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14. ABSTRACT

While a majority of prostate cancers (PCa) remain clinically insignificant, some have the potential to metastasize and become lethal and therefore merit intervention. Thus, identification of men most at risk and most likely to benefit from therapy is a major clinical and public health challenge. Recent evidence suggests that the clinical-pathologic criteria used to assess eligibility for active surveillance and to define progression requiring intervention do not capture molecular changes that may more accurately predict progression of tumors from indolent to aggressive. Based on published results and preliminary data, we hypothesize that truly indolent Gleason pattern (Gp) 3 tumors are a molecularly distinct subset from potentially aggressive Gp3. During this period, we evaluated somatic copy number alteration (SCNA) landscape between tumor foci from patients who did not progress with long-term follow-up on active surveillance versus those from patients who did have to pursue primary therapy. We identified an overall quiet SCNA landscape in clinically indolent prostate cancer. We also evaluated circulating tumor DNA (ctDNA) as a biomarker in perioperative plasma samples from patients undergoing prostatectomy for intermediate/high-risk disease and found limited amounts of ctDNA.

15. SUBJECT TERMS
Prostate cancer, active surveillance, biomarkers

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Table of Contents

Page

1. Introduction……..……1

2. Keywords……..……1

3. Accomplishments……..……..1

4. Impact…….……5

5. Changes/Problems..……5

6. Products……..……6

7. Participants & Other Collaborating Organizations…….……7

8. Appendix

1. INTRODUCTION

AS has emerged as an approach for sparing men the morbidity associated with primary therapies for indolent PCa, while closely monitoring them for disease progression that would require such therapy before the development of lethal disease. However, while it appears that deferring therapy does not have major impact on survival, there are concerns that the delayed therapy may negatively impact survival in a subset of men, and may in some cases lead to more aggressive local therapy than would have been indicated on initial discovery. Conversely, concerns that an aggressive tumor was missed on biopsy or may emerge during surveillance lead many men with indolent disease to opt for RP or radiation therapy (with approximately half of patients on AS programs eventually undergoing primary therapy). Therefore, more refined methods are needed to separate patients at low risk for progression, who should be spared morbidity of primary therapy and perhaps even serial biopsies, from those at higher risk for progression who need more intensive management and should possibly proceed directly to primary therapy. To address this need, our purpose is to identify features that identify candidate AS patients whose tumors are at increased risk of progression, or of having an undetected higher grade tumor. Based on published results and our preliminary data, we hypothesize that truly indolent Gp3/Gs6 tumors are a molecularly distinct subset and will have a relatively silent SCNA landscape, while potentially aggressive Gp3 tumors will have extensive SCNA including losses in established tumor suppressor genes. This hypothesis will be tested in Aim 1 by examining the landscape of SCNA in indolent Gs3 from AS patients who have not progressed for >5 years, versus in Gp4-associated Gp3. Our second hypothesis is that indolent Gp3/Gs6 PCa will have very low or undetectable levels of ctDNA, while potentially aggressive tumors will have higher levels that will also increase over time (which may reflect greater tumor volume, increased cell turnover, or micrometastatic disease).

2. KEYWORDS

Prostate cancer, active surveillance, biomarkers

3. ACCOMPLISHMENTS

What were the major goals of the project?

Research-Specific Tasks

Aim 1. Determine the somatic copy number alteration (SCNA) landscape of Gleason pattern 3 from men undergoing active surveillance.

Aim 2. Determine whether circulating tumor DNA prior to radical prostatectomy is a biomarker of aggressive PCa.

Training-Specific Tasks

Major Task 1: Training and educational development in prostate cancer research

What was accomplished under these goals?

Research-Specific Tasks

Aim 1:

Subtask 1: Identify appropriate tissue samples (ongoing, 75% completed)

We are evaluating SCNA as a prognostic biomarker regarding probability of clinical progression on active surveillance. We previously identified cases of patients who remained clinically indolent with long-term follow-up on active surveillance as well as a few cases of patients who were upgraded from low-risk initial disease to higher-risk disease subsequently (clinically non-indolent), requiring primary therapy. We did not include any patients in the non-indolent cohort who were upgraded on first re-biopsy, since this is typically thought to reflect sampling error rather than true disease progression. Thus, all non-indolent patients in this study were not found to have higher-risk disease until after several years' follow-up. From each case, we identified biopsies taken at baseline; in patients who had no malignancy on initial biopsies, we selected the first biopsy that showed malignancy.

In the past year, I identified BIDMC active surveillance patients enrolled in the PASS study (NCT00756665) who ultimately required primary therapy, allowing us to expand the cohort of clinically non-indolent cases, and we are now requesting tissue (no tissue requests possible during COVID-19 pandemic).

Subtask 2: Microdissect (ongoing, 75% completed)

After selecting appropriate blocks from each case, we previously performed punch biopsies from the areas most involved by tumor for subsequent cases. We also obtained benign tissue for comparison. The same procedure is planned for the newly identified samples described above.

Subtasks 3 and 4: Evaluate SCNA from tumor and from normal prostate tissue and perform cross-platform analyses (ongoing, 75% completed)

We previously extracted DNA from these samples and performed ultra-low-pass whole-genome sequencing (ULP-WGS), and these results were included in last year's progress report. SCNA will be analyzed in the newly identified samples described above.

Subtask 5: Begin expansion to larger cohort if indicated (ongoing, 50% complete)

We have decided to further investigate the SCNA landscape of clinically non-indolent cases in order to see whether a quiet landscape at diagnosis is predictive of subsequent outcomes. As above, I identified an additional cohort of patients to expand our non-indolent cases. I have assembled a list of appropriate blocks and have confirmed clinical data.

Sub-Aim 1b: Characterize the immune tumor microenvironment of Gp3 versus Gp4-associated Gp3 in patients on AS (not yet initiated)

All subtasks related to this sub-aim have not been started yet, as we are focusing our efforts on the SCNA investigations as well as immune TME characterization in high-grade localized disease. Our preliminary findings suggest that it may be difficult to capture immune TME in core needle biopsies given tissue heterogeneity in prostatectomy samples.

Aim 2:

We planned to first study ctDNA as a potential biomarker in patients with intermediate-/high-risk localized prostate cancer with the rationale that if it could not be reliably detected or correlated with outcome in these patients, that it would also likely be limited as a biomarker in earlier disease. We published our results from this study last year (Hennigan ST et al., JCO Precision Oncology 2019).

Major Task 1: Identify tumors overexpressing ERG (completed)

We performed IHC to establish ERG status of tumors, and we selected concordantly positive or negative foci (supplement table 5 in manuscript cited above).

Major Task 2: Identify TMPRSS2:ERG breakpoint (completed)

We successfully microdissected tumor foci, extracted DNA, and constructed a genomic DNA library. We performed whole-genome sequencing to identify the breakpoint and used these results to generate breakpoint-specific primers.

Major Task 3: Quantification of breakpoint in ctDNA (completed)

We extracted DNA from plasma samples and attempted to amplify the TMPRSS2:ERG fusion with primers generated above. In one of two ERG-positive cases for which WGS was performed, we successfully read through the TMPRSS2:ERG breakpoint (Supplement Figure 3a-c in cited manuscript). However, even a nested PCR approach failed to amplify the fragment of DNA containing the breakpoint from plasma (Supplement Figure 3d-e in cited manuscript).

Major Task 4: Perform sequencing of RP specimens and look for identified tumor mutations in ctDNA (completed)

In plasma collected pre-RP from 112 patients, we did not find any SCNAs via ULP-WGS. This contrasted with results from patients with metastatic disease, where 4/7 patients had detectable ctDNA by ULP-WGS (see cited manuscript for full details).

We then tried a personalized ultradeep sequencing approach. This method involved laser capture microdissection of multiple geographically and phenotypically distinct tumor foci from prostatectomy specimens in order to identify truncal mutations. Once identified, these would serve as targets for ultradeep sequencing of matching ctDNA. After confirming this method's sensitivity with spike-in experiments, we attempted this approach in nine patients with localized intermediate-/high-risk disease undergoing prostatectomy. However, we were unable to detect any ctDNA in plasma from any of these patients before or after RP, even in a patient who subsequently experienced biochemical recurrence (and therefore, by definition, had micrometastatic disease present at the time of surgery).

Major Task 5: Expand analysis to lower-risk tumors (will not be performed)

Based on these findings and according to criteria set forward in the Statement of Work, we previously concluded that ctDNA was unlikely to be present in sufficient amounts in lower-risk tumors to be useful as a biomarker in this setting. We will instead investigate other strategies as detailed below.

Training-Specific Tasks

Subtask 1: Attend and present at an international scientific meeting (completed and ongoing)

I presented an abstract at ASCO GU 2020 and was co-author on six other abstracts presented at international scientific meetings, one of which was selected for an oral abstract at the ASCO Virtual Scientific Program in 2020.

Subtask 2: Organize and present research at weekly GU tumor board (completed and ongoing)

I coordinate our weekly multidisciplinary GU oncology tumor board, assembling lists of patients to be discussed, distributing this to radiologists and pathologists, and presenting new literature in the field for discussion. Moreover, in light of COVID-19, I completely shifted our tumor board to an online format and worked together with a programming team to develop an online case submission system.

Subtask 3: Complete courses in biostatistics, biomarker development, and computational biology (completed biostatistics course; not yet initiated biomarker development or computational biology courses)

I obtained a certificate in biostatistics from the Harvard Catalyst program.

Subtask 4: Publish results in a peer-reviewed journal (completed)

I was part of a team that previously published our investigation of ctDNA in localized prostate cancer in the Journal of Precision Oncology. In addition, I published describing similar ctDNA work in a patient with esophageal cancer (Einstein DJ et al., JCO Precision Oncol 2020).

Subtask 5: Develop, write, obtain regulatory approval, and activate a trial of polo-like kinase inhibitor in patients with metastatic castration-resistant prostate cancer and early resistance to Abiraterone (completed)

I am overall PI of NCT03414034, which has accrued over 40 patients to date to test the combination of onvansertib (PLK1i) and Abiraterone.

Subtask 6: Develop, write, obtain regulatory approval, and activate a trial of PD-1 inhibitor in patients with high-risk biochemically recurrent prostate cancer (completed)

I am overall PI of NCT 03637543, which has accrued over 10 patients to date to test the use of nivolumab in high-risk biochemically recurrent prostate cancer.

Subtask 7: Collect tumor tissue and blood samples from patients undergoing radiation plus androgen deprivation therapy for localized prostate cancer, evaluate for presence of T cells capable of recognizing tumor neoantigens identified in biopsy samples (ongoing, 25% completed)

We have completed tumor and blood sample collection from 12 patients. We performed WES from four cases, predicted neoantigens, and generated peptides based on these neoantigens. We performed exploratory experiments stimulating PBMCs with these peptides.

Subtask 8: Establish a rapid autopsy program for patients deceased of prostate and other genitourinary cancers, develop a tissue bank, perform IHC studies, establish xenografts and organoids from autopsy tissue (completed and ongoing)

I have set up a successful program for performing rapid autopsies. This program is a component of the Pathology Core in the recently submitted Prostate SPORE application and is intended to generate collaboration between DF/HCC scientists and clinicians, including investigators at both Dana-Farber Cancer Institute (DFCI) and Beth Israel Deaconess Medical Center (BIDMC). Since its inception and through the incredible generosity of our patients and their families, we have performed 10 rapid autopsies, eight of which have been in patients deceased of prostate cancer. At the time of autopsy, which is typically within three hours of death, we collect material from approximately 10-20 sites including bone, nodal, and visceral metastases. We collect both fixed formalin paraffin embedded tissue and matched frozen tissue. We have also collected fresh tissue for viable freezing and have created a patient-derived xenograft (PDX) from one case. All of these patients had been treated with standard hormone therapy, including androgen signaling inhibitors, and several have additional archival specimens available from time of diagnosis—in the localized or metastatic setting—and before and/or after subsequent therapies. In some cases, we have matched pre/post-treatment biopsies, and some of these patients have also been treated with investigational agents and/or specialized therapies such as immune checkpoint inhibitors for microsatellite-high disease and poly(ADP)-ribose polymerase inhibitors for tumors with deficiencies in homologous recombination repair. This program is IRB reviewed and involves patient research consent for obtaining tissue for research purposes, including establishment of cell lines, organoids, and PDXs.

What opportunities for training and professional development has the project provided?

This project has offered a number of opportunities for my training and professional development. My overall goal is to advance my career as a translational physician-scientist in the field of prostate cancer. During the course of this project, I have developed skills that are essential for this career path. I have worked closely with colleagues in pathology to develop a better understanding of tissue preparation including how to isolate small amounts of tumor from core biopsies and assemble a tissue micro-array. I have worked with Drs. Balk and Sowalsky to analyze and interpret sequencing data. Finally, I have worked with regulatory specialists to better understand regulatory issues surrounding tissue banking studies. I have leveraged all of these skills for other projects, especially the neoantigen project and rapid-autopsy protocol described above and below.

The salary support offered by this award has also protected time to pursue a number of projects ranging from exploratory pre-clinical work to phase II clinical trials.

My first exploratory project is a study of neoantigens in localized prostate cancer. I am working together with immunology experts as well as Drs. Balk and Bhasin to identify tumor neoantigens in diagnostic core biopsies from patients undergoing radiation and hormonal therapy for intermediate-to-high-risk localized prostate cancer. I have then collected serial blood specimens with the goal of identifying whether any T cells are present that are capable of recognizing the identified tumor neoantigens.

In addition, I have set up a rapid-autopsy protocol as above. With tissue obtained from these autopsies and prior tissue obtained during these patients' clinical care, we are performing investigations of tumor heterogeneity and alterations in androgen receptor as well as genomic alterations in response to treatment. We are working on a manuscript outlining findings from our first case. We are also considering single-cell Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq); a grant proposal has been submitted outlining this work.

I have had the opportunity to design and run two phase 2 clinical trials. One involves an inhibitor of polo-like kinase 1 (PLK1) in combination with abiraterone for metastatic castration-resistant prostate cancer (mCRPC). The other involves the PD-1 inhibitor nivolumab for patients with high-risk biochemically recurrent prostate cancer. Both trials are currently open and accruing patients, and both have led to successful grant proposals for correlative studies. I have also successfully obtained funding for a third phase 2 clinical trial involving neratinib in a biomarker-selected population of patients with mCRPC, and I am finalizing a protocol currently.

Finally, I have used some of my protected time to contribute to several research manuscripts and reviews, currently under review. I have also written the newest version of the Genitourinary Oncology section of the ASCO Self-Evaluation Program and added six-month updates.

How were the results disseminated to communities of interest?

The paper describing ctDNA results was published in the Journal of Clinical Oncology Precision Oncology.

What do you plan to do during the next reporting period to accomplish the goals?

Aim 1:

As noted above, we are expanding our ULP-WGS approach to more cases of patients on AS who ultimately develop non-indolent prostate cancer. This will enable a more robust comparison of the quiet landscape noted in clinically indolent disease to similar patients who ultimately are upgraded. We plan to make tissue requests as the COVID-19 pandemic passes and begin punching tissue and extracting DNA. Towards sub-Aim 1b, we will begin evaluating core biopsies to see if lymphocytes can be identified by IHC (subtask 1) in order to perform the remaining subtasks.

Aim 2:

We working with collaborators to pursue an alternative liquid biopsy approach using the DNA methylome of circulating tumor DNA, described more below. In parallel, we are currently expanding our analysis of the proteome of these samples using the SOMAscan platform. We will also continue following our existing patients and try to obtain tissue from any metastatic recurrences to confirm that we were targeting the correct clone, also described more below.

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

CHANGES/PROBLEMS

Changes in approach and reasons for change

Aim 1:

No changes other than including more cases as noted above.

Aim 2:

Given the difficulty detecting ctDNA even in more aggressive localized tumors, even one with biochemical recurrence, we decided that this approach is likely to be limited as a biomarker in more indolent early-stage disease, where ctDNA is even less likely to be present.

One other approach is to use a potentially more sensitive liquid biopsy tool, cell-free methylated DNA (cfMeDNA). By assaying the methylation status of millions of DNA targets rather than attempting to find small, infrequent genetic mutations, sensitivity is greatly increased. This has been recently shown to distinguish patients with early-stage kidney cancer from normal controls (Shen SY et al., Nature 2018). We are working together with local collaborators to begin developing a cfMeDNA signature in prostate cancer, beginning with metastatic patients and then moving into the localized intermediate/high-risk space. Eventually, this could be applied to active surveillance patients.

In parallel, we are investigating a proteomic assay (SOMAscan) that can quantify a large spectrum of protein analytes in a small volume of plasma. Using our previously collected specimens for the ctDNA studies, we will also be able to examine the proteome and investigate whether there are systematic differences between patients who did and did not experience biochemical recurrence.

In addition, we will continue to follow patients analyzed in our previous cohort to see if they develop metastatic recurrence. If so, we will try to obtain biopsy material. This would allow us to verify that our personalized primers were targeting the correct clone, the one ultimately responsible for metastatic recurrence.

Actual or anticipated problems or delays and actions or plans to resolve

Nothing to Report.

Changes that had a significant impact on expenditures

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report.

PRODUCTS

Publications, conference papers, and presentations

Publications

1. **Einstein DJ**, Liang N, Malhotra M, Aleshin A, Moshkevich S, Billings PR, Pectasides E. Assessment of Molecular Remission in Oligometastatic Esophageal Cancer with a Personalized Circulating Tumor DNA Assay. JCO Precision Oncology 2020;4:239-243. [DOI: 10.1200/PO.19.00339]
2. **Einstein DJ** and Garnick MB. Genitourinary Cancers chapter of American Society of Clinical Oncology Self-Evaluation Program, 7th Edition.
3. Garnick MB and **Einstein DJ.** Editorial comment. Urology. 2019;131:182-183. [PMID: 31451158]
4. Garnick MB and **Einstein DJ.** Editorial comment. Urology. 2020. *In press*.

Presentations

1. Patell R, **Einstein DJ**, Halleck J, Buss MK. Patient perceptions of treatment benefit in advanced cancer. ASCO Supportive Care in Oncology Symposium 2019. San Francisco, CA.
2. Shaw K, Calagua C, Russo J, **Einstein DJ**, Balk S, Ye H. Tumor PD-L1 expression is detected in a significant subset of high-risk localized and metastatic prostate cancer but is rare in ductal subtype. United States and Canadian Academy of Pathology (USCAP) Annual Meeting 2019. Baltimore, MD.
3. Gupta S, Sonpavde G, Weight CJ, McGregor BA, Gupta S, Maughan BL, Wei XX, Gibb E, Thyagarajan B, **Einstein DJ**, Dechet CB, Lowrance WT, Murugan PJ, Kilbridge KL, Agarwal N, Davicioni E, Eckstein M, Mossanen M, Preston MA, Konety BR. Results from BLASST-1 (Bladder Cancer Signal Seeking Trial) of nivolumab, gemcitabine, and cisplatin in muscle-invasive bladder cancer (MIBC) undergoing cystectomy. ASCO Genitourinary Cancers Symposium 2020, San Francisco, CA. (selected oral abstract presented by Dr. Shilpa Gupta)
4. **Einstein DJ,** Choudhury AD, Saylor PJ, Werner L, Erlander MG, Ridinger M, Bubley G. A phase II study of onvansertib (PCM-075) in combination with abiraterone and prednisone in patients with metastatic castration-resistant prostate cancer. ASCO Genitourinary Cancers Symposium 2020, San Francisco, CA.

5. Kelly WK, Leiby B, **Einstein DJ**, Szmulewitz RZ, Sartor AO, Yang ES, Sonpavde G. Radium-223 and niraparib treatment in castrate-resistant prostate cancer patients with and without prior chemotherapy. ASCO Virtual Scientific Program 2020.
6. Choudhury AD, Xie W, Parikh M, Lee D, Kessler ER, **Einstein DJ,** Kochupurakkal B, Mouw KW, Van Allen EM, Doyle LA, D'Andrea AD, Taplin ME, Shapiro G. A phase II study of M6620 in combination with carboplatin compared with docetaxel in combination with carboplatin in metastatic castration-resistant prostate cancer. ASCO Virtual Scientific Program 2020.
7. McKay RR, Xie W, Fennessy FM, Zhang Z, Lis R, Rathkopf DE, Laudone VP, Bubley G, **Einstein DJ**, Chang P, Wagner A, Preston MA, Kilbridge KL, Chang SL, Choudhury AD, Pomerantz M, Trinh QD, Kibel AD, Taplin ME. Results of a phase II trial of intense androgen deprivation therapy prior to radical prostatectomy in men with high-risk localized prostate cancer. ASCO Virtual Scientific Program 2020. (selected oral abstract presented by Dr. Rana McKay)
8. Patell R, **Einstein DJ**, Miller EJ, Halleck J, Dodge L, Buss MK. "Where did you read that?" External sources of information and patients' perceptions of prognostic goals. ASCO Virtual Scientific Program 2020.
9. Miller EJ, Patell R, **Einstein DJ**, Halleck J, Dodge L, Buss MK. Trends in patient misperception and decisional regret during treatment for advanced cancer: a prospective study. ASCO Virtual Scientific Program 2020.

Website(s) or other Internet site(s)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: David Einstein, MD
Project Role: PI
Researcher Identifier: 0000-0001-9163-3281
Nearest person month worked: 6
Contribution to Project: Organizing clinical data, generating research questions, analyzing SCNA and ctDNA data

Funding Support: this award plus P20, Bridge Grant, and PCF Challenge Award noted below

Name: Steven Balk, MD/PhD
Project Role: Mentor
Researcher Identifier: 0000-0002-4546-7371
Nearest person month worked: 1
Contribution to Project: Supervising research questions and data analysis
Funding Support: NIH R01, P01, P50 grants; DoD Impact Award W81XWH-16-1-0431 and Idea Development Award PC170715

Name: Adam Sowalsky, PhD
Project Role: Collaborator
Researcher Identifier: 0000-0003-2760-1853
Nearest person month worked: 2
Contribution to Project: Conducting WES and ctDNA sequencing
Funding Support: DoD W81XWH1610433 and W81XWH1510710

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

No new changes, as previously reported:

P20-CA233255 (Co-PIs: Balk & Einstein) 04/01/19-08/31/20 0.12 CM
NIH/NCI TDC: $50,000
"Genomic Features of Immunogenic Prostate Cancer in African-American Patients"
Aim 1. Identify somatic genomic alterations associated with immunogenic PCa in AA patients
Aim 2. Identify germline genomic variants associated with immunogenic PCa in AA patients

Bridge Project (Co-PIs: Balk, Einstein, Yaffe) 03/01/19-02/28/21 0.6 CM
Koch Institute TDC: $330,434
"Optimizing Plk1 Therapeutics for Clinical Translation"
Aim 1. Co-clinical trial to assess predictive biomarkers of synergy between Plk1 inhibitors and abiraterone.
Aim 2. Identification of mechanisms of synergistic cancer cell killing to expand the utility of this combination to other cancer types.

18CHAL09 (PI: Balk) 11/02/18-11/02/20 1.2 CM
Prostate Cancer Foundation TDC: $1,000,000
"Identifying and Targeting Immunogenic Prostate Cancer at High Risk for Lethal Metastatic Progression"
(I am PI of the phase 2 study that supports Aim 2, and I am PI of the translational protocol #17-048 that supports Aim 3.)
Aim 1. Identify genomic and microenvironmental features associated with immunosuppressive mechanisms in PD-L1-positive primary prostate cancer.
Aim 2. Determine predictive ability of PD-L1 expression in primary prostate cancer for response to nivolumab in men with biochemical relapse.
Aim 3. Examine antigen-specific T cell responses to mutated peptides expressed in prostate cancer cells, and whether these antigen-specific T cells are expanded by PD-1 blockade.

What other organizations were involved as partners?

Nothing to Report.