Adjuvant melanoma therapy with new drugs: should physicians continue to focus on metastatic disease or use it earlier in primary melanoma?

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It is important to differentiate between two concepts of adjuvant therapy in melanoma—what we have come to call late adjuvant and early adjuvant therapy. Early adjuvant therapy is defined as a medical intervention that is done after resection of a primary melanoma to eradicate possible undetectable minimal residual disease, whereas late adjuvant therapy is done when an overt metastatic disease (nodal or visceral) has been completely resected, to control disease better than if the same treatment were given at a later time, in the presence of multiple metastases. Early adjuvant therapy is thus a preventive treatment strategy, whereas late adjuvant therapy aims at anticipating treatment of metastatic disease. For patients with melanoma, 1-year treatment with targeted therapies and immunotherapy have only been assessed in late adjuvant settings, the outcomes of which more or less reproduce the same dramatic effect as they have in metastatic disease. However, early adjuvant therapy could provide greater benefits in terms of public health, since thin melanomas without nodal metastases are so common that they account for most deaths by melanoma. In the early adjuvant setting, a treatment course of less than 1 year might be sufficient to control the disease, with less toxicity and at reduced costs. In this Personal View, we discuss the potential benefit of short-term early adjuvant treatment in patients with stage II melanoma, with the hope that sentinel-node biopsy and the American Joint Committee on Cancer staging will soon be replaced by more relevant biomarkers to identify the most suitable candidates for early adjuvant therapy for this disease.

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Introduction

Recent publications have reported outstanding results in the adjuvant treatment of stage IIIA, to fully resected stage IV, melanoma (we use staging as per the American Joint Committee on Cancer [AJCC] guidelines across the text, unless otherwise specified).[1–5] We would like to differentiate between two quite different concepts of adjuvant therapy, which we define as late adjuvant and early adjuvant treatments. Herein, we propose to develop early adjuvant strategies, with the objective of treating the cancer before it becomes overtly metastatic, to increase chances of cure, and substantially influence melanoma-specific mortality.

Treatment in the early adjuvant setting can be defined as a medical intervention after resection of a primary melanoma without any clinically or radiologically detectable metastasis to eradicate any undetectable minimal residual disease potentially present, so that it never becomes overtly metastatic. In some patients, a subset of primary tumours with no radiographically or clinically detectable metastases, with or without sentinel-node involvement, has the propensity to further progress, metastasise, and eventually lead to death. However, markers to identify this subset of aggressive primaries are missing and this patient group would benefit from receiving early adjuvant treatment with the intention of bringing cancer cells under control.

By contrast, treatment in the late adjuvant setting can be defined as a medical intervention in overt metastatic disease once the detectable component of the metastatic disease (nodal or visceral) has been surgically resected. This treatment route is based on the concept that a lower tumour burden increases the likelihood of complete tumour control, as suggested by the improved outcome of many therapies (ie, immunotherapy and targeted therapy) in low tumour burden and low lactate-dehydrogenase metastatic disease compared with more extensive disease.[6,7] It is expected that such a treatment strategy will control tumour spread more effectively or for longer periods than using the same treatment given at a later time. From this point of view, late adjuvant treatment can be regarded as an anticipated metastatic treatment as opposed to a preventive strategy. It must be noted that recent attempts at neoadjuvant strategies in stage III–IV melanoma[8] can be considered similar to those used in the late adjuvant concept because they both target the metastatic disease earlier than the standard of care, although in neoadjuvant therapy the treatment is given before rather than after surgical resection of the metastatic tumour.

Selection of patients for early or late adjuvant therapy

Although the AJCC database contains stage-dependent melanoma-specific survival data,[9] the database is unable to identify which individuals have aggressive primary tumours that are destined to progress, and thus is unable to identify those patients that would benefit from an early adjuvant treatment or those with resectable metastases who are likely to benefit from late adjuvant therapy. Therefore, AJCC is not suitable to indicate early or late adjuvant treatments and guide treatment decision making. Furthermore, the 2018 changes to the AJCC staging system make it difficult to compare the effects of different adjuvant-therapy strategies in a given group of patients.[10] Nevertheless, early adjuvant treatment is mainly appropriate for patients with disease currently classified as stage IIA, IIB, and IIC, and could potentially also

involve stage I, should diagnostic tools become available to focus on the rare patients in this category who are at risk. Conversely, late adjuvant treatment is appropriate for patients with disease currently classified as stages IIIB, IIIC, and fully resected stage IV. Patients with stage IIIA melanoma, who are identified through the sentinel-node biopsy procedure and have a 5-year melanoma-specific survival of 93%,[9] represent an ambiguous group of patients since, depending on the case, their cancer could be assumed to be either only a primary melanoma with an immunological conflict around a few tumour cells in the first nodal relay, or as an already active metastatic disease. For the first biological situation, we would consider an early adjuvant strategy, whereas a late adjuvant strategy would be considered for the second. However, these two biological situations in stage IIIA disease are difficult to distinguish despite the efforts to do so according to the size of melanoma deposits in the sentinel node.[11]

It is noteworthy that published adjuvant-therapy trials with active drugs in melanoma[1–5] and the main ongoing trials (ie, US Intergroup E1609, SWOG 1404, and CheckMate 915) of the same setting, are all trials of late adjuvant treatment. Indeed, they all select patients with stage IIIB and IIIC disease,[1–5] and, depending on the trials, fully resected stage IV melanoma[3] or a selected subgroup of patients with stage IIIA melanoma.[2,4] Patients with stage IIIA melanoma are selected if the diameter of their tumour load in the sentinel node was more than 1 mm, which is more likely to indicate true active metastases that are likely to progress than a focus of immune conflict around a few tumour cells, the course of which is yet to be established.

No new active targeted or immunological drug has ever been tested using an early adjuvant strategy for melanoma. The only exception are the patients with stage IIC melanoma (n=27) who were included in the BRIM8 trial.[4] The findings of this trial could not provide any conclusive information about the efficacy of BRAF inhibitors in stage II melanoma because of the low number of patients who were recruited and the particularly severe prognosis of patients with IIC melanoma (more severe than IIIA) among those with stage II disease.[9] However, many historical trials that used much less active drugs, including interferons and vaccines, were at least in part trials that applied the early adjuvant concept in patients with stage II melanoma.[12–16] Unfortunately, these trials were done before sentinel-node biopsy became a routine procedure and when stage II labelling was defined differently to how it is now. It is therefore impossible to establish whether the protective and adjuvant effect of interferon treatment resulted from early adjuvant treatment alone or from the effects of early and late adjuvant treatments.

Effect of adjuvant therapies on the mortality burden of melanoma

The table summarises the major differences between early and late adjuvant treatments, and underlines the importance of separating the two concepts despite their formal designation (ie, after surgery) as adjuvant treatment.

There are two reasons why patient groups receiving early adjuvant treatments might be a better public-health target than those with more advanced-stage disease who are treated with late adjuvant strategies. First, because active immunotherapy or targeted molecules might have higher chances of curing patients before, rather than after, they become overtly metastatic. Second, primary melanomas with a Breslow depth of less than 1 mm or 1–2 mm are so common that they account for nearly half of future deaths by melanoma, according to data from Queensland, Australia,[17] and the USA,[18] including the SEER registry.[19] Unexpectedly, the greatest number of all deaths from melanoma occur in patients initially diagnosed with T1 cancer (according to the tumour, node, and metastasis [TNM] staging).[19] Despite low individual risk of death (5-year melanoma-specific survival rates range between 82% and 99% in the total patient population with T1a–T4b N0M0 melanoma, or about 98% in patients with stage I melanoma, and 90% in those with stage II melanoma[9]), most future deaths from melanoma will be from patient cohorts with T1 and T2 stage.[17–19] Unfortunately, few assay systems are able to discern patients with higher death risk among the large heterogeneous group of patients with stages I and II melanoma,[20–22] and these assays have mostly been tested on patient cohorts outside clinical trials. Despite the high mortality burden due to melanoma among these groups of patients, giving them early adjuvant treatment constitutes a challenge for the pharmaceutical industry. Trials in populations of unselected patients with stage I–IIIA melanoma are characterised by high numbers of individuals to treat and delayed clinical results because event occurrence (ie, relapse and death) is rare and delayed. Moreover, a potential risk exists for severe drug adverse events, which is difficult to accept for patients in these groups who would do well even without adjuvant treatment. Whether this unfavourable therapeutic ratio can be improved by decreasing the duration (or the doses, or both) of adjuvant treatments while still maintaining their clinical benefit is currently unknown. However, negative sentinel-node biopsy is clearly not a relevant biomarker to exclude candidates for early adjuvant therapy, since many patients with negative sentinel nodes (stage I and II) contribute to melanoma mortality. It might thus be worth considering stopping the use of the sentinel-node procedure as a selection tool for indicating early adjuvant treatment, in the same way as it has been abandoned by a large part of the medical community as a tool for indicating systematic extensive nodal surgery.[23,24]

Nevertheless, physicians should be aware of the potentially greater effect of an early adjuvant than a late adjuvant strategy on the mortality burden of melanoma. Most deaths by melanoma occur in individuals who are initially diagnosed with low-thickness melanoma and

	Early adjuvant therapy	Late adjuvant therapy
Setting	After surgical resection of a primary tumour, with no overt metastatic disease	After surgical resection of overt metastatic disease (usually nodal)
Concept	Eradicate possible residual disease so that it never becomes overt metastatic disease	Take advantage of the tumour-load reduction in an active metastatic process rendered provisionally undetectable by surgery
Main objective	Real cure could be realistic in many cases	Better disease control than a delayed medical intervention
Ideal patient target (theoretically)	All patients with a primary melanoma without detectable metastasis but who ultimately contribute to melanoma mortality; in the absence of a relevant biomarker, all patients who do not achieve favourable outcomes from surgery of the primary malignant melanoma	All metastatic patients who can be rendered apparently metastasis-free after surgery
American Joint Committee on Cancer-stage correspondence for ideal target	I, IIA, IIB, and IIC; IIIA is ambiguous but often probably corresponds to an immune conflict around a few tumour cells	IIIB, IIIC, and IV fully resected; IIIA is ambiguous but sometimes could correspond to an active metastasis
Expected effect on melanoma-specific mortality of the population	Important because these patients are contributing a lot to overall collective mortality, even if their individual risk is statistically low; full patient recovery can be expected	Mitigated because these patients are not major contributors to overall mortality for melanoma; cure is unlikely; the efficacy of a treatment used in late adjuvant therapy might be compromised if used later in case of relapse
Optimal duration and regimen	Short duration (<1 year) might be enough to eradicate an early cancer and would decrease toxic effects and cost	Long duration (>1 year) and treatment combination might increase benefit
Reading of the effect	No easy early reading: a benefit in relapse-free survival with a long plateau* can be expected; overall-survival effect might be important but late	Rapid effect on relapse-free survival; hazard ratio might decrease with time; overall-survival effect is the only way to know whether a drug benefit is higher when used first in late adjuvant setting or in a distant metastatic-disease setting
Ideal drug	Lowest possible risk of lethal or permanent serious adverse events (many patients with low individual risk will be exposed)	Highest effectiveness (severe adverse events are tolerable because there are only patients with high individual risk)
BRAF and MEK inhibitors	Rapid tumour eradication possible, adverse events are always transient; risk of induction of new resistance mechanism in dormant cells if treatment is prolonged	High rate of efficacy; transient efficacy with frequent secondary resistance
Effect of immunotherapy	Could be an easy situation for an immune therapy (ie, it is more likely to be effective when the tumour load is low, and the immune system intact); risk of lethal adverse events and permanent complications is not null, conflicting with the low individual risk of dying from a melanoma	Protective effect persisting after discontinuation; high rate of primary resistance

*We interpret a long plateau to mean that the patient might be cured

Table: **Differences between early adjuvant and late adjuvant therapy in melanoma**

not with advanced-stage disease.[17–19] Additionally, use of drugs in a late adjuvant treatment setting is unlikely to lead to a cure and might compromise the efficacy of the same drugs when metastatic disease becomes clinically apparent again. If this were the case, the initial overall-survival benefit attributed to late adjuvant therapy might be eventually lost. However, this benefit loss might not occur, as clinical experience shows that, some months after the onset of secondary resistance to targeted therapies, therapy rechallenge sometimes becomes active again.[25] This observation suggests that using a drug in the adjuvant setting might not always compromise efficacy of the same drug in the metastatic setting.

Despite these limitations, the late adjuvant setting is easy for pharmaceutical companies to develop for several reasons. First, when effective treatments are available for the metastatic stage, as they are for melanoma, trials of late adjuvant therapy are expected to reproduce at least the same results as in distant metastatic disease, since late adjuvant trials are just trials in a favourable setting of patients with already active metastatic disease. Second, as late adjuvant strategy is targeting only people with a very high risk of relapase, adverse events are more tolerable than in the early adjuvant strategy, in which a lot of low-risk patients are potentially exposed to adverse events. Third, results (eg, relapse-free survival as an accepted regulatory endpoint) are obtained much faster in the late adjuvant than early adjuvant therapy setting. Moreover, the first reported interim analysis of late adjuvant treatment trials, which are likely to provide the best protective hazard ratios, is what the community will use to judge the trials. Indeed, there is a low probability that a treatment discontinued at one year can have a long-term effect in already metastatic disease and obtain a real cure in a majority of patients, which might result in lower protective hazard ratios in late than in early analyses of the trials.

Duration of adjuvant treatments

The 1-year duration period used for most recent adjuvant treatment trials[1–5] for melanoma is arbitrary. A 1-year adjuvant treatment strategy can be either too short when

dealing with already overt metastatic disease (late adjuvant setting), or too long when treating the residual disease after resection of a primary-melanoma (early adjuvant setting). In published trials[1–5] of late adjuvant treatment, the adjuvant therapy effect is visible on relapse-free survival curves from the first evaluation at 3 months. In the context of an early adjuvant-treatment trial, the objective to change the prognosis of disease could be achieved with a course of immune or targeted treatments of less than 1 year. Furthermore, a short duration of treatment might not only improve the toxicity-to-benefit ratio and lower the treatment cost, which are crucial characteristics of testing treatment in the early adjuvant setting, but might also reduce the occurrence of premature discontinuation of treatment and increase patient adherence. Because of the precocity of the medical intervention, we expect the effects of an early adjuvant treatment to be clearcut and rapid: either the early adjuvant treatment successfully and definitively eradicates an early melanoma, or the early cancer proves resistant to these treatments. In the case of the cancer proving resistant to the treatment, not only prolonging the treatment by a few months is unlikely to lead to a cure of the disease, but it might also be counterproductive, inducing new molecular mechanisms of resistance in a dormant disease or pointlessly exposing patients to toxic effects. In contrast to early adjuvant therapy, late adjuvant treatments deal with an already active metastatic disease and the expected outcome is to control rather to cure. In agreement with the model of metastatic melanoma, it could thus be logical to intensify late adjuvant therapy for stage IIIB–IIIC melanoma with a combination of treatments or by prolonging the adjuvant treatment to more than 1 year, or both.

Other models suggest that increasing the duration of adjuvant treatments can be beneficial in advanced forms of cancers. Increasing the duration of imatinib therapy to more than 1 year in high-risk gastrointestinal stromal tumours can improve relapse-free survival and overall survival.[26] In hormone-positive breast cancer, for example, extending the duration of adjuvant therapy with different drugs (ie, tamoxifen) to more than 5 years can improve treatment outcomes, particularly in patients with axillary nodal metastases.[27] Although the use of immunotherapy or targeted therapy in the early or late adjuvant treatment of melanoma are completely different, in terms of mechanism of action, more clinical trials are needed to test different durations and intermittent regimens[28] in the adjuvant setting, with different protocols tailored to the mechanisms of action of the drug and the tumour load.

Biomarkers for the indication of early adjuvant therapy

The major advantages of early adjuvant therapy compared with late adjuvant therapy represent an argument for the medical community to test new active immune and targeted treatments in patients with stage I and stage II melanoma. The main obstacle is that these tests entail treating a high number of disease-free patients, with the risk of triggering rare but severe complications. From this point of view, the respective theoretical advantages and disadvantages of immunotherapy and targeted therapies are not the same when early or late adjuvant strategies are considered (table). The ideal solution for early adjuvant therapy would be to wait for the next generation of individual biomarkers to identify aggressive primary melanomas more reliably than sentinel-node biopsy. Many strategies are currently being tested, including liquid biopsies (especially circulating tumour DNA), gene expression profiling of the primary melanoma, and immunological scoring.[29,30] However, once suitable biomarkers are identified, it will possibly take years to validate them. Therefore, physicians must find a way of successfully doing a trial of early adjuvant therapy with poorly selected patients before ideal biomarkers are available.

Recommendations for future trials of early adjuvant therapy

An acceptable toxicity-to-efficacy ratio for targeted therapy and for anti-programmed cell death protein-1 (PD-1) treatment in the early adjuvant setting can probably be obtained. Shortening the duration of early adjuvant treatment will not avoid adverse events, since most of them develop during the first months, often even in the first weeks, of treatment. However, a short duration of treatment will make adverse events that affect quality of life, which can last for months with the use of targeted therapies, more tolerable for patients. A short treatment duration with anti-PD-1 might avoid some of the few but very rare and life-threatening adverse events (ie, myocarditis) or permanent severe complications (ie, type 1 diabetes), at least in those cases when such events develop late. However, in the early adjuvant setting, physicians might also want to consider more restrictive criteria for the exclusion of any fragile or hyper-reactive patients, insist on a closer monitoring of adverse events, and impose stricter interruption rules than those that are used in the late adjuvant setting. Combined with the increased recognition and early treatment of adverse events, these precautions will probably make trials of early adjuvant treatment acceptable even with the use of immunotherapies.

Trials with interferon[12,13] in a similarly unselected population showed, without recruiting large population samples, that a drug much less active than anti-PD-1 or than BRAF and MEK inhibitors can show a substantial early adjuvant effect in a reasonable timeframe and a numerically reasonable population of patients. Once the early adjuvant strategy is validated, the number of patients needed to select for this new approach will be easy to decrease by restricting it to populations enriched with the more aggressive primary malignant melanoma.

Search strategy and selection criteria

References for this Personal View were identified through searches of MEDLINE and of the European Society for Medical Oncology, American Society of Clinical Oncology, European Association of Dermato Oncology, and Society for Melanoma Research databases using the search terms "adjuvant" AND "melanoma" from Jan 1, 1998 to Aug 31, 2018. Only papers published in English were considered.

New technologies and biomarkers will hopefully help to select these subpopulations more accurately than the use of tumour thickness or sentinel-node biopsy.

Until such selection tools have been developed, it might be worth testing an early adjuvant treatment given over a short duration. Several types of trials could be proposed on the basis of this concept: simple randomised trials of patients with stage II cancer (selection still based on sentinel node) or of all patients with T1b–T4 cancer with no clinically detectable nodes (without doing sentinel-node biopsy) could evaluate 3–4 months adjuvant treatment (targeted or anti-PD-1) versus placebo. However, more complex designs could simultaneously assess the duration of the therapy and the relevance of sentinel-node biopsy to select patients for adjuvant therapy. For example, a randomised trial of patients with T1b–T4 melanoma without clinically detectable nodes could compare a reference group undergoing sentinel-node biopsy followed either by 1-year adjuvant treatment in patients with positive nodes or by no treatment in patients with negative nodes, with another group without sentinel-node biopsy, but systematically given adjuvant treatment for 3–4 months. At present, we are only aware of one future trial of immunotherapy in early adjuvant treatment (ClinicalTrials.gov, NCT03553836), which is testing pembrolizumab. However, it will still use a selection procedure based on sentinel-node biopsy (AJCC stage II cancer), will only focus on highest-risk stage II cancers, and will still use the a 1-year regimen that has been validated in the late adjuvant setting.

Melanoma is a good model to test the major public-health question of when and how cancer should be approached in the adjuvant setting, when active drugs have already been approved. In our view, an early adjuvant strategy is likely to have a better chance of decreasing melanoma mortality than any late adjuvant strategy and should be invested on more heavily in the future.

Contributors

JJG wrote the project proposal and the first draft of the paper. All authors contributed to the decision of the precise objectives of the study, the literature review, and manuscript discussion and revision. JL edited the manuscript, and all authors approved the final version.

Declaration of interests

JJG has served as an adviser for Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Merck Pfizer, Novartis, Pierre Fabre, Roche, and Sun Pharma. CG has served as an adviser for Amgen, Bristol-Myers Squibb, Leo, Roche, Merck Sharp & Dohme, and Novartis; and has received grants from Array, Bristol-Myers Squibb, Novartis, and Roche. PA has served as an adviser for Amgen, AstraZeneca, Array, Bristol-Myers Squibb, Genmab, Incyte, Merck Sharp & Dohme, Novartis, Pierre Fabre, Medimmune, Roche, and Syndax; and has received grants from Array, Bristol-Myers Squibb, and Roche. JL has served as an adviser for Amgen, Bristol-Myers Squibb, Eisai, Eusa pharma, Merck Sharp & Dohme, Novartis, Pfizer, Pierre Fabre, Roche, and Sun pharma; and has received grants from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Pfizer. RD has served as an adviser for Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sun pharma, and Takeda; and has received grants from Bristol-Myers Squibb, Roche, and Array. DS has served as an adviser for Amgen, Array, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Incyte, Merck Sharp & Dohme, Merck-EMD, Novartis, Pfizer, Pierre Fabre, Regeneron, and Roche.

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