

2007 AACR-NCI-EORTC International Conference

Molecular Targets and Cancer Therapeutics:

Discovery, Biology and Clinical Applications

October 22-26, 2007 • San Francisco, California

Colette D. Lukan, MD, FRCPC
Communications Manager, EORTC

Introduction

This article presents highlights from the recent 19th International Conference on Molecular Targets and Cancer Therapeutics jointly sponsored by the American Association for Cancer Research (AACR), National Cancer Institutes (NCI), and European Organization for Research and Treatment of Cancer (EORTC).

The AACR-NCI-EORTC conference, which is held every year, alternating between Europe and the United States, brings together world leaders to discuss and debate novel cancer therapeutic approaches spanning the research spectrum from molecular targets and drug discovery to target validation, preclinical studies and early clinical trials. This year's meeting proved to be as attractive and successful as past events, featuring well over 800 scientific papers and drawing an attendance of over 3600 delegates.

The following report will focus on molecular target diagnostic, predictive and therapeutic discoveries of clinical relevance. Although much of the data presented are preliminary, it is likely that some of the new agents discussed here will be in advanced clinical research within the coming few years.

First in Class and Novel Targeting Agents

GSK923295A is a first-in-class potent, selective inhibitor of the mitotic kinesin centromere-associated protein E (CENP-E). This compound has demonstrated significant anti-tumor activity in multiple tumor cell lines including breast, lung and colon, ovarian and prostate with some tumors types showing complete regression. Researchers expect that GSK923295A will result in minimal myelosuppression and less side-effects compared with the mitotic inhibitors, taxanes and vinca alkaloids due to its selective targeting of rapidly dividing cells and a 10-fold difference between the sensitivity of bone marrow and the most sensitive tumor cell lines (i.e. breast). The drug, administered intravenously, is currently being tested in patients with advanced solid tumors and may prove to be effective across a broad spectrum of tumor types.¹

OSI-906 is the first selective IGF-R1 kinase inhibitor to enter phase I trials. Insulin-like growth factor receptor is a cell surface enzyme expressed by many human cancer cells and is known to drive tumor growth. In laboratory experiments OSI-906 reduced growth of 15 cell lines including colorectal, lung, breast, pancreatic and pediatric tumors and mouse models. When OSI-906 was tested in mice with human colorectal cancer tumors in combination with erlotinib, thus ensuring the blockade of both IGF-R1 and EGFR tumor receptors, colorectal tumor growth was completed arrested and tumor size reduced by 22%. Phase I studies are ongoing.^{2,3}

Two leukemia stem cell (LSC) specific targeting agents were discussed for the treatment of AML.⁴ Cancer stem cell research is the most advanced in leukemia where a well-defined cell population has been identified. Parthenolide (PLT), a sesquiterpene lactone, occurring naturally in the plant feverfew, is used for the relief of migraine, to help prevent blood clots, as an anti-inflammatory for arthritis and has been shown to induce death of human LSC *in vivo*. The clinical use of PLT is limited by its poor pharmacological properties and therefore, dimethylamino-parthenolide (DMAPT), a PTL analog was developed which has shown very selective LSC toxicity and potent inhibition of NF-KB. In preclinical studies it demonstrated 70% oral bioavailability and was well-tolerated. A second compound, TDZD-8 is a non-parthenolide, LSC-specific compound that selectively induces apoptosis, eradicating both primary AML stem and progenitor cells at a much faster rate (i.e. within 2 hours or less) when compared to PLT without significant normal hematopoietic stem and progenitor cell toxicity. TDZD-8 may employ a unique and previously unknown mechanism to rapidly target leukemia cells. Drug manufacturing is underway and phase I studies are scheduled to begin.

Phase I study results⁵ of the orally administered novel synthetic triterpenoid RTA 402 (CDDO-Me), a first-in-class targeted anti-inflammatory modulator (AIM) that inhibits the activity of transcription factors known to promote tumor progression and resistance to therapy, were reported. In preclinical studies, RTA 420 has shown potent anti-tumor activity as a single agent, the ability to potentiate effects of other agents and to protect against major radiation and chemotherapy-induced toxicities. In a dose-finding and PK study, RTA 402 was well tolerated at doses of up to 900 mg/day in 27 patients with advanced solid tumors exposed for up to 11 months. Stable disease was achieved in 9/12 (75%) patients with melanoma, renal cell or medullary thyroid carcinoma. Phase II studies are ongoing in patients with metastatic melanoma and pancreatic carcinoma.

Researchers have studied the genetically engineered non-virulent oncolytic herpes simplex virus NV1023 as a targeted therapy for human cancers in which neural invasion is common. An animal model was created in which human carcinoma cells were implanted into the sciatic nerve of mice. Nerve function was maintained and significant tumor regression was observed in mice given NV1023, while all control animals developed limb paralysis within 5-7 weeks after tumor injection, indicating that NV1023 selectively targets nerves invaded by metastases, killing malignant cells while leaving healthy neural cells undamaged, thereby preventing paralysis. The clinical implications of these findings are significant and Phase I studies are currently underway.⁶

Anti-angiogenesis Agents and Functional Imaging

Researches and clinicians are using functional imaging to study the effects of anti-angiogenesis agents and to identify biomarkers predictive of response that may help to select patients for treatment with these agents. Dynamic contrast-enhanced MRI and US (DCE-MRI, DCE-US), and functional CT and PET, can be used to measure parameters such as tumor blood flow, vessel permeability and blood volume distribution as well as to analyze potential tumor biomarkers. The results of four phase I studies are presented that highlight the utility of functional imaging as an aid in drug development.

Preliminary results of the first clinical study⁷ combining combrestatin A4 phosphate (CA4P), a vascular disruptive agent (VDA), and bevacizumab were reported. Single agent CA4P causes significant tumor necrosis as a result of vascular shutdown. However, tumor re-growth can occur due to blood vessels that survive in the tumor rim. Preclinical models show that this re-growth can be prevented by an anti-VEGF antibody agent which acts to inhibit the neo-vasculature of the surviving tumor rim. This synergistic anti-tumor activity was confirmed in patients with advanced solid tumors administered CA4P (45, 54 or 63 mg/m²) and bevacizumab (10 mg/ kg) every 14 days. Functional DCE-MRI demonstrated that CA4P induced statistically significant reductions in tumor perfusion and vascular permeability that were sustained by the co-administration of bevacizumab. Stable disease lasting more than 2-4 months and improved tumor marker levels were observed in 3/6 patients and no grade 3 / 4 toxicities were recorded. Additional studies are required to support the use of this novel drug combination.

The results of a phase II study evaluating sunitinib monotherapy in 30 patients with advanced hepatocellular carcinoma, a highly vascular tumor with high levels of the angiogenic factors VEGF and VEGFR2, were presented. Sunitinib, an oral tyrosine kinase inhibitor known to target many receptors including VEGFR2, was given orally at 37.5 mg/m² once a day for 4 weeks followed by a 2 week drug-free period and then repeated. One patient achieved a partial response lasting 14 months while 48% of patients had stable disease for 3 or more months and 6 patients remain on study. The KM estimate of overall survival reached 10 months. DCE-MRI showed decreased tumor permeability after 2 weeks of therapy and relevant tumor necrosis in 35% of patients. The investigators believe that the currently evaluated sunitinib dose and schedule are safe and that further investigation is warranted.⁸

The results of a phase I study, examining the use of dynamic contrast-enhanced ultrasonography (DCE-US) parameters as predictors of response to targeted therapy, were reported for patients treated with the multikinase inhibitor sorafenib and dacarbazine. Data from 115 DCE-US examinations, performed prior to, during and at study completion, identified a significant difference between pre- and post-treatment average peak intensity to blood volume measurements between “good” compared to “poor” responders, evident as early as 8 days after treatment initiation.⁹ These data support further evaluation of DCE-US as a tool for predicting early response to targeted therapies.

The EORTC trial 16041, “A biological and pharmacologic phase I study of NGR-TNF, a novel vascular targeting agent in patients with refractory solid tumors”, was a dose escalation study in which 67 patients with malignant solid tumors refractory to standard chemotherapies were given NFR-TNF by intravenous infusion once every 3 weeks at a starting dose of 0.2µg/m². DCE-MRI vascular parameter measurements confirmed the biological activity of NFR-TNF. The PK data were linear with dose. Although no responses were observed, stable disease was recorded in 9/55 patients and drug toxicity was generally mild. The recommended dose for future single agent studies is 45µg/m² as a 1-hour infusion every 3 weeks.¹⁰

Molecular Markers and Patient Selection

Researchers presented their work on microRNAs and the potential clinical applications of microRNA let-7 in lung cancer. MicroRNAs are single-stranded RNA molecules which regulate gene expression and are known to control a host of cell activity, including cell cycle progression, differentiation and apoptosis. They serve as excellent diagnostic and prognostic markers, may be involved in tumorigenesis and therefore themselves could be potential therapeutic molecules. In lung cancer, let-7 is poorly expressed or deleted which predicts for poor prognosis. However, when over-expressed, tumor growth is inhibited, indicating a role for let-7 as a tumor suppressor in lung tissue.

In mammalian cell lines, the loss of let-7 results in radioresistance and overexpression induces radiosensitivity. In 20% of lung cancer patients, an alteration in the let-7 binding site of an important oncogene has been identified and the researchers hypothesize that this may be an inherited, genetic predisposition to smoking-induced cancers therefore defining a subset at very high risk of developing smoking-related cancers.

The therapeutic application of microRNAs is being investigated in cell and animal models and the various small synthetic microRNA molecules studied to date have all shown a dose-dependent effect on cultured lung cancer cell proliferation, a profound effect when given repeatedly and to enhance the effects of some anticancer drugs. Synthetic microRNAs are retained in the body for 15-20 days without any liver or kidney toxicity but require a drug delivery system which is the current focus of development in preparation for testing in humans.^{11,12,13}

Results from a landmark phase III EORTC/NCIC study¹⁴ demonstrated that the presence of a methylated MGMT gene promoter in tumor tissue was an independent positive predictive factor

of patient response to TMZ and established temozolomide (TMZ) and radiotherapy (RT) as the new standard of care for newly diagnosed glioblastoma (GBM)¹⁵.

The use of MGMT as a predictive biomarker was confirmed in a phase I/IIa EORTC study¹⁶ in which patients with GBM were prospectively stratified for MGMT status prior to treatment with dose-intense adjuvant TMZ/RT in combination with cilengitide, a highly selective integrin inhibitor targeting the tumor and its vasculature. The study reached the predefined primary endpoint with 69% of patients alive and progression free at six months and a median PF survival of 8.1 months. In a defined patient subgroup with methylated MGMT gene promoter in the tumor tissue, 91% of patients had a PFS of six months and the median has not yet been reached. A phase III study is currently underway.

Researchers are hoping to optimize anti-cancer therapy through the use of pharmacogenomics in non-small cell lung (NSCL), pancreatic and colorectal cancer patients.¹⁷ A cluster of stage I NSCL cancer patients at high risk for disease recurrence and who might therefore benefit from adjuvant chemotherapy, have been identified through genetic testing for ERCC1 gene expression.¹⁸

Similarly, results of a phase III trial in metastatic NSCL cancer patients have shown that assessment of ERCC1 mRNA expression in patient tumor tissue predicts response to docetaxel and cisplatin.¹⁹ ERCC1 is the lead single gene in lung cancer and high ERCC1 expression predicts for a poor response to platinum therapy and therefore can be used to customize chemotherapy. ERCC1 overexpression has also been shown to predict for poorer survival in metastatic colorectal cancer patients treated with FOLFOX.²⁰

Likewise, genetic risk profiling in pancreatic cancer patients has also identified a subset with significantly worse survival that might benefit from the addition of post-operative adjuvant systemic therapy. The current goal of research is to use pharmacogenomics to develop tailored therapeutic strategies for individual patients with the hope of maximizing benefit and minimizing toxicity.

Rational Drug Combinations

The rationale behind EGFR combination therapy is to augment the anti-tumor effects and to mitigate the observed skin toxicity. Successful drug combinations achieving this goal include cetuximab/irinotecan in colorectal cancer, cetuximab/radiation in head and neck cancer and erlotinib/gemcitabine in pancreatic cancer. In NSCL cancer, however, combination studies have been largely negative.

The sequence in which these agents are administered may be important when treating tumors that rely on the EGFR pathway for proliferation. This reliance can be overcome by administering drugs in sequence or by giving the anti-EGFR agent in a pulse-like manner followed by the cytotoxic agent. Increasing knowledge of the mechanisms of resistance to EGFR inhibitors has led to clinical studies evaluating the combination of EGFR inhibitors with a second anti-EGFR drug or with inhibitors of HSP90, protein glycosylation (i.e. tunicamycin), mTOR, IGFR, AKT1 or MAPK. The dose-limiting skin rash seen with EGFR-inhibitors can be antagonized, without mitigating the antitumor effect, with topical anti-inflammatories, immunosuppressants, moisturizing agents and phosphatase inhibitors such as Vitamin K.²¹

PM02734, a novel marine-derived product has demonstrated antiproliferative activity in breast, colon, pancreas, lung and prostate cancer cell lines. PM02734 sensitivity correlates with the expression levels of ErbB3 receptor. It proved to be synergistic when administered with erlotinib even in erlotinib resistance non-small cell cancer cell lines. PM02734 has been selected for clinical development based on its *in vivo* activity in human tumor xenografts, as well as an acceptable non-clinical toxicology profile. A new, international, multi-center phase I clinical trial of PM02734 in patients with advanced malignant solid tumors is currently underway.²²

The efficacy of anti-angiogenesis agents can be improved by the addition of chemotherapy, targeted therapy and radiation or with a second anti-angiogenic agent. When the anti-angiogenic agent is given first, a 'window of normalization' in the tumor vasculature occurs when perfusion increases and hypoxia decreases. More cytotoxic drug is delivered to the tumor if given during this 'window'. This sequential approach to combination therapy has not yet been tested in the clinical trial setting.

Anti-angiogenic agents also enhance the anti-endothelial effects of cytotoxics (i.e. taxanes, topotecan, topoisomerase inhibitors) and lower doses of anti-angiogenic agents may prove as effective as higher doses, as suggested by the recent findings of the phase III "Avastin in Lung" ("AVAIL", BO17704) study which showed that Avastin at doses of either 7.5 or 15 mg/kg given every 3 weeks in combination with gemcitabine/cisplatin chemotherapy prolonged progression-free survival in patients with advanced non-small cell lung cancer when compared to chemotherapy alone.²³

The results of the EORTC 16023-10051 phase I dose escalation study of lonafarnib, a farnesyl transferase inhibitor, given in combination with trastuzumab plus paclitaxel to 23 patients with HER2 overexpressing metastatic breast cancer were reported. Standard regimens of trastuzumab and paclitaxel were used and lonafarnib was administered orally twice daily at increasing doses. Five dose levels were tested prior to reaching the MTD and study interruption. Nineteen patients were discontinued, 10 due to toxicity and 4 due to progressive disease. The toxicity profile was characteristic of the drug combination. Radiologic responses were observed for 10/17 patients (1 CR, 9 PR) and 5 patients with disease stabilization. To date, with a median follow-up 8 months, the 6 month PFS is 85%. These positive results support phase II/III investigation.²⁴

Conclusions

This summary is only a snapshot of the findings presented at this year's AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics: *Discovery, Biology and Clinical Applications*. The quality of the research and the spirit with which this knowledge was shared made this a truly premier international meeting featuring novel cancer therapeutics. More randomized trials of targeted agents, now approaching clinical implementation, will help to further advance the diagnoses and treatment of cancer. The results of studies carried out for targeted agents presented at this conference are encouraging and will in all likelihood be updated at meetings over the next few years.

References

1. Sutton D, Gilmartin AG, Kusnierz A, et al. A Potent and Selective inhibitor of the mitotic kinesin CENP-E (GSK923295A), demonstrating a novel mechanism of inhibiting tumor cell proliferation and shows activity against a broad panel of human tumor cells *in vitro*. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California. Abstract A111
2. Buck E, Eyaguirre A, Rosenfeld-Franklin M, et al. Inhibition of INF-IR by OSI-906 potentiates efficacy of various molecular targeted agents by blocking feedback loops converging at the level of IRS-1. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California PR-1
3. Ji QS, Mulvihill M, Rosenfeld-Franklin M, et al. Preclinical characteristics of OSI-906: A novel ICF-IR kinase inhibitor in clinical trials. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California Abstract C192

-
4. Jordan C. Characteristics and targeting of human leukemia stem cells. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California. Abstract PL01-03
 5. Hong D, Kurzrock R, Supko JG, et al. Phase I trial with a novel orally administered synthetic triterpenoid RTA 402 (CDDO-Me) in patients with solid tumors and lymphoid malignancies. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California. Abstract B82
 6. Gil, ZA, Rein A, Brader P, et al. Nerve-sparing therapy with oncolytic herpes virus for cancers with neural invasion. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California. PR-8
 7. Nathan P, Judson I, Padhani A, et al. A phase I study of the safety, tolerability and antitumor activity of escalating doses of combretastatin A4 phosphate (CA4P) given in combination with bevacizumab to subjects with advanced solid tumors. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California. Abstract B7
 8. Zhu AX, Sahani DS, di Tomaso E, et al. Efficacy, safety, and changes in angiogenic markers following sunitinib monotherapy in patients with advanced hepatocellular carcinoma: Experience from a phase II study. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California. Abstract PR-7
 9. Lassau N, Benatsou B, Chami L, et al. Study of tumor perfusion parameters obtained using contrast enhanced ultrasonography (DCE-US) in a phase I trial of patients treated with sorafenib and dacarbazine. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California. Abstract PR-9
 10. Van Herpen C, Fiedler W, Marreaud S, et al. A biological and pharmacologic phase I study of NGR-TNF, a novel vascular targeting agent, in patients with refractory solid tumors (EORTC 16041). Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California. Abstract B78
 11. Slack F. MicroRNAs in Cancer. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California. ED02-01
 12. Weidhaas JB. MicroRNAs as biomarkers in cancer risk and response. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California. ED02-02
 13. Brown D. miRNAs as Oncogenes, Tumor Suppressors, and Therapeutic Intervention Points. Oral Presentation 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California ED01-04
 14. Heigi M, Stupp R. Right silencing and stratified therapy in glioblastoma. Oral Presentation 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California PL02-03
 15. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352 (10): 987-96, 2005.
 16. Stupp R. et al. *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 2000
 17. Danenberg K. Optimizing Therapy through Pharmacogenomics. Oral Presentation 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California PL06-03
 18. Harpole D, Petersen R, Mukherjee S, et al. A genomic strategy to refine prognosis in early stage non-small cell lung carcinoma (NSCLC). *Proc Am Soc Clin Oncol*. 2006;24:370s. Abstract 7026

-
19. Cobo M, Isla D, Massuti B. *Journal of Clinical Oncology*, Vol 25, No 19 (July 1), 2007: pp. 2747-2754
 20. Shirota Y, Stoecklacher J, Brabender J. *ERCC1* and Thymidylate Synthase mRNA Levels Predict Survival for Colorectal Cancer Patients Receiving Combination Oxaliplatin and Fluorouracil Chemotherapy *Journal of Clinical Oncology*, Vol 19, Issue 23 (December), 2001: 4298-4304
 21. Perez-Soler R. Synergistic schedules with combination of EGFR inhibitors and cytotoxic agents. Oral presentation 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California Abstract CN07-01
 22. PharmaMar PRNewswire: “PharmaMar's Sixth New Compound, PM02734, Enters Clinical Trials”, MADRID, Spain, October 4 / 2005
 23. Heymach J. Combinations with Angiogenesis Inhibitors. Oral presentation 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California Abstract CN07-03
 24. Schellens JH, Dieras V, Roelvink M, et al. A Phase I study of Lonafarnib, a farnesyl transferase inhibitor in combination with herceptin plus paclitaxel in Her 2/neu overexpressing breast cancer. Proceedings of the 2007 AACR-NCI-EORTC International Conference – Molecular Targets and Cancer Therapeutics; October 22-26, 2007; San Francisco, California Abstract B116