Ann Surg Oncol (2022) 29:3694–3708
https://doi.org/10.1245/s10434-021-11236-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CONTINUING EDUCATION– MELANOMA

Neoadjuvant Systemic Therapy (NAST) in Patients with Melanoma: Surgical Considerations by the International Neoadjuvant Melanoma Consortium (INMC)

Alexander C. J. van Akkooi, MD, PhD[1], Tina J. Hieken, MD[2], Elizabeth M. Burton, MBA[3], Charlotte Ariyan, MD, PhD[4], Paolo A. Ascierto, MD, BC[5], Salvatore V. M. A. Asero, MD, PhD[6], Christian U. Blank, MD, PhD[1], Matthew S. Block, MD, PhD[2], Genevieve M. Boland, MD, PhD[7], Corrado Caraco, MD, PhD[5], Sydney Chng, MBBS, PhD, FRACS[8,9,10], B. Scott Davidson, MD[11], Joao Pedreira Duprat Neto, MD, PhD[12], Mark B. Faries, MD[13], Jeffrey E. Gershenwald, MD, FACS, FAAAS[3], Dirk J. Grunhagen, MD, PhD[14], David E. Gyorki, MBBS, MD, FRACS[15], Dale Han, MD[16], Andrew J. Hayes, MBBS, PhD[17], Winan J. van Houdt, MD, PhD[1], Giorgos C. Karakousis, MD, MS[18], Willem M. C. Klop, MD, PhD[1], Georgina V. Long, BSc, PhD, MBBS, FRACP, FAHMS[8,10,19,20], Michael C. Lowe, MD, MA, FACS, FSSO[21], Alexander M. Menzies, MBBS, PhD[8,10,19,20], Roger Olofsson Bagge, MD, PhD[22], Thomas E. Pennington, BSc, MBBS, MS, FRACS[8,10], Piotr Rutkowski, MD, PhD[23], Robyn P. M. Saw, MBBS, MS, FRACS[8,9,10], Richard A. Scolyer, MBBS, MD, FRCPA, FRCPath, FAHMS[8,9,10], Kerwin F. Shannon, MBBS, FRACS[8,10], Vernon K. Sondak, MD[24], Hussein Tawbi, MD, PhD[3], Alessandro A. E. Testori, MD[25], Mike T. Tetzlaff, MD, PhD[26], John F. Thompson, MD, FRACS, FACS[8,9,10,20], Jonathan S. Zager, MD, FACS[24], Charlotte L. Zuur, MD, PhD[1,27], Jennifer A. Wargo, MD[3], Andrew J. Spillane, MD[8,10,19,20], Merrick I. Ross, MD[3] on behalf of International Neoadjuvant Melanoma Consortium (INMC)

[1]Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands; [2]Mayo Clinic, Rochester, MN; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Memorial Sloan Kettering Cancer Center, New York City, NY; [5]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Napoli, Italy; [6]Azienda di Rilievo Nazionale e di Alta Specializzazione Garibaldi, Catania, Italy; [7]Massachusetts General Hospital, Boston, MA; [8]Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; [9]Royal Prince Alfred Hospital, Sydney, NSW, Australia; [10]Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; [11]Northside Hospital Cancer Institute, Atlanta, GA; [12]AC Camargo Cancer Center, São Paulo, Brazil; [13]The Angeles Clinic, Cedars Sinai Medical Center, Los Angeles, CA; [14]Erasmus MC – Cancer Institute, Rotterdam, The Netherlands; [15]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [16]Oregon Health and Science University, Portland, Oregon; [17]Royal Marsden NHS Foundation Trust, London, UK; [18]Hospital of the University of Pennsylvania, Philadelphia, PA; [19]Royal North Shore Hospital, St. Leonards, NSW, Australia; [20]The Mater Hospital, North Sydney, NSW, Australia; [21]Winship Cancer Institute, Emory University, Atlanta, GA; [22]Sahlgrenska Center for Cancer Research, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [23]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [24]Moffit Cancer Center, Tampa, Florida; [25]Skin Oncology Division, Image Regenerative Clinic, Milan, Italy; [26]University of California San Francisco (UCSF), San Francisco, CA; [27]Department of Otorhinolaryngology, Leiden University Medical Center, Leiden, The Netherlands

Alexander C. J. van Akkooi, Tina J. Hieken, and Elizabeth M. Burton shared first authorship.

Andrew J. Spillane and Merrick I. Ross shared senior authorship.

First Received: 10 August 2021
Accepted: 10 December 2021;
Published Online: 28 January 2022

A. C. J. van Akkooi, MD, PhD
e-mail: a.v.akkooi@nki.nl

ABSTRACT Exciting advances in melanoma systemic therapies have presented the opportunity for surgical oncologists and their multidisciplinary colleagues to test the neoadjuvant systemic treatment approach in high-risk, resectable metastatic melanomas. Here we describe the state of the science of neoadjuvant systemic therapy (NAST) for melanoma, focusing on the surgical aspects and the key role of the surgical oncologist in this treatment paradigm. This paper summarizes the past decade of developments in melanoma treatment and the current evidence for NAST in stage III melanoma specifically. Issues of surgical relevance are discussed, including the risk of progression on NAST prior to surgery. Technical aspects, such as the definition of resectability for melanoma and the extent and scope of routine surgery are presented. Other important issues, such as the utility of radiographic response evaluation and method of pathologic response evaluation, are addressed. Surgical complications and perioperative management of NAST related adverse events are considered. The International Neoadjuvant Melanoma Consortium has the goal of harmonizing NAST trials in melanoma to facilitate rapid advances with new approaches, and facilitating the comparison of results across trials evaluating different treatment regimens. Our ultimate goals are to provide definitive proof of the safety and efficacy of NAST in melanoma, sufficient for NAST to become an acceptable standard of care, and to leverage this platform to allow more personalized, biomarker-driven, tailored approaches to subsequent treatment and surveillance.

With the rapid evolution of effective, available therapies for advanced melanoma and their subsequent approval in the adjuvant setting, the field of neoadjuvant systemic therapy (NAST) is an area of intense interest and ongoing research—following success in other cancers where NAST is now standard practice. The International Neoadjuvant Melanoma Consortium (INMC) goal is to harmonize NAST research to accelerate discoveries and new therapeutic approaches for patients with resectable metastatic melanomas. Here, the INMC describes the current state of NAST from a surgical oncology perspective, highlighting the important role of the surgical oncologist in the clinical research team, and we also describe research strategies that may lead to better insights into tailored surgical management and improved patient outcomes, particularly for patients with stage III melanoma.

BACKGROUND

Patients with clinically detected (= macroscopic, palpable, or imaging-detected) nodal stage III melanoma represent approximately 10–20% of all melanoma cases diagnosed yearly.[1,2] Historically, therapeutic lymph node dissection (TLND) has been the cornerstone of treatment for these patients. TLND is associated with significant morbidity and frequently does not result in cure, as 20–80% of patients progress to stage IV melanoma.[1,3–5]

During the past decade, there have been enormous improvements in systemic therapies, with safety and efficacy first demonstrated for patients with stage IV melanoma. Currently, widely available effective systemic therapy can be categorized into two groups: immune checkpoint blockade (ICB) and targeted therapy (TT). ICB consists of anti-CTLA-4 antibodies (e.g., ipilimumab) and anti-PD-(L)1 antibodies (e.g., nivolumab, pembrolizumab, spartalizumab, atezolizumab) or combinations of these.[6–12] TT consists of combined BRAF & MEK inhibitors (dabrafenib & trametinib, encorafenib & binimetinib, or vemurafenib & cobimetinib) of *BRAF* mutated melanoma directed at the MAP kinase pathway.[13–20] Finally, combinations of TT and ICB or sequential approaches are also being studied, but the optimal sequence or combination is not yet clear.[21–23]

These agents have also demonstrated efficacy in the adjuvant setting by improving relapse-free survival (RFS). In patients with resected stage III melanoma (including in-transit metastases as well as regional lymph node disease), single agent ICB and dabrafenib & trametinib for patients with *BRAF*-mutated disease are approved options.[24–26] Ipilimumab is the only agent with a demonstrated overall survival (OS) benefit, which has not yet been reported for newer adjuvant therapies.[27–33] Thus, the current standard of care treatment paradigm for patients with clinically detected stage III melanoma has become surgery followed by adjuvant systemic therapy.[34,35] While these new options are effective overall, approximately one third of patients still recur within 2 years, demonstrating the need for a more aggressive and personalized approach in the neoadjuvant setting.[29,36–38]

In the slipstream of these developments, neoadjuvant systemic therapy (NAST) is being increasingly investigated, as it is for other cancers, e.g., breast, rectal, pancreas. Importantly, all NAST studies to date have been investigator-initiated phase II trials and there have not (yet) been phase III registration trials to gain regulatory approvals by FDA/EMA.

The benefits of NAST may include:

1. Improving relapse-free and distant metastasis-free survival, with the ultimate goal of improving overall/disease-specific survival compared with the adjuvant setting.
2. Identifying a cohort of patients who have drug-responsive disease and might be treated with less extensive surgery, and possibly without surgery.
3. Identifying a cohort of patients with a favorable prognosis who may not require adjuvant radiotherapy and/or systemic therapy, and tailored follow-up.
4. NAST response might give important prognostic/predictive and toxicity information, and help direct the choice of adjuvant therapy.
5. Identifying patients with resistant disease to direct towards clinical trials of novel therapies or new drug combinations.
6. Reducing tumor burden to facilitate resection and potentially lessening the morbidity of resection.
7. Model for drug development.
8. Exploring biomarkers of response and resistance with the provision of unique high-value specimens collected routinely in the NAST paradigm, including sequential tissue and blood specimens before, during, and after NAST.
9. No delay in initiating effective systemic therapy.

The INMC is a multidisciplinary group consisting of medical, surgical, and radiation oncologists, pathologists, imaging experts, translational research scientists, and patient advocates, as well as representatives of regulatory and pharmaceutical bodies. The mission of the INMC is to bring together the appropriate stakeholders to maximize collaboration, with the goal of achieving an aligned and consistent approach to demonstrating the place of NAST, including pooled analyses, in the management of patients with melanoma. The members have conducted a number of phase II trials of NAST and there is an ongoing coordinated schedule of trials investigating the neoadjuvant paradigm for patients with stage III melanoma.

The INMC seeks to harmonize considerations related to key aspects of NAST research in the context of clinical trials. For example, a state-of-science paper by Amaria et al. outlined important areas for alignment and made recommendations for trial design, target patient populations, clinical endpoints, and biospecimen collection.[39] Another INMC manuscript by Tetzlaff et al. described the detailed standardized pathologic criteria for accurately assessing response to NAST—essential to ultimately establishing pathologic response as a potential surrogate for clinical endpoints.[40] This can be best exemplified in the pooled analysis of INMC trials reported by Menzies et al. where RFS and OS outcomes following NAST were based on pathologic response.[41] Here, we focus on the role of the surgical oncologist in NAST for patients with melanoma.

CURRENT EVIDENCE FOR NAST IN STAGE III MELANOMA

NAST phase II studies of ICB and TT have been completed or are in progress.[42–47] To date there have been no phase III trials. The landmark early studies of NAST were reviewed recently in this journal.[48] Novel to the studies reported in the landmark series are some updates of these previous trials as well as the recent first report of NAST using the combination of the anti-LAG3 antibody relatlimab with nivolumab. This study showed again a high rate of pathological complete response (pCR) of 59%.[49]

In summary, to date, nearly all patients evaluated after treatment with neoadjuvant dabrafenib plus trametinib have some clinical and pathologic response. Patients who achieve pCR have an improved prognosis, but pCR is not as reliable a predictor of improved long-term outcome as it is after neoadjuvant ICB. pCR or near-pCR ($\leq$ 10% viable tumor cells) have been defined as major pathologic response (MPR). Patients with any response to ICB, but particularly those with an MPR, have a seemingly vastly improved prognosis compared with historical expectations. In the OpACIN-neo study after 17.6 months median follow-up, only 1/64 patients (2%) with pathologic response ($\leq$ 50% viable tumor cells) had recurred, vs 13/21 of the non-responders (62%).[45,50] MPR on ICB might therefore be a valid surrogate endpoint for the FDA/EMA.

At present, ASCO guidelines for systemic therapy for patients with melanoma indicate that no recommendation can be made for or against the routine use of NAST. Patients should be offered or referred for enrollment in clinical trials where possible (Type: No recommendation; Evidence quality: Low; Strength of recommendation: Not applicable).[34] The INMC supports this ASCO recommendation and aims to investigate NAST further to demonstrate its potential benefits in melanoma.

ISSUES RELEVANT TO THE SURGEON REGARDING NAST FOR STAGE III MELANOMA

Concerns from surgeons and oncologists have been raised that during evaluation and treatment with NAST, patients with resectable disease might progress to become unresectable. To date there is little evidence that this is an issue. The Amaria et al. neoadjuvant ICB study was terminated early, in part because of disease progression in 2 patients on single agent nivolumab.[43] However, within the short neoadjuvant time frame, these patients progressed

systemically as well as loco-regionally, which indicates aggressive biology and that it is likely that these patients were spared from potentially morbid and futile surgery. Similar low trends of progression to stage IV disease and of loco-regional progression beyond regional salvage were seen in the OpACIN-neo and PRADO trials.[50,51] The proportion of patients who progressed prior to surgery was even higher in the neoadjuvant study of talimogene laherparepvec (T-VEC) + surgery versus surgery (NCT02211131), in which 11/76 (14%) patients did not undergo surgery due to progression prior to surgery, and again most cases involved distant sites of disease progression.[52] However, one might argue that T-VEC is not a systemic therapy, but rather a locoregional one.

It is important to note that similar patients with aggressive tumor biology manifesting early distant metastases were not enrolled on the adjuvant therapy trials if they developed distant relapses prior to randomization. A recent report by Bloemendal et al. from a prospective phase III randomized, controlled trial of adjuvant dendritic cell therapy vs placebo (NCT02993315) demonstrated that 18% of patients showed progression on restaging imaging within 12 weeks after surgery, despite negative imaging for distant disease prior to surgery. These patients were considered screen failures and not included in the EORTC 18071, 1325/Keynote 054, Combi-AD and Checkmate 238 studies. It has to be remembered that NAST trials do not include sentinel node (SN) patients, but do include patients with aggressive tumors with early distant metastases.

Nearly all patients with *BRAF* mutated melanoma treated with NAST BRAF/MEK inhibition will respond, lowering the likelihood of progression to unresectable disease in the interval between treatment initiation and surgery. Conversely, patients treated with combined NAST of ipilimumab & nivolumab demonstrated discordance between clinical and pathological response (patients may not seem to be responding clinically and radiographically to NAST, but still demonstrate a similarly high rate of pathological responses). The pooled analysis by Menzies et al. showed a 4% rate of progression of disease prior to surgery, all in patients on immunotherapy (7/140, 5%).[41]

CLINICAL AND OPERATIVE CONSIDERATIONS FOR PATIENTS ENROLLED ON NAST CLINICAL TRIALS

The current standard of care approach to macroscopic (palpable/imaging detected) melanoma lymph node metastases is a TLND, followed by adjuvant systemic therapy. There has been debate for decades on what constitutes a TLND. For example, in the groin: is a femoral-inguinal dissection sufficient, or should it always include an iliac-obturator dissection too? Similar discussions are ongoing for the axilla and neck. High level evidence has been lacking to support either a more limited or a more extensive approach. The prospective EAGLE FM trial (NCT02166788) was designed to answer the pelvic TLND question, but the trial was terminated prematurely due to a lack of accrual.

While the standard of care is still TLND followed by systemic adjuvant therapies, the challenge is how to correctly select patients for whom radical surgery might shift from the primary treatment modality to consolidation and confirmation of pathologic treatment response after NAST. If the future of melanoma surgery evolves to be the latter in responders to NAST, the next step is to define the extent of surgery required to confirm pathological response.

Potential benefits of NAST that resonate with surgical oncologists are that it may be possible to offer the majority of patients surgery that is less morbid than upfront surgery, and secondly that the pathologic response to NAST might inform the decision for, and/or duration of, adjuvant therapy resulting in a significantly shorter duration of systemic therapy than the current adjuvant standard of 1 year. A reduction in surgical morbidity could stem from a number of potential surgical modifications in technique and lower overall costs by adopting a shorter duration of systemic therapy.

The most obvious surgical modification for a bulky yet resectable tumor which responds favorably to NAST is that the subsequent TLND could be a more straightforward procedure and potentially less morbid because of the decrease in the volume of tumor in the operative field, even if the same surgical and anatomical principles of the TLND are adhered to. Surgeons have reported that decreased tumor volume by NAST appeared to increase the ease of resection, although the data on surgical complication rates are insufficient to confirm that this translated into less surgical morbidity.[46]

An alternative future strategy that could be evaluated is the potential reduction of the extent of the TLND that is undertaken. For example, in patients with axillary lymphadenopathy, a dissection could be limited to the level(s) involved, or for patients with cervical lymphadenopathy, a more selective neck dissection could be considered. For patients with clinical inguinal lymphadenopathy, controversy still exists about the role of elective iliac and obturator nodal clearance.[3,53,54] Many patients without radiographical evidence of iliac/obturator involvement will have micro-metastatic disease identified; however, the prognostic impact of elective dissection of these nodes remains uncertain. In the future, the response to neo-adjuvant therapy may aid in this decision-making. For patients with evidence of response to therapy in inguinal nodes, the iliac/obturator dissection might be

avoided, whereas in those patients without evidence of response, more thorough regional therapy may be important to compensate and assist with regional disease control.

Developing these approaches may reduce the short-term and long-term morbidity of surgery; however, previous studies have not necessarily demonstrated a correlation between reduced anatomical extent of dissection within a regional lymph node area and a reduction in morbidity. An example of this is the MSLT-I study where patients who had macroscopic disease had similar morbidity with inguinal or ilio-inguinal dissection.[55] These MSLT-I data suggest that less morbidity might be from less burden of disease rather than less extent of surgery. However, in the NAST situation, this is complex as pCR after immune checkpoint blockade can be associated with residual bulky nodal mass. More data are required before making firm conclusions regarding impact of NAST on surgical morbidity.

Another theoretical route by which surgical morbidity of TLND could be minimized is by altering the surgical approach and intent entirely. In this approach, the role of surgery would not be clearance of all potentially affected lymph nodes within a defined lymph node basin, but the assessment of the extent of response to NAST. As a substudy of the OpACIN-neo trial, placement of a magnetic seed to identify the index biopsy-proven lymph node was studied.[45,56] This index node was then selectively removed during TLND and examined separately by the pathologist and compared with the remaining nodal basin response. This showed excellent concordance in this pilot study. The principle of identifying an index node using a fiducial (magnetic seed marker, clip, iodine seed or other form of localization) placed in the tumor prior to NAST that can be readily localized by surgeon and pathologist was utilized in the PRADO study to determine response and further tailor treatment.

Using a localization marker is particularly helpful in those patients who have achieved a significant clinical response to ensure that surgery has included the area of original disease. The adoption of such a strategy will be critical moving forward as we continue to assess NAST in less extensive, but very targeted, surgical resections.

This approach of 'personalized response-driven surgery' was adopted in the recently presented PRADO study (NCT02977052) where, following NAST, patients underwent excision of the index node and, if this demonstrated an MPR, no further surgery was recommended.[51] Of 99 patients, 60 achieved an MPR. In patients with a less robust response, TLND was recommended, resulting in only 30/99 who underwent a TLND. Currently, follow-up is too short to report the relapse rate for the nodal basin. Regardless of the limited follow-up, the PRADO study was a proof of concept study and too small to be able to recommend a departure from the current standard of care TLND. At least one large prospective phase III trial with sufficient follow-up will be required to justify changing this treatment paradigm.

RESECTABILITY IN METASTATIC MELANOMA

Although "resectability" is an eligibility issue not only in NAST clinical trials, but also in most other trials of systemic therapy in metastatic disease, "resectable" does not have a universally agreed definition among melanoma surgeons. In other malignancies, where this issue has been more formally addressed (e.g., pancreatic adenocarcinoma, oral cancer, hepatic colorectal cancer metastases) the definition is primarily based on the technical ability to remove all evident disease and have the patient survive the operation.[57–59] In melanoma, the issue is often more complicated. Whilst there are clearly cases in which all evident tumor cannot technically be removed, in a large number of other situations technical removal of all disease would be possible, but considered either futile or overly morbid. For example, extensive in-transit metastases might be able to be removed as numerous individual excisions, but early recurrence would be a predictable result. Similarly, disease clearance could be achieved by a forequarter amputation, but the morbidity of such an approach might be considered unreasonable, especially when such radical surgery would still be unlikely to be associated with cure. Noting this, three overall categories become apparent: (1) resectable, (2) technically unresectable, and (3) unresectable due to likely futility or unacceptable morbidity.

The availability of more effective systemic therapies obviously influences these somewhat subjective considerations. Where no medical option exists, the acceptability of a more aggressive or morbid surgical approach increases. By definition, NAST can only be considered in "resectable" cases. Until more analyses of resectability in metastatic melanoma are available, trial protocols should clearly state how the issue is adjudicated in subject screening. For example, eligibility determination in the context of a multi-disciplinary setting. In addition, the reasons for unresectability in any patients who progress in the preoperative period (e.g., loco-regional versus distant progression) should be reported. Surgical oncologists should consider this issue and define resectable, borderline resectable, and unresectable states.

RESPONSE ASSESSMENT TO NAST

Preoperative Imaging

Assessment of the response to NAST requires both radiographic and pathologic evaluation. Data from early

NAST studies show discordance between radiographic and pathologic assessments of response, with imaging often underestimating responses.[43–45,50] While the limitations of current imaging with either contrast-enhanced CT or fluorodeoxyglucose (FDG)—positron emission tomography (PET)/CT are well-documented in assessments of early response to systemic therapies, particularly immunotherapy, imaging remains crucial for evaluating disease progression. As stated in the previous INMC White Paper, contrast-enhanced CT is recommended at baseline and prior to surgical intervention at the completion of the neoadjuvant course.[39] While PET/CT has advantages, such as whole-body evaluation and better detection of distant disease, it is limited by thicker CT slices, poor liver evaluation, and lower specificity for melanoma; and is even more prone to picking up pseudo-progression. Contrast-enhanced CT provides the additional advantage of greater anatomic detail, which may be useful for the surgeon's assessment of resectability and extent of surgery necessary to increase the likelihood of R0 resection. Additional imaging techniques, such as fluorothymidine (FLT) PET (NCT04221438) or CD8 T cell-specific isotopes, are being evaluated in an attempt to increase radiographic-pathologic concordance of response to NAST.

Pathological Response Assessment

The INMC has developed standardized criteria to assess the pathological response to NAST in melanoma.[60] This was a key step in harmonizing and quantifying response assessment across different NAST trials and towards the ultimate goal of establishing surrogate endpoints for clinical outcomes. Different patterns of histological responses were identified and categorized. Interestingly, response to NAST can be quite heterogeneous within the same lymph node, with areas of complete response adjacent to viable tumor cells. Therefore, TLND or, in principle pending further data on safety, resection of the previously involved (index) lymph node(s), rather than percutaneous needle biopsy, is required for accurate assessment of pathological response to NAST.

CONSIDERATION OF ADJUVANT RADIOTHERAPY

Adjuvant radiotherapy (RT) following TLND is used less frequently than previously following the publication of the ANZMTG/TROG randomized trial. However, it is still considered for patients at high risk of regional relapse to improve regional control.[61] There is limited prospective data from adjuvant or neoadjuvant studies to guide this decision. Patients with a good pathological response to NAST have a lower risk of recurrence overall and therefore may safely avoid adjuvant RT. In those patients with persistent bulky lymphadenopathy following NAST (without an MPR), especially when extranodal extension and/or adjacent soft tissue disease is present, adjuvant RT should be discussed. Particular consideration should be given to options available for salvage in the setting of regional recurrence. If R0 resection is performed and adjuvant systemic therapy is planned, it may be reasonable to omit radiation and reserve it as a component of salvage therapy in the event of later regional relapse. We recommend neoadjuvant trial protocols include specific language regarding whether or not adjuvant nodal radiation is permitted.

SPECIFIC SURGICAL AND ANESTHETIC CONSIDERATIONS

The overwhelming majority of patients entered into NAST trials will have resectable disease with standard TLND at the time of entry into the study. The definitions of resectable or unresectable disease have been previously discussed above. The single arm phase II Reductor study showed that cytoreductive neoadjuvant or induction therapy with dabrafenib & trametinib was safe and highly potent, allowing radical dissection in 17/21 (81%) patients previously judged to have unresectable loco-regionally advanced melanoma.[62] For the remainder of this paper, we will focus on resectable disease.

TLND is usually well tolerated and major life-threatening complications are extremely rare, although wound related surgical morbidity is common, particularly with inguinal dissections.[63] The most common long-term surgical complications are chronic lymphedema and sensory changes.[64]

NAST itself or the disease response to NAST may cause necrosis and inflammation. Currently, it is still unclear if a dense fibrotic inflammatory response to NAST might cause a higher rate of surgery-related complications. As it is unclear when the surgeon is operating whether this is residual tumor or a fibrotic treatment response, this finding sometimes results in en-bloc removal of adjacent structures including muscle and nerves to encompass the fibrotic area, even in cases of a pCR.[40] The frequency of such extensive resection due to fibrosis from NAST is not well characterized at present. It seems to be seen more frequently in patients with isolated resistant disease who are offered surgery for oligo-metastatic disease after long-term immunotherapy treatment. It is important that surgeons work together to register such surgery-related complications in a uniform manner to determine whether there might be an increase in such complications after NAST.

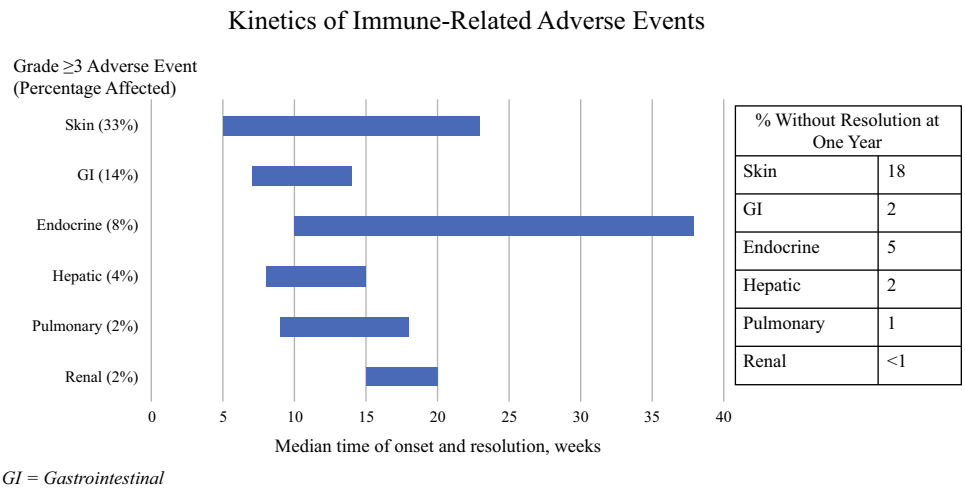

FIG. 1 Kinetics and frequency of immune-related adverse events from anti-PD-1 agents (adapted from Weber J.S. et al., J Clin Oncol 2017 Mar;35(7):785-792. https://doi.org/10.1200/JCO.2015.66.1389). *GI* gastrointestinal

As mentioned above, a potential future benefit of NAST is de-escalating the extent of the surgery, because smaller tumor residua can be removed after an MPR, hopefully with less morbidity. Some studies are attempting such surgical de-escalation, but until there is robust evidence of the safety of this novel approach, we recommend formal TLND according to the definitions used by, for example, MSLT and EORTC.[27,30,64]

However, it is not clear at this time whether the decrease in tumor volume at the time of surgery influences the rate of surgical complications, for example reported as occurring in 63% of patients, despite surgeons reporting improved resectability in approximately half the patients after undergoing NAST with TT.[46]

Another way NAST might influence surgical decision making is through the potential side effects and/or the treatment(s) given to counter adverse events (AEs) associated with NAST, particularly with ICB, which may adversely influence the patient's tolerance of general anesthesia and surgery. For example, high-dose steroids are often given to patients who develop immune related AEs (irAEs), which are well known to impair wound healing and are associated with a higher rate of anastomotic leaks in colorectal surgery.[65]

For TT, constitutional symptoms are extremely common including fever, chills, and fatigue, mostly grade 1–2. None of these AEs are likely to have an impact on the patient's progression though surgery. However, they may raise concerns during preoperative assessment, suggesting a potential secondary site of infection that will need to be excluded, and they may cause the patient to be debilitated at the time of surgery. Rashes associated with TT remain a common AE that could theoretically negatively impact upon surgery if co-localized with a surgical wound, although they are much less common with combined BRAF/MEK inhibition than with BRAF therapy alone. Hypertension is an AE that may potentially delay surgery if requiring treatment. However, in general TT is well tolerated and most medical oncologists would encourage therapy up to or even through surgery to avoid any potential flare reactions on discontinuing treatment. Other less common AEs that should be excluded preoperatively include elevation of liver enzymes, serous retinopathy, and left ventricular dysfunction.[66]

In contrast, for ICB there is potential for significant irAEs which may increase perioperative complications. The typical time frames for development of irAEs are shown in Fig. 1. Hepatic complications are common and grade 3 and above hepatotoxicity is seen in 10–20% of cases. Severe colitis is infrequent, but may be a contraindication to surgery until resolution occurs. Autoimmune endocrinopathies, particularly hypothyroidism, are frequent, but rarely pose major surgical or anesthetic risk. This can be different in rare cases of adrenal insufficiency or pan-hypopituitarism. Pneumonitis is a known irAE and could have a significant effect on anesthetic tolerance. It is critical that surgeons and anesthesiologists are aware of these potential immune-related toxicities so that appropriate preoperative evaluation is undertaken including clinical and laboratory assessment of endocrine and hepatic function. This should allow easy identification and the instigation of treatment prior to surgery. Furthermore, some irAEs develop at later time points and may occur after surgical treatment has been completed. Close multidisciplinary collaboration between the surgeon, medical oncologist, and other clinicians is warranted.

Treatment of irAEs with steroids is not a contraindication to proceeding with surgery. The immunosuppressive effect of steroids is manifested principally on T cells because of their expression of the glucocorticoid receptor, while neutrophil and B cell function is preserved. Hence, in contrast to cytotoxic chemotherapy, which may globally

decrease all immune function, most surgeons agree that proceeding with an operation is reasonable for patients who are clinically asymptomatic once steroids are being tapered. However, patients should be warned of an increased rate of infectious complications and asked to report any symptoms promptly so that evaluation can be undertaken and antibiotics commenced promptly.

There are a few rare irAEs that might preclude proceeding to an immediate operation, for instance a severe case of pneumonitis, peri- or myocarditis, or myositis might render general anesthesia unsafe. Interestingly, most patients with severe irAEs have significant pathologic responses.[67]

There is no consensus on a specific time frame between surgery and the resumption of any potential adjuvant therapy, beyond what the phase II clinical trials have mandated in their protocols. In most of the pivotal adjuvant trials, treatment was initiated within 12 weeks of surgery, after recovering from surgery and AEs. Obviously, there is less urgency to start adjuvant therapy in patients with MPR.

TRANSLATIONAL RESEARCH OPPORTUNITIES WITH NAST

One of the greatest benefits and opportunities of NAST is being able to do serial biopsies of the tumor whilst it is in situ and during treatment. This enables assessment of biomarkers that may predict response and long-term outcomes. As has been shown in other diseases, like breast cancer, endpoints such as clinical, radiographical, and pathological response are valuable ways of assessing effectiveness of NAST and can correlate with long-term survival outcomes. In breast cancer the FDA recognizes improvement of pCR rate as a biomarker for registration of new drugs or combinations.[68] To date, phase II trials of NAST in patients with stage III melanoma have confirmed that pCR is a reliable biomarker of improved response and progression-free survival.[41] In addition, patients on IT who have a near-pCR or even any pathological response seem to have improved outcomes compared with either historical controls or those without an MPR.

Additional biomarkers that have been evaluated include tumor mutational burden (TMB),[33] interferon gamma (IFN-γ) gene expression signature,[45,50] patterns of lymphoid immune infiltrates,[69] and clonal T cell repertoire.[43,44] There is no doubt that a huge range of potential biomarkers or combinations of biomarkers need evaluation and this is a key priority in designing NAST trials. An example of this is the DOMINI study (NCT04133948), currently open for accrual. In this study, patients are randomized, based on their IFN- γ gene expression signature to either receive nivolumab or nivolumab + domatinostat (HDAC inhibitor) for (IFN-γ)-high or nivolumab + domatinostat or ipilimumab + nivolumab + domatinostat for (IFN-γ)-low tumors.

DATA COLLECTION RECOMMENDATIONS

Currently, the INMC recommends use of NAST for resectable stage III melanoma only in the context of clinical trials. At the same time, we recommend that responses to NAST in those trials are reported as described by Tetzlaff et al.[40] With respect to surgical morbidity, it is important that the reporting methods are uniform.

Therefore, we have developed a number of relevant data items to be recorded in the case record forms (CRFs), which are pivotal to allow adjustments for case-mix when assessing surgical outcomes/morbidity. For example, weight and height (BMI), smoking habits, and diabetes need to be recorded. Moreover, lymphedema is considered one of the most important surgical AEs, and to adjust for the many different ways this is historically assessed, we recommend measuring the circumference of arms and legs according to the methodology used in the MSLT-II trial.[64]

Finally, we have developed 2 simple surgical questionnaires (1 preoperative, 1 postoperative) to record surgical experience (ease or difficulty of surgery) after NAST ("Appendices A and B"). The phase II DONIMI study (NCT04133948) is the first worldwide study from the INMC network using these questionnaires, which are also being tested in the smaller phase II NeoACTIVATE trial (NCT03554083) testing combinatorial NAST for both *BRAF*m and *BRAF*wt melanoma.[70] We envision that these data collection recommendations will provide useful information for surgical oncologists and will need to evolve over time.

FUTURE DIRECTIONS

Melanoma has become the prototype tumor for immunotherapy development and the NAST model has been instrumental in achieving this. In the slipstream, ICB has also been shown to be safe and effective in the treatment of non-melanoma skin cancers, such as Merkel cell carcinoma (MCC), locally advanced/metastatic cutaneous squamous cell carcinoma (SCC), and basal cell carcinoma (BCC).[71–76] This led to the first NAST trials for non-melanoma cutaneous malignancies, for instance the Checkmate 358 trial for MCC.[77] This showed disease progression in 3 patients (7.7%) prior to surgery, but also demonstrated a significant response rate with 18 patients (54.5%) having a pathological response to single-agent nivolumab x 2 doses at week 0 and week 2 (surgery at week 4).[77] As in many centers the same multidisciplinary

team cares for patients both with melanoma and non-melanoma cutaneous tumors, we strongly recommend also applying the INMC principles to NAST trials for non-melanoma skin cancer.

SUMMARY AND CONCLUSIONS

NAST has shown tremendous promise in phase II studies. NAST might have huge benefits compared with the current standard of care: TLND followed by a year of adjuvant systemic therapy. These benefits might include: tailoring the extent of surgery, reducing morbidity, personalizing or avoiding adjuvant therapy based on pathologic response, and improving survival (relapse-free, distant metastasis-free, and melanoma-specific overall survival). The phase III NADINA trial (NCT04949113) might be the first trial that leads to NAST becoming a standard of care approach. Further support for NAST might come from the enrolling phase II SWOG 1801 trial (NCT03698019) testing neoadjuvant pembrolizumab, followed by TLND and adjuvant pembrolizumab vs TLND followed by adjuvant pembrolizumab. Until then, a TLND + adjuvant systemic therapy is still recommended (Table 1).

The INMC recommends the use of NAST in clinical trials and for those trials to align with INMC principles to allow for structured outcome reporting (according to the INMC criteria for pathological assessments), collection of morbidity data (INMC questionnaires), and tissue and blood biomarker analyses to allow comparison of results across trials to facilitate rapid testing of new agents to ensure a comprehensive and complete understanding of the biological impacts of these modern therapies on various aspects of clinical outcomes. The perspective and role of the surgical oncologist is pivotal in the determination of appropriate patients for each of these trials and harmonization across disciplines to ensure a cohesive evaluation and assessment of the response to treatment and outcomes related to surgery.

APPENDIX A

TABLE 1 Overview of NAST study results

Trial	Regimen	N	pCR %	Med RFS (mo)	2-year RFS	Med FU (mo)
Targeted therapy (TT)						
Amaria et al.[42]	Dabrafenib & Trametinib	21	58	19.7		18.6
Long et al.[46]	Dabrafenib & Trametinib	35	49	23.0	43.4%	27.0
Immunotherapy (IT)						
Blank et al.[44,50]	Ipi + Nivo	10	33	NR	80%	48
Amaria et al.[43]	Nivo	12	25	NR		20
	Ipi + Nivo	11	45	NR		
Huang et al.[47]	Pembrolizumab	30	19	NR		18
Rozeman et al.[45,50]	Ipi + Nivo	86	57	NR	83.6%	24.6
Amaria et al.[49]	Rela + Nivo	30	59	NR		16.2

Ipi ipilimumab, *Nivo* nivolumab, *Rela* relatlimab, *N* number, *pCR* pathologic complete response, *Med* median, *RFS* relapse-free survival, *mo* months, *FU* follow-up

Questionnaire 1 (Baseline)

Questionnaire 1 (baseline)

- Surgeon name: ……..
- Patient identifier (first 3 digits site code, last 3 digits is patient code) _ _ _ / _ _ _
- Date of questionnaire : _ _ / _ _ / _ _ (YY / MM / DD)
- Suspected fixation or narrow margin to adjacent anatomic structure? (can be more than one)
    - o No
    - o Yes,
  - If Yes, please specify:
    - o Skin
    - o Muscle/fascia
    - o Artery
    - o Vein
    - o Nerve
- On a scale of 1-5 how difficult do you anticipate the surgery will be if done now?
  - 1 (much easier)
  - 2 (easier)
  - 3 (average)
  - 4 (more difficult)
  - 5 (much more difficult)
- Any remarks?

  ……

  ……

  ……

  ……

APPENDIX B

Questionnaire 2, Directly After Surgery (< 24 h)

Questionnaire 2 Directly after surgery (< 24 hours)

- Surgeon name: …….
- Patient identifier (first 3 digits site code, last 3 digits is patient code) _ _ _ / _ _ _
- Date of questionnaire : _ _ / _ _ / _ _ (YY / MM / DD)
- Date of surgery : _ _ / _ _ / _ _ (YY / MM / DD)
- Which basin(s) did you resect? (can be more than 1)
  - ☐ Femoral/Inguinal (below the level of the inguinal ligament)
  - ☐ Iliac/obturator (above the level of the inguinal ligament)
  - ☐ Axilla
  - ☐ Cervical
    - o Parotid
    - o Level 1
    - o Level 2
    - o Level 3
    - o Level 4
    - o Level 5
    - o Occipital
  - ☐ Popliteal
  - ☐ Epitrochlear
  - ☐ Other, specify : …….
- Did you need to resect other structures?
  - ☐ No
  - ☐ Yes

    If yes, please specify:
    - o Skin

  - Muscle/fascia
  - Artery
  - Vein
  - Nerve
- What was the (incision to close) surgical time? _ _ _ minutes
- Estimated blood loss:
  - ☐ less then
  - ☐ as expected
  - ☐ more than expected
-
- Was this quicker or longer than normal?
  - ☐ Quicker
  - ☐ Same
  - ☐ Longer
- On a scale of 1-5 how difficult was the surgery for you now?
  - ☐ 1 (much easier)
  - ☐ 2 (easier)
  - ☐ 3 (average)
  - ☐ 4 (more difficult)
  - ☐ 5 (much more difficult)
- Do you think the resection was easier or more difficult compared to patients not undergoing neoadjuvant therapy?
  - ☐ Easier
    - Why?
  - ☐ Harder
    - Why?
  - ☐ No difference
- Did you notice more bleeding than normally?
  - ☐ No
  - ☐ Yes
- Did you notice more fibrosis than normally?
  - ☐ No
  - ☐ Yes
- Did you notice any other changes than normally?

- ☐ No
- ☐ Yes, specify .....

- Did you have to make alterations in the surgery or perioperative management as a consequence of the neoadjuvant treatment?
- If so, please describe .....
- Any remarks?

ACKNOWLEDGMENT The authors gratefully acknowledge assistance from colleagues at their respective institutions.

FUNDING RAS and JFT are recipients of an Australian National Health and Medical Research Council (NHMRC) Program Grant (APP1093017), and RAS is supported by an NHMRC Practitioner Fellowship (APP1141295). RPMS is supported by the Melanoma Institute Australia. GVL is supported by an NHMRC Practitioner Fellowship and The University of Sydney Medical Foundation.

DISCLOSURE RAS has received fees for professional services from Evaxion, Provectus Biopharmaceuticals Australia, Qbiotics, Novartis, Merck Sharp & Dohme, NeraCare, AMGEN Inc., Bristol-Myers Squibb, Myriad Genetics, GlaxoSmithKline. DEG Advisory boards—Amgen, Bayer, Q Biotics; Speaker Fee—BMS. RPMS has received honoraria for advisory board participation from MSD, Novartis, and Qbiotics and speaking honoraria from BMS and Novartis. GVL is consultant advisor for Aduro Biotech Inc, Amgen Inc, Array Biopharma Inc., Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Evaxion Biotech A/S, Hexel AG, Highlight Therapeutics S.L., Merck Sharpe & Dohme, Novartis Pharma AG, OncoSec, Pierre Fabre, QBiotics Group Limited, Regeneron Pharmaceuticals Inc., SkylineDX B.V., Specialised Therapeutics Australia Pty Ltd. ROB has received institutional research grants from Bristol-Myers Squibb (BMS) and SkyLineDx, speaker honoraria from Roche and Pfizer, and has served on advisory boards for Amgen, BD/BARD, Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Novartis, Roche and Sanofi Genzyme. MCL has received honoraria for advisory board participation from BMS. JFT has received honoraria for advisory board participation from BMS Australia, MSD Australia, GSK and Provectus Inc, travel support from GSK and Provectus Inc, and support for conference attendance from Novartis. GCK PI of Investigator Initiated Trial (IIT) sponsored by Merck. AAET travel support for meetings from Agenus. PR has received honoraria for lectures and Advisory Boards from Novartis, MSD, BMS, Roche, Bayer, Pierre Fabre, Sanofi, Merck, Blueprint Medicines. PAA has/had a consultant/advisory role for Bristol Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Array, Merck Serono, Pierre-Fabre, Incyte, Medimmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Alkermes, Italfarmaco, Nektar, Boehringer-Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, Oncosec, Nouscom, Takis, Lunaphore, Seagen, iTeos. He also received research funding from Bristol Myers Squibb, Roche-Genentech, Array, Sanofi and travel support from MSD. TJH Research funding (to her institution) from Genentech, SkylineDX. JPDN Speaker for BMS and MSD. JSZ Relevant to the work are advisory board for Merck, Novartis. MSB Institutional research support from Genentech (related to this work) and from Bristol-Myers Squibb, Immune Design, Pharmacyclics, Marker Therapeutics, Sorrento Therapeutics, Transgene, Viewpoint Molecular Targeting, and Merck (unrelated to this work). Unpaid consultant for Sorrento Therapeutics, Viewpoint Molecular Targeting, and TILT Biotherapeutics. MTT Past advisory board relationships with Myriad Genetics, Nanostring, Bristol Meyers and Seattle Genetics (all closed); currently performing central pathology review for a Merck sponsored trial. AMM Advisory Boards—BMS, MSD, Novartis, Roche, Pierre-Fabre, Qbiotics. MBF Advisory boards—BMS, Novartis, Merck, Sanofi, Nektar, Pulse Bioscience. HT has received consulting fees from Merck, BMS, Novartis, Genentech, Eisai, Iovance, Karyopharm and Boxer Capital, and research funding to institution from Merck, BMS, Novartis, Genentech, GSK. CUB Advisory role: BMS, MSD, Roche, Novartis, GSK, AZ, Pfizer, Lilly, GenMab, Pierre Fabre, Third Rock Ventures. GMB: Sponsored Research Agreement, Olink Proteomics, Palleon Pharmaceuticals, InterVenn Biosciences; Scientific Advisory Board: Nektar Therapeutics, Novartis, Ankyra; Consulting: InterVenn, Merck. VKS: Dr. Sondak is a compensated consultant for Bristol Myers Squibb, Eisai, Merck, Novartis, Regeneron, and Replimune and receives research funding from Neogene Therapeutics. All other authors declare no conflicts of interest.

REFERENCES

1. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67:472–92.
2. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med*. 2006;355:1307–17.
3. van der Ploeg AP, van Akkooi AC, Schmitz PI, et al. Therapeutic surgical management of palpable melanoma groin metastases: superficial or combined superficial and deep groin lymph node dissection. *Ann Surg Oncol*. 2011;18:3300–8.
4. Madu MF, Wouters MW, Klop WM, et al. Clinical prognostic markers in stage IIIB melanoma. *Ann Surg Oncol*. 2016;23:4195–202.
5. Madu MF, Schopman JHH, Berger DMS, et al. Clinical prognostic markers in stage IIIC melanoma. *J Surg Oncol*. 2017;116:244–51.
6. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711–23.
7. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369:122–33.
8. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014;384:1109–17.
9. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373:23–34.

10. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. 2015;16:908–18.
11. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372:2521–32.
12. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372:320–30.
13. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364:2507–16.
14. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012;367:1694–703.
15. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367:107–14.
16. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380:358–65.
17. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med*. 2014;371:1877–88.
18. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*. 2015;386:444–51.
19. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015;372:30–9.
20. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19:603–15.
21. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF(V600) mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;395:1835–44.
22. Ascierto PA, Mandala M, Ferrucci PF, et al. First report of efficacy and safety from the phase II study SECOMBIT (SEquential COMBo Immuno and Targeted therapy study). *Ann Oncol*. 2020;31(Supplement 4):S1173–4.
23. Dummer R, Lebbe C, Atkinson V, et al. Combined PD-1, BRAF and MEK inhibition in advanced BRAF-mutant melanoma: safety run-in and biomarker cohorts of COMBI-i. *Nat Med*. 2020;26:1557–63.
24. USFDA: FDA grants regular approval to nivolumab for adjuvant treatment of melanoma 2017.
25. USFDA: FDA approves pembrolizumab for adjuvant treatment of melanoma.
26. USFDA: FDA approves dabrafenib plus trametinib for adjuvant treatment of melanoma with BRAF V600K or V600K mutations.
27. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med*. 2016;375:1845–55.
28. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N Engl J Med*. 2017;377:1813–23.
29. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med*. 2017;377:1824–35.
30. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med*. 2018;378:1789–801.
31. Hauschild A, Dummer R, Schadendorf D, et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600-mutant stage III melanoma. *J Clin Oncol*. 2018;36:3441–9.
32. Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial. *Eur J Cancer*. 2019;119:1–10.
33. Dummer R, Brase JC, Garrett J, et al. Adjuvant dabrafenib plus trametinib versus placebo in patients with resected, BRAF(V600)-mutant, stage III melanoma (COMBI-AD): exploratory biomarker analyses from a randomised, phase 3 trial. *Lancet Oncol*. 2020;21:358–72.
34. Seth R, Messersmith H, Kaur V, et al. Systemic therapy for melanoma: ASCO guideline. *J Clin Oncol*. 2020; 38(33):3947–3970. https://doi.org/10.1200/JCO.20.00198
35. Michielin O, van Akkooi ACJ, Ascierto PA, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30:1884–901.
36. Hauschild A, Dummer R, Santinami M, Atkinson V, Mandalà M, Kirkwood JM, Chiarion Sileni V, Larkin JM, Nyakas M, Dutriaux C, Haydon AM. Long-term benefit of adjuvant dabrafenib + trametinib (D + T) in patients (pts) with resected stage III BRAF V600–mutant melanoma: five-year analysis of COMBI-AD 2020.
37. Hauschild A, Dummer R, Schadendorf D, et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600–mutant stage III melanoma. *J Clin Oncol*. 2018;36:3441–9.
38. Long GV, Schadendorf D, Del Vecchio M, et al. Adjuvant therapy with nivolumab (NIVO) combined with ipilimumab (IPI) vs NIVO alone in patients (pts) with resected stage IIIB-D/IV melanoma (CheckMate 915). In: *Clin Cancer Res* Presented at: AACR Annual Meeting 2021; April 10–15, 2021; Virtual. Abstract CT004, 2021.
39. Amaria RN, Menzies AM, Burton EM, et al. Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium. *Lancet Oncol*. 2019;20:e378–89.
40. Tetzlaff MT, Messina JL, Stein JE, et al. Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma. *Ann Oncol*. 2018;29:1861–8.
41. Menzies AM, Amaria RN, Rozeman EA, et al. Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). *Nat Med*. 2021;27:301–9.
42. Amaria RN, Prieto PA, Tetzlaff MT, et al. Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2018;19:181–93.
43. Amaria RN, Reddy SM, Tawbi HA, et al. Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. *Nat Med*. 2018;24:1649–54.
44. Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. *Nat Med*. 2018;24:1655–61.
45. Rozeman EA, Menzies AM, van Akkooi ACJ, et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. *Lancet Oncol*. 2019;20:948–60.

46. Long GV, Saw RPM, Lo S, et al. Neoadjuvant dabrafenib combined with trametinib for resectable, stage IIIB-C, BRAF(V600) mutation-positive melanoma (NeoCombi): a single-arm, open-label, single-centre, phase 2 trial. *Lancet Oncol*. 2019;20:961–71.
47. Huang AC, Orlowski RJ, Xu X, et al. A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma. *Nat Med*. 2019;25:454–61.
48. Spillane AJ, Menzies AM, van Akkooi ACJ. The landmark series: Neoadjuvant Systemic Therapy (NAST) for stage 3 melanoma patients—a potential paradigm shift in management. *Ann Surg Oncol*. 2020;27:2188–200.
49. Amaria R, Postow M, Tetzlaff MT, et al. Neoadjuvant and adjuvant nivolumab (nivo) with anti-LAG3 antibody relatlimab (rela) for patients (pts) with resectable clinical stage III melanoma. *J Clin Oncol*. 2021;39:9502.
50. Rozeman EA, Hoefsmit EP, Reijers ILM, et al. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. *Nat Med*. 2021;27:256–63.
51. Blank CU, Reijers ILM, Pennington T, et al. First safety and efficacy results of PRADO: a phase II study of personalized response-driven surgery and adjuvant therapy after neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in resectable stage III melanoma. *J Clin Oncol*. 2020;38(15):10002.
52. Dummer R, Gyorki D, Hyngstrom J, et al. Primary 2-year (yr) results of a phase 2, multicenter, randomized, open-label trial of efficacy and safety for talimogene laherparepvec (T-VEC) neoadjuvant (neo) treatment (tx) plus surgery (surg) vs surg in patients (pts) with resectable stage IIIB-IVM1a melanoma. *Ann Oncol*. 2019;30(suppl 5):v851–934.
53. Egger ME, Brown RE, Roach BA, et al. Addition of an iliac/obturator lymph node dissection does not improve nodal recurrence or survival in melanoma. *J Am Coll Surg*. 2014;219:101–8.
54. Henderson MA, Gyorki D, Burmeister BH, et al. Inguinal and ilio-inguinal lymphadenectomy in management of palpable melanoma lymph node metastasis: a long-term prospective evaluation of morbidity and quality of life. *Ann Surg Oncol*. 2019;26:4663–72.
55. Faries MB, Thompson JF, Cochran A, et al. The impact on morbidity and length of stay of early versus delayed complete lymphadenectomy in melanoma: results of the Multicenter Selective Lymphadenectomy Trial (I). *Ann Surg Oncol*. 2010;17:3324–9.
56. Schermers B, Franke V, Rozeman EA, et al. Surgical removal of the index node marked using magnetic seed localization to assess response to neoadjuvant immunotherapy in patients with stage III melanoma. *Br J Surg*. 2019;106:519–22.
57. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol*. 2006;13:1035–46.
58. Rocha FG, Helton WS. Resectability of colorectal liver metastases: an evolving definition. *HPB (Oxford)*. 2012;14:283–4.
59. Kreeft A, Tan IB, van den Brekel MW, et al. The surgical dilemma of 'functional inoperability' in oral and oropharyngeal cancer: current consensus on operability with regard to functional results. *Clin Otolaryngol*. 2009;34:140–6.
60. Tetzlaff MT, Adhikari C, Lo S, et al. Histopathological features of complete pathological response predict recurrence-free survival following neoadjuvant targeted therapy for metastatic melanoma. *Ann Oncol*. 2020;31:1569–79.
61. Henderson MA, Burmeister BH, Ainslie J, et al. Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. *Lancet Oncol*. 2015;16:1049–60.
62. Blankenstein SA, Rohaan MW, Klop WMC, et al. Neoadjuvant cytoreductive treatment with BRAF/MEK inhibition of prior unresectable regionally advanced melanoma to allow complete surgical resection, REDUCTOR: a prospective, single arm, open-label phase II trial. *Ann Surg*. 2021;274:383–9.
63. van Akkooi AC, Bouwhuis MG, van Geel AN, et al. Morbidity and prognosis after therapeutic lymph node dissections for malignant melanoma. *Eur J Surg Oncol*. 2007;33:102–8.
64. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med*. 2017;376:2211–22.
65. Eriksen TF, Lassen CB, Gogenur I. Treatment with corticosteroids and the risk of anastomotic leakage following lower gastrointestinal surgery: a literature survey. *Colorectal Dis*. 2014;16:O154–60.
66. Dickson D, Johnson J, Bergan R, et al. The master observational trial: a new class of master protocol to advance precision medicine. *Cell*. 2020;180:9–14.
67. Eggermont AMM, Kicinski M, Blank CU, et al. Association between immune-related adverse events and recurrence-free survival among patients with stage III melanoma randomized to receive pembrolizumab or placebo: a secondary analysis of a randomized clinical trial. *JAMA Oncol*. 2020;6:519.
68. Pathological complete response in neoadjuvant treatment of high-risk early-stage breast cancer: use as an endpoint to support accelerated approval by United States Food and Drug Administration: Center for Drug Evaluation and Research; 2020: FDA-2012-D-0432.
69. Helmink BA, Reddy SM, Gao J, et al. B cells and tertiary lymphoid structures promote immunotherapy response. *Nature*. 2020;577:549–55.
70. Hieken TJ, Price DL, Piltin MA, et al. Surgeon assessment of the technical impact of neoadjuvant systemic therapy on operable stage III melanoma. *Ann Surg Oncol*. 2021;29(2):780–786. https://doi.org/10.1245/s10434-021-11112-9
71. D'Angelo SP, Russell J, Hassel JC, et al. First-line (1L) avelumab treatment in patients (pts) with metastatic Merkel cell carcinoma (mMCC): preliminary data from an ongoing study. Abstract 9530. *J Clin Oncol Suppl*. 2017.
72. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:1374–85.
73. Levy S, Aarts MJB, Eskens F, et al. Avelumab for advanced Merkel cell carcinoma in the Netherlands: a real-world cohort. *J Immunother Cancer*. 2020;8:e001076.
74. Nghiem P, Bhatia S, Lipson EJ, et al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. *J Clin Oncol*. 2019;37:693–702.
75. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. *N Engl J Med*. 2016;374:2542–52.
76. Migden MR, Khushalani NI, Chang ALS, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. *Lancet Oncol*. 2020;21:294–305.
77. Topalian SL, Bhatia S, Amin A, et al. Neoadjuvant nivolumab for patients with resectable Merkel cell carcinoma in the CheckMate 358 Trial. *J Clin Oncol*. 2020;38:2476–87.