The management of early and late stage melanoma in the modern era

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General Discussion and Future Perspectives

Resectable melanoma

Surveillance of melanoma

The rising incidence of cutaneous melanoma poses an important challenge for cancer control and public health globally, specifically in populations with fair skin and of Caucasian descent.[1,2] National guidelines recommend surveillance of patients with familial melanoma. Another risk factor for the development of melanoma is multiple (atypical) naevi. However, whether patients with multiple common naevi and or atypical naevi should receive thoroughly skin surveillance is less clear.[3,4] Shedding light on this unclarity is important, as this can provide new insights in potential novel clinical managements in patients with multiple (atypical) naevi.

In chapter 2 we assessed the incidence of melanoma in patients with multiple atypical and or common naevi. We identified specific risk factors (multiple actinic keratoses, history of melanoma, sunburns in childhood, fair skin, blue eyes) for developing melanoma in patients with more than 100 naevi and or 5 atypical naevi.[5] Moreover, we found that the majority of melanoma cases in patients with multiple atypical nevi were detected by a dermatologist, without having been noted by the patient. Additionally, we observed that melanoma originated more frequently from pre-existing naevi in this patient population, while sporadic melanomas developed more frequently from normal appearing skin in the general population.[6] Considering these results, we recommend that patients with multiple atypical naevi (>5) and or numerous common naevi (>100) and additional identified risk factors multiple actinic keratosis, history of melanoma, sunburn in childhood, fair skin and or blue eyes should be monitored on an annual basis by a dermatologist.

Concurrently, patients with a *CDKN2A* germline mutation are already seen by a dermatologist on a biannual basis, as these patients have an estimated risk of melanoma development of 70%.[7,8] It is important to assess whether melanoma develops from a preexistent naevus or de novo in this patient group, as these findings might alter surveillance and or clinical management. In **chapter 3**, we analyzed melanoma cases in HMel^{CDKN2A} patients, and examined total body photography to determine whether melanoma arose from a preexistent nevus of normal appearing skin. Our findings demonstrate that the majority of melanoma cases arose from a preexistent naevus (78%). This result supports the routine use of total body photography and sequential dermoscopy to determine alterations in melanocytic naevi. Additionally, since melanoma emerged from a preexistent naevus in a relatively high proportion of cases, this suggesting that HMel^{CDKN2A} patients might benefit from more frequent removal of melanocytic naevi.

Regarding patients who develop melanoma, no concrete consensus in follow-up guidelines for cutaneous melanoma exists.[4,9] The conventional follow-up schedule suggests biannually follow-up for patients diagnosed with stage IB (T1bN0), IIA (T1BN0) melanoma for a total of 5 years.[10,11] Since

existing lack of consensus, the MELFO study was performed in 2022, a multicenter randomized clinical trial in which conventional follow-up care was compared with an experimental follow-up interval.[12] Interestingly, no differences were observed in recurrence free survival between the conventional and experimental follow-up scheme. Seemingly the support for an appropriate, safe and cost-effective follow-up regimen. As a consequence, the MELFO follow-up scheme has been implemented into the Dutch Melanoma Guideline and has been adopted into clinical care practice.

The current follow-up schedule is based on the TNM melanoma classification. Important is to identify additional prognostic factors next to the traditional T,N,M variables. For instance histologic subtype. To explain the importance of this, the subtype nodular melanoma is associated with an increased local and distant recurrence rate, regardless of Breslow thickness.[13] Additionally, melanoma subtypes such as acral melanoma and mucosal melanoma are also associated with lower recurrence-free survival rates and should therefore also be regarded as a prognostic marker for melanoma recurrence.[14,15] These identified subtypes should have their own specific follow-up regimen, in order to detect melanoma recurrence in early stage and thereby improving melanoma-specific survival.

Lymph nodal management for stage III melanoma

In addition to changes in follow-up for melanoma patients, the standard of care for sentinel node-positive status has also evolved. In 2017, the MSLT-II trial demonstrated no improvement in melanoma-specific survival for patients with micro metastatic lymph node disease in the sentinel node who underwent complete lymph node dissection compared to those who had only ultrasonic lymph node observation.[16] As a result, immediate complete lymph node dissection for sentinel lymph node-positive patients has been omitted and this has been adopted in clinical practice since 2018. A real-world study published in 2021 confirmed the adoption and implementation of active nodal surveillance instead of immediate complete lymph node dissection in sentinel node-positive patients, demonstrating similar melanoma-specific survival rates in both patient groups.[17,18,19]

Regarding patients with macroscopic lymph node disease, there is currently no clear consensus on the optimal surgical management.[20] Historically, the standard of care involved complete lymph node dissection. However, influenced by the findings of the MSLT-II study and the emergence of (neo)adjuvant therapies, complete lymph node dissection is omitted more frequently and surgical management is moving towards dissection of affected lymph nodes only, so-called lymph node picking.

The PRADO study, published in 2022 by Reijers and colleagues, assessed the efficacy of neoadjuvant ipilimumab/nivolumab in clinical stage IIIB-D melanoma patients.[21] The study found that therapeutic lymph node dissection could be safely omitted in patients who achieved a major pathological response (<10% viable tumor) to neoadjuvant immunotherapy. In addition, the study showed that patients who omitted therapeutic lymph node dissection reported significantly higher scores in specific health-related quality of life domains, including physical functioning, role functioning, global functioning, and social functioning, compared to those who underwent lymph node dissection.

Currently, a Dutch study is underway to investigate the outcomes of performing only a therapeutic index lymph node dissection in resectable high risk stage III melanoma patients, to assess the response to neoadjuvant treatment, thereby omitting complete therapeutic lymph node dissection. If this study confirms the safety of this approach, it will likely lead to a further shift in the management of lymph nodal melanoma disease towards less extensive surgical interventions.

Adjuvant therapy for stage II-III melanoma

These alterations in surgical management have significantly changed the treatment landscape, reducing potential surgery-related side effects and decreasing associated costs. Beyond these adjustments in follow-up care and lymph node management, the introduction of anti-PD-1 and *BRAF/MEKi* therapies in the adjuvant setting has further transformed the treatment paradigm.[22-27] The FDA has approved adjuvant anti-PD-1 therapy for stages IIB, IIC, IIIA, IIIC, and IIID melanoma. In the Netherlands, adjuvant anti-PD-1 therapy has received EMA approval for stage IIIA-D disease. Similarly, adjuvant *BRAF/MEKi* therapy has been approved for stage IIIA-D disease, and its efficacy for stage II disease is currently under investigation.

Clinical trials exploring the effectiveness of adjuvant therapy required complete lymph node dissection for stage IIIA-D melanoma patients. As a result, the effectiveness of adjuvant therapy in stage III melanoma patients who did not undergo complete lymph node dissection is unclear.

In Chapter 4, we describe that resected stage III melanoma patients who omitted complete lymph node dissection and were treated with adjuvant anti-PD-1 and adjuvant *BRAF/MEKi* had an improved progression free survival, compared to patients treated with surgery only. This suggests that adjuvant therapy may also be effective in eradicating occult regional disease. Regarding the timing of recurrence, patients treated with anti-PD-1 therapy experienced an earlier onset of disease recurrence compared to those in the *BRAF/MEKi* group. Although, our study was limited by a relatively short follow-up period, a larger study with an extended follow-up period, published by Broman and colleagues in 2021, demonstrated similar results.[18]

Despite reported improvement in local disease control, no improved overall survival has been observed in stage II/III melanoma patients treated with adjuvant anti-PD-1 therapy and *BRAF/MEKi*.[28] This raises the question whether it is more effective to treat with adjuvant therapy or to perform regular follow-ups consisting of clinical-radiological and blood assessments until disease recurrence is detected. As of now, there is no clear answer to this question.

While adjuvant treatment enhances local and distant disease control, it is important to note that this benefit can come at a cost. Approximately 30% of patients undergoing adjuvant therapy may experience immune therapy-related adverse events (irAEs).[29-31] Our study in **Chapter 4** highlights that immune therapy and *BRAF/MEKi* related adverse events were not uncommon and occurred more frequently in *BRAF/MEKi*-treated patients. This aligns with adjuvant trial data showing a higher frequency of any grade adverse event with targeted therapy compared to anti-PD-1 treatment.[25,27,32]

Regarding irAEs, these can include adrenal insufficiency, hypophysitis, colitis, hepatitis, thyroiditis, arthritis, diarrhea, pneumonitis, and toxic epidermal necrolysis.[33] These adverse events can be severe, long-lasting, and require additional treatment, significantly impacting the quality of life.[29,31] Similarly, adverse events related to *BRAF/MEK* inhibitors can have a serious impact on the quality of life, however, these side effects often resolve within a few days after discontinuation of therapy.[34,35]

Adjuvant therapy patient selection

Given the potential impact of treatment-related adverse events, patient selection must be conducted carefully to identify individuals at higher risk of developing irAEs, considering factors like comorbidities (including autoimmune diseases), age, and ECOG performance status.[30,36-39] While these risk factors for adverse event development are well established in the advanced treatment setting, it remains unclear whether this hold true in the adjuvant setting. Additionally, it is unclear whether patients treated with adjuvant therapy experience adverse events more frequently than advanced melanoma patients treated with systemic immune checkpoint inhibitors.

To address this, we analyzed the incidence and severity of adverse events in both adjuvant-treated and systemically treated advanced melanoma patients in **Chapter 5**, and assessed prognostic factors associated with adverse event development. Our results show that patients receiving adjuvant therapy had fewer comorbidities and pre-existing autoimmune conditions compared to those with advanced melanoma, indicating that relatively healthier patients are selected for adjuvant therapy This seemingly logical, as the importance of immunotherapy might be less essential in the adjuvant setting compared to the advanced setting.

Our study found that ECOG performance status and any type of comorbidity were independently associated with the development of adverse events in patients receiving adjuvant therapy. Therefore, these factors should be taken into consideration when advising patients adjuvant anti-PD-1 therapy. Additionally, we did not observe a significant difference in the incidence and severity of adverse events between adjuvant-treated and systemically treated advanced melanoma patients. This may be due to the low absolute number of adverse events captured in our study, as we only recorded grade III-IV irAEs. Therapy cessation due to adverse events was observed more frequently in the adjuvant group than in the systemic therapy group, suggesting a potential less therapy compliance, as treatment is less crucial, in adjuvant treated patients.

Further research is needed to include all grades of adverse events to determine if there is a significant difference across the full spectrum of adverse events between these patient groups.

In addition to identifying risk factors associated with adverse event development, it is important to pinpoint patients who can benefit most from adjuvant therapy. Patients with a relatively good prognosis, such as those with stage IIB and IIIA melanoma, can likely forego additional adjuvant treatment. In contrast, those with a less favorable prognosis, such as resected stage IIIC-D and stage IV-M1c-d disease, should be prioritized for adjuvant therapy consideration.[40]

Identifying patients at risk for disease recurrence can be complex, and biomarkers like circulating tumor DNA (ctDNA) may aid in therapy selection. Recent studies have shown that stage III melanoma patients with detectable ctDNA have an increased risk of relapse, suggesting that ctDNA, in conjunction with the AJCC classification scheme, could be valuable in making adjuvant therapy decisions for stage III melanoma patients.[41,42]

Another emerging biomarker is tumor mutational burden (TMB), which quantifies the number of somatic mutations per megabase of genomic DNA. Studies have suggested a correlation between TMB and the number of neo-antigens generated by the tumor, as well as the response of melanoma patients to immune checkpoint inhibitors. However, a significant proportion of patients with high TMB do not respond to anti-CTLA-4 or anti-PD-1 therapies, leaving the clinical utility of TMB uncertain.[43]

Interferon gamma (IFN-γ), which influences immune response and PD-1 expression, may also play a role in predicting response to adjuvant anti-PD-1 therapy. Several studies have demonstrated that upregulated IFN-γ expression correlates with a higher response to neoadjuvant therapy in stage III melanoma patients.[44,46] However, it is unclear whether the presence of an IFN-γ signature could aid in monitoring therapy response in adjuvant-treated patients, especially since a portion of these patients are rendered disease-free. The lack of tumor-related neo-antigens in patients who are disease free might result in a less potent immune response.

In summary, while identifying patients who would benefit most from adjuvant therapy remains challenging, advancements in biomarkers like ctDNA, TMB, and IFN-γ offer promising approaches for improving patient selection and treatment efficacy.

Critical view on adjuvant therapy

Despite the booked advancements in adjuvant immune checkpoint inhibition and targeted therapy for melanoma, the Dutch Society for Medical Oncology and Lung Oncology has recently updated its criteria for recommending adjuvant treatments. The Dutch healthcare association is currently developing a new framework for assessing and making reimbursement decisions regarding these therapies. There is growing criticism against the indiscriminate use of immune-checkpoint inhibitors in the adjuvant setting, with a preference emerging for more targeted, personalized neoadjuvant or adjuvant therapy approaches. Additionally, there is a trend towards deferring immunotherapy until a later stage, particularly in cases of disease relapse.[28] This approach is praised for its efficient resource utilization, prevention of potential therapy-induced drug resistance, avoidance of overtreatment, and preservation of the quality of life for patients without cancer-related symptoms who are susceptible to side effects from immune checkpoint inhibitors.

In conclusion, while adjuvant therapy can play a pivotal role in preventing local and distant disease recurrence, it is crucial to weigh the potential benefits and drawbacks for each individual patient. Since no overall survival benefit has been demonstrated yet for adjuvant therapy, clinical decisions should be made on a case-by-case basis to optimize patient selection for adjuvant treatment.

Neo-adjuvant therapy for stage III melanoma

Although the revolutionary progress that has been made with the introduction of adjuvant therapy, the outcomes of adjuvant therapy treated stage IIIC-D melanoma patients remain poor.[40] The relapse rate for these patients at 2 year follow-up has been estimated to be 40% for adjuvant immunotherapy and 40% at 3 years with adjuvant targeted therapy.[26,32,47] Our study in **chapter 4**, confirms indeed that adjuvant treated patients with macroscopic disease (stage IIIC-D) had a worse prognosis compared to stage IIIB melanoma in the post-MSLT-II era.

The advent of neo-adjuvant therapy has the potential to further improve outcomes for melanoma patients with resectable high risk stage III disease. The rationale for neo-adjuvant therapy stems from the observation of an increased immune response in patients exhibiting tumor neo-antigens, whereas those with completely resected melanoma might not show such potent immune responses due to the absence of tumor neo-antigens.[44,48]

Several studies have been conducted to analyze the efficacy of neo-adjuvant therapy. A pooled analysis of six melanoma neo-adjuvant trials in 2021 demonstrated that, at a 12-month follow-up, neo-adjuvant anti-CTLA-4/anti-PD-1 combination therapy had the highest response rate compared to anti-PD-1 monotherapy in patients with clinical stage III melanoma, with recurrence-free survival rates of 84% and 64%, respectively.[49] In addition, the SWOG trial in 2023 comparing neo-adjuvant pembrolizumab versus adjuvant pembrolizumab in patients with clinically detectable stage IIIB to IVc melanoma, demonstrated greater benefits from neo-adjuvant pembrolizumab, with a two-year recurrence-free survival of 72% in the neo-adjuvant group compared to 49% in the adjuvant-only group.[50]

Moreover, the results from the recently published NADINA study underscores the efficacy of neo-adjuvant immunotherapy. In this phase 3 trial, patients with resectable macroscopic stage III melanoma were randomly assigned to receive neo-adjuvant ipilimumab plus nivolumab followed by surgery or surgery followed by 12 cycles of adjuvant nivolumab. Patients who developed a partial or no response response to immunotherapy received adjuvant nivolumab therapy, while patients with a major pathological response received neoadjuvant treatment only.

During a follow period of 9.9 months, the estimated 12 month event free survival was 84% in the neoadjuvant group and 57% in the adjuvant group. In addition, in patients with a major pathological response to immunotherapy, the recurrence free survival was 95%, suggesting that solely neoadjuvant therapy might be sufficient for this response group.

In light of these results, neo-adjuvant therapy seems more effective in disease recurrence reduction compared to adjuvant treated patients in patients with clinical stage III melanoma. If studies with a longer follow-up period confirms these findings, then neo adjuvant therapy should be selected as preferred treatment choice in melanoma patients with macroscopic nodal disease.

Regarding neo-adjuvant *BRAF/MEK* inhibitors for clinical stage III melanoma patients, a pooled analysis showed a recurrence-free survival rate of 75% at 12 months and 47% at 24 months in treated high risk stage III melanoma patients.[49] Interestingly, in resectable stage IIIB/C melanoma patients with a partial response, the two-year recurrence-free survival was significantly higher in the neo-adjuvant immunotherapy group compared to the neo-adjuvant *BRAF/MEK* cohort, with rates of 64% versus 13%, respectively.[49] This highlights the importance of achieving a pathological (near) complete response in patients treated with targeted therapy, whereas a partial response to immunotherapy might be sufficient to improve recurrence-free survival.

Interestingly, the DOMINI trial showed that an upregulation of IFN-Y signature is associated with an improved response to neo-adjuvant ipilimumab/nivolumab therapy.[51] The IFN-Y signature could aid in optimizing the neo-adjuvant and adjuvant treatment scheme and potentially alter

surgical management in these patients. For example, patients who develop a partial response to neo-adjuvant therapy with a low IFN-Y signature, should be selected and or guided for additional surgery and or adjuvant therapy.

Potential disadvantages of neo-adjuvant treatment include delay in surgery, risk of disease progression to unresectable disease state and immune therapy related adverse events which could potentially impact surgical resection and outcomes. Despite these drawbacks, the potential benefits of neo-adjuvant treatment appear to outweigh the disadvantages. Hopefully, neo-adjuvant immune checkpoint inhibition will soon be approved for clinical use in patients with stage III resectable high-risk melanoma.

Prognostic factors for systemic therapy response in advanced melanoma

The emergence of systemic immune checkpoint inhibition has significantly shifted the treatment paradigm for metastatic melanoma.[24,52-54] Despite the progress made in improving overall survival, several knowledge gaps regarding prognostic factors in advanced melanoma still exists. Established prognostic indicators for cutaneous metastatic melanoma include LDH value, cerebral involvement, ECOG status, and the overall number of affected organ sites with metastases.[55] Our study in **Chapter 6** confirmed that increased LDH values, the presence of cerebral disease, multiple affected organ sites, and decreased ECOG status are all associated with poorer survival outcomes in patients treated with systemic anti-PD-1 or *BRAF/MEKi* therapies.

However, there is limited knowledge regarding other prognostic factors related to treatment response, such as histologic subtype, age, mutation status, gender, PD-L1 status, comorbidities, therapy-related adverse events, and ethnicity. Identifying and understanding these factors are crucial for optimizing treatment strategies and improving patient outcomes in advanced melanoma.

Histologic subtype

Melanoma subtypes characterized by a higher tumor burden tend to exhibit a more favorable response to therapy compared to those with a lower tumor burden.[56,57] Specifically, metastatic acral and metastatic mucosal melanomas, which harbor a lower tumor mutation burden, have been shown in retrospective studies to have worse treatment-related survival outcomes compared to advanced superficial spreading melanomas. Given that the histologic subtype nodular melanoma is associated with worse recurrence-free survival than superficial spreading melanoma, regardless of Breslow thickness, we conducted a study (**Chapter 6**) to assess the efficacy of immunotherapy and targeted therapy in advanced nodular- and superficial spreading melanoma patients.[13,58]

This study in **Chapter 6** demonstrates that treatment-related survival outcomes for nodular melanoma were similar to those for superficial spreading melanoma. However, despite similar treatment-related survival, overall survival was worse for nodular melanoma patients. This can be explained by the shorter time to metastasis for nodular melanoma compared to superficial spreading melanoma. Earlier metastasis in nodular melanoma ultimately leads to a worse prognosis. Traditionally, the histologic subtype NM has not yet been regarded as a prognostic variable for metastasis, highlighting the need to reevaluate follow-up protocols for nodular melanoma patients.

Given these findings, it is important to consider the histologic subtype for both melanoma specific follow-up scheme and the histologic subtype should be assessed when deciding on adjuvant or advanced immunotherapy for melanoma patients. By doing so, we can aim to improve the outcomes in melanoma patients.

Age and comorbidity

Since clinical trial participants typically consist of relatively healthy individuals, it was uncertain whether older patients with advanced melanoma were suitable for systemic therapy. However, a large population-based retrospective study conducted by Glas and colleagues demonstrated that the response rates and toxicity of checkpoint inhibitors did not vary with increasing age or comorbidity.[59] Despite similar grade III-IV toxicity rates, elderly patients discontinued therapy more frequently than their younger counterparts. This could be due to older patients experiencing a higher frequency of immune therapy-related adverse events of any grade, which may lead to a deterioration in quality of life and physical functioning. Additionally, therapy might be discontinued more frequently as its clinical utility potentially has less impact on the life span of elderly patients nearing the end of life.

Mutation status

The prognostic role of pathogenic mutations in treated advanced melanoma is complex. A recently published meta-analysis demonstrated that *NRAS* mutated melanoma is associated with a higher likelihood of partial or complete tumor response compared to *NRAS*-wildtype melanoma.[60] Therefore, the presence of a *NRAS* mutation status might be considered a prognostic marker for response to immune checkpoint inhibition therapy. Albeit this, advanced *NRAS*-mutated melanoma can only be treated with immune checkpoint inhibitors and no *BRAF/MEK* inhibitors, the prognostic value of the *NRAS* mutation remains uncertain.

In parallel, a study conducted by van Not and colleagues, investigating the efficacy of anti-PD-1 in advanced melanoma patients, reported no survival difference between *BRAF* or *NRAS* mutated

melanoma patients.[61] Interestingly, the study observed an improved survival for *BRAF*-mutated melanoma patients treated with the ipilimumab/nivolumab combination therapy compared to patients with *NRAS*-mutant and wild-type melanoma. Suggesting that BRAF mutation status is a prognostic factor to consider when deciding between mono- and dual-checkpoint inhibition therapies.

Gender

The prognostic role of gender in response to immune checkpoint inhibition therapy is not fully clarified. It has been suggested that response to immune checkpoint inhibition may differ based on gender due to differences in autoimmune comorbidities: women have a higher susceptibility to autoimmune disorders. A large meta-analysis published in 2018 in the Lancet, which included more than 110,000 patients with melanoma (32%) and non-small-cell lung cancer (31%) treated with immune checkpoint inhibitors, reported a pooled overall survival hazard ratio of 0.72 (95% CI 0.65-0.79) for females and 0.86 (95% CI 0.79-0.93) for males.[62] This suggests that the magnitude of response to immune checkpoint inhibition might be sex-dependent. However, this analysis might be biased due to the relatively low proportion of melanoma patients and the exclusion of patients with a history of autoimmune disorders in clinical trials, which is more prevalent in women. The presence of autoimmune comorbidities might lead to more frequent adverse events and therapy cessation. On the other hand, the occurrence of immune-induced adverse events could also potentially be associated with a good prognostic value.

A study published in 2021 by Jang et al. in JAMA Oncology observed a higher mortality hazard ratio for women with melanoma treated with ipilimumab/nivolumab compared to men, though no difference was seen in patients treated with anti-PD-1 monotherapy.[63] Conversely, a more recent study by van der Kooij and colleagues demonstrated no gender related differences in immune checkpoint inhibitor-related survival overall.[64] However, they did observe a survival advantage in female patients aged 60 years and older with *BRAF* V600 mutant melanoma compared to their male counterparts. This finding was in line with a study published in 2022 in Nature, which reported improved survival for females versus males in *BRAF/MEKi*-treated advanced melanoma patients, even after adjusting for age, LDH, disease load, affected organ sites, and ECOG performance status.[65] Given these inconsistent results, additional research is needed to understand the specific effects of gender on the effectiveness of immune checkpoint inhibitors and targeted therapy.

Ethnicity

A more recent focus in advanced melanoma research is the role of ethnicity. An international multicenter observational study involving 1135 patients examined the outcomes of anti-PD-1

monotherapy across different ethnic groups.[66] Interestingly, white patients with non-acral cutaneous melanoma had significantly higher objective response rates and longer progression-free survival compared to East Asian, Hispanic, and African patients. This was after adjusting for age, gender, anatomical location, metastasis stage, baseline lactate dehydrogenase levels, mutational status, and prior systemic treatment. In contrast, no survival benefit related to ethnicity was observed in patients with advanced acral/mucosal/uveal melanoma treated with anti-PD-1 therapy.

This finding challenges the prevailing notion that the connections between the effectiveness of PD-1 blockade and ethnicity are solely due to differences in melanoma histologic subtype. Other factors, such as sociodemographic variables and access to healthcare, may contribute to these outcome differences, particularly in regions with rural areas and healthcare disparities. However, the exact reasons behind the variations in treatment benefits remain unclear.

Additional research is needed to explore the effect of therapy response across different demographic groups and to assess biomolecular factors, including genomic assessments and immune activation and exhaustion status assays, across different ethnicities. As such, no firm conclusions can be drawn based on current study results.

Immune therapy related adverse events

Recently, a study published in JAMA Open in 2022 demonstrated that patients experiencing immune therapy-related adverse events had better survival compared to those without such events.[67] Additionally, a study by Eggermont and colleagues reported an association between immune-related adverse events and improved recurrence-free survival in stage III melanoma patients treated with adjuvant anti-PD-1 therapy.[68]

Despite these findings, to date only immune therapy induced vitiligo has been directly linked with improved survival. Additional research is needed to identify other specific adverse events associated with improved outcomes, in order to enhance response prediction in immunotherapy treated patients.

Radiological response

Mixed response

Immunotherapy has significantly improved overall survival in metastatic melanoma. However, evaluating individual patient responses to immunotherapy can be complex.[69-71] The dynamics and configurations of immunotherapy response are still being comprehensively characterized. A distinct subgroup of patients with stable disease according to RECIST criteria (less than 20% tumor

progression and less than 30% tumor regression) display intermediate survival rates.[72] Nuanced response patterns often elude detection with current radiographic methods like RECIST, prompting the development of alternative immunotherapy-specific assessments, such as iRECIST.[73] While iRECIST can be beneficial, its implementation in clinical care can be complex and cumbersome.

A specific radiological response is pseudoprogression, in which tumors initially increase in size but eventually regress.[74,75] Additionally, patients may exhibit regression in some tumors while others progress, known as a mixed response. Alternatively, some patients experience progression in a solitary site or organ, termed oligometastatic progression.

The management of these specific responses is less clear. In **Chapter 7**, we describe the occurrence and management of mixed responses to immunotherapy in patients with advanced melanoma. Mixed response most closely aligned with stable disease, demonstrating a dynamic state as mixed responders eventually continued to partial response or disease progression. Notably, patients with a mixed response who eventually responded to therapy underwent surgery more frequently than those who did not respond. Unsurprisingly, patients who underwent surgical treatment exhibited an enhanced overall survival compared to those who did not.

Our study supports an observation period of approximately three months for advanced melanoma patients with a mixed response to immune checkpoint inhibition, with re-assessment using serial imaging. We identified prognostic factors related to therapy response in this specific group, including higher median LDH levels, the presence of metastases in three or more organ sites, and brain metastases. Surgery could be suitable for mixed responders with later no response, if progressive symptoms are present and no other systemic therapy options are available.

Further refinement of clinical classification systems and identification of features associated with better or worse outcomes may guide clinical decision-making in these challenging situations. The use of consolidative surgery in mixed response patients should be considered on a case to case basis.

Heterogeneous response

In **Chapter 8**, we reported the clinical outcomes and management of mixed response, pseudoprogression, and sarcoid-like reaction in advanced melanoma patients treated with immune checkpoint inhibition therapy. We found that mixed response occurred most frequently, while pseudoprogression and sarcoid-like reactions were less common. We emphasize the importance of recognizing mixed response, as it is not uncommon, and clinicians should be aware of this clinicoradiological phenomenon.

Patients who develop a mixed response should be evaluated in more detail, with attention to previously identified prognostic factors to potentially predict further therapy response. Since therapy response can still occur in these complex cases, it is important not to halt therapy too early.

For patients who develop pseudoprogression, these were all classified as having progressive disease (PD) according to RECIST criteria. Despite PD classification, these patients had good overall survival outcomes, consistent with findings from several other studies. These findings support continuing immune checkpoint inhibition when pseudoprogression is suspected, and underlines the importance of assessing response clinically next to radiological evaluation.

Given the complexity of radiological disease assessment in patients with heterogeneous responses, additional biomarkers may be helpful in identifying those who will eventually respond to therapy. By documenting and reporting the occurrences of these specific radiological phenomena, we hope that national databases will begin to register these unique responses in the coming years. This could significantly improve clinical management for this patient group.

Conclusion

Early detection of melanoma is crucial for enhancing melanoma-specific survival. Personalized surveillance for who are at risk for melanoma development can aid in improving early melanoma detection. We identified specific phenotypic clinical risk factors associated with melanoma development in patients with multiple (atypical) naevi, and these should be taken into consideration when determining whether follow-up is necessary in this patient group.

Patients with a *CDKN2A* germline mutation have a 70% lifetime risk of developing melanoma, necessitating regular skin examinations for early detection. Understanding whether melanoma arises from pre-existing nevi or normal appearing skin in these patients can enhance clinical management. Our study using total body photography (TBP) found that most melanomas developed from pre-existing nevi, supporting the use of TBP and sequential dermoscopy. Surgical removal of melanocytic nevi in patients with *CDKN2A* germline mutations might help prevent melanoma development.

The introduction of immune checkpoint inhibitors has significantly improved outcomes for stage III/IV melanoma in both adjuvant and systemic settings. Our study found that adjuvant anti-PD-1 or *BRAF/MEKi* therapies improves locoregional disease control in resected stage III/IV melanoma patients who did not undergo standard complete lymph node dissection.

Despite improved outcomes in the adjuvant setting, immunotherapy can induce severe long lasting adverse events. Therefore, it is important to identify clinical prognostic variables

associated with adverse event development. In our study, we identified that the presence of any type of comorbidity and decreased ECOG performance status were associated with an increased risk on adverse event development in adjuvant treated stage III/IV melanoma patients. We observed no significant difference in adverse event occurrence rates in adjuvant versus advanced immunotherapy treated patients, suggesting that the extent of disease is of little influence in adverse event development.

Currently, the advent of neo-adjuvant immunotherapy revolutionized the treatment for stage III melanoma even further, as it has demonstrated greater benefits than adjuvant therapy alone, suggesting it may become the primary treatment for high risk stage III melanoma patients.

For advanced melanoma, predictive factors for systemic therapy response include age, LDH levels, cerebral disease, the number of affected organ sites, ECOG status, mutation status, immune therapy-related adverse events, and histologic subtype. We observed similar treatment-specific survival in advanced nodular melanoma patients treated with anti-PD-1, compared to stage IV superficial spreading melanoma patients. However, despite this, we observed a shorter overall survival in advanced nodular melanoma due to its tendency to metastasize earlier than superficial spreading melanoma. Therefore, histologic subtype should be assessed when determining optimal follow-up for primary melanoma patients. Additionally, histologic subtype could potentially play a role in adjuvant therapy considerations.

Clearly the kinetics and heterogeneity of immune checkpoint inhibitor responses are insufficiently captured by RECIST 1.1, which is cumbersome to use in real-world clinical management outside of clinical trials. We identified that a heterogeneous response was not uncommon to immunotherapy and we observed specific radiological patterns; mixed response, pseudoprogression and a sarcoid like reaction. Mied response patients had an intermediate survival outcome, and we show that these responses are dynamic and can evolve over time. Clinical characteristics associated with progression of disease after initial mixed response included higher LDH, brain metastases, and ≥ 3 organ sites with metastases. Surgical treatment for highly selected patients with a mixed response was associated with improved outcomes. Patients with pseudogrogression were all staged as progressive disease (PD), underlining the shortcoming of RECIST criteria for this patient group, and all had benefit from therapy continuation.

We recommend to perform serial imaging with a low threshold in patients with a heterogeneous response to immunotherapy and not to halt therapy too early, as response to treatment may still occur. In-depth analysis of immunogenic and tumoral responses is required in these complex cases and could potentially shed light on this phenomenon in the future.

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