DGMC – Human Research
Final Report

1. DATE: 10 April 2014

2. Protocol Number: FDG20010007H RTOG9902

3. Title: A Phase III Protocol of Total Androgen Suppression (TAS) and Radiation Therapy (RT) vs TAS and RT Followed by Chemotherapy with Paclitaxel, Estramustine, and Etoposide (TEE) for Localized, High-Risk, Prostate Cancer

4. Risk: ☒ **Greater than Minimal Risk** ☐ **Minimal Risk**

5. Date of Approval: 6 Nov 2000

6. Start Date: 17 Nov 2000

7. Study Staff

Name	Rank	Study Role	Date of Investigator Training	Staff/ Resident/ Fellow/ Civilian	Dept/ Office Symbol	Phone	E-mail
Mitchell, James	Maj	PI	11/26/12	Staff	SGQXO	423-7691	James.mitchell.6@us.af.mil
David Eastham	Lt Col	AI	2/10/13	Staff	SGQXO	423-7691	David.eastham@us.af.mil
David J Hoopes	Maj	AI	8 April 2011	Staff	SGQXO	423-3673	David.Hoopes.1@us.af.mil
Natalia I Knezienski	Civ	CRC	4 April 2012	Civ	SGQXO	423-7691	Natalia.Knezienski.1@us.af.mil

8. Study Status:
(Check one only)
☐ Inactive, protocol never initiated
☐ Inactive, protocol initiated but has not/will not be completed
☒ All approved procedures/uses have been completed

9. Number of Subjects Entered into the Study: For multiple sites, add rows to the table below for each site.

	Number approved to enroll	**Number enrolled**	**Withdrawals**
Number of subjects enrolled at DGMC	not determined	2	0
Number of subjects enrolled at National RTOG Cooperative Sites	1440	397	17 (not eligible)

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
13 MAY 2014	**Final**	**06 NOV 2000 - 13 MAY 2014**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
FDG20010007H, RTOG #99-02 A Phase III protocol of androgen suppression and radiation therapy Vs and RT followed by chemotherapy with paclitaxel, estramustine, and etoposide for localized, high risk, prostate cancer.	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S) **Lt Col Davis Eastham, Maj James Mitchell, Maj David Hoopes, Maj Hristov Borislav, Lt Col Ronald Engel**	5d. PROJECT NUMBER **FDG20010007H**
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Clinical Investigation Facility David Grant Medical Center 101 Bodin Circle Travis AFB, CA 94535**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) **Clinical Investigation Facility David Grant Medical Center 101 Bodin Circle Travis AFB, CA 94535**	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Summary of Protocol Objectives: The primary objectives were to assess the relative efficacy of the combination of androgen suppression (AS) plus radiation therapy (RT) followed AS vs. AS plus RT followed by chemotherapy (CT) plus AS in high risk, unfavorable prognosis prostate cancer (PCa) population. In order to measure the efficacy of the treatments the endpoints being evaluated were overall survival, disease free survival, local control and freedom from distant metastasis. Differences in toxicities between the two treatments were also going to be evaluated. The RTOG 9902 investigators hypothesize that adjuvant CT would improve the survival rate of high-risk PCa when used in combination with RT and AS. Methods: The purpose and methods were reviewed and approved by the local IRB. The voluntary and full informed consent of participants was obtained prior to study procedures. Volunteer participants who met eligibility criteria were stratified, enrolled and randomized as per protocol. In brief, eligibility criteria included men with high risk non metastatic prostate cancer histologically confirmed with PSA level of 20-100ng/mL and a Gleason score > 7, stage T2 or greater. Volunteer participants were randomized into one of two treatments. RT began 8 weeks after androgen suppression treatment and followed weekly by their radiation oncologist during the RT, every 3 months for two years, then every 6 months for three years and yearly after that for the remainder of the participants natural life. Results: Study was locally approved on November 2000 and assigned number FDG20010007H, receiving 10 continuing approval before IRB oversight was transferred to Wilford Hall (WHMC) under protocol number FWH20110083H. IRB oversight was transferred back DGMC in May 2012. This study opened nationally in Jan 2000 and prematurely closed to accrual in Oct 2004 with a total of 397 participants (380 eligible); 2 from DGMC. The protocol has been deemed terminated by national RTOG-9902. We have one participant still enrolled in the study from which data collection will cease and monitoring will continue as standard of care throughout the remainder of his natural life as per latest RTOG broadcast (Nov2013). RTOG 9902 investigators previously reported on the chemotherapy combination toxicities that led to early protocol closure (Rosenthal, et al. IJROBP 73:672, 2009), also reported with local yearly reviews (2005, 2012). Nevertheless, participants have been followed for the primary endpoint. Overall study compliance was 98-99% for Arm-1 and Arm-2, respectively. Median follow-up was 6 years; 5-yr overall survival was 86% for both the RT+AS and RT+AS+CT arms (p=0.79). Conclusions: RTOG 9902 failed to reach its accrual goal due to toxicity. Investigators found no difference in overall survival with the addition of adjuvant CT. Of note, small sample size due to premature closure may have reduced the ability to detect a significant difference. However the study revealed that patients are willing to be randomized into chemotherapy and that chemotherapy as an adjuvant does not present significant late gastro and genitourinary toxicities and it is being evaluated. A similarly designed trial, RTOG 0521, completed accrual in 2009, will shed light into adjuvant chemotherapy with a different combination (rather than TEE).

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**SAR**	**7**	

9.1. Summary of Unanticipated Problems and Adverse Events:

The study had *Local* Unanticipated Problems:
☐ Yes ☒ No
The study had *Local* Adverse Events:
☒ Yes ☐ No
All *Local* adverse, serious adverse and unexpected events were reported IAW SGSE 40-402-01:
☒ Yes ☐ No ☐ N/A

List all the local and sponsor reported unanticipated problems, serious and non-serious adverse events, reported to the sponsor and protocol deviations that resulted in subject harm for the entire study. **If none occurred, state NONE.**

FDG20010007H/RTOG-9902 ran active enrollment for a total of 4 years. Study was prematurely halted due to higher than anticipated SAE on one of the randomization arms (Arm-2) of the trial. At DGMC we had two participants (as of 2004) one of which was enrolled in Arm-2. As per RTOG direction participant was re-assigned to Arm-1 with a treatment change (2005 CR report). RTOG 9902 study also reported 2 deaths in Arm-2 (due to sepsis). At DGMC we reported one death in 2004. There were no reported protocol deviations at DGMC that resulted in subject harm.

Type of Event*	Date of Event	Date Reported	Description of Event	Site of Event (for multisite)	Outcome
SAE	17 APR 02	23 APR 02 by RTOG	Increased thromboembolic and other toxicities	RTOG-Nat	DSMB-temporary halt study APR02-JUN02. Protocol amendment to address anticoagulation regimen
SAE	30 JUL 04	4 OCT 04 by RTOG	Persistent thromboembolic and other toxicities	RTOG-Nat	DSMB-premature closure. Continue follow up of enrolled
SAE	4 FEB 04	24 JUN 04	Participant expiration	DGMC	Report/Notification of death

*Unexpected adverse event, severe adverse event, or adverse event

Reminder if these events were study related, caused harm or increased the risks to subjects or others, they should have already been reported when discovered, using the Adverse or Unexpected Adverse Event report form. This is only a summary of those events.

9.2. Summary of Withdrawals from the Study: If none occurred, state NONE. List all subjects who withdrew (please specify if the subject withdrew, is lost to follow-up, deceased or any other reasons from your study)

For the Entire Study Chronologically

Date of Withdrawal	Subject Number	Reason for Withdrawal
none		

9.3. Consent Process:

Each participant was recruited in accordance with the recruitment plan approved by the IRB.
☒ Yes ☐ No

Each participant was consented in accordance with the consent process approved by the IRB.
☒ Yes ☐ No

Each participant was given a copy of the signed, dated informed consent document.
☒ Yes ☐ No

As the PI, I have retained a copy of each participant's signed, dated informed consent document and provided a copy to the Protocol Office for record.
☒ Yes ☐ No

10. Study Deviations

Have any minor non-compliance events occurred? ☒ Yes ☐ No
Have any serious non-compliance events occurred? ☐ Yes ☒ No

List any instances of non-compliance minor or serious

Local minor non-compliance activities were noted during an audit conducted on 1MAR2010. Protocol deviation was reported for a consent form misplaced on 02APR2009. These activities did not cause harm or affect the rights and/or welfare of study participants and have been reported appropriately to the respective regulatory bodies. Furthermore, corrective/preventive actions were put in place to prevent reoccurrence.

I certify that no changes have occurred in the protocol since the previous IRB review. ☒ Yes ☐ No

11. Complaints about the Study:

Have there been any reported complaints regarding the study?
☐ Yes ☒ No

List all complaints about your study, for the Entire study. **If no complaints occurred, state NONE and delete the table below. Do not use N/A**

NONE

12. Amendments:

List all amendments/changes made to the protocol, Informed Consent or investigator's brochure. **IF none occurred, state NONE. Do not use N/A.**

Date of Change	Date of Approval	Summary of the Change
18-Oct-01	18-Oct-01	**DGMC Amendment 1:** Change of PI from Col William Dickerson to Maj Roland Engel. Addition of Col William Dickerson as AI
1-Aug-02	1-Aug-02	**DGMC Amendment 2:** Deletion of Col William Dickerson due to military transfer
31 Jul 03	4-Aug-03	**DGMC Amendment 3:** RTOG National Amendments #1, #2 and #3: Changes in protocol content and ICD
18 Apr 04	16 Apr 04	**DGMC Amendment 4:** RTOG National Amendment# 4: Changes in protocol content and ICD
5 Apr 04	21 Apr 04	**DGMC Amendment 5:** Addition of Dr. Belinda Ark and Capt

		Carolyn A. Wild as AIs
2 Sep 09	4 Oct 09	**DGMC Amendment 6:** Adding two AIs: Maj Vincent Lee and Capt Borislav Hristov, and RTOG National Amendment#5: Changes in protocol content
23-Jul-10	2 Aug 10	**DGMC Amendment 7:** Deletion of Maj Vincent Lee due to separation from the AF
12-Oct-10	1-Nov-10	**DGMC Amendment 8:** Personnel Change in PI from Col Engel (PCS) to Maj David Hoopes
18 Apr 13	26 Apr 13	**DGMC Amendment 9:** Change of PI from Maj Hoopes to Maj James Mitchell; Maj Hoopes will remain as AI. Also to add Lt Col David Eastham as an AI

13. Funding:

(Complete as appropriate, delete the others, some of this information is contained in your protocol and or amendments – suggest you cut and paste info. As a reminder, requests for additional funding must be submitted using the Protocol Amendment form.

Funding from:

☐R&D ☐SGO ☐O&M ☐HMJ ☒OTHER (explain source): RTOG/JROC

in the amount of $__N/A____ was approved in my original protocol. Of that money, I will need $__N/A___ for the remainder of this fiscal year.

I have received External Resources to support this study in the form of:
(select all those applicable):

- ☐ Loaned equipment
- ☐ Consumable supplies
- ☐ Drugs from a non-DoD source

14. Summary of Research Findings:

Summary of Protocol Objectives: The primary objectives were to assess the relative efficacy of the combination of androgen suppression (AS) plus radiation therapy (RT) followed AS vs. AS plus RT followed by chemotherapy (CT) plus AS in high risk, unfavorable prognosis prostate cancer (PCa) population. In order to measure the efficacy of the treatments the endpoints being evaluated were overall survival, disease free survival, local control and freedom from distant metastasis. Differences in toxicities between the two treatments were also going to be evaluated. The RTOG 9902 investigators hypothesize that adjuvant CT would improve the survival rate of high-risk PCa when used in combination with RT and AS.

Methods: The purpose and methods were reviewed and approved by the local IRB. The voluntary and full informed consent of participants was obtained prior to study procedures. Volunteer participants who met eligibility criteria were stratified, enrolled and randomized as per protocol. In brief, eligibility criteria included men with high risk non metastatic prostate cancer histologically confirmed with PSA level of 20-100ng/mL and a Gleason score > 7, stage T2 or greater. Volunteer participants were randomized into one of two treatments. RT began 8 weeks after androgen suppression treatment and

followed weekly by their radiation oncologist during the RT, every 3 months for two years, then every 6 months for three years and yearly after that for the remainder of the participant's natural life.

Results: Study was locally approved on November 2000 and assigned number FDG20010007H, receiving 10 continuing approval before IRB oversight was transferred to Wilford Hall (WHMC) under protocol number FWH20110083H. IRB oversight was transferred back DGMC in May 2012. This study opened nationally in Jan 2000 and prematurely closed to accrual in Oct 2004 with a total of 397 participants (380 eligible); 2 from DGMC. The protocol has been deemed terminated by national RTOG-9902. We have one participant still enrolled in the study from which data collection will cease and monitoring will continue as standard of care throughout the remainder of his natural life as per latest RTOG broadcast (Nov2013). RTOG 9902 investigators previously reported on the chemotherapy combination toxicities that led to early protocol closure (Rosenthal, et al. IJROBP 73:672, 2009), also reported with local yearly reviews (2005, 2012). Nevertheless, participants have been followed for the primary endpoint. Overall study compliance was 98-99% for Arm-1 and Arm-2, respectively. Median follow-up was 6 years; 5-yr overall survival was 86% for both the RT+AS and RT+AS+CT arms (p=0.79).

Conclusions: RTOG 9902 failed to reach its accrual goal due to toxicity. Investigators found no difference in overall survival with the addition of adjuvant CT. Of note, small sample size due to premature closure may have reduced the ability to detect a significant difference. However the study revealed that patients are willing to be randomized into chemotherapy and that chemotherapy as an adjuvant does not present significant late gastro and genitourinary toxicities and it is being evaluated. A similarly designed trial, RTOG 0521, completed accrual in 2009, will shed light into adjuvant chemotherapy with a different combination (rather than TEE).

15. Publications and Presentations for this research study:
List all presentations **Authored by study staff** (Include lectures, abstracts, posters, etc), for the Entire study. **For RTOG and other national collaborations please include publications and presentations directly tied to the approved protocol only.**

Date	Authors	Title
1 Nov 2012	Hamstra D.A., Hunt D., Grignon D., Hanks G.E., Peters C.A., Rosenthal S.A., Lock M.I., Zeitzer K.L., Souhami L., and Sandler H.	Gleason Pattern 5 is Associated With an Increased Risk for Metastasis Following Androgen Deprivation Therapy (ADT) and Radiation: An Analysis of RTOG 9202 and 9902 *Int J Radiat Oncol Biol Phys. 2012 doi:10.1016/j.ijrobp.2012.07.240* *Oral Scientific Session 225*
4-8 June 2010 Proc of American Society of Clinical Oncology (ASCO) Annual Meeting	Sandler H, Hunt D, Sartor A, Gomella L, Hartford A, Zeitzer K, Rajan R, Kerlin K, Michalski J, Rosenthal S.	A Phase III Protocol of Androgen Suppression (AS) and Radiation Therapy (RT) versus AS and RT Followed by Chemotherapy with Paclitaxelkestramustine, and Etopside (TEE) for Localized, High-Risk, Prostate Cancer Poster Presentation
1 March 2009	Rosenthal S, Bae K, Pienta K, Hartford A, Asbell S, Rajan R, Kerlin K, Michalski J, Sandler H.	Phase III Multi-Institutional Trial of Adjuvant Chemotherapy (CT) with Paclitaxel, Estramustine, and Oral Etoposide in Combination with Long-Term Androgen Suppression (AS) Therapy and Radiation Therapy (RT) vs. Long-Term AS + RT Alone in the Management of High-Risk Prostate Cancer: Preliminary Toxicity Analysis of RTOG 99-02. *Int J Radiat Oncol Biol Phys.* 2009; 73 (3): 672-678. http://www.ncbi.nlm.nih.gov/pubmed/18990504 *Journal Article*

These presentations/publications were approved by the CIF Director and Public Affairs Office.
☐Yes☐No **NON applicable**, non-local publications

16. Signature of Principal/Associate Investigator:

James O. Mitchell, MD
Type/Print Name of Investigator

Signature

4/18/14
Date

CC: Research Monitor (RM) Name
(Forward a copy of this report to RM.)

Attachments:
Please list attachments below and attach to Progress Report
e.g. amendments, publications