Pancreatic Cancer: Making the Intractable Tractable

Moderator: Jordan D. Berlin, M.D. Professor of Medicine Ingram Professor of Cancer Research Clinical Director, GI Oncology Program Director, Phase I Program, Vanderbilt-Ingram Cancer Center

Panelists:

- Margaret A. Tempero, MD, Director, UCSF Pancreas Center and Leader, Pancreas Cancer Program, UCSF Helen Diller Family Comprehensive Cancer Center
- David Tuveson, MD, PhD, Professor and Deputy Director of Cancer Center Cold Spring Harbor Laboratory
- Charles J. Link, Jr. MD, Chairman, Chief Executive & Scientific Officer at NewLink Genetics Corp

CANCER PROGRESS by Defined Health

Ductal Pancreatic Cancer – Pushing for Progress

David Tuveson MD PhD

CSHL

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PDAC: The numbers

- 38,000/43,000 USA deaths/cases/yr
- 250,000 worldwide/yr
- 6% alive 5 years
- 4% enroll on clinical trials
- NCI spend approx 98M/yr until now; USA Foundations add another 10-20M

- Many in the public and private space view this as a problem and not an opportunity

PDAC - the clinic

- 50% patients are sick when diagnosed
- Other 50% only 10-15% have localized tumor and can go for surgery
- Following surgery up to 20% are alive at 5 years
- In the advanced metastatic setting there are two recent positive RP3 trials: FOLFIRINOX (+6mo) and Gem/Abraxane (+1.8mo)

How can we do better in PDAC?

1. Early diagnosis – this is why cervical cancer mortality has dropped, and already spiral CT in smokers has had a measureable impact

2. Better therapies – Both before and after surgery, and when surgery isn't possible. We need a penicillin for this disease and the basic science is guiding us to an extent

Science of PDAC

+ The disease is a recognized preneoplastic condition, and in the advanced setting PDAC possesses a dominant driver mutation, KRAS, making it more uniform genetically than other carcinomas.

- Unfortunately there isn't a "KRAS inhibitor"

+ We do have animal models of PDAC and they have helped illuminate certain limitations

Mouse PDAC and therapies - 1

A. There is a general drug delivery defect in PDAC tumors in mice. This is likely the case in humans also. The causes are multi-factorial and include various physical barriers:

1. Lack of blood vessels in the tumor
2. Compression of blood vessels in the tumor
3. Distance of stromal material drugs must travel
4. Lack of fenestrae in tumoral blood vessels

Mouse PDAC and therapies - 2

B. The tumor microenvironment poses a biochemical and immune barrier to therapeutic responses:

1. Biochemical barrier: PDAC stromal fibroblast cells can suppress the response to cytotoxic drugs such as gemcitabine (Todd Golub Nature 2012). Mechanism unknown.
2. Immune barrier: PDAC immune cells are oftentimes immature myeloid cells, and there is a paucity of T cells (R Vonderheide, D Bar-Sagi Cancer Cell 2012)

Suggested approaches for PDAC

- 1. Clinical Science Trials – fewer patients, repeat biopsies. First ensure that scientific hypothesis is justified prior to doing a Ph2 or Ph3 trial.
- 2. Enable the academics to design and conduct this study. Provide the therapies and material support so the science can be conducted properly.
- 3. Consider combination trials in the early space with multiple partners.
- 4. Co-clinical trials with mouse modeling groups

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