PERSONAL STATEMENT	
Impact of award on applicant's career	In the short term, the ASCO Career Development Award will significantly support my dedicated research efforts and provide structured mentorship in clinical and translational oncology research initiatives. Together- my mentor, [redacted], and I- have constructed an in-depth training plan to develop my skills in surgical and clinical oncology leadership and hypothesis-driven research that will enable me to meet my future goals as an independent investigator pursuing thematic, potentially practice-changing research objectives. He has helped me devise structured career development and mentoring plans, including establishing important milestones during the execution of my research proposal and regular weekly meetings with my mentorship team in clinical surgical oncology and basic Immunology. Quarterly progress reports will be provided to my membership committee for regular review. Each of these mentors has a tremendous track record of independent funding while maintaining positions of leadership at both our institutional level and national societies of clinical and surgical oncology. It is without question that their initiative and investment in my career will successfully guide me in my endeavors. I believe these relationships have consistently demonstrated the ideal components of mentoring, reliant on strong communication, frank honesty in their review, defined objectives, critical time management in the demands of a busy clinical practice, prompt feedback and accountability. Not only will the support allow me to protect my time pursuing education and research goals, this funding specifically will apply to translational biomarker studies that are not explicitly supported already in the clinical trial IIT with [redacted] We feel these analyses are the crux of the potential impact of this trial, beyond the clinical outcomes, and receipt of this award will dramatically impact the ability to complete those studies.
Applicant's career plan	I am a fellowship trained and board certified Complex General Surgical Oncologist with a significant history of training and commitment to academic medicine and oncology research. I aim to be a basic/translational researcher with specific focus in mechanisms of evasive resistance to immunotherapy in melanoma. I currently conduct collaborative laboratory investigations as part of a robust immuno-oncology multi-disciplinary group.

	To strengthen the scientific rigor of my work, I am also concurrently obtaining a PhD in Immunology at [redacted] with anticipated graduation in 2022. Long term, I aim to maintain at least 50% effort devoted to bench-to-bedside-to- bench translational research. I feel this dual presence is critical for understanding the relevant clinical questions in oncology, as well as understanding the obstacles to implementation of pre-clinical studies that are often successful in isolation but significantly less effective in clinical practice. As surgeons, we must challenge ourselves to stay intimately in tune with advancing technologies and therapies, making ourselves oncologists first and technicians second. I believe this is a key component to clinical leadership, and in fact leads to the progression of our field with forward thinking/novel interventions that naturally influence the field. It will be increasingly important as our treatment approaches become more complex, as evidenced by the multitude of immuno-oncology clinical trials, that these investigative efforts continue in tandem with rigorous molecular and biomarker correlatives to strengthen our understanding of treatment failure and personalize combination strategies. Surgeons are particularly impactful in oncology research in their unique capacity to investigate important questions about management of local and regional disease. I also intend to continue my commitment to service and leadership in clinical oncology by applying to the ASCO leadership program when eligible.
Percentage time on research activities	With the immense support of my division and department leadership, I am 75% research committed for at least the next three years. This support was given to me in effort to pursue my current K12 Award in Translational Immuno-Oncology. While this award would be relinquished if receiving the ASCO Career Development Award, this protected time will continue to be supported during the duration of the grant.
Sources of salary support	1. 75% by K12 Award in Translational Immuno-Oncology 2. 5% support collaborative R01 funding - [redacted] 3. 5% support by an institutional grant mechanism directly related to this project 4. 10% salary support is provided by Investigator-Initiated Trial Agreement with [redacted] Pharmaceuticals directly related to the proposed clinical trial 5. Remaining support guaranteed by the Department of Surgery

Applicant's role	My role is to serve as Primary Investigator on the proposed clinical trial and the correlative analysis. My mentor, Dr. [redacted], has a significant track record of mentored and independent research in translational immuno-oncology and is a previous recipient of the ASCO CDA. He will serve as mentor and sponsor of my development as well as serve as advisor in two roles: both as lead of my mentorship committee, comprised also of my Division Chief in Surgical Oncology and the director of our Immuno-Oncology Core Facility; but also, as part of my advisory committee in my graduate studies. As a current PhD candidate in Immunology, the proposed research is ongoing in preparation of my thesis and we have selected a core committee to include basic scientists in immunology and translational physician-scientists to oversee my continued research. In this way, the support and scientific review of my work is quite robust with considerable feedback from experts in my field to facilitate my development. Dr. [redacted] will continue to guide me in developing this proposal and other research projects into R funding and we have already identified such grant mechanisms for which I would be competitive. We aim to secure my independent funding in this capacity by the completion of the CDA term. He has also provided significant sponsorship to date for society engagement opportunities and will continue to guide me in leadership development opportunities within ASCO as well as our field specific societies.
Collection and analysis of data	This trial is under the oversight of the Office of Clinical Research within our [redacted] Comprehensive Cancer Center. Clinic visit metrics have been defined and will be extracted by our trained clinical research associates. Tissue and blood specimens will be collected per protocol and banked within our Immune Core Facility. Histology analysis will be reviewed by two independent dermatopathologists who serve as co-Investigators to the trial. Further data analysis from flow cytometry, immunohistochemistry, and ELISA will be collected within our Immune Core Facility and analyzed by myself in conjunction with senior Facility technicians. Statistical analysis will be performed by our trained biostatisticians within the cancer center.
Clinical potential of research project	Strategies to improve survival in this population are urgently needed and present opportunity to further our understanding and application of immunotherapeutics. Our ability to predict non-responder from responder to immunotherapeutic agents such as [redacted] is not yet

	defined and the risk of universal exposure to systemic agents may outweigh the hypothesized benefit given the potential for immune-mediated toxicity as well as associated costs. Therefore, the overall goal of this proposal is to perform a novel bedside-to-bench evaluation of an established and efficacious immunotherapy, with oncolytic virus [redacted] with in-depth mechanistic dissection of molecular and immunologic signatures in response to [redacted] to define a more rational and targeted selection of immunotherapy to maximize benefits and minimize risks. This study would be first in kind to target high risk earlier stage melanoma in the neoadjuvant setting using a less toxic intra-tumoral immunotherapy with key correlative endpoints regarding immune mechanisms of response. We have identified a novel, targetable pathway (AXL/GAS6) in the adaptive resistance of melanoma and we seek to define the role of this molecular pathway following stimulatory immunotherapy with [redacted] We expect to demonstrate efficacy of intra-lesional [redacted] in the histologic clearance of primary melanoma while allowing standard of care surgical excision. We anticipate significant major response and anticipate correlative reduction in sentinel burden. If positive, this clinical therapy represents a significant therapeutic advantage to a population not currently eligible for modern immunotherapy and may be practice changing in approach to high risk primary melanoma. Additionally, we aim to elucidate pretreatment signatures of response to facilitate precision application of immunotherapy in melanoma.
Other funding sources	Initial funding for clinical trial including IRB fees, clinical care, drug provision, clinical histology and partial salary support have already been secured by IIS with [redacted] Salary support is currently provided by my K12 Award in Translational Immuno-Oncology, which I acknowledge will be relinquished if receiving this award. I am requesting this additional support to conduct the proposed in depth biomarker analysis of trial samples. We anticipate utilization of the preliminary data generated from the support of this opportunity to enhance our application for extramural funding in response to the National Cancer Institute's Investigator-Initiated Early Phase Clinical Trials for Cancer Treatment and Diagnosis (R01) request for proposals (RFP). We will be competitive for multiple cycles of review with this RFP open per standard cycle dates through January

	2021. Additionally, if eligible, this project will be submitted for the Society for Surgical Oncology, and Melanoma Research Alliance Young Investigator Award. Initial feedback indicates very positive scoring and capacity to expand correlative studies for initial data will contribute significantly to the likely success of these funding applications.
Concurrent Career Development Award	I do have concurrent appointment to a K12 development award. I understand policy guidelines will require me to relinquish this K12 if receiving the ASCO CDA. I will apply during this time for other societal awards if eligibility is not mutually exclusive but do not have any currently outstanding applicatons.
Involvement of Drug(s) in Research	Yes
Name of Drug(s)	[redacted]
Name of Drug Manufacturer(s)	[redacted]

PROJECT TIMELINE

Milestone/Activity:	Open Enrollment
Milestone Type:	Project
Status:	In Progress
Expected Date:	[redacted]
Is Deliverable:	Yes
Description:	Contract between [redacted] is near completion, protocol and budget have received final approval by both entities. Enrollment expected early [redacted]

[redacted] **Activity:**	IND Completion
Milestone Type:	Project
Status:	Completed
Expected Date:	[redacted]
Is Deliverable:	[redacted]
Description:	IND application has been approved by FDA

Milestone/Activity:	Enrollment Complete
Milestone Type:	Project
Status:	Not Started
Expected Date:	[redacted]
Is Deliverable:	Yes
Description:	Trial conclusion

Milestone/Activity:	Abstract submission
Milestone Type:	Project
Status:	Not Started
Expected Date:	[redacted]
Is Deliverable:	Yes
Description:	Interim analysis of tolerability and enrollment, surgical outcomes to be submitted to ASCO conference

Milestone/Activity:	Clinical Analysis
Milestone Type:	Project
Status:	Not Started
Expected Date:	[redacted]
Is Deliverable:	Yes
Description:	Clinical outcomes analysis to be completed immediately following final surgical procedure

Milestone/Activity:	Biomarker analysis complete
Milestone Type:	Project
Status:	Not Started
Expected Date:	[redacted]
Is Deliverable:	Yes

Description:	Completion of correlative studies, collection of RFS data

Milestone/Activity:	Preliminary manuscript submission
Milestone Type:	Project
Status:	Not Started
Expected Date:	[redacted]
Is Deliverable:	Yes
Description:	Submission of manuscript describing clinical tolerability and surgical outcomes

Milestone/Activity:	R01 Submission
Milestone Type:	Project
Status:	Not Started
Expected Date:	[redacted]
Is Deliverable:	Yes
Description:	Submission of this project to R01 RFP for early phase IIT

BUDGET and JUSTIFICATION

	Year 1	Year 2	Year 3	Total
Indirect Costs	$4,200	$4,200	$4,200	$12,600
Indirect/Facilities and Administrative Costs	$4,200	$4,200	$4,200	$12,600
Direct Costs	$62,466	$62,467	$62,467	$187,400
Consortium/Contractual Costs	$0	$0	$0	$0
Consultant Costs	$0	$0	$0	$0
Equipment	$0	$0	$0	$0
Other Expenses	$0	$0	$0	$0
Patient Care Costs (Inpatient)	$0	$0	$0	$0
Patient Care Costs (Out-patient)	$0	$0	$0	$0
Personnel Costs	$45,028	$47,905	$48,228	$141,161
Subcontracts	$0	$0	$0	$0
Supplies	$14,938	$14,562	$14,239	$43,739
Travel	$2,500	$0	$0	$2,500
Total Indirect Costs	$4,200	$4,200	$4,200	$12,600
Total Direct Costs	$62,466	$62,467	$62,467	$187,400
Total	$66,666	$66,667	$66,667	$200,000

Budget Notes

Year	Note
Year 1	A. Key Personnel i. [redacted], will serve as Principal Investigator on this project. [redacted] is an [redacted]. Funds are requested for partial salary support of Dr. [redacted] who will dedicate a minimum of 75% of her effort to this research project. Her salary will be voluntarily capped per NIH levels to maximize funding for this project and only 15% of her

salary and fringe benefits is being requested at this time. As Principal Investigator, [redacted] will be responsible for the overall design, direction, conduct of the research, and oversee the publication of data. She will ensure the on-time completion of all milestones. [redacted] is an expert in the surgical resections of melanoma and has extensive experience in the study of the tumor microenvironment, immune-modulation by primary tumors, and the mechanisms of resistance to standard therapies in vitro and in pre-clinical mouse models. She will coordinate and integrate all aspects of the research proposal in order to demonstrate the impact of neoadjuvant oncolytic viral therapy in early stage melanoma. (Total salary and fringe benefits costs for entire life of the project is [redacted] 986).

ii. Funds are requested for partial salary support of [redacted] She will dedicate a minimum of 2% of her time in year 1 and then 3 % for years 2 and 3, to this project for clinical research coordination. She will coordinate all specimen processing and banking, schedule coordination, as well as perform data analysis pertinent to this proposal. She will be fully trained to assist in medication injection through our Melanoma Continuity Clinic. (Total salary and fringe benefits costs for entire life of the project is [redacted]

iii. Funds are requested for statistical support from [redacted]. She will dedicate a minimum of 2% of her time on this project. Funds are requested to further utilize her expertise with large databases and complex statistical analyses. (Total Salary and Fringe Benefits: [redacted]

B. Travel:

i. Funds are requested to cover travel costs to attend the mandatory Conquer Cancer Foundation Grants and Awards Ceremony. ($2,500).

C. Supplies Funds are requested for the following supplies:

i. Fluorescent probes and stains for immunofluorescence. (Total $12,300).

ii. Multi-analyte profiling of serum/plasma samples for inflammatory cytokines will be performed using Luminex kits as well as individual ELISA plates, including coated plates, protein standard, detection antibody, and streptavidin-HRP for sample detection

	by optical density. ($11,250). iii. Antibodies for flow cytometry consumables such as pipettes, pipette tips, tubes, and general laboratory supplies. Antibodies for immunophenotyping, processing of specimens for flow cytometry (tubes, reagents, tissue filters), and costs associated with the use of the flow cytometry facility including the Coulter Q-prep. (Total $20,189).
Year 2	A. Key Personnel i. [redacted] MD, will serve as Principal Investigator on this project. [redacted] Funds are requested for partial salary support o [redacted], who will dedicate a minimum of 75% of her effort to this research project. Her salary will be voluntarily capped per NIH levels to maximize funding for this project and only 15% of her salary and fringe benefits is being requested at this time. As Principal Investigator, [redacted] will be responsible for the overall design, direction, conduct of the research, and oversee the publication of data. She will ensure the on-time completion of all milestones. [redacted] is an expert in the surgical resections of melanoma and has extensive experience in the study of the tumor microenvironment, immune-modulation by primary tumors, and the mechanisms of resistance to standard therapies in vitro and in pre-clinical mouse models. She will coordinate and integrate all aspects of the research proposal in order to demonstrate the impact of neoadjuvant oncolytic viral therapy in early stage melanoma. (Total salary and fringe benefits costs for entire life of the project is [redacted] ii. Funds are requested for partial salary support of [redacted], NP. She will dedicate a minimum of 2% of her time in year 1 and then 3 % for years 2 and 3, to this project for clinical research coordination. She will coordinate all specimen processing and banking, schedule coordination, as well as perform data analysis pertinent to this proposal. She will be fully trained to assist in medication injection through our Melanoma Continuity Clinic. (Total salary and fringe benefits costs for entire life of the project is [redacted] iii. Funds are requested for statistical support from [redacted], PhD. She will dedicate a minimum of 2% of her time on this project. Funds are requested to further utilize her expertise with large databases and complex statistical analyses. (Total Salary and Fringe Benefits: [redacted]

	B. Supplies Funds are requested for the following supplies: i. Fluorescent probes and stains for immunofluorescence. (Total $12,300). ii. Multi-analyte profiling of serum/plasma samples for inflammatory cytokines will be performed using Luminex kits as well as individual ELISA plates, including coated plates, protein standard, detection antibody, and streptavidin-HRP for sample detection by optical density. ($11,250). iii. Antibodies for flow cytometry consumables such as pipettes, pipette tips, tubes, and general laboratory supplies. Antibodies for immunophenotyping, processing of specimens for flow cytometry (tubes, reagents, tissue filters), and costs associated with the use of the flow cytometry facility including the Coulter Q-prep. (Total $20,189).
Year 3	A. Key Personnel i. [redacted] will serve as Principal Investigator on this project. [redacted] Funds are requested for partial salary support of [redacted], who will dedicate a minimum of 75% of her effort to this research project. Her salary will be voluntarily capped per NIH levels to maximize funding for this project and only 15% of her salary and fringe benefits is being requested at this time. As Principal Investigator, [redacted] will be responsible for the overall design, direction, conduct of the research, and oversee the publication of data. She will ensure the on-time completion of all milestones. [redacted] an expert in the surgical resections of melanoma and has extensive experience in the study of the tumor microenvironment, immune-modulation by primary tumors, and the mechanisms of resistance to standard therapies in vitro and in pre-clinical mouse models. She will coordinate and integrate all aspects of the research proposal in order to demonstrate the impact of neoadjuvant oncolytic viral therapy in early stage melanoma. (Total salary and fringe benefits costs for entire life of the project is [redacted]. ii. Funds are requested for partial salary support of [redacted] NP. She will dedicate a minimum of 2% of her time in year 1 and then 3 % for years 2 and 3, to this project for clinical research coordination. She will coordinate all specimen processing and banking, schedule coordination, as well as perform data analysis pertinent to this proposal. She will be fully trained to assist in medication injection through our Melanoma

	Continuity Clinic. (Total salary and fringe benefits costs for entire life of the project is [redacted] iii. Funds are requested for statistical support from [redacted] PhD. She will dedicate a minimum of 2% of her time on this project. Funds are requested to further utilize her expertise with large databases and complex statistical analyses. (Total Salary and Fringe Benefits: [redacted] B. Travel: B. Supplies Funds are requested for the following supplies: i. Fluorescent probes and stains for immunofluorescence. (Total $12,300). ii. Multi-analyte profiling of serum/plasma samples for inflammatory cytokines will be performed using Luminex kits as well as individual ELISA plates, including coated plates, protein standard, detection antibody, and streptavidin-HRP for sample detection by optical density. ($11,250). iii. Antibodies for flow cytometry consumables such as pipettes, pipette tips, tubes, and general laboratory supplies. Antibodies for immunophenotyping, processing of specimens for flow cytometry (tubes, reagents, tissue filters), and costs associated with the use of the flow cytometry facility including the Coulter Q-prep. (Total $20,189).

Category	Note
Indirect Costs	
Indirect/Facilities and Administrative Costs	
Direct Costs	
Consortium/Contractual Costs	
Consultant Costs	
Equipment	
Other Expenses	
Patient Care Costs (Inpatient)	

Patient Care Costs (Out-patient)	
Personnel Costs	
Subcontracts	
Supplies	
Travel	

PROJECT INFORMATION	
Project Title	[redacted]
Abstract	Despite the recent notable advances in the treatment of advanced melanoma with application of growing immunotherapies, patterns of response and factors resulting in treatment failure are poorly understood. The application of these therapeutics has been limited in the neoadjuvant setting, particularly in earlier stage disease, even though this strategy has improved tolerance and efficacy with other modalities of therapy in most solid cancer types. Survival remains significantly poorer for thick and ulcerated lesions (T3b/T4) with less than 50% survival at 5 years independent of other prognostic indicators. Oncolytic viral therapies (OVT) stimulate or suppress the immune system in different ways to stop cancer cells from growing and intra-lesional OVT has demonstrated comparable efficacy and durability with greater tolerability than most effective systemic therapy. [redacted] is the only phase III approved intra-lesional therapy in melanoma and has demonstrated significant overall response rate (64%) and bystander effect (34% in uninjected lesions) in the therapeutic setting for advanced disease. We propose an open-label, Phase 2 study of [redacted] in the neoadjuvant setting for patients with high-risk, resectable primary cutaneous melanoma prior to definitive excision. This strategy has not yet been explored in early phase disease despite positive results in advanced melanoma. The central hypothesis of this proposal is that neoadjuvant intralesional therapy with [redacted] in high risk melanoma will effectively treat local and subclinical distant disease by enhanced immune recognition, immunomodulation of the nodal basin, and still allow for standard of care surgery. The primary aim of this study will be to evaluate for histologic response of melanoma with secondary aim to determine changes in immune response and draining sentinel nodes as well as relationship of immune phenotype to response rate and nodal burden. We plan for thorough exploratory analysis of genetic and microenvironmental changes to identify actionable targets in incomplete response as well changes in sentinel burden and subsequent rates of locoregional disease control and recurrence-free survival in long term follow up. We predict that histologic clearance of the primary tumor in the surgical specimen will be associated with improved RFS. Our ability to predict non-responder from responder to immunotherapeutic agents such as [redacted] not yet defined and the risk of universal exposure to systemic agents may outweigh the hypothesized benefit. Importantly, mechanistic dissection of pathways and immunological signatures of response offer the promise of a more rational and targeted selection of immunotherapy. This study would be first in kind to target earlier stage melanoma in the neoadjuvant setting with a less toxic intra-tumoral immunotherapy with key correlative endpoints regarding mechanisms of response.
Specific Aims	AIM 1: Evaluate for histologic clearance (pathologic major response rate) of melanoma following intra-lesional [redacted] in the neoadjuvant setting prior to standard of care surgery for primary cutaneous melanom with wide resection and sentinel lymph node biopsy. AIM 2: A. Evaluate the effect of [redacted] on the tumor immune microenvironment in primary tumor and in the draining sentinel lymph node and correlation to

	histologic response, disease stag, sentinel node positivity and recurrence free survival. B. Evaluate the relationship of immune changes and histologic response to AXL tyrosine kinase signaling in the tumor, drainging lymph node and serum detectable markers APPROACH: We propose a single-arm phase II clinical trial design at [redacted] This is an investigator initiated study (IIS) funded with support by [redacted]. [redacted] will be injected intratumorally on Day 1 [redacted] One week after [redacted] injection, wide-local excision and sentinel lymph node biopsy will be performed. Tissue biopsies and peripheral blood will be collected at enrollment, prior to third [redacted] treatment when possible, and at time of surgery. The sample size is based on the primary objective (the pathologic response on surgical histology specimen). Based on the response rates of 64% (P1) in advanced melanoma, a null hypothesis would present a response rate no greater than 45% (P0), a level that would not support further development. A sample size of 62 patients will provide 91% power to detect a clinically significant change, a difference (P1-P0) of 19% using a one-sided binomial test and a 5% type I error rate. Pathologic response has been associated with and predicted by presence of CD8 T cell infiltrate in previous studies. The expected response rates of high CD8 group versus low CD8 group are 83% versus 50% based on prior data. Our sample size of 62 (31 in high CD8 group and 31 in low CD8 group) would achieve 82% power to detect a difference between the two groups of 83%-50%=33%, with the significance level of 0.05. Primary and Secondary Endpoints/Criteria for Evaluation: Primary • Pathologic response: complete pathologic response (pCR) (defined as 0% residual tumor; major response defined as 50% residual tumor; partial response defined as at least 50% residual tumor or stable disease) will be measured by our specialized dermatopathologist Secondary • Flowcytometry of fresh tumor samples and multiplex immunohistochemistry of formalin fixed paraffin embedded (FFPE) tumors, will be used to determine immune cell type and phenotype, and checkpoint immune expression (PD-L1). T cell infiltration will be calculated as a percentage of total intratumoral cells. • Sentinel lymph node positivity (based on presence of fibrosis and melanophage) • RFS will be measured from the time of surgery Analysis Plans and Correlative Studies: A total of 62 patients will be enrolled in the study at an accrual rate of about 3patients per month at 2 major cancer centers over a period of 12 months with a 24 months follow up time. Toxicity and adverse events assessments will be performed at time of first [redacted] and at each subsequent treatment appointment. Post-operative wound complications will be documented per routine at surgical follow up. Clinic and radiological assessment will be performed every 3 months per routine surveillance protocol. For the correlative analysis tissue biopsy and peripheral blood samples will be collected at first and third [redacted] treatments. Surgical specimen will be collected

	at time of surgery. Flowcytometry, IHC and RNA sequencing will be used to investigate the expression of genes including BRAF, IDO, arginase, iNOS, CTLA-4, PD- 1, PD-L1. To determine if certain clones of T cells are preferentially expanding after therapy, samples will be used for TCR deep sequencing. We will classify histologic, genetic and immunologic differences in responders vs non-responders by evaluating pathologic responses in CD8 T cell low/high groups. All study oversight is our responsibility and correlative studies will be performed at [redacted].

Resubmission of Prior Application	Yes
Prior Application	

CLASSIFICATION

Subject Area	Melanoma/Skin Cancers If Other:

Focus Area(s)	Biomarkers, Clinical Trials, Melanoma, Surgery, Immunotherapy/Vaccines, Resistance to Therapeutics If Other:

ASSURANCES

Animal Use

Animal Use	No
Assurance Status	
IACUC Approval Date	
IACUC Expiration Date	
Assurance Number	

Human Use

Human Use	Yes
Assurance Status	Pending
IRB Approval Date	
IRB Expiration Date	
Assurance Number	
Exemption Number	

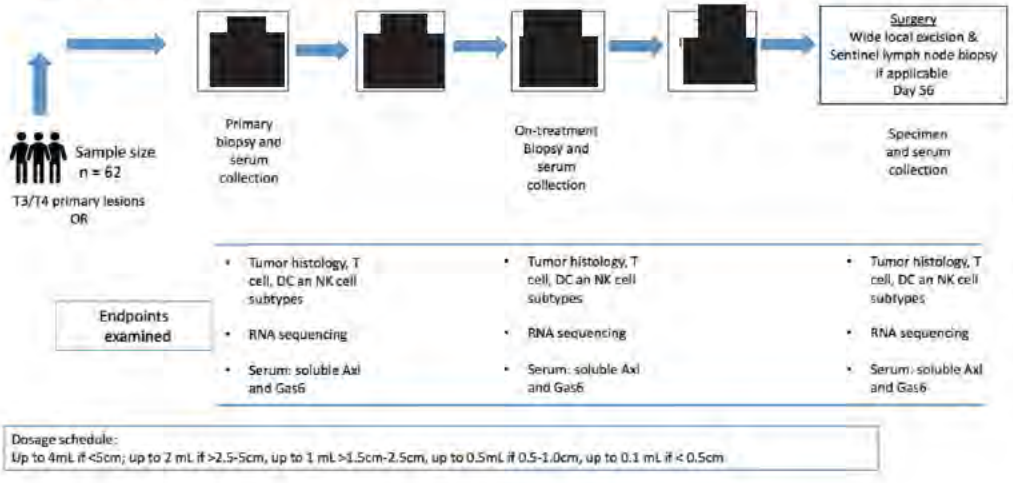
SIGNFICANCE AND BACKGROUND:

Overall survival (OS) outcomes for thicker and ulcerated melanomas (T3b and T4 lesions) remains significantly poor with less than 50% 5-year OS independent of other prognostic indicators (1). Despite the recent notable advances of novel immunotherapeutics for the treatment of advanced melanoma (2), exploration of these therapeutics has been limited in the neoadjuvant and earlier stage disease setting. Furthermore, the response patterns and factors leading to treatment failure are poorly understood (3). While, neoadjuvant strategies are employed frequently for high risk patients in many other solid tumors, development of this application in melanoma has been limited to date. In part, this may be due to the potential for significant adverse events with systemic immunotherapy and current lack of predictive biomarkers to identify patients likely to respond to therapy.

[redacted] is an oncolytic virus that mediates tumor regression through selective replication within and lysis of tumor cells as well as induction of systemic antitumor immunity capable of eradicating tumor at distant, uninjected sites. [redacted] is derived from HSV type I and genetically modified to preferentially replicate in tumor cells and enhance immunity by increased 1) antigen loading of MHC class I molecules and 2) expression of granulocyte-macrophage colony- stimulating factor to increase tumor-antigen presentation by dendritic cells [4,5]. Intratumoral [redacted] has been shown to be safe and is approved as intralesional therapy for patients with unresectable stage IIIB through IV melanoma. Significant overall response rate (64% in injected lesions) and bystander effect (34% in uninjected lesions) was observed in Phase III studies with minimal side effect profile [6,7]. Mechanistically, [redacted] increases intratumoral infiltration of T cells, decreases immunosuppressing Treg population and may generate long lasting immunity leading to durable control at uninjected sites [8-10].

In this proposal, our primary goal is to define the molecular and local, regional and circulating immunological changes in response to [redacted] after neoadjuvant administration for high risk, locally advanced (T3/4) primary melanomas. This analysis will be performed as part of a novel, first in application IIS of neoadjuvant [redacted] prior to definitive excision and sentinel lymph node biopsy (Figure 1). This study is being conducted with the objective of clinical efficacy as assessed by major pathologic response as well as characterization of immunologic changes in the tumor and draining nodal basin in response to [redacted]. Pathologic Complete Response (pCR) is a recognized surrogate of overall response rate (ORR) and recurrence free survival (RFS) and increasingly evaluated in neoadjuvant trials in many cancer types. Early data of neoadjuvant trials in advanced melanoma have demonstrated relationship between pCR and improvement of 1 year disease free survival although this has not been studied to date in

Figure 1. Study Schema



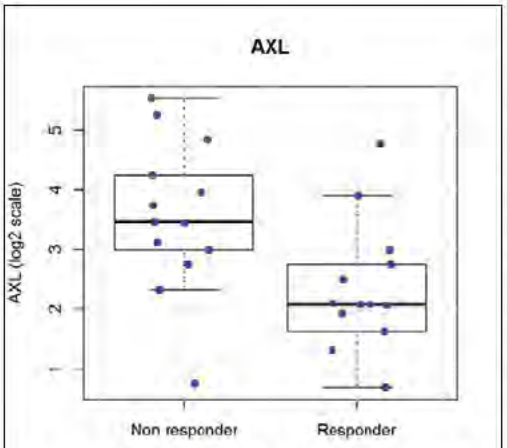


Figure 2. High AXL expression correlates to resistance to anti-[redacted] in advanced melanoma[redacted]

primary melanoma [11-13]. In our group we have extensive experience with intralesional therapies for melanoma and have demonstrated capacity for complete clearance of primary melanoma in poor surgical candidates with intra- lesional therapy [14,15]. As primary melanoma exerts significant influence over immune function in the draining nodal basin and [redacted] has demonstrated significant response in uninjected bystander lesions, we expect change in nodal disease burden [16, 17]. Given its direct and indirect pro-inflammatory effects, we also hypothesize that intra- lesional [redacted] will influence immune cell recognition and infiltrate. We specifically aim to validate the relationship between AXL tyrosine kinase receptor signaling in relationship to therapeutic resistance to neoadjuvant [redacted].

The AXL tyrosine kinase receptor has been implicated with poorer prognosis in many human cancers, including certain resistant phenotypes of melanoma and failure to respond to targeted therapy or checkpoint blockade (Figure 2) [18-21]. Exact contribution to tumor progression remains unknown, as paradoxical oncogenic and anti-inflammatory properties of the AXL receptor have been described, which carries implications for potential anticancer therapy.

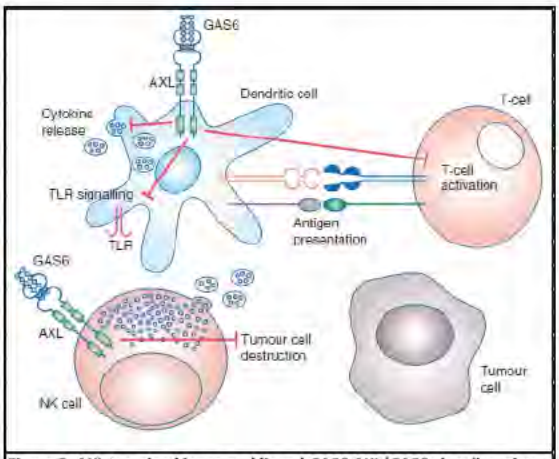


Figure 3. AXL tyrosine kinase and ligand GAS6 AXL/GAS6 signaling plays a regulatory role in innate immune effector cells, influences antigen presentation,T cell priming, and is a novel target for therapeutic intervention Adapted from Gay, BJC 2017

Early preclinical data demonstrates Axl ligand, Growth Arrest- Specific 6 (GAS6) influences suppressive function of regulatory T cells (Treg) and inhibits Natural Killer (NK) and dendritic cell (DC) cell maturation. Similar to immune "checkpoint," AXL serves as a negative immune regulator in response to inflammation and injury, a mechanism that is highjacked in the tumor setting to promote unchecked growth (Figure 3)[19, 21-23]. AXL receptor function significantly manipulates epithelial to mesenchymal plasticity in the tumor microenvironment, influencing ligand secretion by macrophages. This correlated in vivo with significant increase in metastatic potential for Axl expressing tumors and with metastatic events eliminated by multiple strategies of AXL inhibition in prior investigator studies. Response was greatest in immunocompetent models, highlighting the interplay between this pathway and immune cell function [17].This pathway may critically contribute to adaptive/evasive immune resistance as it is seen to be significantly activated in chemotherapy resistant breast and pancreatic models (Figure 4) as well as radio-insensitive melanoma[23,24].

The corresponding influence on immune cell function and infiltrate in these models remains underappreciated. In clinical samples, immune cell/AXL relationship remains highly complex and poorly understood with a number of host factors including age, gender, and obesity influencing inflammatory cascade. In our preliminary data, AXL expression by immune populations increases by stage and is correlated with an immunosuppressing phenotype and poorer overall survival. Based on our preliminary data showing that Axl tyrosine kinase is a

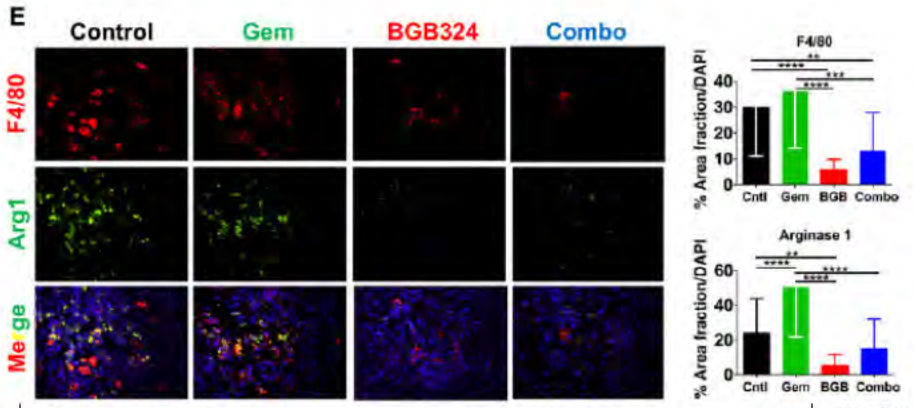


Figure 4. Axl inhibition alters immune landscape AXL inhibition reduces tumor associated macrophages and Arginase-1 expression in M2/immunosuppressive skewed macrophages Gem=Gemcitabine, BGB= AXL small molecule inhibitor [redacted]

potent driver of mesenchymal transition and immune evasion in the tumor microenvironment, we hypothesize that inflammatory mileu associated with [redacted] failure will be associated with increased expression and activity of AXL tyrosine kinase by influencing regulatory T-cell migration and Natural Killler maturation and dampening anti-viral immune response that is responsible for observed bystander effect with [redacted]. We propose response to [redacted] will be associated with improved clinical outcome.

HYPOTHESIS: ***We hypothesize that neoadjuvant intra-lesional therapy with [redacted] in high risk early stage melanoma will effectively treat local and subclinical distant disease by enhanced immune recognition and immunomodulation of the nodal basin and still allow for standard of care surgery.*** We expect that neoadjuvant intralesional [redacted] injection will be well-tolerated and predict that histologic clearance of the primary tumor in the surgical specimen will be associated with improved recurrence free interval and potentially positively impact overall survival. This study will be the first of its kind for primary melanoma and has the potential to advance both our understanding and treatment of malignant melanoma.

We will test our central hypothesis through the following specific aims:

AIM 1: Evaluate for histologic clearance (pathologic major response rate) of melanoma following intra-lesional [redacted] in the neoadjuvant setting prior to standard of care surgery for primary cutaneous melanom with wide resection and sentinel lymph node biopsy.

AIM 2:

- **A.** Evaluate the effect of [redacted] on the tumor immune microenvironment in primary tumor and in the draining sentinel lymph node and correlation to histologic response, disease stage, sentinel node positivity and recurrence free survival.
- **B.** Evaluate the relationship of immune changes and histologic response to AXL tyrosine kinase signaling in the tumor, drainging lymph node and serum detectable markers Gas6 and sAXL.

INNOVATION

This study will include in-depth analysis to help identify the mechanism of action and resistance, changes in immune signature, identify biomarkers of response, and provide a foundation for further improving these approaches. One of the major shortcomings of immunotherapy trials has been the lack of studies that identify these mechanisms. If successful, this study will be the first of its kind for primary melanoma; a crucial first step for later studies. Scientific data documenting immune response may tailor further treatment in the event of relapse or progression and improve utilization of available adjuvant therapies. We aim to study treatment strategies that can render intra-lesional [redacted] even more effective and develop insights into the molecular and cellular targets at play. In summary, this study will be the first of its kind and has the potential to advance

both our understanding and treatment of malignant melanoma.

APPROACH:

We propose a single-arm phase II clinical trial design at [redacted] Comprehensive Cancer Center (investigator-initiated study PI: [redacted]) funded by [redacted] see Figure 1), followed by wide-local excision and sentinel lymph node biopsy. Tissue biopsies and peripheral blood will be collected at enrollment, prior to third [redacted] treatment when possible, and at time of surgery. The sample size is based on the primary objective (major pathologic response). Based on the response rates of 64% (P1) in advanced melanoma, a null hypothesis would present a response rate no greater than 45% (P0). A sample size of 62 patients will provide 91% power to detect a clinically significant change, a difference (P1-P0) of 19% using a one-sided binomial test and a 5% type I error rate. Based upon a conservative expected improvement in 1 year RFS in [redacted] rials from 52% in non- responders to 83% in patients with a complete response (pCR), and the estimation that 15% of patients will have a pCR, 62 evaluable patients will provide 80% power to detect this 31% increase in 1-year RFS for patient with pCR using a one-sided log-rank test with 5% Type 1 error rate. Exclusionary criteria are defined in supplementary clinical protocol to include patients in which [redacted] injection is contraindicated per standard clinical guidelines including but not limited to significant immunosuppression, pregnant or breastfeeding women and patients with competing comorbidities that preclude standard of care surgery.

RESEARCH PLAN

A total of 62 patients will be enrolled in the study at an accrual rate of about 3 patients per month at 2 major cancer centers over a period of 12 months with a 24 months follow up time. Toxicity and adverse events assessments will be performed at time of first [redacted] injection and at each subsequent treatment appointment. Post- operative wound complications will be documented per routine at surgical follow up. Clinic and radiological assessment (when appropriate) will be performed every 3 months per routine surveillance protocol.

For the correlative analysis, tissue biopsy and peripheral blood samples will be collected at first and third [redacted] treatments. Surgical specimen will be collected at time of surgery. All study oversight is our responsibility and correlative studies will be performed at [redacted]. This protocol is Scientific Review Committee approved [redacted]. Final IRB approval is pending, IND, submitted 5/21/2019 has been approved by FDA. [redacted] is contracted as second enrollment site under [redacted] oversight. Tissue procurement and drug administration will be conducted per protocol at both sites with banking of tissue and analysis performed at [redacted]. All proposed correlative studies will be conducted in the Immune Monitoring Core at [redacted] unless otherwise indicated. Hazardous materials, including oncolytic virus, will be handled per pharmacy protocol as described in detail in supplementary clinical protocol. Please see attached statistical analysis plan for further endpoint definition and statistical justification.

Primary and Secondary Endpoints/Criteria for Evaluation:

Primary

- Pathologic response: complete pathologic response (pCR) (defined as 0% residual tumor; major response defined as <50% residual tumor; partial response defined as at least 50% residual tumor or stable disease) will be measured independently by two of our specialized dermatopathologists

Secondary:

- Sentinel lymph node positivity (based on presence of fibrosis and melanophages)
- RFS will be measured from the time of surgery
- RNA sequencing and multiplex immunohistochemistry of formalin fixed paraffin embedded (FFPE) tumors, will be used to determine immune cell type and phenotype not limited to but focused upon macrophage markers arginase, iNOS; CTLA-4, PD- 1, PD-L1; BRAF, AXL TK related signaling, IL-10 and IFN-gamma. To determine if certain clones of T cells are preferentially expanding after therapy, samples will be used for TCR deep sequencing. We will classify histologic, genetic and immunologic differences in responders vs non-responders by evaluating pathologic responses in CD8 T cell low/high groups. T cell infiltration will be calculated as a percentage of total intratumoral cells.
- Plasma will be evaluated for systemic cytokine and chemokine signatures using Luminex technology and ELISA for sAXL/GAS6

APPLICANT ROLE

This proposal is an original Investigator-Initiated Study designed and written by [redacted]. She will be responsible for patient screening, enrollment, data and safety monitoring, and oversight of data collection and analysis. She will also be responsible for administering drug to patients at [redacted] and training of all co-Investigators as well as the surgeon of record for all standard of care surgeries for study patients. She will be responsible for oversight of data analysis in coordination with the Immune Monitoring Core and Dermatopathology.

OUTCOMES

We expect to demonstrate efficacy of intra-lesional [redacted] in the histologic clearance of primary melanoma while allowing standard of care surgical excision. We anticipate significant major response and anticipate correlative reduction in sentinel burden. We will use immunohistochemistry, next generation sequencing and serum proteomic analysis measuring outcomes as described to include pathologic response rate, changes in sentinel lymph node disease, tumor immune cell infiltrate, and ultimately recurrence free survival (RFS). We aim to perform in depth analysis of genetic and microenvironmental changes as well as identify actionable targets in incomplete responders.

Initial funding for clinical trial including IRB fees, clinical care, drug provision, clinical histology and salary support have already been secured by IIS with [redacted] We are requesting this additional support to conduct the proposed in depth biomarker analysis of trial samples. We anticipate utilization of the preliminary data generated from the support of this opportunity to enhance our application for extramural funding in response to the National Cancer Institute's Investigator-Initiated Early Phase Clinical Trials for Cancer Treatment and Diagnosis (R01) request for proposals (RFP). We will be competitive for multiple cycles of review with this RFP open per standard cycle dates through January 2021.

POTENTIAL PITFALLS

Potential limitations of the study include failure to meet recruitment goals. We have a robust patient population for our proposed study group and recruitment efforts are considered attainable given current clinical practice at both recruitment sites. Extensive outreach and education has been provided through our regional dermatological societies to streamline referral practice and raise community awareness of trial goals and need to early recruitment to enroll for trial eligibility. Accrual rate will be reviewed at the conclusion of the first year. If target completion is less than expected, additional study sites have been recruited to include [redacted].

Other potential limitations include toxicity precluding completion of standard of care surgery or failure of efficacy to justify application of therapy. Trial monitoring parameters have been established as such:

To ensure that the patients are treated with an efficacious and safe regimen, the response rate in surgical specimen and toxicity during the whole study will be monitored simultaneously using the Bayesian stopping boundaries calculated based on beta-binomial distribution. Response is defined as any type of partial response, major response, or complete response in the surgical specimen. Toxicity is defined as Grade 3 or higher.

The combination regimen will be considered promising if the response rate in surgical specimen is at least 40% and the toxicity rate is maintained at most 20%. The prior probabilities of response and toxicity for the regimen are modeled by beta distributions (Beta(0.8, 1.2) and Beta(0.3, 1.7), respectively), and response and toxicity are assumed to be independent. Denoting the probabilities of response and toxicity by $\{\theta_{RES}, \theta_{TOX}\}$, and they are compared to fixed targets of response and toxicity rates. The following decision criteria will be applied:

1) stop if Prob$\{ \theta_{RES} < 0.40 \mid data\} > 0.97$, and
2) stop if Prob$\{ \theta_{TOX} > 0.20 \mid data\} > 0.97$

Patients will be monitored by a cohort size of 15 (except 17 for last cohort) according to the following stopping boundaries for response in surgical specimen and toxicity during the whole study. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses are observed.

Number of Patients Evaluated	Stop if Number of Response Observed	Stop if Number of Toxicity Observed
15	0-2	7-15
30	0-7	11-30
45	0-11	15-45
62	Always stop with this number of patients	

RESOURCES

The [redacted] has over 2000 square feet of newly built laboratory space located in the [redacted] campus. Core facilities available to investigators including, but not limited to, Luminex, Cytomation MoFlo cell sorter, LSR Fortessa with plate reader, Compucyte iCys laser scanning cytometer, genomics, proteomics, and metabolomics. Core in vivo animal imaging facilities are available and include PET, MRI, and bioluminescence. Pathology services, including TMA construction, immunohistochemistry, and immunofluorescence are available through the [redacted]. There are core services provided by the [redacted] including Flow Assisted Cell Sorting (FACS), Microscope and Videomicroscopy Core, and Vector Core.

The [redacted] designated Comprehensive Cancer Center physicians and staff maintain Extensive experience in clinical trials. The Center for Clinical Trials is an integrated resource which works closely with other campus institutions including the School of Veterinary Medicine's academic departments, the School of Medicine, the Clinical and Translational Science Center. Clinical investigators have active trials aimed at accelerating the identification and development of diagnostics and therapeutics for the benefit of our patients, and numerous oncology trials are ongoing. Clinical trial support is provided by Investigator Initiated Study with [redacted], supporting contract documentation and approved budget is provide in supplementary materials.

STATISTICAL CONSIDERATIONS

Primary endpoints

Pathologic response defined as: Complete Response (pCR, defined as 0% residual tumor), Major Pathologic Response (defined as ≤10% residual tumor)
Partial Pathologic Response (pPR, defined as less than or equal to 50% viable tumor cells), Pathologic Non-Repsonse (pNR, defined as greater than 50% viable tumor cells)
The analysis will be based on intent-to-treat (ITT). If a patient fails to complete treatment or disease reassessment, then he/she will be counted as a non-responder, even though the exact response is unknown.

Secondary endpoints

Sentinel lymph node positivity will be a secondary endpoint, based on fibrosis and melanophage presence. Recurrence free survival (RFS) will be calculated as the time from start of treatment to first documented evidence of disease recurrence or death, whichever comes first.

Sample size justification/power analysis:

Evaluation of pathologic responses: Based on previous study for injected lesions [2], the major response rate is expected to be 64% (P_1). The null hypothesis is that the major response rate is no greater than 45% (P_0), a level that would not support further development. A sample size of 62 patients will provide 91% power to detect a difference (P_1-P_0) of 19% using a one-sided binomial test, with the target significance level as 0.05.
Evaluation of RFS in responders/non-responders: Based on previous study for advanced disease, there is improvement in 1-year RFS in [redacted] trials from 15% in non-responders to 73% in patients with a complete response (pCR). For our study, the 1-year RFS in non-responders is expected to be similar to the untreated historic group (around 52%). Based upon a conservative expected improvement in 1 year RFS in [redacted] trials from 52% in non-responders to 83% in patients with a complete response (pCR), and the estimation that 15% of patients will have a pCR, 62 evaluable patients will provide 80% power to detect this 31% increase in 1-year RFS for patient with pCR using a one-sided log-rank test with 5% Type 1 error rate [22].

Statistical analysis plan:

Our primary objective will be to validate capacity to achieve pathologic response with short course neoadjuvant [redacted] in high risk melanoma patients. The proportion of patients who experience a pathologic complete response (pCR) or major response will be calculated as the ratio of the number of eligible patients who experienced the response, divided by the total number of eligible patients who began treatment; exact 95% confidence intervals will be constructed. To assess changes over time and association between sentinel node positivity and immune phenotype, a logistic regression model accommodating repeated measures will be applied to sentinel node positivity, including immune phenotype as covariates.

Descriptive analysis of histologic/immunologic/genetic resultsTo study histologic/immunologic/genetic differences in responders vs non-responders, we will have descriptive statistics for PD-1, PDL-1, BRAF, Axl/TK expression, T-/B-/NK-Cell, macrophage, dendritic cell, CD3, CD4, CD8, CD20, CD16, CD56, Granzyme B, cleaved caspase 3, Ki-67, and others. We will compare them in responders vs non-responders using nonparametric Wilcoxon test.

Analysis of OS and RFS: Kaplan-Meier plots and confidence intervals will be used to summarize OS and RFS. The median and associated 95% confidence intervals will be reported.Furthermore, RFS will be calculated for non-responders and responders respectively, and 1-year RFS and associated 95% confidence intervals will be calculated. The difference of RFS curves between non-responders and responders will be tested using logrank test.

Immunotherapy has dramatically impacted outcomes for late stage melanoma; however, high risk patients without the involvement of lymph nodes are not currently candidates for most types of this type of therapy. Additionally, there is significant evidence that immunotherapies, like other treatments such as chemotherapy, may have better efficacy when given before surgical removal of tumors (neoadjuvant). Application of the most common type of immunotherapy, checkpoint blockade, has been very limited in this fashion to due unpredictable response rate and risk of adverse side effects.

Oncolytic viral therapy (OVT) can stimulate or suppress the immune system in different ways to stop cancer cells from growing and injecting OVT directly into tumors has shown overall tumor control comparable to other immunotherapies with greater tolerability. [redacted] is the only phase III approved intra-lesional therapy in melanoma and has demonstrated not only ability to locally destroy tumors with direct injection; but, also, induces a subsequent immune response that attacks distant tumors throughout the body.

We aim to specifically improve treatment options for patients with thick and ulcerated (T3b/T4) melanoma who are considerable risk for melanoma related death. Without evidence of nodal disease, these patients do not currently have effective therapeutic options and are typically observed until time of melanoma relapse; which, unfortunately occurs in greater than 60% of patients. Less than 50% of these patients will be alive at 5 years from diagnosis.

We propose a Phase II clincal trial of [redacted] in which patients with these high risk tumors would undergo OVT injection prior to standard surgical excision. We hypothesize that applying [redacted] prior to surgery will still allow for routine surgery but also produce immune response in distant sites such as draining lymph nodes. We will measure degree of response in the injected melanoma as a predictor of overall clinical outcome.

Neoadjuvant therapy has the added benefit of allowing for a comparison of tumor samples before and after surgery to allow us to better understand which tumors may respond better to a certain therapy and why other patients may fail the same therapy. We plan for thorough exploratory analysis of genetic and microenvironmental changes to identify possible alternative targets in patients who do not respond. This strategy has not yet been explored in early stage melanoma despite dramatic results seen with neoadjuvant therapeutics in other cancer types. Our ability to predict non-responder from responder to immunotherapeutic agents such as [redacted] is not yet defined and the risk of universal exposure to these systemic agents may outweigh the hypothesized benefit given the potential for immune-mediated toxicity as well as associated costs to patients. This study would be first in kind to target high earlier stage melanoma in the neoadjuvant setting with a less toxic intra-tumoral immunotherapy with key correlative endpoints regarding immune mechanisms of response.

If the results of this trial are successful, this could be practice changing for all high risk melanoma patients, altering the standard of care approach. Barriers to accrual have been identified, the most pertinent of which is the need to capture patients with residual melanoma for injection. We have a broad outreach program through our very active [redacted] this trial proposal has been presented extensively in the region. With the overwhelming support of our dermatologists, patients are being directed for trial evaluation immediately, even prior to biopsy, in order to ensure eligibility. Additionally, there has been great interest in participation by our network of surgical oncologists such that we have identified well connected sites, such as [redacted] as potential additional recruitment sites if we fail to meet accrual goals at one year benchmarks. Interim results will be monitored for efficacy and reported at relevant scientific platforms such as the Society for Melanoma Research and Society of Immunotherapy for Cancer.

We anticipate minimal trial burden to patients. Travel will be required for the preoperative injections as well as potential low side effect profile associated with injection; however, the benefit of potential improved melanoma survival and disease control significantly outweighs these minimal risks. To minimize this burden, we have streamlined injection clinic protocol to

facilitate appointments. We have also created measures to pre-screen eligible patients and have drug storage capacity on campus such that patients could initiate therapy at intake rather than requiring repeated multiple visits for enrollment. Remaining treatment is per standard of care and does not present additional burden.

[redacted]

[redacted], Applicant
ASCO Conquer Cancer Career Development Award

Dear Selection Committee,

I am delighted to write this letter of support for [redacted] application for the ASCO Conquer Cancer Career Development Award. I am writing this strong letter of recommendation to express my enthusiasm for [redacted] research efforts and future career as an independent clinical and translational surgeon-scientist. Receipt of this award will certainly allow her to continue to conduct translational research in the area of surgical diseases as well as utilize the unique resources available at [redacted] to examine a very exciting, first in class application of neoadjuvant immunotherapy in high risk malignant melanoma. I am strongly committed to [redacted] career development, and I believe she has the potential to be a successful clinical and translational cancer researcher who can perform high-impact bedside-to-bench translational immunotherapy research. For this application, she has conceived and developed a novel and innovative proposal which has significant scientific merit that has launched her on the path to an independent research program likely to meaningfully impact the field of translational immunotherapy and neoadjuvant strategies for locally advanced melanoma patients. With appropriate mentoring and career development, I think [redacted] has strong potential to conceive and develop further proposals that are competitive and has already successfully secured independent external funding with an independently conceived investigator initiated trial sponsored by [redacted]

[redacted] is in her third year of faculty appointment in the Division of Surgical Oncology during which time she has developed a robust clinical melanoma program and serves as co-Investigator on several clinical trials as well as translational correlative studies of gastric cancer and melanoma. She is the current holder of the [redacted] award supporting her progress from a mentored position to one of independence and compliments her background of T32 training as a Physician-Scientist in Oncology at the [redacted]. I have known [redacted] since her recruitment in 2016 following completion of her training in [redacted]. She comes from a highly trained clinical background of surgery and original basic science experience resulting in multiple high impact publications as well as national awards for Basic/Translational Science.

[redacted] is supported by a very talented and successful mentorship team led primarily by [redacted] has an impressive track record of success in his development under the K12 program, as well as being a previous recipient of the SSO Clinical Investigator Award, and has demonstrated strong capacity for clinical/translational immunotherapy research. He has expressed great interest and enthusiasm for continued mentorship of [redacted] development. As part of this productive relationship, [redacted] will continue to oversee her development as a surgeon, including her ability to successfully lead a team-science enterprise, prepare successful proposals for extramural funding, and conduct the proposed clinical trial. Together, they have outlined a thoughtfully in-depth plan to further develop her skills in hypothesis-driven immuno-oncologic research and surgical leadership, augmenting her clear potential as an independent investigator of practice-changing research objectives. I expect great success from this collaboration given his track record of outstanding mentorship of numerous junior Faculty and surgical residents, and we are fully committed to [redacted] research and development irrespective of whether she receives this award.

In summary, [redacted] is a highly motivated and qualified individual who has the potential to have a highly successful career in translational immunotherapy and high impact melanoma research. The Division of Surgical Oncology and Department of Surgery has released 75% of her time from any clinical, educational, or administrative duty to allow protected time to carry out the responsibilities of the proposed research. It remains extremely important to our departmental mission to attract and maintain surgical scientists to conduct novel clinical studies and ask questions of critical translational impact. Therefore, [redacted] investigations remain a central component of our multidisciplinary evaluation of patients undergoing oncologic care for melanoma and gastric cancer. I strongly endorse her application for the ASCO Conquer Cancer Career Development Award, and fully support her efforts to become a productive translational immunotherapy surgeon-scientist.

Please contact me if you would like additional information.

Sincerely,

[redacted]

[redacted]

Dear Selection Committee,

It is my pleasure to very enthusiastically support [redacted] application for the 2019 ASCO Conquer Cancer Career Development Award. I am currently serving as Dr. [redacted]s mentor for her ongoing research and career development, including a [redacted] Oncology award, and I am committed to continuing to serve as her mentor for this prestigious award should she be selected for it. Overall, [redacted] has demonstrated to me that she has the potential to be a successful translational cancer researcher in immuno-oncology who can perform high-impact bedside-to-bench translational immunotherapy research along with clinical trials. Moreover, I think this award will significantly foster her development in this direction. For her application, she has conceived and developed a novel and innovative proposal which has significant scientific merit and will launch her on the path to an independent research program likely to meaningfully impact the field of translational immunotherapy and neoadjuvant [redacted] for locally advanced melanoma patients. With appropriate mentoring and career development, I think [redacted] has strong potential to conceive and develop further proposals that are competitive for independent external funding.

As a surgeon who has been productive as a clinical/translational immunotherapy researcher, I will serve as [redacted] primary mentor. I have known [redacted] she joined the faculty of the Division of Surgical Oncology in the Department of Surgery at [redacted] in 2016, and we have developed a productive mentoring relationship. As a surgeon-scientist, I understand the unique challenges which surgeons face as clinician-scientists, and it has been my pleasure to mentor her career development as a surgeon thus far, including her ability to prepare successful research proposals based on important surgical questions, and her ability to effectively lead a successful team-science research enterprise. As I have been working closely with [redacted], it is clear to me that she has conceived and formulated a novel and significant research proposal which will serve to supplement funding for the exploratory aims of her ongoing clinical trial with support from [redacted] as well as her K12 Clinical Oncology Award.

The focal point of [redacted] current proposal is molecular mechanisms of resistance to intralesional [redacted] immunotherapy in melanoma via AXL tyrosine kinase signaling. Her clinical/ translational trial will be focused on therapeutic intervention applied neoadjuvantly with [redacted]a first in kind study in melanoma. This proposal is a direct extension of [redacted]

experience during her Surgical Oncology Fellowship when she identified AXL and Gas6 as potent mediators of metastatic programming with specific modulation of host cell recruitment and function in the tumor microenvironment. Targeting of this pathway dramatically improved survival in preclinical models as well as augmented chemotherapeutic efficacy. Her current work is based on preliminary observations that AXL may also play a critical role in adaptive resistance to immunotherapy and be a novel target for improving overall response to modern systemic and intralesional immunotherapeutic agents. Overall, Dr. [redacted] is passionate about this research proposal as she feels it creates a foundation for future work and productive translational science. If she continues in her ongoing progress, she will be competitive as a new NIH investigator, and we specifically aim to submit this work in response to a R01 request for proposals to the National Cancer Institutes's Investigator-Initiated Early Phase Clinical Trials for Cancer Treatment with an alternative an NIH/K08 Career Development award as a secondary alternative approach.

Ultimately, regardless of the mechanism, [redacted] maturity and progress to date indicate to me that she has a successful career ahead of her as a clinician-scientist in translational immunotherapy research. I believe that I can offer [redacted] guidance and assistance in her career goals. [redacted] has recruited a team of clinician-scientists to serve as a mentorship committee including [redacted], both successfully funded, independent investigators in translational science. [redacted] has also been accepted to the [redacted] graduate program in Immunology with a specially-designed curriculum under her K12 award in Translational Immuno-oncology. Through this course work and dedicated oversight, she will have rigorous evaluation of the proposed project and the guidance to significantly strengthen the scientific rigor of the immunologic mechanistic studies proposed as well as the support of the Immunology Core to conduct these studies.

As noted above, I think [redacted] proposal for the current funding opportunity demonstrates her potential to conduct innovative and impactful translational cancer immunotherapy research. By evaluating the histologic immune response to [redacted] in both primary tumors and sentinel disease in relation to AXL and Gas6 expression, we anticipate important insights into the mediators of response vs non-response to neo-adjuvant immunotherapy. Clinically, we also anticipate improved survival in [redacted] responders given the known bystander effect established in oncolytic viral therapies. It is a clear sign of [redacted] research potential that her original ideas have developed into the proposed research studies. Since [redacted] has formulated a worthy research project and will make an excellent recipient of this award, I am committed to supporting her career development. I have mentored numerous junior Faculty and surgical residents in original research projects during my tenure as Faculty of the [redacted] School of Medicine, and it is clear to me that [redacted] has outstanding potential as a translational physician-scientist. I also understand and fully support the need for departmental and mentor support for mentored physician scientists such as Dr. [redacted] to succeed, and I am committed to [redacted] research and career development irrespective of whether she receives this award.

I will meet independently with [redacted] on a bi-weekly basis to discuss research progress and troubleshooting. During these formal meetings, we will discuss short and long range plans for this proposed project and appraise the milestones set and progress achieved

for successful completion of this research. As part of [redacted], she will participate in weekly laboratory meetings with the Laboratory of Cancer Immunology along with journal clubs and research symposia. She will present her data and research findings locally and nationally at basic/translational scientific meetings, including SITC (meeting which I regularly attend) and the Society of Melanoma Research. As her mentor, I will have regular one-on-one meetings with her to review data, discuss hypotheses, and plan follow-up assays/ experiments. As part of her didactic training, I will help her initiate collaborations with colleagues at [redacted] and elsewhere, acquaint her with members of the Immunology research community, and assist her in writing and submitting peer-review articles in order to publish her findings. I actively teach graduate level coursework in Cancer Immunology at [redacted], and I will ensure that Dr. [redacted] is adequately trained in this area. In addition, she will receive formal coursework in immunology, tumor immunology, cancer/ vascular biology, and grant writing as part of her research training. I will also ensure that [redacted] participates in continuing education on professionalism and responsible conduct in research.

In summary, [redacted] is a highly qualified and motivated individual who has the potential to have a highly successful career in translational immunotherapy and high impact melanoma research. I strongly endorse her application for the 2020 ASCO Conquer Cancer Career Development Award, and I fully support her efforts to become a productive translational immunotherapy surgeon-scientist. Please contact me if you would like additional information.

Sincerely,