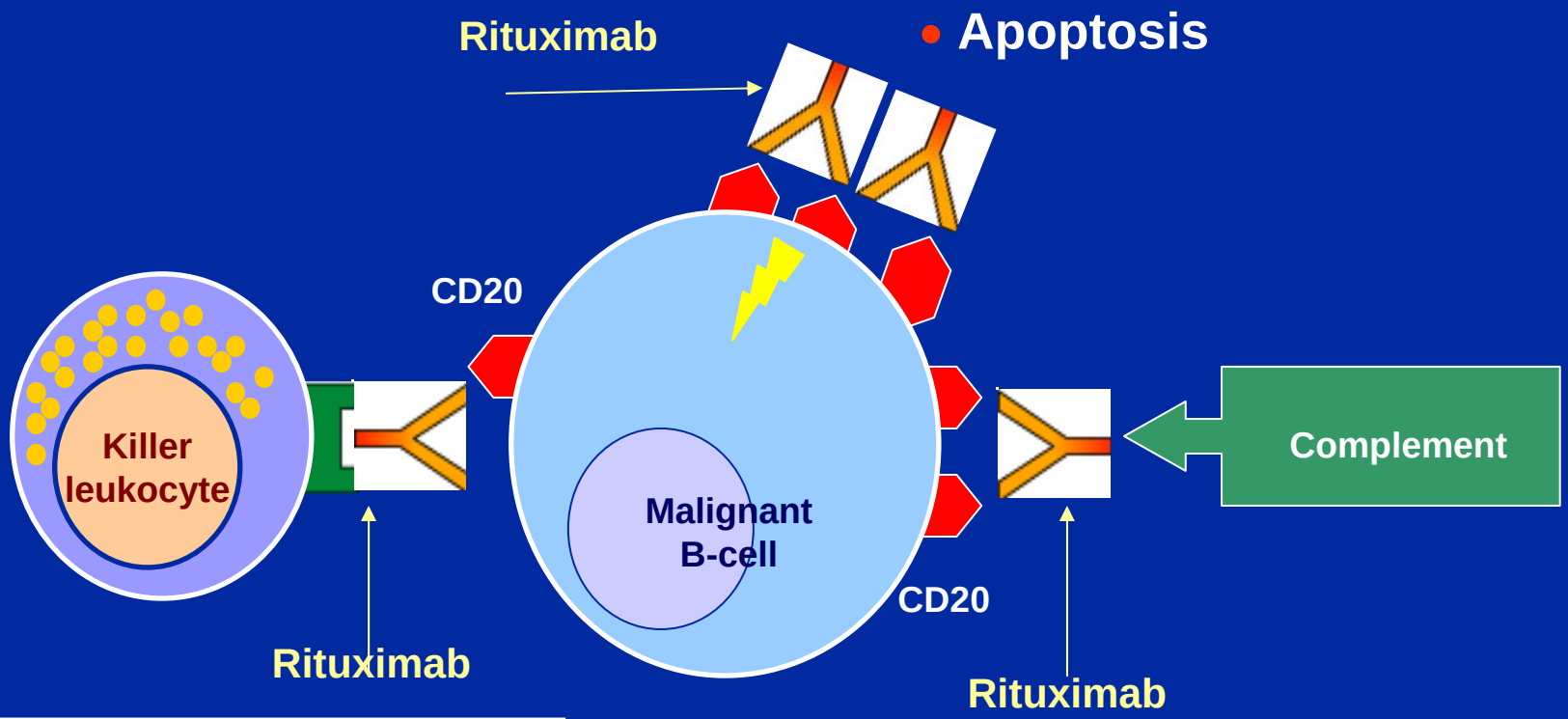


Figure 1. Ten-year relative survival estimates by age group and calendar period. All patients had non-Hodgkin lymphoma.

Pulke et al. Archives Int Med 2008

Rituximab: Mechanisms of Action



- ADCC = Antibody-dependent cell-mediated cytotoxicity

- CDC = Complement-dependent cytotoxicity

New generations of anti-CD20 MoAb

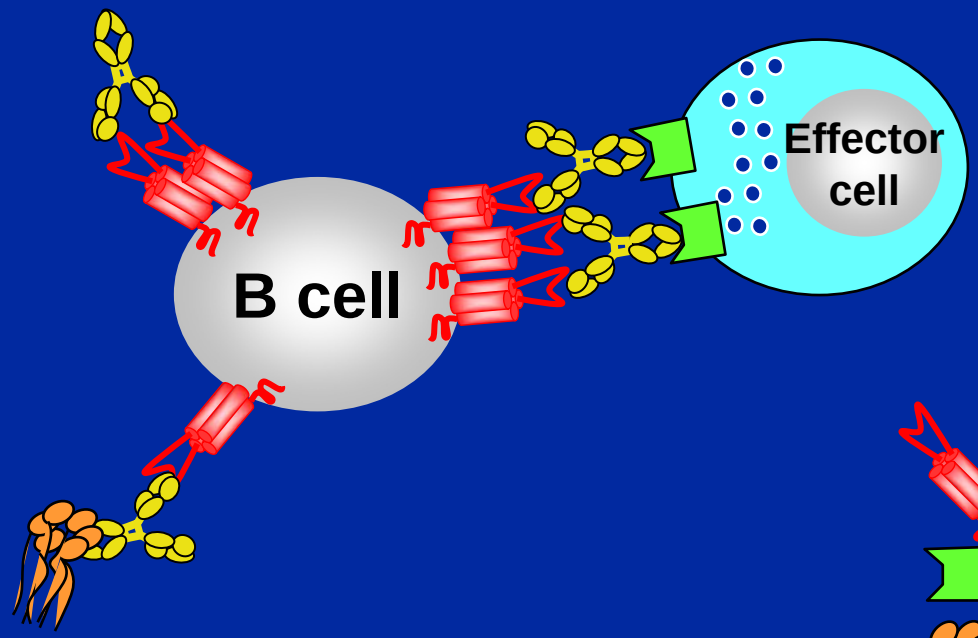
Rituximab	Roche/Genentech	chIgG1	+	+	+
Ocrelizumab	Roche/Genentech	huIgG1	+	+/-	+
Veltuzumab	Immunomedics	huIgG1	+	+	+
Ofatumumab	GenMab/GSK	huIgG1	+	++	+/-
AME-133	Lilly	huIgG1	++	+	+
PRO131921	Genentech	huIgG1	++	+/-	+
GA101	Roche/Glycart	huIgG1	+++	0	+++
EMAB-6	LFB	huIgG1	+++	+	+
KM3065	Kyowa	huIgG1	+++	+	+
Autres	Macogenics, Biolex				

Guillaume Cartron

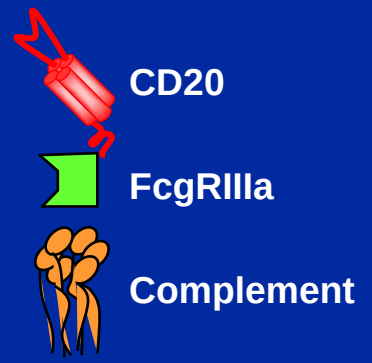
GA101: mechanisms of action
Versus type I antibodies

Increased direct cell death
Unique type II epitope & elbow-hinge modification

Increased ADCC
via increased affinity to the 'ADCC receptor' FcgRIIIA



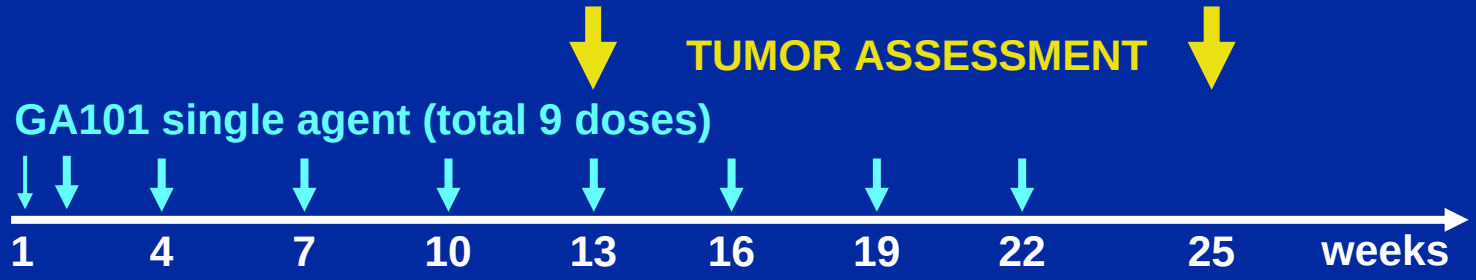
Lower CDC activity
Due to recognition of type II epitope



Early phase I development of GA101

- **First contacts: June 2006**
  - the team in charge of clinical development at Roche
  - 2 academic investigators + 1 scientist with June 2006
- **During 12 months**
  - Framework of the phase I study
  - Discuss on several meeting opportunities
    - Optimize the protocol (dose, scheme, patients selection, …)
    - Discuss preclinical safety results
    - Discuss additional translational studies
  - 7 hem-onc centers selected in one country
  - Less than 12 months to accrue the first 6 cohorts of 3 patients

Study BO20999: Phase I dose-escalation (3+3 design)



- CD20+ malignant disease for whom “no therapy of higher priority was available”
- n = 3 per cohort
  - Successive cohorts initiated if no DLT
- Started in September 2007 at 7 sites in France

Cohort group	GA101 dose Dose 1 / doses 2–9
1	50 / 100 mg
2	100 / 200 mg
3	200 / 400 mg
4	400 / 800 mg
5	800 / 1200 mg
6	1200 / 2000 mg
7	1600 / 1600 / 800 mg

GA101 administered as per rituximab administration guidelines

TC every 2 weeks

- Discussion about safety AND efficacy
- Discussion about early biological endpoints (cytokines/complement fractions ; PK data, …)
- Discussion of the dose escalation scheme
- One day meeting with all available data
  - For the interpretation of the phase I results
  - For the design of the phase II

Other inputs through the collaboration

- **Some unexpected toxicities encountered in patients with a particular subsets of B-cell disease**
  - **Discuss mechanisms, require additional data, interpretation of "out of study" investigations…**

- **Discussion of phase II dose:**
  - **Responses observed as low and high dose levels,**
  - **no clear indication of an optimal dose through PK data**

    - **Choice for a randomized (= 2 dose levels) phase II study**
    - **2 cohorts of 40 pts each accrued in < 6 months in 13 centers in one country !**

Questions from the clinician

- **How to associate clinicians early on ?**
  - **Easy for us since the concepts were familiar to us**
- **Choice of centers**
  - **Specialization for one disease, dynamic of academic oooperative groups used to conduct large phase III studies**
  - ***versus***
  - **center specialized for phase I studies ?**
- **Quality of the discussion**
  - **Ability to discuss early confidential data**
- **Early results interpretation: stop or go decisions**
- **Work load … but enthousiasm !**