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Optimal systemic therapy for high-risk resectable melanoma

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Competing interests

A.M.M.E. has served on data safety monitoring boards for Biocad, BioNTech, GlaxoSmithKline (GSK), Novartis and Pfizer; and has served on scientific advisory boards for Agenus, Biocad, BioInvent, CatalYm, Clover, Ellipses, Galecto, GSK, IO Biotech, Merck, Nektar, Sairopa, Sellas, SkylineDx, TigaTx and TTxDiscovery. O.H. has received speaker's bureau from Bristol Myers Squibb (BMS), Novartis, Pfizer and Sanofi/Regeneron; is a consultant for Aduro, Akeso, Alkermes, Amgen, Beigene, Bioatla, BMS, GSK, lmmunocore, ldera, lncyte, lnstilBio, lovance, Janssen, Merck, NextCure, Novartis, Pfizer, Roche/Genentech, Sanofi/Regeneron, Seattle Genetics, Tempus and Zelluna; and is at a contracted research institution for Arcus, Aduro, Akeso, Amgen, Bioatla, BMS, CytomX, Exelixis, GSK, lmmunocore, ldera, lncyte, lovance, Merck, Moderna, Merck-Serono, NextCure, Novartis, Pfizer, Roche/Genentech, Rubius, Sanofi/Regeneron, Seattle Genetics, Taiga, Torque and Zelluna. G.V.L. is a consultant/adviser for Agenus, Amgen, Array Biopharma, Boehringer Ingelheim, BMS, Evaxion Biotech, Hexal AG (Sandoz Company), Highlight Therapeutics, Merck Sharpe & Dohme, Novartis, OncoSec, Pierre Fabre, Provectus, Qbiotics and Regeneron. J.J.L. has served on data safety monitoring boards for Abbvie, Immutep and Evaxion. He has served on scientific advisory boards without equity consideration for 7 Hills, Bright Peak, Exo, Fstar, Inzen, RefleXion and Xilio, and with equity consideration for Actym, Alphamab Oncology, Arch Oncology, Kanaph, Mavu, NeoTx, Onc.AI, OncoNano, Pyxis, Stipe and Tempest. He has held consultancy roles with compensation for Abbvie, Alnylam, Bayer, BMS, Castle, Checkmate, Codiak, Crown, Day One, Duke St, EMD Serono, Endeavor, Flame, Genentech, Gilead, HotSpot, Ikena, Immunocore, Incyte, Janssen, Kadmon, Macrogenics, Merck, Mersana, Nektar, Novartis, Partner, Pfizer, Regeneron, Servier, STINGthera, Synlogic and Synthekine. He has received research support (all to his institution for clinical trials unless noted) from AbbVie, Astellas, AstraZeneca, BMS (for both investigator-initiated and industry trials), Corvus, Day One, EMD Serono, Fstar, Genmab, Ikena, Immatics, Incyte, Kadmon, KAHR, Macrogenics, Merck, Moderna, Nektar, NextCure, Numab, Palleon, Pfizer (investigator-initiated and industry trials), Replimmune, Rubius, Servier (investigator-initiated trials), Scholar Rock, Synlogic, Takeda, Tizona, Trishula and Xencor. He holds intellectual property on the following patents: Serial #15/612,657 (Cancer Immunotherapy); PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: Diagnostic, Prognostic and Therapeutic Uses Thereof).

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Abstract

Immunotherapy with immune-checkpoint inhibitors and molecularly targeted therapy with BRAF inhibitors were pioneered in the setting of advanced-stage, unresectable melanoma, where they revolutionized treatment and considerably improved patient survival. These therapeutic approaches have also been successfully transitioned into the resectable disease setting, with the regulatory approvals of ipilimumab, pembrolizumab, nivolumab, and dabrafenib plus trametinib as postoperative (adjuvant) treatments for various, overlapping groups of patients with high-risk melanoma. Moreover, these agents have shown variable promise when used in the preoperative (neoadjuvant) period. The expanding range of treatment options available for resectable high-risk melanoma, all of which come with risks as well as benefits, raises questions over selection of the optimal therapeutic strategy and agents for each individual, also considering that many patients might be cured with surgery alone. Furthermore, the use of perioperative therapy has potentially important implications for the management of patients who have disease recurrence. In this Viewpoint, we asked four expert investigators and medical or surgical oncologists who have been involved in the key studies of perioperative systemic therapies for their perspectives on the optimal management of patients with high-risk melanoma.

For which patients does the benefit of systemic perioperative therapy, as opposed to treatment only upon disease recurrence, outweigh the risks?

Georgina V. Long. To answer this question, it is important to first define high-risk resectable melanoma and what is systemic perioperative therapy. High-risk resectable melanoma is best defined using the AJCC 8th edition staging system[1] and includes stage III disease, particularly substages IIIB, IIIC and IIID, as well as the rarer entity of resectable stage IV disease and, more recently, stage IIB and IIC melanomas. Even after all melanoma has been completely removed through surgery and radiographic assessment shows no evidence of residual disease, these patients still have a very high risk of recurrence (for example, approximately 70–80% in those with stage IIID melanoma)[2,3]. Most recurrences occur in the first 2 years following surgery; however, a significant risk of recurrence remains beyond this point. In an effort to reduce this risk, systemic perioperative therapy can be given after complete resection of melanoma, in which case it is termed ‘adjuvant’ therapy, or prior to surgery, termed ‘neoadjuvant’ therapy.

Phase III trials of adjuvant immune-checkpoint inhibition with the anti-PD-1 antibodies pembrolizumab and nivolumab have demonstrated substantial improvements in recurrence-free survival (RFS) when compared with placebo (in the case of pembrolizumab[2,4,5]) and when compared with ipilimumab (in the case of nivolumab[6]) (TABLE 1). Overall, the

risk of recurrence is reduced by approximately 40% for stage III melanoma[2] and by around 35–40% for stage II disease[4,5] as compared with surgery alone. Similarly, in the phase III COMBI-AD trial involving patients with stage III *BRAF*^{V600}-mutant melanoma, adjuvant therapy with the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib substantially improved RFS compared with placebo, with a reduction in the risk of recurrence of almost 50%[3]. Importantly, similar reductions in the risk of distant metastasis were also observed across studies in the setting of resectable stage III–IV disease, and mature data are awaited for stage II disease (TABLE 1). Lastly, the randomized phase II IMMUNED study of adjuvant immunotherapy in patients with completely resected stage IV melanoma showed impressive RFS improvements with either nivolumab or nivolumab plus ipilimumab (at standard doses (TABLE 1)) compared with placebo[7].

Neoadjuvant therapy (both BRAF-targeted treatment and anti-PD-1-based immunotherapy) has shown an unprecedented effect on RFS in patients who have a pathological complete response (pCR)[8], defined as the complete absence of residual viable tumour cells[9]. The results with immune-checkpoint inhibitors (ICIs) are especially compelling: a pooled analysis of multiple phase II studies conducted by the International Neoadjuvant Melanoma Consortium (INMC) demonstrated a 2-year RFS above 95% for those with a major pathological response (MPR; complete or near-complete response with ≤10% viable tumour cells[9]) after only 6–8 weeks of ICI treatment[8]. Importantly, >60% of patients with resectable stage III–IV melanoma have an MPR to anti-PD-1 antibodies combined with either anti-CTLA4 or anti-LAG3 antibodies[10,11] (TABLE 1).

On the basis of the available data from the trials outlined above, nearly all subgroups of patients with resectable stage IIB–C, III or IV melanoma benefit from 12 months of adjuvant systemic therapy with a reduction in the risks of recurrence and distant metastases (that is, prevention of progression to stage IV disease). Thus, the question of perioperative drug therapy comes down to an assessment of the risk of toxicities versus the absolute potential benefit. Currently, neoadjuvant therapy has not been approved for use outside of well-designed clinical trials.

In general, patients with major contraindications to therapy, for example, those with pre-existing clinically significant autoimmune disease prohibitive to ICI-based immunotherapy or patients with substantial comorbidities and/or poor social support for whom toxicities could result in worse outcomes compared with a recurrence of melanoma, may forgo adjuvant therapy. For these patients, systemic therapy can be considered if they develop unresectable recurrent disease, at which point the risk to benefit ratio of therapy becomes easier to quantify — the risk of toxicity is easier to minimize and the benefit can be assessed more quickly (within ~12 weeks) given that the treatment can be tailored according to radiological response when a patient has scan-visible melanoma (which is not possible in the adjuvant setting). For example, an elderly patient with comorbidities might only need 6–12 weeks of therapy to achieve an excellent response with shrinkage of the metastases (as measured clinically or on radiological imaging). This is in contrast to the adjuvant setting, where patients receive 12 months of therapy and one only knows that the therapy has worked if there is a continued absence of recurrence over time.

Notably, data demonstrating an improvement in overall survival (OS) with adjuvant therapy compared with no adjuvant therapy remain insufficient. Indeed, no OS benefit was observed in the CheckMate 238 study of adjuvant nivolumab versus ipilimumab[6] (TABLE 1). Importantly, adjuvant ipilimumab did demonstrate an OS benefit over placebo in the phase III EORTC 18071 trial[12], although this study was conducted in the era when effective therapies for recurrent melanoma were not widely available. Similarly, the first 3 years of recruitment to the COMBI-AD trial of adjuvant dabrafenib plus trametinib, which demonstrated an early OS benefit relative to placebo[3] (TABLE 1), was conducted in an era of ineffective therapies. In the phase III KEYNOTE-054 trial of adjuvant pembrolizumab versus placebo, patients were allowed to cross over to active therapy on melanoma recurrence in an effort to answer the question of whether to treat ‘now versus later’. However, only 155 of 298 patients with disease recurrence crossed over from the placebo arm, and the results of the OS analysis are still awaited[13]. With the now widely available effective systemic therapies for unresectable stage IV melanoma, and the durable melanoma control observed over many years in this population (5-year OS of ~40–50% with most therapies)[14–16], forgoing adjuvant systemic therapy and only treating at the time of relapse with unresectable disease might achieve the same OS outcomes obtained with adjuvant therapy.

However, what is not factored into this argument for treating only at recurrence is the quality of life. Preventing stage IV melanoma might prevent serious psychological distress and/or debilitating symptoms of metastatic disease: a patient who presents with melanoma recurrence in the brain and is subsequently cured by systemic therapy but is left with a neurological deficit would benefit from prevention of the metastatic recurrence in the first place with adjuvant therapy.

The question of what adjuvant therapy for which patient, including the choice between BRAF-targeted therapy and immunotherapy, requires a multi-factorial approach; patient-related factors, drug therapy factors and disease-related factors, including the melanoma substage and absolute risk of recurrence, along with the histological subtype, must be considered together. Other than *BRAF*^{V600} mutation for BRAF-targeted therapies, no highly sensitive or specific tissue biomarkers are available to assist in the selection of therapy. Important patient and drug factors include comorbidities, the risk and types of toxicities, and the patient’s perception of potential benefit as well as their personal attitude towards risk. Of note, toxicities can be reversible (including almost all BRAF-targeted therapy toxicities and the majority of immune-related toxicities) or irreversible (such as endocrinopathies induced by ICIs). Therefore, the perception might be that patients with a low absolute risk of recurrence will benefit from an adjuvant therapy approach that has a low risk of irreversible toxicities, such as BRAF-targeted therapy, although a growing body of both clinical and translational evidence indicates that survival outcomes are improved if ICIs are given before BRAF-targeted therapy in patients with stage IV melanoma[17–19]. Importantly, the *BRAF*-mutant subgroup of patients in the KEYNOTE-054 trial had a similar hazard ratio for the reduction in recurrence risk with pembrolizumab to that observed for dabrafenib plus trametinib in COMBI-AD (TABLE 1), although the gap between the Kaplan–Meier curves for the pembrolizumab and placebo groups is continuing to widen with time[2] — a pattern that differs from BRAF-targeted therapy[3].

Jason J. Luke. Considerations around perioperative therapy, whether neoadjuvant or adjuvant, must weigh the risks of recurrence versus toxicity, and this same consideration now applies across patients with disease ranging from deep primary melanomas to palpable nodal metastases and even completely resected metastatic disease. The field lacks robust data to adequately determine whether OS is improved through early intervention with systemic therapies as compared with treatment at the time of metastatic relapse. Data from small numbers of patients involved in certain trials have begun to indicate that median outcomes might be similar with either approach[13,20] — therein is the rub: individual patients are, of course, not the median and either have or do not have disease recurrence. Some patients with recurrence rapidly deteriorate and die from melanoma despite having multiple treatment options. However, beyond this variability in outcomes, patients have consistently reported that living with the risk of melanoma recurrence is a psychological harm that they rank second only to an actual diagnosis of recurrent disease and higher than the risk of toxicities[21,22]. In this context, then, I believe that, after discussion of risks and benefits, patients whose highest priority is minimizing the risk of melanoma recurrence should be offered perioperative therapy when indicated based on proven therapeutic benefit in rigorous randomized studies or through participation in well-designed clinical trials with this goal.

Ultimately, do you believe the neoadjuvant or adjuvant approach to be superior and why?

Alexander M. M. Eggermont. As described above, perioperative systemic therapy can be adjuvant, neoadjuvant or both. In the field of melanoma, we have rapidly established that adjuvant therapy with drugs that were originally approved in the advanced-stage, unresectable disease setting all provide a benefit in terms of RFS and distant metastasis-free survival (DMFS) in patients with resected stage III–IV disease[2,3,6,12] (TABLE 1). An OS benefit compared with placebo has also been established for adjuvant ipilimumab in EORTC 18071 (REF.[12]) and for adjuvant dabrafenib plus trametinib in COMBI-AD[3]. The situation is slightly more complex for anti-PD-1 antibodies. Although nivolumab improved RFS and DMFS when tested against the active comparator ipilimumab in CheckMate 238, the 6% DMFS benefit at 4 years did not translate into a significant OS benefit[6]. Pembrolizumab was compared with placebo in KEYNOTE-054 and provided an absolute DMFS benefit of 16% at 3.5 years[2], which may well translate into an OS benefit, but the maturity of the OS data is still years away. In the IMMUNED trial involving patients with resected stage IV melanoma, the combination of adjuvant nivolumab 1 mg/kg plus ipilimumab 3 mg/kg administered every 3 weeks was shown to be superior to single-agent nivolumab (3 mg/kg every 2 weeks) in terms of RFS, with both immunotherapy regimens being superior to placebo[7]. A different schedule of nivolumab 240 mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks did not show a benefit over adjuvant nivolumab monotherapy (480 mg every 4 weeks) for patients with IIIB–IV disease in the CheckMate 915 trial, potentially owing to suboptimal dosing of ipilimumab[23]. The first phase III trial of adjuvant immunotherapy conducted in patients with sentinel node-negative stage IIB–C melanoma, KEYNOTE-716, demonstrated a significant improvement in RFS with pembrolizumab versus placebo[4,5], which led to FDA supplementary approval of pembrolizumab for this population in 2021 (TABLE 1).

Despite these advances in the adjuvant setting, the revolution in neoadjuvant ICI therapy is what currently makes all the headlines. The experience with neoadjuvant systemic therapy with anti-PD-1 antibodies alone, and especially in combination with anti-CTLA4 or anti-LAG3 antibodies, in patients with melanoma and macroscopic regional lymph node involvement (stage IIIB–D) and/or resectable distant metastases (stage IV) has been nothing short of sensational, regardless of *BRAF* mutation status (TABLE 1). In the seminal OpACIN study, Blank et al.[24] showed that two cycles of neoadjuvant nivolumab 1 mg/kg plus ipilimumab 3 mg/kg resulted in a pathological response rate (pRR) of 78%. Importantly, they also demonstrated that this neoadjuvant therapy induced much greater expansion of tumour-resident T cell clones already present in the blood at the start of treatment as well as expansion of newly detected T cell clones, resulting in a greater clonal variety, compared with adjuvant nivolumab plus ipilimumab[24]. These findings provided the biological understanding for the superior outcome with neoadjuvant anti-PD-1 and anti-CTLA4 therapy. The substantial toxicities associated with this combination therapy were greatly reduced by 'flipping' the doses (that is, using nivolumab 3 mg/kg plus ipilimumab 1 mg/kg), while retaining an 80% pRR, with pCR (100% necrosis) or pathological near-complete response (pnCR; >90% necrosis) rates of 47% and 23%, respectively, as demonstrated in the randomized OpACIN-neo trial[25]. Moreover, 2-year RFS was 84% for all patients and 97% for patients with a pathological response[10]. We have never ever seen this kind of results in this patient population! In the pooled analysis by the INMC, Menzies et al.[8] confirmed a pCR rate of 43% with neoadjuvant nivolumab plus ipilimumab (versus 20% with anti-PD-1 antibody monotherapy), with 2-year RFS of 96% in patients with a pathological response. In patients with *BRAF*-mutant melanoma, combined BRAF and MEK inhibition induced a similar pCR rate (47%) but 2-year RFS was very much inferior: 79% for patients with a pCR, but 0% for those with a pathological partial response compared with 100% and 95%, respectively, with neoadjuvant ICI therapy[8].

Another major benefit of the high pRRs achieved with neoadjuvant anti-PD-1 and anti-CTLA4 therapy was demonstrated in the PRADO trial by Blank and colleagues[26]. In this study involving 99 patients with macroscopic stage III melanoma, the largest involved lymph node was marked by ultrasound-guided insertion of a tiny magnetic marker and only the marked lymph node was removed for pathological response evaluation after two cycles of neoadjuvant nivolumab plus ipilimumab. Patients with a pCR or pnCR did not undergo completion lymph node dissection (CLND) and did not receive any further adjuvant therapy; 60 (61%) patients had such a response, 58 (97%) of whom did not undergo CLND, resulting in fewer surgery-related adverse events[26]. Patients with a pathological partial response underwent CLND but did not receive adjuvant therapy. Longer follow-up assessment of RFS is needed to confirm the suitability of this approach given that most other neoadjuvant studies included a planned period of adjuvant therapy for all patients. Nevertheless, neoadjuvant therapy has the promise to reduce surgical and adjuvant interventions, and thus adverse events and morbidity, while potentially also increasing cures.

Similar observations with other ICI-sensitive tumour types are of major importance. In 20 patients with localized microsatellite instability-high (MSI-H) and/or mismatch repair-deficient (dMMR) colorectal cancer, Chalabi et al.[27] demonstrated that two cycles of neoadjuvant nivolumab plus ipilimumab resulted in a 100% pRR, including 12 pCRs (60%)

and 7 pnCRs (35%). This is obviously another practice-changing observation: neoadjuvant therapy instead of upfront surgery is likely to become the rule for treating patients with these tumours. Moreover, endoscopic monitoring of response, in lieu of pathological analysis of surgical specimens, will probably be helpful for deciding which patients can safely avoid surgical resection. The initial data suggest that this could be the case for almost all of these patients. Similarly, in a study in which 32 patients with localized MSI-H/dMMR oesophageal or gastric adenocarcinoma received up to six cycles of neoadjuvant nivolumab plus ipilimumab, André et al.[28] reported a 76% pRR, including a 59% pCR rate and a 14% pnCR rate, among 29 evaluable patients who underwent surgery. These results indicate that surgical resection could also potentially be avoided in patients with MSI-H/dMMR gastroesophageal cancers. In the context of muscle-invasive bladder cancer, the objective of clinical research on novel neoadjuvant treatments is to improve the long-term outcome of patients compared with the use of standard-of-care chemotherapy. Neoadjuvant immunotherapy was initially used to determine the benefit of administering short courses of ICI monotherapy before radical cystectomy. Among the pivotal studies of this approach, PURE-01 revealed a pCR rate of 37% with three preoperative cycles of pembrolizumab[29]. Similar findings have been reported with other anti-PD-1/PD-L1 antibodies either alone or combined with anti-CTLA4 antibodies[30–32]. Promising results with neoadjuvant ICI therapy have also been reported in various other settings, including locally advanced cutaneous squamous cell carcinoma, non-small-cell lung cancer, and head and neck cancer[33,34].

In summary, neoadjuvant immunotherapy's future is now and melanoma is leading the way[34]! We are at a defining moment of a paradigm change. Ultimately, I firmly believe that neoadjuvant strategies will be superior in terms of multiple outcome parameters. The data on neoadjuvant ICI therapy seem to indicate superior RFS and OS in patients with resectable stage III–IV melanoma compared with surgery alone and potentially also compared with adjuvant ICI therapy. Moreover, the neoadjuvant approach offers the potential to substantially reduce the extent of surgery by enabling the omission of CLND and, in some patients, the resection of distant metastases. Importantly, all of these benefits can be achieved with a shorter duration of systemic treatment[10,24–26,34].

Omid Hamid. Ultimately, I also believe that the ideas behind neoadjuvant therapy will de facto render it superior to adjuvant therapy — at least in the academic arena. We have reached a breaking point at which therapeutic options are increasing in the adjuvant and metastatic settings, and direction is lacking. Clinical trials of adjuvant therapies combining anti-LAG3 antibodies, pegylated interferon, BRAF and MEK inhibitors, and personalized vaccines with ICIs are in process and threaten to increase the complexity of decision-making in this setting. Answers are not forthcoming. Compounding the complexity is the fact that, currently, no clarity exists in the metastatic arena to translate into adjuvant strategies. The DREAMseq trial[17] was a triumph in that it demonstrated the superiority of nivolumab plus ipilimumab over BRAF-targeted therapy as the initial treatment for patients with metastatic *BRAF*-mutant melanoma; however, the debate over the optimal sequencing of these treatments has been replaced, after the reporting of initial results from the RELATIVITY-047 trial[35], with one regarding the choice of combining anti-CTLA4 versus anti-LAG3 antibodies with PD-1 inhibitors. Pegylated interferon and VEGF-

targeted combination approaches with anti-PD-1 antibodies are also knocking at the door. These questions currently remain unanswered in the metastatic setting and would require mammoth trials in the (neo) adjuvant space. We are presently falling short for our patients.

In this current landscape, neoadjuvant therapy is an educator, a redeemer and a saviour. We have failed to identify appropriate predictive markers to assist with decision-making for even first-line therapy at patient presentation (regardless of whether this relates to the adjuvant, unresectable disease or metastatic setting) since the advent of PD-L1 immunohistochemistry. Although we know that a high tumour mutational burden (TMB) is predictive of a favourable response to ICIs, this biomarker has not emerged as a definitive ally. Neoadjuvant therapy provides us with the ability, in a controlled environment, to utilize pretreatment and post-treatment tissues, circulating tumour DNA, next-generation sequencing data, patient profiles, and so on, to develop predictive and prognostic biomarkers that can be incorporated into prospective trials.

Once curated, this ‘library’ of information, which could never be accomplished in another setting, can illuminate the path towards smaller trials, gating for predetermined success through the selection of biomarker-identified exquisite responders. Although the neoadjuvant paradigm was not conceived in the field of cutaneous oncology, the expertise in immuno-oncology stems from this arena. Melanoma therapy educates and, indeed, informs treatment for all solid tumours.

Through the repurposing of therapeutic agents that ‘failed’ in the metastatic setting, neoadjuvant trials can deliver another major educational pearl. For example, the disappointments with locally delivered therapy, such as STING agonists, oncolytics, electroporated factors and various other injectable agents, on a broad basis might lie in their need to be used when tumour burden is at its lowest. These agents provide tolerable treatment options and high response rates and could potentially achieve improvements in RFS, DMFS and OS if applied in the neoadjuvant setting. Future trials of perioperative therapy will include patients with high-risk stage II melanoma, possibly doubling the number of individuals at risk of substantial toxicities. Thus, the neoadjuvant approach might redeem these injectable agents as major assets for drug development, a concept that is currently being explored in clinical trials (NCT04303169).

Moreover, toxicities from therapy, particularly if they are long term, can limit decision-making not only in the (neo) adjuvant setting but also in the metastatic setting. For example, dual anti-PD-1 and anti-CTLA4 antibody therapy is fraught with toxicity; the nivolumab plus ipilimumab regimen used in CheckMate 915 threatened to shut the door on this combination in the adjuvant setting because inappropriate dosing led to a lack of benefit[23] (TABLE 1). However, through trials such as OpACIN-neo[10,25], we have been able to test for appropriate regimens and introduce flipped dosing with confidence of equal or greater benefit. In addition, the early identification of MPR as a correlate of long-term RFS in this setting has introduced the discussion of biomarker-led shortening of the duration of therapy, and even to the omission of subsequent adjuvant therapy after surgery, in patients with an MPR[26]. Conversely, pathological identification of lack of response can lead to an early switch of therapy to avoid further deleterious therapy, which is particularly important

for patients with *BRAF*-mutant melanoma, for whom another beneficial option exists. Trials in the metastatic setting cannot achieve this goal as imaging evaluation is known to underestimate response to therapy and can even inappropriately indicate progressive disease in some patients, particularly with immunotherapy. This logic is indisputable and paradigm-shifting. Another significant end point, currently being evaluated in the PRADO study[26], is the elucidation of an MPR in the largest lymph node metastasis as a surrogate to obviate the need for CLND and thereby reduce surgical morbidity, as discussed above.

These points present a protocol towards an appropriate armamentarium to illuminate initial decision-making for all patients. I must admit that the support needed for an appropriate neoadjuvant programme might not be available at most community and even academic centres. Currently, most patients are transferred to our clinics after melanoma resection without medical oncology input. How, then, do we advance the care of this population? This constitutes the inflection point where adjuvant therapy then triumphs over neoadjuvant therapy. Adjuvant therapy will always be superior in terms of population access precisely because it lacks the intricacies of the neoadjuvant paradigm. Nevertheless, the wisdom derived from neoadjuvant trials will constitute a roadmap based on easily accessible biomarker data from the initial tumour that will manoeuvre the patient to a bespoke adjuvant regimen. It will take substantial time to persuade our colleagues of this principle — focusing the trajectory of adjuvant decisions will be less complicated.

G.V.L. Randomized phase II (NCT03698019) and phase III (NCT04949113) clinical trials of neoadjuvant versus adjuvant therapy are under way. These studies will give us the definitive answer to this question; however, translational data suggest that the neoadjuvant approach is superior in terms of anticancer immune effects with greater expansion of tumour-specific T cells[10,36]. Furthermore, the neoadjuvant approach provides advantages for clinical care given that patients receive the much-needed feedback after surgery as to whether their melanoma was responsive to systemic therapy. Not only can the clinician use this information to tailor patient follow-up in terms of the imaging surveillance schedule and type or the need for adjuvant therapy, but the patient's risk of recurrence can also be refined based on the biological evidence provided by the degree of pathological response. For example, those with an MPR to ICIs rarely have disease recurrence[8,10], and might, therefore, be spared from adjuvant therapy, intensive surveillance and psychological concerns.

Additionally, the neoadjuvant paradigm provides many other benefits to the field of cancer research. For example, this platform enables rapid drug development, cutting typical trial conduct time from ≥2 years to ~6 months. Furthermore, the collection of large amounts of tissue, including samples of the tumour microenvironment in patients who have excellent pathological responses and of the resistant tumour in those who do not, provides unparalleled opportunities for translational studies to develop novel therapies and biomarkers.

J.J.L. In considering neoadjuvant and adjuvant therapy, I take the view that these therapeutic approaches are not necessarily at odds with each other and should be used together when possible. Obviously, the identification and treatment of patients using an adjuvant approach is more straightforward and will be the prevailing paradigm for the vast majority of

patients in the near term given that a clinical workflow including biopsy sampling, surgical resection and then consideration of systemic therapy is standard throughout the world. This approach also allows for patients with refractory disease that recurs locoregionally to then be considered as good candidates for neoadjuvant therapy. For a subset of the very small group of patients who present outright with bulky disease that is truly resectable, impressive outcomes have been reported with neoadjuvant immunotherapy using combinations of ICIs in small-cohort, single-arm phase II studies[8,10,25,26]; however, trying to compare these outcomes to the robust data from randomized phase III studies of adjuvant therapies is essentially impossible (TABLE 1). In summary, the adjuvant therapy paradigm is supported by the most data, is in keeping with how standard clinical management workflows are constructed and is applicable in settings outside of large multidisciplinary centres (which is most of the world). I applaud the continued pursuit of neoadjuvant studies, but believe it unlikely that they will impact standard perioperative management of melanoma within the next decade.

How could patient selection be improved?

J.J.L. Patient selection for perioperative treatment is one of the most important questions facing oncology in the modern era. In the previous era of chemotherapy, there was little question that early initiation of systemic treatment for the total patient population was justified given the poor outcomes of metastatic disease. In the current era, however, the opportunity for long-term disease control and even treatment-free survival exists for some patients with metastatic cancer, particularly those with melanoma[37]. Unfortunately, the identification of patients with melanoma who will have disease recurrence after surgery or those who would obtain long-term disease control in the context of metastatic disease remains elusive on a molecular level. To date, the presence of a T cell-inflamed tumour microenvironment and a high TMB remain the molecular factors associated with the best treatment outcomes in the metastatic, adjuvant and neoadjuvant settings, regardless of whether immunotherapy or BRAF-directed approaches are taken[10,38,39]. Other tumour gene expression profiles have been associated with an increased risk of disease recurrence and distant metastasis[40], and circulating tumour DNA measurements might also inform these considerations[41]. However, these predictors remain imperfect. These biomarkers and others should continue to be explored, although clinical factors are currently the best predictors of outcomes, with a low initial tumour burden and/or undetectable minimal residual disease being the most likely indicators of long-term survival[42–45]. For these reasons, consideration of adjuvant therapy for all patients with resectable melanoma, weighing the risks and benefits for each individual, remains the standard of care until more reliable approaches to molecular stratification are identified.

G.V.L. Patient selection could be improved by combining clinical factors with tissue biomarkers for risk prediction. Indeed, a crucial need exists in the field of melanoma for highly sensitive and highly specific predictive tools, including tools to predict the risk of recurrence both at diagnosis of resectable melanoma[46] and after perioperative systemic therapy in order to help select patients.

The neoadjuvant setting has provided excellent data to start the process of creating such predictive tools that integrate both tissue, blood or microbiome biomarkers and clinical factors. For instance, patients with both high expression of an IFNγ signature (IFNγ^{hi}) and a high TMB in melanoma tissues all had a pathological response after 6 weeks of neoadjuvant nivolumab plus ipilimumab in the OpACIN-neo trial[10]. This predictive biomarker is highly specific but is not highly sensitive, given that nearly 40% of patients with IFNγ^{lo} and TMB-low tumours also had a pathological response[10]. Nevertheless, we are already using such biomarkers to select patients to de-escalate or escalate systemic therapy in neoadjuvant trials. In the phase Ib DONIMI trial[47], for example, patients with IFNγ^{hi} melanomas received two neoadjuvant cycles of nivolumab with or without the histone deacetylase inhibitor domatinostat, whereas those with IFNγ^{lo} melanomas all received the combination with or without additional ipilimumab.

A.M.M.E. As clearly outlined above, in patients with melanoma[10], as well as in those with bladder cancer[29,31] and other cancer types[27], expression of an IFNγ-related gene signature, a high TMB and the presence of a T cell infiltrate in the tumour have each been demonstrated to be key predictors of a pathological response to neoadjuvant ICI therapy.

Does the choice of prior (neo)adjuvant therapy have implications for the treatment options and outcomes of patients with recurrent disease?

A.M.M.E. We are on a rapid learning curve in this regard. Recurrent disease after neoadjuvant and/or adjuvant therapy might have a distinct biology and lower sensitivity to subsequent systemic therapies, particularly in the context of ICI retreatment[13,48]. It will be some time before we have real-world data to establish, in large numbers of patients, what the response rates are after prior (neo)adjuvant therapy with anti-PD-1 antibodies, dual ICI combinations, or tyrosine kinase inhibitors–ICI combinations that have been introduced over the past 5 years. Nevertheless, we can reasonably expect to encounter patients with a different disease biology that will require the use of additional and potentially novel systemic agents to (re)induce a response to such therapies.

J.J.L. The pursuit of perioperative therapy has important implications for the treatment of recurrent disease but these are informative and not deleterious. If a patient has late recurrence beyond 6 months following adjuvant anti-PD-1 or BRAF-directed therapy, they will often benefit from retreatment with the same agent in the advanced-stage disease setting. By contrast, if the patient has an early relapse, they are then identified as needing a more intensive treatment approach and the idea of ‘reserving’ what would have been an ineffective treatment is illogical. Data already indicate that certain salvage treatments have substantial response rates and the potential for long-term benefit, including combination therapy with anti-PD-1 plus anti-CTLA4 antibodies following progression on anti-PD-1 antibody monotherapy[49], or adoptive cell transfer of tumour-infiltrating lymphocytes[50]. Furthermore, movement of effective therapies into the perioperative setting will homogenize the population of patients with refractory disease, thereby facilitating the development of new treatments for this population. With an expanding genomic and immunobiological toolset, many opportunities are emerging to target previously undruggable targets (such

as RAS and p53) and to develop novel immunotherapies (for example, innate immune stimulators and adoptive cellular approaches involving T cell receptor-transduced T cells) that might improve outcomes for patients with refractory melanoma in the future.

O.H. Unfortunately, the fact remains that many patients will ultimately have disease recurrence after (neo)adjuvant therapy, although this experience will enable further research in a prospective fashion. As outlined in the comments above, some therapeutic success in the past (that is, late relapse) will mandate retreatment with the same regimen, whereas a lack of benefit will avoid wasting additional precious time on an ineffective therapeutic approach. Pathological evaluation of recurrent disease utilizing the experience obtained in the neoadjuvant arena will ensure the greatest chance of therapeutic success. Currently, major institutions and pharmaceutical partners have lent substantial resources to this endeavour, and collectively our efforts will lead to meaningful data with the power to deliver consequential progress.

G.V.L. The goal of perioperative systemic therapy is to cure patients; therefore, if a patient has disease recurrence, the treatment has, by definition, failed — the micrometastatic disease was not eradicated and the cancer is resistant to that therapy. Accordingly, subsequent treatment options need to include drugs with a different mode of action[48,51]. Local therapies, such as surgery or radiotherapy, can often also be utilized, when appropriate. If the recurrence occurs long after adjuvant therapy, occasionally, retreatment can be appropriate[13,48,51,52]. However, in summary, after disease recurrence, response rates to subsequent therapies are often low and outcomes are poor, and this is an area of intense research interest in the field of melanoma[13,51,52].

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Table 1 |

Summary of key clinical trials of perioperative systemic therapy for melanoma

Trial (phase): treatment arms	Disease stage (*n*)	pRR	RFS/EFS[a]	DMFS	OS	Refs
Adjuvant studies						
EORTC 18071 (III): ipilimumab 10 mg/kg vs placebo, every Q3W for 4 doses, then every 3 months for up to 3 years	IIIA–C (951)	NA	Median: 26.1 vs 17.1 months 1-year: 63.5% vs 56.1% 2-year: 51.5% vs 43.8% 3-year: 46.5% vs 34.8% 5-year: 40.8% vs 30.3% 7-year: 39.2% vs 30.9% HR 0.75, 95% CI 0.63–0.88; $P < 0.001$	Median: 48.3 vs 27.5 months 5-year: 48.3% vs 38.9% 7-year: 44.5% vs 36.9% HR 0.76, 95% CI 0.64–0.90; $P = 0.002$	5-year: 65.4% vs 54.4% 7-year: 60.0% vs 51.3% HR 0.73, 95% CI 0.60–0.89; $P = 0.002$	12,53,54
COMBI-AD (III): dabrafenib 150 mg BID plus trametinib 2 mg QD vs placebo for up to 1 year	IIIA–C (*BRAF*^{V600} mutant; 870)	NA	Median: NR (mFU 60 months) vs 16.6 months 1-year: 88% vs 56% 2-year: 67% vs 44% 3-year: 59% vs 40% 4-year: 55% vs 38% 5-year: 52% vs 36% HR 0.51, 95% CI 0.42–0.61; *P* value NA	Median: NR 1-year: 91% vs 70% 2-year: 77% vs 60% 3-year: 71% vs 57% 4-year: 67% vs 56% 5-year: 65% vs 54% HR 0.55, 95% CI 0.44–0.70; *P* value NA	1-year: 97% vs 94% 2-year: 91% vs 83% 3-year: 86% vs 77% HR 0.57, 95% CI 0.42–0.79; $P = 0.0006$	3,55,56
CheckMate 238 (III): nivolumab 3 mg/kg Q2W vs ipilimumab 10 mg/kg Q3W for 4 doses, then every 3 months for up to 1 year	IIIB–IV (906)	NA	Median: 52.4 vs 24.1 months 1-year: 70.5% vs 60.8% 2-year: 62.6% vs 50.2% 3-year: 58% vs 45% 4-year: 51.7% vs 41.2% HR 0.71, 95% CI 0.60–0.86; $P = 0.0003$	Median: NR (mFU 51.1 months) vs 52.9 months 1-year: 80.2% vs 73.4% 2-year: 70.5% vs 63.7% 4-year: 59.2% vs 53.3% HR 0.79, 95% CI 0.63–0.99; *P* value NA	4-year: 77.9% vs 76.6% HR 0.87, 95% CI 0.66–1.14; $P = 0.31$	6,57
KEYNOTE-054 (III): pembrolizumab 200 mg vs placebo Q3W for up to 18 doses	IIIA–C (1,019)	NA	Median: NA 1-year: 75.4% vs 60.2% 2-year: 68.3% vs 47.1% 3-year: 63.7% vs 44.1% 3.5-year: 59.8% vs 41.4% HR 0.59, 95% CI 0.49–0.70; $P < 0.0001$	Median: NA 3.5-year: 65.3% vs 49.4% HR 0.60, 95% CI 0.49–0.73; $P < 0.0001$	NA	2,58,59
IMMUNED (III): nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (followed by nivolumab 3 mg/kg Q2W) vs nivolumab 3 mg/kg Q2W vs placebo for up to 1 year	IV (167)	NA	Median: NR (mFU 28.4 months) vs 12.4 vs 6.4 months 1-year: 75% vs 52% vs 32% 2-year: 70% vs 42% vs 14% HR for combination vs placebo 0.23, 97.5% CI 0.12–0.45; $P < 0.0001$ HR for monotherapy vs placebo 0.56, 97.5% CI 0.33–0.94; $P = 0.011$	NA	NA	7
CheckMate 915 (III): nivolumab 240 mg Q2W + ipilimumab 1 mg/kg Q6W vs nivolumab 480 mg Q4W for up to 1 year	IIIB–IV (1,844)	NA	Median: NR 2-year: 64.6% vs 63.2% HR 0.92, 97.295% CI 0.77–1.09; $P = 0.269$	Median: NR 2-year: 75.4% vs 77.4% HR 1.01, 95% CI 0.83–1.23	NA	23

Trial (phase): treatment arms	Disease stage (*n*)	pRR	RFS/EFS[a]	DMFS	OS	Refs
KEYNOTE-716 (III): pembrolizumab 200 mg or placebo Q3W for up to 1 year	IIB/C (976)	NA	Median: NR 1-year: 90.5% vs 83.1% HR 0.65, 95% CI 0.46–0.92; $P = 0.0066$ 1.5-year: 85.8% vs 77.0% HR 0.61, 95% CI 0.45–0.82; *P* value NA	NA	NA	4,5
Neoadjuvant studies						
NeoCombi (II): dabrafenib 150 mg BID plus trametinib 2 mg QD as neoadjuvant therapy for 12 weeks and as adjuvant therapy for 40 weeks	IIIA–B (*BRAF*^{V600} mutant; 35)	100% (pCR 49%)	Median: 23.3 months (30.6 months in patients with a pCR vs 18.0 months in those with a non-complete pathological response) 1-year RFS: 77.1% (82.4% vs 72.2%) 2-year RFS: 43.4% (63.3% vs 24.4%)	Median: 30.6 months; 38.0 months in patients with a pCR vs 27.7 months in those with a non-complete pathological response ($P = 0.58$)	Median: NR (mFU 27 months) 1-year: 100% 2-year: 93.8%	60
OpACIN (Ib): nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (2 neoadjuvant + 2 adjuvant cycles, or 4 adjuvant cycles only)	IIIB/C (20)	78% in 9 evaluable patients (pCR 33%; pnCR 33%; pPR 11%)	Median: NR (mFU 4 years in responders) 3-year RFS: 80% (vs 60% in 10 patients in adjuvant-only group) 4-year RFS: 60% (in both groups) 3-year EFS: 80% (vs 60%) 4-year EFS: 80% (vs 60%)	NA	3-year: 90% (vs 70% in adjuvant-only group) 4-year: 90% (vs 70%)	10,24
OpACIN-neo (II): 2 cycles of nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (group A) vs nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (group B) vs 2 cycles of ipilimumab 3 mg/kg Q3W followed by 2 cycles of nivolumab 3 mg/kg Q2W (group C)	IIIA–C (group A 30; group B 30; group C 26)	Group A: 80% (pCR 47%; pnCR 23%; pPR 10%) Group B: 77% (pCR 57%; pnCR 7%; pPR 13%) Group C: 65% (pCR 23%; pnCR 23%; pPR 19%)	Median: NR (mFU 2 years) 1-year RFS: 85.5% for all patients (90.0%, 82.8% and 83.3% for groups A, B and C, respectively); 96.9% for responders and 47.7% for non-responders 2-year RFS: 83.6% for all patients (90.0%, 77.6% and 83.3% for groups A, B and C, respectively); 96.9% for responders and 35.5% for non-responders 1-year EFS: 83.7% (90.0%, 80.0% and 80.8% for groups A, B and C, respectively) 2-year EFS: 81.7% (90.0%, 74.3% and 80.7% for groups A, B and C, respectively)	NA	1-year: 97.7% (93.3%, 100% and 100% in groups A, B and C, respectively) 2-year: 94.8% (93.3%, 95.5% and 96.2% in groups A, B and C, respectively)	10,25
NCT02519322 (II): nivolumab 480 mg +relatlimab 160 mg in weeks 1 and 5 (with surgery at week 9, followed by up to 10 additional adjuvant doses)	IIIA–IV (30)	73% (pCR 59%; pnCR 7%; pPR 7%)	Median: NR (mFU 16.2 months) 1-year RFS: 93%; 100% for MPR group vs 80% for non-MPR group ($P = 0.016$) 1-year EFS: 90%	NA	1-year: 95%	11

BID, twice daily; DMFS, distant metastasis-free survival; EFS, event-free survival; mFU, median follow-up; MPR, major pathological response; *n*, number of patients; NA, not available/applicable; NR, not reached; OS, overall survival; pCR, pathological complete response; pnCR, pathological near-complete response; pPR, pathological partial response; pRR, pathological response rate; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; QD, once daily; RFS, relapse-free survival.

[a]For neoadjuvant studies only; this end point captures patients with disease progression prior to surgery.