

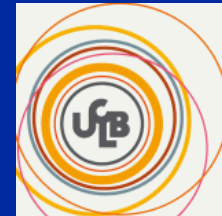
# Phase I studies of MoAbs in Oncology

A clinician point of view

**Gilles SALLES**  
Hematology Department



Service d'Hématologie  
Hospices Civils de Lyon



Université Claude Bernard

# 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

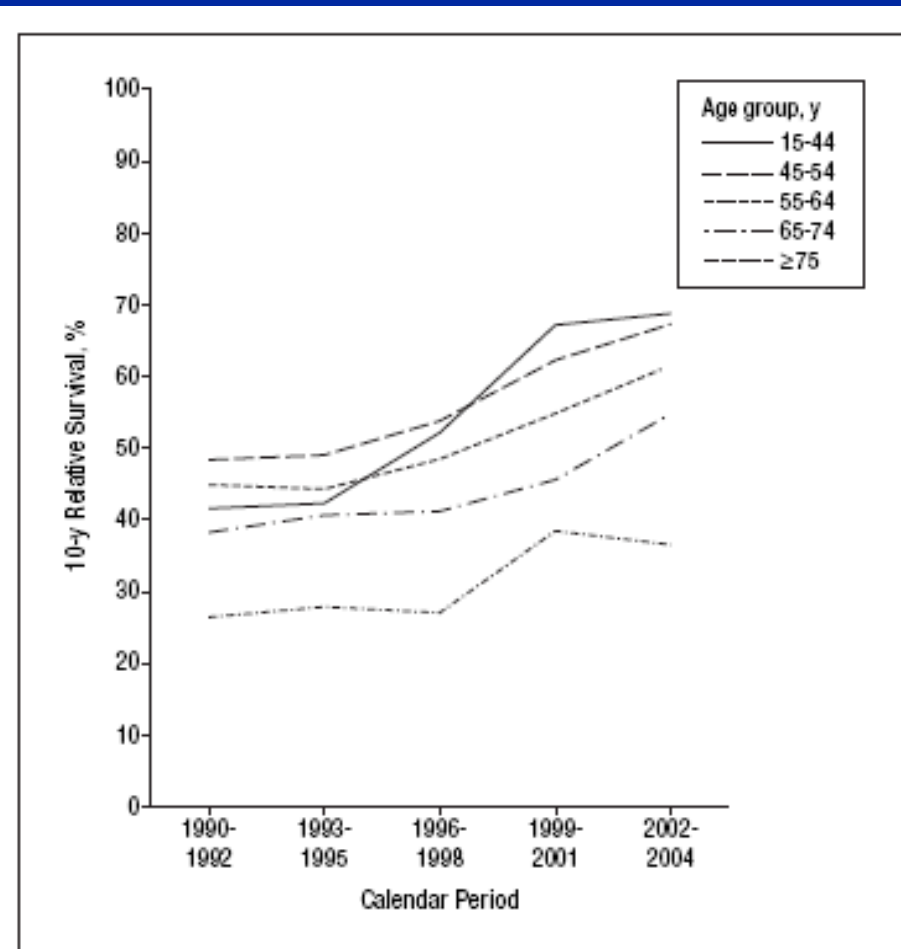
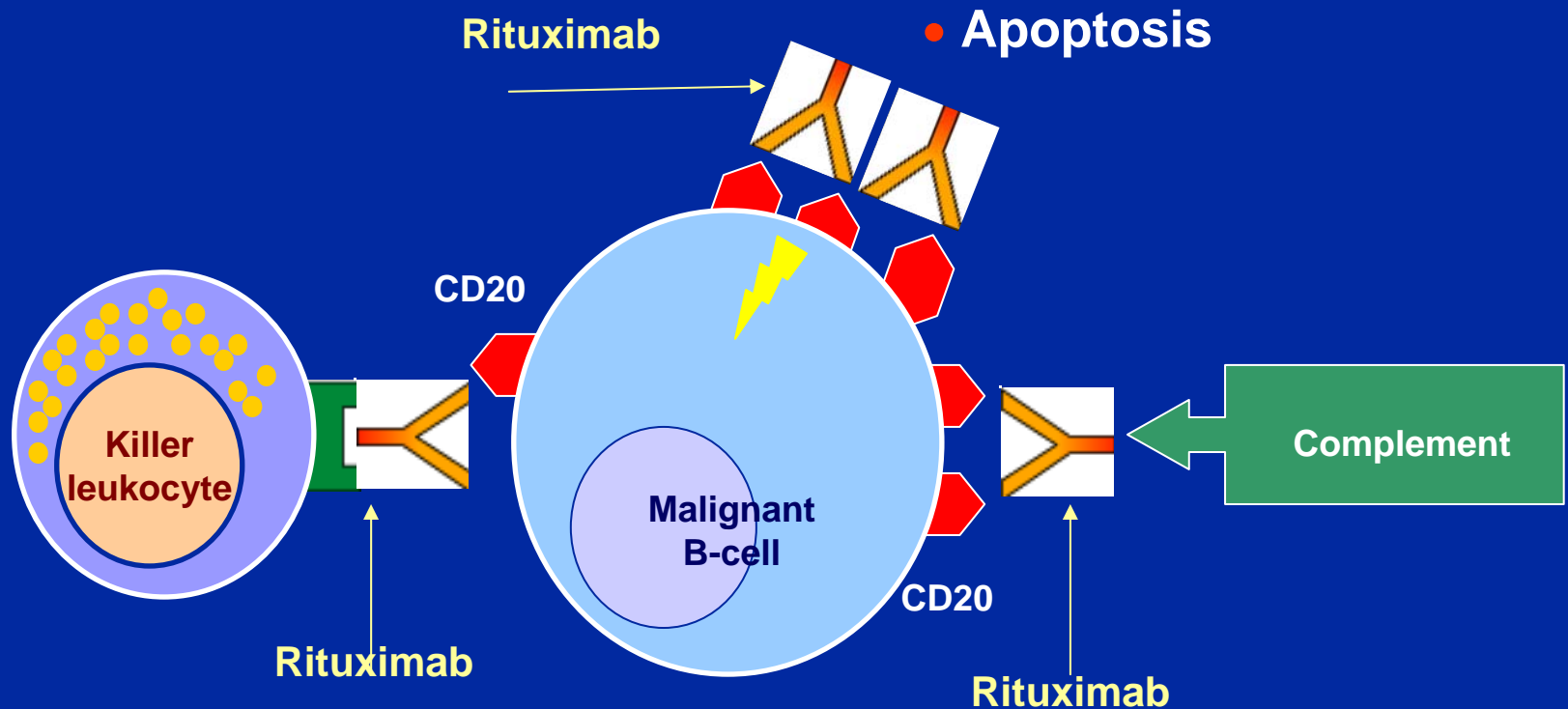


Figure 1. Ten-year relative survival estimates by age group and calendar period. All patients had non-Hodgkin lymphoma.

# Rituximab: Mechanisms of Action



- ADCC = Antibody-dependent cell-mediated cytotoxicity

- CDC = Complement-dependent cytotoxicity

# New generations of anti-CD20 MoAb

Rituximab	Roche/Genentech	chlgG1	+	+	+
Ocrelizumab	Roche/Genentech	hulgG1	+	+/-	+
Veltuzumab	Immunomedics	hulgG1	+	+	+
Ofatumumab	GenMab/GSK	hulgG1	+	++	+/-
AME-133	Lilly	hulgG1	++	+	+
PRO131921	Genentech	hulgG1	++	+/-	+
<u>GA101</u>	Roche/Glycart	hulgG1	+++	0	+++
<u>EMAB-6</u>	LFB	hulgG1	+++	+	+
<u>KM3065</u>	Kyowa	hulgG1	+++	+	+
Autres	Macogenics, Biolex				

# GA101: mechanisms of action

## Versus type I antibodies

### Increased direct cell death

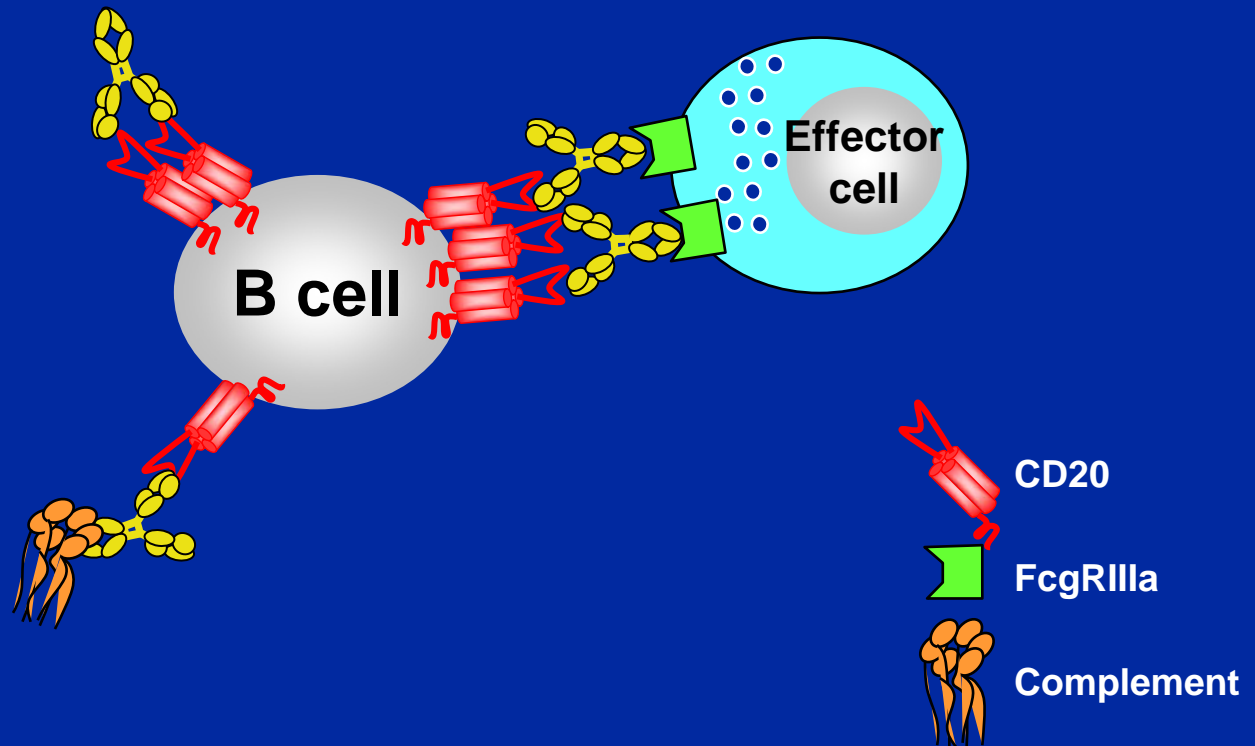
Unique type II epitope & elbow-hinge modification

### Increased ADCC

via increased affinity to the 'ADCC receptor' FcγRIIIa

### Lower CDC activity

Due to recognition of type II epitope

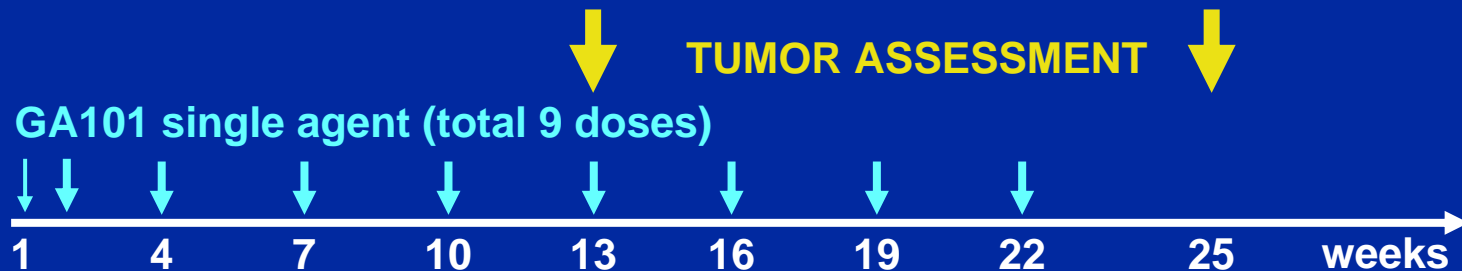


# Early phase I development of GA101

---

- **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 cooperative 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 enthusiasm !**