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**Therapeutic antibody constructs:
State of the art and future developments**

Klaus Bosslet, PhD

Presentation overview

- Critical overview about antibody technology and antibody mimetics evolution
- Treatment barriers in oncology
- Antibody Targeted Radio Therapy: A novel highly efficacious treatment option in oncology: Zevalin, L19-SIP etc.

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Historical evolution of antibody technologies

- Description of polyclonal immunoglobulins selective for tetanus and diphtheria toxins (E. v. Behring 1890)
Pitfalls: Batch to batch variation, virus contamination risk
- Monoclonal antibody technology (Koehler and Milstein 1975)
Pitfalls: Immunogenicity after repetitive long term application
- Chimerized antibodies (Sahagan et al. 1986)
Pitfalls: Induction of HACAs after repetitive long term application
- Humanized antibodies (Riechmann, Winter et al 1985)
Pitfalls: Labour intensive, not always feasible, remaining HAHA risk
- Antibody phage display technology
(Clackson, Hoogenboom, Griffiths, Winter 1991)
Pitfalls: Functional assays to be implemented late, affinity maturation etc
- Antibody ribosomal display technology
(Hanes, ... Plueckthun 1998)
Pitfalls: Challenging technology, similar to Phage display



Antibody mimetic technologies

- DARPINs: Designed ankyrin repeat proteins (Kawe, Forrer, Amstutz, Plueckthun 2006)
- Monobodies: Fibronectin Type III domain containing scaffolds (Olson et al 2007)
- Affibodies: small alpha helical domain (z-domain) of SPA (Hansson et al 1999)
- Nanobodies: single domain antibodies from camel heavy chain antibodies (Muyldermans, Lauwereys 1999)
- Anticalins: a new class of ligand binding proteins (Skerra 2001)

Potential Pitfalls: Immunogenicity, Half-life, Freedom to operate



Antibody formats optimized for efficacy

- Fc- optimized intact function blocking IgGs
(Glycoengineering, Fc-Receptor interaction)
- Half life optimization of fragments (Pegylation, Hesylation)
- BITES: Bispecific immunotherapeutics
- Trispecific antibodies
- Immunoconjugates
- SMIPs: Small modular immunopharmaceuticals
(scFv-Fc, scFv-cytokine, soluble factor-Fc)
- Antibody Targeted Radio Therapeutics: Zevalin*, L19-SIP* etc.

*to be presented in more detail



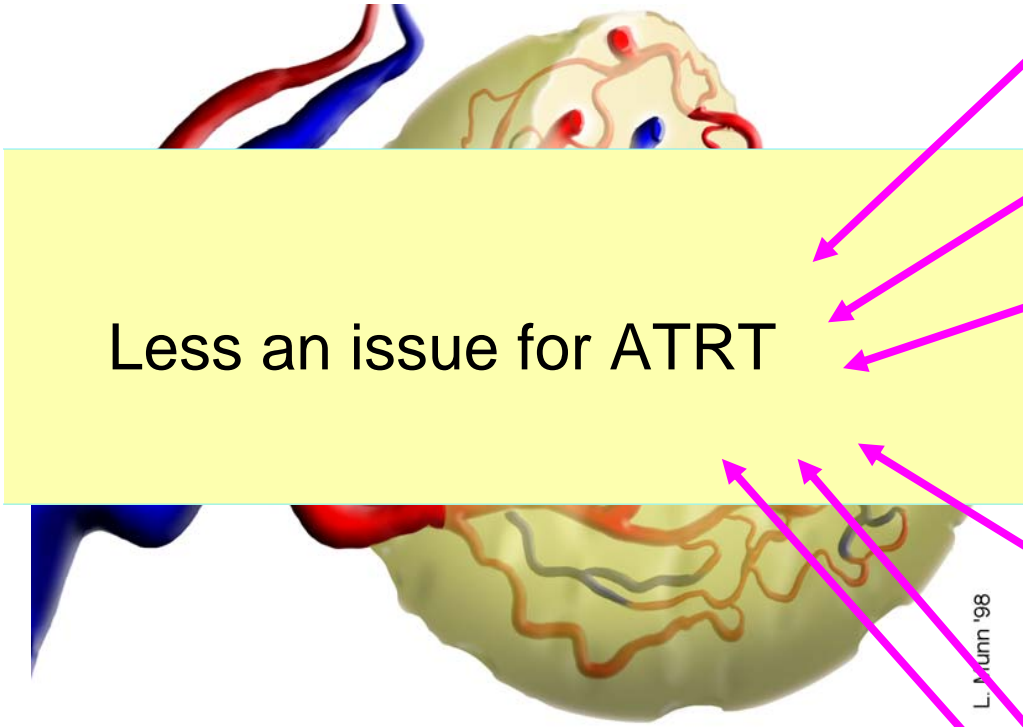
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Presentation overview

- Critical overview about antibody technology and antibody mimetics evolution
- **Treatment barriers in oncology**
- Radioimmunotherapy: A novel highly efficacious treatment option in oncology: Zevalin, L19-SIP etc.



Pathophysiology of cancer



Less an issue for ATRT

Successfully targeted cancer drugs have to overcome these treatment barriers

Treatment barriers

- Molecular and cellular heterogeneity of tumor cell population connected with chromosomal instability
- Presence of cellular clones resistant to antiproliferative drugs
- Induction of MDR during treatment with antiproliferative drugs
- Accumulation of anergic immune and inflammatory cells within the tumor mass (T-reg accumulation)
- Limited accessibility and diffusion within the solid tumor mass associated with altered connective tissue and increased IFP
- Aberrant vascular network
- Cancer stem cell phenotype different from majority of cancer cells



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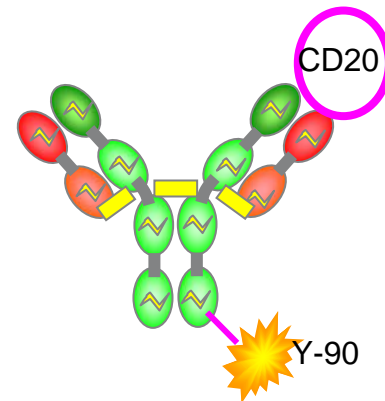
- Critical overview about antibody technology and antibody mimetics evolution
- Treatment barriers in oncology
- **ATRT: A novel highly efficacious treatment option in oncology: Zevalin, L19-SIP etc.**



^{90}Y -Ibritumomab Tiuxetan (Zevalin[®]) Consolidation of First Remission in Advanced Stage Follicular Non-Hodgkin's Lymphoma: First Results of the International Randomized Phase 3 First-line Indolent Trial (FIT) in 414 Patients

Anton Hagenbeek,¹ Angelika Bischof-Delaloye,²
John A. Radford,³ Ama Rohatiner,⁴ Gilles Salles,⁵ Achiel Van
Hoof,⁶ Barbara Putz,⁷ Michael Kunz,⁷
Franck Morschhauser,⁸ for the FIT Investigators

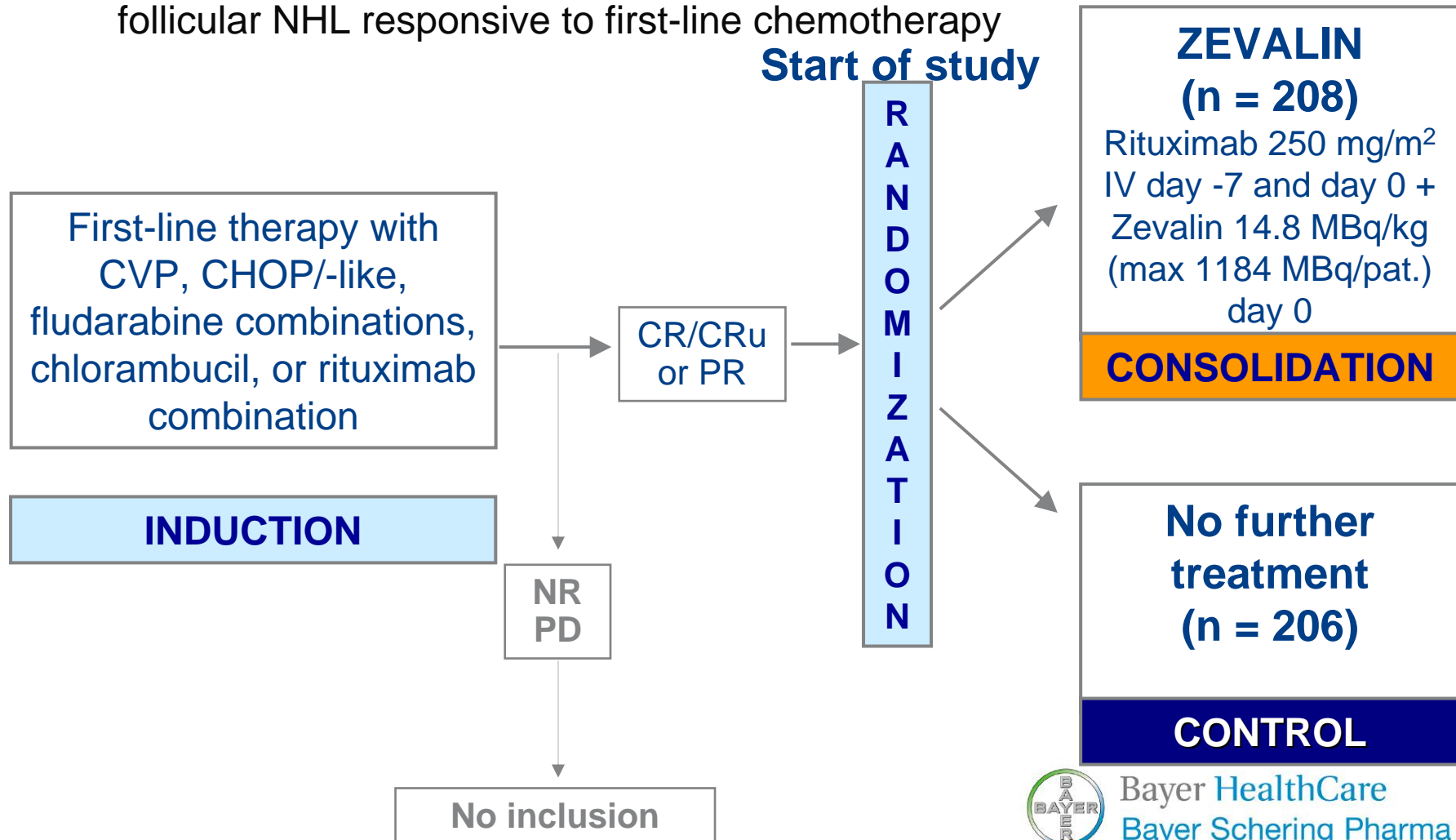
¹UMC Utrecht/HOVON, the Netherlands; ²Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; ³Christie Hospital, Manchester, UK; ⁴St Bartholomew's Hospital, London, UK; ⁵Centre Hospitalier Lyon Sud, Pierre Bénite, France; ⁶General Hospital St-Jan, Brugge, Belgium; ⁷Bayer Schering Pharma AG, Berlin, Germany; ⁸Hôpital Huriez, Lille, France



FIT Study Schema: Consolidation therapy

- Overall study objective

To compare the efficacy and safety of Zevalin consolidation versus no further treatment (control) in patients with advanced-stage follicular NHL responsive to first-line chemotherapy

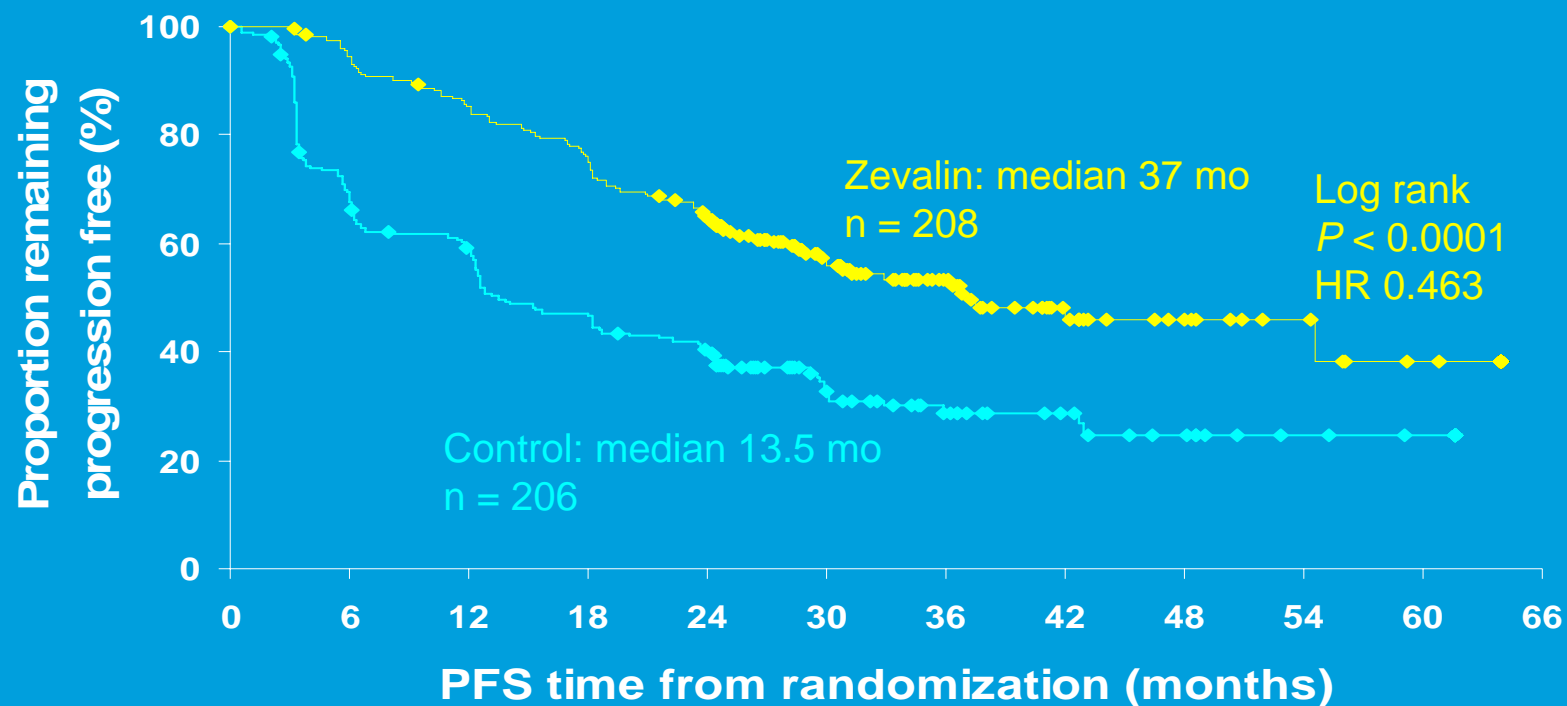


Zevalin Consolidation Improved Response Quality in 77% of Patients: Conversion From PR to CR/CRu

First-line regimen	Control n / N (%)*	Zevalin n / N (%)*	P value
All patients	17 / 97 (17.5)	78 / 101 (77.2)	< 0.001
Chlorambucil	1 / 13 (7.7)	11 / 13 (84.6)	< 0.001
CVP / COP	3 / 29 (10.3)	16 / 22 (72.7)	< 0.001
CHOP	8 / 32 (25.0)	31 / 41 (75.6)	< 0.001
CHOP-like	0 / 8 (0)	10 / 13 (76.9)	< 0.005
Fludarabine comb.	0 / 3 (0)	5 / 5 (100.0)	< 0.05
Rituximab comb.	5 / 12 (41.7)	5 / 7 (71.4)	= 0.34

* Proportion of patients with PR after first-line therapy who converted to CR/CRu post-randomization.

FIT Primary End Point: Median PFS in All Patients*



*Median observation period was 3.5 years.



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Conclusions: 1

- Zevalin consolidation is well tolerated with no unexpected toxicities
 - Low incidence of infectious events despite high proportion of patients with grade 3/4 neutropenia
 - Similar health-related quality of life parameters between treatment arms

(Gondek et al. ASH 2007, abstract 3319; poster no. 2473)
- Zevalin consolidation resulted in:
 - High conversion rates from PR to CR/CRu: 77% regardless of type of first-line treatment regimen administered
 - High overall CR rate: 87%
 - High molecular remission rate in blood: 90%

(Goff et al. ASH 2007, abstract 3412; poster no. 631)

Conclusions: 2

- Zevalin consolidation significantly prolongs median PFS by 2 years compared with no further treatment in patients responsive to first-line induction treatment
 - 2-year PFS advantage seen in patients with CR/CRu after first-line treatment suggests Zevalin benefit in patients with minimal residual disease
 - Zevalin consolidation leads to prolonged PFS in all FLIPI subgroups
- No difference in OS at currently available follow-up

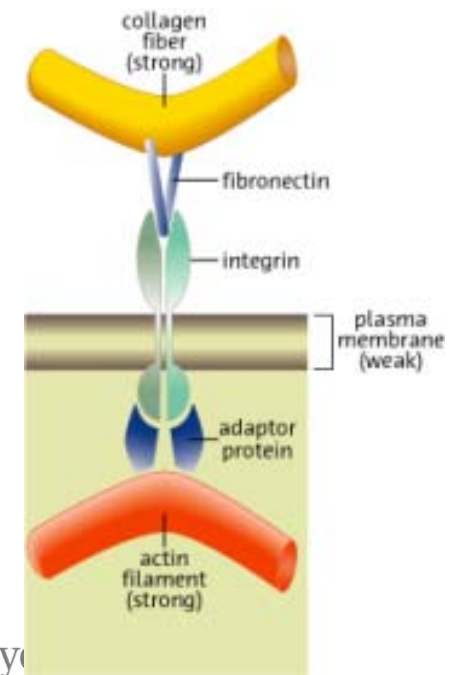
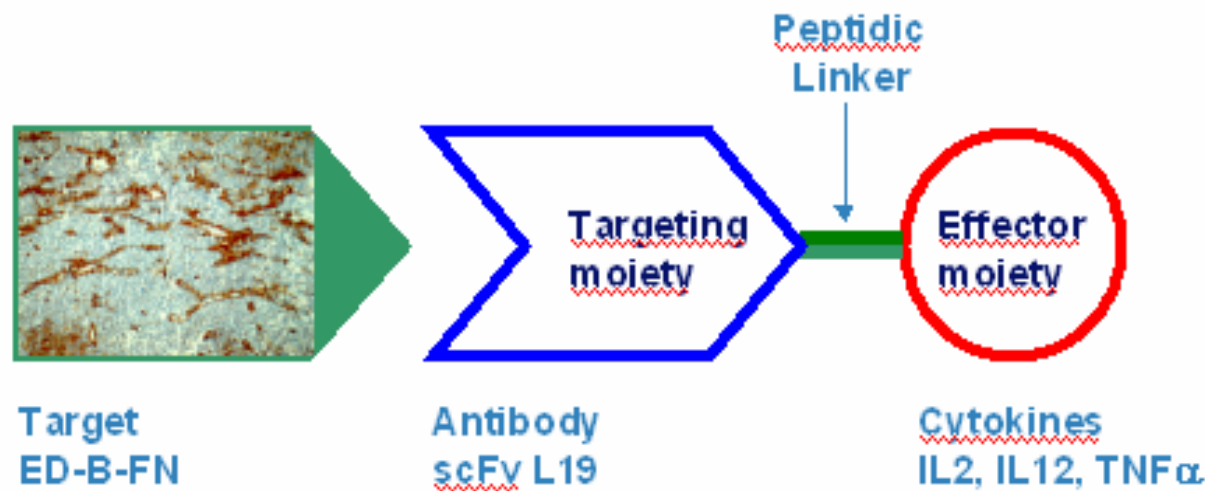
Consolidation with Zevalin has proven to be highly efficacious in patients with advanced stage follicular non-Hodgkin's lymphoma in first remission

EMA approval for first line consolidation treatment granted to BAYER in April 2008



The ED-B Fibronectin antigen - L19 Antibody system

- The extra domain B of Fibronectin (ED-B fibronectin) was found in 1987 by Zardi to be selectively associated with neoangiogenesis (Extracellular matrix glycoprotein)
- Associated with newly formed blood vessels and stromal structures
Not detectable in most normal adult tissues
- Due to the conserved state of ED-B fibronectin, antibodies could not be generated
- With the invention of synthetic phage display antibody technology, high affinity human binders have been generated (L19 antibody, Neri, 1999, protective IP)
- Research collaboration between Philogen, Italy and SAG (2000)
=> exclusive rights on all anti ED-B constructs



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Tissue selectivity of ED-B fibronectin detected by IHC with L19

ED-B FN expressed in many tumors

=> the L19 antibodies can be applied in many tumors

- Renal cell cancer
- Hepatocellular cancer
- Pancreatic cancer
- Colorectal cancer
- Breast Cancer
- Lung cancer, SC & NSC
- Head and neck cancer
- Malignant melanoma
- Glioblastoma
- Hodgkin's lymphoma
- NHL, different entities
- Multiple myeloma

Berndt et al. *Histochem Cell Biol.* 1998;109:249-255. Borsi et al. *Int J Cancer.* 2002;102:75-85.

Santimaria et al. *Clin Cancer Res.* 2003;9:5711-579.

Data on file, Schering AG, Germany.



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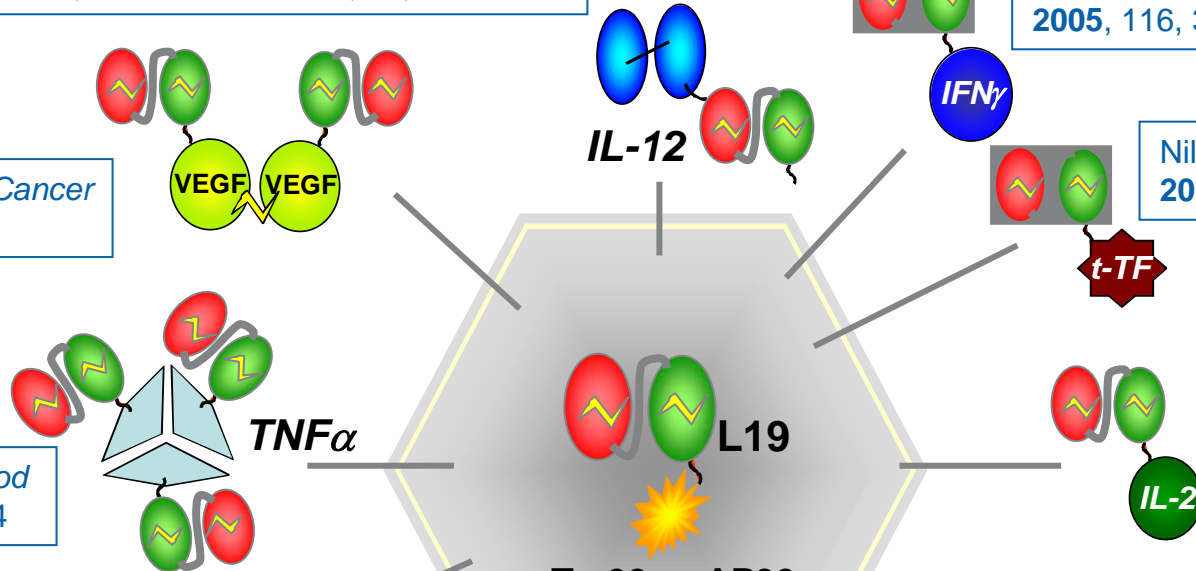
The L19 antibody platform

Halin et al., *Nature Biotechnol.* **2002**, 20, 264
 Halin et al., *Cancer Res.* **2003**, 63, 3202

Ebbinghaus et al., *Int. J. Cancer*, **2005**, 116, 304

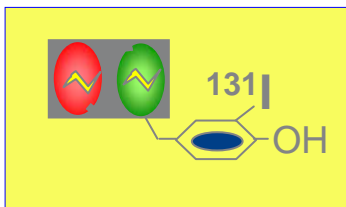
Nilsson et al., *Cancer Res.* **2001**, 61, 711

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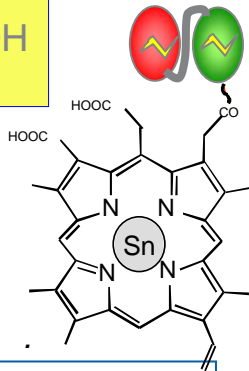


Borsi et al., *Blood* **2003**, 102, 4384

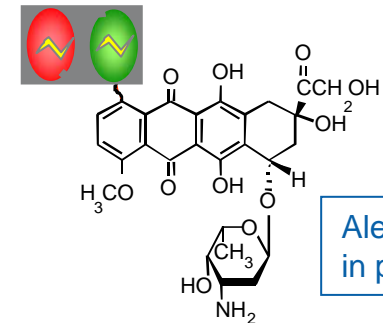
Carnemolla et al., *Blood*, **2002**, 99, 1659



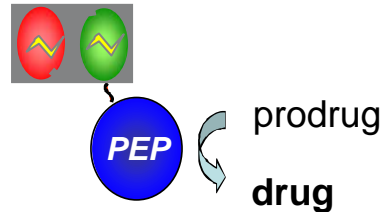
Borsi et al., *Int. J. Cancer* **2002**, 102, 75-85



Tc-99m- AP39



Alessi et al., in preparation

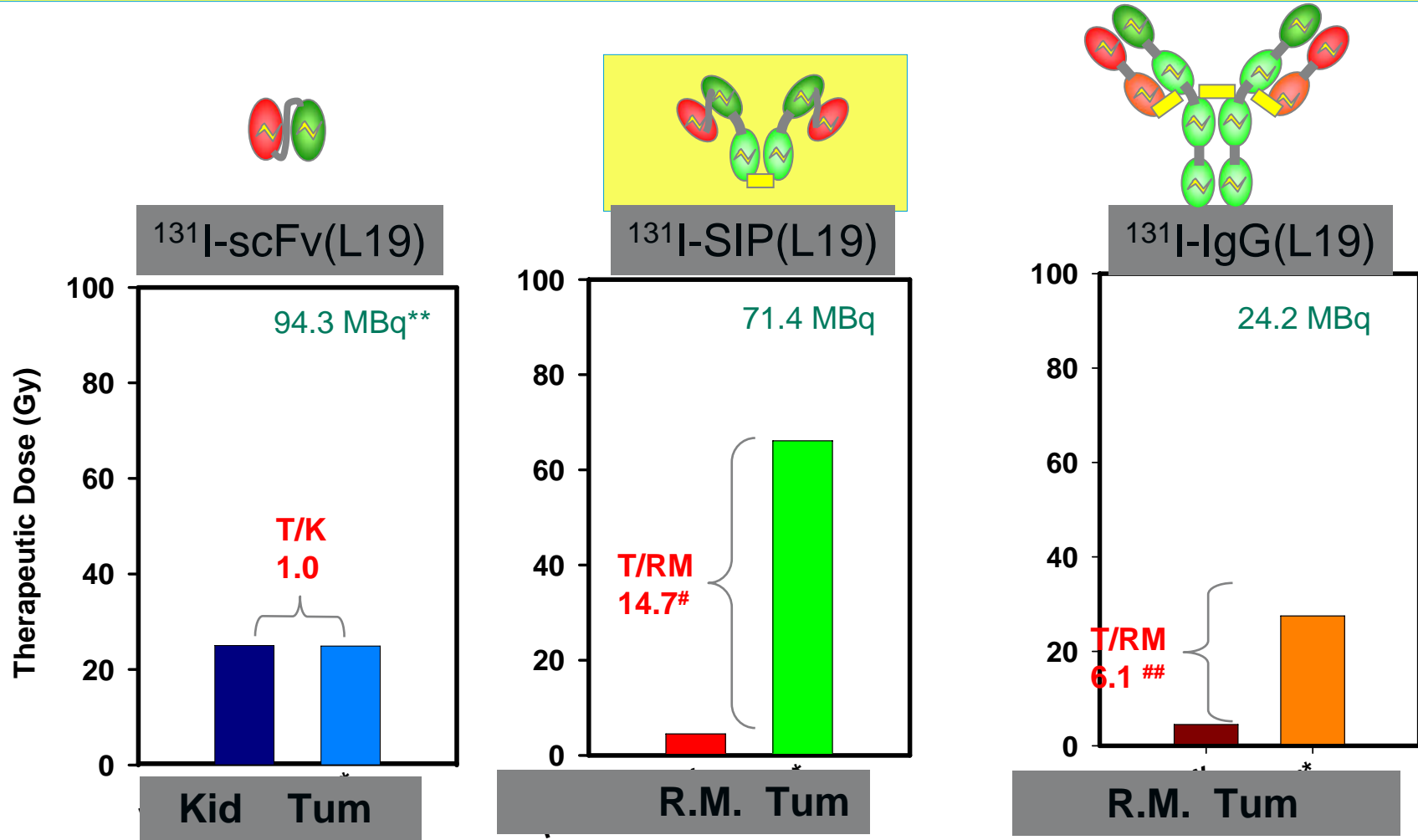


Heinis et al., *Biochemistry* **2004**, 43, 6293

Birchler et al., *Nature Biotechnol.* **1999**, 17, 984
 Fabbrini et al., *Int. J. Cancer* **2005**, Oct 10

What is the best format for Antibody Targeted Radio Therapy?

In vivo biodistribution and retention studies in F6 tumors favour the SIP format



For humans: TD_{50/5} (Red Marrow): 4.5 Gy TD_{5/5} (Kidneys): 25 Gy



Summary of ongoing clinical studies with L19-SIP (Ph 1)

- Results from ongoing Phase I dose escalation study confirm the preclinical biodistribution and efficacy studies
 - Partial remissions and disease stabilizations were observed in patients with therapy resistant bulky tumor masses

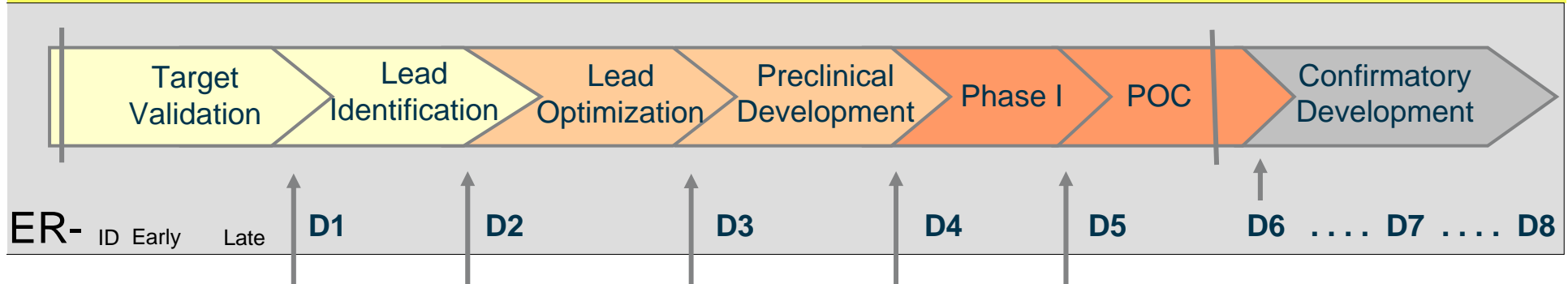
=>

ATRT will deliver treatment options for both bulky tumor masses (L19-SIP) as well as minimal residual disease (Zevalin)



GDD-ONCOLOGY project pipeline

A pipeline with innovative Targeted Biological Therapeutics and Small Molecules



AA

DAST Inhibitor

Nexavar Nexavar

AP

Novel SERD

ZK-PRA

Bonefos

Bonefos

ZK-Epo

TBT

L19-SIP
L19-TNF

L19-IL2

Zevalin

Zevalin

Campath

Campath



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S7

Portfolio Slide Status 12/2007 (nicht mehr ganz aktuell)

Dominik Mumberg; 11.02.2008

A beautiful cancer of the sky: Thank you for your attention



Hubble Aufnahme vom Krebsnebel (eng. *Crab Nebula*, wörtlich übersetzt also *Krabbennebel*, eine Bezeichnung, die im deutschen Sprachraum aber weniger üblich ist). Es ist ein Supernovaüberrest im Sternbild Stier und wird im Messier-Katalog als *M1* geführt.