PHASE 1 TRIAL OF DURVALUMAB IN COMBINATION WITH BCG OR EXTERNAL BEAM RADIATION IN BCG-UNRESPONSIVE NON-MUSCLE INVASIVE BLADDER CANCER PATIENTS (HCRN GU16-243: ADAPT-BLADDER TRIAL)

Noah M. Hahn[1,2,3], Michael A. O'Donnell[4], Jason A. Efstathiou[5,6], Marianna Zahurak[1], Gary Rosner[1], Jeff Smith[7], Max R. Kates[1,2,3], Trinity J. Bivalacqua[1,2,3], Phuoc T. Tran[1,2,3,8], Daniel Y. Song[1,2,3,8], Alex S. Baras[1,2,3,9], Andres Matoso[1,2,3,9], Woonyoung Choi[1,2,3], Kellie N. Smith[1,2,10], Drew M. Pardoll[1,2,10], Luigi Marchionni[1,2,11], Bridget McGuire[1,2,3], Burles Johnson[1,2,3], Tanya O'Neal[1], David J. McConkey[1,2,3], Tracy L. Rose[12,13], Marc Bjurlin[12,14], Emerson A. Lim[15], Charles G. Drake[15], Christopher B. Anderson[15,16], Donald L. Lamm[17], Daniel M. Geynisman[18], Mark A. Hallman[19], Eric M. Horwitz[19], Essel Al-Saleem[20], David YT Chen[21], Alexander Kutikov[21], Gordon Guo[22,23], Timothy A. Masterson[24], Nabil Adra[25], Hristos Z. Kaimakliotis[24]

[1]Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [2]The Johns Hopkins Greenberg Bladder Cancer Institute, Baltimore, MD; [3]The James Buchanan Brady Urological Institute, Baltimore, MD; [4]University of Iowa Carver College of Medicine, Iowa City, IA; [5]Massachusetts General Hospital, Boston, MA; [6]Harvard Medical School, Boston, MA; [7]Hoosier Cancer Research Network, Indianapolis, IN; [8]Johns Hopkins School of Medicine, Department of Radiation Oncology, Baltimore, MD; [9]Johns Hopkins School of Medicine, Department of Pathology, Baltimore, MD; [10]Johns Hopkins Bloomberg Kimmel Institute for Cancer Immunotherapy, Baltimore, MD; [11]Johns Hopkins School of Medicine, Center for Computational Genomics, Baltimore, MD; [12]University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC; [13]University of North Carolina, Department of Medicine, Division of Medical Oncology, Chapel Hill, NC; [14]University of North Carolina, Department of Urology, Chapel Hill, NC; [15]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; [16]Columbia University, Department of Urology, New York, NY; [17]BCG Oncology, Phoenix, AZ; [18]Fox Chase Cancer Center, Department of Hematology and Oncology, Philadelphia, PA; [19]Fox Chase Cancer Center, Department of Radiation Oncology, Philadelphia, PA; [20]Fox Chase Cancer Center, Department of Pathology, Philadelphia, PA; [21]Fox Chase Cancer Center, Department of Urology, Philadelphia, PA; [22]Indiana University Simon Cancer Center, Department of Radiation Oncology, Indianapolis, IN; [23]University Hospitals Cleveland Medical Center, Cleveland, OH; [24]Indiana University Simon Cancer Center, Department of Urology, Indianapolis, IN; [25]Indiana University Simon Cancer Center, Department of Hematology and Oncology, Indianapolis, IN

Introduction

- BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) represents a high-risk form of urothelial carcinoma (UC).
- Previous reports implicate upregulation of the PD-1/PD-L1 immune checkpoint pathway as a resistance mechanism to intravesical BCG therapy and improved preclinical tumor control is demonstrated when immune checkpoint therapy is added to radiation therapy. [1,2]
- Recent FDA approval of systemic PD-1/PD-L1 immune checkpoint inhibitor (CPI) monotherapy represents a new option for BCG-unresponsive NMIBC patients (pts) with carcinoma in-situ (CIS) who face cystectomy as their primary standard alternative. [3]
- Despite initial complete responses (CR) to CPI therapy, durable CRs at 12 months are rare in NMIBC pts indicating a need for novel therapy approaches. [3]
- In metastatic UC, increased objective response rates have been observed with combination immunotherapy approaches. [4]
- Inspired by the 2015 NCI-sponsored NMIBC Clinical Trials Planning Meeting, the ADAPT-BLADDER trial aims to investigate the safety and efficacy of novel combination immunotherapy approaches in NMIBC pts particularly those incorporating anti-PD-L1 durvalumab therapy regimens. Here we report initial phase 1 results. [5]

Materials and Methods

STUDY DESIGN

- Prospective multi-arm, multi-stage, multi-institution phase 1/2 study

KEY PHASE 1 ELIGIBILITY

- Age ≥ 18
- ECOG PS 0-1
- BCG-unresponsive NMIBC with TURBT within 60 days of registration
  - Recurrent CIS within 12 months of adequate BCG treatment (tx)
  - Recurrent high-grade Ta/T1 within 6 months of adequate BCG tx
  - Persistent high-grade T1 at first disease evaluation
  - Prostatic urethral involvement
  - Adequate BCG defined at least 5 of 6 doses of initial induction BCG + at least 2 of 3 doses of maintenance or at least 2 of 6 doses of a second induction course
- Pts who are BCG-unresponsive at any time point in their tx history are eligible
- Pts with prostatic urethral NMIBC and upper tract non-invasive tumors are eligible
- Adequate organ function (CrCl >= 30 ml/min)

PRIMARY ENDPOINT

- Determine the recommended phase 2 dose (RP2D) of each regimen

SECONDARY ENDPOINTS

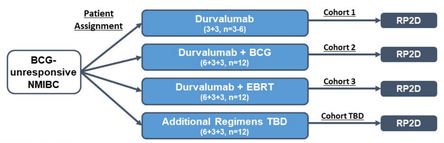
- Complete response (CR) rate of each regimen
- 6-month recurrence free survival (6m RFS) of each regimen
- Safety and toxicity profiles of each regimen studied

TERTIARY ENDPOINTS

- Durability of response (12m and 24m RFS)
- Association between presences of CIS and clinical outcomes
- Association between tumor DNA and RNA genomic signatures and clinical outcomes
- Effect of durvalumab treatment regimens on tumor, peripheral blood mononuclear cell (PBMC), and plasma pharmacodynamic measures (T-cell receptor sequence signatures, immune cell subsets, cytokines)
- Exploratory associations between tumor DNA methylation signatures and circulating antibody profiles with clinical outcomes

Materials and Methods (Continued)

GU16-243 ADAPT-BLADDER Trial – Phase 1 Schema



STUDY TREATMENTS

- Durvalumab (D) 1120 mg iv d1 on q21d cycle x 8 cycles
- TICE BCG 50 mg intravesically weekly x 6, maintenance per urologist's discretion
- EBRT to whole bladder in 3 separate 6 Gy fractions on days 1, 3, 5 of cycle 1 only

DOSE LIMITING TOXICITY (DLT) DEFINITION

- Any grade 3-4 toxicity in first 42 days of tx (exceptions – grade 3 hypothyroidism, grade 3 diarrhea/rash/urinary symptoms/lab abnormalities that resolve < 7 days)
- Any grade 2 toxicity in first 42 days of tx due to study tx that delays tx > 21 days

DISEASE ASSESSMENTS

- Cystoscopy, urine cytology and for-cause biopsies at 3 months; cystoscopy, urine cytology and mandatory bladder biopsy at 6 months; long-term tumor assessments per urologist's discretion
- Deparaffinization and DNA/RNA isolation was performed per manufacturer kit (Qiagen AllPrep DNA/RNA FFPE) instructions
- Library prep and RNA whole transcriptome sequencing was performed using Ion Torrent's AmpliseqRNA platform (Thermo Fisher, Inc) and an S5XL sequencer (Thermo Fisher, Inc)
- T-cell receptor sequencing was performed using the ImmunoSeq platform (Adaptive Biotechnologies)

STATISTICAL CONSIDERATIONS

- Confidence intervals will be reported for CR rate, 6m RFS rate, and toxicities
- Exploratory associations between clinical outcomes and translational investigations will be analyzed by Kaplan-Meier curves, log-rank tests, and univariate Cox regression models.

Results

	All Cohorts (N=28)	Cohort 1 (D) (N=3)	Cohort 2 (D + BCG) (N=13)	Cohort 3 (D + EBRT) (N=12)
Age, Median (IQR)	74.0 (9.0)	72.0 (5.5)	74.0 (6.0)	74.0 (11.2)
Gender, n (%)				
Male	23 (82.1)	3 (100.0)	10 (76.9)	10 (83.3)
Female	5 (17.9)	0 (0.0)	3 (23.1)	2 (16.7)
Race, n (%)				
Caucasian	26 (92.9)	2 (66.7)	12 (92.3)	12 (100.0
African-American	1 (3.6)	0 (0.0)	1 (7.7)	0 (0.0)
Asian	1 (3.6)	1 (33.3)	0 (0.0)	0 (0.0)
ECOG PS, n (%)				
0	22 (78.6)	1 (33.3)	10 (76.9)	11 (91.7)
1	6 (21.4)	2 (66.7)	3 (23.1)	1 (8.3)
Prior BCG regimens, n(%)				
1	6 (21.4)	1 (33.3)	2 (15.4)	3 (25.0)
2	12 (42.9)	0 (0.0)	9 (69.2)	3 (25.0)
3+	10 (35.7)	2 (66.7)	2 (15.4)	6 (50.0)

Table 1: PATIENT DEMOGRAPHICS

(D = Durvalumab; BCG = TICE BCG; EBRT = External Beam Radiation)

	All Cohorts (N=28)	Cohort 1 (D) (N=3)	Cohort 2 (D + BCG) (N=13)	Cohort 3 (D + EBRT) (N=12)
Pure Papillary, n (%)	11 (39.3)	1 (33.3)	5 (38.5)	5 (41.7)
Ta	4 (14.3)	0 (0.0)	3 (23.1)	1 (8.3)
T1	7 (25.0)	1 (33.3)	2 (15.4)	4 (33.3)
Concurrent Papillary + CIS, n (%)	3 (10.7)	1 (33.3)	1 (7.7)	1 (8.3)
Ta + CIS	2 (7.1)	1 (33.3)	1 (7.7)	0 (0.0)
T1 + CIS	1 (3.6)	0 (33.3)	0 (0.0)	1 (8.3)
Pure CIS, n (%)	14 (50.0)	1 (33.3)	7 (53.8)	6 (50.0)

Table 2: BASELINE TUMOR STAGES

(D = Durvalumab; BCG = TICE BCG; EBRT = External Beam Radiation)

Toxicity	Grade	Cohort 1 (D) N, (%)	Cohort 2 (D + BCG) N, (%)	Cohort 3 (D + EBRT) N, (%)	DLT Event
Lipase increased	4	0 (0.0)	0 (0.0)	1 (8.3)	No
UTI	3	1 (33.3)	0 (0.0)	0 (0.0	No
Hyperglycemia	3	0 (0.0)	1 (7.7)	1 (8.3)*	No
Myocardial Infarction	3	0 (0.0)	1 (7.7)	0 (0.0)	No
ALT increased	3	0 (0.0)	0 (0.0)	1 (8.3)*	Yes
AST increased	3	0 (0.0)	0 (0.0)	1 (8.3)*	Yes
Lipase increased	3	0 (0.0)	0 (0.0)	1 (8.3)*	No
Pneumonitis	3	0 (0.0)	0 (0.0)	1 (8.3)	No
Maculopapular rash	3	0 (0.0)	0 (0.0)	1 (8.3)**	No

Table 3: ALL GRADE 3-4 TOXICITY EVENTS

(D = Durvalumab; BCG = TICE BCG; EBRT = External Beam Radiation; *Possibly treatment related; **Definitely treatment related; All other attributions unlikely or unrelated)

Recommended Phase 2 Doses

D – 1120 mg iv d1 on q21d cycle

BCG – 50 mg TICE BCG weekly x 6

EBRT – 6 Gy x 3 on d1,3,5 c1 only

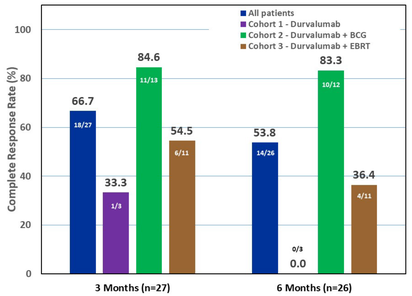


Figure 1: COMPLETE RESPONSE RATE at 3- and 6-MONTHS

Results (Continued)

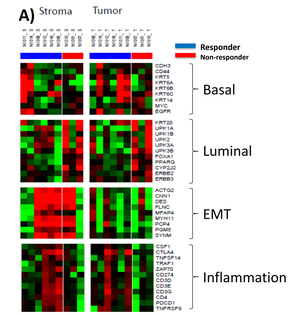


Figure 2: BASELINE TUMOR AND STROMA GENE EXPRESSION SIGNATURES IN RESPONDING vs NON-RESPONDING PATIENTS

(3A – Baseline T-cell Receptor Clonality Responders vs Non-responders; 3B – C1D8 vs C1D1 T-cell Receptor Clonality (All patients))

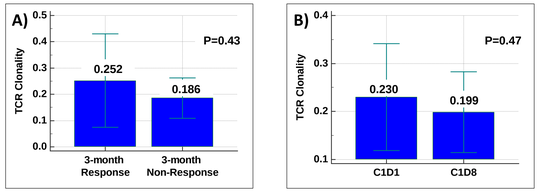


Figure 3: T-CELL RECEPTOR CLONALITY ANALYSIS

(3A – Baseline T-cell Receptor Clonality Responders vs Non-responders; 3B – C1D8 vs C1D1 T-cell Receptor Clonality (All patients))

Conclusions

- Durvalumab in combination with intravesical BCG therapy or EBRT can be safely administered to NMIBC patients.
- Complete response rates in the treated BCG-unresponsive NMIBC population are promising with no unexpected adverse events observed.
- Preliminary translational investigations suggest decreased response in luminal, non-inflamed tumors with no appreciable changes in PBMC TCR clonality at a very early post-treatment time point.
- Longer-term follow up is need to assess the durability of observed responses.
- The multi-arm, multi-stage ADAPT-BLADDER study presents an attractive trial design to optimize assessment of future NMIBC combination strategies.

References

1. Inman BA et al, Cancer 2007;109:1499-1505
2. Fukumoto K et al, Ann Surg Oncol 2018;25(8):2484-91
3. Keytruda (Pembrolizumab) Full Prescribing Information, accessed 9/2/20
4. Powles T et al, ESMO 2020, abstract 6970
5. Lerner S et al, Bladder Cancer 2016;2(2):165-202