

TITLE: Neoadjuvant Therapy for Melanoma: A US Food and Drug Administration - Melanoma Research Alliance Public Workshop

RUNNING TITLE: Neoadjuvant Therapy for Melanoma: Workshop Review

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Abbreviations: EFS, event free survival; DRFS, distant relapse free survival; ICI, immune checkpoint inhibition; irPRC, immune-related pathologic response criteria; MPR, major pathologic response; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; pCR, pathologic complete response; PFS, progression free survival; pPR, partial pathologic response; RCT, randomized controlled trial; RFS, relapse free survival; TRAE, treatment related adverse events; T-VEC, talimogene laherparepvec

ABSTRACT

Tremendous progress has been made in treating patients with metastatic melanoma over the past decade. In that timeframe, the US Food and Drug Administration (FDA) has approved 12 novel treatments for patients with advanced unresectable melanoma, comprising both kinase-targeted therapies and immune checkpoint inhibitors (ICI), and 5 treatments for adjuvant (postoperative) use in patients with high-risk resectable stage III melanoma. It is not known whether outcomes can be further improved by administering kinase inhibitors or ICI in the neoadjuvant (presurgical) setting in patients with high-risk resectable melanomas. Noting research community interest in exploring the neoadjuvant approach for treating melanoma and recognizing that early harmonization of methodologies may expedite the development of therapeutics in this space, the FDA and Melanoma Research Alliance convened a public workshop on November 6, 2019, in National Harbor, Maryland, to discuss key issues. The workshop consisted of 23 faculty and included more than 250 live participants. Topics discussed included opportunities for advancing novel endpoints for regulatory purposes as well as translational research, clinical trial design considerations, and strategies for optimizing patient selection while mitigating risk.

INTRODUCTION

There has been tremendous progress in treating patients with metastatic melanoma in the past decade, with more than a dozen new treatments approved by the US Food and Drug Administration (FDA) since 2011. These include kinase inhibitors targeting mutant BRAF or MEK that inhibit driver pathways active in ~50% of melanomas (1), and immune checkpoint inhibitors (ICI) targeting CTLA-4 or PD-(L)1 that enable the immune system to attack and kill melanoma cells. In 2008, the 3-year overall survival (OS) rate for patients with inoperable, advanced melanoma was ~5%. (2) Now, >30% of patients with advanced melanoma treated initially with concurrent BRAF and MEK inhibitors and >50% of those treated initially with ICI are alive at 5 years. (3-5)

Some drugs shown to be effective in the unresectable or metastatic disease setting have also proven to be effective adjuvant therapies for patients with operable stage III melanomas (i.e., locoregional metastasis). In patients with resectable stage III melanomas with BRAF V600E/K mutations, adjuvant BRAF and MEK inhibitor combination regimens increased the estimated 3-year rate of relapse-free survival (RFS) from 39% for placebo controls to 58% (HR=0.47, 95%CI 0.39-0.58, P<0.001). (6) Similarly, in all comers, the PD-1 blocking monoclonal antibodies pembrolizumab and nivolumab each increased one-year RFS to >70%, compared to 50-60% in patients receiving placebo control or single-agent ipilimumab. (7,8)

Despite progress with adjuvant treatment, a substantial minority of patients with resectable melanoma remain at risk for post-surgical relapse, prompting interest in exploring neoadjuvant therapy to further improve long-term outcomes. Recurrence-free survival was 52% at 5-years of follow-up in patients with BRAF V600E or V600K mutant stage III melanoma

treated with 12-months adjuvant dabrafenib+trametinib; 51.7% at 4-years in patients with stage III/IV melanoma treated with 12-months adjuvant nivolumab; and 63.7% at 3-years in patients with stage III melanoma treated with 12-months adjuvant pembrolizumab. (9-11) Preclinical and clinical data in melanoma and other cancers suggest that this approach justifies additional clinical investigation.(12-15)

The application of neoadjuvant treatment for patients with resectable melanoma should be considered in the context of balancing potential risks and benefits, in a patient population among whom some might be cured by standard available therapies (Table 1).(16) For instance, among patients with stage III locoregional metastasis, 77% are expected to be alive at 5 years (32% - 93%, depending on AJCC substage).(17) The FDA and Melanoma Research Alliance, the largest nonprofit, nongovernmental funder of melanoma research, convened a public workshop entitled “*Approaches to Neoadjuvant Treatment in Melanoma*” on November 6, 2019, to discuss the appropriate design of clinical trials assessing the risks and benefits of presurgical therapies in patients with resectable melanoma. At this meeting, academic and industry researchers, patient advocates, biomedical journalists, and FDA representatives reviewed lessons learned from the neoadjuvant treatment experience in other solid tumors, and the limited number of neoadjuvant clinical trials that have been reported to date in melanoma. Here, we summarize information that was discussed in the Workshop.

LESSONS LEARNED FROM NEOADJUVANT THERAPIES IN OTHER CANCERS

Breast Cancer

Experts believe the greatest opportunity for curing cancer is when it has not yet exhibited clinically detectable metastases.(18,19) Research on neoadjuvant therapy in breast cancer provides a foundational experience that can inform neoadjuvant approaches in melanoma. The breast cancer experience highlights an innovative approach to neoadjuvant clinical trial design with the simultaneous and adaptive testing of multiple regimens in I-SPY-2, a so-called “platform” or adaptive multi-arm, phase II trial enrolling patients with locally advanced tumors.(20) In I-SPY-2, each experimental regimen is compared against a common control arm, giving greater randomization probabilities to regimens that have been successful in a patient’s tumor subtype based on the endpoint of pathologic complete response (pCR). MRI is serially performed, and imaging response is factored into the adaptive randomization. This design accelerates screening new drugs and regimens by patient subtype by minimizing the number of patients and time required to identify active new agents or combinations.

In the I-SPY2 study, the primary endpoint is pCR, defined as no residual invasive cancer cells in the primary breast tissue or draining lymph nodes, which is used as an early surrogate of antitumor activity. Secondary endpoints are residual cancer burden, event-free survival (EFS), and distant relapse-free survival (DRFS).(21) All participating medical centers adhere strictly to standard operating procedures, enabling pooling of data.

The I-SPY2 trial, however, is not powered to determine whether an experimental drug’s effect on pCR rate is predictive of the drug’s effect on a traditional measure of clinical benefit (e.g., EFS or OS). A large pooled analysis of 12 neoadjuvant breast cancer randomized controlled trials (RCTs) that included nearly 12,000 patients found that although individual patients who attain a pCR have better long-term outcomes (confirming that pCR is a prognostic

indicator in breast cancer), a drug's impact on pCR did not correlate with its impact on long-term clinical benefit (EFS and OS) on a trial level.(22) However, the authors pointed out that it would have been difficult to show that treatments that improve pCR rate prolong survival because treatments in the included RCTs showed little or no treatment improvements, because of the low numbers of patients that experienced pCR, the heterogeneous combined study populations, or perhaps because an effect on pCR is not a surrogate for an effect on EFS or OS for some or all of the drugs studied for breast cancer in the neoadjuvant setting.(23) It remains uncertain whether improving pCR rate would lead to lowering of hazard of EFS or OS.

Lung Cancer

Stage II-III A resectable non-small-cell lung cancer (NSCLC) has a five-year survival rate of 30-50% and the use of adjuvant platinum-doublet chemotherapy adds 5% to long-term survival over surgery alone.(24) Such modest treatment effect is seen in a meta-analysis of neoadjuvant and adjuvant chemotherapy treatments for early-stage NSCLC.(25) The recent success of ICI and targeted therapies in advanced metastatic NSCLC has led to the proliferation of neoadjuvant trials testing these treatments for Stage I-III A resectable NSCLC. Because few patients with NSCLC experience a pCR after neoadjuvant chemotherapy (occurring in ~5% of cases), several neoadjuvant studies use the endpoint of major pathologic response (MPR), defined as $\leq 10\%$ residual viable tumor cells in the primary tumor at resection after neoadjuvant treatment. These studies are also collecting data on the long-term endpoints of RFS and OS.

Results of three studies have been reported assessing single agent or combination ICI as neoadjuvant treatment for patients with operable NSCLC. One study found that 9 of 20 patients with Stage I-III A resectable NSCLC who received nivolumab monotherapy for 4 weeks in the

neoadjuvant setting experienced a MPR or pCR.(13) A second study found 10 of 41 patients with Stage I-IIIa resectable NSCLC who received an ICI in the neoadjuvant setting experienced a MPR/pCR.(26) Finally, a third, single-arm, open-label Phase II study found that 35 of 41 patients with Stage I-IIIa NSCLC who received combination neoadjuvant nivolumab plus chemotherapy experienced MPR/pCR.(27)

Platform studies akin to I-SPY2 are planned or underway for NSCLC and offers the opportunity to rapidly evaluate pathologic response to novel treatment combinations (NCT03794544).(28) These trials, along with other trials planned and ongoing, have the potential to accelerate drug development and guide rational combination therapy selection for patients with NSCLC.

NEOADJUVANT MELANOMA TRIALS

In contrast to the neoadjuvant experience in breast and lung cancers, in which patients had their primary tumor in place at the time treatment commenced, the majority of melanoma patients enrolled in neoadjuvant clinical trials had stage III regional metastatic disease after excision of the primary tumor. Furthermore, many neoadjuvant trials in melanoma involve the use of ICI, which have a very different mechanism of action than cytoreductive chemotherapies used in breast cancer. Fifty-eight neoadjuvant melanoma trials were listed in ClinicalTrials.gov as of November 2019, including both systemic and localized treatment approaches in patients with stages II-IV melanoma; many of these studies are ongoing. Two targeted therapy and five immunotherapy neoadjuvant trials in patients with stage IIIB/C or IV melanoma were discussed at the Workshop and recently summarized.(29) Two small studies (n=21 and n=35), of patients with resectable stage IIIB/C or IV melanoma and BRAF V600E/K mutation, demonstrated

complete radiographic responses of 2 of 13, and 16 of 35 patients, after neoadjuvant treatment, and pCR rates of approximately 50% (7 of 12 patients, and 17 of 35 patients), respectively.(30,31)

The majority of neoadjuvant studies that are ongoing in melanoma are testing ICI and use pathologic response as an endpoint. Assessment of pathologic response to ICI in patients with melanoma is a logical endpoint given the precedent for its correlation with improved long-term clinical outcomes in individual patients with breast and lung cancer although the correlation between pathological response and long-term outcome need to be validated in the specific context of melanoma treated with ICI. Five reported small studies of neoadjuvant immunotherapy in melanoma were discussed. Single agent ICI with PD-1 blocking antibodies administered in the neoadjuvant setting resulted in radiographic response rates of ~25%, pCR rates of 19-25%; whereas patients receiving combination ICI with CTLA-4 and PD-1 blocking antibodies experienced radiographic response rates 57-70%, and pCR rates of 33-57%.(32-35) However, patients receiving combination nivolumab 1 mg/kg + ipilimumab 3 mg/kg in the neoadjuvant and adjuvant setting experienced more grade ≥ 3 treatment-related adverse events (TRAE)(~73%-90%).(32,33)

A fourth study, a randomized (1:1:1) trial conducted in 89 patients with stage IIIB/C melanoma, attempted to optimize neoadjuvant dosing of nivolumab + ipilimumab by testing three different schedules: group A, two cycles of ipilimumab 3 mg/kg plus nivolumab 1 mg/kg every 3 weeks; group B, two cycles of ipilimumab 1 mg/kg plus nivolumab 3 mg/kg every 3 weeks; or group C, two cycles of ipilimumab 3 mg/kg every 3 weeks directly followed by two cycles of nivolumab 3 mg/kg every 2 weeks. The authors found that pCR ranged from 23-57%,

depending on the schedule, with pCRs of 47%, 57%, and 25% for schedules A, B, and C respectively. MPR ranged from 46-70%, and an additional 10-19% of patients experienced a partial PR (pPR). Two cycles of ipilimumab 1 mg/kg plus nivolumab 3 mg/kg (arm B) yielded a pathological response rate of 77% with tolerable toxicity (grade 3-4 TRAEs in 20% of patients), supporting the further exploration of this regimen in a randomized study.(36)

A fifth study included 150 patients with stage III-IV melanoma randomized (1:1) to either 6 doses/12 weeks of neoadjuvant, single-agent talimogene laherparepvec (T-VEC) or to surgery alone.(37) The authors found preliminary evidence that neoadjuvant administration of the oncolytic virus T-VEC in patients with resectable Stage III-IV melanoma yielded an OS rate at 2 years of 88.9%, compared to 77.4% for a control group receiving surgery alone (HR 0.49, P=0.050) and a pCR rate of 17.1% (37) However, the post-surgery treatment was not controlled, confounding its interpretation.

A pooled analysis of 6 neoadjuvant trials in a total of 184 patients with stage III melanoma found a 41% pCR rate, 38% (n = 51) with ICI and 47% (n = 24) with kinase inhibitors.(38) Twelve-month RFS was higher in patients with pCR versus those without pCR (95% vs 62%, P<0.001); this difference was observed with ICI (100% vs 72%, P<0.001) as well as with kinase inhibitors (88% vs 43%, P<0.001). These results suggest that neoadjuvant therapy for melanoma, using agents already shown to be effective and safe in the advanced unresectable disease setting, is promising for patients at high risk for relapse after surgery. Interrogation of the degree of pathologic response as an early biomarker demonstrating whether the neoadjuvant therapy received is having an impact on a patient's cancer is warranted. Larger randomized trials, such as SWOG 1801 and other current trials noted by one

panelist, with monitoring of long-term outcomes will be needed to define and identify the potential clinical benefit of neoadjuvant therapy for patients with melanoma.

INTEGRATION OF SYSTEMIC NEOADJUVANT THERAPY WITH SURGERY

Overall, neoadjuvant ICI and targeted therapies have been found to be relatively safe across cancer types in clinical trials with close monitoring, with few patients becoming ineligible for surgery due to TRAEs or disease progression.(13,26,39) However, with ICI, some investigators have reported increased rates of immune-related adverse events in the neoadjuvant compared to advanced unresectable patient populations; this is hypothesized to reflect generally heightened activity in the intact immune systems of patients with lower disease burdens who receive ICI as their first systemic cancer therapy.(40) In some patients with NSCLC progression during the neoadjuvant treatment period, more extensive surgery was required in 7 of 13 patients.(41) This also appears true in patients with melanoma.(30,42) In one melanoma trial, 2 of 11 patients who received neoadjuvant ICI experienced disease progression such that they were unable to undergo surgery.(32) In symptomatic patients with rapidly expanding tumors, the urgent need for surgical palliation may make neoadjuvant treatment unfeasible. Conversely, in patients with a major response to neoadjuvant therapy, the need for surgery could potentially be eliminated, or a more tailored surgical approach could be utilized than originally planned. Major pathologic responses may render the tumor bed difficult to define intraoperatively, thus marking the index area prior to initiation of systemic therapy should be considered.

NEOADJUVANT CLINICAL TRIAL DESIGN AND REGULATORY CONSIDERATIONS

A portion of the Workshop was devoted to discussion of optimal trial design and analysis, as well as regulatory considerations, for the efficient evaluation of investigational agents being tested in patients with melanoma in the neoadjuvant setting.

Eligibility criteria

The ratio of risk to benefit needs to be a primary consideration for patient selection in neoadjuvant melanoma trials because a proportion of operable patients will be cured by surgery alone, or surgery plus conventional adjuvant therapies, despite the high risk of relapse in some clinicopathologically-defined subgroups (Table 1). For patients with melanoma to be eligible for neoadjuvant therapy, their detectable cancer must be deemed to be completely resectable by an experienced surgeon. Patients should be excluded from enrollment if they have co-morbidities relevant to the planned surgery, or conditions that would increase the likelihood of adverse events from the drug(s) being tested. However, eligibility criteria should be designed to not unnecessarily exclude patients with melanoma who might potentially benefit from either arm of a RCT.(43)

Endpoints

Pathological Response

Although Workshop participants agreed that pathologic response is an informative endpoint for neoadjuvant trials, a number of issues remain. For instance, how should pathologic response be defined (e.g., complete, major, or partial pathologic responses)? In the non-melanoma setting, investigators' opinions have varied on whether pCR should be defined as a lack of residual invasive cancer, or lack of residual invasive and in situ-cancer, and whether pCR should be assessed in tumor-draining lymph nodes in addition to the primary tumor.

However, in patients with melanoma enrolling in neoadjuvant trials, the primary tumor site is commonly absent, and surgery is focused on the removal of metastatic draining lymph nodes (stage III) or oligometastatic visceral sites (stage IV). In the context of clinical trials, pathologists should be blinded when conducting tissue-based response assessments, and consensus across the field is needed to standardize analysis methods.(23,44,45) Pathologic evidence of treatment response may be assessed in representative biopsies or completely resected tumors, while the formal definition of pCR requires a full assessment of tumor tissues after complete surgical resection.(44,45)

Participants discussed whether broadening a pathological response endpoint to include not only pCR, but also MPR and pPR should be considered (Table 2). Analyses of eighteen-month RFS rates in patients receiving neoadjuvant ipilimumab + nivolumab, either sequentially or in combination, found that only 2% (1/64) of patients with pPR had relapsed compared to 64% (13/21) of patients with >50% residual viable tumor.(36) Moreover, an earlier study testing combination ipilimumab + nivolumab found that none among seven patients who experienced pCR/MPR/pPR had relapsed at a median follow-up time of 25.6 months.(33) Although the number of patients studied is small, these data suggest that some patients who experience less than a pCR, such as MPR or pPR, might derive durable responses; however, this may depend on the type of therapy administered.

Evaluation of the impact of neoadjuvant kinase inhibitor therapies vs ICI, and local vs systemic therapies in melanoma based on pathologic response rate may differ. While the International Neoadjuvant Melanoma Consortium (INMC) proposes to use the same pathologic response definitions for both ICI and targeted treatments, the kinetics of a pathologic response

with these two treatment modalities having distinct mechanisms of action may differ.(44)
Notably, the pooled analysis from Menzies et al. found that among patients with melanoma experiencing a pCR to neoadjuvant therapy, 0% (0/51) receiving ICI experienced a relapse compared to 41% (7/17) receiving targeted therapies.(38) Therefore, acceptance of degree of pathologic response as a surrogate marker for long-term clinical outcomes will require studying larger patient cohorts, longer follow-up, and consistency in the design and conduct of neoadjuvant trials.

Clinical Endpoints

In FDA guidances, EFS or OS are identified as appropriate efficacy endpoints for neoadjuvant therapy to support regular approval.(23,46) Broadly, EFS needs to be clearly defined as encompassing any clinically significant event that occurs after the time of randomization, including disease progression (local and/or distant tumor recurrence) or death due to any cause. To allow pooling of melanoma trial data for the evaluation of pCR as a validated surrogate endpoint, EFS should be defined in a detailed and consistent way across all trials, with a consensus definition of what comprises an “event”; because EFS is a composite endpoint, the specific event should be captured for each patient in all the studies included in the analysis. Data on duration of follow-up, frequency of disease progression assessments, and how missing assessments and drop-outs due to toxicity are evaluated in each study are also important in considering pooling of data from several melanoma clinical trials.

Safety endpoints should assess the number of patients who could not proceed to surgery due to disease progression or TRAEs during the neoadjuvant treatment period; on the other hand, patients who require less aggressive surgery due to tumor down-staging should

also be enumerated. Safety endpoints should assess the TRAE profile of neoadjuvant treatments and ensure that patients not only live longer but experience a good quality of life.

Approval pathways

The FDA has published guidance on two main approval pathways for new drugs to enter the market: accelerated or regular approval.(47) An accelerated approval may be granted to a “product for a serious or life-threatening disease or condition ... upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.”(47) Accelerated approval may require post-marketing trials that verify and describe clinical benefit. In contrast, regular approval is based on demonstration of clinical benefit on endpoints such as OS, PFS, RFS, EFS, other patient benefit (e.g., improved function, decrease in disease-specific symptoms), or a validated surrogate marker of clinical benefit.

Accelerated approval: Single versus multiple trials

For new drugs with unproven efficacy, the FDA described in the treatment of early stage breast cancer two design options for neoadjuvant therapy trials aimed at garnering accelerated approval followed by regular approval.(23,48) One is to conduct a single, well-designed and powered RCT add-on design in which an investigational agent is added to a standard regimen in the pre-surgical setting. In the single-trial model, pCR is the surrogate endpoint upon which to seek accelerated approval, and EFS or OS is the primary endpoint to assess clinical benefit for

regular approval. The trial must be powered appropriately to demonstrate a benefit in EFS or OS.

An alternative pathway using multiple trials, would rely upon separate trials to support accelerated and regular approval. In this model, applicants conduct one or more neoadjuvant RCT, powered to detect an absolute improvement in pCR rate between arms, to support accelerated approval. A subsequent larger RCT, which should be conducted in either the neoadjuvant or adjuvant setting, powered for EFS (neoadjuvant), DFS (adjuvant), and/or OS (either disease setting), would be used to confirm clinical benefit and provide the basis for regular approval. This approach may be most appropriate for drugs for which there is existing substantial evidence of efficacy in the advanced unresectable disease setting and well-described safety profiles.

Novel designs and biomarkers

With the complete resection of post-treatment tumors, neoadjuvant therapy provides a unique opportunity for exploratory correlative analyses that are expected to garner new insights into drug mechanisms and provide biomarkers for long-term treatment outcomes. Workshop participants suggested that a concerted and organized “team science” approach is needed in melanoma to interrogate novel biomarkers and strategies to improve therapeutic response. For instance, regarding neoadjuvant ICI, expression of tumor and immune profiling of checkpoints such as PD-1, TIM-3 and LAG-3; a high interferon-gamma gene expression signature; and high tumor mutational burden at baseline are being assessed as potential biomarkers to select patients for treatment with one or more therapies.(30,35)

A pathologic signature of immune-mediated response to ICI treatment has been described, which includes features of immune activation, tumor clearance, and tissue repair. These features were used to develop immune-related pathologic response criteria (irPRC), with strong inter-observer reproducibility among five pathologists assessing the tissue.(49) The pathologic features were originally described in lung cancer and melanoma, and the findings were subsequently extended to include both primary tumors and metastases from more than ten different tumor types.(45,49,50) These findings suggest that a pan-tumor scoring system for pathologic response to immunotherapy may be possible, allowing for a unified approach to scoring and facilitating comparisons across different studies and indications for a given immunotherapy regimen.

Incentives should be developed that encourage drug developers to pursue novel trial designs and collaborations. The INMC has made progress in galvanizing an international coalition of many of the multidisciplinary experts leading neoadjuvant ICI and kinase inhibitor melanoma trials.(29)

CHALLENGES AND FUTURE RESEARCH DIRECTIONS IN NEOADJUVANT TREATMENT FOR MELANOMA

Due to the limited number of melanoma neoadjuvant trials reported to date, with modest-sized patient populations, ongoing survival analyses, and inconsistencies in defining relevant endpoints, there are still many unknown factors that make it challenging to interpret overall results and design future studies. For instance, it is difficult to contextualize the efficacy of neo-adjuvant therapies in comparison to adjuvant therapies for melanoma due to the few

studies that have been conducted to directly compare these treatment modalities, as well as the small number of neo-adjuvant trials that have reported RFS, a common endpoint used for adjuvant trials. Rapidly changing standards of care in melanoma, coupled with different preferences in oncology practice across the globe, make it difficult to combine findings across neoadjuvant studies. Moreover, many clinics appear to be providing off-label neoadjuvant treatments to patients with high-risk resectable melanomas, so that it may become difficult to enroll treatment-naïve patients in neoadjuvant therapy trials.

To address these and other challenges, Workshop participants identified a need to align trial design, recruit sufficient patients, obtain data to validate the clinical meaningfulness of a specific effect on pathological response, standardize endpoint criteria to assess efficacy and safety, facilitating the potential approval of neoadjuvant melanoma therapies. Shared strict definitions and standards for pathologic response determinations may facilitate the pooling of data from studies or study arms. One set of possible guidelines for trial design and pathological assessment has been put forth by the INMC, recommending 6-8 weeks' duration of preoperative neoadjuvant therapy plus one year of adjuvant therapy, and standardized reporting of pathological response (pCR, MPR, pPR).(29) However, not all pathologists and clinical researchers agree with these guidelines.

Along with aligning trial design, Workshop participants pointed toward the need to pursue correlative studies to identify biomarkers of treatment response and resistance. Correlative studies conducted in conjunction with already-completed neoadjuvant immunotherapy trials suggest that many of the immunologic features distinguishing responders from non-responders in late-stage disease, such as increased CD8+ T cell infiltration into

tumors, interferon-gamma signature, B-cell signatures and tertiary lymphoid structures, and tumor mutational burden, may predict outcomes in the neoadjuvant setting as well.(31,32,34,35,44,51,52) Determining which markers correlate with pathological response, clinical response, or both is an important goal and could also inform appropriate treatment regimens for patients whose melanoma eventually metastasizes. Neoadjuvant trials that use pathologic response as the primary efficacy endpoint are useful in guiding decisions made during drug development, even if they ultimately do not assess the long-term efficacy endpoints intended to demonstrate clinical benefit.

Workshop participants identified additional research avenues that should be explored. Several noted that the on-treatment and/or serial biopsy format of neoadjuvant trials enables mechanism-of-action studies and (in the case of ICI) delineation of immune cell types involved in tumor behavior. Such studies also have the potential to reveal how other factors such as sex hormones, the microbiome, and tumor-secreted factors, among other variables, may affect therapeutic response. Novel imaging approaches are also needed given the limitations of RECIST and other approaches in accurately predicting responses. However, caution should be used in obtaining serial biopsies in registration trials, as this may affect the assessment of pCR.

CONCLUSIONS

Early clinical and correlative scientific results from neoadjuvant melanoma trials suggest that this approach is feasible to screen drugs for early activity, provide an opportunity for exploring biomarkers for appropriate patient selection, and to assess the effects of drugs in the neoadjuvant setting. These studies also reveal some of the challenges involved in ensuring the development of safe and effective neoadjuvant treatments that are personalized, such that the

right patient receives the right treatment at the right time. These include clarifying nuances in patient eligibility, consistently defining and validating early surrogate markers (pathologic or other) for long-term clinical benefit, and clearly defining EFS and other clinical outcome measures. Future development of safe and effective neoadjuvant therapies for patients with melanoma will require close collaborations among stakeholders from diverse clinical specialties and research sectors, such as those convened at the FDA-MRA Workshop.

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Table 1. Potential Benefits and Risks of Neoadjuvant Therapy for Melanoma

POTENTIAL BENEFITS	POTENTIAL RISKS
<p>Clinical Outcome</p> <ul style="list-style-type: none"> • Potential for durable responses in patients with resectable tumors at high risk for recurrence • Treating when tumors are present may lead to more effective priming of the systemic anti-tumor immune response • Potential for less complicated surgeries due to reduced tumor burden • Possibility of eliminating the need for surgery in some patients needs to be studied <p>Pathology</p> <ul style="list-style-type: none"> • Assessment of pathological response at time of surgery can inform choice of subsequent therapy and provide a marker of long-term clinical outcomes • Ability to collect high quality biospecimens to facilitate translational research and identification of biomarkers of response/resistance 	<p>Clinical Outcome</p> <ul style="list-style-type: none"> • Tumor may progress and become inoperable during the neoadjuvant treatment period • Tumor growth during neoadjuvant treatment period may lead to more complicated surgeries and increased surgical morbidity • Potential for increased adverse events in neoadjuvant setting, depending on the regimen under study • Over-treatment: >50% of stage III patients will be cured by surgery alone <p>Pathology</p> <ul style="list-style-type: none"> • Difficult to identify regressed tumors for tissue resection and loss of prognostic factors <p>Toxicity</p> <ul style="list-style-type: none"> • Drug toxicity may limit wound healing/ability to undergo surgery at scheduled time

Table 2. Endpoints to Consider

<p>Clinical Standard of Care Endpoints</p> <ul style="list-style-type: none"> • EFS, RFS, OS • QOL / AE measures • Number of patients who lose surgical option due to neoadjuvant therapy • Number of patients down-staged or spared from surgery due to complete response to neoadjuvant therapy
<p>Translational Research Endpoints</p> <ul style="list-style-type: none"> • pCR (no residual tumor in tumor bed or lymph nodes), MPR ($\leq 10\%$ residual viable tumor), pPR ($\leq 50\%$ residual viable tumor) • Combine pathological response with novel imaging results • Scoring by immune-related pathologic response criteria (irPRC) to optimize thresholds of residual viable tumor as predictors of patient outcomes to immunotherapy • Gene expression signatures and other tissue markers correlating with pCR/RFS/OS

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