The Phase 1 Unit
Departments of Oncology and Haematology
Rigshospitalet

Martin Hutchings

Invest in Denmark Roundtable Meeting - 27 May 2021

Phase 1 Unit

- Established in 2005
- Focus on Phase I trials and personalized medicine
- Only dedicated unit in Denmark
- Dedicated staff only working with early clinical trials – no standard treatments
- Collaboration between Dept. of Oncology and Dept. of Haematology

The Phase 1 Unit - Staff

- Full time consultants (only phase 1 – no other sub-speciality):
  - Kristoffer Staal Rohrberg, MD, PhD (Head of Phase 1 Unit)
  - Iben Spanggaard, MD, PhD
  - Martin Højgaard, MD, PhD
- Part time consultants (with additional appointments besides phase 1):
  - Ulrik Lassen, Professor, MD, PhD (Head of Dept. of Oncology)
  - Camilla Qvortrup, MD, PhD
  - Martin Hutchings, MD, PhD (Hematology)
  - Anna Caroline Riley, MD, PhD (Hematology)
- Residents
- PhD students
- 9 Nurses and hiring
- 4 Secretaries and 2 research coordinators
- Data management by oncology and haematology CRUs
  - Oncology: 15 research nurses/study coordinators dedicated to phase 1 studies
  - Haematology: 7-8 research nurses/study coordinators primarily dedicated to phase 1 studies

The staff is highly experienced in developing, planning, implementing and running clinical trials, as well as processing the emerging data.

Premises

- 10 fulltime beds with staff 24/7 - expanding
- Outpatient clinic for treatment and follow-up
- Four oncology specialists plus residents
- Two hematology specialists
- Staff office (core unit)
- On site laboratory for immediate PK and PD handling
- Access to and routine in serial tumor and skin biopsies
- Access to advanced imaging
  (CT; PET/CT; MRI; PET/MRI; small animals imaging)
- Easy access to ICU

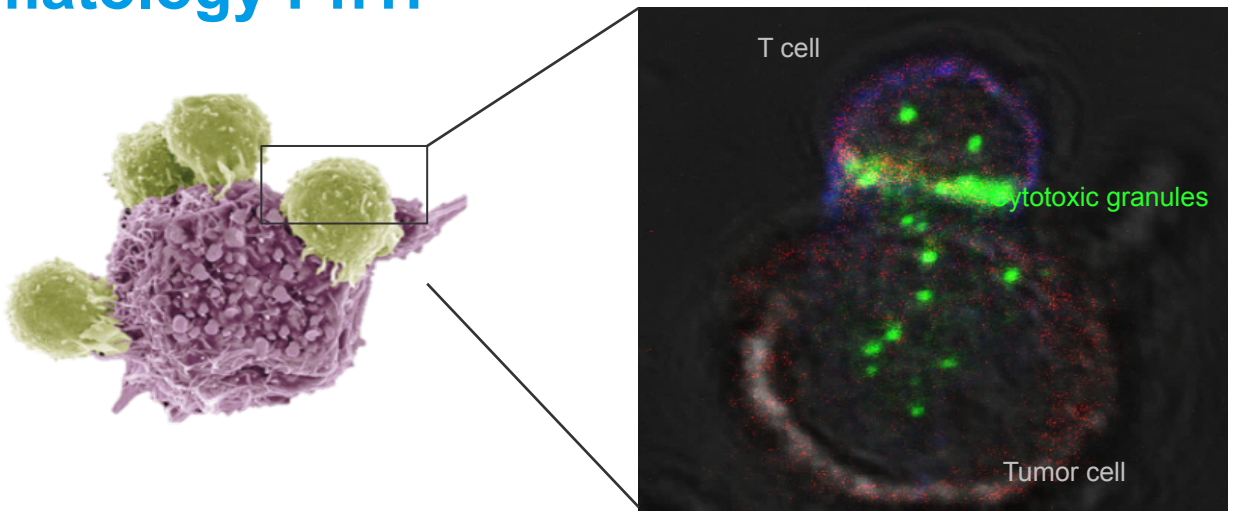
Studies performed in The Phase 1 Unit

- **First-in-human**
- Dose-finding (including add-on)
- PK/PD interaction studies (DDI)
- Standardised diets
- **Basket trials targeting specific driver mutations**
- Phase 1b
- Early phase 2
- Randomised phase 2 with PK/PD

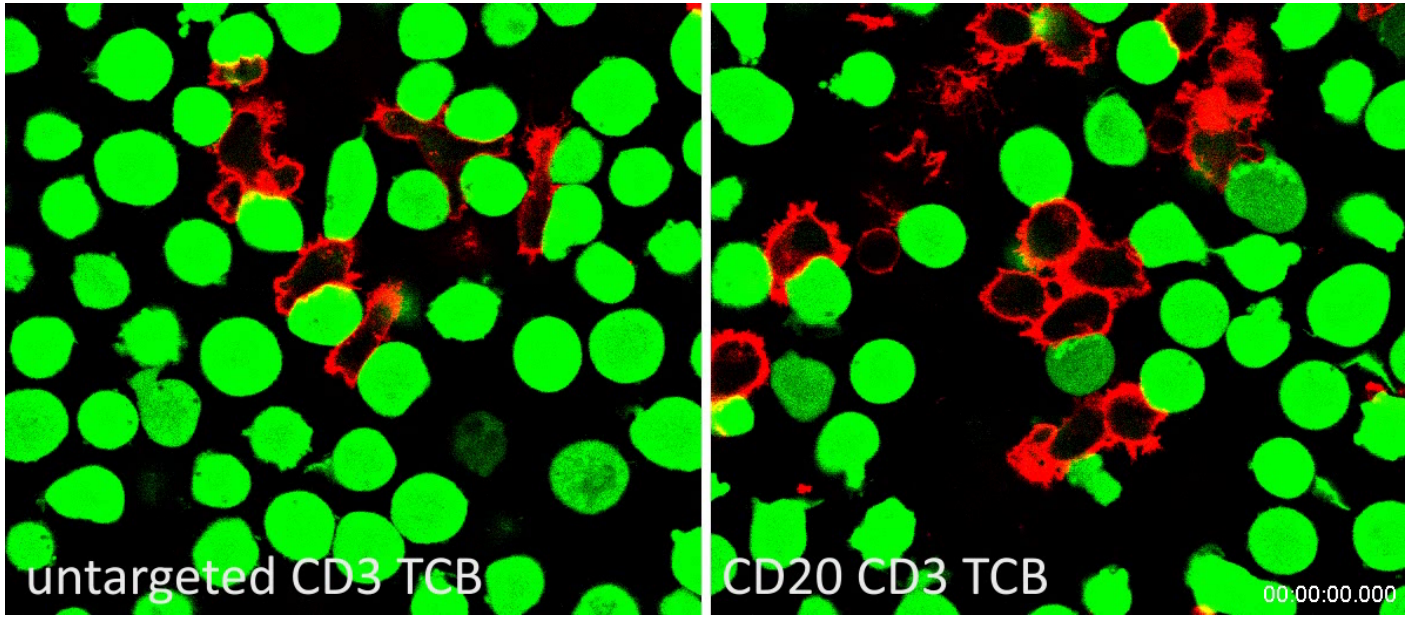
Our key area of excellence in haematology Ph1: Bispecific antibodies

The antibody binds to the tumor cell, leading to:

- T cell activation and cell kill using cytotoxic granules (green)
- Local **T cell proliferation** & cytokine/chemokine release resulting in enhanced T cell recruitment



T cells (red) kill CD20 positive tumor cells (green) when exposed to the active CD20/ CD3 bispecific (CD20-TCB/ RG6026) , but not when exposed to an inactive bispecific



Courtesy of M Bacac, Roche.

Subcutaneous epcoritamab induces complete responses with an encouraging safety profile across relapsed/refractory B-cell non-Hodgkin lymphoma subtypes, including patients with prior CAR-T therapy: updated dose-escalation data

Martin Hutchings, MD, PhD[1], Rogier Mous, MD, PhD[2], Michael Roost Clausen, MD, PhD[3], Peter Johnson, MD, FRCP[4], Kim M. Linton, MBChB, PhD[5], Martine E.D. Chamuleau, MD, PhD[6], David John Lewis, MD[7], Anna Sureda Balari, MD, PhD[8], David Cunningham, MD, FRCP, FMedSci[9], Roberto S. Oliveri, MD, PhD[10], Dena DeMarco[11], Brian Elliott, MD[11], Kuo-mei Chen, PhD[11], Pieternella J. Lugtenburg, MD, PhD[12]

American Society of Haematology – annual meeting December 2020

Glofitamab Step-Up Dosing Induces High Response Rates in Patients with Hard-to-treat Refractory or Relapsed (R/R) Non-Hodgkin Lymphoma (NHL)

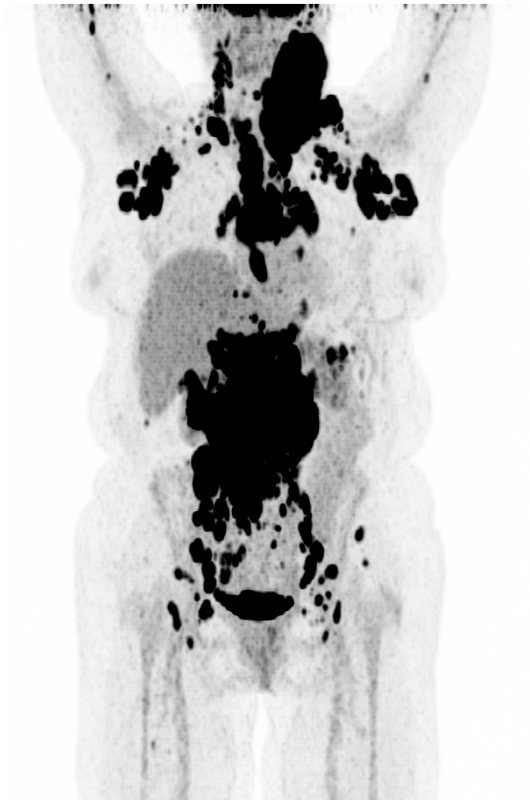
• **Martin Hutchings,**[1] Carmelo Carlo-Stella,[2] Emmanuel Bachy,[3] Fritz C Offner,[4] Franck Morschhauser,[5] Michael Crump,[6] Gloria Iacoboni,[7] Anna Sureda,[8] Joaquin Martinez-Lopez,[9] Linda Lundberg,[10] Anesh Panchal,[11] David Perez-Callejo,[10] James Relf,[11] David Carlile,[11] Emily Piccione,[12] Kathryn Humphrey,[11] Michael J Dickinson[13]

American Society of Haematology – annual meeting December 2020

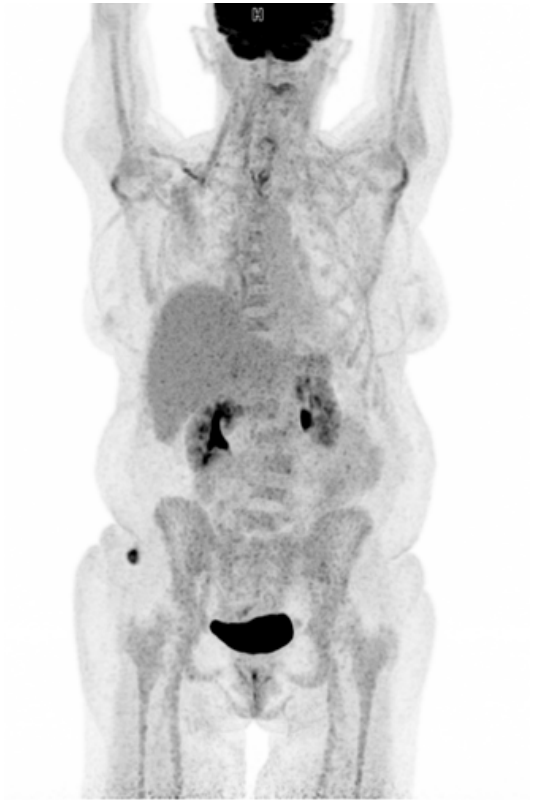
Accepted as an Oral Presentation at the 62nd ASH Annual Meeting and Exposition

- 76-year old lady with Richter transformation
- 8 prior lines of treatment
- Refractory to the 3 most recent lines

Before treatment

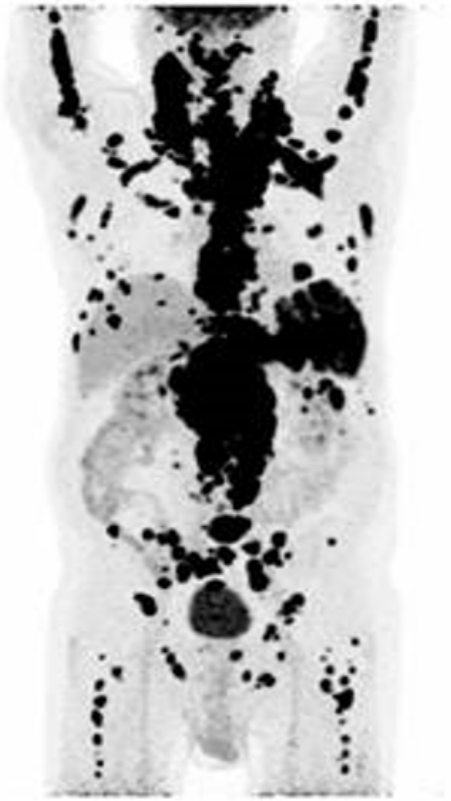


After 2 cycles = CR



- 69-year old man with non-GCB DLBCL
- 3 prior lines of treatment
- Refractory to the 2 most recent lines

Before treatment

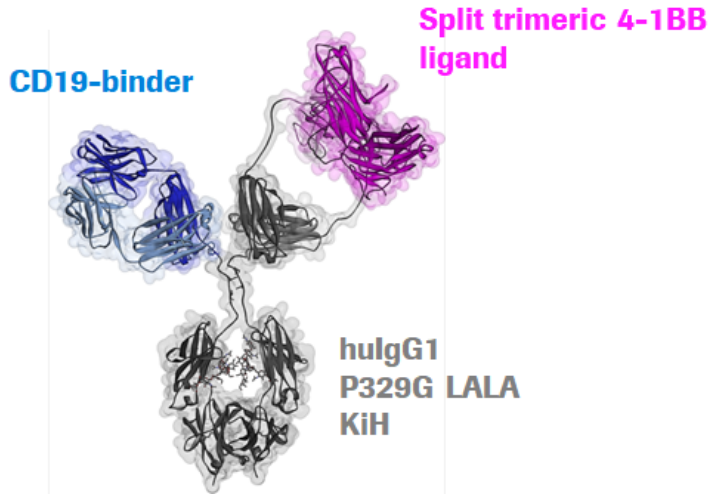


After 2 cycles = PR

CD19-targeted 4-1BBL (RO7227166)

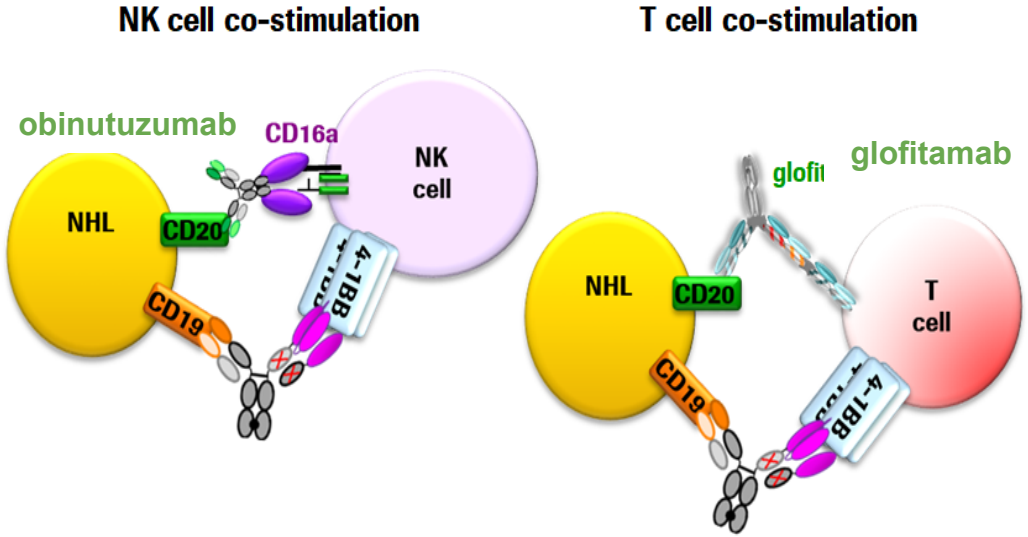
CD19 4-1BBL is a bispecific antibody targeting CD19 B cell antigen and the 4-1BB costimulatory domain on immune effector cells

RO7227166



- Costimulation of activated NK cells and T cells is **strictly dependent on CD19+ B cell crosslinking.**
- **Fc part is silenced** to prevent crosslinking with Fc-gamma receptors and related toxicity.

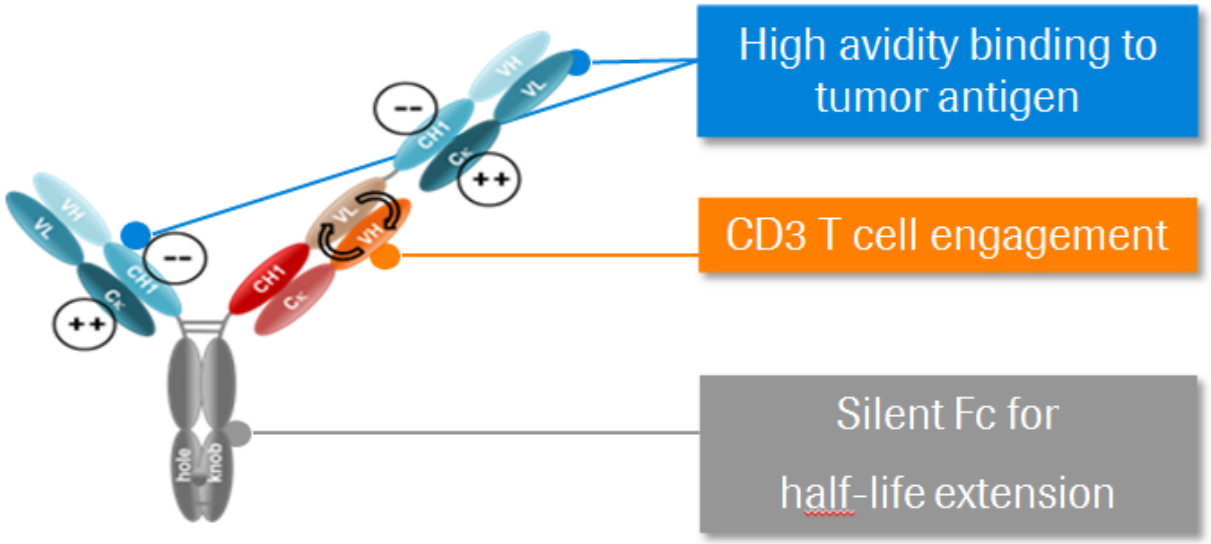
Mode of action



- **Signal 1** (NK or T cell activation) is delivered by **obinutuzumab** or **glofitamab** respectively
- **Signal 2** delivered by **CD19 4-1BBL** leads to **enhanced NK and T cell activation** and promotes of a **durable immune response**

Bispecific HLA-A2 WT1/CD3 antibody in acute myeloblastic leukemia

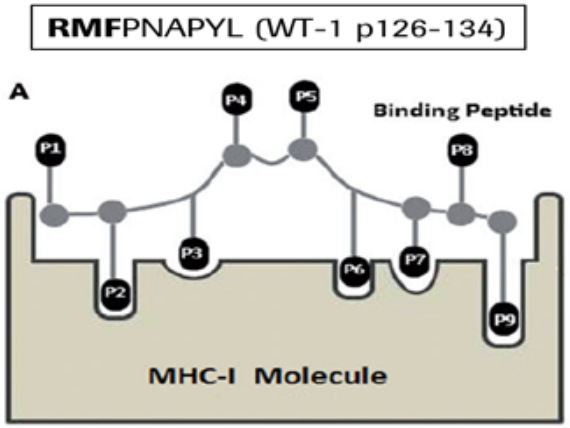
First human treated at Rigshospitalet 04 November 2020

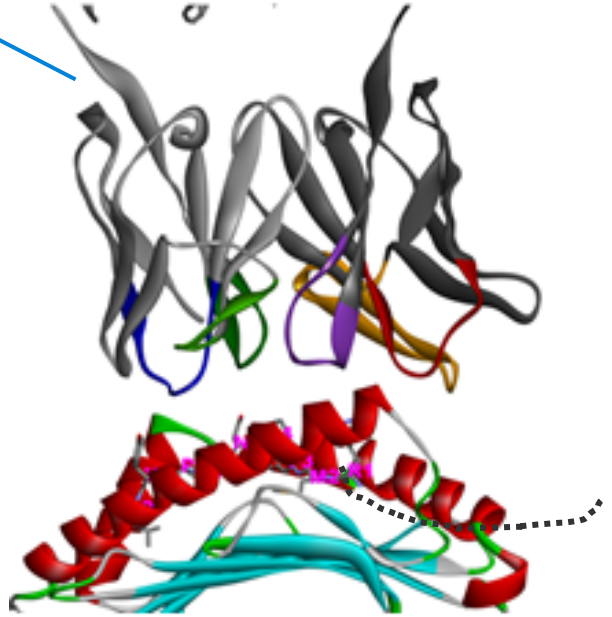


High avidity binding to tumor antigen

CD3 T cell engagement

Silent Fc for half-life extension



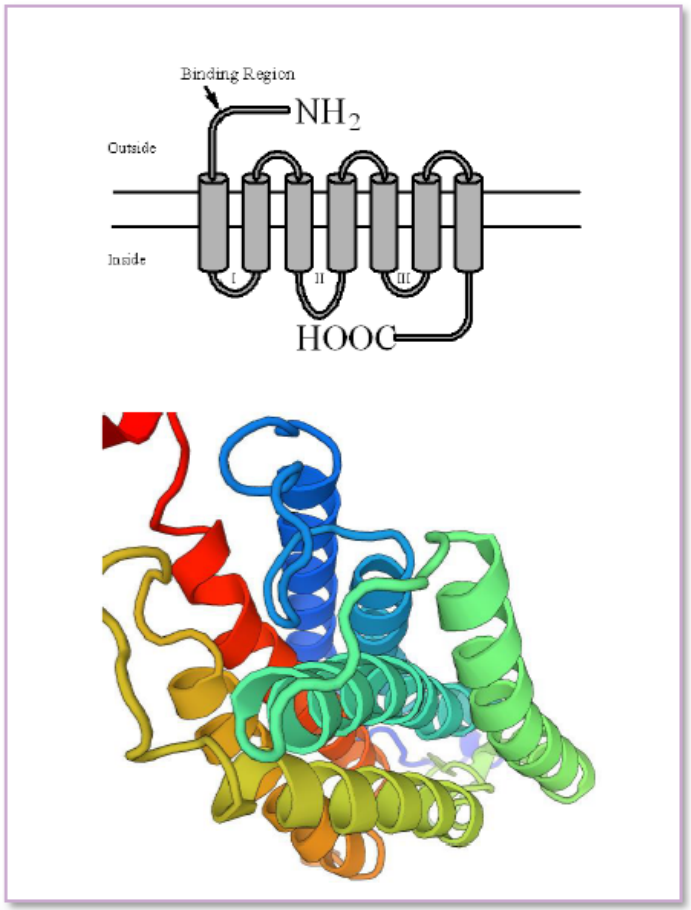


Affinity pMHC	Avidity pMHC	Affinity CD3
50 nM	450 pM	35-50 nM

Bispecific GPRC5D/CD3 antibody in multiple myeloma

First human treated at Rigshospitalet 11 November 2020

- G-protein coupled receptor family C group 5 (PRC5D) is an **orphan receptor** with **no known ligands or functions** in human (and human cancer)
- GPRC5D has **seven transmembrane** segments and is expressed in cell membranes
- The GPRC5D gene that is mapped on **chromosome12p13.3 contains three exons and spans about 9.6 kb**. The large first exon encodes the seven-transmembrane domain
- **Biological Function in MM not known**, but GPRC5D described to be **associated with poor prognosis and high tumour load** (plasma cell number) in MM patients[1, 2, 3]. GPRC5D does not seem to correlate with International Staging System score or any evaluated common cytogenetic abnormality[4]



[1]Venkateshaiah, Blood 2013; [2]Atamaniuk, ESCI 2012; [3]Cohen, Hematology 2013; [4]Smith, Sci Transl Med 2019

Rigshospitalet – ongoing phase 1 haematology studies

Protokol	Sponsor	EuDraCT	PI	Design	Status	Indication
BRF117019	Novartis	2012-001705-87	Martin	Basket	Inclusion completed	BRAF+ (MM + HCL)
INCB 50465-102	Incyte	2016-002829-11	Martin	Fase 1b	Inclusion completed	Follicular lymphoma
NP39461	Roche	2017-000357-39	Martin	Fase 1	Inclusion completed	DLBCL
CC-92480-MM-001	Celgene	2017-001236-19	Annette V	Fase 1 FIH	Open	Multiple myeloma
NP30179	Roche	2016-001185-28	Martin	Fase 1 FIH	Open	B-NHL
NP40126	Roche	2017-003648-18	Martin	Fase 1	Open	DLBCL/FL
M15-654	AbbVie	2017-002099-26	Annette V	Fase 1	Open	Multiple myeloma
NP39488	Roche	2017-004835-36	Martin	Fase 1	Open	B-NHL
GCT3013-01	Genmab	2017-001748-36	Martin	Fase 1 FIH	Open	B-NHL
BP41072	Roche	2019-000416-28	Martin	Fase 1 FIH	Open	B-NHL
CINC424H12201 (ADORE)	Novartis	2019-000373-23	Caroline	Fase 1-2	Open	Myelofibrosis
WP42004	Roche	2020-000216-30	Martin	Fase 1 FIH	Open	AML
BP42233 (GRACE)	Roche	2020-002012-46	Caroline	Fase 1 FIH	Open	Multiple myeloma
GO41582	Genentech	2019-003540-76	Annette V	Fase 1 FIH	Open	Multiple myeloma
GCT3009-01	Genmab	2019-002752-16	Martin	Fase 1 FIH	Open	B-NHL
GCT3013-02	Genmab	2020-000845-15	Martin	Fase 1b	Open	B-NHL
GCT3013-03	Genmab	2020-000848-57	Martin	Fase 1b	Open	CLL

Haematology FIH studies with first-patient-in at Rigshospitalet

Protokol	Sponsor	EuDraCT	PI	Design	Status	Indication
BRF117019	Novartis	2012-001705-87	Martin	Basket	Inclusion completed	BRAF+ (MM + HCL)
INCB 50465-102	Incyte	2016-002829-11	Martin	Fase 1b	Inclusion completed	Follicular lymphoma
NP39461	Roche	2017-000357-39	Martin	Fase 1	Inclusion completed	DLBCL
CC-92480-MM-001	Celgene	2017-001236-19	Annette V	Fase 1 FIH	Open	Multiple myeloma
NP30179	Roche	**2016-001185-28**	**Martin**	**Fase 1 FIH**	**Open (2017)**	**B-NHL**
NP40126	Roche	2017-003648-18	Martin	Fase 1	Open	DLBCL/FL
M15-654	AbbVie	2017-002099-26	Annette V	Fase 1	Open	Multiple myeloma
NP39488	Roche	2017-004835-36	Martin	Fase 1	Open	B-NHL
GCT3013-01	Genmab	2017-001748-36	Martin	Fase 1 FIH	Open	B-NHL
BP41072	Roche	**2019-000416-28**	**Martin**	**Fase 1 FIH**	**Open (2019)**	**B-NHL**
CINC424H12201 (ADORE)	Novartis	2019-000373-23	Caroline	Fase 1-2	Open	Myelofibrosis
WP42004	Roche	**2020-000216-30**	**Martin**	**Fase 1 FIH**	**Open (2020)**	**AML**
BP42233 (GRACE)	Roche	**2020-002012-46**	**Caroline**	**Fase 1 FIH**	**Open (2020)**	**Multiple myeloma**
GO41582	Genentech	2019-003540-76	Annette V	Fase 1 FIH	Open	Multiple myeloma
GCT3009-01	Genmab	2019-002752-16	Martin	Fase 1 FIH	Opens Jan 2021	B-NHL
GCT3013-02	Genmab	2020-000845-15	Martin	Fase 1b	Opens Jan 2021	B-NHL
GCT3013-03	Genmab	2020-000848-57	Martin	Fase 1b	Opens Feb 2021	CLL

Translational reasearch @ the Phase 1 Unit

- Targeted therapies
  - Clonal evolution and drug resistance
    - Repeated biopsies, ctDNA, CTC
    - Expression analysis
    - Organoids
  - Proteomics
  - Metabolomics
  - Drug repurposing
- Immunotherapy
  - Tumor mutational landscapes and neoepitopes
    - CTC, ctDNA, PBMC
  - PET: PD-L1, CD4, CD8
- Fusions and variants of unknown significance
  - Cell lines

The Phase 1 Unit

- Established in 2005
- Annual referrals: +600 pts
- Annual accrual 120-150 pts
- More than 50 ongoing phase I trials and early phase II (basket)
- Highly experienced in conduction of first-in-human trials
  - Oncology
  - Hematology
- Highly experienced in handling of CRS
- Fast track approval of phase 1 trials (approval often within 3 weeks)
- Serial biopsies, PD and PK
- Genomic profiling program since 2013
  - +2000 included (WES, RNA seq and SNP)
  - Preclinical program for drug-resistance and immunotherapy
- Pre-screening programs for mutations in ctDNA
- Pre-clinical drug testing program

Rigshospitalet – phase 1 Unit haematology studies

- National phase 1 unit for haematological malignancies since 2014
- Patients included from all over Denmark and Southern Sweden
- Among the leading centres in the World for early clinical development in lymphoma
- Over the last three years 40-50 patients included per year into haematology phase 1 studies, the majority in first-in-human studies and with a special focus on bispecific antibodies
- Four times since 2017 first site to administer a new, immunotherapeutic agent to patients with malignant lymphoma, multiple myeloma, and acute myeloid leukemia, respectively
- RH phase 1 unit represented as first or last author of oral presentations of phase 1 studies at every ASH, EHA, ASCO, and ICML meetings since 2018
- Currently 17 active haematology phase 1 studies, including 14 studies open for inclusion, plus 4-5 new studies opening in the coming six months
- Two haematology consultants, working in seamless collaboration with oncologists and nursing staff in the phase 1 unit

Recent publications from the Haematology Phase 1 Unit

- **Hutchings M**, Morschhauser F, Iacoboni G, et al. Glofitamab, a Novel, Bivalent CD20 Targeting T-cell Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed/Refractory B-cell Lymphoma: a Phase I Trial. **J Clin Oncol 2021** Mar 19;JCO2003175. doi: 10.1200/JCO.20.03175. Online ahead of print.
- **Hutchings M**, Mous R, Clausen MR, et al. Subcutaneous Epcoritamab in Patients With Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma: Results From the Dose-Escalation Part of a First-in-Human, Open-Label, Phase 1/2 Study. **Lancet 2021**, accepted for publication