METASTATIC CASTRATE RESISTANT PROSTATE CANCER: AN INTEGRATED APPROACH TO OPTIMIZE PATIENT THERAPY

TEAM PROSTATE:
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JILL GALLAHER, SHILPA GUPTA, CONOR LYNCH, JONG PARK, JULIO POW-SANG AND JAKE SCOTT
SINCE THE BEGINNING OF THIS MEETING, 232 MEN IN THE USA ALONE HAVE DIED FROM METASTATIC PROSTATE CANCER (WWW.CANCER.ORG)

90% OF MEN THAT DIE FROM PROSTATE CANCER WILL HAVE BONE METASTASIS

INITIALLY, PROSTATE CANCER RESPONDS TO HORMONAL THERAPY; HOWEVER, RESISTANCE IS INEVITABLE

CASTRATE RESISTANT METASTATIC PROSTATE CANCER

AND CURRENT THERAPIES ARE INEFFECTIVE
TREATMENT STRATEGIES FOR CASTRATION RESISTANT PROSTATE CANCER @ MOFFITT

NCCN Guidelines Version 1.2013
Prostate Cancer

ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER

- Maintain castrate serum levels of testosterone and Denosumab (category 1) or zoledronic acid (category 1) if bone metastases

Studies positive for metastases

→ Symptomatic

Yes

- Palliative RT or radionuclide for symptomatic bone metastases
- Clinical trial

No

- Docetaxel (category 1)
- Mitoxantrone (category 1)
- Abiraterone acetate (category 1)
- Enzalutamide (category 1)
- Sipuleucel-T (category 1)
- Secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Abiraterone acetate
  - Enzalutamide
  - Ketoconazole
  - Steroids
  - DES or other estrogen
- Docetaxel
- Clinical trial

Is there a way to integrate personalized targeted therapies into this regimen?

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NCCN Guidelines Index
Prostate Table of Contents
Discussion

See Principles of Androgen Deprivation Therapy (PROS-E).
See Principles of Chemotherapy/Immunotherapy (PROS-F).
Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. Sipuleucel-T is not indicated in patients with hepatic metastases or life expectancy <6 months.

Although most patients without survival benefit reported for Docetaxel may be considered...
POTENTIAL TARGETED THERAPIES

NOVEL THERAPIES

- BASED ON PATIENT’S CANCER PATHWAY ACTIVATION
- JAK/STAT PATHWAY
- AKT PATHWAY (LOSS OF PTEN)
QUESTION?

Can we optimize the use of conventional and novel targeted therapies to improve survival of patients with castrate-resistant metastatic prostate cancer? We will use an integrated clinical, biological, and mathematical modeling approach to address our question!
### INDEX PATIENT-MR. SMITH: A MODEL CASE

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**Metastatic Prostate Bone Biopsy From Moffitt Patient, Jas Dhillon**
JAK/STAT inhibitor

Bone uEnv
- PTEN
- AR
- JAK

AKT/mTOR inhibitor

Tumor
- PTEN +/−
- AR +/−
- JAK +/−

Immuno Tx

Immune
- PTEN
- AR
- JAK

Bone remodeling agent

Chemo

Hormone

Hormone Tx
Bone uEnv

Bone remodeling agent

JAK/STAT inhibitor

AKT/mTOR inhibitor

Tumor

PTEN +/-

AR +/-

JAK +/-

Chemo

Hormone

Hormone Tx
FINAL WORKING MODEL
Model Implementation - 1st Order Linear Ordinary Differential Equations

\[ \dot{T}_i = \left( \begin{array}{c} \alpha_i \\ \beta_i B \\ \gamma_i J_i (1 - J_x) \\ \rho_i P_i (1 - P_x) \\ \sigma_i A_i H \\ \eta_i C_x \end{array} \right) T_i \]

\[ \dot{B} = \left( \begin{array}{ccccccc} -P_x \nu_p & -J_x \nu_J & -C_x \nu_C & -R_x \nu_R & H & \sum_{i=1}^{8} T_i \nu_T \\ \end{array} \right) B + \sum_{i=1}^{8} T_i \nu_T \]

\[ H = H_0 - H_x \eta \]

\[ J_i, P_i, A_i = \begin{cases} 1 & \text{if mutation is present} \\ 0 & \text{otherwise} \end{cases} \]

\[ J_x, R_x, P_x, H_x, C_x = \begin{cases} 1 & \text{if treatment is applied} \\ 0 & \text{otherwise} \end{cases} \]
Parameterization...

**Initial conditions (i.e. baselines):**
- amount of bone (I know it's abstract - any parameters welcome) Human femur volume = 1x106 mm3, Bone = 0.14x106 mm3
- amount of immune cells (cells?)
- hormone (testosterone?)

**Tumor growth rate 3mm3 per day (PMID 15330153)**

- Cx: chemo every 3 weeks for 12 weeks (based on scans and regression, continue until progression)
- Hx: hormonal AR directed therapy 12 weeks (based on scans - if tumor regressing by scan, they stay on it)
- Ix: immune 9 weeks with 3 courses
- Jx: JAK inhibitor Daily treatment for 8 weeks (based on follow up and regression continue until progression)
- Px: AKT (PTEN loss) Oral daily for 8 weeks (based on scan and regression continue until progression)
- Rx: RANK Once overt met is detected by scan, Indefinite (always on)

**T-independent:**
- tumor stimulation of bone (i.e. rate of tumor increase per volume bone) 0.656um per day PMID: 3455637
- hormonal stimulation of immune (i.e. rate of bone increase per mol hormone)
- hormonal stimulation of bone (i.e. rate of bone increase per mol hormone) 1.5x (0.656um per day)
- bone stimulation of tumor (i.e. rate of bone increase per tumor population) 3 fold increase in LNCAP growth in response to OB conditioned media over 5 days (Blaizcev et al., Clin Can Res, 10, 2004)
- tumor PTEN population inhibition of bone (i.e. rate o' bone destruction per tumor PTENness)
- hormonal stimulation of the tumor: 7mm3 per day (PMID 15330153)

**T-dependent:**

**On Tumor Cells:**
- rate of tumor decrease from Ix
- AKT Tumor death: 60% kill over one week at conc. (Cancer J, 2008)
- JAK/STAT Tumor death: 60% kill over one week at conc. of (Jaksch KB, PLOS one 7(4) 2012)
- AKT Tumor death: 80% kill over one week at conc. of (Cancer, J, 2007)
- JAK/STAT Tumor death: 80% kill over one week at conc. of (Cancer, J, 2007)

**On Hormone:**
- depletion from residual hormone in castrate resistant men
- single dose of inhibitore reduces systemic testosterone from 3.5nm/l to 0.7nm/l in over 7 days (80% reduction) (O'Donnell A et al. Br J Cancer, 2004)
INDEX PATIENT-MR. SMITH: A MODEL CASE

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METASTATIC PROSTATE BONE BIOPSY FROM MOFFITT PATIENT, JAS DHILLON
GENETIC ALGORITHM
GENETIC ALGORITHM

NEW POPULATION
UNTREATED TUMOR GROWTH

\[ \sum_{i=1}^{8} T_i = 10^9 \text{ tumor cells} \]

average size of detectable tumor \( \sim 10^7 \)
\( \sim 100 \) detectable tumors
RESULTS
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<th>HORMONE</th>
<th>CHEMO</th>
<th>BONE TARGETED</th>
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**JAK/STAT**

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CONCLUSIONS

☐ Personalized therapy for “Mr. Smith” can be tailored based on the evolving molecular profile of future biopsy using real-time dynamic predictions.

☐ The results of the mathematical modeling confirms standard of care improves overall survival.

☐ Our integrated approach may optimize conventional and novel therapeutic strategies.
SHORT TERM IMPLICATIONS

☐ WILL ALLOW FOR AN IMMEDIATE RETROSPECTIVE STUDY OF MODEL IMPLICATIONS FOR OUR PROSTATE CANCER PATIENTS USING THE TCC DATABASE.

☐ INTERROGATION OF THE TCC DATABASE = 50 PATIENTS WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER TISSUE SPECIMENS AVAILABLE FROM THE LAST 5 YEARS (JAS DHILLON)

☐ MODELING

☐ INTRATUMORAL

☐ IN VITRO

☐ IMMUNOTHERAPY

Subjects with metastatic banked tissue N=

Quantitative Immunofluorescence for Stat5, AR, PTEN

Targeted Therapy (Jak2 inhibitor, AK inhibitor, PI3 Kinase inhibitor, mTOR inhibitor)

Standard Therapy (Chemotherapy, Hormonal therapy, Immunotherapy)

RETROSPECTIVE VALIDATION
SHORT TERM IMPLICATIONS

PLATFORM FOR PROSTATE CANCER RESEARCH @ MOFFITT BY:

1) PROMOTING TEAM SCIENCE (CLINICAL/BIOLOGICAL/MATHEMATICAL/STATISTICAL/EPIDEMIOLOGICAL)

2) ADDRESSING KNOWLEDGE GAPS IN CLINICAL CARE

3) UNDERSTANDING THE COMPLEXITIES OF CELLULAR AND MOLECULAR PATHWAYS AND THEIR INTERACTIONS
LONG TERM IMPLICATIONS

- RESEARCH IMPLICATIONS
  1) CLINICAL TRIAL DESIGN DRIVEN BY MATHEMATICAL MODELING
  2) EXTRAMURAL FUNDING TO SUPPORT PROSPECTIVE TRIALS

- CLINICAL IMPLICATIONS
  1) CO-ORDINATION WITH MOFFITT DRUG DISCOVERY TEAMS TO ACCELERATE THE TRANSLATION OF THERAPIES TO THE CLINIC
  2) OPTIMIZE THE CURRENT MOFFITT CLINICAL PATHWAY
  3) MAKE MOFFITT A GLOBAL LEADER IN THE FIELD OF PERSONALIZED MEDICINE

- NEWLY DIAGNOSED SUBJECTS WITH METASTATIC PROSTATE CANCER
  - QUANTITATIVE IMMUNOFLOUORESCENCE FOR STAT5, AR, PTEN ON METASTATIC SITE BIOPSY/CTC
  - TARGETED THERAPY BASED ON BIOMARKER ELIGIBILITY
  - STANDARD THERAPY BASED ON BIOMARKER ELIGIBILITY

PROSPECTIVE TRIAL
## BUDGET

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IMO FEEDBACK