FOX CHASE CANCER CENTER
TEMPLE HEALTH

Novel Combinatorial Treatment of Cancer

(Ref. No. 326-NB)

Background

One major approach for treating cancer is the induction of DNA damage, by chemotherapeutic agents or radiation, to further prevent propagation of the cancer cells. However, all cells have DNA damage checkpoint safety mechanism that senses the damage and delays cell cycle progression until the DNA is repaired. In cancer cells, the checkpoint mechanism may contribute to resistance, because it allows the cells to repair their damaged DNA and thus continue to proliferate once the drug has been metabolized. Overcoming the DNA damage checkpoint, by targeting the proteins involved in the DNA damage checkpoint pathways, is a powerful approach for improving cancer patient treatment outcomes. Agents targeting the DNA damage checkpoint proteins, like the tyrosine kinases Chkl and Weel, have been tested in clinical trials. Early generation Chk1 inhibitors were found to be toxic to patients. There has been more promising clinical data with Wee 1 inhibitors. Thus, fine-tuning of the interplay between chemotherapeutics and DNA damage checkpoint inhibitors is an attractive solution that allows discovering and re-purposing FDA approved drugs as novel chemosentitizers. The repurposing of existing drugs for new uses can save significant amounts of time and money for the drug to reach the clinic.

Summary of the Invention

Scientists from Fox Chase Cancer Center have discovered that Bosutinib (myeloma drug; inhibitor of Src/Abl tyrosine kinases) and its isomer Bos-I are inhibitors of Chkl and Weel kinases, and can override the DNA damage checkpoint. *In vitro* and xenograft studies showed that Bosutinib and Bos-I were able to sensitize pancreatic cancer cells to killing by sublethal concentrations of Gemcitabine (chemotherapeutic; DNA-damaging agent). The *in vitro* data show that both Bosutinib and Bos-I (and possibly other chemical derivatives of these compounds) reduce Gemcitabine LC_{50} dose significantly, and side by side comparison showed that Bos-I was more potent as a sensitizer than Bosutinib. This is consistent with *in vitro* kinase inhibitor experiments that showed Bos-I as a stronger inhibitor of Chk1 and Wee1 than Bosutinib (*Ref. 1*). Taking into account the mode of action of both these drugs as chemosensitizers that can override the DNA damage checkpoint, their use is likely to extend beyond pancreatic cancer, and can be used for combination treatments for lung, head and neck, kidney, hematopoietic system, breast, ovary, colon, lymph nodes, bladder, prostate gland, stomach, or esophagus tumors. Indeed, recent *in vitro* studies showed efficacy of Bosutinib and Bos-I with checkpoint override activity in acute lymphoblastic leukemia (*Ref. 2*).

References:

(1) Beeharry N. *et al.* (2014), "Re-purposing clinical kinase inhibitors to enhance chemosensitivity by overriding checkpoints", *Cell Cycle*, 13:14, 2172-2191, DOI: 10.4161/cc.29214

(2) Ghelli A. *et al.* (2018), "Targeting WEE1 to enhance conventional therapies for acute lymphoblastic leukemia", *J Hematol Oncol* 11(1): 99. DOI: 10.1186/s13045-018-0641-1

Advantages

- Potent and safe combination therapy of various cancers
- Drugs based on solid science

IP Status

Patent US 9,421,203 issued in 2016.

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