

National Horizon Scanning Centre

**INGN 201 (contusugene
ladenovec; Advexin)**

**for Li-Fraumeni syndrome associated
cancers**

December 2007



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INGN 201 (contusugene ladenovec; Advexin) for Li-Fraumeni syndrome associated cancers

Target group

- Li-Fraumeni syndrome associated cancers (LFS)

Background

Li-Fraumeni syndrome is a rare autosomal dominant disorder, which is caused by mutations in p53, a tumour suppressor gene (identified in approximately 70-80% of patients with clinical characteristics of LFS). P53 is the most frequently mutated gene in cancer and loss of one normal copy of p53 in the germline leads to a very high risk of developing a variety of cancers at an early age. The most frequent cancers in carriers of germline p53 mutations are breast carcinoma, soft-tissue sarcomas, brain tumours, osteosarcoma, and adrenocortical carcinoma, however, other types of tumour can also arise and multiple primary cancers frequently occur^{1,2}. Several members of the same family can suffer from the condition, for which there are no specific therapies.

Technology description

INGN 201 (contusugene ladenovec, Advexin) is an adenoviral p53 gene therapy system which combines the p53 tumour suppressor with a non-replicating, non-integrating adenoviral delivery system. The company anticipates that INGN 201 will be used as a monotherapy, administered directly into tumours (intratumoural).

INGN 201 is in phase III clinical trials for head and neck cancer and in phase II clinical trials for breast cancer and non-small cell lung cancer.

Innovation and/or advantages

There are currently no licensed therapies to specifically treat LFS associated cancers. It is anticipated that INGN 201 will be used with a view to prolonging survival.

Developer

Introgen Therapeutics.

Place of use

- | | | |
|---|---|--|
| <input type="checkbox"/> Home care e.g. home dialysis | <input type="checkbox"/> Community or residential care e.g. district nurses, physio | <input type="checkbox"/> Primary care e.g. used by GPs or practice nurses |
| <input type="checkbox"/> Secondary care e.g. general, non-specialist hospital | <input checked="" type="checkbox"/> Tertiary care e.g. highly specialist cancer centres | <input type="checkbox"/> Emergency care e.g. paramedic services, trauma care |
| <input type="checkbox"/> General public e.g. over the counter | <input type="checkbox"/> Other: | |

Availability, launch or marketing dates, and licensing plans:

The company anticipate a licence application in Europe by the end of 2007. INGN 201 has been designated an orphan drug for this indication in Europe. INGN 201 is pre-registration in the EU for LFS.

NHS or Government priority area:

This topic is relevant to the NHS Cancer Plan.

Relevant guidance

LFS leads to an increasing susceptibility to cancers, including breast cancer and soft tissue sarcomas. Relevant guidance is listed below:

Breast cancer

- NICE clinical guideline. Familial breast cancer, 2006³.
- NICE clinical guidelines in progress (due January 2009):
 - Advanced breast cancer – diagnosis and treatment
 - Early breast cancer – diagnosis and treatment
- SIGN clinical guideline. Management of breast cancer in women, 2005⁴.

Sarcoma

- NICE: Improving outcomes for people with sarcoma, 2006⁵.

Clinical need and burden of disease

It is difficult to estimate the incidence of this rare disease because the frequency of germline p53 mutations among patients with cancers characteristic of LFS is not known with any accuracy. The disease affects predominantly young people and the historical definition is based on family-related criteria, i.e. the diagnosis of a sarcoma in a patient under 45 years, who has a first-degree relative diagnosed with any cancer before the age of 45, and another first or second degree relative in the same lineage diagnosed with any cancer before the age of 45 years or sarcoma at any age⁶.

The risk of developing a cancer for a patient carrying deleterious mutation of the p53 gene is, 15% by age 15 years, 84% by age 45 years in women and 41% by age 45 years in men with the significant difference between the sexes almost entirely explained by breast cancers⁷. Breast cancer can account for more than 40% of cancers in females affected by LFS. Other than breast cancer, no evidence exists of increased penetrance of cancer predisposition related to sex⁶. The risk of developing a second cancer, especially a radiation-induced cancer, is high⁸.

The incidence of LFS in the general population is not well identified, but expert opinion suggests that LFS is exceedingly rare. Approximately 260 families with LFS have been described worldwide⁹. Of children with soft tissue sarcomas, 5-10% have family histories of malignancies consistent with LFS or other syndromes with an autosomal dominant inheritance pattern⁶.

Existing comparators and treatments

- Genetic counselling and genetic testing
- Prevention of second cancers e.g. regular MRI breast screening

There are currently no approved therapies to specifically treat LFS-related cancers and successful treatment can be problematic due to the frequency of multiple malignancies, and the development of treatment resistance. An additional problem is that conventional cytotoxic therapies (chemotherapy and radiotherapy) that induce DNA damage also contribute to the high incidence of treatment related secondary malignancies in these patients¹⁰.

Efficacy and safety

Trial name	P53 therapy (INGN 201) in a patient with LFS
Sponsor	Grant support: Introgen Therapeutics Inc.
Status	Published ¹⁰
Location	USA
Design	Non-randomised; uncontrolled
Participants	n=1; 25-year-old female from a family with LFS; refractory to previous cytotoxic therapy, progressive LFS embryonal carcinoma. The patient had three pelvic tumours with only one accessible for intra-lesional injection with INGN201. Received INGN201 at a dose of 2×10^{12} viral particles per injection, twice weekly on days 2 and 4 of week 1, then every 28 days for 2 additional treatments.
Follow-up	4 months
Primary outcome	Complete remission
Secondary outcome	Improvement of tumour-related symptoms
Key results	Treatment led to improvement of tumour-related symptoms and a complete remission at 4 months, determined by fusion fluorodeoxyglucose (FDG) positron emission tomography (PET) scans.
Adverse effects	Well tolerated; grade 1 pain at injection site and transient fever.

Estimated cost and cost impact

The cost of INGN 201 has yet to be determined.

Potential or intended impact – speculative**Patients**

- | | | |
|---|---|---|
| <input checked="" type="checkbox"/> Reduced morbidity | <input checked="" type="checkbox"/> Reduced mortality or increased survival | <input checked="" type="checkbox"/> Improved quality of life for patients and/or carers |
| <input type="checkbox"/> Quicker, earlier or more accurate diagnosis or identification of disease | <input type="checkbox"/> Other: | <input type="checkbox"/> Non identified |

Services

- | | | |
|---|--|---|
| <input checked="" type="checkbox"/> Increased use e.g. length of stay, out-patient visits | <input type="checkbox"/> Service reorganisation required | <input type="checkbox"/> Staff or training required |
| <input type="checkbox"/> Decreased use | <input type="checkbox"/> Other: | <input type="checkbox"/> Non identified |

Costs

- | | | |
|--|--|---|
| <input type="checkbox"/> Increased unit cost compared to alternative | <input type="checkbox"/> Increased costs: more patients coming for treatment | <input type="checkbox"/> Increased costs: capital investment needed |
| <input checked="" type="checkbox"/> New costs: | <input type="checkbox"/> Savings: | <input type="checkbox"/> Other: |

References

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The National Institute for Health Research National Horizon Scanning Centre Research Programme is funded by the Department of Health.
The views expressed in this publication are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health

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