SynteractHCR

Innovative Therapies in Oncology

Overview of Experience

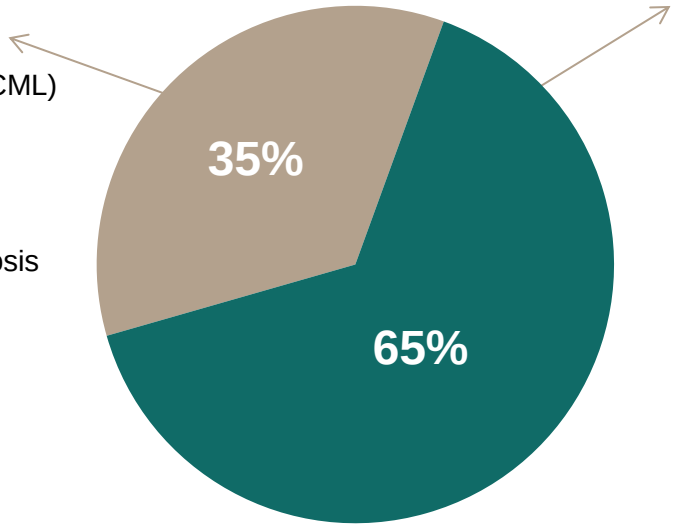
October 2015

Oncology Experience By Indication

We have performed nearly 500 Phase I-IV oncology projects

Hematological malignancies

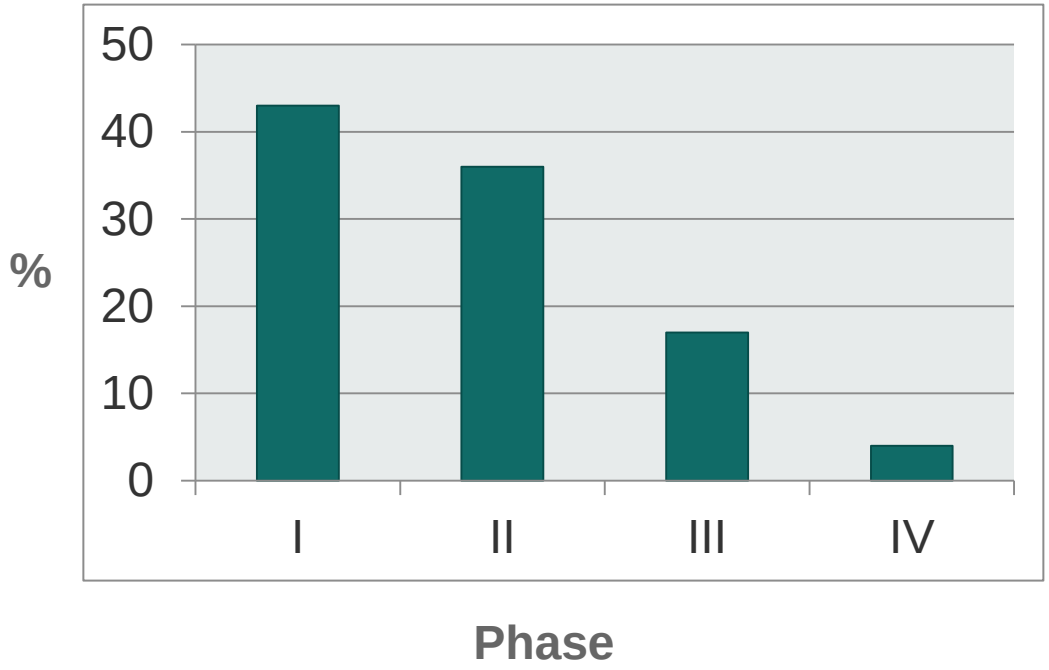
- Leukemia (ALL, CLL, AML, CML)
- Lymphoma
- Non-Hodgkin Lymphoma
- Multiple Myeloma
- Light chain amyloidosis
- Chronic idiopathic myelofibrosis



Other cancer types

- Melanoma
- Breast
- Lung (NSCLC/SCLC)
- Colorectal
- Gastro-intestinal
- Liver
- Kidney
- Pancreatic
- Head and eck
- Thyroid
- Brain
- Prostate
- Cervical
- Ovarian
- Soft tissue sarcoma

Oncology Study Experience by Phase

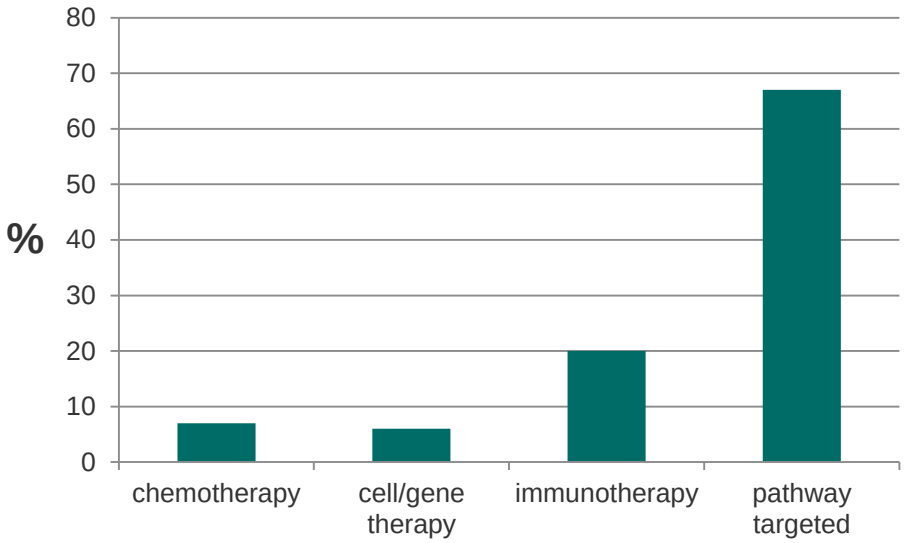


Global oncology study experience across all phases

Expertise With Innovative Therapies

SynteractHCR has built extensive experience in innovative therapeutic approaches including:

- ***Pathway-targeted therapies***
- ***Immunotherapy***
- ***Cell-based therapies***
- ***Gene-based therapy***



Specific Immunotherapy Experience

Studies have been performed with:

- Dendritic cell-based therapeutic cancer vaccines
- Cytotoxic T-cell therapy
- Monoclonal antibodies (passive and active therapy)
- Immune checkpoint inhibitors
- Cytokines (e.g. granulocyte colony-stimulating factor)

Dendritic Cell-Based Vaccines Experience

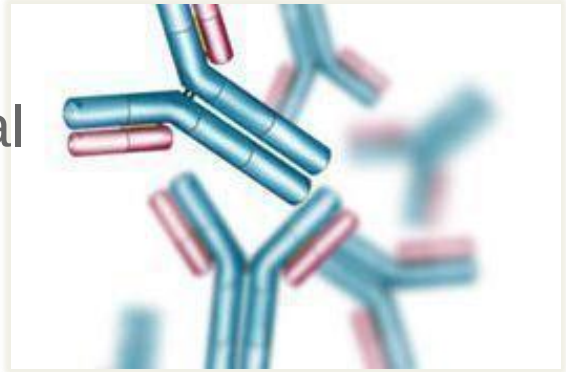
- Phase II study with **autologous mature dendritic cells transfected with mRNA encoding human telomerase reverse transcriptase (hTERT),** in patients with acute myeloid leukemia (AML) in complete clinical remission (US; 2014 – 2015)
- Global phase III study with **autologous dendritic cells pulsed with tumor lysate antigen (DCVax-L)** for treatment of glioblastoma multiforme (US, CAN, DEU, UK; 2007 – 2015)

Cytotoxic T-cell Therapy Experience

- Phase I study of tolerability and safety of repeat administrations of autologous lymphoid effector cells in prostate cancer patients (DNK; 2011 – 2012)

- Phase II study with **cytotoxic T-cell therapy** in combination with imatinib in chronic myeloid leukemia (ITA; 2008 – 2013)

Monoclonal Antibodies (mAbs) Experience



- First-In-Human phase I dose escalation trial of the **humanized anti-CD47 monoclonal antibody** in acute myeloid leukemia (UK; 2015 – 2017)
- Phase II study with repeated dosing of a trifunctional anti-HER2/neu x anti-CD3 monoclonal antibody for hormone therapy refractory patients with HER2/neu 1+ or 2+ expressing advanced or metastatic breast cancer (DEU, ITA, ESP, FRA, AUT; 2008 – 2010)
- Randomized, double-blind, placebo-controlled phase II trial of **bavituximab** plus docetaxel in patients with previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (IND, US; 2010 – 2012)

Monoclonal Antibodies (mAbs) Experience (cont.)

- Pivotal, multicenter, phase II with **BITE monoclonal antibody** in adults with beta-precursor acute lymphoblastic leukemia (2010 - 2014)
- Study performed in **11 European countries** (BEL, NLD, DEU, AUT, FRA, ITA, ESP, GBR, POL, ROU, CZ) and Russia
  - 80 investigational sites and ~ 200 patients enrolled
- **Timely study start-up** (including regulatory submissions) in all participating countries
- **Challenging inclusion/exclusion criteria**
  - Pre-screening strategy implemented to cope with the recruitment challenge, resulting in the expected patient enrollment

Immune Checkpoint Inhibitors Experience

- Phase I/II study to assess safety and efficacy of Toll-like receptor 9 agonist in combination with **ipilimumab targeting CTLA-4**, in patients with metastatic melanoma (US; 2015 – 2020)

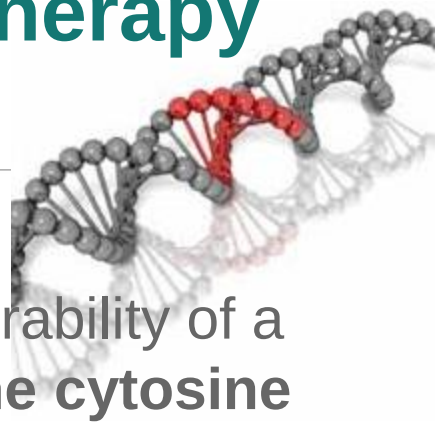
- Phase II study evaluating combination therapy using autologous dendritic cells pulsed with tumor lysate antigen and **anti-PD-1 antibody nivolumab** in patients with recurrent glioblastoma multiforme (US; 2015 – 2018)

Cytokines (G-CSF) Experience

- Randomized, double-blind, parallel-group, multi-center phase III comparative study investigating efficacy and safety of **pegfilgrastim (G-CSF)** in breast cancer patients treated with myelosuppressive chemotherapy (DEU; 2012 – 2013)

- Phase IV study with dose-dense chemotherapy in combination with **pegfilgrastim (G-CSF)** to treat B-cell lymphoma in patients older than 65 years and in low-risk patients younger than 65 years (ESP; 2005 – 2013)

Cell-based and Gene-based Therapy Experience



- Phase I ascending dose trial of the safety and tolerability of a **retroviral replicating vector encoding transgene cytosine deaminase** in patients undergoing subsequent resection for recurrent high grade glioma and followed by treatment with the prodrug 5-fluorocytosine (US; 2009 – 2016)
- Open-label, uncontrolled phase I/II study with **genetically modified allogeneic mesenchymal stem cells** to treatment of advanced gastrointestinal adenocarcinoma (DEU; 2015 – 2017)
- Randomized, controlled phase II study with **myeloid progenitor cell therapy** in patients receiving chemotherapy for acute myeloid leukemia (US; 2014 – 2016)

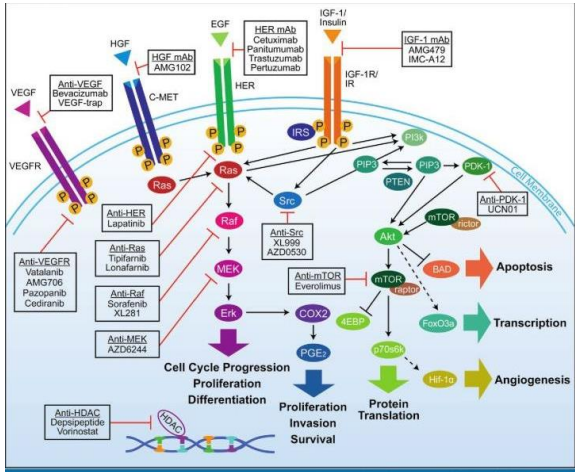
Experience With Pathway-Targeted Therapies

Performed studies with therapies targeting:

Hematological malignancies	Other tumor types
Hepcidin Kinase (incl. Tyrosine kinase) Aminopeptidase Metalloenzyme Telomerase TORC1/2 Sam68 Histone deactylase Proteasome Notch signaling Lysine-specific histone demethylase BET bromodomain	Kinase (incl. Tyrosine kinase, MEK, serine/threonine, polo-like) Epidermal growth factor receptor Telomerase Lysyl oxidase Estrogen receptor Nucleolin TORC1/2 Topoisomerase Notch signaling Wnt signaling Proteasome Coagulation factor VIIa Proto-oncogene BRAF Toll-like receptor

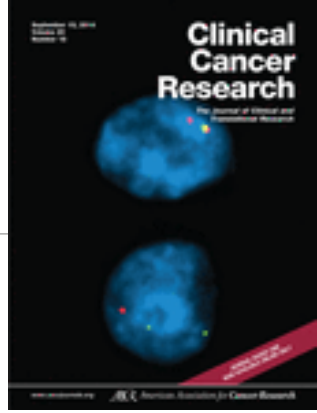
Pathway-Targeted Therapy Experience

- Phase I study of a **telomerase inhibitor** in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (US; 2009 – 2011)
- Phase Ib study to assess the safety of a **receptor tyrosine kinase inhibitor** and paclitaxel in patients with advanced solid tumors (US; 2015 – 2017)
- Phase II two-arm trial of **HDAC inhibitor** with decitabine in elderly patients with newly diagnosed acute myeloid leukemia (AML) (US; 2013 – 2015)
- Phase Ib/II safety and efficacy study of **anti-Notch antibody therapy** with etoposide and platinum therapy in small cell lung carcinoma (FRA, ESP, US; 2014 – 2017)



Source: J Natl Cancer Inst © 2009 Oxford University Press

Pathway-Targeted Therapy Case Study



Study performed by SynteractHCR (NLD; 2008 – 2012) published in
Clinical Cancer Research, 20 (18), 4776 – 83 (2014)

Phase I Study of RGB-286638, A Novel, Multitargeted Cyclin-Dependent Kinase Inhibitor in Patients with Solid Tumors – Abstract:

- **Purpose:** RGB-286638 is a multitargeted inhibitor with targets comprising the family of cyclin-dependent kinases (CDK) and a range of other cancer-relevant tyrosine and serine/threonine kinases. The objectives of this first in human trial of RGB-286638, given i.v. on days 1 to 5 every 28 days, were to determine the maximum tolerated dose (MTD) and to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of this new drug.

- **Experimental Design:** Sequential cohorts of 3 to 6 patients were treated per dose level. Blood, urine samples, and skin biopsies for full PK and/or PD analyses were collected.

- **Results:** Twenty-six patients were enrolled in 6-dose levels from 10 to 160 mg/d. Four dose-limiting toxicities were observed in 2 of the 6 patients enrolled at the highest dose level. These toxicities were AST/ALT elevations in 1 patient, paroxysmal supraventricular tachycardias (SVTs), hypotension, and an increase in troponin T in another patient. The plasma PK of RGB-286638 was shown to be linear over the studied doses. The interpatient variability in clearance was moderate (variation coefficient 7%–36%). The PD analyses in peripheral blood mononuclear cells, serum (apoptosis induction) and skin biopsies (Rb, p-Rb, Ki-67, and $p27^{KIP1}$ expression) did not demonstrate a consistent modulation of mechanism-related biomarkers with the exception of lowered Ki-67 levels at the MTD level. The recommended MTD for phase II studies is 120 mg/d.

- **Conclusions:** RGB-286638 is tolerated when administered at 120 mg/d for 5 days every 28 days. Prolonged disease stabilization (range, 2–14 months) was seen across different dose levels.

Diane A.J. van der Biessen, Herman Burger, Peter de Bruijn, Cor H.J. Lamers, Nicole Naus, Hannes Loferer, Erik A.C. Wiemer, Ron H.J. Mathijssen, and Maja J.A. de Jonge,*

To learn more call +1-760-268-8200
or visit www.SynteractHCR.com