Clinical Protocol

2A Pilot Presurgical Study of Daratumumab (CD38 antagonist) or JNJ-40346527 in Men with High-Risk Localized Prostate Cancer Followed by Radical Prostatectomy

Protocol 2017-0103

JNJ-54767414 Daratumumab
JNJ-40346527

Principal Investigator: Sumit K. Subudhi, M.D., Ph.D.
U.T. M. D. Anderson Cancer Center
Department of Genitourinary Medical Oncology
1155 Pressler, Unit 1374
Houston, Texas 77030
Phone: (713) 792-2830
Fax: (713) 745-1625
Email: sksubudhi@mdanderson.org

Co-Principal Investigators: Brian F. Chapin, M.D.
U.T. M. D. Anderson Cancer Center
Department of Urology
1155 Pressler, Unit 1373
Houston, Texas 77030
Phone: (713) 792-3250
Fax: (713) 794-4824
Email: bfchapin@mdanderson.org

Ana Aparicio, M.D.
U.T. M. D. Anderson Cancer Center
Department of Genitourinary Medical Oncology
1155 Pressler, Unit 1374
Houston, Texas 77030
Phone: (713) 792-2830
Fax: (713) 745-1625
Email: aaparicio@mdanderson.org

Collaborators: Padmanee Sharma, M.D., Ph.D.
Email: padsharma@mdanderson.org

Additional Collaborators see the institutional database page

Biostatistician: Rebecca Slack, MS
Email: rsslack@mdanderson.org

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Version 00	01/31/2017	Pre-Submission packet
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Version 01	03/27/2017	CRC IRB packet
Version 02	03/27/2017	IRB approved (initial)
Version 03	03/27/2017	Administrative edits
Version 04	07/14/2017	Clarifications
Version 05	12/27/2017	Additional study arm JNJ-527
Version 06	05/07/2018	Administrative con med language
Version 07	06/18/2018	Drug infusion rate correction

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2A Pilot Presurgical Study of Daratumumab (CD38 antagonist) or JNJ-40346527 in Men with High-Risk Localized Prostate Cancer Followed by Radical Prostatectomy

Table 1: Time and Events Schedule for Assessments and Procedures

Daratumumab:

All events have a window of +/- 7 days		**Screening Phase**	**Open- label Treatment Phase**				**Surgery Phase**	**End of Study**
	Notes	**Within 28 days of enrollment**	**W1**	**W2**	**W3**	**W4**	**W6**	**W18**
Screening/Administrative								
Informed consent		X						
Inclusion/Exclusion Criteria		X						
Medical History		X						
Laboratory Evaluations[b]								
Hematology and Serum Chemistry		X	X	X	X	X	X	X
Testosterone		X					X	X
Blood Type and Screen for daratumumab arm only			X	X	X	X	X	
PSA		X			X		X	X
Safety								
12-lead ECG		X						
Physical examination		X	X	X	X	X	X	
Weight, Height	Height at screening only	X	X	X	X	X	X	
Vital signs	for drug infusion (excludes weight): at arrival to infusion center; change in status; upon completion of medication or prior to discharge	X	X	X	X	X	X	
ECOG PS		X					X	X
Ongoing Subject Review								
Concomitant medications		Record in medical record from signing informed consent to date of prostatectomy (not required to be entered to the electronic case report form)						
Adverse events		Record from signing informed consent to a minimum of 90 days after **last dose** of study drug						X[a]
Study Drug Administration								
Daratumumab			X	X	X	X		
Surgery Phase								
Prostatectomy	On or after week 6						X	

CD=cluster of differentiation; W=week; ECOG PS=Eastern Cooperative Oncology Group Performance Status; PSA=prostate-specific antigen

a Minimum of 90 days after last dose of daratumumab for end of study visit.
b Laboratory evaluations details located on Table 2: Collection Time points for laboratory evaluation.

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JNJ-527:

All events have a window of +/- 7 days		**Screening Phase**	**Open- label Treatment Phase**				**Surgery Phase**	**End of Study**
	Notes	**Within 28 days of enrollment**	**W1**	**W2**	**W3**	**W4**	**W5**	**W18**
Screening/Administrative								
Informed consent		X						
Inclusion/Exclusion Criteria		X						
Medical History		X						
Laboratory Evaluations[b]								
Hematology and Serum Chemistry		X	X	X	X	X	X	X
Testosterone		X					X	X
PSA		X			X		X	X
Safety								
12-lead ECG		X						
Physical examination		X	X	X	X	X	X	
Weight, Height	Height at screening only	X	X	X	X	X	X	
Vital signs	for drug infusion (excludes weight): at arrival to infusion center; change in status; upon completion of medication or prior to discharge	X	X	X	X	X	X	
ECOG PS		X					X	X
Ongoing Subject Review								
Concomitant medications		Record in medical record from signing informed consent to date of prostatectomy (not required to be entered to the electronic case report form)						
Adverse events		Record from signing informed consent to a minimum of 90 days after **last dose** of study drug						X[a]
Study Drug Administration								
JNJ-527			X	X	X	X[c]		
Surgery Phase								
Prostatectomy	On or after week 5						X[c]	

CD=cluster of differentiation; W=week; ECOG PS=Eastern Cooperative Oncology Group Performance Status; PSA=prostate-specific antigen

a Minimum of 90 days after last dose of JNJ-527 for end of study visit.
b Laboratory evaluations details located on Table 2: Collection Time points for laboratory evaluation.
c. A minimum of a 3 day wash-out of JNJ-527 is required before surgery

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Table 2: Collection Time points for laboratory evaluation

Daratumumab:

Laboratory Evaluations (± 7 days from time points)								
Laboratory Name	**Study Required Tests**	**Screening Phase**	**W1**	**W2**	**W3**	**W4**	**Surgery Phase: W6**	**End of Study: W18**
CDC w Diff	hemoglobin	X	X	X	X	X	X	X
	white blood cell (WBC) count	X	X	X	X	X	X	X
	platelet count	X	X	X	X	X	X	X
	absolute neutrophil count (ANC)	X	X	X	X	X	X	X
	absolute lymphocyte count	X	X	X	X	X	X	X
	absolute monocyte count	X	X	X	X	X	X	X
	absolute eosinophil count	X	X	X	X	X	X	X
Comprehensive Metabolic Panel	potassium	X	X	X	X	X	X	X
	creatinine	X	X	X	X	X	X	X
	glucose (fasting)	X	X	X	X	X	X	X
	albumin (screening only)	X						
	total bilirubin	X	X	X	X	X	X	X
	AST	X	X	X	X	X	X	X
	ALT	X	X	X	X	X	X	X
	Alkaline phosphatase (ALP)	X	X	X	X	X	X	X
	direct bilirubin	X	X	X	X	X	X	X
	indirect bilirubin	X	X	X	X	X	X	X
	PSA	X			X		X	X
	Testosterone	X					X	X
	Blood Type and Screen		X	X	X	X	X	

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JNJ-527:

Laboratory Evaluations (± 7 days from time points)								
Laboratory Name	**Study Required Tests**	**Screening Phase**	**W1**	**W2**	**W3**	**W4**	**Surgery Phase: W5**	**End of Study: W18**
CDC w Diff	hemoglobin	X	X	X	X	X	X	X
	white blood cell (WBC) count	X	X	X	X	X	X	X
	platelet count	X	X	X	X	X	X	X
	absolute neutrophil count (ANC)	X	X	X	X	X	X	X
	absolute lymphocyte count	X	X	X	X	X	X	X
	absolute monocyte count	X	X	X	X	X	X	X
	absolute eosinophil count	X	X	X	X	X	X	X
Comprehensive Metabolic Panel	potassium	X	X	X	X	X	X	X
	creatinine	X	X	X	X	X	X	X
	glucose (fasting)	X	X	X	X	X	X	X
	albumin (screening only)	X						
	total bilirubin	X	X	X	X	X	X	X
	AST	X	X	X	X	X	X	X
	ALT	X	X	X	X	X	X	X
	Alkaline phosphatase (ALP)	X	X	X	X	X	X	X
	direct bilirubin	X	X	X	X	X	X	X
	indirect bilirubin	X	X	X	X	X	X	X
	PSA	X			X		X	X
	Testosterone	X					X	X

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ABBREVIATIONS

AAP	abiraterone acetate plus prednisone (or prednisolone)
ADT	androgen deprivation therapy
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
CD4	cluster of differentiation 4
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
ICS	intracellular cytokine staining
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IgG	serum immunoglobulin G
IHC	Immunohistochemistry
IRB	Institutional Review Board
ITT	intent-to-treat
IV	Intravenous
MDSC	myeloid-derived suppressor cells
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PCWG3	Prostate Cancer Working Group 3
PK	Pharmacokinetics
PSA	prostate-specific antigen

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1. INTRODUCTION

Daratumumab (previously known as JNJ-54767414) is a first-in-class, human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds CD38-expressing malignant cells with high affinity. Daratumumab is approved by the Food and Drug Administration (FDA) for the treatment of patients with multiple myeloma (MM).

JNJ-40346527 is a potent, selective, orally available, small-molecule inhibitor of the colony stimulating factor-1 receptor (CSF-1R) tyrosine kinase (also known as the cellular homolog of the feline McDonough sarcoma virus oncogene [v-fms] or FMS receptor tyrosine kinase). So far, the safety and preliminary efficacy of JNJ-40346527 has been evaluated in 3 clinical trials conducted in healthy volunteers, subjects with rheumatoid arthritis and subjects with Hodgkin lymphoma. Based on safety, pharmacokinetic and pharmacodynamic data JNJ-40246527 administered orally (po), twice daily (BID) at a dose of 150 mg has been identified as the recommended dose and schedule for future studies conducted in patients with malignant diseases.

For the remainder of this protocol, study drug will collectively refer to daratumumab or JNJ-40346527 (JNJ-527).

For the most comprehensive nonclinical and clinical information regarding the study drugs refer to their latest, respective version of the Investigator's Brochure and Addenda.

1.1. Prostate Cancer and Immunological Correlates

Historically, the prostate gland was considered an immunologically privileged site as initial reports suggested there were no lymphatics within the prostate; we now know this is not accurate and can identify lymphatic vessels traversing all aspects of the prostate. However, mounting evidence suggests that the prostate is precariously balanced between a state of immune unresponsiveness and a state of immune recognition. For the most part, in younger men, the host immune system appears to be largely indifferent to the prostate; however, in older patients, it is well-documented that there is a high incidence of inflammatory disorders of the prostate that occur in the absence of an identifiable pathogen and encompasses the clinical definition of prostatitis. Furthermore, in the setting of prostate cancer, it has been shown that a low density of tumor-infiltrating lymphocytes (TILs) is a predictive factor for a poor outcome thus highlighting the significance of immune responsiveness to tumor presence within the prostate (1).

Our group has previously demonstrated in a presurgical clinical trial that the immune checkpoint therapy, ipilimumab, increases the frequency of activated T cells within malignant and non-malignant prostate tissues (2). More recently, it has been shown in a presurgical trial that the prostate cancer vaccine, sipuleucel-T, promotes the recruitment of activated lymphocytes within the tumor microenvironment (3). Together, these studies demonstrate that immunotherapies can illicit systemic T cells responses and recruit effector T cells within the prostate tumor microenvironment.

1.2. Pelvic Lymphadenectomy During Radical Prostatectomy

A standard lymph node dissection during routine radical prostatectomy has involved the removal of nodes from the obturator fossa only. However, it has been known for a long time, but commonly neglected, that primary lymph node metastases may occur in a much larger template. Lymphangiography studies have long demonstrated that the prostate lymphatics drain into the periprostatic subcapsular network, from which three groups of ducts originate, namely the ascending duct from the cranial prostate draining into the external iliac lymph nodes, the lateral duct running to the hypogastric lymph nodes and the posterior duct draining from the caudal prostate to the subaortic sacral lymph nodes of the promontory. The levels of lymph node drainage are segregated into the hypogastric (primary), obturator (secondary), external iliac (tertiary) and presacral (quaternary) lymphatics (4-6). Based on these anatomical and lymphographic studies it becomes evident that standard pelvic lymphadenectomy misses the primary and quaternary lymphatics of the prostate; thereby, decreasing the opportunity for adequate regional staging. While nomograms like Partin's are commonly used to estimate the risk of nodal involvement, these are based upon a pelvic lymph-node dissection (PLND) of the obturator fossa only and will therefore underestimate the risk of lymph node metastases to a great extent (7).

A prior study demonstrated that the detection rate of small solitary lymph node metastases markedly increases when performing an extended PLND, and almost half of the metastases would have been missed by a PLND of the obturator fossa only (8). Another study observed a higher incidence of metastases in extended PLND as compared to standard PLND (26 versus 12%) without a significant difference in morbidity. Stone et al. noted that the incidence of positive lymph nodes was three times higher (23.1 versus 7.3%) with extended PLND (9).

Because of the importance of an in situ systemic immune response to become manifest as a result of immunotherapy, drainage of tumor derived dendritic cells to the lymph nodes may be essential. These questions need to be answered to optimize trials of immune system co-modulatory agents. Significant information regarding the effects of novel immunotherapies may be gained through more meaningful pelvic lymph node dissection using an extended template. In addition, it should be remembered that a PSA relapse of up to 30% occurs after radical prostatectomy, and it is quite certain that some of these relapses are due to missed lymph node metastases. Patients undergoing an extended lymph node dissection may benefit not only from the underlying diagnostic value, but also its potential therapeutic value. Thirty-nine percent of patients with a single positive node after extended lymph node dissection in the report of Bader and colleagues remained free of relapse compared to only 10% of those from whom two or more nodes were removed (8). This observation has been recently confirmed by other groups: Among men with lymph node-positive disease involving less than 15% of extracted nodes, the 5-year PSA progression-free rate for extended lymph node dissection was 43 versus 10% for the more limited lymph node dissection (10). Thus a radical prostatectomy with extended PLND may offer long-term survival beyond the information gained from interrogating additional lymph nodes following immunotherapy.

1.3. Neoadjuvant (Presurgical) Therapy in Prostate Cancer

There are no neoadjuvant standard of care treatment strategies for patients with localized prostate adenocarcinoma who are scheduled to undergo radical prostatectomy. We have previously conducted several neoadjuvant clinical trials in the setting of localized prostate cancer to identify biological markers that correlate with specific therapies (11-17).

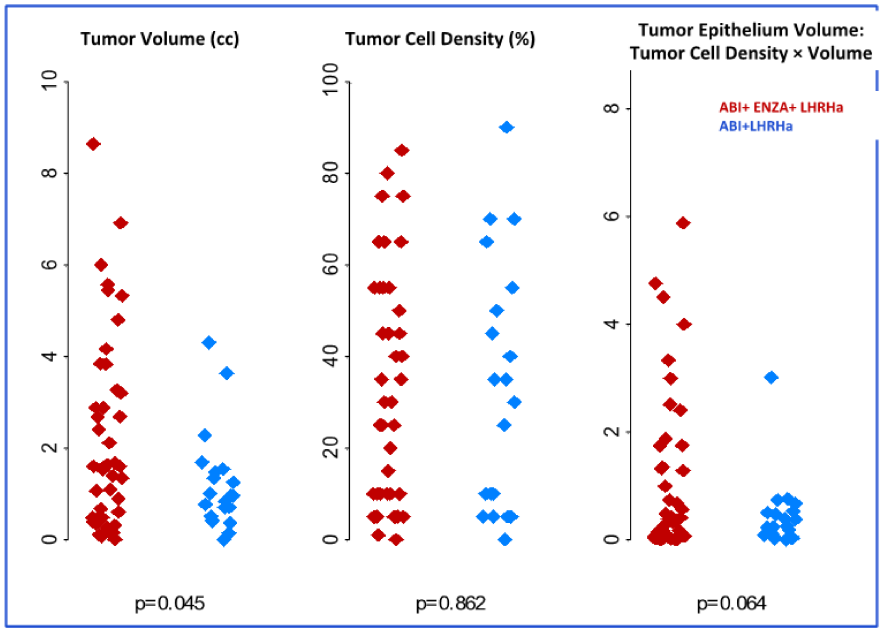
We and others believe the timing of curative treatment for high-risk prostate cancer within a 3-month window from the time of diagnosis is critical (18). Therefore, in the presurgical setting examination of novel therapeutic agents without the use of hormonal therapies (e.g., LHRH analogues) should occur within 3 months of the initial prostate biopsy.

The challenges to developing immunotherapy for prostate cancer are daunting. Although prostate cancer is the first common adult solid tumor that has an approved vaccine which prolongs survival, it has been difficult to build upon. The challenges that may account for this in our view are: 1) there are no immune-related biomarkers that can monitor efficacy in easily accessible tissues; 2) immunologic changes within the peripheral blood have been relatively uninformative; 3) there is disease stage heterogeneity (men with “early cancers” may have an different benefit than those with more aggressive cancer); 4) relationship of immunotherapy efficacy may be therapy-specific (i.e., immune checkpoint therapies may be more effective in cancers with “high mutational loads”, whereas vaccines may be more effective early in progression).

To address these issues we have developed a presurgical model to assure that study patients have uniform and clinically high-risk cancers. We have previously quantified viable tumor volume for high-risk localized cancers that allow the estimation of efficacy. These measures account for total tumor volume, the cancer cell density, and an integration of the two (Figure 1). The dynamic range observed allow us to link novel therapies to residual viable tumor volume in small sample sizes. In this study, we will attempt to link this to a favorable immune profile in treated tissues.

Figure 1: Residual Tumor Quantification

Residual Tumor Quantification



Our departmental experiences with presurgical trials in localized prostate cancer have recently demonstrated drug activity based on tumor epithelial cell density and/or changes in tumor biomarkers (e.g., immune infiltration [% CD3 or % CD68 cells]). In addition, we have successfully identified adaptive resistance mechanisms to these active agents by examining pre- and post-treatment tissues in the presurgical clinical trials that have served to inform the development of subsequent trials.

We believe that in this clinical trial, our biomarker and safety data will better inform which drug(s) demonstrate a potential favorable impact on the treatment of prostate cancer and therefore; warrant further pursuit. We will be able to preliminarily link changes in the immune profile to potential antitumor activity, and correlate this with tumor cell density. For example, we would expect an inverse relationship between immune cell density and tumor epithelial density (e.g., increased CD3 density [pre-treatment vs post-treatment] would correlate with lower post-treatment tumor epithelial density).

1.4. Daratumumab

Daratumumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards cells that express high levels of CD38. Daratumumab induces lysis of CD38-expressing cells, by a wide spectrum of mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity

(ADCC), antibody-dependent cellular phagocytosis (ADCP), and direct apoptosis through activation of complement proteins, natural killer (NK) cells, macrophages, and antibody crosslinking, respectively. Recent investigation of single-agent study the multiple myeloma setting has also revealed favorable immunomodulatory effects such as increases in T cell numbers and clonality and higher CD8 ratios with respect to CD4s and regulatory populations of T-regulatory and myeloid derived suppressor cells (unpublished data).

1.4.1. Nonclinical Experience with Daratumumab

1.4.1.1. Toxicology of Daratumumab

Toxicology data have been derived from studies with daratumumab in chimpanzees and with a surrogate anti-CD38 antibody in cynomolgus monkeys. The primary toxicities identified in chimpanzees were infusion-related reactions (IRRs) during the first, but not subsequent, daratumumab infusions and thrombocytopenia. The binding affinity of daratumumab is ≥15-fold higher for chimpanzee platelets than for human platelets, suggesting that thrombocytopenia may be less pronounced in humans. Anemia was observed in cynomolgus monkeys. The cynomolgus anti-D38 binds strongly to cynomolgus monkey red blood cells (RBCs), while daratumumab shows only a low level of binding to human RBCs, suggesting that the anemia may have limited clinical relevance in humans. The effects on platelets and RBCs were reversible.

Depletion of specific lymphocyte phenotypic cell populations, as expected, based on the intended pharmacological effect of daratumumab, was observed in both chimpanzees and cynomolgus monkeys. No genotoxicity, chronic toxicity, carcinogenicity, or reproductive toxicity testing has been conducted.

1.4.2. Clinical Experience with Daratumumab

1.4.2.1. Pharmacokinetics and Immunogenicity of Daratumumab

The PK of daratumumab following IV administration was evaluated in subjects with relapsed and refractory MM at dose levels from 0.1 mg/kg to 24 mg/kg, and included the recommended 16 mg/kg dose and regimen. The population PK analysis included 223 subjects with MM receiving daratumumab in 2 clinical trials, GEN501 and MMY2002 (150 subjects received 16 mg/kg). Over the dose range from 1 to 24 mg/kg, increases in area under the concentration-time curve (AUC) were more than dose-proportional. Clearance decreased with increasing dose and repeated dosing, indicating target-mediated PK. Following the recommended schedule and dose of 16 mg/kg, the mean [standard deviation (SD)] serum Cmax value was 915 (410) µg/mL at the end of weekly dosing, approximately 2.9-fold higher than following the first infusion. The mean (SD) pre-dose (trough) serum concentration at the end of weekly dosing was 573 (332) µg/mL. Based on the population PK analysis, daratumumab steady state is achieved approximately 5 months into the every-4-week dosing period (by the 21st infusion), and the mean (SD) ratio of Cmax at steady-state to Cmax after the first dose was 1.6 (0.5). The mean (SD) linear clearance and mean (SD) central volume of distribution are estimated to be 171.4 (95.3) mL/day and 4.7 (1.3) L, respectively. The mean (SD) estimated terminal half-life

associated with linear clearance was approximately 18 (9) days. Population PK analyses indicated that the central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Population PK analyses also showed that age (31 to 84 years) and gender do not have clinically important effects on the PK of daratumumab.

Of the 199 total subjects in Studies GEN501 and MMY2002 that were evaluable for immunogenicity, none were positive for anti-daratumumab antibodies.

1.4.2.2. Efficacy and Safety Studies of Daratumumab

The FDA approval of daratumumab for the treatment of patients with MM who have received at least 3 prior lines of therapy including a PI and an IMiD or who are double-refractory to a PI and an IMiD was based on data from the pivotal study MMY2002 and key supportive study GEN501.

Among the heavily pre-treated population of subjects in Study MMY2002 (97% of subjects refractory to last line of therapy, 95% were refractory to both a PI and IMiD; 63% refractory to pomalidomide, and 48% refractory to carfilzomib); daratumumab monotherapy at 16 mg/kg achieved an overall response rate (ORR) of 29%. The response data are further supported by Study GEN501, which had an ORR of 36% among subjects treated with 16 mg/kg daratumumab. Integration of data from Study MMY2002 and Part 2 of Study GEN501 resulted in an ORR of 31% with duration of response of 7.6 months. Median time to first response is slightly less than 1 month, corresponding with the first disease assessment.

The response at the proposed dose of 16 mg/kg was consistent across all subgroups, regardless of the number of prior lines of therapy, refractory status, or geographic region. The depth of response (very good partial response [VGPR] or better) induced by single-agent daratumumab was 11% across Study MMY2002 and Study GEN501. Following treatment with daratumumab, 3 stringent CRs (sCRs), 2 CRs, and 12 VGPRs were observed across both studies. The CR/sCR rate is 3%.

At the time of primary analysis, with a median follow up of over 9 months, 44 of 46 subjects who responded to treatment were still alive. The estimated 12-month OS rate was 69% across Study MMY2002 and Study GEN501.

The main safety finding is IRRs. No organ-specific toxicity has been identified. The safety profile is favorable for relapsed and refractory multiple myeloma, where patients are often fragile after a multitude of prior therapies and suffer from drug-induced or disease-related myelosuppression.

1.5. JNJ-40346527

JNJ- 40346527 will be named JNJ-527 for the remainder of this protocol. JNJ-527 is a small molecule with a molecular weight of 498.06 and a molecular formula of $C_{27}H_{35}N_5O_2.HCl$. It is available as free-base equivalent (eq.) 50and 150 mg hard gelatin capsules.

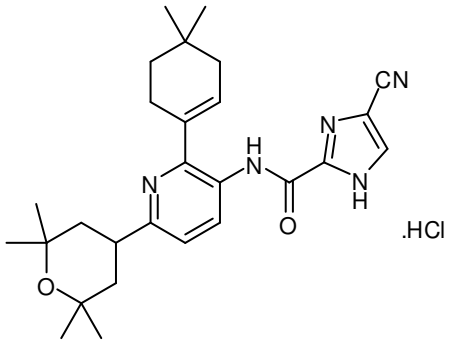


Figure: JNJ-527 – Molecular Structure

The inhibitory activity of JNJ-527 was tested at 0.1 and 0.3 µM in vitro against a panel of 214 kinases and the results are shown below.

Table: JNJ-527 Inhibition (IC50) of Kinase Activity In Vitro					
	CSF-1R	KIT	FLT3	TRKA	PDGFRß
IC50, mean (µM)	0.0032	0.020	0.19	0.22	0.50
Key: CSF-1R=receptor for colony stimulating factor-1; FLT3=FMS-related tyrosine kinase 3 including D835Y mutation; IC50=concentration required to produce 50% inhibition; KIT=product of the kit proto oncogene; PDGFRß=platelet derived growth factor receptor beta; TRKA=neurotrophin receptor kinase A.					

JNJ-527 demonstrated potent activity against CSF-1R tyrosine kinase at low nanomolar concentrations. In addition, JNJ-527 had limited activity against 6 additional wild-type kinases including KIT (Mast/stem cell growth factor receptor or SCFR), FMS-like tyrosine kinase 3 (FLT3), FLT3(D835Y), JAK2 JH1 JH2, KIT, MAP4K5, TRKA, RET(V804L), STK24, and STK25.

The primary molecular target of JNJ-527, the CSF-1/CSF-1R pathway, controls the recruitment, differentiation, and survival of tumor associated macrophages (TAMs), which, as part of the tumor stroma, contribute to the malignant tumor phenotype by promoting tumor cell proliferation and invasion, as well as by inducing angiogenesis and sustaining an immunosuppressive microenvironment. Recent pre-clinical investigation support the hypothesis that JNJ-527 mediated

CSF-1R inhibition impacts TAM polarization and leads to a depletion of the tumorigenic M2-TAMs. The impact of JNJ-527 treatment on the immune-suppressive tumor microenvironment and specifically the recruitment and differentiation of TAM in men with high-risk localized prostate cancer will be investigated in this study.

The most comprehensive nonclinical information regarding JNJ-527 are provided in the Investigator's Brochure.

1.5.1. Nonclinical Experience with JNJ-527

1.5.1.1. Toxicology of JNJ-527

Toxicology data have been derived from studies with JNJ-527 in multiple species including rats, rabbits, and dogs. The primary toxicities identified across these species affected the (1) hematopoietic system (decrease in erythrocytes and leukocytes), (2) electrolyte hemostasis (decreased urinary calcium), (3) coagulation (decreased activated partial thrombin time), (4) liver (transaminase elevation, (5) kidney (progressive nephropathy), (6) blood vessels (arteritis), (7) connective tissue (mucinous accumulation), (8) and testicles (testicular degeneration). The toxicities were generally mild to moderate and fully reversible following JNJ-527 withdrawal and wash out. Most toxicities were dose dependent and occurred only after multiple administrations and at the highest JNJ-527 dose tested. JNJ-527 did not demonstrate genotoxicity or developmental toxicity. In rabbits reproductive toxicity was shown with JNJ-527.

The most comprehensive toxicology data regarding JNJ-527 are provided in the Investigator's Brochure.

1.5.2. Clinical Experience with JNJ-527

1.5.2.1. Pharmacokinetics of JNJ-527

The PK of JNJ-527 following oral administration was evaluated in 3 independent clinical studies conducted in healthy volunteers (n=120 subjects), subjects with rheumatoid arthritis (n=96 subjects), and subjects with Hodgkin lymphoma (n=21 subjects). Multiple JNJ-527 oral, daily doses up to a total of 900 mg as single dose and up to 600 mg as repeat dose were evaluated in these 3 studies.

Following single-dose administration, absorption of JNJ-527 was rapid (median t_{max} ranged from 1 to 3.5 hours). JNJ-527 demonstrated a large apparent volume of distribution (V_d/F >~800 L). Mean C_{max} and AUC both increased with dose, but appeared to be less than dose-proportional. The JNJ-527 concentration-time profile demonstrated multiphasic decline with an overall mean terminal $t_{1/2}$ of about 70.6 (range of mean: 49.4 to 98.8) hours.

Following repeat-dose administration, the Cmax and AUC on Day 14 appeared to increase in a dose proportional manner. The JNJ-527 concentration-time profile demonstrated multiphasic

decline with an overall mean terminal t1/2 of approximately 140 hours (mean of 85.2 to 183 hours). The observed systemic accumulation of JNJ-527 appeared to be dose-related, with mean accumulation ratios ranging from 1.53 at lower doses to 3.02 at higher doses. Following repeat dose, daily administration, JNJ-527 reached steady state by Day 21. Systemic exposure (C_{max} and area under the concentration-time curve from hour zero to hour 24 [AUC_{24}]) on Day 21 increased with increasing dose from 150 to 450 mg once daily (QD). Exposure was paradoxically lower at 600 mg QD compared to 450 mg QD. Mean AUC_{24} values were comparable between 300 mg QD and 150 mg BID on Day 21, while mean C_{max} was lower following BID dosing.

JNJ-527 is a reversible inhibitor of primarily CYP3A4 and CYP2C8 and to a lesser extent of several other CYP isoforms (i.e., CYPs 2B6, 2C9, 2C19, and 2D6) in vitro. JNJ-527 increased the plasma exposure of midazolam (by ~65%) in a clinical Phase 1 study, suggesting a weak inhibition of CYP3A4 at clinically relevant doses.

JNJ-527 is an inhibitor of P-gp mediated transport of digoxin in vitro but was not a substrate for P-gp in vitro. Care should be taken if JNJ-527 is to be administered with P-gp substrates, especially those with narrow therapeutic index. The clinical impact of co-administration of JNJ-527 with known inhibitors and inducers of CYP3A4/5, CYP2C8, or CYP2C19 are not fully understood. An increase or decrease of the systemic exposures of JNJ-40346527 and its active metabolites has to be anticipated.
The most comprehensive pharmacology data regarding JNJ-527 are provided in the Investigator's Brochure.

1.5.3. Efficacy and Safety Studies of JNJ-527

JNJ-527 is currently under clinical development for the potential therapy of chronic inflammatory- and malignant diseases. So far only limited clinical efficacy was observed with JNJ-527 in the treatment of malignant diseases. In a Phase 1/2 study conducted in subjects with relapsed or refractory Hodgkin lymphoma (B. von Tresckow et al., Clin Cancer Res; 21(8); 1843–50, 2015) 1 out of 20 evaluable subjects treated with JNJ-527 at a dose of 150 mg QD experienced a complete response with a progression-free survival of 352 days. An additional 11 out of 20 evaluable subjects (55%) achieved stable disease (duration of 1.5 to 8 months) and 8 subjects (40.0%) had progressive disease. In this study, almost all subjects (19 of 21 subjects [90.5%]) experienced at least 1 adverse event (AE). The most frequent AEs (occurring in ≥20% of subjects) were pyrexia (52%), nausea (33%), headache (33%), vomiting (29%), and anemia (24%). Severe (CTCAE Grade 3) AEs were reported in 7 subjects (33%) and included anemia, lymphopenia, gastric obstruction, peripheral edema, abnormal hepatic function, increased lipase, and hypoalbuminemia. A single subject experienced a CTCAE Grade 4 laryngeal inflammation. Serious Adverse Events (SAEs) were observed in 4 subjects (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1 acute phase reaction, CTCAE Grade 2 dyspnea, CTCAE Grade 3 gastric obstruction, CTCAE Grade 4 dyspnea, and CTCAE Grade 5 lung disorder). No deaths considered related to JNJ-527 by the investigator occurred in the study.

The most comprehensive safety **data regarding JNJ-**527 are provided in the Investigator's Brochure.

1.6. Biomarker Rationale

1.6.1. Daratumumab:

Recent daratumumab biomarker studies of Phase 1 and Phase 2 multiple myeloma patient samples (from studies GEN501 and MMY2002, respectively) have revealed previously unknown immunomodulatory effects of daratumumab (20). For example, blood samples from patients treated with daratumumab exhibit the elimination of highly immunosuppressive subsets of CD38+ T-regulatory cells (Tregs), CD38+ myeloid derived suppressor cells (MDSCs), and CD38+ regulatory B cells. It has also been shown that daratumumab can modulate the intrinsic enzymatic activity of CD38, and may potentially lead to a reduction in immunosuppressive adenosine levels. This shift away from an immunosuppressive environment may lead to the generation of protective immune responses. Indeed, a concomitant induction of helper and cytotoxic T-cell increases in absolute cell counts and production of IFNγ in response to viral peptides has been observed following daratumumab treatment. Additionally, an increase in T-cell clonality in patients who responded to daratumumab versus patients who did not respond was observed, indicating an improved adaptive immune response that may contribute to clinical response. In the current study, flow cytometry and IHC will be performed on the tumor and blood samples to evaluate changes in immunosuppressive cell types and enhanced adaptive immunity.

1.6.2. JNJ-527:

The CSF-1/CSF-1R pathway, the molecular target of JNJ-527, controls the recruitment, differentiation, and survival of tumor associated macrophages (TAMs), which, as part of the tumor stroma, contribute to the malignant tumor phenotype by promoting tumor cell proliferation and invasion, as well as by inducing angiogenesis and sustaining an immunosuppressive microenvironment. TAMs are derived from circulating lymphocyte antigen 6C (Ly6C)-expressing monocytes originating from the bone marrow and spleen. Inflammatory cytokine signals such as CSF-1 secreted from stressed and apoptotic tumor cells attract these monocytes that migrate from the tumor blood vessels into the tumor microenvironment. Within the tumor stroma, the monocytes undergo differentiation into macrophages with a very distinct and divergent state of activation. Linked to the arms of the adaptive immune response with which they interact, the emerging TAMs are described as either “classical” M1 macrophages (interacting with T helper 1 [TH1] cells) involved in efficient antigen presentation and pathogen killing or “alternative” M2 macrophages (interacting with T helper 2 [TH2] cells) and showing high phagocytotic and anti-inflammatory activity. In the tumor microenvironment, M1-like TAMs secrete high amounts of pro-inflammatory cytokines and are thought to promote anti-tumor immunity. In contrast, M2-like TAMs produce low amounts of pro-inflammatory cytokines and higher amounts of the anti-inflammatory cytokine interleukin-10. In addition, M2-like TAMs overexpress CSF-1R and continuous activation of the CSF-1/CSF-1R pathway promotes the M-2 like polarization (MA Canarile, J. Immunother. Of Cancer, 5, 53, 2017).

The stroma of a majority of prostate carcinomas is characterized by an abundance of TAMs and a significant correlation has been proclaimed between an increased density of TAMs in the tumor

micorenvironment and higher proliferation rate, enhanced tumor vascularization (i.e. microvessel density) and inferior prognosis in prostate cancer patients (CE Lewis, JW Pollard. Cancer Res. 66, 605, 2006). Targeting the CSF-1/CSF-1R pathway with the therapeutic intention to impact the TAMs is emerging as an attractive paradigm for novel anti-tumor immune-therapies in prostate cancer (J Escamilla et al., Cancer Res., 75, 1-13, 2015). Based on pre-clinical data, it can be hypothesized that inhibition of the CSF-1/CSF-1R pathway with JNJ-527 in prostate cancer (1) decrease the number of TAMs in the prostate microenvironment, (2) affect the polarization of TAMs towards the M1-like phenotype, (3) change the cellular composition of the prostate cancer microenvironment (i.e. density of CSF-1R-expressing dendritic cells, neutrophils, and myeloid suppressor cells), (3) increase the number of tumor-infiltrating lymphocytes (TILs), and (4) decrease prostate cancer cell proliferation and tumor angiogenesis.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Objectives	Endpoints/Assessments
Primary	
Safety and tolerability of therapy with the study drugs in men with high-risk localized prostate cancer.	• Incidence of adverse events
Secondary	
To assess the proportion of patients who achieve pathological CR with the study drugs in men with high-risk localized prostate cancer.	• pT0 or pathologic complete remission rate
Exploratory	
To study immunological changes in tumor tissues and peripheral blood in response to the study drugs in men with high-risk localized prostate cancer.	• Immunological variables will be measured based on peripheral blood samples and tumor tissue samples.

2.2. Hypothesis

The primary hypothesis of the study is that presurgical treatment with each study drug will be safe and tolerable when given as therapy for primary prostate cancer.

3. STUDY DESIGN AND RATIONALE

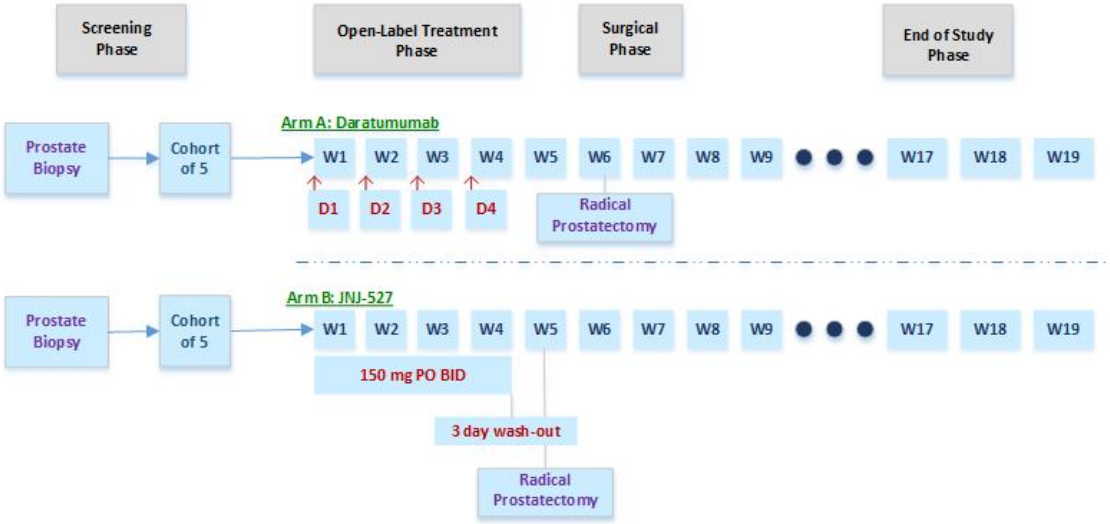
3.1. Overview of Study Design

This is a single center, open-label, presurgical study to determine the safety and tolerability of the study drugs in patients with high-risk localized prostate cancer. There are two arms: Arm A-Daratumumab or Arm B – JNJ-527. Up to 15 subjects, who meet all the inclusion criteria and none of the exclusion criteria, will be enrolled on each arm to receive one of the study drugs. The patients will be assigned treatment arms in cohorts of 5 as described in Section 9.3 Treatment Assignment of this protocol.

The study will consist of a Screening Phase, an Open-label Treatment Phase, Surgical Phase, and a Follow-Up Phase. Subjects on Arm A will receive 4 weekly doses of daratumumab prior to

surgery. Subjects on Arms B will receive 4 weeks of JNJ-527 daily oral administration with a wash-out of 3 days prior to surgery.

Figure 2: Schematic Overview of the Study



W = week; D = Dose

3.2. Study Design Rationale

Rationale for Subject Population

In patients with high-risk localized disease, surgery and radiation therapy results in PSA-progression-free survival under 50% at 5 years. Even among men with Cancer Stage II, T1c-T2b prostate adenocarcinoma who undergo radical prostatectomy more than 33% will have biochemical recurrence within 8 years (19).

Daratumumab is an immunomodulatory agent that targets CD38 and enhances systemic immune responses (20). Prostate luminal cells expressing CD38 are localized in proximity to prostatic inflammation, and their presence in patients with localized prostate cancer is prognostic for biochemical recurrence and metastasis (21).

In prostate cancer secretion of CSF-1 by tumor cells and activation of the CSF-1 receptor pathway in monocytes, macrophages and myeloid-derived suppressor cells is important for the maintenance of an immune-suppressive microenvironment. JNJ-527 is a small molecule targeting the CSF-1 receptor tyrosine kinase which may render prostate cancer sensitive to immune-stimulating therapies by depleting M-2 like TAMs and myeloid suppressor cells in the tumor stroma.

In this clinical trial, we propose to determine the safety and tolerability of each study drug in patients with high-risk localized prostate cancer. Depending on the toxicity profile, changes in the peripheral blood and prostate tissue immune profile, and residual tumor quantification, future studies may investigate any of the study drugs in combination with other agents.

Rationale for Dose Selection

The dose and regimen for daratumumab is 16 mg/kg given weekly for a total of 4 weeks intravenously based on the approved dosing for multiple myeloma.

The dose and regimen for JNJ-527 is 150 mg given orally, twice daily for a total of 4 weeks based on the recommended dosing established in a previous Phase 1/2 study conducted in patients with Hodgkin lymphoma.

4. SUBJECT POPULATION

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Consent to MD Anderson laboratory protocol PA13-0291.
2. Histological documentation of adenocarcinoma of the prostate reviewed at MD Anderson Cancer Center. Patients with small cell, neuroendocrine, or transitional cell carcinomas are not eligible.
3. Patients with high-risk prostate cancer (at least 1 core with Gleason sum $\geq$8) must have at least three core biopsies involved with cancer (a minimum of 6 core biopsies, must be obtained at baseline). A prostate biopsy within 3 months from screening is allowed for entry requirements.
4. No evidence of metastatic disease as documented by technetium-99m (99mTc) bone scan and by computed tomography (CT) or magnetic resonance imaging (MRI) scans.
5. Eugonadal state (serum testosterone >150 ng/dL).
6. Localized or locally advanced disease deemed by the surgeon to be resectable. Patients must be appropriate candidates for radical prostatectomy plus pelvic lymph node dissection.
7. No prior treatment for prostate cancer including prior surgery (excluding transurethral resection of the prostate [TURP]), cryoablation, pelvic lymph node dissection, radiation therapy, hormonal therapy or chemotherapy.
8. Subject must be ≥18 years of age.
9. To avoid risk of drug exposure through the ejaculate (even men with vasectomies), subjects must use a condom during sexual activity while on study drug and for 3 months following the last dose of study drug. If the subject is engaged in sexual activity with a woman of childbearing potential, a condom is required along with another effective contraceptive method consistent with local regulations regarding the use of birth control

methods for subjects participating in clinical studies and their partners. Donation of sperm is not allowed while on study drug and for 3 months following the last dose of study drug.

10. ECOG performance status (PS) grade of 0 or 1.
11. Clinical laboratory values at screening:
    - Hemoglobin, platelet count, absolute neutrophil count, absolute lymphocyte count within institutional normal limits. Administration of growth factors or blood transfusions will not be allowed to confirm eligibility
    - Serum chemistries, renal and liver panels within institutional normal limits or meets the requirements for radical prostatectomy
12. Each subject must sign an informed consent form (ICF) indicating that he understands the purpose of and procedures required for the study and is willing to participate in the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Prior hormone therapy for prostate cancer including orchiectomy, antiandrogens, ketoconazole, or estrogens (5-α reductase inhibitors allowed), or LHRH agonists/antagonists.
2. Currently enrolled in another interventional study.
3. Concurrent treatment with systemic corticosteroids (prednisone dose >10 mg per day or equivalent) or other immunosuppressive drugs <14 days prior to treatment initiation. Steroids that are topical, inhaled, nasal (spray), or ophthalmic solution are permitted.
4. History of or known or suspected autoimmune disease (exception(s): subjects with vitiligo, resolved childhood atopic dermatitis, hypothyroidism, or hyperthyroidism that is clinically euthyroid at screening are allowed).
5. Known evidence of an active infection requiring systemic therapy such as human immunodeficiency virus (HIV), active hepatitis, or fungal infection.
6. History of clinically significant cardiovascular disease including, but not limited to:
    - Myocardial infarction or unstable angina ≤6 months prior to treatment initiation
    - Clinically significant cardiac arrhythmia
    - Deep vein thrombosis, pulmonary embolism, stroke ≤6 months prior to treatment initiation
    - Congestive heart failure (New York Heart Association class III-IV)
    - Pericarditis/clinically significant pericardial effusion
    - Myocarditis
    - Endocarditis
7. History of major implant(s) or device(s), including but not limited to:

- Prosthetic heart valve(s)
- Artificial joints and prosthetics placed ≤12 months prior to treatment initiation
- Current or prior history of infection or other clinically significant adverse event associated with an exogenous implant or device that cannot be removed

8. Other prior malignancy (exceptions: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) ≤2 years prior to enrollment.
9. Any medical, psychological or social condition that in the opinion of the investigator, would preclude participation in this study.

5. TREATMENT BLINDING

Blinding

As this is an open-label study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

6.1. Study Drug Administration

For the purposes of this study, 'study drug' refers to daratumumab or JNJ-527. If a dose of any of the study drugs is missed, it should be omitted and will not be made up or taken with the next dose.

6.1.1. Arm A: Daratumumab

Infusion solution will be prepared as a 1,000-mL (first dose) or 500-mL (second and subsequent doses) dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 μM) during the infusion.

Daratumumab will be administered as a dose of 16 mg/kg. If toxicities are observed refer to Section 6.2. Daratumumab will be administered once weekly for a total of 4 doses. Daratumumab will be administered as an IV infusion as per the infusion rate recommendations in Table3. The dose will be calculated based on the subject's weight rounded to the nearest kilogram. Dosing calculations do not need to be changed for weight changes that are <10% from baseline. The study pharmacist will then calculate the required volume from the vial. All infusions will be planned as outpatient visits. Subjects will receive pre-infusion medications and post-infusion medications as detailed in the protocol.

Daratumumab infusion reactions are frequently observed in patients with multiple myeloma, particular during the first infusion (91% of patients experienced infusion reactions on first dose only). The prevalence of infusion reactions in patients with prostate cancer is unknown, but is anticipated to be less than that observed in patients with multiple myeloma. The daratumumab infusion rate, optimized for the treatment of subjects with multiple myeloma, will be utilized**.**

The dilution volumes, initial infusion rates, and increment for the first, second, and subsequent doses are provided in Table 3. The first infusion, with a volume of 1,000 mL, takes approximately 8 hours; the second and subsequent infusions, with volumes of 500 mL, take approximately 4 hours. The maximum infusion rate for all infusions is 200 mL/hour. Additional details for administration times and rates, as well as pre-infusion medications, will be provided in the administration guidelines.

Refer to the daratumumab package insert for information related to drug preparation, handling, and administration. Vital signs (excluding weight) will be performed at arrival to outpatient infusion center. If the patient has a change in status (e.g. shortness of breath, rash, flush) vital signs will be checked again. Finally they will be rechecked at the completion of all medications or prior to discharge from the infusion center.

6.1.1.1. Guidelines for the Prevention and Management of Toxicities for Daratumumab

Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions, and resources necessary for resuscitation (e.g., agents such as epinephrine and aerosolized bronchodilators, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an infusion-related reaction develop, the infusion should be paused. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice the following guidelines may apply:

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.

- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, daratumumab may be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied.

If an infusion is paused, then a long-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as a serious adverse event.

6.1.1.1.1. Pre-infusion medication

Table 3: Daratumumab Infusion Rate

Daratumumab Infusion Rate	**Dilution Volume**	**Initial Infusion Rate (first hour)**	**Increments of Infusion Rate[a]**	**Maximum Infusion Rate**
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] consider titration of the infusion rate only in the absence of infusion reactions.

[b] Dilution volume of 500 mL should be used only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL

[c] Use a modified initial rate for subsequent infusions (ie, third infusion onwards) only if there were no Grade 1 (mild or greater infusion reactions during a final infusion rate of >/= 100 mL/hr in the first two infusions. Otherwise, continue to use instructions for the second infusion.

Pre-infusion medications for subjects receiving daratumumab will be administered as described in the Time and Events Schedules. On daratumumab infusion days, subjects will receive the following medications up to 3 hours prior to daratumumab infusion:

- Acetaminophen 650-1000 mg IV or PO
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent but avoid IV use of promethazine).
- Methylprednisolone 100 mg IV or PO or equivalent. Substitutions for methylprednisolone are allowed.

- Leukotriene Inhibitor (optional) on Cycle 1 Day 1: montelukast 10 mg PO, or equivalent.
- If necessary, all PO pre-infusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.
- Pre-infusion medications will be documented in the medical record but not entered to the electronic case report form. Patient self-medication should be documented on an institutionally approved medication diary.

6.1.1.1.2. Post-infusion Medication

For the prevention of delayed infusion-related reactions, all subjects will receive long- or intermediate-acting corticosteroid orally (20 mg methylprednisolone or equivalent in accordance with local standards) on the 2 days following all daratumumab infusions (beginning the day after the infusion).

In the absence of infusion related AEs after the first 3 infusions, post-infusion corticosteroids should be administered per investigator discretion.

For subjects with a higher risk of respiratory complications, the following post-infusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as albuterol aerosol
- Control medications for lung disease (e.g., inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)
- Post-infusion medications will be documented in the medical record but not entered to the electronic case report form.

6.1.1.1.3. Grade 1-2 (mild to moderate):

Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate as outlined in Table 3

6.1.1.1.4. Grade 3 (severe):

Once reaction symptoms reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 3. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion-related reaction.

6.1.1.1.5. Grade 4 (life threatening):

Permanently discontinued daratumumab treatment.

6.1.2. Arm B: JNJ-527

JNJ-527 is available as free base equivalent (eq.) 50 mg, and 150 mg hard gelatin capsules. The eq. 50 mg capsules are size 3, opaque capsules and the eq. 150 mg capsule is a size 00 opaque capsule.

JNJ-527 will be administered as a dose of 150 mg po BID. Participants should be instructed to take the JNJ-527 capsules with a large glass of water (~250ml) at the same time each day. Participants should be instructed to swallow the JNJ-527 capsules whole and not to chew, crush or open them. If vomiting occurs, no re-dosing is allowed before the next scheduled dose. Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.

JNJ-527 can be taken without regard to meals, preferably right after breakfast and dinner. Anti-acids may affect absorption; if needed, take antacids

2 hours or more before or after any doses of study drug. If a subject is taking frequent antacids, always take JNJ-527 with food (e.g. within ~ 30 minutes after breakfast and within ~ 30 minutes after their evening meal).

Participants must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medication, due to potential CYP3A4 interaction with the study medication. Orange juice is allowed.

Due to potential interactions with JNJ-527, no herbal or dietary supplements are permitted, including St. John's Wort. If treatment-related toxicities are observed that based on the investigator's best clinical judgement require a dose reduction, the dose of JNJ-527 can be reduced to 100 mg po BID. The dose of JNJ-527 can be reduced only once. In case of another episode of treatment-related toxicity which based on the investigator's best clinical judgement requires a dose reduction, the study treatment with JNJ-527 needs to be discontinued.

JNJ-527 will be administered BID for a total of 4 weeks with a minimum of a 3 day wash-out before surgery to minimize potential wound-healing complications. Any longer wash-out may compromise the pharmacokinetic evaluation of the tissue. If there is a longer delay, the surgery should go forward to provide the appropriate cancer treatment for the patient.

7. STUDY EVALUATIONS

7.1. Study Procedures

7.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, biomarker, and safety measurements applicable to this study.

The study is divided into 4 phases: a Screening Phase, an Open-label Treatment Phase, Surgical Phase and an End of Study Phase. Assessments/procedures should be completed on the day indicated; if this is not possible because of a weekend, holiday, or emergency, the assessment/procedure should be completed within the timeframe noted in Table 1.

Clinical laboratory results must be available and reviewed by the investigator before any study drug is administered. Repeat or unscheduled samples may be collected for safety reasons or for technical issues with the samples.

7.1.2. Screening Phase

All subjects must sign an ICF prior to the conduct of any study-related procedures. Screening procedures will be performed up to 28 days before treatment enrollment. Laboratory tests noted in the inclusion criteria must be within the limits specified prior to treatment initiation. Testing may be repeated for this purpose. The last result obtained prior to treatment initiation will be used to determine eligibility. Assessments performed as part of the subject's routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to treatment initiation.

7.1.3. Open-Label Treatment Phase

The Treatment Phase will begin at Week 1 with initiation of study drug. For Arm A, daratumumab will discontinue after Week 4. For Arm A, prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase, as per investigator. For Arm B, JNJ-527 will discontinue at the end of Week 4 with a 3 day wash-out before surgery.

The study will be conducted in an outpatient setting.

Investigators will review clinical and laboratory data to determine suitability of the next week's dose of treatment of the study drug during the Treatment Phase.

Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated.

7.1.4. Surgical Phase

Radical prostatectomy dissection (Open or Robotic Assisted Laparoscopic) shall be performed in accordance with good surgical planning and technique on or after Week 6 (Arm A:

daratumumab) or during Week 5 (Arm B: JNJ-527). Extended lymph node dissection shall be performed (at the discretion of the operating surgeon) during the course of radical prostatectomy. The boundaries of bilateral pelvic lymph node dissection will be the crossing of the ureter over the common iliac artery cranially, the circumflex iliac vein and Cooper's ligament caudally, the genitofemoral nerve and obturator internus medially the obturator nerve dorsally and along the internal iliac vessels. All fatty, connective and lymphatic tissue of the obturator fossa along the obturator muscle will be removed, leaving the obturator nerve and vessels bare. Lymph nodes from the 3 different locations on each side, called external iliac vein, obturator fossa and internal iliac vessels, will be collected.

7.1.5. End of Study Phase

A clinic visit to obtain follow-up information (see Table 1) will occur on Week 18 (±7 days) unless the subject is lost to follow-up, or has withdrawn consent to study participation.

7.2. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. The study will include the following evaluations of safety and tolerability according to the time -points provided in the Time and Events Schedule Table 1.

7.2.1. Adverse Events

All adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 90 days following the last dose of study treatment. Adverse events will be followed by the investigator as standard of care. Prostatectomy will follow current practice guidelines and the attending surgeon will document the progress of the surgical procedure. Adverse events related to surgery will not be collected in the eCRF. Serious adverse events will be collected per Section 10.

7.2.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

The following tests will be performed:

- Hematology Panel
  -hemoglobin
  -white blood cell (WBC) count
  -platelet count
  -absolute neutrophil count (ANC)
  -absolute lymphocyte count
  -absolute monocyte count
  -absolute eosinophil count
  -absolute basophil count

- Serum Chemistry Panel

-potassium	-AST
-creatinine	-ALT
-glucose (fasting)	-alkaline phosphatase (ALP)
-albumin (screening only)	-total bilirubin, perform direct and indirect bilirubin (screening only if Gilbert's disease is suspected)

Other Laboratory Evaluations

- Testosterone
- PSA
- Blood Type and Screen prior to every infusion and prior to surgery for daratumumab only

In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required.

7.2.3. Concomitant Medication

Concurrent medications to manage symptoms, concurrent diseases, supportive care, including vitamins, and herbal medications will be recorded in the electronic medical record but not required to be entered to the electronic case report form.

Cytochrome (CYP) inhibition

The clinical impact of co-administration of JNJ-527 with known inhibitors and inducers of CYP3A4/5, CYP2C8, or CYP2C19 are not fully understood. An increase or decrease of the systemic exposures of JNJ-527 and its active metabolites has to be anticipated. (Section 1.5.2.1)

Drugs that induce CYP3A4 activity may decrease JNJ-527 plasma concentrations. For participant in which CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used (Refer to Appendix X for detailed list of agents).

JNJ-527 is a substrate of CYP450 and is primarily metabolized through oxidative biotransformation catalyzed by CYP3A4 leading to the formation of carboxymetabolites. Minor pathways are catalyzed by CYP2C8 and CYP2C9 leading to monooxygenated metabolites. Concomitant use of JNJ-527 and drugs that inhibit CYP3A4 may increase exposure to certain kinase inhibitors. Caution is warranted when administering JNJ-527 to participants taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. Systemic exposures to these medications could be increased while receiving JNJ-527.

Additionally, strong to moderate CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin) may significantly increase concentrations of JNJ-527 and should be used with caution when administered concurrently with JNJ-527.

P-glycoproteins (P-GP)

JNJ-527 is an inhibitor of P-gp mediated transport of digoxin in vitro but was not a substrate for P-gp in vitro. Care should be taken if JNJ-527 is to be administered with P-gp substrates. especially those with narrow therapeutic index (e.g., digoxin) and consultation with oncology pharmacist and Investigator is required (Refer to Attatchment 3 for detailed list of agents).

7.2.4. Electrocardiogram (ECG)

Electrocardiograms (ECGs) (12-lead) to be performed at Screening. Clinically relevant abnormalities noted at screening should be included in the medical history. Additional cardiovascular assessments should be performed as clinically appropriate to ensure subject safety. Abnormalities noted should be collected as adverse events.

7.2.5. Vital Signs

Vital sign measurements including weight, temperature, pulse, and resting systolic and diastolic blood pressure will be collected each clinic visit. Height will be measured at screening. Patient will have a set of vital signs (excluding weight) on arrival to the infusion center. If the patient has a change in status (e.g. shortness of breath, rash, flush) vital signs will be checked again. Finally they will be rechecked at the completion of all medications or prior to discharge from the infusion center.

7.2.6. Physical Examination

The Screening physical examination will be performed. Height and weight will be measured at screening. During the Treatment Phase, limited symptom-directed physical examination and recording of weight are performed. The frequency is provided in Table 1. Abnormalities noted should be collected as adverse events.

7.2.7. ECOG Performance Status

The ECOG PS grades, provided in Attachment 1, will be used to grade changes in the subject's daily living activities. The frequency of ECOG PS assessment is provided in Table 1.

7.2.8. Biomarker Evaluations

The Immunotherapy Platform will perform immune monitoring, including but not limited to evaluation of CD4 and CD8 T cells in peripheral blood and available tumor samples as previously published (15, 22-24, 28-31). All samples will be collected and analyzed as per a separate IRB-approved lab protocol.

PAXgene and Peripheral Blood collection timepoints for biomarker analysis

All events have a window of +/- 7 days		**Screening Phase[a]**	**Open- label Treatment Phase**				**Surgery Phase**	**End of Study**
	Notes	**Within 28 days of enrollment**	**W1**	**W2**	**W3**	**W4**	**W6**	**W18**
Whole blood (PAXgene) for RNA[b, c]	W1 samples prior to dose 1	X	X		X		X	X
Peripheral Blood [b, c]	W1 samples prior to dose 1	X	X		X		X	X

W = week; PSA = prostate specific antigen

a. Within 28 days of enrollment
b. W1 sample prior to dose 1
c. Variation, alterations and deletions will not be considered deviations from the protocol

8. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

8.1. Completion

A subject will be considered to have completed the study if he has completed all protocol-specified procedures, has not been lost to follow up, has not withdrawn consent for study participation before the end of the study or has died. Subjects in the End of Study Phase will be considered to have completed the study when the end of the study has been reached.

8.2. Discontinuation of Study Treatment

Study drug must be discontinued for the following:

- Occurrence of unacceptable toxicity
- The investigator believes that for safety reasons (e.g., adverse event) it is in the best interest of the subject to discontinue study treatment
- Subject refuses further treatment with study drug
- Noncompliance with study requirements

8.3. Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Adverse Events causing permanently discontinuation of daratumumab per section 6.24 and 6.25.
- Lost to follow-up
- Withdrawal of consent

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before prostatectomy, the reason for withdrawal is to be documented in the eCRF and in the source document. These subjects will be replaced (up to 3) for the primary endpoint, and they will be evaluated for toxicity. In the absence of adverse events, patients will be evaluable for toxicity at the next scheduled visit. Patients who experience adverse events will be evaluable for toxicity.

9. STATISTICAL METHODS

Safety Population: The safety population includes all subjects who received at least 1 dose of study drug as treated.

Biomarker Population: The 'biomarkers' analysis population will consist of all subjects who received at least 1 dose of study drug and have biomarker measurements from pretreatment biopsy and prostatectomy specimen.

9.1. Sample Size Determination

An accrual rate of 1 patient per month is anticipated. A maximum sample size of 30 patients, for 15 patients per treatment group will be enrolled. No hypotheses will be tested, but with 15 patients per treatment group we can determine whether an unreasonable proportion of patients have high grade toxicities and gather estimates of immune and molecular changes in tumor and serum and down staging at surgery. These measures will be used to design a larger, hypothesis-based trial.

9.2. Endpoints

Primary Endpoint

Adverse events by CTCAE v4.03 will be recorded for all patients, recording name, grade, start and end dates, attribution to study drug, and whether the event was alleviated or controlled with relevant appropriate care similar to Phase I trials.

Secondary Endpoints

Pathologic response will be measured from the surgical specimen. Pathologic CR is defined as the absence of residual tumor in the radical prostatectomy specimen (ie, pT0). Patients who do not undergo surgery for any reason will be counted as not having a pathologic CR.

Exploratory Endpoints

Immune changes in blood and tumor tissue will be assessed as per section 7.2.7.

9.3. Treatment Assignment

Patient cohorts will alternate treatment assignments. Due to the delay between cohorts, when the first cohort is waiting for assessment, the next 5 patients will be enrolled in the alternative treatment. The first 5 patients were treated with Daratumumab. Patients 6-10 will be enrolled as the first cohort receiving JNJ-527. While those 5 patients are waiting for assessment, patients 11-15 will then be enrolled as the second cohort for the Daratumumab group, and so on. Enrollment of each 5-patient cohort will be completed before starting the next cohort for the other study treatment.

9.4. Interim Monitoring

A Bayesian sequential monitoring design will be used to monitor the trial for toxicity (25, 26) separately for each treatment group. Interim assessments will be performed in cohorts of 5 patients, with accrual held for safety evaluation for each cohort. The treatment group will continue if patients are exhibiting reasonable toxicity rates to continue. Calculations were performed in MultcLean Desktop version 2.1.0.

9.4.1. Interim Analyses for Toxicity

Toxicities will be monitored assuming an *a priori* probability of toxicity following Beta(0.2, 1.8). Trial limiting toxicities (TOX) are defined as:

- grade 3 infusion reactions lasting > 6 hours,
- grade 2 toxicity at least possibly related to study drug lasting > 14 days,
- grade 3-4 events that are at least possibly related to study drug with the following exceptions:
    a. asymptomatic grade 3-4 neutropenia and anemia lasting ≤ 5 days,
    b. asymptomatic grade 3 thrombocytopenia lasting ≤ 5 days
- major surgical complications (ie, rectal injury, ureteral injury, vascular injury) due to toxicity at least possibly related to study drug, or
- surgery is delayed > 4 weeks from the originally scheduled date due to toxicity at least possibly related to study drug

The trial will be terminated if Prob(TOX > 0.10 | data) > 0.80. The specific rules for stopping after each cohort are included in Table 4:

Table 4: Specific Rules for Stopping

If there are this many patients (or more) with TOX	2	3	3
Stop the treatment group if there are this many (or fewer) patients who are evaluable (have TOX, had surgery without TOX, or reached planned surgery date without TOX but will not undergo surgery)	5	10	15*

* The treatment group will stop at 15 patients regardless of the number of patients with TOX, but if there are 3 or more, then the toxicity is too great for future trials at this dose and schedule for this patient population.

Five patients will be accrued before the first analysis. If 2 or more of the 5 patients have TOX, stop the trial and the treatment will be declared as too toxic for this population. If there are 0 or 1 TOXs, enroll the next 5 patients. The operating characteristics are summarized in the following table:

Table5: Operating Characteristics

	Stop if Prob{TOX > 0.10 | data} > 0.80		
True Toxicity Rate	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
0.05	0.03	14.7	15 (15, 15)
0.075	0.06	14.4	15 (15, 15)
0.1	**0.11**	**14.0**	**15 (15, 15)**
0.15	0.24	13.0	15 (15, 15)
0.20	0.39	11.7	15 (5, 15)
0.3	0.67	9.3	10 (5, 15)

The Investigator is responsible for completing a Toxicity/Efficacy summary report and submitting it to the IND office Medical Monitor for review. This should be submitted after the first 5 evaluable patients per cohort, complete 6 weeks of study treatment, and before prostatectomy; and every 5 evaluable patients per cohort, thereafter. Accrual must be halted until summary is reviewed, and study continuation is approved.

9.5. Analysis Plan

Patients' demographic information at baseline will be analyzed by treatment group, with data summarized in tables listing the number and percentages. Adverse events, SAEs, and TOX events will be summarized by grade and attribution in descriptive tables and figures. Overall biomarker response rates and their 90% credible intervals will be estimated using a beta distribution with a prior of Beta (1.5, 0.5). Findings will be used to as preliminary data to plan a hypothesis-driven trial.

10. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

10.1. Definitions

10.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The Sponsor collects adverse events starting with the signing of the ICF (refer to Section 10.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require

intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (e.g., death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For the study drugs, the expectedness of an adverse event will be determined by whether or not it is listed within the Reference Safety Information in their respective Investigator's Brochures.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 10.1.2, Attribution Definitions.

10.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

10.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE Version 4.03 Any adverse event or serious adverse event not listed in the NCI- CTCAE Version 4.03 will be graded according to investigator clinical judgment by using the standard grades as follows:

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities

Grade 4: Life-threatening or disabling adverse event

Grade 5: Death related to the adverse event

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (e.g., laboratory abnormalities).

10.2. Special Reporting Situations

Safety events of interest on a Sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study drug
- Suspected abuse/misuse of a Sponsor study drug
- Accidental or occupational exposure to a Sponsor study drug
- Medication error involving a Sponsor product (with or without subject/patient exposure to the Sponsor study drug, e.g., name confusion)
- Exposure to a Sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

10.3. Procedures

10.3.1. All Adverse Events

All adverse events and special reporting situations will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study drug (or 90 days for serious adverse events), or until start of subsequent anticancer therapy or the subject withdraws consent for study participation, if earlier, which may include contact for follow-up of safety. For subjects who have

received subsequent treatment with therapeutic intent for NSCLC during the adverse event reporting period, only adverse events that are considered to be possibly, probably, or definitely related to the study drugs need to be reported. Serious adverse events, including those spontaneously reported to the investigator, must be reported using the Serious Adverse Event Form. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 10.1.1). Death should not be recorded as an adverse event or serious adverse event, but as the outcome of an adverse event. The adverse event that resulted in the death should be reported as a serious adverse event. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

The Sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the Sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The Sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the Sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the institute).

The investigator (or Sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study

- Investigator's name and 24-hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Blood type and IAT (as described in Section 7.2.2)

10.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate Sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following infusion of daratumumab, then the hospitalization should not be reported as a serious adverse event
- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be

considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

10.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

11. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

11.1. Procedures

All initial PQCs must be reported to the Sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the Sponsor according to the serious adverse event reporting timelines (refer to Section 10.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

11.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

11.3. Serious Adverse Event Reporting (SAE) for M.D. Anderson Sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of study drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 90 days' time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

11.4. Reporting to FDA

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

11.5. Investigator Communication with Supporting Companies

Adverse events classified as "serious" require 24 hour handling and reporting to Janssen to comply with regulatory requirements.

The following method are acceptable for transmission of safety information to Janssen:

- Electronically via Janssen SECURE Email service (preferred): CISCO System
- For business continuity purposes, if SECURE email service is non-functional: facsimile (fax) transmission report to 1-866-451-0371.

Janssen Severity Criteria

The NCI-CTCAE (Version 4.03) will be used to grade the severity of AEs.

Any AE not listed in the NCI-CTCAE will be graded according to the investigator's clinical judgment using the standard grades as follows:

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity.

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Grade 4 (Life-threatening): Urgent intervention indicated.

Grade 5 (Death): Death.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (e.g., laboratory abnormalities).

11.5.1. Serious Adverse Events Exceptions

- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. Hospitalization for a complication of therapy administration will be reported as a serious adverse event.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, sampling for laboratory tests, or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse even that results in prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

11.5.2. Adverse Events of Special Interest

Adverse events indicative of inflammatory cytokine release will be followed as part of standard safety monitoring activities by the supporter, Janssen. These events will be reported to the sponsor's medical monitor within 24 hours of awareness irrespective of seriousness (i.e., serious and nonserious adverse events) following the procedure described above for serious adverse events and will require enhanced data collection.

Pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event.

12. STUDY DRUG INFORMATION

12.1. Physical Description of Study Drug

12.1.1. Daratumumab

The daratumumab supplied for this study is a colorless to pale yellow, preservative-free, sterile concentrate for intravenous infusion.

Daratumumab will be manufactured under the responsibility of the supporting company. Refer to the package insert for a list of excipients.

12.1.1.1. Packaging

Daratumumab

Daratumumab is supplied in sterile glass vials containing daratumumab at a concentration of 20 mg/mL. It will be supplied to the site/pharmacy as bulk supply 100 mg/5 mL single-dose vial or 400 mg/20 mL single-dose vial.

12.1.1.2. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number.

12.1.1.3. Preparation, Handling, and Storage

Daratumumab

Since daratumumab does not contain a preservative, the administration of the diluted solution should be initiated as soon as possible at room temperature 15°C–25°C (59°F–77°F) and in room light. If not used immediately, please store the diluted solution at **refrigerated** conditions 2°C – 8°C (36°F–46°F) and protected from light for up to 24 hours prior to administration. Do not freeze.

If the daratumumab preparation must be stored for longer than 1 hour, then it must be kept at 2°C to 8°C. For the subjects' comfort, the solution should be kept at room temperature (15-25˚ C) for approximately 1 hour before the start of the infusion. The infusion should be completed within 15 hours.

12.1.2. JNJ-527

JNJ-40346527 is available as free-base equivalent (eq.) 10 mg, 50 mg, and 150 mg hard gelatin capsules. The eq. 10 mg and 50 mg capsules are size 3, opaque capsules and the eq. 150 mg capsule is a size 00 opaque capsule.

12.1.2.1. Labeling

The storage conditions and expiry date are indicated on the label

12.2. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids should be disposed per institutional policy.

Study drug will be supplied only to subjects participating in the study.

13. ETHICAL ASPECTS

13.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who provide their consent voluntarily will be enrolled.

13.2. Regulatory Ethics Compliance

13.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

13.2.2. Institutional Review Board

The investigator will provide the IRB with current and complete copies of the protocol and appendices (as required by local regulations).

13.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by the reviewing IRB and be in a language that the subject can read and understand per policy. The informed consent should be in accordance with applicable regulatory requirements, and policy.

13.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

Data will be entered into MD Anderson institutionally approved and compliant database(s). The database(s) have secure portal that requires users to login with validated credentials, uses approved encryption protocols as defined by institutional information security standards. Systems have granular data access controls to ensure that the minimal amount of information required to complete a task is presented, can handle de-linking and de-identification of patient information to maintain patient confidentiality if necessary. The system(s) are 21 CFR 11 compliant. Standard data collection, storage procedures, and quality assurance procedures will be followed, to ensure integrity and auditability of all information entered.

All patients will be registered in the University of Texas MD Anderson Cancer Center Office of Research Administration database. Registration will occur following informed consent process and prior to initiation of investigational intervention(s). All eligibility criteria must be satisfied.

13.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored according to local regulations for additional research with patient consent to daratumumab.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research.

14. ADMINISTRATIVE REQUIREMENTS

14.1. Record Retention

In compliance with the regulatory guidelines, the investigator/institution will maintain all eCRF and source documents that support the data collected from each subject, Regulatory or Essential Documents for the Conduct of a Clinical Trial, and any additional study documents.

14.2. Use of Information and Publication

All information, including but not limited to information regarding the study drugs or the supporter's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the supporter to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the supporter. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the supporter's prior written consent.

14.3. Registration of Clinical Studies and Disclosure of Results

The supporting company will register and disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENT 1: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS GRADES

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Eastern Cooperative Oncology Group (27).

ATTACHMENT 2: NEW YORK HEART ASSOCIATION CRITERIA

The following table presents the New York Heart Association classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Classification of Functional Capacity and Objective Assessment. Available at http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp Accessed 22 January 2015.

ATTACHMENT 3: SUMMARY OF MEDICATIONS TO BE USED WITH CAUTION

Strong CYP3A4/5 inhibitors:
Voriconazole, Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole

Strong CYP3A4/5 inducers:
Avasimibe[2,3], carbamazepine, mitotane, nafcillin, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3]

CYP3A4/5 substrates with NTI[1]:
Terfenadine, Alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine

Pgp inducers:
Aliskiren, colchicine, dabigatran, digoxin, everolimus, fexofenadine, loperamide, marovirac, posaconazole, ranolazine, saxigliptan, sirolimus, sitagliptin, and tolvaptan

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
[2] Herbal product
3 P-gp inducer