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RESEARCH ARTICLE

The Current Successes (and Failures) in the Treatment of Cutaneous Metastatic Melanoma

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ABSTRACT

The contemporaneous treatment of cutaneous metastatic melanoma (CMM) has been revolutionized in a process started decades ago with the better understanding of cancer genetics, cancer biology and the functioning mechanisms of the immune system, which were more recently translated from basic and clinical research into efficacious and effective new drugs. At the turn of the 21st century, patients with CMM had very few treatment options and their survival was measured in few months. Traditional chemotherapy or cytotoxic drugs had very limited non curative potential, with OS in the ranging from 6 to 12 months, at best.

Currently, the use of immune check point inhibitors (ICIs) and drugs directed at blocking mutated BRAF gene proteins as well as MEK inhibitors have transformed the landscape of CMM treatment, with immense positive impact on hard surrogates such as overall survival (OS) and disease-free survival (DFS) and on the quality of life (QoL) of such patients.

Our objective here is to review the last ten years of data regarding this evolution, as well as acknowledging its pitfalls and limitations, while trying to look forward in the search for biomarkers that could better tail treatment choices while preventing unnecessary toxicities.

Introduction

The contemporaneous treatment of cutaneous metastatic melanoma (CMM) has been revolutionized in little more than a decade when the acquired knowledge about cancer genetics, biology and the functioning mechanisms of the immune system were translated from basic and clinical research into efficacious and effective new drugs. A qualified, well-coordinated and obsessive conduction of clinical trials was able to finally demonstrate robust treatment benefits that we can, currently, offer to our patients in this previously gruesome scenario. At the turn of the 21st century, patients with CMM had very little treatment options and could hope for a survival which was measured in few months. Traditional chemotherapy or cytotoxic drugs, used as single agents (Dacarbazine was the usual prototype) or in combination (Carboplatin and Paclitaxel) demonstrated either in randomized trials or metanalyses a very limited non curative potential, with OS in the ranging from 6 to 12 months, at best.[1,2]

The role of the immune system in either allowing development or in the maintenance of cancer has been investigated for a long time. Its manipulation initially through the use cytokines such as interferons or interleukins, was tested in variable regimens. With the exception of pioneering studies by Rosenberg at the National Cancer Institute (NCI) that have demonstrated that a small fraction of patients could achieve long term survival with high dose Interleukin-2 (IL-2), most of those trials using cytokines failed to demonstrate a significative survival advantage and also presented a very difficult toxicity and safety profile, which usually limited their use to very experienced therapeutic or research groups.[3,4]

The tentative combination of cytotoxic agents and cytokines, known as biochemotherapy, was developed from single institutions initiatives, but failed to reach efficacy and safety standards in randomized trials, preventing it to be an acceptable therapeutic option for patients with CMM. [5–7]

During the first decades of the current century, two principles of cancer development, or hallmarks, were successfully explored to form the basis of the existing therapies of CMM. These approaches have built upon the previous scientific knowledge, allowing the oncologic community to abandon chemotherapy or cytokines interventions, with rare exceptions and in very specific scenarios.

With recent technological developments such as gene sequencing, and the newly acquired knowledge about genetics of the cancer cell (cancer genomics) we were able to identify specific gene mutations, gene fusions or deletions associated with the development and maintenance of the malignant process. As we better understood the pathophysiologic mechanism of cancer development and driver mutations, this knowledge was translated into drug targeting of specific enzymes, such as tyrosine kinases, allowing the development of tyrosine kinase inhibitor drugs. One of the first validations of the effectiveness of this approach was the use of inhibitors of the product of gene fusion BCR-ABL that changed the natural history of Chronic Myelogenous Leukemia (CML) carrying the Philadelphia chromosome. [8]

In the last decade, a recognized hallmark of cancer development and maintenance, the capacity of avoiding immune elimination, opened another avenue for investigation. As we revisited the immune system capacities and with the crescent recognition of the role of the activated cytotoxic CD8+ T lymphocytes as a competent control system against cancer, it was soon demonstrated that CD8+ T cells were inhibited and nonfunctional in most patients in whom cancer had developed beyond its initial stages. The knowledge about the mechanisms behind T-cell inhibition form the basis of recently developed agents that led to the emergence of drugs known as immune check-point inhibitors (ICIs). The concept that the immune system could be reactivated in its capacity to identify and eliminate tumor cells, through the recognition of cancer antigens, previously under a negative immune influence of the cancer cell, through the expression of negative checkpoints, was successfully explored and proven in a series of revolutionizing clinical trials. These ICIs are one of the mainstays of the current the treatment of CMM and a growing number of different cancer types. [9–11]
Again, the therapeutic agents (immune checkpoint inhibitors and small molecules inhibitors of tyrosine kinases, such as *BRAF* and *MEK*) that were developed and subsequently tested derived from basic research knowledge. Their clinical use, goals and landmark results, shortcomings and toxicities are described in this review.

A major challenge remaining today is to recognize that these therapies are not effective for many CMM patients. The search for biomarkers that can better guide our treatment choices is of paramount importance, as is the investigation as to how to better deal with their toxicities, both acute and long term. Lastly, but not less important, the financial toxicities associated with these new treatment options must be addressed if we want to transform

the outcomes not only for CMM patients, but of all cancer patients, in the present and in near future.

Immune Checkpoint Inhibitors

As previously stated, the rationale for the use of immunotherapy for the treatment of CMM is not recent, coming from previous experiences with the use of high doses of IL-2 and Interferon which demonstrated very low response rates, in the range of 5-10%. [4] Furthermore, these treatments were associated with high rates of toxicity that often led to treatment discontinuation due to adverse effects. However, the fortunate few patients who did respond and could tolerate the adverse effects were experiencing long periods of remission, much superior to any cytotoxic therapy regimen.

The advent of a better understanding of carcinogenesis with Hanahan and Weinberg's article on the Hallmarks of cancer, emphasizing the role of immune evasion mechanisms of tumor cells, particularly the interaction of antigen-presenting cells (APCs), T-lymphocytes, and tumor cells, as well as the proteins involved in this process, led to the beginning of the modern era of immunotherapy with the use ICIs. [10] These series of surface proteins or receptors act together in multiple combination mechanisms, sometimes activating and other times inhibiting the activation of T-cells, triggering an immune response. [12] Tumors can exploit these pathways to modulate immune response to its advantage.

Immune activation is achieved by the binding of Major Histocompatibility Complex (MHC) receptors, a kind of "individual identity," on each cell, with T-cell receptors (TCRs) present on CD8+ T lymphocytes. They “read” and identify whether the cell belongs to that individual person or is considered foreign (non-self). This mechanism is how humans develop immune responses to microorganisms and tumor cells as well. When a protein is identified as foreign, the immune response process is initiated to eliminate those cells, activating cytotoxic and humoral responses.

To avoid excessive responses from the immune system, a negative regulatory mechanism exists to maintain homeostasis. This is achieved by the binding of CTLA-4 (cytotoxic T lymphocyte-associated protein 4) on CD8+ T surface to B7-1 and B7-2 receptors on APCs. The interaction between CTLA-4 and its ligand carries a negative regulatory signal, blocking IL-2 transcription and therefore the progression through the cell cycle, preventing lymphocyte replication and differentiation. [13,14]

The second negative tunning pathway is programmed death protein 1 (PD-1). Its function is to control the replication and activation of lymphocytes through regulatory T cells (Tregs), reducing periodicity and inducing apoptosis. [12] More recently discovered, lymphocyte activation gene 3 (LAG-3), is an inhibitor expressed in exhausted lymphocytes, which performs negative regulation by inhibiting lymphocyte activation. [15]

ICIs use is based on the rationale of releasing the immune system brakes, stimulating the patient’s immune response against cancer. [16] This mode of action contrasts with classical cytotoxic or targeted therapies that directly act against neoplastic cells. This shift of focus also implies a different profile of adverse effects, discussed below.

The first drug to improve survival in metastatic melanoma using this pathway was Ipilimumab, a CTLA-4 inhibitor that, in the MDX010-20 trial demonstrated a median overall survival (OS) of over 10 months for previously treated patients. [17] However, the most significant data came from long-term follow-up, showing that the survival rate at 12 and 24 months was 46% and 24%, respectively, demonstrating the existence of patients alive after 2 years, a result previously unreached in patients with CMM.

PD-1 receptor inhibitors achieved even better results. The CheckMate 066 study compared Nivolumab to chemotherapy (Dacarbazine) in patients with unresectable stage III or stage IV disease who were previously untreated. [18] Patients who used nivolumab had a 58% lower chance of death compared to the chemotherapy group. Pembrolizumab showed similar benefits, as demonstrated in the 7-year follow-up update of the Keynote 006 study, where pembrolizumab remained superior to ipilimumab in terms of OS (37.8% *vs.* 25.3%) and progression-free survival (PFS) (9.4 *vs.* 3.8 months; 95% CI: 6.7-11.6). [19] Atezolizumab, an anti-PD-L1 drug, has also demonstrated good results used as monotherapy, with a response rate (RR) and disease control rate of 35% and 46%, respectively. [20,21]

These promising first results led to the investigation of combining immune activation mechanisms. A phase III study compared Nivolumab-Ipilimumab (Anti-PD-1 + anti-CTLA-4) versus Ipilimumab alone, showing a significant increase in PFS and a higher rate of patients alive after 6.5 years: 49% for Ipilimumab-Nivolumab, *vs.* 23% for Ipilimumab alone. Detailed subgroup analyses of these ICI trials demonstrated that the benefits remained, even in patients without PD-L1 expression and in *BRAF*

mutated patients. [19,22,23] This finding of marker-independent analyses led to the current practice of not incorporating PD-L1 expression to the decision-making process of CMM treatment. [24] Across different trials, there have been around 10% complete responses with ICI monotherapy and up to 15-20% in ICI combinations, with disease control of over 50 months, raising the question of whether these patients could be actually cured.

The utility of another immune pathway inhibition was recently illustrated with the combination of Relatlimab (anti-LAG3) with Nivolumab, in a study that has demonstrated an increase in median PFS of 10.2 *vs.* 4.6 months and a response rate of 43.1 *vs.* 32.6%. [25,26]. Unfortunately OS results have not yet been achieved. [26] Unlike in treatments with anti-PD1 and CTLA-4, PD-L1 and LAG-3 expression > 1% proved to be predictive of response, with a RR of 53% *vs.* 30% when both biomarkers were negative. [26]

Patients treated with ICIs may develop immune-mediated toxicities. The most common ones are skin rash, diarrhea, hepatitis, hyper- or hypothyroidism, and pituitary insufficiency. [27] The incidence is higher with either anti-CTLA-4 in monotherapy or its combinations. While toxicities generally respond well to the management with corticosteroid therapy physicians must be aware and provide comprehensive clinical care for patients receiving ICIs.

BRAF inhibitors

BRAF mutation constitutively activates the mitogen-activated protein kinase (MAPK) pathway, promoting cell proliferation and acting as a driver for transformation into malignant cells. [28] In 2002, a comprehensive analysis of solid cancers revealed that approximately 60% of melanomas, and 8% of all cancer types carry an activating mutation in the gene encoding *BRAF*. [29] Among all tumors harboring a *BRAF* mutation, the V600E mutation occurs in 80 to 90 percent of cases, while the V600K mutation occurs in approximately 15 percent of cases. [30]

Focusing on this target, *BRAF* inhibitors (*BRAF*i) have been developed, with very significant results. Vemurafenib, an orally available inhibitor of mutated *BRAF*, was the first selective *BRAF* inhibitor evaluated in clinical trials. In 2010 a phase I study demonstrated an overall RR of 69% in solid tumors refractory to standard therapy. In the melanoma cohort, the RR was 81%. [31] Subsequently a phase II study of vemurafenib confirmed a RR of 50% in patients with previously treated CMM carrying the V600E or V600K *BRAF* mutations. [32]

These initial trials led to a phase III study comparing Vemurafenib to Dacarbazine, the standard of care chemotherapy at the time. Comparatively to chemotherapy, patients in the Vemurafenib group experienced a significant reduction in the risk of progression of 74% and a reduction in the risk of death of 63%, which ultimately resulted in the regulatory approval of Vemurafenib. [33] In March 2014, the updated follow up confirmed these favorable outcomes, with a median OS of 13·6 months in the Vemurafenib group compared with 9·7 months in the Dacarbazine group. [34]

Dabrafenib, another *BRAF* inhibitor, was subsequently developed and demonstrated comparable activity to Vemurafenib. [35] In a phase III trial that included 250 patients with previously untreated advanced melanoma, with *BRAFV600E* mutation-positive and compared Dabrafenib with Dacarbazine, objective responses were reported in 53% of the patients in the experimental group, with a median time to response of 6·2 weeks. The median PFS was also superior with Dabrafenib (5.1 vs. 2,7 months). [36]

The toxicity profile of these two *BRAF*i monotherapy drugs differ from chemotherapy. The most common adverse events on these trials were cutaneous (hyperkeratosis, papillomas, palmar-plantar erythrodysaesthesia), as well as arthralgia and fatigue. Vemurafenib causes more phototoxic effects and cutaneous squamous cell carcinomas (SCC), whereas fever, pyrexia and chills occur more often with Dabrafenib. [33,36]

MEK inhibitors

Given that Dabrafenib and Vemurafenib provide only a limited 5 to 7-months until disease progression, research has focused on understanding the mechanisms of acquired resistance. The findings suggested a potential reactivation of the MAPK pathway upstream of *MEK* as a contributing factor. [32,36]

Trametinib, an oral selective inhibitor of *MEK*1 and *MEK*2 activation and kinase activity, previously demonstrated RR of 33% in a phase I trial in 2012, used as monotherapy in previously treated patients. [37] This led to a phase III trial for patients with advanced melanoma with a V600E or V600K *BRAF* mutation to Trametinib versus chemotherapy, as first or second line after progression to chemotherapy. The median PFS was only 4.8 months in the Trametinib versus 1.5 months in the chemotherapy group. Notably, no cutaneous SCC were observed while treatment with Trametinib. The most common adverse events in the trametinib group were rash, diarrhea, peripheral edema, fatigue, and

dermatitis acneiform, but most grade 2 or lower. Central serous retinopathy and retinal-vein occlusion have been uncommon but worrisome events associated with this *MEK* inhibitor (*MEK*i), as well as ventricular dysfunction, observed in 7% of patients. [38] Although trametinib was approved by the FDA in 2013, the use as monotherapy was overtaken by the superior efficacy with single-agent *BRAF*i and the posterior use of combination of *BRAF*i and *MEK*i.

Combined *BRAF*/*MEK* inhibition

The co-targeting of mutated *BRAF* and *MEK* was assessed in a phase I/II study that combined the *BRAF*i Dabrafenib with the *MEK* inhibitor Trametinib in patients with metastatic *BRAFV600* melanoma. This approach revealed a good safety profile, despite an increased occurrence of pyrexia and chills noted with the combination. Additionally, more frequent gastrointestinal toxic effects were observed, most of grade 1 or 2 severity. Interestingly, proliferative skin lesions, including cutaneous SCC, were less commonly observed with Dabrafenib–Trametinib combination (7% vs 19%), supporting the hypothesis that concurrent *MEK*i attenuates paradoxical MAPK activation. [39]

The combination of Dabrafenib with Trametinib was evaluated in two phase III trials, compared with single-agent *BRAF*i using either Vemurafenib (COMBI-v) or Dabrafenib (COMBI-d). COMBI-v randomized 704 patients to the combination of Dabrafenib and Trametinib or Vemurafenib alone, as first-line therapy to *BRAFV600E/K* mutated advanced melanoma patients. The objective RR was significantly higher in the combination therapy (64% vs. 51%), the median PFS was 11.4 months vs. 7.3 months to Vemurafenib and OS was also significantly increased with the combination. Cutaneous SSC and keratoacanthoma occurred in 1% of patients in the combination-therapy group and 18% of those in the Vemurafenib alone group. [40] In extended follow-up, the combination continued to improve both PFS and OS after three years (PFS 25% *vs.* 11%; OS 45% *vs.* 32%). [41] The COMBI-d trial included a similar population as COMBI-v. The results confirmed the combination superiority, with 3-year PFS of 22% *vs.* 12% and 3-year OS of 44% vs. 32%. The combination also increased the non-cutaneous toxicity such as diarrhea (18 versus 9 percent), pyrexia (52 versus 25 percent), and chills (28 *vs.* 14%), leading to 11% of discontinuation. [42]

A different *BRAF*i/*MEK*i combination was evaluated in a phase III trial with Vemurafenib and Cobimetinib. The COBRIM trial randomized 495 patients with previously untreated advanced *BRAFV600* mutation–positive melanoma to combination versus monotherapy Vemurafenib. [43] The updated efficacy results confirmed a significant survival benefit with combination therapy, with median PFS of 12·3 months versus 7·2 months and median OS of 22·3 months versus 17·4 months. [44] Overall, 70% of patients in the combination group had an objective response, as compared with 50% in the control group. Some toxic events were observed at a lower frequency in the combination group than in the control group, including alopecia, arthralgias, keratoacanthomas and cutaneous SCC. The rate of grade 3 events was 60% with combination vs. 52% with vemurafenib.

The third *BRAF*i/*MEK*i combination approved was that of Encorafenib and Binimetinib. The COLUMBUS phase III trial compared this combination with Vemurafenib or Encorafenib monotherapy in treatment of naive patients with advanced melanoma, harboring *BRAFV600E/K* mutation. [45] The median PFS was longer for patients in the Encorafenib plus Binimetinib group than for those in the Encorafenib (14.9 *vs.* 9·6 months) or Vemurafenib (7·3 months) groups, showing a significant reduction in the risk of progression or death (HR 0.54) with combination compared with Vemurafenib. The overall response also was improved with combination (63% vs. 51% with Encorafenib and 40% with Vemurafenib).

Grade 3–4 adverse events were reported in fewer patients in the combination group (58%) than in either the Encorafenib (66%) or Vemurafenib (63%) groups. The most common grade 3–4 adverse events were increased γ-glutamyltransferase, creatine phosphokinase and hypertension with combination; compared to palmoplantar erythrodysaesthesia syndrome, myalgia, and arthralgia in the Encorafenib group; and arthralgia in the Vemurafenib group. SCC affected 3% in the combo group, 8% in the Encorafenib group, and 17% in the Vemurafenib group.[45]

Overall survival results were published in 2018, demonstrating a 39% reduction in the risk of death for patients treated with Encorafenib plus Binimetinib compared to Vemurafenib. [46] The median OS was 33.6 months and 16.9 months, respectively. The difference between combination and Encorafenib monotherapy was lower and non-statistically significant.

The trials above have established these three combinations of *BRAF*i and *MEK*i as standard first-line targeted therapies for patients with *BRAFV600*–mutant melanoma. Since they have

not been directly compared in randomized trials, choice is made based on the toxicity profile, accessibility, and patient/physician preference.

Combined Immunotherapy and Targeted therapy

Early-phase trials indicated that three-drug combinations had promising anti-cancer properties, with very few subjects witnessing disease progression as the first evaluable response. [47–50] For example, the combination of Dabrafenib, Trametinib, and Durvalumab reported a 76% ORR, with all 15 subjects in the *BRAF*-mutant cohort of the trial achieving disease control [47]. Similarly, a combination of Vemurafenib, Cobimetinib, and Atezolizumab yielded an 85.3% preliminary RR, with roughly 69% of the subjects still showing disease control during the final data review. [49]

These promising results from early-phase trials with triple therapies led to randomized studies, aiming to evaluate the efficacy of three-drug combinations with *BRAF*i/*MEK*i as the control groups. Both the KEYNOTE-022 and COMBI-I trials examined the enhanced efficacy of a *BRAF*i/*MEK*i doublet when paired with anti-PD1 agents (Pembrolizumab and Spartalizumab, respectively) compared to just the *BRAF*i/*MEK*i combo. [51,52] Similarly, the IMspire150 study explored the effectiveness of a combination of Vemurafenib, Combimetinib, and Atezolizumab, comparing it with a regimen of Vemurafenib and Cobimetinib. [53] Nonetheless, these studies have presented mixed outcomes, leaving the definitive role of three-drug combinations still in debate.

In the phase II KEYNOTE-022 trial, researchers assessed the effectiveness of combining Dabrafenib with Trametinib and Pembrolizumab versus the standard *BRAF*i/*MEK*i combo, in treating *BRAFV600*-mutant CMM patients in the first line setting. Although the three-drug regimen showed a numerically longer median PFS (16.0 months *vs.* 10.3 months), the primary study endpoint did not reach statistical significance. Furthermore, there was no observed advantage in overall survival OS and RR with the triplet regimen (63.3% compared to 71.7% in the standard treatment). [51] Subsequent findings from the initial analysis of the phase III COMBI-i trial did not demonstrate the combination of Dabrafenib, Trametinib and Spartalizumab to be superior to the same placebo-controlled combo, in terms of PFS. During this analysis, OS was not evaluated for statistical significance. The ORR appeared comparable between both groups (68.5% *vs.* 64.2%).[52] On a contrasting note, the phase III IMspire 150 trial achieved a PFS advantage with the combination of Vemurafenib, Cobimetinib, and Atezolizumab compared to a placebo-based combo treatment. The median PFS was 15.1 months for the three-drug combination *vs.* 10.6 months for the doublet. After around 18 months of follow-up, 43.6% of patients on the triplet regimen were progression-free compared to 31.6% on the dual treatment. No subgroup of patients seemed to benefit more than others. Additionally, the Atezolizumab group showed a longer duration of response (DoR) (21.0 months *vs.* 12.6 months). [53]

Since the results of these trials have not yielded particularly impressive outcomes and the lack of comparative trials with combination immunotherapy, the role of triple therapy is still to be determined.

Sequencing treatment for *BRAF* mutated patients

Patients with CMM that harbor the *BRAFV600 E/K* mutation can be treated either with ICIs or targeted therapy. The use of *BRAF*i/*MEK*i tends to produce higher initial overall RR, while the immunotherapy approach, especially using the combination of Nivolumab and Ipilimumab demonstrates longer duration of response and OS. [25,42,46,54,55] When results from randomized trials were not yet available, a usual approach among clinical oncologists was to treat patients with a higher volume of disease or those more symptomatic with targeted therapy first, while those patients that were asymptomatic or with fewer sites of metastatic disease, usually received ICIs, either as monotherapy or combination therapy.

In 2022 the first randomized data on sequencing were presented and published. In the phase III DREAMseq trial, patients with *BRAF* mutant melanoma were randomly assigned to receive either immunotherapy (Nivolumab plus Ipilimumab) or targeted therapy (Dabrafenib plus Trametinib) as first line treatment, with a cross-over to the alternate regimen at the time of disease progression by RECIST. [56] This trial was positive for its primary endpoint, 2-year OS, with the sequence of immunotherapy followed by targeted therapy having almost 72% of patients alive *vs.* 52% with the opposite sequence. A trend towards improvement in PFS (11.8 months *vs.* 8.5 months) and in the median duration of response were also observed. All patient subgroups presented a trend of towards benefit when immunotherapy was the frontline treatment, including those with high volume of disease or worse prognostic factors. The toxicity profile was similar in both groups.

Another recently published trial, the phase II randomized trial SECOMBIT also evaluated the

best sequence approach comparing immunotherapy and targeted therapy in the *BRAFV600* mutant CMM patients. [57] In the same manner as with the DREAMseq, starting treatment with immunotherapy followed by targeted therapy demonstrated a trend to better survival outcomes, with higher PFS and OS, although this trial was not statistically designed to compare between treatment arms. The SECOMBIT trial also evaluated an alternative treatment regime initiating with a short course (8 weeks) of targeted treatment followed immunotherapy until progression. The rational for this third arm, also called "sandwich arm", was based on preclinical data and from a series of sequential biopsies of 16 patients collected during the first 14 days of treatment with *BRAF*i/*MEK*i and at the time of progression. In these patients, an immunomodulatory effect of the targeted treatment in the tumor microenvironment, leading to an increment in the antigen presentation and pro inflammatory cytokines. [58,59]

Both trials support the benefit of ICIs as first line treatment in the CMM patient harboring a *BRAF* mutation. Also, the overall RR of immunotherapy as front-line treatment was superior in comparison of those who started with targeted treatment (45% vs. 25%). [57] The benefits of immune approach first could be explained by recent published data suggesting that targeted treatment induces an immunosuppressive tumor microenvironment. [60,61]

While this data supports the use of combined immunotherapy as frontline therapy in patients with *BRAFV600E/K* mutant CMM, there are still many caveats and unanswered questions. We still need to understand which are the patients that benefits most with each strategy and develop biomarkers that could guide patient selection more efficaciously.

Conclusions and future perspectives

The estimated incidence of cutaneous melanoma in the United States by the year 2040 will make it the second most common malignancy in both men and women, surpassing lung, and colorectal cancers and second only to breast cancer. [62] CMM is a complex illness, demanding multidisciplinary management. Surgical approach was once the therapy of choice for oligometastatic patients as a first line of treatment, but now is now restricted for very selected oligometastatic patients or those in whom metastatic disease that has failed targeted therapy or immunotherapy.[63] Currently, even patients with brain metastases can be efficaciously and safely treated with the novel approaches . [60,64]

In the last couple of years, novel agents, including personalized melanoma vaccines (mRNA-based, for example) or drugs targeting other immune checkpoints (TIGIT, LAG-3) or bispecific T-cell antibodies have shown promise in early trials, and more mature randomized data are eagerly awaited. [26,65,66] Another important point is the search and development of biomarkers that could better tailor treatment, selecting patients, improving results, diminishing toxicities for patient and costs for health providers. [55,67–69]

In conclusion, many efforts from the last 20 years have resulted in dramatic improvements in survival for CMM patients. Further efforts should be in search for improving early diagnosis, stratification factors, response predictors, and quality of life. These will be fundamental for increasingly individualizing therapy, further improving outcomes, reducing unnecessary toxicities, and reducing financial impacts.

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