

Advancements in prostate cancer research provide hope for finding a cure and lead to the discovery of new treatments to minimize the impact of a man's prostate cancer and maximize his quality of life. This regular *Hot SHEET* supplement includes some of the latest research from the Prostate Cancer Foundation (www.pcf.org).

26th Annual PCF Scientific Retreat – Top New Discoveries for Patients – Part 2

PCF held its 26th Annual Scientific Retreat in late 2019. In attendance were 665 participants from 188 institutions from 18 countries. Scientific Retreat is an opportunity for PCF-funded investigators and other experts in the field of prostate cancer research to learn from each other through presentations and informal networking.

From 42 total panels and presentations, PCF's Director of Research Dr. Andrea Miyahira has curated the Top New Discoveries for Patients – this is Part 2. Stay tuned for more next month!

CD46 as a Novel Target in Metastatic Castration Resistant Prostate Cancer

CD46 is a protein that helps cancer cells to evade killing by immune cells, and is highly upregulated in castrate resistant prostate cancer (CRPC) but not normal cells. CD46 expression may be particularly high in cases of neuroendocrine prostate cancer. Thus, CD46 represents a promising target for prostate cancer immunotherapy. Drs. Rahul Aggarwal, Eric Small, Bin Liu, and Larry Fong, and the prostate cancer team at the University of California, San Francisco have developed a CD46-targeting treatment (CD46 ADC), with potent anti-tumor activity in preclinical prostate cancer studies. Early studies suggest CD46-ADC may be synergistic with checkpoint immunotherapy and androgen receptor (AR)-targeted therapy.

The team has recently initiated a first-in-human Phase I clinical trial to test the efficacy and safety of CD46-ADC in patients with metastatic CRPC. Based on results from this study, the team may pursue trials testing CD46-ADC in combination with checkpoint immunotherapy and AR-targeted therapy. Dr. Rob Flavell, a nuclear medicine physician scientist at UCSF, is also developing a novel PET radio tracer targeting CD46 that may be used as a companion biomarker and theranostic agent to image CD46 expression. Studies in mice are promising thus far.

What this means to patients: Dr. Aggarwal and the UCSF team have identified CD46 as a promising new therapeutic target in prostate cancer, that may also have synergy with checkpoint immunotherapy and AR-targeted therapy. The team have developed a novel CD46-targeting agent, have completed preclinical development and have recently initiated a first-in-man Phase I trial.

The Biology and Therapeutic Impact of Targeting IL-23 in Prostate Cancer

Myeloid-derived suppressor cells (MDSCs) are a class of immune cells that infiltrate tumors in large numbers and promote cancer growth. Their role in driving prostate cancer and as treatment targets is an important area in need of study. Dr. Andrea Alimonti and his team at the Institute of Oncology Research, Switzerland found that MDSCs are significantly increased in mouse models of castrate-resistant prostate cancer (CRPC) and promote the development of resistance to androgen deprivation therapy (ADT) via secretion of IL-23. ADT, part of the standard of care for advanced prostate cancer, stops testosterone from being produced or directly blocks it from acting on prostate cancer cells. Treatment of these models with an anti-IL-23 antibody enhanced the efficacy of ADT.

IL-23 and MDSCs were also increased in metastatic CRPC tumors compared with hormone-sensitive prostate cancer. Based on these findings, in collaboration with the team of Dr. Johann de Bono of the Institute of Cancer Research and Royal Marsden NHS Foundation Trust (UK), a Phase I/II clinical trial is being initiated in mCRPC patients assessing the safety and efficacy of IL-23a (a powerful anti-psoriasis drug) combined with ADT.

What this means to patients: New treatment strategies are urgently needed for mCRPC. Dr. Alimonti and team have identified MDSCs and IL-23 as novel drivers and therapeutic targets in CRPC and will initiate a clinical trial to test an IL-23-targeting therapy for the treatment of CRPC. This drug is used for psoriasis, and represents a novel drug repurposing approach.

The PCF is the world's leading philanthropic organization funding and accelerating prostate cancer research. Founded in 1993, the PCF has raised more than \$745 million and provided funding to more than 2,000 research programs at nearly 200 cancer centers and universities.