



an integrated
strategy
to cure cancer



PRODUCT

Recombinant fusion protein combining a vessel-specific tumour-homing peptide (NGR) with the human cytokine TNF

CONCEPT

First-in-class vascular targeting agent (VTA) in the class of peptide-cytokine complexes

INDICATIONS

Currently investigated in Phase III clinical trial in mesothelioma, and in Phase II clinical trials in colorectal, liver, lung (SCLC and NSCLC) and ovarian cancer

Orphan Drug status in the EU and in the US for the treatment of MPM, and for the treatment of HCC

CLINICAL STATUS

- 1 Phase III trial as monotherapy in mesothelioma
- 2 Phase II trials as monotherapy, in colorectal and liver cancer
- 4 Phase II trials in combination therapy: with Xelox in colorectal cancer; with doxorubicin in small-cell lung and ovarian cancer; with platinum-based regimens in non-small-cell lung cancer
- 1 Phase I trial exploring escalating doses in the high-dose range

MARKET

Sales of targeted cancer therapies in the 7 major pharma markets expected to grow to US\$ 29,1 billion by 2015

PARTNERSHIP

Available for co-development and out-licensing agreements

NGR-hTNF

A unique vascular targeting agent for the treatment of solid tumours

PRODUCT PROFILE

NGR-hTNF is a vascular targeting agent characterised by a unique mode of action, and is first-in-class in the class of peptide-cytokine complexes targeting tumour blood vessels. It is a fusion protein obtained by combining a tumour homing peptide (NGR) with the human cytokine Tumour Necrosis Factor (hTNF).

CONCEPT

NGR-hTNF acts directly and specifically on blood vessels feeding the tumour mass, causing their functional alteration: its peptide moiety NGR binds to a particular form of CD13, a receptor selectively expressed by endothelial cells of human tumour blood vessels during the formation of new vessels, while it does not home to tumour-unrelated human tissues. The binding of NGR-hTNF to tumour endothelial cells induces cell death by eliciting defined signalling pathways through the surface receptors for both moieties of the molecule, i.e. CD13 and TNF-R.

Functional alteration of tumour blood vessels induced by NGR-hTNF leads *inter alia* to an increase in vascular permeability, thus allowing improved penetration into the tumour tissue of other anticancer drugs administered in combination, enhancing their therapeutic efficacy. Therefore, NGR-hTNF can be used both as new single-agent therapeutic option, and in synergical combinations with most cytotoxic regimens currently available.

NGR-hTNF acts independently of tumour type and has a low risk of inducing pharmacological resistance: therefore, it has therapeutic potential for most vascularised solid tumours.

ADDRESSING INDICATIONS WITH HIGH UNMET NEED

MolMed's clinical development plan for NGR-hTNF is focused on solid tumours with very different growth patterns and very different levels of incidence: however, they all share the common traits of severity and actual need of new therapeutic options.

On one hand, MolMed is addressing tumours considered to be either rare or with limited diffusion - although with ever-growing incidence - that have no or very few therapeutic options available, such as malignant pleural mesothelioma, primary liver cancer and small-cell lung cancer (SCLC).

NGR-hTNF - A unique vascular targeting agent for the treatment of solid tumours



On the other hand, clinical investigation of NGR-hTNF includes much more widespread indications - such as colorectal, ovarian and non-small cell lung cancer - that have a much wider range of treatments available or in development, but with many patients becoming either intolerant or refractory to all possible treatment lines over time. For these heavily pre-treated patients with no options left, MolMed intends to offer a new and efficacious treatment thanks to the unique mode of action of NGR-hTNF, overcoming pharmaco-resistance developed towards previous treatments.

CLINICAL DEVELOPMENT

NGR-hTNF is undergoing clinical development in two different programmes:

- As novel monotherapy option
- In combination therapy with different cytotoxic regimens

Monotherapy - Phase III trial

- Mesothelioma - pivotal randomised (NGR015)

Monotherapy - Phase II trials

- Colorectal cancer (NGR006)
- Liver cancer (NGR008)

Positive preliminary results of these trials presented in 2008 at ASCO (*Abstracts 4110, 15544*), at ESMO (*Abstracts 397P, 546P*), and in 2009 at ASCO (*Abstracts 4088, 15500*) and at ESMO (*Abstracts 6062, 6617*)

Monotherapy - Phase I trial

- Dose-escalating, investigating administration at high doses (NGR013)

Combination with chemotherapeutic agents - Phase II trials

- Colorectal cancer, with Xelox (NGR005) - results presented at ESMO 2009 (*Abstract 6066*)
- Small-cell lung cancer, with doxorubicin (NGR007)
- Ovarian cancer, with doxorubicin (NGR012)
- Non-small-cell lung cancer, with either of two platinum-based regimens (cis/gem or cis/pem) - randomized (NGR014)

MARKET

MolMed plans to develop NGR-hTNF as a novel therapeutic option for relapsing disease in indications with high unmet medical need: colorectal, liver, lung (small cell and non-small cell) and ovarian cancers, malignant pleural mesothelioma and soft tissue sarcoma.

The overall market potential of NGR-hTNF is considerable: it has use as a single agent therapy, as part of combination therapy with standard chemotherapy regimens, and in pre-surgery treatment as a neoadjuvant. Sales of innovative and targeted cancer therapies across the seven major pharmaceutical markets generated US\$ 22 billion sales in 2006, and forecasted sales are expected to grow to US\$ 29,1 billion by 2015 (*Source: Business Insight 2007*).

ORPHAN DRUG STATUS

NGR-hTNF was granted Orphan Drug designation in the EU and in the US for the treatment of malignant mesothelioma in 2008, and for the treatment of liver cancer in 2009.

PARTNERSHIP OPPORTUNITIES

MolMed is available to co-development and out-licensing partnerships for completion of the NGR-hTNF clinical program and product commercialisation. MolMed is particularly interested in collaborations with major pharmaceutical or medical biotech companies interested in strengthening their existing oncology portfolio.

CONTACT

Holger Neecke
Director Business Development
e-mail: holger.neecke@molmed.com

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