OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Vaccines and Vaccination

August 20-22, 2012 Hilton Chicago/Northbrook, USA

Combining targeted therapy with immunotherapy (interferon-α): Rational, efficacy in gastrointestinal stromal tumor model, and implications in other malignancies

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Imatinib (IM) revolutionized gastrointestinal stromal tumor (GIST) treatment but median-progression-free-survival of unresectable/metastatic disease is <2 years. B-RAFV600-mutated-melanoma responds to vemurafenib dramatically but median-progression-free-survival is <9 months. Despite continuing discoveries of new effective therapeutic targeted agents, drug-resistance and early relapse will maintain recurrent themes using monotherapy. Our preclinical study demonstrated that terminal cancer patient's lymphocytes can be converted into effective cytotoxic T-lymphocytes in vitro killing patient's own tumor cells. We investigated a new strategy combining targeted therapy (IM) with immunotherapy (peginterferon α-2b) for stage III/IV GIST with the rational that peginterferon α-2b serves as danger signals while IM's effective killing supplies GIST-specific-antigens in vivo without leucopenia, thus allowing for dendritic cell and cytotoxic T-lymphocyte differentiation toward Th1 adaptive cell-mediated immunity (Th1 response). Analysis of eight patients showed significant induction of IFN-γ–producing–CD8+, –CD4+, –NK cells, and robust IFN-γ–producing-tumor-infiltrating-lymphocytes, signifying induction of innate and Th1 response. Complete remission (CR) + partial response (PR)=100%; overall survival=100%; one patient died of unrelated illness while in PR; after a median follow-up of 5 years (3.9 to 5.0 years), Six of 7 evaluable patients are either in continuing remission or showed progression-free-survival (PFS) more than doubling the median-genotype-specific PFS of the phase III IM-monotherapy trial (CALGB150105/SWOGS0033). We conclude that combination of effective non-marrow-suppressive-targeted therapy with peginterferon α-2b is safe, induced significant innate and Th1 response, and demonstrated highly promising clinical efficacy in GIST model, thus warranting development in other tumors including melanoma, prostate, breast, colon, pancreatic cancer, and NSCLC harboring EGFR mutations or EML4-ALK.

Biography

Lei L Chen received medical education at Albert Einstein Medical College, completed medical oncology fellowship at Memorial Sloan-Kettering Cancer Center. Prior to medical education, she worked as a post-doctoral fellow with Ralph Steinman at the Rockefeller University. Her most recent affiliations include MD Anderson Cancer Center (2000-2006) where she focused in sarcoma, gastrointestinal stromal tumor, completed pre-clinical studies, and designed the combination targeted therapy with immunotherapy; and Huntsman Cancer Institute, University of Utah (2006-2011) where she conducted the GIST study (DOI:10.1007/s00262-011-1185-1). She just retired—relinquishing clinical duties concentrating in research and planning of some of the clinical trials mentioned above.

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