Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium

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Advances in the treatment of metastatic melanoma have improved responses and survival. However, many patients continue to experience resistance or toxicity to treatment, highlighting a crucial need to identify biomarkers and understand mechanisms of response and toxicity. Neoadjuvant therapy for regional metastases might improve operability and clinical outcomes over upfront surgery and adjuvant therapy, and has become an established role for drug development and biomarker discovery in other cancers (including locally advanced breast cancer, head and neck squamous cell carcinomas, gastroesophageal cancer, and anal cancer). Patients with clinically detectable stage III melanoma are ideal candidates for neoadjuvant therapy, because they represent a high-risk patient population with poor outcomes when treated with upfront surgery alone. Neoadjuvant therapy is now an active area of research for melanoma with numerous completed and ongoing trials (since 2014) with disparate designs, endpoints, and analyses under investigation. We have, therefore, established the International Neoadjuvant Melanoma Consortium with experts in medical oncology, surgical oncology, pathology, radiation oncology, radiology, and translational research to develop recommendations for investigating neoadjuvant therapy in melanoma to align future trial designs and correlative analyses. Alignment and consistency of neoadjuvant trials will facilitate optimal data organisation for future regulatory review and strengthen translational research across the melanoma disease continuum.

Lancet Oncol 2019; 20: e378–89

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Introduction

High-risk resectable melanoma (clinically detectable stage III with or without in-transit metastases) represents 10–20% of all melanoma cases diagnosed yearly and has a risk of relapse (up to 70%) when treated with surgery alone.[1,2] Positive results of studies of targeted therapies and immunotherapies for stage IV melanoma have ushered in a new era of adjuvant therapies for resected stage III disease, but patients with clinical stage III disease remain at a high risk of recurrence even with these adjuvant therapy advances. Therefore, improving existing therapies, innovating new therapeutic drugs, and investigating new combination regimens is greatly needed in the neoadjuvant setting (ie, drug is given before definitive resection) for patients with high-risk clinical stage III melanoma.

Neoadjuvant systemic therapy is part of the established standard of care therapy in the management of other malignancies. This approach has several advantages: it might reduce tumour burden and facilitate surgical resection; it provides potentially valuable information regarding pathological response, which has been used as a surrogate endpoint of improved patient outcomes in treatment of other cancer types (such as locally advanced breast cancer, head and neck squamous cell carcinomas, gastroesophageal cancer, and anal cancer); and provides deep insights into mechanisms of disease resistance and response, and enables identification of biomarkers for response and survival.[3–6] The response to neoadjuvant systemic therapy might also give important prognostic and toxicity information, and help direct the choice of adjuvant therapy, if needed, after definitive surgical resection. The neoadjuvant approach might also provide a mechanism through which novel drugs and combinations might be studied.[7,8] Finally, evidence from preclinical models suggests that neoadjuvant therapy might provide a survival benefit over adjuvant therapy in the context of treatment with an immune checkpoint blockade, along with promising initial clinical trial results in patients.[9] Despite all the listed potential benefits with neoadjuvant therapy, the therapy also has potential risks. Specifically, administration of neoadjuvant systemic therapy delays initiation of what is considered standard of care surgery because patients with poor treatment response could develop unresectable disease. Additionally, toxic effects from neoadjuvant therapy might result in long-term patient morbidity or further delay surgical resection, and thereby increase surgical risk. Thus, there is a need to clearly define the ideal patient population, duration of treatment, and toxicity of neoadjuvant systemic therapy to balance the potential risks of this investigational approach. In addition, patients remain at risk of the same toxicity as they would be exposed to when receiving standard of care adjuvant therapy.

Several neoadjuvant systemic therapy trials have been done for patients with melanoma using contemporary targeted and immunotherapies with promising early

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data (table).[10–15] A pooled analysis of two targeted therapy trials (dabrafenib with trametinib) and two immunotherapy trials (nivolumab with or without ipilimumab; total of 65 evaluable patients in the four trials; 44 treated with dabrafenib and trametinib and 21 treated with immunotherapy) showed that high rates of complete pathological response were achievable with either regimen, and that complete pathological response correlated with improved relapse-free survival, particularly in patients treated with immunotherapy.[16] Nonetheless, these trials had disparate patient populations, designs, endpoints, and small sample sizes. Thus, the generalisability of these results is limited, and underscores the need for a standardised approach to the design and conduct of neoadjuvant systemic therapy trials for melanoma. It is crucially important for the melanoma community to be organised around basic tenets of neoadjuvant therapy to achieve a meaningful impact in advancing clinical outcomes and the scientific discovery necessary for acceptance of a neoadjuvant approach into the mainstay of melanoma therapy.

Consensus formation

The collective vision was to establish a strong organisational framework (figure 1) to harmonise approaches to the investigation of neoadjuvant systemic therapy in the treatment of patients with high-risk, resectable metastatic melanoma. Central to these efforts is the development of a comprehensive and holistic approach with the goal of maximising collaborative clinical and translational research opportunities among individual investigators and across numerous institutions worldwide.

Since 2016, the INMC has met regularly to identify fundamental opportunities and challenges in establishing neoadjuvant systemic therapy within the armamentarium of treatment options for high-risk, resectable melanoma and has worked together to develop guiding principles for future research in this area (figure 1). The disciplines of medical oncology, surgical oncology, pathology, translational research, imaging, and statistics organised working groups to address clinical trial development (including patient population and study design and endpoints), pathological evaluation, surgical principles, and biomarker evaluation. The groups evaluated existing data and trial designs and developed recommendations organised under three themes: patient selection and treatment duration; trial endpoints, including radiological, pathological, survival, safety, and surgical endpoints; and biospecimen collection and translational research (panel 1).

Patient selection and treatment duration

Patient selection

Melanoma recurrence and survival are highly dependent upon stage at the time of diagnosis. However, within each stage, patients have heterogeneous outcomes, particularly for patients with stage III disease.[1,2] Accordingly, patient selection for such clinical trials is crucial and stratification should be considered when disparate groups are included in a single study. This approach has been used in most neoadjuvant systemic therapy trials to date for patients with high-risk resectable clinical stage III melanoma; results show that patients have measurable disease in regional lymph nodes as measured by Response Evaluation Criteria in Solid Tumours (RECIST) imaging.[17] Few trials have included patients with in-transit disease, unresectable stage III or stage IV disease, and those who received previous systemic therapy (table). The experimental nature of neoadjuvant therapy must be explained in detail to patients and they must be informed that the neoadjuvant approach might be associated with higher risks than the standard approach of upfront surgery and adjuvant therapy.

The INMC generally recommends limiting the enrolment of patients with clinically detectable stage IIIB, IIIC, and IIID (American Joint Committee on Cancer [AJCC] 8th edition)[1,18] melanoma who have surgically resectable disease, as determined by a multidisciplinary team consisting of surgical and medical oncologists and radiologists evaluating measurable lesions by RECIST criteria (with disease confined to lymph nodes with a short axis of >15 mm). This criterion is particularly important in studies exploring the utility of pathological complete response and major (or near complete) pathological response (major pathological response or near complete response, ie, ≤10% viable residual tumour) as a surrogate endpoint for survival outcomes. The effect of previous adjuvant therapy (including radiotherapy, as well as systemic adjuvant therapy with targeted therapy or immune checkpoint blockade) should be considered, because it might affect late response to neoadjuvant systemic therapy.

Inclusion of patients with resectable in-transit metastases or oligometastatic stage IV melanoma and borderline-resectable melanoma might also be considered. However, this approach should be carefully planned and studied as a separate cohort from patients with surgically resectable stage IIIB, IIIC, and IIID nodal disease, because the biology of this presentation (and risk of relapse) might differ substantially.[1] The likelihood of achieving disease control for the proposed therapy should be carefully considered in trials, including for patients with borderline resectable disease, because progression on therapy can occur and has been observed in a completed neoadjuvant melanoma trial (NCT02519322).[12] In addition, close clinical and imaging monitoring for potential progression during neoadjuvant therapy is recommended. Trials focused on patients with low-risk disease, including stage II disease or stage IIIA disease, have a high chance of cure with upfront surgery and standard of care adjuvant therapy and further investigation into the potential benefit of neoadjuvant

	Patient population*	Regimen	Number of participants	Primary endpoints	Pathological responses†	RECIST response	Median follow up (months)	Relapse-free survival (months) or proportions	Safety
NCT00972933	Clinical stage IIIB or IIIC and oligometastatic stage IV; patients with in-transit metastases included	Two neoadjuvant doses of ipilimumab (10 mg/kg), surgery, then followed by two adjuvant doses of ipilimumab	35	Pathological responses	0 pathological complete responses; 15% of participants had microscopic-only disease†	9% participants	18	11	Grade 3 adverse events: 32%
NCT02231775	Clinical stage IIIB or IIIC and oligometastatic stage IV with BRAF V600E or V600K mutation; patients with in-transit metastases allowed	Neoadjuvant dabrafenib (150 mg twice a day) plus trametinib (2 mg daily) for 8 weeks followed by surgery and 44 weeks of the same adjuvant treatment versus surgery	21	Event-free survival	58% participants had pathological complete responses	85% participants	18·6	19·7 months for neoadjuvant systemic therapy group *vs* 2·9 months for surgery group	A: Grade 3: 47% of participants in the neoadjuvant systemic therapy group had grade 3 adverse events
NCT01972347	Clinical stage III with BRAF V600E or V600K mutation; patients with in-transit metastases included	Dabrafenib (150 mg twice a day) plus trametinib (2 mg daily): 12 weeks neoadjuvant therapy and 40 weeks of adjuvant therapy	35	Pathological complete response proportion and RECIST response proportion	49% participants had pathological complete responses	86% overall RECIST response rate; 46% participant had complete responses	27	23 months of overall relapse-free survival (30 months of pathological complete response, 18 months of non-pathological complete response)	57% participant had any grade 3 adverse events; 3% had any grade 4 events; and 26% had surgical grade 3 events; 26% had drug-related grade 3 events and 3% drug-related grade 4 events
NCT02437279	Clinical stage III	Surgery plus 12-week adjuvant ipilimumab (3 mg/kg) and nivolumab (1 mg/kg); 6 weeks of neoadjuvant and 6 weeks of adjuvant ipilimumab (3 mg/kg) and nivolumab (1 mg/kg)	10 participants per group	Safety, tumour specific T-cell expansion	33% participants had pathological complete responses; 33% had near pathological complete responses; and 11% had pathological partial responses (neoadjuvant group only)	57% participants in the neoajuvant group	32	70% in the surgery group *vs* 80% in the neoadjuvant therapy group	Grade 3 adverse events: 90% of participants in the surgery group *vs* 90% of participant in the neoadjuvant therapy group
NCT02519322	Clinical stage III and oligometastatic stage IV; patients with in-transit metastases included	4 doses of nivolumab (3 mg/kg) neoadjuvant therapy, surgery, and 24 weeks of nivolumab adjuvant therapy; 3 courses of ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) neoadjuvant therapy, surgery, and 24 weeks of nivolumab adjuvant	12 participants in the nivolumab-only group and 11 in the ipilimumab plus nivolumab group	Pathological complete response	Pathological complete response: 25% participants in the nivolumab-only group *vs* 45% participants in the ipilimumab plus nivolumab group	25% participants in the nivolumab-only group *vs* 73% participants in the ipilimumab plus nivolumab group	20	Relapse-free survival: 56% participants in the nivolumab-only group *vs*81% participants in the ipilimumab plus nivolumab group	Nivolumab-only: 8% participants had grade 3 adverse events; ipilimumab plus nivolumab: 73% participants had grade 3 adverse events; no grade 4 or 5 events in any group

(Table continues on next page)

	Patient population	Regimen	Number of participants	Primary endpoints	Pathological responses*	RECIST response	Median follow up (months)	Relapse-free survival (months) or proportions	Safety
(Continued from previous page)									
NCT02434354	Clinical stage III or resectable stage IV; patients with in-transit metastases included	Pembrolizumab (one course of 200 mg), surgery, and then 1-year pembrolizumab	30	Feasibility, safety	19% participants had Pathological complete response and 11% near pathological complete response	Not recorded	18	100% relapse-free survival for patients with or near pathological complete response	Grade 3 adverse events not reported; no grade 4 or 5 toxic effects identified or reported
NCT02977052	Clinical stage III	Group A: two courses of ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) once every 3 weeks; Group B: two courses of ipilimumab (1 mg/kg) plus nivolumab (3 mg/kg) once every 3 weeks; Group C: two courses of ipilimumab (3 mg/kg) once every 3 weeks plus two courses of nivolumab (3 mg/kg) every 2 weeks	30 in group A; 30 in group B; and 26 in group C	Safety	Pathological complete response 47% in group A vs 57% in group B vs 23% in group C; near pathological complete response 23% vs 7% vs 23%; pathological partial response 10% vs 13% vs 19%; pathological non-response 20% vs 23% vs 35%	60% in group A; 60% in group B; and 42% in group C	8·3	43% of pathological non-responders relapsed; no relapses reported in the other response groups	Grade 3 or 4 adverse events: 40% in group A vs 20% in group B vs 50% in group C

*Staging according to the American Joint Committee on Cancer, seventh edition. †Pathological complete response is defined as no viable tumour; near pathological complete response is defined as less than 10% of viable tumour; pathological partial response is defined as less than 50% viable tumour. †Denotes pathology reviewed before definitions used by other trials included in this table.

Table: **Modern (since 2014) neoadjuvant trials for patients with melanoma with available data**

Figure 1: **Timeline of the International Neoadjuvant Melanoma Consortium and guideline development**
INMC=International Neoadjuvant Melanoma Consortium. ASCO=American Society of Clinical Oncology.

systemic therapy would require differing trial designs, the discussion of which are not considered in this Policy Review. Clinical trial design in the neoadjuvant setting should be adaptive and strike a balance between risk of recurrence and risk of toxicity or surgery delay. Although high toxicity might be acceptable in high-risk populations with low 5-year overall survival (stage IIIC and IIID disease according to AJCC, eight edition),[1] alternative dosing schemes or other better tolerated combination therapies need to be identified for low-risk disease.

Data should be collected regarding clinical stage, including standard clinicopathological factors (eg, detailed primary tumour features and previous sentinel node status if applicable) and previous adjuvant therapy, to inform future prognostic models. Complete staging and prognostic assessments should be done and data collected, which should include established prognostic (eg, lactate dehydrogenase) and predictive (eg, BRAF, NRAS, PD-L1) biomarkers.

Duration of neoadjuvant and adjuvant therapy

Duration of neoadjuvant therapy in clinical trials has ranged from 3–12 weeks with proposed schedules based on dosing regimens of individual drugs, putative mechanisms of action, likelihood or kinetics of response, and potential toxicity (table). Although longer treatment duration might increase the likelihood of achieving a pathological complete response, particularly for drugs with slower kinetics of response, a risk of both local and systemic disease progression exists with this approach,

with the possibility of the disease becoming unresectable. Additionally, longer treatment durations might increase the likelihood of toxicity and associated morbidity, which might delay surgery or increase the risk of surgical complications. Based on all available data, the INMC recommends 6-week to 8-week duration of preoperative therapy as a standard recommendation in the design of neoadjuvant systemic therapy trials. Longer duration of therapy might be considered as novel approaches evolve; however, a standardised approach following this recommendation will promote consistency and empower future cross-trial comparisons.

In addition to neoadjuvant treatment, the majority of trials have included a component of adjuvant therapy, with a total duration of systemic treatment (neoadjuvant plus adjuvant) of 1 year in most trials (table). This design was, in part, informed by approved regimens of adjuvant systemic therapy in melanoma.[18–21] In the future, the degree of pathological response from neoadjuvant therapy might direct the inclusion of an adjuvant phase, but this approach remains an area of active investigation. At present, the INMC suggests that neoadjuvant trials include a conventional postoperative adjuvant therapy phase (with or without the drugs under investigation), to bring the total duration of systemic therapy to 1 year for purposes of standardisation and cross-trial comparability. Exceptions could be made but should be based on a strong scientific or clinical rationale (eg, to evaluate outcomes after pathological complete response in the absence of postoperative therapy).

Trial endpoints

Assessment of drug toxicity

Safety is a key outcome measure reported in all clinical trials. Given the multimodality therapy involved in neoadjuvant systemic therapy trials, both drug toxicity and surgical complications should be evaluated and recorded in detail. To date, no evidence that neoadjuvant BRAF and MEK inhibitors result in significant delays in surgery or increased post-operative complications is available.[11,14] Patients with earlier-stage disease have less systemic immunosuppression than patients with widespread metastatic disease,[22] and thus more toxicity have been observed in neoadjuvant immunotherapy trials compared with available data in patients with stage IV disease, particularly with combined ipilimumab and nivolumab treatment.[10,12,15] In some situations, these toxic effects have led to omission of treatment administration and surgical delays.[12] The INMC recommends that neoadjuvant systemic therapy trials record and report the nature of all pharmacological toxic effects, the reason for and duration of surgical delays, surgical complications, and a careful record of attribution of causality.

Drug-associated toxic effects should be reported using Common Terminology Criteria for Adverse Events.[23] The proportion of patients requiring steroids, other immunosuppressive drugs, or other supportive medications (eg, hormone replacement), doses, and the duration of use should also be recorded. Any immunosuppression-related complications, such as infections, should also be recorded. Close cooperation with colleagues from different specialities (gastroenterology, endocrinology, neurology, dermatology) is crucial because immune-related adverse events can be potentially complex and require additional consultation.

The inclusion of standard quality-of-life assessments might also be included in neoadjuvant systemic therapy trials as secondary endpoints to better understand the effect of treatment-induced toxic effects on long-term quality of life.

Panel 1: **The International Neoadjuvant Melanoma Consortium recommendations for neoadjuvant melanoma clinical trial design**

Cohort and treatment duration

- Stage III, RECIST measurable, resectable melanoma, and confined to lymph nodes
- Patients with resectable in-transit metastases or oligometastatic stage IV as unique cohorts
- No previous radiotherapy to the nodal basin
- Randomised trials stratified by stage for studies with clinical endpoints
- 6–8-week duration of neoadjuvant therapy
- Adjuvant therapy to complete 1 year of systemic therapy in total

Endpoints

- Safety: drug toxicity, need for supportive medications, surgical delays or complications, and quality-of-life assessments
- Radiological: RECIST 1.1 response evaluation at completion of neoadjuvant therapy
- Pathological: standardised reporting of pathological response with adherence to definition of pathological complete response, non-pathological response, near complete or major pathological response, and , pathologic al partial response
- Survival: relapse-free survival, event-free survival, and distant metastasis-free survival as key survival endpoints
- Exploratory translational or biomarker evaluations incorporated into all trials

Statistical considerations

- Randomised trials stratified by stage for studies with clinical endpoints

Other study considerations

- Rigorous collection of data on perioperative morbidity and ease of surgical resection
- Longitudinal biospecimen collection and subsequent analysis to provide insights into predictors of response and mechanisms of resistance

Radiographical assessment of response and relapse

Radiographical response is a key outcome in the neoadjuvant setting and might be associated with pathological response, survival, or both. Contrast-enhanced CT is the most widely used imaging modality for the assessment of treatment response and is the recommended primary imaging modality for neoadjuvant systemic therapy trials. Although fluorodeoxyglucose (FDG)-PET/CT has greater sensitivity for detecting distant metastatic disease than CT alone and has the advantage of whole-body coverage, limitations include low spatial resolution (~6 mm), poor visualisation of the lungs and liver, and overall poor specificity. Additionally, brisk immune infiltrates and granulomatous inflammatory reactions induced by immunotherapy[24] might make the interpretation of FDG-PET/CT challenging in neoadjuvant immunotherapy trials.[25] Finally, the feasibility of PET/CT to determine response in the metastatic setting at early timepoints remains unclear because it is not routinely available, and radiation concerns need to be considered because PET scans have higher radiation exposure than traditional CT scans. Ultrasound of the involved nodal basin might provide the best guide of treatment response in the neoadjuvant setting, but this modality is highly operator dependent and has not yet been systematically evaluated in the neoadjuvant systemic therapy setting. CNS imaging is imperative because of the propensity for melanoma to metastasise to the brain, including as the first site of stage IV disease or systemic therapy failure.[26,27] MRI with intravenous gadolinium-based contrast is superior to other imaging modalities because of improved soft tissue contrast and should be done if clinically feasible.

The INMC recommends CT imaging at baseline and after the completion of neoadjuvant treatment, just before surgical resection. Although numerous standardised imaging response criterion have been developed for use in clinical trials, CT-based RECIST 1.1 remains the most frequently used criteria.[17] For patients treated with neoadjuvant immunotherapy, alternative response criteria, such as the immune-related response criteria, immune-related RECIST, or immune RECIST might be considered;[28–30] however, the INMC recommends using RECIST 1.1 as the default radiological criteria used in these trials, with other criteria as secondary analyses.[31]

Following neoadjuvant systemic therapy and surgical resection, we recommend that patients should be evaluated for disease relapse by regular surveillance imaging. Scans should include imaging of the body (by CT) and the brain (by MRI when feasible, otherwise CT). Follow-up imaging is typically done every 3 months for at least 2 years after surgery, every 6 months up to 5 years, and yearly thereafter, and ideally should use the same imaging protocols across the duration of follow-up.

Although these standard imaging modalities are essential, there is also a strong rationale to identify new imaging technologies. Trials of neoadjuvant systemic therapy for melanoma with both targeted and immunotherapies have reported discordant findings between imaging and pathological responses.[11,12]

Surgical resection of disease and surgical endpoints

Upfront surgical resection is currently considered standard of care for stage IIIB, IIIC, and IIID melanoma. However, in light of advances in systemic therapy and as explained in the introduction, our recommendation is to strongly consider enrolling these patients in a clinical trial of neoadjuvant therapy. The surgical approach per se should not deviate from standard procedures involved in a therapeutic lymph node dissection for the indicated nodal basin, because most candidates for neoadjuvant systemic therapy have bulky nodal disease.

In the case of satellite or in-transit disease, resection of oligometastatic disease, or disease outside the standard draining nodal basin, the surgical and medical oncology teams might consider placing a radiographical marker (by interventional radiology) into the lesions so that they might be identified even in the setting of marked tumour reduction. This strategy not only allows for resection of residual disease if present, but also facilitates pathological assessment in the rare instance that the treated tumour bed is not readily identifiable. Although a more limited approach to nodal resection is being used in other disease types, such as breast cancer, the INMC currently recommends a complete resection of the lymph node basin. However, the need for extensive surgery in patients with deep pathological responses will be a focus in a clinical trial (NCT02977052) that is currently recruiting patients with melanoma.

Data to evaluate how neoadjuvant systemic therapy affects the ease of surgical resection has not been consistently collected across melanoma neoadjuvant trials. One study of neoadjuvant *BRAF*-targeted therapy showed an improvement in surgeon-assessed resectability in 47% of cases (and no change in the remainder cases);[14] however, anecdotally, other therapies might make the procedure more difficult. Similarly, relative complications following surgical resection have not been thoroughly studied, although early evidence suggests that surgical complications are not markedly higher compared with upfront surgery, even in the setting of treatment with corticosteroids for immune-related adverse events in the neoadjuvant setting (NCT02437279, NCT02977052, NCT02519322).[10,12,15] Nonetheless, a careful assessment of surgical feasibility before the initiation of neoadjuvant systemic therapy and complication data after surgery should be collected in all trials. The INMC Surgery Working Group is preparing a specific surgical assessment tool that addresses this point that should be implemented in future trials.

Pathological assessment of response

Since pathological response is a critical endpoint in most neoadjuvant therapy trials, the pathology team are key

members in assessing pathological response. The team should be informed when a surgical case is anticipated, and information regarding the extent of disease before treatment and the type of neoadjuvant therapy used should be included in the pathology requisition form. A thorough pathological assessment should be done and should be balanced with the collection of relevant biospecimens as indicated by treatment protocol and planned translational studies.

From a pathology standpoint, all lymph nodes (whether grossly positive or negative for tumour) should be identified and submitted for histopathological assessment. The presence of grossly matted nodes or extranodal extension of tumour should be documented in the gross description of the pathology report, together with three-dimensional measurements of the largest grossly evident metastatic deposit, since the amount of tissue submitted proceeds according to gross tumour size. In addition to standard AJCC parameters recommended for staging and clinical care,[1,18] the pathology report should describe and quantify evidence of therapy-specific effects, including the relative percentage of tumour bed occupied by viable tumour, tumoural necrosis or pigmented macrophages, inflammatory infiltrate, and fibrosis. These features contribute to the calculation of the percent residual viable tumour (ie, the ratio of surface area of residual viable tumour occupying the surface area of the total tumour bed over the surface area of the total tumour bed). The tumour bed is defined as the area of tissue occupied by viable tumour or evidence of tumoural regression (necrosis, clusters or sheets of pigmented macrophages, fibrosis or fibroinflammatory stroma, or a combination of these features).[32] If multiple lymph nodes were involved by melanoma, the percentage of residual viable tumour is the sum of the surface areas of the multiple residual viable tumour deposits divided by the sum of the surface areas of the tumour beds occupying the involved nodes.

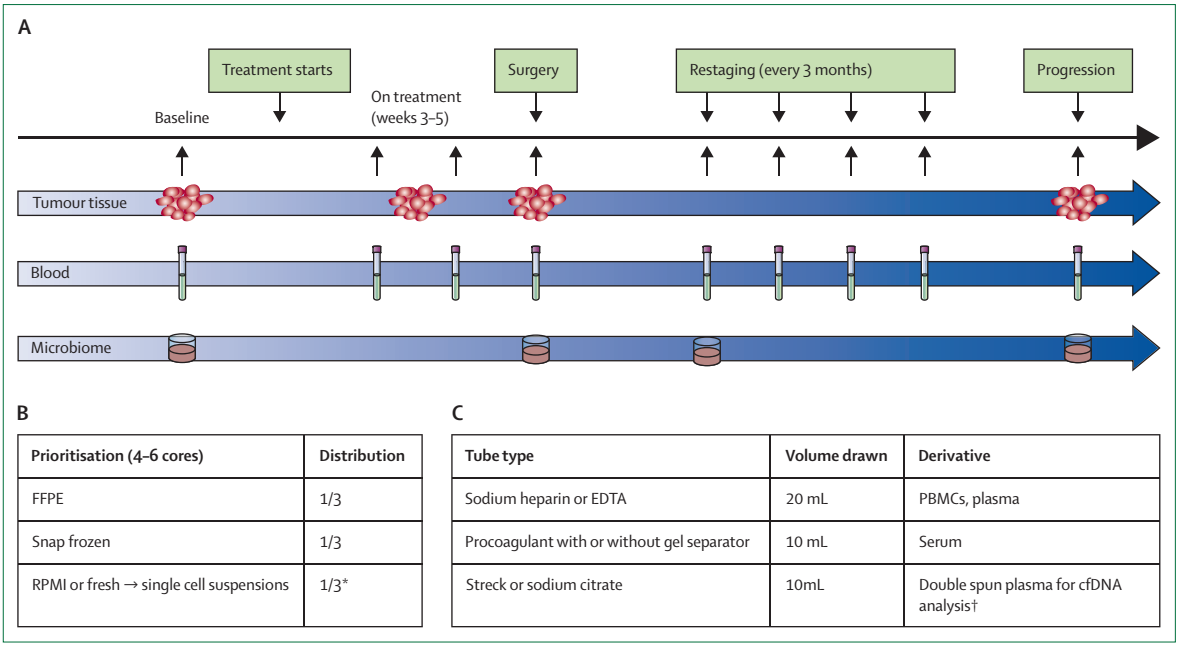
Adhering to these recommendations is most important because pathological responses have been shown to be a robust and crucial predictor of outcomes of neoadjuvant systemic therapy in other cancer types (breast cancer, head and neck squamous cell carcinomas, gastro-esophageal cancer, and anal cancer),[4–6,8,33,34] and are being actively explored as surrogate endpoints for melanoma. This determination depends strongly upon standard practices for sample processing and pathological review, and standardised methods for scoring and reporting pathological responses. The INMC Pathology Working Group published a thorough set of detailed recommendations in 2018,[32] and we provide a summary in this Policy Review.

A continuum of pathological responses has been observed in patients with melanoma treated with neoadjuvant targeted therapy or immune checkpoint therapy. Pathological complete response is defined as the complete absence of residual viable tumour. In early neoadjuvant systemic therapy trials for patients with melanoma, pathological partial response was empirically defined as 50% or less of the tumour bed occupied by viable tumour cells and pathological non-response as more than 50% of the tumour bed occupied by viable tumour cells (figure 2). Some neoadjuvant immunotherapy studies have also used a category of near pathological complete response or major pathological response that was defined as 10% or less viable tumour cells as these patients seem to have similar outcomes to patients with pathological complete response.[35,36] Additional grading systems to score residual viable tumour as a continuous variable have been proposed.[36] The INMC recommends that all neoadjuvant systemic therapy trials adhere to standardised definitions of pathological response reporting including pathological complete response, near pathological complete response or major pathological response, pathological partial response, and pathological non-response. Studies are ongoing to determine optimal thresholds for the percentage of residual viable tumour associated with long-term patient outcomes.

It is possible that the percentage of residual viable tumour associated with improved melanoma-specific survival following neoadjuvant therapy varies depending on the drugs used because of the differing mechanisms of targeted and immune therapies. Notably, different histological patterns have been observed in tumours harvested after neoadjuvant systemic therapy.[32] Continued collection, reporting, and analysis of pathological features in these trials will be essential to optimally define pathological criteria that are clinically robust surrogates of patient outcomes in the future.

Survival endpoints

Relapse-free survival is a key survival outcome showing that applied neoadjuvant and adjuvant treatment could prevent or delay disease relapse. Although relapse-free survival might be an accepted surrogate endpoint for long-term overall survival in both early and advanced melanoma settings,[37] additional mature data will continue to inform the validity of relapse-free survival and pathological response as surrogate endpoints in the neoadjuvant setting. Assessment of event-free survival is also important to include to report the data of relapse before planned surgical intervention. Event-free survival is also an important early parameter for comparison with adjuvant trials because it records early relapses occurring before adjuvant therapy, which is currently not documented in adjuvant trials and accounts for around 15% of relapses.[19] Assessment of distant metastasis-free survival is important in determining whether disease progression is limited to local recurrence or distant metastases. Notably, the validity of such endpoints for comparison of regimens will depend in part on standardised use of adjuvant therapies in trial designs. Assessment of overall survival is important, although likely to be heavily and increasingly



B

Prioritisation (4–6 cores)	Distribution
FFPE	1/3
Snap frozen	1/3
RPMI or fresh → single cell suspensions	1/3*

C

Tube type	Volume drawn	Derivative
Sodium heparin or EDTA	20 mL	PBMCs, plasma
Procoagulant with or without gel separator	10 mL	Serum
Streck or sodium citrate	10mL	Double spun plasma for cfDNA analysis†

Figure 2: **Biospecimen collection for neoadjuvant systemic therapy trials**
(A) Longitudinal sample collection schedule. (B) Tumour tissue prioritisation and distribution (ie, how tissue and blood are allocated for analyses). (C) Blood collection and prioritisation. FFPE=formalin-fixed paraffin-embedded. PBMC=peripheral blood mononuclear cell. cfDNA=cell-free DNA. RPMI= Roswell Park Memorial Institute. *Assuming 4-6 core are obtained, divided out as above; single cell suspensions would be dependent upon site capabilities and should use a minimum of 2 cores. †Might also be done using ethylenediaminetetraacetic acid (EDTA) tubes.

confounded by subsequent therapies in the metastatic setting. Every effort should be made to collect date and cause of death. The INMC recommends that these trials include assessment of landmark 1-year, 2-year, and 3-year relapse-free survival, event-free survival, distant metastasis-free survival, and overall or melanoma-specific survival as survival endpoints.

Biospecimen collection and translational research

One particularly advantageous attribute of the neoadjuvant treatment approach is the opportunity to do in-depth characterisation of high-quality biospecimens collected in the context of therapy, as well as residual tissue collected at the time of surgery. The INMC strongly recommends that all neoadjuvant systemic therapy trials include prospective translational endpoints and study designs that allow robust assessments of biospecimens derived from the study. Indeed, the primary (or secondary) endpoint of many of these trials might be associated with a change in a relevant biomarker (depending on the drug being studied and alongside other crucial endpoints studied such as radiographical and pathologic responses, as well as survival endpoints). Notably, even though these trials are typically designed to enrol a small number of patients, the yield of robust translational data per patient is very high. Thus, investment into these efforts is clearly warranted.

The INMC recommends that all neoadjuvant systemic therapy trials collect biospecimens and facilitate translational research to better understand response and resistance (primary or innate and acquired) to systemic therapy. All translational endpoints should be incorporated into either the secondary or exploratory trial objectives. Analysis of data should be in the context of pathological response (eg, pathological complete response or major pathological response *vs* pathological partial response *vs* pathological non-response) and survival, including relapse-free survival.

Biospecimen collection

The INMC recommends collecting tumour samples at baseline, early during treatment (week 3–5 of treatment depending on therapy), at surgical resection, and at relapse (figure 2). Every effort should be made to obtain tissue specimens specifically for translational evaluation, as opposed to archived samples after standard pathological processing. The preferred and ideal method of collecting tumour tissue before surgery is to obtain core biopsies (14 gauge, 3–7 cores per timepoint) because fine needle aspirates are insufficient material for the complete analyses recommended. Although most of the surgical resection specimens must be submitted for pathological assessment of response, obtaining a portion of the residual tumour and the treated tumour bed for translational studies at this timepoint is crucially important to facilitate evaluation of translational endpoints. These needs (ie, need for formal pathological assessment of resonse and need to reserve tissue for biospecimen analysis) should be balanced accordingly,

and tissue should be prioritised and distributed to maximise impact (figure 2).

In addition to collecting tumour biopsies, longitudinal blood sampling should also be done in the context of these trials, with a suggested timing of collection in parallel with tumour biopsies, and also with restaging in the adjuvant setting (figure 2). In addition to peripheral blood mononuclear cells, blood derivative samples should include sufficient serum and plasma to analyse plasma exosomal cell-free DNA (sequencing), and cytokines (figure 2; panel 2).

Besides blood and tumour samples, growing evidence suggests that the gut microbiome might have a role in response to melanoma therapy.[38,39] The pathological assessments in combination with translational information generated from blood and tumour specimens has the potential to provide invaluable insights into the mechanisms of response and resistance to therapeutic interventions being tested. Thus, collection of such samples is highly recommended, with timepoints indicated (figure 2). Additional samples might be collected based on therapeutic drugs, trial design, or specific hypotheses.

Translational research and analysis of biospecimens

INMC guidelines and recommendations for downstream analysis are outlined in panel 2, although these and additional analyses might be customised per the therapeutic target being studied. As a rule, samples should be processed as soon as possible, and then batched for analyte extraction or slide preparation and analysis to limit variability. Processing of samples should be dictated by the correlative priorities of the study to maximise yield and flexibility in downstream analyses. Resulting raw data should be stored in a Health Insurance Portability and Accountability Act-compliant, password protected site with regular, scheduled back-up of data. Relevant metadata, including pathological and radiological responses, staging and treatment information, and survival data, should be collected in the context of the clinical trial and shared within the confines of data use agreements. Ultimately, coordinated biospecimen collection and analysis with data sharing will allow tremendous insights to be gained with the potential to guide future clinical research and treatment.

Regulatory considerations

With these guidelines, the goal of the INMC is to standardise neoadjuvant clinical trial methods to create a path for regulatory review and approval of novel drugs and combinations in melanoma. This goal will be best achieved through consistent and cohesive collaboration within the context of the INMC and in close consultation with regulatory authorities around the world.

In the era of several active treatments for melanoma, the challenge for a novel drug or combination to become accessible to patients is very high nowadays. At present, several drugs are being tested in small phase 1 trials in treatment-naive patients with metastatic melanoma, with decisions to proceed into large-scale and expensive phase 3 trials made with little clinical or translational data, and almost always in unselected patients. There is a crucial need to test combinations quickly and efficiently, to understand the mechanistic reasons for their activity, and to identify predictive biomarkers that might select patients most likely to benefit from therapy, and to investigate mechanisms of resistance in a homogeneous dataset. In this context, it is logical to test promising combinations in the neoadjuvant setting and assess their effect on pathological complete response, major pathological response, or both, and relapse-free survival. In the case of breast cancer, neoadjuvant therapy has emerged as a viable regulatory path for novel drugs but has required a coordinated effort of investigators and establishment of pathological complete response as a valid surrogate endpoint for clinical benefit.[6,7] Data generated from thoughtfully designed studies with aligned approaches and endpoints, coupled with translational data from high-quality biospecimens providing insights into biological activity, are crucial, and positions the neoadjuvant setting as a platform for rapid and efficient evaluation, and prioritisation of promising novel drugs and combinations for testing in large phase 3 studies for melanoma.

Panel 2: **Biospecimen analysis prioritisation**

Prioritisation of analysis platforms is highly dependent upon sample availability, mechanism of therapeutic intervention, site capabilities, and funding. The International Neoadjuvant Melanoma Consortium makes the following recommendations for the consideration of investigators, customisable to these variables:

Tumour tissue

- Formalin-fixed paraffin-embedded: single-stain immunohistochemistry (IHC), multiplex-IHC, and extraction of analytes for other analyses as appropriate (eg, DNA, RNA)
- Snap frozen: RNA sequencing, whole-exome sequencing, T-cell or B-cell receptor sequencing and other analyses as appropriate (methylation studies, targeted sequencing panels)
- Roswell Park Memorial Institute or single-cell suspensions: flow cytometry, mass cytometry, single-cell sequencing, or use as supplement material for assays done on snap frozen samples

Blood

- Peripheral blood mononuclear cells: genomic DNA or flow cytometry
- Plasma or serum: exosomal and cytokine analyses, and cell-free DNA

Microbiome

- 16S rDNA gene sequencing or whole-genome sequencing

Conclusion

A coordinated and harmonised global effort is paramount to translate the strategy of neoadjuvant systemic therapy efficiently and effectively into optimal therapies for patients. Thus, the INMC was established to provide consensus recommendations and best practices that will facilitate and accelerate clinical and translational research. Through a strong organisational framework, the INMC is dedicated to help facilitate collaborations among international experts and across multiple disciplines to advance the field of neoadjuvant therapy for patients with melanoma. Because some patients with clinical stage III melanoma might otherwise be cured with upfront surgery and standard of care adjuvant therapy, in accordance with standard clinical trial practices, it is important to stress the investigational nature of neoadjuvant trials to patients and to ensure the consent is well informed. Additionally, the risk of delaying standard of care surgery must be mitigated by closely monitoring patients in the neoadjuvant treatment phase. Indeed, toxicity from combination ipilimumab and nivolumab in patients with clinical stage III melanoma has been higher than what has been observed for patients with stage IV disease and, thus, this risk should be limited to patients with clinical stage III disease.[10,12]

A report[10] published in 2018, has suggested improved clinical outcomes for patients with stage III melanoma treated with neoadjuvant ipilimumab with nivolumab compared with those treated with the same drugs in the adjuvant setting, albeit in a small cohort of patients. However, the need to carefully evaluate short-term clinical endpoints (relapse-free survival) and long-term endpoints (overall survival) of neoadjuvant therapy against those of adjuvant therapy remains.

As we move forward with this approach, several important questions remain. Will pathological complete response and major pathological response correlate with relapse-free survival and overall survival, and will this correlation differ according to the neoadjuvant therapeutic approach? Pathological complete response correlated with significantly improved relapse-free survival and distant metastasis-free survival with neoadjuvant targeted therapy,[11,14] and neoadjuvant immunotherapy trials.[10,12,13,15] Further, both pathological complete response and major pathological response have been associated with markedly improved 5-year survival following treatment with immunotherapy for patients with advanced melanoma.[40] However, whether treatment outcomes are different between patients with pathological complete response versus major pathological response following neoadjuvant immunotherapy, and whether specific features of the pathological response are associated with patient outcomes remain unclear.[10,12,13,15] Ultimately, results from large cohorts of patients will be needed to validate pathological (or radiographical or other features) surrogates of clinical benefit following neoadjuvant systemic therapy. Such validation will crucially depend upon standardised pathology processing, review, and scoring.[32] Integration of translational analyses with these clinical outcomes will provide important insights that can refine further therapy approaches and inform subsequent treatment decisions, thus advancing the field of melanoma management.

On the basis of input from members of the consortium, we have established several recommendations regarding clinical trial design and monitoring, as well as analysis of samples. Standardisation of trial designs, endpoints, and correlative biomarker studies are essential for acquiring data that can be compared and combined meaningfully between trials. Insights gained from this collaborative approach will probably translate into improved biomarkers of response, resistance, and possibly toxicity, as well as the identification or validation of new therapeutic targets. This approach also represents an ideal platform for testing novel therapeutic combinations, prioritise them for testing in phase 3 trials, and might ultimately help guide personalised melanoma therapy in the adjuvant setting based on the assessment of pathological response. Importantly, these results are likely to affect treatment decisions for stage IV melanoma. For example, analysing whether signatures associated with favourable outcomes in stage III melanoma are also relevant for stage IV disease.

Collaborative efforts are needed to realise precision neoadjuvant cancer care for patients with high-risk resectable metastatic melanoma. Such efforts might provide the opportunity to translate what has been learned to earlier-stage disease, and to prioritise new strategies in the metastatic setting as well. This approach will critically inform future drug and biomarker development in patients with melanoma, with insights that might be applicable to other tumour types.

Search strategy and selection criteria

We searched PubMed using the search terms "neoadjuvant" and "melanoma", and sorting by "clinical trial" under article type, from Jan 1, 2011, to July 15, 2018. Only English language publications were referenced. Additionally, data presented in abstract form at major oncology meetings (American Society of Clinical Oncology, European Society of Medical Oncology, Society for Melanoma Research, and American Academy of Cancer Research) were searched to find trials that had completed accrual and had reported data by the time of manuscript preparation in July 15, 2018.

Contributors

All authors developed, reviewed, and approved the manuscript.

Declaration of interests

RNA receives grant funding from Bristol Myers-Squibb (BMS), Merck Sharpe & Dohme (MSD), Roche-Genentech, Array Biopharma, and Iovance Biotherapeutics, outside the submitted work. AMM reports personal fees as a consultant advisor to BMS, MSD, Novartis, Pierre-Fabre, and Roche. MTT reports personal fees from Novartis for advisory board roles associated with *BRAF* testing of clinical specimens; and personal fees from Myriad Genetics, Seattle Genetics, and Galderma, outside the

submitted work. LAF receives trial research funding from BMS, MSD, Incyte, Merck Serono, and SU2C-MRA; and consultant fees from Elsevier (Via Oncology) and Hoosier Cancer Research Network, outside the submitted work. JEG reports personal fees from Novartis, MSD, BMS, Syndax, and Castle Biosciences, outside the submitted work. MAP reports consulting fees from BMS, MSD, Array BioPharma, Novartis, Incyte, NewLink Genetics, and Aduro, outside the submitted work; honoraria from BMS and Merck, outside the submitted work; and institutional Support from RGenix, Infinity, BMS, MSD, Array BioPharma, and Novartis, outside the submitted work. EAR reports travel support from NanoString and MSD, outside the submitted work. RPMS reports honoraria and service on advisory committees for Amgen, BMS, MSD, and Novartis, outside the submitted work. RJS reports grants and personal fees from Amgen and Merck, and personal fees from Novartis, Array, and Roche-Genentech, outside the submitted work. JMT is a consultant or adviser for BMS, MSD, Amgen, and Astra Zeneca; and reports grants from BMS. AME reports personal fees for a scientific advisory board or independent data monitoring committee membership from more than at last 3 years from Actelion, Bayer, BMS, CellDex, GlaxoSmithKline, HalioDX, Incyte, IO Biotech, ISA pharmaceuticals, Merck-Serono, MSD, Novartis, Polynoma, Sanofi, and Sellas. ZMAD reports personal fees from Novartis, BMS, AstraZeneca, MSD, Vaccinex, and Array; grants and personal fees from Roche-Genentech and Sanofi-Aventis; and consulting with Nanostring, all outside the submitted work. PAA has or had a consulting or an advisory role for BMS, Roche-Genentech, MSD, Array, Novartis, Merck Serono, Pierre Fabre, Incyte, Genmab, Newlink Genetics, Medimmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, and Ultimovacs; and has received research funds from BMS, Roche-Genentech, and Array. ACJvA receives grant funding from Amgen and Novartis, and was part of the advisory board or received consultancy honoraria from Amgen, BMS, Novartis, MSD, Merck-Pfizer, and Roche, outside of the submitted work. JAW is an inventor on a US patent application (PCT/US17/53.717) submitted by the University of Texas MD Anderson Cancer Center that covers methods to enhance immune checkpoint blockade responses by modulating the microbiome; is a paid speaker for Imedex, Dava Oncology, Omniprex, Illumina, Gilead, MedImmune, and BMS; is a consultant or an advisory board member for Roche-Genentech, Novartis, Astra-Zeneca, GlaxoSmithKline, BMS, MSD, and Microbiome DX; receives clinical trial support from GlaxoSmithKline, Roche-Genentech, BMS, and Novartis; has received compensation for Speaker's Bureau and honoraria from Dava Oncology, BMS, and Illumina; and has served on advisory committees for GlaxoSmithKline, Roche-Genentech, Novartis, and AstraZeneca, outside submitted work. CUB receives funding from BMS, within the submitted work, and from MSD, Novartis, and NanoString, outside the submitted work; has advisory roles for BMS, MSD, Roche, Novartis, Pfizer, GlaxoSmithKline, Lilly, Pierre Fabre, and GenMab, through payments made to the Netherlands Cancer Institute. HAT receives personal fees from Novartis; grants and personal fees from BMS and Roche-Genentech; and grants from Merck and Celegene, outside the submitted work. GVL reports personal fees as a consultant adviser to Aduro, Amgen, Array, BMS, MSD, Novartis, Oncosec, Pierre-Fabre, and Roche, outside the submitted work. EMB, RAS, RA, CA, RB, BC, AD, MF, KTF, OH, AH, JMK, SL, KM, JM, HR, MIR, VS, JFT, BAvdW, and AJS have nothing to declare.

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