

# LOR-2040

A novel RNA-targeted therapy being developed for the treatment of relapsed or refractory acute myeloid leukemia

## MARKET OPPORTUNITY

- Significant unmet medical needs exist in oncology for:
  - Effective targeted therapies with utility in many cancers
  - Less toxic agents that can be combined with existing cytotoxic drugs for more tolerable and effective treatment
  - Effective salvage therapies for refractory and relapsed patients to overcome resistance

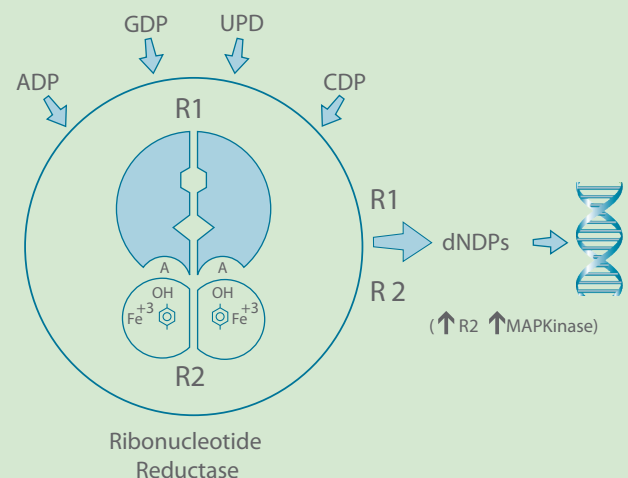
LOR-2040 has been designated Orphan Drug status for the treatment of AML by the U.S. FDA, providing seven years of market exclusivity in the U.S. upon the drug's approval for this indication.

LOR-2040 offers broad-spectrum activity in a variety of hematological and solid tumor diseases, representing considerable market potential.

| Cancer indication | US incidence (2011) | LOR-2040 US Market Potential (USD) | LOR-2040 Global Market Potential (USD) |
|-------------------|---------------------|------------------------------------|--|
| AML               | 13,000              | 60M                                | 170M                                   |
| MDS               | 12,000              | 110M                               | 335M                                   |
| Bladder           | 70,000              | 240M                               | 710M                                   |
| Prostate          | 241,000             | 1.5B                               | 4.3B                                   |
| NSCLC             | 188,000             | 7.0B                               | 20B                                    |
| Breast            | 230,000             | 6.5B                               | 19B                                    |
| Colorectal        | 142,000             | 3.4B                               | 10B                                    |

## MECHANISM OF ACTION

- LOR-2040 is a 20-mer antisense oligonucleotide that specifically targets the R2 subunit of ribonucleotide reductase (RNR), resulting in inhibition of DNA synthesis, cell division, and tumor growth.
- R2 is a highly regulated, cell cycle-controlled protein whose activity is required for DNA synthesis and repair.
- R2 has been identified as a genetic determinant that can profoundly alter the malignant potential of cancer cells.
- Elevated expression of R2 and RNR activity have been noted in a variety of primary tumors and tumor cell lines, and activation of the raf/ras/MAPK pathway can be induced through deregulated expression of the R2 RNR component.
- Overexpression of R2 increases the invasive potential of cancer cells. R2 expression can also determine tumor sensitivity to a variety of drugs with different modes of action.



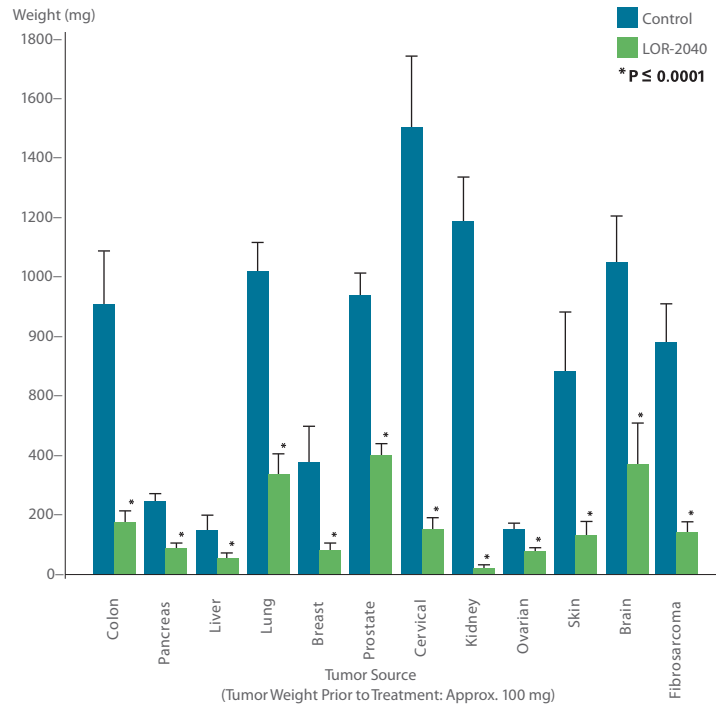
# PRECLINICAL RESULTS:

- LOR-2040 has broad-spectrum activity in preclinical models, showing excellent antitumor efficacy.
- Antitumor activity of LOR-2040 is achieved at much lower doses than toxic dose, demonstrating a broad therapeutic window.
- Strong cooperative efficacy has been demonstrated preclinically with LOR-2040 in combination with a variety of chemotherapeutic regimens.
- Antimetastatic activity of LOR-2040 has been demonstrated in standard *in vivo* metastasis assays.
- Of importance to leukemia indications, LOR-2040 was highly effective in lymphoma and erythroleukemia survival models in mice in preventing almost all mortality, and this benefit was sustained in a discontinuation experiment even after the drug treatment was stopped.
- GLP-toxicology studies determined that LOR-2040 is well tolerated at doses up to 80 mg/kg in acute iv study in rhesus monkeys and at doses up to 50 mg/kg/day in 21-day repeat dose studies in rats and rhesus monkeys.
- Additional target validation studies conducted by Lorus using R2-specific siRNA showed that R2 downregulation correlated with dose-dependent antitumor activity in mouse models of renal cell carcinoma, and that specific knockdown of R2 expression resulted in antiproliferative activity and cell cycle arrest *in vitro*.
- The experimental evidence confirms that the antitumor activity of LOR-2040 is attributable to R2 target downregulation and not immunostimulatory factors.
- For further information, please refer to references 1 and 2.

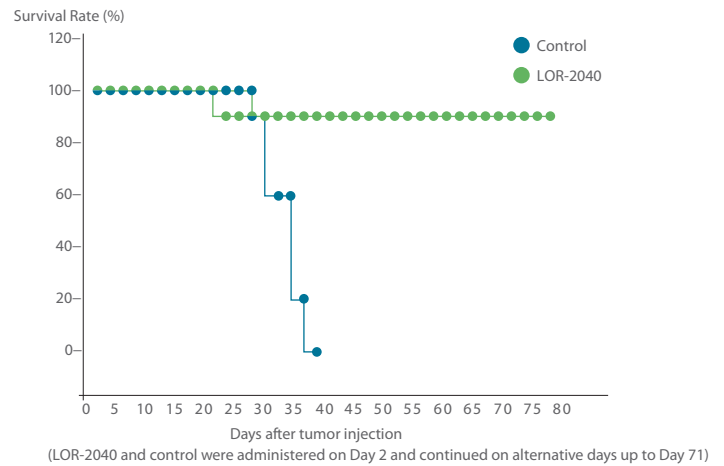
## LOR-2040 CLINICAL DEVELOPMENT PROGRAM

- LOR-2040 development strategy in the clinic is focused primarily on combination administration with established chemotherapy due to strong cooperative activity seen preclinically, and the role of R2 downregulation in sensitizing many cancers to chemotherapy. Early clinical results have validated this strategy.
- Based on the target specificity and excellent single-agent tolerability of LOR-2040, it was anticipated that it would contribute minimal additional toxicity when added to many chemotherapy or immunotherapy regimens, while providing a more effective treatment opportunity.
- The following table summarizes all currently active clinical development programs with LOR-2040, including a number of studies sponsored by the U.S. National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP).

LOR-2040 PRECLINICAL EFFICACY IN VARIOUS HUMAN XENOGRAFT MODELS



SURVIVAL RATE OF CB-17 SCID MICE BEARING ERYTHROLEUKEMIA (CB7) TREATED WITH LOR-2040



### Current and Completed Trials

| Cancer Indication                                   |
|---|
| Acute Myeloid Leukemia (Refractory/Relapsed)        |
| Acute Myeloid Leukemia (Refractory/Relapsed)        |
| High-Grade Myelodysplastic Syndromes/Acute Leukemia |
| Bladder (Superficial and Non-Invasive)              |
| Prostate  |
| Non-Small Cell Lung                                 |
| Breast  |
| Colorectal  |
| Solid Tumors  |
| Renal Cell Carcinoma                                |
| Solid Tumors  |

# CLINICAL RESULTS:

## Acute Myeloid Leukemia Program:

- **Phase Ib** LOR-2040/high-dose cytarabine combination study in AML patients < 60 years of age with pharmacodynamic dose ranging and efficacy objectives:

- This study evaluated a range of clinically active doses of this combination and established a 6 day course of 5 mg/kg LOR-2040 c.i.v. combined with cytarabine 3 g/m2 twice daily for 4 of 5 days as the recommended Phase II dose.

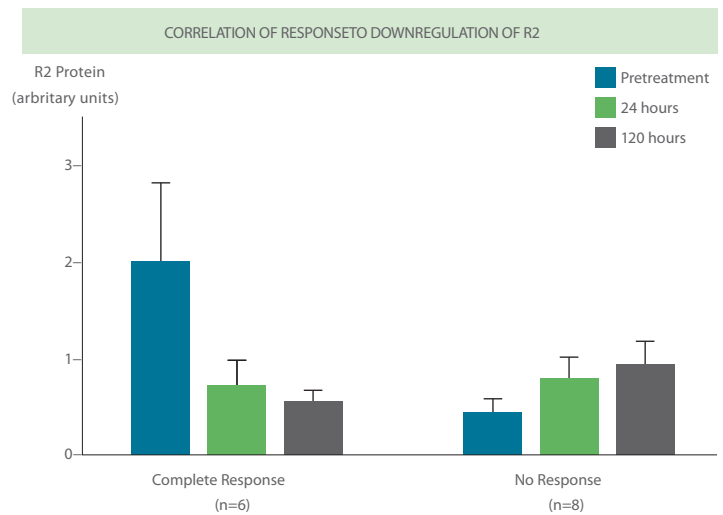
- Favorable disease responses included complete responses in 8 (35%) of the 23 patients and significant cyto-reduction of leukemic blasts in 2 others. Seven of these 10 patients were further able to progress to a successful transplant, a desired outcome of successful salvage therapy. Notably, the study population included unfavorable patients with at least one adverse prognostic characteristic, in whom 50% were prior refractory and 50% relapsed in a median of <6 months.

| Cancer indication | Pts <60 years (n=23)                         | Proceeded to Successful Allogeneic SCT |
|-------------------|--|--|
| CR                | 8<br>(5 prior relapsed, 3 prior refractory*) | 5                                      |
| MRD               | 2<br>(cyto-reduction to <10% BM blasts)      | 2                                      |

CR : Complete Remission; MRD : Minimal Residual Disease  
 \* Historically expected 2<sup>nd</sup> CR rate in refractory/relapsed (with <12 mo duration of 1<sup>st</sup> CR) is only 10-20% (Additionally some prior refractory patients had failed prior high dose cytarabine)

- Intracellular LOR-2040 levels were achieved within 24 hours:
  - Maintained over time with continuous infusion dosing in peripheral blood mononuclear cells (and for at least 2 days after end of dosing).
  - Increased to even higher levels over 5 days in bone marrow, suggesting accumulation in bone marrow.

- Changes in R2 protein level correlated with disease response:
  - R2 downregulation was seen in patients who achieved CR, and this downregulation occurred rapidly within 24 hours;
  - Pre-Treatment R2 levels were significantly higher in patients who eventually achieved CR;
  - Downregulation of R2 over 1 and 5 days in responding patients is shown below.



- Higher intracellular levels of LOR-2040 in more overtly leukemic CD34+ blasts correlate with more R2 downregulation
- Toxicities were comparable to those expected from high-dose cytarabine therapy alone and were not dose limiting.
- For further information, please refer to references 3 and 4.

- **Phase II** LOR-2040/high-dose cytarabine combination study in relapsed/refractory AML patients < 60 years of age:
  - Steering Committee favorably reviewed top line results:
    - Stage 1 protocol criterion achieved
    - Efficacy justifies expansion to large comparative trial to support registration
  - Results confirm and extend prior Phase Ib results:
    - Response rate for CR was twice that of risk-matched historical treatment
    - Finding robust across risk categories
    - Full analysis and peer reviewed presentation and publication planned

## Solid Tumor Programs:

- A series of 5 exploratory studies in various solid tumors, including colon cancer, breast cancer, non-small cell lung cancer (NSCLC), and hormone-refractory prostate cancer were undertaken by the U.S. NCI-CTEP under a clinical trials agreement with Lorus following a review of prior preclinical and clinical data.

- Interim findings include: 47% with PSA response and only 7% with progression in combination with docetaxel and prednisone in hormone-refractory prostate cancer; minor activity in combination with docetaxel in NSCLC; preliminary evidence of R2 downregulation associated with clinical activity in combination with capecitabine in breast cancer.

- Dose schedule optimization studies conducted in the laboratory by Lorus in parallel with the clinical program have shown strong schedule-dependent synergy in support of an optimized sequential schedule for further clinical development of this combination.

- For further information, please refer to references 5 - 7.

| Combination Agent(s)     | Status               | Sponsor |
|--------------------------|----------------------|---------|
| Cytarabine               | Phase II Completed   | Lorus   |
| Cytarabine               | Phase I Completed    | NCI     |
| -                        | Phase I Ongoing      | NCI     |
| -                        | PD Trial (Plan)      | Lorus   |
| Docetaxel/Prednisone     | Phase II Completed   | NCI     |
| Docetaxel                | Phase I/II Completed | NCI     |
| Capecitabine             | Phase II Completed   | NCI     |
| Capecitabine/Oxaliplatin | Phase I Completed    | NCI     |
| Gemcitabine              | Phase I Completed    | NCI     |
| Capecitabine             | Phase I/II Completed | Lorus   |
| -                        | Phase I Completed    | Lorus   |

# DEVELOPMENT STATUS

## - NEXT STEPS

- Acute Myeloid Leukemia Program:
  - Plan to initiate a randomized, placebo-controlled, Phase IIb/III multinational trial with co-development or licensing support in 2012 to **support registration**:
    - In relapsed/refractory AML < 60 yrs
    - LOR-2040 + HiDAC vs. HiDAC
    - Adaptive design appropriate to AML provides high probability of success
    - Primary endpoint: Overall survival and/or complete response
    - Feedback and guidance from FDA on study protocol plan provides development clarity
- Myelodysplastic Syndrome Program:
  - Lorus has undertaken, with U.S. NCI-CTEP sponsorship, a Phase I study of single-entity LOR-2040 in myelodysplastic syndrome (MDS) and related acute leukemias (AL). This ongoing study is intended to explore the opportunity for development of LOR-2040 in an MDS indication and for future potential combination with established first line drugs.
- Solid Tumor Programs:
  - The Lorus program with LOR-2040 in solid tumors includes 5 studies sponsored by NCI-CTEP that have been completed. Future development in solid tumors will require selection of the best indication from the study programs in NSCLC, prostate cancer, breast cancer, colon cancer, and solid tumors, with various chemotherapies in combination with LOR-2040 and strategies for optimizing the combination dose schedule.
- Bladder Cancer Program (intravesicular route):
  - Intravesicular administration of LOR-2040 has the potential advantage of directly targeting an accessible tumor in the bladder wall in order to achieve high local uptake by tumors without systemic effects.
  - The preclinical program of LOR-2040 in support of the bladder cancer program was completed in Q3 2008.
  - A pilot study study of LOR-2040 as a single agent administered intravesically in patients with superficial and non-invasive bladder cancer has been designed and prepared for IND submission.

## Partnering Status

Lorus Therapeutics is seeking partners who are interested in co-development and commercialization of LOR-2040 in the U.S., Europe and rest of the world.

For further enquiries:

[www.lorusthera.com](http://www.lorusthera.com)

Email: [bd@lorusthera.com](mailto:bd@lorusthera.com)

Phone: +1-416-798-1200 x 394



# LOR-2040 - POINTS OF DIFFERENTIATION

- Excellent Target
  - Validated (HU, siRNA and others) - loss of activity can not be compensated
  - Highly over-expressed in cancer cells - modifies malignancy related pathways
  - Cooperates with a variety of oncogenes to enhance cellular transformation and malignant potential
- Specific and selective anti-tumor agent
  - Excellent antitumor efficacy in tumor growth, metastasis and survival assays in a broad range of cancers
  - Strong efficacy in combination with standard therapeutic regimens
- Clinically relevant target down regulation
  - Demonstrated in target and surrogate tissues
- Tumor stabilization and regression
  - Demonstrated in renal, non-small cell lung, and breast cancer, and AML trials
- Favorable preclinical comparative data versus other antisense targets
  - Highlights potential advantage of R2 target in multiple cancers

## Intellectual Property

LOR-2040 is protected under several patents both for composition and cancer uses in a number of countries worldwide, including Canada, Europe, Australia, China, and the U.S. For more details, please visit our website at [www.lorusthera.com](http://www.lorusthera.com).

## References

1. Lee Y et al. GTI-2040, an antisense agent targeting the small subunit component (R2) of human ribonucleotide reductase, shows potent antitumor activity against a variety of tumors. *Cancer Res.* 2003 Jun 1;63(11):2802-11.
2. Orr RM. GTI-2040. *Lorus Therapeutics. Curr Opin Investig Drugs.* 2001 Oct;2(10):1462-6.
3. Klisovic RB et al. Phase I Study of GTI-2040, an Antisense to Ribonucleotide Reductase, in Combination with High-Dose Cytarabine in Patients with Acute Myeloid Leukemia. *Clin Cancer Res.* 2008 Jun 15;14(12):3889-3895.
4. Wei X et al. Metabolism of GTI-2040, a phosphorothioate oligonucleotide antisense, using ion-pair reversed phase high performance liquid chromatography (HPLC) coupled with electrospray ion-trap mass spectrometry. *AAPS J.* 2006;8(4):E743-55.
5. Stadler WM et al. A Phase I/II study of GTI-2040 and capecitabine in patients with renal cell carcinoma. *Cancer Chemother Pharmacol.* 2008 Apr;61(4):689-94.
6. Juhasz A et al. Analysis of ribonucleotide reductase M2 mRNA levels in patient samples after GTI-2040 antisense drug treatment. *Oncol Rep.* 2006 May;15(5):1299-304.
7. Desai AA et al. A phase I study of antisense oligonucleotide GTI-2040 given by continuous intravenous infusion in patients with advanced solid tumors. *Ann Oncol.* 2005 Jun;16(6):958-65.