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Epidemiology and Risk Factors of Melanoma: A Review

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Guest Editors

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ABSTRACT

We are currently witnessing a worldwide increase in the incidence of melanoma. Incidence in Europe is about 25 cases per 100,000 population, while in Australia it reaches a rate of 60 new cases per 100,000. While the epidemiological curves of the 1980’s and 1990’s suggested an increase in the incidence of melanoma across all age groups, the last 10 years’ data indicates a 5% reduction in the incidence of thin melanoma in young individuals aged between 15 and 24. This suggests a positive impact of primary prevention campaigns [1-2]. The risk factors associated with melanoma are different and multifactorial: on one hand there is a genetic predisposition, as evidenced by the increased risk in patients with dysplastic nevus syndrome, with familial melanoma or familial melanoma syndromes; on the other hand, the unprotected interaction between UV rays and phototypes I-II increases the risk of developing melanoma, especially in case of sunburns in pediatric age. This review aims to summarize melanoma epidemiology and risk factors.
Introduction

Melanoma incidence is increasing in white skin populations, especially where fair-skinned individuals are subject to excessive sun exposure, as attested by incidence and prevalence data of skin cancers in Australia [3]. In Europe, the incidence rate is about <25 new cases of melanoma per 100,000 population; in the United States (US), 30 per 100,000; and in Australia, where the incidence rate is extremely high, it reaches 60 cases per 100,000. In recent years, there has been a dramatic increase in incidence in people over 60 years of age and in general in all age groups. Incidence curves suggest that the incidence will continue to increase in the coming years [4].

The most common phenotypic risk factor is sunburn-prone skin, whereas melanocortin-1 receptor (MC1R) gene variants are the most important underlying genetic determinants studied in the last decade. Individuals with a high number of common nevi and those with large congenital, multiple, and/or atypical nevi are at higher risk, and this phenotype is also genetically determined [5]. Melanoma is more likely to be diagnosed in these groups of patients, which is why they need thorough follow-up and clinical monitoring. The genetic component is part of the increased risk although it is not the main factor. The most important exogenous factor of melanoma is UV exposure, particularly intermittent sun exposure [6].

Epidemiology and Risk Factors of Melanoma

Incidence Trends

Cutaneous melanoma (CM) is by far the most common subtype of melanoma, accounting for more than 90% of melanoma cases [3].

Since the Second World War, the incidence of CM has increased while Australian and North American data showed a stabilization of CM rates [7].

In these countries, primary and secondary prevention campaigns have increased allowing to limit the damage mediated by UV rays. This has been obtained by increasing information diffusion on the importance of sun protection, by implementing diagnostic systems, such as dermoscopy, allowing for early suspicious diagnosis.

Queensland (Australia) epidemiological trends during the last 10 years, show a 5% decrease of thin melanoma incidence in young individuals between 15 and 24 years, suggesting that primary prevention efforts are being carried out successfully [7-8]. On the other hand, a significant reduction in mortality in all age groups has not yet been observed [8].

Melanoma is reported as the 19th most common cancer worldwide, with estimated age-adjusted incidence rates of 2.8-3.1 per 100,000 [9].

The analysis of CM trends in Europe between 1995 and 2012, shows an incidence rate ranging from 5.6/100,000 inhabitants in Spain to 24/100,000 in Switzerland where there is the highest number of diagnosed in situ melanomas [7].

The median age at diagnosis is 61 years for men, 56 for women. In situ melanomas constituted 25% of diagnosed melanomas, while superficial spreading melanoma (SSM) was the most frequent variant constituting 46% of diagnoses. As regards lesions’ distribution, this varied between men and women: in men the most frequent site was the trunk (43%), in women the legs (57%) [7].

Otherwise, Australia and the US have higher incidence rates compared to Europe. The reason for this marked incidence variation is unclear and could be associated with cultural and wealth differences influencing the sun exposure time. Another reason could be due to the fact that many European countries do not have a cancer registry, or this is not rigorously updated [6].

The incidence of melanoma is increasing at a greater rate than other types of cancer. The mean age at diagnosis is 57 years with higher incidence in women in the younger age groups while the ratio reverses in old age with higher incidence in men. Estimates from the US report a lifetime risk of melanoma of 1 in 56 for women and 1 in 37 for men. In general, mortality rates are higher among men than women [5,6], possibly due to the later presentation of the disease.

Risk Factors: Photo-Type, Nevus Count, Ultraviolet Rays

Several risk factors thought to be significant in the development of cutaneous melanoma have been identified by epidemiologic studies. These can be divided into environmental factors and genetic factors, but there is clearly an interaction between genetics and environment.

Pigmentation has an indisputable and significant influence on skin susceptibility to malignant change. Melanocortin 1 receptor (MC1R) is a cell surface receptor in melanocytes that induces pigment production. There are many polymorphisms of MC1R gene, which determine the different skin phenotypes; variants such as red hair and fair skin phenotype express low pigmentation, resulting in increased sensitivity to ultraviolet (UV) light and an increased risk of associated melanoma.

In addition to characterizing the phototype, melanin, is involved in defending melanocytes and keratinocytes from UV light; this explains why phototypes I and II are at higher risk of developing melanocytic and keratinocytic cancers, being more susceptible to UV damage.

A high number of acquired melanocytic nevi, the red hair phenotype and MC1R R alleles all independently increase melanoma risk.

This is supported by a study carried out in Queensland, Australia, reporting that individuals with ≥ 20 nevi (≥ 5 mm diameter) and MC1R R/R genotype have a 25-fold increased...
melanoma risk, compared to people with 0 to 4 nevi and the MC1R WT/WT genotype; while individuals with ≥ 20 nevi and the MC1R R/R genotype have an absolute melanoma risk to age 75 of 23.3% for men and 19.3% for women [10]. Several studies have shown that the main factors associated with the development of melanoma are the number of melanocytic nevi, family history of melanoma, and genetic susceptibility. Melanoma in most cases arises on healthy skin, although 25% of melanomas are associated with a preexisting nevus and this justifies the double incidence of nevus associated melanoma in young adults and elderly. In addition, the number of moles is associated with the risk of developing melanoma especially in cases of more than 100 moles or moles with dysplastic appearance [11].

Most cutaneous melanomas arise on skin sporadically (rather than chronically) exposed to the sun, in sites and individuals who are more prone to sunburn. The highest rates are seen in individuals with repeated intense sun exposure. This theory is further strengthened by the observation that patients with melanoma who actively reduce their sun exposure after initial diagnosis are consequently at reduced risk of developing a second primary melanoma [8]. In contrast, individuals with dark skin, or skin that darkens easily in response to sunlight but does not burn, have demonstrably lower rates of melanoma [12-13]. However, sun exposure is not directly related to melanoma development, as evidenced by the fact that melanoma can also occur in sites that are not chronically exposed to the sun.

The age at which sun exposure and/or sunburn occurs also appears to be important. A systematic review [14] strongly associated intermittent sun exposure in childhood or adolescence with an increased risk of melanoma. Specifically, individuals who experienced more than 5 episodes of severe sunburn had a 2-fold increased risk of melanoma [15].

One of the most important modifiable risk factors in the etiopathogenesis of melanoma is certainly UV-B exposure [16]. Personal history of sunburn in childhood is associated with a higher risk, intermittent exposure is associated with melanoma, and chronic exposure is associated with actinic keratosis and keratinocyte cancers.

Although the melanoma-effects of UV-B exposure are well evidenced, UV-A exposure does not come without risks [17]. Artificial UV exposure may play a role in the development of melanoma; in fact, the amount of UV-A exposure in a typical tanning bed session is significantly higher than exposure during normal outdoor activities or even during sunbathing.

Sunbeds emit UV-A radiation and a meta-analysis of studies [18] that explored the incidence of melanoma following sunbed use reported a 75% increased risk in individuals under 35 years of age with a history of sunbed use. Because of the increased risk of melanoma in tanning bed users, their use has been banned in many states [19]. Instead, smoking, a common carcinogen, has not been independently associated with melanoma [20].

Finally, there is an interesting association between melanoma and comorbidities. For instance, immunosuppressed individuals, who underwent organ transplantation, are at demonstrable risk for melanoma, including recurrence in individuals with primary melanomas resected before transplantation, although the greatest risk for these patients is to develop keratinocyte cancers. In fact, the pooled relative risk (pRR) for melanoma, among liver and heart transplant patients was 5.27 (95% CI 4.50-6.62), higher than the pRR in kidney transplant patients 2.54 (95% CI 2.18-2.96). According to recent data, transplant recipients are at more than double the risk of developing melanoma overall when compared to the general population [21].

In addition, patients who present other skin malignancies (basal cell or squamous cell carcinomas or mycosis fungoides) are at higher risk of developing melanoma and subsequent death from the disease [22,23].

Genetic Factors

A family history of melanoma is a strong risk factor for the disease. Considering that familial clustering of a disease is an indicator of possible heritable causes, there has been an explosion of research in the past 2 decades directed at elucidating the genetic basis of melanoma [24]. This explains why it is important to also consider the individual genetics when determining personal risk. Genetic factors such as skin phenotype, clearly influence risk, as well as familiarity that counts for 5-10% of melanomas origin [25]. Some of these occur in specific syndromes—such as atypical familial multiple moles and melanoma syndrome (FAMMM) or dysplastic nevus syndrome (DNS)—where individuals have multiple, phenotypically variable moles at high risk for malignant transformation, thus presenting an almost guaranteed lifetime risk of melanoma. Many individuals do not meet the diagnostic criteria for these syndromes, but still have numerous nevi, often due to cumulative sun exposure [25].

Observational studies suggest a strong association between a high number of nevi and melanoma [26]. A personal history of cutaneous melanoma is also a known risk factor for additional primary melanomas [27]. All of these criteria are of great clinical value because patients with so many nevi, with familiarity for melanoma, and with dysplastic nevus syndrome are monitored nowadays with digital videodermatoscopy by performing quarterly or semiannual total body dermatoscopic examination.

To assess individual risk and to carry out successfully prevention interventions risk prediction models have been developed in recent years. Clinicians and patients have now
access to a series of online calculators assisting in prevention stages, early detection, and optimum treatment of melanoma, ultimately saving lives [28]. There are several variables considered in these scores, the most common being the presence of moles, freckle density, history of sunburns, and hair color [29].

Mucosal Melanoma

Mucosal melanoma is the least common of the 3 melanoma subtypes, accounting for less than 1.5% of all melanomas [30]. The incidence of mucosal melanoma varies with both gender and age [30], the median age at diagnosis is 70, except for oral cavity melanomas which tend to occur in younger patients. Incidence increases with age, over 65% of cases are in fact diagnosed in patients over 60. The incidence in women is almost twice as high as in men, possibly because of the higher rates of genital tract melanomas [31] amongst women. The absolute incidence of mucosal melanoma in white populations is higher (2:1) than in non-whites [30-33].

Mucosal melanomas occur most often in the head and neck region, the female genital tract, and the anorectal region [30]. No clear risk factors for mucosal melanoma are known. Because mucous membranes are not exposed to the sun, UV radiation is not considered an important etiologic factor. The role of viruses-such as human papillomavirus (HPV) or human herpes virus (HHV) implicated in other malignancies of the oral cavity-has not been demonstrated [32] while smoking has been reported to be associated with a higher prevalence of oral pigmented lesions [34].

Conclusion

Worldwide data indicates an increase in the incidence of melanoma, although primary and secondary prevention campaigns have led to a 5% reduction in the incidence of thin melanoma in individuals between 15-24 years of age, suggesting the effectiveness of preventive measures [1-2].

While it is possible to intervene with early diagnosis, there are non-modifiable risk factors that must be evaluated for each patient. Among these, photo type, number of nevi, familiarity for melanoma are independent variables associated to melanoma.

It is therefore necessary to intervene on the removal of known risk factors such as avoiding sunburn, avoiding the use of tanning lamps, and exposing to the sun without using sunscreen.

A recent study showed that broad-spectrum sunscreens that prevent erythema are unlikely to compromise vitamin D status in healthy populations. This explains the futility of avoiding sunscreen to produce Vitamin D, a theory often expressed by patients who fear the side effects of sunscreen. Based on these data, a daily broad-spectrum sunscreen with high UV-A protection does not compromise vitamin D status in healthy people and should always be used, regardless of the season [35].

On the other hand, it is necessary to implement screening campaigns even in younger age groups and carry out informative campaigns to stress the importance of an annual dermatological checkup. Moreover, to improve secondary prevention it is essential to disclose easy rules, such as the ABCDE rule (asymmetry, irregular borders, uneven color, size greater than 6 mm, and history of evolution) or the ugly duckling (a mole different from the others) that are still effective today for the early diagnosis of melanoma.

The development of new technologies, such as dermoscopy, videodermoscopy and confocal microscopy, have also increased the diagnostic capacity in small melanocytic lesions [36, 37].

This fact allows earlier diagnoses, but it increases the diagnostic capacity and therefore the incidence of the disease. From 1975 to 2015, the incidence of melanoma increased approximately 6-fold in the US. The cause of this increase, according to some authors, is not due to UV-induced sun damage or to personal risk factors but to an increased clinical and histological ability to diagnose melanoma [38,39]. In fact, according to some studies, although the incidence of melanoma has increased in most continents, mortality has remained stable. A recent work points out that the cause of the increase in diagnosis and therefore incidence of melanoma is due to a medical-legal problem, ie, more dermatologists perform biopsy analysis on suspicious lesions and more pathologists tend to diagnose melanoma, even when they are faced with “gray spaces” as in the case of dysplastic nevi [38]. According to the authors, this cycle of overdiagnosis is intensified by the use of the dermatoscope by dermatologists, which increases the number of lesions excised. The authors’ suggested solution to limit overdiagnosis would be to stop mass dermatological screening.

The data reported in our review confirms an increase in the incidence of melanoma, although mortality remains stable. However, primary and secondary prevention campaigns have had a positive impact in reducing the diagnosis of melanoma, particularly in younger populations, as previously reported and discussed. Moreover, dermoscopy, has not only increased the number of removed melanomas, it has also allowed to avoid benign lesions’ removal. On this point we disagree with the authors who claim that screening campaigns should be suspended because an annual examination allows the early detection of melanomas and the identification of high-risk patients (eg patients with more than 100 nevi or with dysplastic nevus syndrome) who need a closer monitoring. Future studies are needed to identify the effectiveness of primary and secondary prevention, to assess its impact on worldwide incidence, and to solve current controversies.
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Evolution of the Clinical, Dermoscopic and Pathologic Diagnosis of Melanoma

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ABSTRACT

The conventional narrative states that the steadily rising incidence of melanoma among fair-skinned Caucasian populations during the last decades is caused by excessive UV-exposure. There is, however, no doubt that other factors had a significant impact on the rising incidence of melanoma. Pre-1980s the clinical diagnosis of melanoma was based on gross criteria such as ulceration or bleeding. Melanomas were often diagnosed in advanced stages when the prognosis was grim. In the mid-1980s education campaigns such as the propagation of the ABCD criteria, which addressed health care professionals and the public alike, shifted the focus towards early recognition. Dermatoscopy, which became increasingly popular in the mid-1990s, improved the accuracy for the diagnosis of melanoma in comparison to inspection with the unaided eye, especially for flat and small lesions lacking ABCD criteria. At the same time, pathologists began to lower their thresholds, particularly for the diagnosis of melanoma in situ. The melanoma epidemic that followed was mainly driven by an increase in the number of in situ or microinvasive melanomas. In a few decades, the landscape shifted from an un-
Introduction

A conventional introduction of an article on melanoma diagnosis usually includes statements on the rising incidence and mortality of melanoma in general, and that melanoma is the most lethal type of skin cancer. While the latter is not true (the lethality of Merkel cell carcinoma is higher), the incidence and mortality rates of melanoma seem to have peaked recently[1]. Furthermore, a conventional introduction will also include a statement that the steadily rising incidence of melanoma among fair-skinned Caucasian populations is caused by excessive intermitted UV-exposure[2-4], but will not mention that increased public awareness, early recognition campaigns, technical innovations, and lower thresholds of pathologists had a significant impact on the rising incidence of melanoma.

A Pubmed literature search using “melanoma” and “diagnosis” keywords yields 68102 articles if unrestricted and 9621 articles if the search is limited to the past 3 years. It is obvious that even the most ambitious review cannot cover all aspects of melanoma diagnosis. Like any type of scientific research, a review should not only collect data but also create a narrative with explanatory power. The aim of this review is not to be exhaustive but to focus on the evolution of the criteria and concepts for melanoma diagnosis. While melanoma was exceedingly rare pre-1980, we observed a dramatic increase in the incidence in some parts of the world [5,6]. This statement deserves an explanation. It is the major underlying hypothesis of this review that this epidemic can in most parts be explained by changing diagnostic concepts and progress in the field of in-vivo examination techniques. This interpretation is increasingly shared by others, although with different conclusions [7]. Advocates of early recognition, dermatologists and general practitioners alike, are faced with increasing criticism [8,9].

According to the opinions of critics, the increased incidence of melanoma is due to overdiagnosis, that goes hand in hand with an increase in the number of unnecessary biopsies and excisions driven by in vivo examination techniques such as dermatoscopy. In this scenario overdiagnosis and unnecessary surgery lead, according to critics, to increased morbidity and anxiety, while at the same time there is no evidence supporting improved survival following early recognition.

As a solution, Welch et al recently suggested not to biopsy pigmented lesions with a diameter smaller than 6 mm [7]. While Welch et al rightly addressed many problematic issues in the field of melanoma diagnosis, this suggestion indicates a lack of knowledge of and a lack of confidence in current diagnostic techniques.

Clinical Diagnosis

By clinical diagnosis we refer to the diagnosis of melanoma with the unaided eye, which was state-of-the art before the introduction of the dermatoscope. The natural starting point for a review on the clinical diagnosis of melanoma are the ABCD criteria. These were popularized in the mid-1980s, mainly in the US [10]. Before the 1980s the diagnosis of melanoma was based on gross features such as ulceration or bleeding. The ABCD criteria mark the first attempt to summarize melanoma criteria in a simple mnemonic that is easy to remember. It includes asymmetry (A), border irregularity (B), color variegation (C), and diameter larger than 6mm (D) criteria. The ABCD criteria were developed following the increasing need to educate physicians and the public to recognize melanoma at earlier stages. In the words of Darrel Rigel, who was part of the team that popularized the ABCD criteria in the 1980s, it was “intended to be a simple tool that could be implemented in daily life, a mnemonic as easy as ABC to alert both laypersons and healthcare professionals to the clinical features of early melanoma” [11].

Along the same line, Rona McKie propagated a 7-point checklist to support non-dermatologists in recognizing possible melanomas[12,13]. The checklist was known as the Glasgow 7-point checklist and was quite popular in the UK. The clinical ABCD criteria and the Glasgow 7-point checklist became blueprints for other simple mnemonics, such as the ABCD rule [14] or the 7-point checklist for dermatoscopy [15], which even in terms of their naming, directly refer to their historic models. Interestingly, neither the ABCD criteria...
nor the Glasgow 7-point checklist were derived from statistical evidence but rather from the best judgements of expert clinicians. At the same time in 1985, A Bernard Ackerman, who was an influential figure in the field of dermatology and dermatopathology, wrote a lively plea for early recognition of melanoma entitled “No one should die of malignant melanoma” [16]. In a series of articles and book chapters, Ackerman and his coworkers set forth and refined criteria for the clinical and histopathologic diagnosis of melanoma in situ. Pre 1980s, the recognition of melanoma in situ was not widely accepted and it was rather viewed as a precursor but not as authentic melanoma. The combined effect of increased public awareness and education of healthcare professionals to recognize the early stages of melanoma had a major impact on the diagnosis of melanoma. The incidence of melanoma increased, and the epidemic of melanoma started.

From an early recognition point of view, the most critical parameter in the ABCD criteria was the diameter. A size threshold puts a limit to how early melanomas can be diagnosed. The ABCD rule gives credit to the fact that small melanomas are difficult to diagnose because melanomas smaller than 6 mm are usually not asymmetric and multicolored, at least when viewed with the unaided eye. Size limits were also part of other algorithms. The Glasgow 7-point checklist established a size limit of 7 mm. A popular algorithm for the diagnosis of acral melanoma developed by Saida et al determined a size limit of 7 mm for the diagnosis of acral melanoma [17]. The diagnosis of melanoma of the nail matrix is discouraged if the pigmentation covers less than 1/3 of the nail plate [18]. Size limits have the problem that, at least in theory, all melanomas start smaller than 6 mm. A reevaluation of the ABCD criteria in 2004, however, concluded that the size limit of 6 mm should not be lowered[19]. In light of the fact that melanomas smaller than 6 mm were increasingly recognized, the authors suggested that “the ABCD should be expanded to ABCDE (E standing for enlargement or evolution) to emphasize the significance of evolving pigmented lesions for the diagnosis of melanoma”.

The disadvantage of the newly added E criterion relies on the fact that it depends on information collected over time. Although the self-reported history of patients or information provided by a spouse or partner can at times be a valuable source for this type of information, it is not perfectly reliable[20, 21]. Total body photography (TBP) on the other hand, helps to detect new and changing lesions independent from the attention of the patient and thereby facilitates the detection of small and inconspicuous melanomas [22–24]. It also reduces the number of unnecessary excisions of benign lesions [25]. In a recent meta-analysis, Ji-Xu calculated that total body photography of high-risk individuals significantly reduced the number of biopsies needed to detect one melanoma from 14.8 to 8.6 [26]. Most melanomas detected by TBP were in situ, highlighting the impact of TBP for early recognition. TBP is especially useful for individuals with multiple nevi, in whom melanomas are more difficult to detect because of the abundance of nevi [27].

The “ugly duckling” approach addresses this difficulty in attempting to find the one outlier among multiple similar looking lesions. The first attempts to popularize the “ugly duckling” approach can be attributed to the French dermatologist JJ Grob, who co-authored an article on this topic in 1998 [28]. Unlike the ABCD criteria, the “ugly duckling” method is a comparative approach that takes into account the landscape of nevi in a particular patient. It tacitly assumes that individuals have a nevus archetype and that deviations from this archetype may indicate malignancy. It is an informal method as there is no rigorous definition regarding the kind of deviation that is significant. All kinds of deviation have been used to identify the outlier lesion, such as a pink lesion among pigmented lesions, a large lesion among small lesions, and a chaotic lesion among symmetric lesions. This approach can also be used to increase specificity in patients with multiple “atypical” nevi. If all nevi look atypical and none is standing out the significance of “atypia” decreases. This inverse interpretation of the “ugly duckling” approach has been more formally investigated in the field of dermatoscopy by Argenziano and coworkers [29]. In 2021, Soensken et al. successfully used the “ugly duckling” approach to automatically detect outlier lesions from photographic overviews with artificial intelligence (AI) [30].

Dermatoscopy

The seminal paper of Pehamberger on pigmented skin lesions pattern analysis, published in 1987 [31] paved the way for future developments of the dermatoscopic diagnosis of melanoma. It described patterns of benign and malignant pigmented skin lesions and introduced and defined dermoscopic criteria that are still used today. A closer look at this classical article, however, reveals that the melanomas shown in the figures are large and could have been diagnosed without dermatoscopy. The method of dermatoscopy was still evolving and the world of dermatology was not ready to accept that melanomas can be small (smaller than 6 mm) and inconspicuous (Figure 1). Soon thereafter other groups followed and presented their own interpretation of pattern analysis. Old concepts such as the ABCD criteria and the Glasgow 7-point checklist were reused for dermoscopy. Stolz et al invented the ABCD rule of dermoscopy and Argenziano et al the 7-point checklist[14,15]. Both methods aimed to differentiate melanomas from nevi. Other noteworthy algorithmic approaches include Menzies rule [32], the CASH algorithm [33], and the chaos and clues method, which appeared later [34]. Over the years 3 meta-analysis showed how dermatoscopy improved diagnostic accuracy for melanoma, compared to an unaided
Another milestone was the Second Consensus Conference of Dermoscopy, which was virtually held [38]. This was a turning point for the evolution of dermatoscopy because it marks the beginning of a fruitful international collaboration among different groups that tried to establish a consensus for criteria and terminology. Prior to this milestone event, the study of dermatoscopy was fragmented into different small research groups that often antagonized each other.

In the following years dermatoscopy differentiated into a complex science and criteria for melanoma were refined. Special criteria were described for acral melanoma [39–41], facial melanoma [42–44], amelanotic and hypomelanotic melanomas [45,46], nodular melanomas [47,48], mucosal melanoma [49], nail matrix melanoma [50–53], and melanomas on chronic sun damaged skin [54]. Smaller and smaller lesions were identified as melanomas thanks to dermatoscopy pushing the diagnostic boundaries, also in dermatopathology [54–58]. Furthermore, Argenziano et al demonstrated that when applied by experienced users, dermatoscopy reduces the number of biopsies or excisions needed to detect 1 melanoma [59]. Despite these advancements, it became clear that dermatoscopy had its limitations [59–63]. It was reported that some small and flat melanomas lack melanoma clues at the beginning and can only be diagnosed by observing changes over time with sequential digital dermatoscopy [64–68]. The finding was immediately criticized as just another way to inflate the melanoma epidemic [69]. The introduction of sequential dermatoscopy to recognize changes over time, mirrors the letter E (for evolving) addition to the ABCD criteria.

Finally, dermatoscopic images are increasingly used for training of machine learning algorithms [70–75]. Computer algorithms based on deep learning outperformed dermatologists in some studies and increased the expectations that AI will replace human expertise, at least for some applications such as teledermatoscopy. The expectations are likely exaggerated because AI-based algorithms still lack the kind of adaptive general knowledge that is necessary to act independently from humans. It is likely, though, that AI will transform images-based diagnostic medicine in many ways. As recently demonstrated by Tschandl et al, collaboration between humans and computers is more promising than competition [72].

**Histopathologic Diagnosis**

While it is easy to pin down the beginning of the clinical and dermatoscopic diagnosis of melanoma evolution, the same does not apply to histopathology. A possible choice is the work of LV Ackerman in the late 1940s. It was one of the first to systematically describe the pathology of “melanocarcinoma”, as defined then [76]. All clinical photos and micro-images of a tiny melanoma (<3 mm).

![Figure 1](image_url)
graphs in his original publication of a series of 75 cases show advanced cases of melanoma. Of 40 patients who underwent dissection of the local lymph nodes, 37 already had lymph node metastasis at the time of diagnosis. The article is mostly interesting for its summary of beliefs about melanoma prevalent in those days. According to LV Ackerman melanoma usually starts in a mole and “it is most unusual to find the changes of malignant melanoma entirely within the epidermis with no change in the dermis.” Interestingly, among the suggested treatments mentioned in this article there was also castration, because it was believed that hormones have an impact on the course of the disease. In 1953, A Allen and S Spitz co-authored an article, in which they set forth their belief that all melanomas start in a preexisting mole, especially in a so called “active junctional nevus” [77]. The micrograph of the “activated junctional nevus immediately preceding the development of infiltrating melanocarcinoma” shown in figure 9 in their 1953 article shows a melanoma in situ. From the current point of view, most of what has been published on the pathology of melanoma pre-1970s is only of historical interest. The articles, however, witness the different concepts of Ackerman, Allen, Spitz, and other pioneers of melanoma pathology, compared to our current view, particularly regarding melanoma in situ. What has been defined a precursor by Allen and Spitz, would be called a melanoma today.

In the early 1970s WH Clark and coworkers propagated a “histogenetic” classification of melanoma, which continues to be relevant until today [78,79]. In its original form the classification included 3 subtypes: nodular melanoma, superficial spreading melanoma, and lentigo maligna melanoma. Nodular melanoma was typified by pure vertical growth, while superficial spreading melanoma expands along the epidermis (radial or horizontal growth phase). The fourth subtype, acral lentiginous melanoma, was added later. Around the same time in the early 1970s, A Breslow introduced the invasion thickness as prognostic marker for primary skin melanoma [80,81], and in the mid-1970s, AB Ackerman and coworkers set forth histopathologic criteria for the diagnosis of melanoma that are still widely used by dermatopathologists (Table 1) [82]. Ackerman also popularized the concept of melanoma in situ, clinically and pathologically, and denied the concept of precursor lesions such as “Allen’s active junctional nevus”, “Hutchinson’s melanotic freckle”, “Koskard’s lentigious dysplastic nevus of the elderly”, and “precancerous melanosis of Dubreuilh”. According to his opinion, these were evasions from the correct diagnosis of melanoma in situ.

In 1992 the National Institutes of Health (NIH) held a consensus conference to discuss the clinical and histological characteristics of early melanoma [83]. The panel of the consensus conference agreed that melanoma in situ is a distinct entity. With this official acceptance of “melanoma in situ” as authentic melanoma, the stage was finally set for early recognition to lift off. The increased public awareness, the availability of a new, accurate, and affordable in vivo examination technique, and the lower hesitancy of pathologists to diagnose melanoma in situ acted in accordance: The incidence for melanoma skyrocketed and increased more than for any other type of cancer.

Conventional pathology is still the gold standard for melanoma diagnosis but it is far from perfect. There is a large discrepancy of opinions and concepts among pathologists who tend to disagree on classification, terminology, the significance of subtypes, and on the model of tumor progression, but most importantly, they tend to disagree on the diagnosis [84–87]. For certain types of lesions there is large inter- and intra-observer variability among community-based pathologist whether a given lesion is benign or malignant. The most common issues of this sort concern the diagnosis of small or flat lesions and lesions with a spitzoid morphology. For these lesion categories, the community suggested terms with uncertain prognosis such as atypical Spitz tumor (AST) [88] and superficial atypical melanocytic proliferation of uncertain malignant significance (SAMPUS) [89]. There is certainly a need for such categories in practice but there are different

<table>
<thead>
<tr>
<th>Table 1. Significant histopathologic features of superficial spreading melanoma according to Price, Rywlin, and Ackermann 1976</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor circumscription of the intraepidermal melanocytic component of the lesion with lateral extension of individual melanocytes</td>
</tr>
<tr>
<td>Increased number of melanocytes, solitary and in nests, within and above the epidermal basal-cell layer and within adnexal epithelium (pagetoid appearance)</td>
</tr>
<tr>
<td>Marked variation in size and shape of the melanocytic nests</td>
</tr>
<tr>
<td>Confluence of melanocytic nests rather than discrete nests.</td>
</tr>
<tr>
<td>Absence of maturation of melanocytes with descent into the dermis.</td>
</tr>
<tr>
<td>Melanocytes with nuclear atypia</td>
</tr>
<tr>
<td>Melanocytes in mitosis</td>
</tr>
<tr>
<td>Necrosis or degeneration of melanocytes</td>
</tr>
</tbody>
</table>
views about the best way to express this ambiguity. One school of thought will blame the lesion (“the lesion does not know what it is”), the other the ignorance of the reporting pathologist (“the pathologist does not know what it is”).

In the early 2000s the molecular revolution in medicine gained momentum and new observations challenged our concepts of melanoma biology. The first turning point was the discovery of the significance of BRAF mutations in melanoma and in nevi [90]. This was soon followed by the detection of other tumorigenic mutations in other oncogenes [91] and climaxed in the description of the genomic landscape of melanoma [92]. While some of these discoveries translated into the identification of “druggable” biologic targets [93], the new insights into the genetic landscape of melanoma did not translate into reliable diagnostic methods for borderline lesions. Although molecular techniques such as fluorescence in situ hybridization (FISH) [94] or comparative genomic hybridization (CGH) [95] have been used to better classify borderline lesions such as Spitz tumors, they remain auxiliary techniques, requiring an integration with clinical and dermoscopic observations as well as with conventional pathology[96].

The recent hype associated with AI and deep learning in image based diagnostic medicine did not leave dermatopathology untouched [97]. Using random crops of digitized whole slide scans, Hekler et al showed that an algorithm trained by deep learning was capable off differentiating melanoma from nevi as accurate as pathologists [98]. It is, however, currently unknown how such algorithms will perform in the everyday practice.

Summary and Interpretation

There can be no doubt that the clinical, dermoscopic, and histopathologic criteria for the diagnosis of melanoma changed significantly over time. New inventions such as dermoscopy, TBP, and new developments in the field of AI and molecular medicine continuously modify the way we diagnose melanocytic proliferations. These developments in conjunction with increased public awareness shifted the landscape of melanoma diagnosis towards an increased detection of borderline lesions, especially with early melanomas. In a few decades we passed from an era of significant underdiagnosis to overdiagnosis. By overdiagnosis we refer to the inflation of the diagnosis of in situ or microinvasive melanomas with unknown prognostic significance. The undesired consequences of overdiagnosis should not be taken lightly. Apart from putting a significant financial burden on health care systems, overdiagnosis is associated with increased anxiety and morbidity of affected individuals. However, the recent suggestion of Welch and coworkers, that we should stop performing biopsies for lesions smaller than 6 mm, indicates lack of knowledge of current diagnostic techniques such as dermoscopy. Some, albeit not all melanomas, can be diagnosed with confidence by dermoscopy even when they are smaller than 6 mm (Figure 1). If early recognition of melanoma translates into improved survival is still a matter of debate. This question is not easy to answer. It would demand a randomized controlled trial with 2 arms. In 1 arm all lesions smaller than 6 mm that can be identified as melanomas by dermoscopy would be excised, in the other arm these lesions would be left alone until they reach the size of 6 mm. Since such a trial has not been performed and will not be completed in the near future, we have to rely on indirect evidence such as invasion thickness.

It is also true that early recognition has become a business. Feeding the business demands that the melanoma epidemic is constantly rising. However, to attribute the recent decline of melanoma mortality solely to the invention of new therapies is a slap in the face of all clinicians who dedicated their work to early recognition. Dermatologists or primary care clinicians, who work on the forefront of early diagnosis, are not greedy businessmen who stir up and exploit anxiety only for their own profit, in the same way as basic researchers and the pharmaceutical industry, who invent and develop new treatments against cancer, are not altruistic cure-alls.

Instead of turning back the wheel of time and ignoring the innovations of the last 30 years the inflated melanoma epidemic is best tackled otherwise. First, like any other diagnostic technique dermoscopy needs training and expertise and it can have undesired side effects if used by inexperienced users. Better training will produce better dermatoscopists, who know the limitations of the technique and will make better decisions. If used appropriately by sufficiently trained and experienced clinicians, dermoscopy will reduce and not inflate the number of excisions and biopsies. Second, pathologists who sign out melanocytic lesions need specific training in clinical dermatology. They need to be aware that borderline lesions are best diagnosed with an integrated approach taking into account clinical, dermoscopic and, in some cases, also molecular findings. Third, clinicians and pathologist should not be paranoid of missing a melanoma. Overdiagnosis should be as undesirable as underdiagnosis. In some parts of the world vulnerability to malpractice lawsuits leads to over anxiousness, which leads to excessively low thresholds and overdiagnosis. Forth, we need a shift of policy with regards to incentives. Reimbursements for monitoring techniques such as TBP or digital dermatoscopy should be in the range of excisions. Reimbursement of clinicians, who need a disproportionally large number of biopsies to detect one melanoma, should be capped. Fifth, slides of pathology labs with a disproportionally large number of melanoma diagnoses should be reviewed by an expert panel. If the panel concludes that the threshold for melanoma diagnosis is below current standards, pathologists should be offered retraining.
I acknowledge that some of these suggestions will be unpopular among dermatologists and pathologists. There is, however, no other way to restore the trust in the accuracy of melanoma diagnosis. Without this trust, all efforts directed towards early recognition of melanoma will be in vain.

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Melanoma: Staging and Follow-Up

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Key words: Melanoma; staging; follow-up

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ABSTRACT

Cancer staging is the process determining to which extent a cancer has spread and where it is located in the body. A thorough staging is of utmost importance, not only because it provides the most accurate prognostic estimation, but also because several crucial decisions, such as the treatment choice and the follow-up strategy, vary according to the tumor’s stage. The current staging system for melanoma is based on the 8th edition of TNM classification issued by the American Joint Committee on Cancer (AJCC) in 2017. It includes a clinical and a pathological staging, both consisting of 5 stages (0-IV). The stage of a melanoma is determined by several factors, among which the Breslow thickness, the pathological presence or absence of ulceration in the primary tumor, the presence and the number of tumor-involved regional lymph nodes, the presence or absence of in-transit, satellite and/or microsatellite metastases, and the presence of distant metastases. Following melanoma diagnosis, an accurate medical workup, in line with the stage and the physical examination, should be performed.
Introduction

Staging is a process determining the extent to which a cancer has spread in a person’s body and where it is located. Cancer stage is categorized from 0 to IV, with stage IV cancer corresponding to a cancer that has metastasized at distant locations. The most used system to stage solid tumors, including melanoma, is the universally accepted TNM (Tumor, Node, Metastasis) staging system. Cancer staging can be divided into clinical and pathological staging. Clinical and pathological stages are defined by different criteria and may differ but are generally considered as complementary to each other. In general, clinical staging is based on all the available information obtained before surgical excision of the tumor (eg by physical examination, blood tests, and imaging), while pathological staging is performed by a pathologist and relies on the information provided by microscopic examination of the tumor following surgical resection.

The clinical stage of a melanoma can be determined only following a complete excision of the primary tumor, a clinical examination of the skin and lymph nodes, and a radiologic assessment for regional and distant metastases’ detection. Pathological staging of a melanoma takes into account not only the microstaging of the primary tumor and the wide excision but also considers the information on regional lymph nodes after partial or complete lymphadenectomy, when performed. A proper staging is extremely important, because it provides the most accurate prognostic estimation and allows to take several crucial decisions, such as the treatment choice and the follow-up strategy, that are based on clinical tumor stage.

Table 1. Clinical staging according to AJCC 8th edition [1].

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M0</td>
</tr>
</tbody>
</table>

Melanoma Staging System

The current staging system is based on the 8th edition of TNM classification for staging of melanoma issued by the AJCC in 2017 and is summarized in Tables 1-5 [1]. This relatively new system has been broadly accepted after its publication and is considered the cornerstone for classifying melanomas [2,3].

There is both a clinical and a pathological staging, both consisting of 5 stages as follows:

Clinical Staging:

- 0: in situ disease
- I and II: localized disease

Stage I is further divided into substages IA and IB, while stage II includes substages IIA, IIB and IIC. The determining
factors for staging and substaging are the Breslow thickness and the presence or absence of ulceration after the pathological assessment of the primary tumor (Tables 1 and 2). Of note, mitotic rate and Clark’s level of invasion, previously used for sub-classification, no longer influence melanoma staging.

### Table 2. Pathological staging according to AJCC 8th edition [1].

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1a/b, T2a</td>
<td>N1a, N2a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T1a/b, T2a</td>
<td>N1b/c, N2b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2b, T3a</td>
<td>N1a/b/c, N2a/b</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T0</td>
<td>N1b/c, N3b/c</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1a/b, T2a/b, T3a</td>
<td>N2b, N3a/b/c</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3b, T4a</td>
<td>Any N ≥ N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>N1a/b/c, N2a/b/c</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIID</td>
<td>T4b</td>
<td>N3a/b/c</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T, Tis</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

• III: regional disease

Regional disease is defined by the presence of metastases in regional lymph nodes and/or “in transit metastases”, “satellite metastases”, and microsatellite metastases. Satellite metastases are defined as cutaneous or subcutaneous metastatic lesions up to 2 cm from the margin of the primary tumor. In-transit metastases are defined as cutaneous or subcutaneous lesions located between 2 cm from the primary tumor and the regional nodal basin. Microsatellite metastases are defined as tumor nests larger than 0.05 mm in diameter in the reticular dermis, subcutis, or vessels beneath the primary invasive tumor, but separated from it by at least 0.3 mm of normal tissue on the section in which the Breslow measurement was taken.

Regional lymph nodes metastases are defined as metastases in the lymph node basin that drains lymph from the region around the tumor. Involvement of regional lymph nodes is confirmed by their pathological examination after sentinel lymph node (SLN) biopsy (for clinically occult lymph node metastases) or therapeutic lymph node dissection when performed (for clinically evident regional lymph node disease). Involvement of regional lymph nodes may be also detected by clinical, radiologic examination and/or diagnostic biopsies (clinical staging). Therefore, there is only 1 stage group for clinical stage III. In contrast, pathological stage III is divided into A, B, C, and D stage groups depending on Breslow thickness, the pathological presence or absence of ulceration in the primary tumor, the number of tumor-involved regional lymph nodes, and the presence or absence of in-transit, satellite and/or microsatellite metastases (Table 4).

### Table 3. Definition of T according to AJCC 8th edition [1].

<table>
<thead>
<tr>
<th>Category</th>
<th>Thickness</th>
<th>Ulceration</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX: Primary tumor cannot be assessed</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>T0: No evidence of primary tumor</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Tis (in situ)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>T1</strong></td>
<td>≤1 mm</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>&lt;0.8 mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T1b</td>
<td>0.8-1.0 mm</td>
<td>With ulceration</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>&gt;1.0-2.0 mm</td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>&gt;1.0-2.0 mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T2b</td>
<td>&gt;2.0-4.0 mm</td>
<td>With ulceration</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>&gt;2.0-4.0 mm</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>&gt;2.0-4.0 mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T3b</td>
<td>&gt;4.0 mm</td>
<td>With ulceration</td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td>&gt;4.0 mm</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>&gt;4.0 mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T4b</td>
<td>&gt;4.0 mm</td>
<td>With ulceration</td>
</tr>
</tbody>
</table>
Table 4. Definition of N according to AJCC 8th edition [1].

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Tumor-Involved Regional Lymph Node</th>
<th>Presence of In-transit, Satellite, and/or Microsatellite Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX: Patients in whom the regional nodes cannot be assessed</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>N0: No regional metastases detected</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>N1</td>
<td>1 tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved node</td>
<td></td>
</tr>
<tr>
<td>N1a</td>
<td>1 clinically occult (ie, detected by SLN biopsy)</td>
<td>No</td>
</tr>
<tr>
<td>N1b</td>
<td>1 clinically detected</td>
<td>No</td>
</tr>
<tr>
<td>N1c</td>
<td>No regional lymph node disease</td>
<td>Yes</td>
</tr>
<tr>
<td>N2</td>
<td>2 or 3 tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with 1 tumor-involved node</td>
<td></td>
</tr>
<tr>
<td>N2a</td>
<td>2 or 3 clinically occult (ie, detected by SLN biopsy)</td>
<td>No</td>
</tr>
<tr>
<td>N2b</td>
<td>2 or 3, at least 1 of which was clinically detected</td>
<td>No</td>
</tr>
<tr>
<td>N2c</td>
<td>1 clinically occult or clinically detected</td>
<td>Yes</td>
</tr>
<tr>
<td>N3</td>
<td>4 or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases</td>
<td></td>
</tr>
<tr>
<td>N3a</td>
<td>4 or more clinically occult (ie, detected by SLN biopsy)</td>
<td>No</td>
</tr>
<tr>
<td>N3b</td>
<td>4 or more, at least one of which was clinically detected, or presence of any number of matted nodes</td>
<td>No</td>
</tr>
<tr>
<td>N3c</td>
<td>2 or more clinically occult or clinically detected and/or presence of any number of matted nodes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

• IV: distant metastatic disease

This stage includes distant metastases to lung, central nervous system (CNS) or other organs as well as to skin, soft tissue and nonregional lymph nodes. Although there is no further division to substages, a sub-classification according to the number of organs involved, which organs are involved, and serum levels of lactate dehydrogenase (LDH) is essential for prognostic reasons (Table 5).

Staging workup

Histopathologic Examination

When a suspicious lesion is detected, a biopsy should be performed. A narrow-margin (1-3 mm) excisional biopsy is strongly preferred. In case of primary melanoma, the histopathological features along with clinical examination are determining factors for staging and further management. Therefore, the pathology report should include the Breslow thickness, the ulceration status, the dermal mitotic rate, the margin status, the presence, or absence of microsatellitosis, and the presence or not of pure desmoplasia.

Physical Examination

Special attention should be paid to the physical examination of the entire skin surface to look for satellites or in-transit metastases but also for a second primary melanoma. Physical examination of the regional lymph node basin should be included.

Sentinel Lymph Node Biopsy and Imaging

Patients with a melanoma in situ and a clinical stage IA melanoma with normal physical examination and no other symptoms need no further imaging or laboratory tests. They also are not candidates for SLN biopsy at baseline. The staging procedure is completed with the performance of wide excision [1].

Patients with clinical stage IB melanoma with normal physical examination and no other symptoms need no further imaging or laboratory tests at baseline. Concerning SLN biopsy, this should be considered in patients with T1b melanoma. The decision depends on several factors, such as comorbidities, age, mitotic rate or lymphovascular invasion [1]. Patients with a T2a melanoma, should undergo SLN biopsy.
Patients with clinical stage II melanoma with normal physical examination and no other symptoms need no further imaging or lab tests at baseline, but a SLN biopsy should be offered [1,4,5].

In melanoma patients of any stage, if an equivocal regional lymph node is detected during clinical examination, an ultrasound (US) should be considered prior to SLN biopsy. However, a negative nodal basin US is not a substitute for biopsy of clinically suspicious lymph nodes and histopathology should be warranted. Moreover, abnormalities or suspicious lesions on nodal basin US should be histopathologically confirmed. The presence of lymph node metastasis can be confirmed either with core biopsy or fine-needle aspiration (FNA) [6-8]. Similarly, if clinical or microscopic satellite/in-transit metastases are suspected, a biopsy is mandatory.

If a SLN biopsy is indicated, it should be performed at the same time with the wide excision of the primary melanoma. Noteworthy, SLN biopsy was shown to have only prognostic (and not therapeutic) significance [9-13]. A positive SLN biopsy would directly upstage a patient to stage III, which highlights its significance as a staging procedure, especially after the introduction of adjuvant systemic therapy for stage III. A complete lymph node dissection is not anymore recommended in case of positive SLN biopsy, since it does not offer any therapeutic benefit, it has little prognostic value, and is associated with surgical morbidity [14-17]. It is, however, indicated for the treatment of lymph node metastases diagnosed clinically or by imaging, in the absence of distant metastases.

Imaging for baseline staging should be considered in patients with pathological stage IIIA melanoma and should be performed in all patients with stage IIIB/C/D [1]. Imaging modalities include chest/abdominal/pelvic CT with intravenous (iv) contrast or whole-body PET/CT, with or without brain MRI with iv contrast. Moreover, if clinically indicated, neck region should be also checked with CT with iv contrast.

Finally, stage IV melanoma patients need careful total body medical imaging (CT or PET/CT, brain MRI). Moreover, plasma LDH should also be assessed [1].

Follow-Up

After melanoma diagnosis, the role of ongoing surveillance of disease-free patients is of paramount importance. The main goals of the follow-up are the following:

1. Early identification of relapse (local, distant) and subsequent guidance for adjuvant treatment, where appropriate.
2. Early detection of a second primary melanoma and/or non-melanoma skin cancer.

Early detection of relapse is associated with a higher survival rate, highlighting the importance of an adequate follow-up. The likelihood of recurrence varies according to melanoma stage at first presentation. Patients with melanoma in situ, are very unlikely to recur following wide excision. There are a few exceptions though, such as lentigo maligna type [18-20]. In general, patients with earlier stage melanoma at first presentation are less likely to recur compared to...
those with more advanced stages. Accordingly, the timing of relapse varies according to the stage. Patients with advanced melanoma tend to recur more quickly compared to those with earlier stage [21-23]. Nonetheless, the vast majority of relapses are recorded in the first 5 years and most of them within 2-3 years following surgery. Moreover, the risk of recurrence tends to decrease over time for melanoma stages, but late recurrence (more than 10 years after the initial diagnosis) cannot be excluded [21,22,24-26].

Patients with a personal history of melanoma are at high risk of developing a second primary melanoma. Concerning the risk of developing a second primary melanoma, data reported in the literature is very heterogeneous. The reported percentage of melanoma patients developing a second primary melanoma ranges between 2% and 20% [23, 27-30]. In a cohort of prospectively monitored melanoma patients, the cumulative 5-year risk of second primary melanoma was 8% [30]. Interestingly, the risk appears to be higher within the first year after the diagnosis of the first melanoma, but it remains considerable for at least 5 years and very possibly even more [23, 27-30]. Therefore, individuals with melanoma history should rather be considered at a life-long increased risk of developing a new primary melanoma.

Although the need for a follow-up in patients with melanoma is not a matter of debate, surveillance recommendations vary widely in terms of methods and frequency of visits, and examinations. As there is currently lack of evidence regarding the efficacy of follow-up strategies, different follow-up schemes have been proposed and are mainly based on expert opinions. The suggested follow-up schemes consider the melanoma stage and the presence or not of additional risk factors.

As mentioned above, the first 5 years following the excision of the primary tumor are the most crucial due to high rates of relapse. This is why current guidelines suggest adopting higher intensity follow up strategies during this period. Still, because of the lifetime increased risk of a second primary melanoma or a non-melanoma skin cancer, as well as the risk for late recurrence, monitoring programs for melanoma patients should go beyond 5 years, including at least 1 strongly recommended annual skin exam lifelong [31].

The modalities used to monitor melanoma patients include whole body skin examination, physical examination of the regional lymph nodes, blood tests, and imaging exams, such as chest X-ray, ultrasound, CT, PET/CT, and MRI. More analytically, a clinical evaluation performed by a dermatologist is mandatory at any stage and includes a total body skin examination (with or without a total body clinical and dermoscopic digital documentation) to identify local recurrences (scar, satellite/in-transit recurrence) and subsequent primary melanoma or other skin cancers. Clinical evaluation should also include the examination of the regional lymph nodes and the evaluation of patients’ symptoms and/or signs that would direct appropriate imaging if needed. Ultrasound of the lymph nodes is the most accurate method to detect nodal disease and is generally recommended in patients with equivocal lymph node during physical examination, in patients with AJCC T1b stage and above, in patients who were offered SLN biopsy but it was not performed or in patients with positive SLN biopsy who did not undergo complete lymph node dissection [32]. Other imaging modalities (CT, PET/CT, MRI, chest x-ray) should be considered for monitoring asymptomatic patients in more advanced stages or when signs and symptoms may suggest distant metastasis [33]. In any clinical scenario, if there is a recurrence suspect, this should be confirmed by histopathologic analysis whenever possible.

Finally, routine blood testing (LDH, S100 protein) to detect recurrence is generally not recommended as low positive predictive values have been demonstrated. Ongoing research focuses on liquid biopsies, namely the detection of molecular alterations in plasma and serum of melanoma patients by characterization of circulating tumor cells and cell-free circulating tumor DNA [34,35]. This may provide

| Table 6. Example of follow up schedule examinations based on melanoma stage proposed by European consensus-based interdisciplinary guidelines [2]. |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Stage**   | Clinical-dermatological examination | Lymph node sonography | Laboratory examination: LDH, S-100 | CT neck, thorax, abdominal, pelvic or PET/CT - MRI head |
| Year        | 1 to 3 | 4 to 10 | >10 | 1 to 3 | 4 to 10 | 1 to 3 | 4 to 10 |
| IA          | 6 m | 12 m | 12 m | - | - | - | - |
| IB-IIB      | 3-6 m | 6 m | 12 m | 6 m | - | - | - |
| IIC-IIIC    | 3 m | 6 m | 12 m | 3-6 m | - | 3-6 m | 6 m | - |
| IIIId       | 3 m | 6 m | 12 m | 3-6 m | - | 3-6 m | 6 m | - |
| IV NED (resected, CR under therapy) | 3 m | 6 m | 12 m | 3-6 m | - | 3-6 m | 6 m | - |
| IV (M1a-M1d) (distant metastasis) | Individualized; otherwise staging every 12 weeks |

* NED= No evidence disease, CR= Complete response
valuable information on prognostic outcomes and assessment of treatment response or resistance in the future.

The National Comprehensive Cancer Network (NCCN), an alliance of 31 cancer centers in the United States, has released follow-up recommendations per melanoma stage [1]. According to them, no routine imaging is recommended for stage 0 (in situ) melanoma. For patients with stage IA to IIA with no evidence of disease, routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended. Clinical visits should be scheduled every 6 to 12 months for 5 years and annually thereafter, as clinically indicated. Clinical examination in these visits should emphasize on the regional nodes and skin. For patients with stage IIB to IV (with no evidence of disease), scheduled visits should be conducted every 3 to 6 months for the first 2 years, every 3 to 12 months for the next 3 years and annually thereafter, as clinically indicated again emphasizing on the regional nodes and skin. Moreover, in these stages, imaging (chest x-ray, CT and/or PET/CT) every 3 to 12 months could be considered to screen for asymptomatic recurrence. Regarding central nervous system (CNS), a periodic brain MRI should be performed for up to 3 years to screen for asymptomatic brain metastases in high-risk patients with stage IIIC or higher melanoma, while more frequent surveillance is recommended for patients with prior brain metastases. However, routine imaging is not recommended after 3 to 5 years. Nonetheless, in any case and at any time of follow-up period, when clinically indicated, an appropriate imaging should be offered to evaluate specific signs or symptoms.

Finally, if relapse occurs, imaging is recommended to assess the extent of the disease. In addition, when complete surgical resection of relapse is not feasible and active non-surgical treatment is initiated, clinical examination and/or imaging may be appropriate throughout treatment to assess treatment response.

In Europe, follow-up schemes vary among countries, ranging in frequency from 2 to 4 times per year for 5-10 years, again with higher-intensity strategies in more advanced stages and during the first years. Current European consensus-based interdisciplinary guidelines for melanoma have proposed an example of follow-up schedule examinations based on stage and is shown in Table 6 [2].

Irrespective of the selected follow-up scheme, an individualized approach taking into consideration patient’s risk factors, such as risk for recurrence, prior primary melanoma, family history of melanoma and atypical mole syndrome, is optimal. Moreover, patients’ education must be an integral part of the surveillance strategy and should include:

a. Communication on what to expect from follow-up examinations and why it is important to be compliant with the regular follow-ups.

b. Awareness that family members often have an increased melanoma risk.

c. Guidance on how to perform regular self-examination of the skin and peripheral lymph nodes.

d. Information regarding correct sun exposure behavior.

Conclusion

In conclusion, although there is still no universally adopted follow-up strategy program to monitor melanoma patients, current recommendations, as described above, could serve as a guide for clinicians while future prospective studies are necessary to better standardize this follow-up protocols.

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Current Landscape and Open Questions on Adjuvant Therapies in Melanoma

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ABSTRACT

Melanoma is a form of skin cancer that is frequently diagnosed at early stages. In most cases, surgical resection is curative. In case of thicker melanomas (> pT1b) without clinical or instrumental evidence of metastasis, a sentinel lymph node biopsy is recommended for staging purposes. If the lymph nodes are the only site of disease (macroscopic or microscopic> 1mm), configuring stage III, the international guidelines recommend the use of adjuvant therapy with checkpoint inhibitors (nivolumab or pembrolizumab) or targeted therapies (dabrafenib plus trametinib). These drugs have shown a significant increase in recurrence-free survival, although some doubts and open questions remain. Specifically, none of the available treatments has shown a clear benefit in the overall survival rates, the advantages they give in stage IIIA are not well known, and finally there are still no prospective clinical studies.
Introduction

Melanoma is the deadliest of skin cancers and occurs primarily in young adults, particularly in women [1]. About 50% of patients with cutaneous melanoma harbor a mutation in exon 15 (codon 600) of BRAF proto-oncogene, conferring a worse prognosis [2]. According to the new 8th edition of the American Joint Committee on Cancer (AJCC) staging, patients with early-stage (I-II) have an overall favorable prognosis, whereas patients with stage III melanoma have a rather heterogeneous prognosis [3]. The discovery of immune checkpoint inhibitors and targeted therapies (TT) revolutionized the treatment scenario of metastatic melanoma and with the latest evidence these drugs were also added in adjuvant setting. In this work, we will review the state of art and the unresolved questions of adjuvant therapy. Finally, we will examine future directions for stage III cutaneous melanoma.

Immunotherapy (IT)

Until few years ago, only interferon-α (IFN-α) showed a survival benefit in this setting, although it had a very modest efficacy and was limited to ulcerated melanoma [4]. Anti-programmed cell death-1 (anti-PD-1) antibodies such as nivolumab and pembrolizumab and anti- cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4) antibodies such as ipilimumab clearly exhibited a benefit in terms of progression free survival (PFS) and overall survival (OS) in patients with metastatic melanoma [5]. For this reason, several trials have evaluated the efficacy of these drugs in reducing the risk of relapse in stage III radically resected melanomas. In 2015, EORTC 18071 trial evaluated ipilimumab at a dose of 10mg/kg versus placebo for up to 3 years in patients who had undergone complete resection of stage III melanoma [6]. Both recurrence-free survival (RFS) and OS were significantly superior in the ipilimumab group compared to placebo group at the cost of very high percentage of serious adverse events (5 patients died for immune-related toxicities). Ipilimumab was therefore considered too toxic and was not approved by the European Medicines Agency (EMA) in patient populations who are potentially cured (HR 0.59, p<.001). Adverse events were similar to those reported with other anti-PD1 inhibitors [9]. Very recently, the last update of the S1404 trial was presented, in which pembrolizumab was compared with 1 year of high dose interferon or up to 3 years of ipilimumab in radically resected stage III or IV melanoma: HR for RFS was 0.74 (p<0.001) [10]. After these strong evidences, nivolumab and pembrolizumab were approved by EMA as adjuvant therapy for all stage III melanomas (nivolumab also for radically resected stage IV).

Finally, also the combination of nivolumab and ipilimumab has been tested in adjuvant settings in IMMUNED trial and CheckMate-915 trial with conflicting results. In the first case, a German phase II trial, patients with radically resected stage IV melanoma were randomly assigned to nivolumab-ipilimumab or nivolumab alone, or placebo. HR for recurrence for the doublet group vs placebo was 0.23 and median RFS was not reached after median follow-up of 28.4 months [11]. On the contrary, phase III CheckMate-915 examined adjuvant nivolumab vs combination of nivolumab and ipilimumab in resected stage III-B-D or IV melanomas, but it did not meet its endpoint [12]. These results might be due to the different study population and to the different dose/frequency of ipilimumab, nonetheless further studies are needed.

Targeted therapy (TT)

As immunotherapies, BRAF and MEK inhibitors represented a turning point for the treatment of BRAF mutant metastatic melanomas with very high response rates and a significant benefit in terms of PFS and OS. Regarding the efficacy in the adjuvant setting, COMBI-AD trial tried to show the efficacy of these drugs also in the adjuvant setting. It compared dabrafenib (BRAF inhibitor) 150 mg twice daily plus trametinib (MEK inhibitor) at a dose of 2 mg once daily, versus placebo in stage IIIA-B-C melanoma. In the last update, 3-years RFS was 58% in the experimental arm and 39% in the placebo arm (HR 0.47 p<0.001) [13]. Adverse events were repre-
sented by pyrexia, fatigue, nausea, headache, chills, diarrhea, arthralgia, and rash. These were of grade 3 to 5 in 41% of cases. However, also dabrafenib plus trametinib became a valid option as adjuvant therapy.

Open Questions on Adjuvant Therapy and How to Manage Recurrences

Despite the undoubted effectiveness of these therapies, a number of open questions still remain open. These concern for instance the timing of their use and the risk/benefit ratio in some subgroups of patients. First of all, there is still no evidence regarding the benefit in survival rates: although ipilimumab had already demonstrated an OS advantage vs placebo, in the CheckMate-238, following a 48 months follow-up there are no differences in OS between nivolumab and ipilimumab (78% vs 77%, HR 0.87 p=0.315)[8]. However, fewer events than expected occurred in the trials, so it is underpowered. Also, for pembrolizumab in S1404 no benefit in OS was observed [10]. Moreover, in the COMBI-AD trial the statistical significance did not reach the prespecified target of p=0.000019 (3-years OS: 86% vs 77%, HR 0.57 p=0.0006) [13]. Definitive data of these 2 studies and of KEYNOTE-054, the only study in which a cross-over between treatments was allowed, will clarify if starting the therapy at the time of relapse affects survival rates.

A second important aspect is that all these studies started before the definitive data of Multicentre Selective Lymphadenectomy Trial II [14] and the German Dermatologic Cooperative Oncology Group-selective lymphadenectomy trial [15], that did not report an improvement in melanoma specific survival (MSS) for complete lymph node dissection versus periodic ultrasonographic surveillance in patients with positive sentinel lymph node. This suggests that the study population does not correspond to patients treated in current clinical practice.

Moreover, the new edition of AJCC staging was approved and the main changes concerned stage III: stage IIID was added, and the subgroups were re-distributed. More in detail, stage IIIA now includes T1a-b N1-2a and T2a N1-2a [16]. In the adjuvant trials, only patients categorized as stage IIIA with nodal metastases >1mm (CheckMate-238 did not include them), were included. Furthermore, patients enrolled in these trials with positive SLN have had lymphadenectomy, indicating that some of the stage IIIA may be up-staged. On the other hand, in clinical practice, several patients without nodal dissection could be downgraded to IIIA (for example if they have metastatic non-sentinel lymph nodes). However, taking into account the high melanoma specific survival in this stage (80%-93%) [17], and the risks of durable and serious adverse events, adjuvant therapy should be carefully discussed with these patients [18].

Finally, an unmet need that originated from adjuvant trials is the management of relapses during and after treatment. There is in fact a lack of prospective randomized studies investigating this question, as only retrospective experiences are reported. What we know is that the majority of recurrences are with distant metastases (including locoregional+distant metastases) and they are mostly on-treatment during anti-PD-1 therapy [19] and after treatment with targeted therapies [20, 21]. This observation led to support the idea that treatment with BRAF- and MEK-inhibitors should be prolonged to more than a year (2-3 years?) to improve its efficacy. However, when the relapse occurs during adjuvant therapy (or within few months from its conclusion), it is good practice to switch to another treatment, particularly in BRAF mutant patients (TT→TT and TT→IT). On the contrary, a rechallenge approach, adopting the same drugs, when the relapse occurs off treatment, could be a good option because of good response rates, especially for TT. Nevertheless, data from pembrolizumab rechallenge in the KEYNOTE-054 study, performed on patients who recurred after 6 months from the completion of adjuvant therapy, were very disappointing [22]. Furthermore, radical surgery followed or not by systemic adjuvant therapy, should be done when recurrence is locoregional and when radical surgery is achievable.

A Step Forward

There are several ongoing trials trying to solve the open questions for the management of locoregional melanoma. One of these issues concerns adjuvant therapy for melanomas without involvement of lymph nodes: paradoxically, 5-year survival of stage IIB (87%) and IIC (82%) is worse than stage IIIA (93%). KEYNOTE-716 and CheckMate-76K will compare the efficacy of pembrolizumab and nivolumab, respectively, versus placebo in these patients. Results are expected for 2023-24.

A closer change in clinical practice will probably come from neoadjuvant studies for clinical stage III melanoma. Up to now, the relapse rate for radically resected melanoma with nodal macro metastases was 40% at 2 years with immunotherapies and 40% at 3 years with targeted therapies (without considering 15-20% of patients in the trials occurred during the screening period before the start of adjuvant therapy) [23]. Neoadjuvant therapy could improve outcome from surgery, could personalize adjuvant treatment based on treatment response, and could safely provide tissue for analysis of resistance mechanisms from those who do not have a pathological response. For this reason, in the last years several trials have evaluated this strategy and a recent pooled analysis summarized the results of 6 of them (2 with targeted therapy, 4 with immunotherapy) [19]. In particular, pathological complete response (pCR) was found to be a good surrogate of RFS and OS. pCR rate was 39.7% in the whole cohort: worst
results were found for single agent nivolumab (pCR 20%), while similar outcomes were found for dabrafenib+trametinib (47%) and for nivolumab+ipilimumab (42.7%). The RFS was similar between combination immunotherapies and targeted therapies after 1 year (84% vs 75%) while a significant difference was seen at 2 years (80% vs 47%). Furthermore, with nivolumab+ipilimumab, impressive OS were achieved in patients who obtained a pCR, or a near pCR, or a partial response (about 2/3 of patients) reaching 99% after 2 years. Despite this very promising result, larger studies are needed to confirm these findings and to clarify other open questions such as understanding the mechanisms underlying the relapse in 21% of patients with pCR to targeted therapy.

**Conclusion**

The efficacy of immunotherapy and targeted therapy as adjuvant treatment in stage III melanoma is unquestionable. Something could change soon when the overall survival and relapse-free-survival (RFS) in the intergroup S1404 phase III randomized trial comparing either high-dose interferon (HDI) or ipilimumab or pembrolizumab in patients with high-risk resected melanoma. JCO. 2021;39(15_suppl):9501-9501. DOI:10.1056/NEJMoa1709030. PMID: 28891423.

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Treatment of Advanced Metastatic Melanoma

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Key words: Metastatic melanoma treatment, anti-PD1, target therapy, metastatic melanoma survival, response rate

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The introduction in clinical practice of new drug compounds both targeted therapies anti-BRAF and checkpoint inhibitors have largely improved our potential to manage advanced metastatic melanoma patients. This has led to a significant improvement in terms of response rates and particularly in the overall survival (OS). The long-term results of trials with follow-up data of patients treated with targeted or immunotherapies reported median OS rates around 24 months, with 5-year survival rates around 35-40%.

As to the drugs currently available and reimbursed by the Italian National Health System, 3 combinations of anti-BRAF/anti-MEK inhibitors are available (dabrafenib/trametinib, vemurafenib/cobimetinib and the most recently introduced encorafenib/binimetinib).

As for checkpoint inhibitors, first line immunotherapy is represented by anti-PD1 blockers (nivolumab and pembrolizumab), whilst the anti-CTLA-4 ipilimumab can be used as second line immunotherapy.

ABSTRACT

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Guest Editors

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The decision-making factors that define the best treatment approach in stage IV patients with metastatic melanoma include the mutation pattern, performance status, high/low tumor load, brain metastases, progression pattern (low/fast), and availability of clinical trials. This review will analyze the current therapeutic tools adopted for the treatment of metastatic melanoma patients. It will then focus on the latest results obtained by novel treatments (checkpoint inhibitors and targeted therapies) which can be used in the clinical daily practice.

Introduction

The presence of distant metastases with soft tissues or internal organs’ involvement is classified as stage IV metastatic melanoma. According to the 8th edition American Joint Committee on Cancer (AJCC) 2018, M1 is defined by both the anatomic site of distant metastatic disease (“a” for soft tissue, “b” for lung, “c” for other sites, and the new “d” designation added to include distant metastasis to the central nervous system), and serum lactate dehydrogenase (LDH) values (designated as “0” for not elevated and “1” for elevated [1]). Only a minority of melanoma patients develop distant metastases during the course of their disease, thanks to early diagnosis.

Even if the prognosis for stage IV patients is still severe, the introduction of the new drug compounds, both targeted therapies anti-BRAF and checkpoint inhibitors, have largely improved our potential to manage these patients inducing a significant improvement in terms of response rates (RR) and particularly overall survival (OS). The unsatisfactory results obtained by (bio)-chemotherapy were clearly summarized in a review study by Korn et al [2], which analyzed clinical data obtained from more than 2,000 patients enrolled since 1975 in 42 phase II trials. An overall 1-year survival rate of 25.5% and a median OS of 6.2 months were achieved, with no significant improvement during the last 30 years. The long-term results of the trials with follow-up data of patients treated with targeted or immunotherapies reported median OS rates around 24 months, with 5-year survival rates around 35-40% [3].

Currently, the main criterion adopted to decide the best therapeutic option for an advanced patient is the presence or absence of the BRAF gene mutation. The BRAF mutation is harbored by approximately 50% of melanomas. More frequently, those arising without chronic sun-induced damage, induce the hyperactivation of the MAP-kinase molecular cascade, leading to an uncontrolled proliferation of cancer cells [4]. In the presence of BRAF mutation, both anti-BRAF targeted therapies and checkpoint inhibitors can be used, whilst in the presence of a BRAF wild pattern, only immunotherapy can be prescribed [5]. As to the drugs currently available and reimbursed by the Italian National Health System, 3 combinations of anti-BRAF/anti-MEK inhibitors are available (dabrafenib/trametinib, vemurafenib/cobimetinib and the most recently introduced encorafenib/binimetinib). As to checkpoint inhibitors, first line immunotherapy is represented by anti-PD1 blockers (nivolumab and pembrolizumab), whilst the anti-CTLA-4 ipilimumab can be used as second line.

The decision-making factors defining the best treatment option in a stage IV metastatic melanoma patient are represented by: mutation pattern, performance status, high/low tumor load, brain metastases, progression pattern (low/fast), and availability of clinical trials.

This review will analyze the therapeutic tools available for the treatment of patients with metastatic melanoma and will focus on an update of results obtained by the new treatments (check point inhibitors and targeted therapies) which can be used in the clinical daily practice.

Anti-BRAF and Anti-MEK Inhibitors

The pharmacological inhibition of the mitogen-activated protein kinases (MAPK) pathway by targeting the mutant v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) is a milestone in the management of metastatic melanoma.

2 randomized phase III studies highlighted the efficacy of the dabrafenib-trametinib combination as first-line treatment in metastatic melanoma: COMBI-d (n=423, comparing the combination of dabrafenib/trametinib versus dabrafenib alone (p=0.0014). The median PFS was 11 months for the dabrafenib-trametinib combination and 8.8 months for dabrafenib monotherapy (p=0.0004); the median OS was 25.1 months and 18.7 months, respectively (p=0.01) [6]. Furthermore, the dabrafenib-trametinib combination had a better safety profile and improved health-related quality of life as well as reducing pain [6, 7]. As for the COMBI-v, the objective RR was 69% in the dabrafenib-trametinib combination arm and 51% in the vemurafenib arm (p<0.001) [8]. The dabrafenib-trametinib combination significantly improved OS compared to vemurafenib monotherapy (26.1 compared...
The combination showed a significantly higher clinical activity in terms of RR (68% vs 45%), PFS (median: 9.9 vs 6.2 months), and survival (9 months OS 81% vs 73%) [15]. At a median 14.2-month follow-up, the median PFS was 12.3 months for the combination versus 7.2 months for placebo and vemurafenib (p<0.0001). Median OS was 22.3 months for cobimetinib and vemurafenib versus 17.4 months (for placebo and vemurafenib; p=0.005). The safety profile for cobimetinib and vemurafenib was tolerable and manageable, and no new safety signals were observed with longer follow-ups [16].

The clinical activity of a third combination schedule of anti-BRAF/anti-MEK was investigated in the clinical trial COLUMBUS. COLUMBUS was a 2-part, randomised, open-label, phase III study. During part 1, patients were randomly assigned (1:1:1) to receive oral encorafenib 450 mg once daily, plus oral binimetinib 45 mg twice daily (encorafenib plus binimetinib group), oral encorafenib 300 mg once daily (encorafenib group), or oral vemurafenib 960 mg twice daily (vemurafenib group). Part 2 of the study compared encorafenib 300 mg once daily plus binimetinib 45 mg twice daily with encorafenib 300 mg once daily alone. At 3-year analysis, median OS was 33.6 months with encorafenib plus binimetinib and 16.9 months with vemurafenib [17, 18]. Median PFS was 14.9 months in the encorafenib plus binimetinib group and 7.3 months in the vemurafenib group. A confirmed overall response by blinded independent central review occurred in 63% of patients in the encorafenib plus binimetinib group compared with 51% in the encorafenib group, and 40% in the vemurafenib group. The median time to response was 1.8 months for the encorafenib plus binimetinib group. The most common grade 3-4 adverse events seen in more than 5% of patients in the encorafenib plus binimetinib group were increased γ-glutamyltransferase (9%), increased creatine phosphokinase (7%), and hypertension (6%).

Anti-CTLA4
Iplimunab is a fully humanized monoclonal antibody that binds to CTLA-4, a receptor expressed on the T-cell surface that interacts with CD80 (B7-1) and CD86 (B7-2) on the Antigen-Presenting-Cells (APCs) and downregulates T-cell response. CTLA-4 blockade allows CD28 to bind to B7-1 receptors, leading to immune activation, IL-2 secretion, cytotoxic T-cells expansion, and proliferation [19]. The interaction between CTLA-4 and B7-1/2 takes place in an early phase of the immune response, involving “naive” T lymphocytes and the APCs. This mechanism of action explains the characteristics of the clinical activity as well as the common side effects of this drug, consisting of immune-mediated reactions (irAEs) developing more frequently in the skin, gastro-intestinal tract (mainly diarrhea), liver and endocurinal glands. The trial that led to registration of ipilimumab in melanoma was a phase III clinical trial.
trial in which ipilimumab a glycoprotein 100 peptide (gp100) vaccine was compared with gp100 vaccine monotherapy in patients with unresectable stage III or stage IV melanoma. Ipilimumab monotherapy significantly improved median OS compared with gp100 vaccine monotherapy (10.1 months vs. 6.4 months) [20]. In another important randomized phase III trial, the combination of ipilimumab (10 mg/kg) and dacarbazine (850 mg/sqm) resulted in significantly superior OS compared to dacarbazine (850 mg/sqm) plus placebo (11.2 months vs. 9.1 months) [21].

Ipilimumab produced a plateau in the survival curves: a recent pooled analysis of OS data for 1,861 patients enrolled in 10 prospective and 2 retrospective trials, with up to 10-year follow-up, showed that the survival curve began to plateau around 3 years after treatment. 3-year OS rates were 22%, 26%, and 20% for all, treatment-naive, and previously treated patients, respectively [22]. Moreover, the results of the ipilimumab expanded access programme (EAP) in Italy resulted consistent with these data, confirming the activity of the drug also in specific patient's subsets such as the elderly, the mucosal or uveal primaries, and in the presence of brain metastases [23].

**Anti-PD1**

PD-1 represents a co-inhibitory receptor involved in the negative regulation of T-cell activation [24]. The expression of PD-1 ligand (PD-L1) on tumor cells induces the development of an immunosuppressing environment through the ligand with the PD-1 expressed on T lymphocytes, thus leading to T-cell inhibition and cancer immune system escape.

Two anti-PD-1 monoclonal antibodies are available in the clinical practice and can be used for the treatment of metastatic melanoma patients, ie nivolumab and pembrolizumab.

The CheckMate 066 trial investigated nivolumab mono-therapy as first-line treatment for patients with previously untreated BRAF wild-type advanced melanoma. In this multicenter, double-blind, phase III study, 418 patients with previously untreated, unresectable, stage III/IV, wild-type BRAF melanoma were randomly assigned 1:1 to receive nivolumab or dacarbazine, with OS as primary endpoint. The results demonstrated superior overall RR (40% vs. 13.9%, respectively) and increased 1-year OS (72.9% vs. 42.1%, respectively). Moreover, nivolumab treatment-related adverse events occurred in 11.7% of the patients receiving nivolumab and 17.6% of the patients receiving dacarbazine, respectively [25]. At 5-year analysis [26], ORR was 42% with nivolumab and 14% with dacarbazine. Five-year OS rates were 39% with nivolumab and 17% with dacarbazine; PFS rates were 28% and 3%, respectively. Among patients treated with nivolumab who had a complete response (20%), 88% (37 of 42) were alive as of the 5-year analysis.

In CheckMate 037 phase III trial, patients were randomly assigned 2:1 to receive nivolumab 3 mg/kg every 2 weeks or investigators’ choice chemotherapy (ICC) in ipilimumab-refractory patients with advanced melanoma [27]. Primary endpoints were the proportion of patients who had an objective response and OS. At first interim analysis on 120 and 47 randomized patients, confirmed objective responses were reported in 31.7% of patients in the nivolumab group vs. 10.6% of patients in the ICC group; no treatment-related deaths occurred. In the final 2018 report [28], the overall RR (27% vs 10%) and median duration of response (32 versus 13 months) were significantly higher for nivolumab versus ICC. Fewer grade 3 and 4 treatment-related adverse events were observed in patients on nivolumab (14% vs 34%). Median OS was 16 months for nivolumab versus 14 months for ICC; this data should however be interpreted with caution as patients enrolled in the ICC group could thereafter be treated by anti-PD1 or anti-BRAF targeted therapies.

As to pembrolizumab, KEYNOTE-006 was an open-label, multicenter, randomized, controlled, phase 3 study in which 834 patients with advanced melanoma were randomized to receive pembrolizumab at a dose of 10 mg/kg every 2 or every 3 weeks, or with 4 doses of ipilimumab (3 mg/kg every 3 weeks). The estimated 6-months PFS rates were 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab, respectively. Estimated 1-year OS rates were 74.1%, 68.4%, and 58.2%, respectively. The RR was improved when pembrolizumab was administered either every 2 or 3 weeks, as compared with ipilimumab. Treatment-related adverse events of grade 3–5 severity were lower in the pembrolizumab groups (13.3% and 10.1%) [29]. At the final 5-year follow-up data, median overall survival was 32.7 months in the combined pembrolizumab groups and 15.9 months in the ipilimumab group (p=0.00049). Median PFS was 8.4 months and 3.4 months, respectively [30]. A relevant analysis from this study was done in patients who stopped pembrolizumab after 24 months as per protocol. After a median follow-up of 34.2 months from completion of pembrolizumab, the estimated 24-month PFS from treatment interruption for all 103 patients was 78.4% and 36-month OS was 93.8%. Estimated 24-month PFS was 85.4% for patients with complete response, 82.3% for patients with partial response, and only 39.9% for patients with stable disease. These data pave the way for the possibility of interruption of anti-PD1 treatment in responding patients after 2 years of therapy.

KEYNOTE-002 study was a randomized phase II multicenter trial in which advanced melanoma patients with progression after ipilimumab and/or BRAF/MEK inhibitors were randomized to pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks or investigator-choice chemotherapy. Cross-
over to pembrolizumab was allowed following progression on chemotherapy.

A total of 180 patients were randomized to pembrolizumab 2 mg/kg, 181 to pembrolizumab 10 mg/kg and 179 to chemotherapy. 6-month PFS was 34% in the pembrolizumab 2 mg/kg group, 38% in the 10 mg/kg group, and 16% in the chemotherapy group [31]. At the final post-hoc 5-year analysis, the ORR was 22% and 28% in patients receiving pembrolizumab, versus 4% in patients receiving chemotherapy (p=0.0001 for both pembrolizumab doses versus chemotherapy) [32].

**Anti-CTLA-4/anti-PD-1 Combo Regimens**

Preclinical models have shown that double inhibition of CTLA-4 and PD-1, when compared with single-molecule inhibition alone, synergistically increases anticancer responses 173.

In the double-blind phase II CheckMate 069 study, patients were randomized to treatment with ipilimumab + nivolumab or with ipilimumab + placebo. At a median follow-up time of 24.5 months, the two-year survival was 63.8% for patients treated with nivolumab and ipilimumab in combination and 53.6% for patients treated with ipilimumab alone. In patients with wild type BRAF melanoma, the RR was 61% in the group of patients who received combination therapy compared to 11% of patients who received ipilimumab + placebo (P <0.001), with complete responses reported in 22% of patients in the first group and none in patients treated with ipilimumab alone [33].

The Phase III CheckMate 067 [34,35] study assigned patients with previously untreated advanced melanoma to receive one of the following regimens: nivolumab (at a dose of 1 mg per kilogram of body weight) plus ipilimumab (3 mg per kilogram) every 3 weeks for 4 doses, followed by nivolumab (3 mg per kilogram every 2 weeks); nivolumab (3 mg per kilogram every 2 weeks) plus ipilimumab-matched placebo; or ipilimumab (3 mg per kilogram every 3 weeks for four doses) plus nivolumab-matched placebo. The 2 primary end points were PFS and OS in the nivolumab-plus-ipilimumab group and in the nivolumab group, as compared with the ipilimumab group. 945 patients with advanced melanoma not treated with previous therapies were recruited. Combination therapy showed significantly higher PFS (11.5 months, 95% CI 8.9-16.7) than nivolumab monotherapy (6.9 months, 95% CI 4.3-9.5), or ipilimumab (2.9 months, 95% CI 2.8-3.4). The risk of death or tumor progression was reduced by 58% compared with ipilimumab monotherapy (HR 0.42; 99.5% CI 0.31-0.57). The ORR was 57.6% (95% CI, 52.0-63.2) in the combination cohort versus 43.7% in nivolumab (95% CI, 38.1-49.3) and 19% (95% CI, 14.9-23.8) in the ipilimumab monotherapy group. Patients treated with the combination therapy showed a complete response in 11.5% (compared with 8.9% with nivolumab and 2.2% with ipilimumab monotherapy). Most interestingly, when patients were stratified for PD-L1 negativity or immunohistochemical staining positivity (less or more than 5% of PD-L1 stained tumor cells in a section of at least 100 tumor cells), the median PFS was 14.0 months for patients with PD-L1 positive tumors in both the nivolumab-plus-ipilimumab group, and the nivolumab group. In contrast, in patients with PD-L1-negative tumors, PFS was longer with combination therapy than with nivolumab alone (11.2 months [95% CI, 8.0 a not achieved] vs. 5.3 months [95% CI, 2.8 to 7.1]). In this study, nivolumab combination therapy was superior to nivolumab monotherapy or ipilimumab alone in patients with PD-L1 negative tumors, whereas in patients with PD-L1 positive tumors there was no significant difference between nivolumab monotherapy and combined therapy. Overall survival at 5 years was 52% in the nivolumab-plus-ipilimumab group and 44% in the nivolumab group, as compared with 26% in the ipilimumab group. No sustained deterioration of health-related quality of life was observed during or after treatment with nivolumab plus ipilimumab or with nivolumab alone [36]. Grade 3 or 4 treatment-related adverse events occurred in 59%, 23%, and 28% of the patients in the nivolumab-plus-ipilimumab, nivolumab, and ipilimumab groups, respectively.

This combination therapy was approved in Europe by the EMA on May 2016, regardless of patients’ PD-L1 status.

**cKIT Inhibitors**

Mutations and amplification of the KIT oncogene are more frequent in melanomas arising in the skin with chronic sun damage, acral sites, or mucosal melanomas. A number of evidences from laboratory analysis and preclinical studies showed that hot-spot mutations, most frequently constituted by substitutions at exons 11 and 13, induce a pathological activation of the KIT, thus an upregulation of the downstream signal transduction pathways, which are not only the MAP-kinase, but also the PI3K/AKT, and JAK/STAT pathways. KIT gene expression has been correlated with activating mutations, which indicates the role of KIT in tumorogenesis in melanoma. Therefore, KIT has been suggested to be a potential therapeutic target for malignant melanoma.

Several trials have been conducted using KIT-targeted tyrosine kinase inhibitors in melanoma in both selected and unselected patient populations. Trials with imatinib showed responses if KIT was mutated but not if it was wild-type and amplified [37-39]. Other KIT inhibitors such as dasatinib, sunitinib, and nilotinib have also exhibited responses in KIT-mutant melanomas. However, taken together, these studies showed a percentage of responses around 20% and 30%, mostly of short duration without a significant impact on survival. Moreover, all these studies were performed on a relatively small number of patients and there is no available
randomized trial. In a recent retrospective analysis of 78 patients with metastatic melanoma harboring c-Kit mutations or amplifications treated with imatinib, ORR and DCR were 21.8% and 60.3%, respectively. The median OS and PFS of all patients were 13.1 [40]. The limited clinical activity of targeting cKIT imply that cKIT mutant patients should be treated as first line with immune check point inhibitors and only after the failure of these regimens, consider the potential of cKIT inhibitors.

NRAS Mutant Patients

NRAS mutations (codons 12, 13, and 61) can be detected in 15-20 % of all melanomas. These alterations have been associated with aggressive clinical behavior and a poor prognosis; however, a recent retrospective multicenter Italian study did not confirm the unfavorable prognostic significance of NRAS mutation. A cohort of 331 patients treated with immunotherapy as first-line were retrospectively recruited: 162 NRAS-mutant/BRAF wild-type (mut/wt) and 169 wt/wt. Regarding the outcomes, no significant differences were reported in overall RR, PFS or OS. Irrespective of the mutational status, a longer OS was significantly associated with normal LDH, <3 metastatic sites, lower white blood cell and platelet count, lower neutrophil-to-lymphocyte (N/L) ratio [41].

Some studies have been reported analyzing the clinical activity of anti-MEK inhibitors in these patients. Based on these data, a randomized phase III trial was designed, comparing binimetinib with dacarbazine. The study enrolled 269 patients in the binimetinib arm and 133 in the dacarbazine arm. Binimetinib significantly prolonged PFS and improved RR with respect to the control arm even if the clinical benefit is slow, with median PFS of 2.8 months compared to 1.5. Furthermore, no differences in OS were achieved. An interesting point was that the benefit in terms of PFS appear to be higher in patients with a prior immunotherapy (median 5.5 months) even if this is a retrospective analysis and thus caution should be taken [42].

Patients with Brain Metastases

The presence of brain metastases is now classified as stage IV M1d and it is associated with a poor prognosis (median survival 4 months) [43, 44] Patients with active brain metastases are in fact in most cases excluded from phase III clinical trials, particularly those involving immunotherapies [45,46]

As to targeted therapies, the COMBI-MB was a multicenter, multicohort, open-label, phase 2 study evaluating the combination of dabrafenib/trametinib in 4 patient cohorts with melanoma brain metastases (based on the presence of symptoms, ECOG, and previous radiotherapy). Percentages of intracranial responses ranged from 44% to 59% with PFS lower than that found in patients with no brain metastases (19% PFS at 12 months). Dabrafenib plus trametinib was active with a manageable safety profile in this melanoma population that was consistent with previous dabrafenib plus trametinib studies in patients with BRAFV600-mutant melanoma without brain metastases, but the median duration of response was relatively short [47].

In phase II studies that involved the use of nivolumab or pembrolizumab alone in patients with brain metastases, the percentage of responses varied from 16% to 25%, that is clearly lower than the standard immunotherapy RR of around 40% -50%. The duration of the responses was also significantly shorter [45].

The results of 3 studies carried out in patients with active brain metastases have instead highlighted the clinical activity of the combination of anti-PD1 nivolumab with ipilimumab in these patients with RR ranging from 46% to 55%.

In particular, the ABC study is a phase 2 study that randomized patients with asymptomatic brain metastases to receive the combination nivolumab + ipilimumab, versus nivolumab alone. A third arm involved the inclusion of patients with symptomatic brain metastases to receive exclusively nivolumab. Intracranial RR were 51% in patients treated with the combination, 20% in asymptomatic patients treated with nivolumab, and 6% in symptomatic patients treated with nivolumab. The rate of intracranial responses increased to 59% with the combination in naive, non-pre-treated patients, compared to 21% with monotherapy. PFS was also significantly different, 43% at 3 years with the combination versus 15% and 6% with monotherapy, respectively. The safety profile did not report significant differences with respect to that highlighted in previous studies of immune combo with a percentage of adverse events grade ¾ higher than monotherapy but still manageable from a clinical point of view in a patient setting with such a severe prognosis as those included in the study [48].

A second study reporting the results of the ipi nivo combination in patients with brain metastases is the Phase II CheckMate 204 study, which enrolled 75 patients, with 55% intracranial and 53% global RR, 2.8 months’ time to response and median duration of responses not yet achieved [49].

The third NIBIT-M2 study is a randomized phase 3 study that included patients with brain metastases randomizing them into three arms (fotemustine, fotemustine + ipilimumab, and nivolumab + ipilimumab). The arm treated with the immune combo obtained 44% intracranial response with PFS 36% at 4 years and 41% OS at 4 years [50].

New Scenarios: Combining Targeted and Immunotherapies

A novel approach which is emerging for BRAF-mutant patients is represented by the combination of targeted therapies and immune-checkpoint inhibitors [51], commonly
referred as “triplets”. The rationale for this association is 2-fold. From the clinical point of view, it could couple the principal benefits of the 2 regimens, thus the high response rate of the targeted therapies and the remission duration of immunotherapies in an attempt to overcome the development of acquired resistance. From the biological point of view, anti-BRAF targeted therapies have been recognized to positively modulate the immune regulation, by promoting T-cell infiltration with reduction of regulatory T-cells, inducing melanoma antigen-expression, and restoring the impaired MHC-I surface expression, thus reducing the immunosuppression and immune escape associated with the BRAF mutated oncogenic pathway [52].

The KEYNOTE-022 trial [53], the first phase II trial investigating a triplet in melanoma, randomized 120 patients to receive dabrafenib/trametinib plus pembrolizumab or placebo, with PFS as primary endpoint. The study did not show a statistically significant difference in PFS, even if a non-statistically longer PFS was found in patients treated with the triplet (16.9 vs 10.7 months at 36 months follow-up); moreover, median duration of response was 25.1 months in the triplet cohort and 12.1 months in the control group. Patients treated with the triplet experienced however higher toxicity rates, with 58.3% developing grade 3-5 treatment-related adverse event versus 26.7%.

The IMspire150 trial was a randomized phase 3 study comparing the triplet atezolizumab, vemurafenib, and cobimetinib versus vemurafenib, cobimetinib and placebo, with the primary endpoint of PFS. A total of 514 patients were enrolled. At a median 18.9 month follow-up, investigator–assessed PFS was significantly longer in the triplet group versus control (15.1 vs 10.6 months; p=0.025). The triplet

<table>
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<th>ENDPOINT</th>
<th>COMBI-D DBARAFENIB+ TRAMETINIB VS. DABRAFENIB</th>
<th>COBRIM+ COBIMETINIB + VEMURAFENIB VS. VEMURAFENIB</th>
<th>COMBI-V+ DABRAFENIB + TRAMETINIB VS. VEMURAFENIB</th>
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<tr>
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<td>22.3</td>
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**Figure 1.** Clinical activity of the 3 main combinations of targeted therapy. ORR: Overall response rate; PFS: progression-free-survival; OS: overall survival

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<tr>
<th>COMBI-D DBARAFENIB+ TRAMETINIB VS. DABRAFENIB</th>
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<tbody>
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<td>25.1</td>
<td>22.3</td>
<td>25.6</td>
<td>33.6</td>
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**Figure 2.** (A, B) Development of response in a representative patient with BRAF mutant metastatic melanoma with lung and skin metastases: response achieved as clinically evident at the 7th week from the beginning of treatment. (C-F) CT scan performed 3 months after the beginning showing the complete clearance of lung metastases.
was approved by FDA; however, even if the study met its primary endpoint, the values of the median PFS reached is similar to that of the Keynote-022. The frequency of grade 3-4 adverse events was similar (79% versus 73%); no major adverse events were found in the triplet group and the percentage of patients who stopped all treatment due to adverse events was similar (13% in the triplet versus 16%) [54].

More recently, the results of the part 3 of the COMBI-I trial were presented [55]. This phase III randomized clinical trial enrolled 532 patients to compare the combination of dabrafenib and trametinib plus spartalizumab or placebo. The PFS was longer in the triplet group even if the difference did not meet a statistical significance (16.2 versus 12 months). The objective response rate was 69% versus 64%. The percentage of patients showing grade 3 or more treatment related side effects was 55% in the triplet group versus 33% in the control arm.

The results of the large randomized trials comparing the triplets versus the standard targeted regimens did not completely confirm thus until now the promising preliminary data, also showing a less favorable toxicity profile for this associations. However, all the studies identified a longer PFS of the triplet versus the control arm (with a statistical significance only in the IMspire trial but with similar values across the different studies), thus it is justified to wait for a longer follow-up time to better characterize the role of the combination of targeted and immunotherapies, and to identify which could be the patients that could benefit more from this treatment.

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**Table:**

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<th>% CR</th>
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<td>NIVOLUMAB</td>
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<td>36-37%</td>
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<td>NIVOLUMAB+IPILIMUNAB</td>
<td>58.3%</td>
<td>21.3%</td>
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</table>

**Figure 3.** Clinical activity of immune check point inhibitors. RR= response rate; CR= complete response

**Figure 4.** (A) Pattern of response following immune therapy in a patient with multiple in-transit skin metastasis localised in the lower limb. (B-D) Response developed during 1 year of treatment with induction of inflammation. (E) Immune activation around the skin metastases, towards complete clearance confirmed at histology with development of peri-lesional vitiligo.
Conclusions

The comparison between OS rates before the development of new drugs (1-year survival 2.5%, median survival 6 months) [2] and those achieved with both targeted therapies and immune checkpoint inhibitors (5-year survival 35%, median survival 24 months) clearly highlights the relevant impact that these new treatment approaches are having in the disease course of advanced metastatic melanoma and this is well recognized by the main Italian national, European and American guidelines [5,56,57]. However, when considering the curves from the other side, it is evident that at 5 years, 65% of patients die due to disease progression, supporting the need of more active treatment strategies or combinations. The results from the trials analyzing the clinical activity of the so-called triplets (combo-target plus anti-PD1) gave conflicting results and it is reasonable to think that more follow-up is needed. In the daily clinical practice, the challenges are represented by the management of patients with aggressive disease and/or multiple visceral sites, as well as those with brain metastases or mucosal/coroidal primaries. The availability of adjuvant treatments is improving the disease course in stage III patients disease-free after surgery but the management of the progressions occurring during adjuvant treatment, particularly in BRAF wild-type patients, still represents another clinical challenge. The availability of data coming from real life experiences together with the results of ongoing clinical trials will provide relevant informations to improve the management of these patients, as well as the identification of both prognostic and predictive factors associated with the disease course and response to treatment.

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