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PARP1 in Melanoma: Mechanistic Insights and Implications for Basic and Clinical Research

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ABSTRACT
Targeted therapies and immunotherapies have revolutionized the treatment of metastatic melanoma and have set a successful example for the treatment of other cancers. A similar breakthrough was achieved with the advent of PARP inhibitors (PARPi) in breast and ovarian cancer.
Recent evidence highlights the critical role of PARP1 in melanoma initiation and progression. High PARP1 expression correlates with aggressive melanoma characteristics and poor patient outcomes. Preclinical and clinical data suggest that PARPi, alone or in combination, can effectively reduce melanoma cell viability and inhibit tumor growth. However, integrating PARPi with current treatment approaches and identifying patients who could benefit the most from such combinations remain underexplored areas of investigation.
This review highlights the need for further basic and clinical research on PARP1 in melanoma, to better understand its role and to tackle major challenges in the field, such as resistance to targeted therapies and immune checkpoint inhibitors.

KEYWORDS
PARP1, PARPi, melanoma, targeted therapy, immunotherapy, patient stratification

RUNNING TITLE
Opportunities for PARPi in melanoma treatment

INTRODUCTION

The past 15 years of melanoma research can be described as exciting and a true example of how basic and translational research has improved the patient expectancy of life. In these years, we have achieved more than ten approved melanoma therapies [1].

Melanoma standard of care includes targeted inhibitors of mutant B-Raf proto-oncogene, serine/threonine kinase (BRAFV600E) and of Mitogen-activated protein kinase kinase 1/2 (MAP2K1/2 also known as MEK1/2) in the MAPK pathway, as well as Immune Checkpoint Inhibitors (ICIs), alone or in combination. Other therapeutic options are used for some subsets of patients and include interferon therapy, immunotherapy with inter-leukin-2 (IL-2), or immunotherapy with an oncolytic virus.

These treatments have dramatically improved patient outcomes and nowadays half of patients do obtain long-term survival [2]. Despite tremendous progress, many patients relapse after immunotherapy or become resistant to targeted therapy [3], thus curing melanoma remains a major health challenge and mission.

Within the same years, the treatment of breast and ovarian cancers has experienced a leap forward in therapy with the approval of PARP inhibitors (PARPi) [4]. Poly(ADP-ribose) polymerase 1 (PARP1, HGNC:270), the major member of the PARP protein family, uses NAD+ as a substrate to catalyze the attachment of ADP-ribose polymers (PAR) to target proteins and is best known as a DNA repair enzyme [5]. In cancers defective of genes involved in DNA repair mechanisms (e.g. *BRCA1/2* genes), PARPi induces “synthetic lethality” and tumor death [4].

Melanoma tumors show a high mutational burden, with a predominant UV signature due to sun exposure [6], [7]. In addition, approximately 20% of patients have at least one mutation in a gene involved in DNA repair [8]. *PARP1* gene is altered in melanoma and is involved in onset and progression, providing the rationale for testing the efficacy of PARPi.

In this review, we discuss what we currently know about PARP1 in melanoma and the ongoing clinical trials of PARP inhibitors. We also raise questions about PARP1 biology and targeting that need to be further investigated, to address the major needs of the field and to achieve breakthroughs in melanoma therapeutic applications.

1. PARP1 structure and functions

1.1 PARP1 structure

The poly(ADP-ribose) polymerase 1 (*PARP1*) gene encodes a nuclear protein that performs a specific post-translational modification called PARylation, and regulates a wide number of cellular processes, such as DNA repair, chromatin remodeling, RNA metabolism, cell metabolism, and cell death.

PARP1 protein is composed of three main domains: an N-terminal DNA/RNA-binding domain (Zn), an auto-modification domain (AUTO), and a catalytic domain at the C-terminal (CAT). In the N-terminal domain, there are three zinc finger DNA-binding domains that are important for recognition and binding to DNA damage and for activation of DNA repair enzymes. This domain also harbors a caspase cleavage site, which is cleaved during apoptosis determining the formation of cleaved-PARP1 [9]. The auto-modification domain contains a BRCA1 C-terminal (BRCT) motif and the WGR subdomain. The BRCT motif comprises amino acids that undergo PARylation, particularly Glu and Lys residues. PARP1 auto-PARylation is essential for its activity, as it allows detachment from DNA after damage recognition and subsequent recruitment of downstream repair factors [10]. Finally, the CAT domain contains the NAD+ acceptor site, as well as residues contributing to the initiation, elongation, and branching of PAR [11] **Fig.1a**.

1.2 PARP1 enzymatic activity: PARylation

PARylation is a dynamic reaction, which consists in the covalent attachment of a single ADP-ribose (MAR) or numerous long and branched chains of poly(ADP-ribose) (PAR) on target proteins, regulating their activities. The ADP-ribose donor is the oxidized form of nicotinamide adenine dinucleotide (NAD+), while the reaction product is nicotinamide, which is reconverted to NAD+ through an ATP-dependent biosynthetic process **Fig.1a**.

Proteomic approaches have identified several amino acids that are acceptors for PARylation, such as Lys, Arg, Glu, Asp, Cys, Ser, Thr, His, and Tyr [12], [13], although interaction with cofactors can switch preference for specific residues [14].

Almost all eukaryotes possess *PARP* genes and can perform PARylation [15]. In *H. sapiens*, 18 PARP family members have been identified, but only PARP1, PARP2, and PARP3 as well as PARP4 and PARP5 (also known as Tankyrase 1 and 2), can perform PARylating activity [16], with PARP1 promoting most of it in response to DNA damage [17].

PARylation is a very dynamic reaction and PAR polymers are degraded as quickly as they are generated, in a sort of “write” and “erase” process [18]. Degradation of PAR polymers is carried out by enzymes such as poly(ADP-ribose) glycohydrolase (PARG) and ADP-ribose hydrolases (ARHs). The rapid turnover of PAR polymers is crucial for efficient DNA repair [19] and defects in their catabolism are deleterious to cells [20], [21], as we describe below.

1.3 Role of PARP1 in DNA repair (SSBs and DSBs)

The main role of PARP1 is within DNA damage response (DDR) at lesions that involve single (SSBs) and double (DSBs) strand breaks. DNA damage results in rapid recruitment of PARP1 to lesion sites through its DNA-binding ability [22]. In turn, this induces conformational changes [23] leading to NAD+ binding, and activates PARylation of PARP1 itself, of histones, and other target proteins involved in DNA repair [24], [25] **Fig.1b**.

Recently it has been shown that at early stages of DDR, PARP1 activity is highly dependent on its co-factor Histone PARylation factor 1 (HPF1). The interaction between these two proteins favors PARylation of Ser residues on proteins located in close proximity to DNA breaks, thus promoting the rapid unfolding of chromatin and facilitating access of other repair factors to sites of damage [26].

Proteins involved in DDR bind to PAR through non-covalent interactions and this mediates their recruitment to DNA damage. To perform this interaction, these proteins rely on specific PAR binding domains, such as PAR-binding zinc finger motifs (PBZs), macrodomain folds, RG/RGG repeats, BRCT, RRM, OB-fold domains, PIN domains, and PAR-binding consensus motifs (PBMs) [27].

Within SSBs, the main repair pathways are represented by base excision repair (BER) and nucleotide excision repair (NER). The choice depends on the type of damage: an abasic and oxidized base or a bulky lesion that distorts the double helix, respectively. In both cases, PARP1 plays an important role in damage recognition and recruitment of repair factors, although its role in NER is more established and essential [28], [29]. Within DSB repair, the most important pathways

are non-homologous end joining (NHEJ) and homologous recombination (HR). NHEJ is an error-prone pathway that involves DNA processing at the lesion, searching for homologies between strands before ligation, and leads to a small deletion. HR is an error-free pathway that uses the complementary sequence on the sister chromatid or the homologous chromosome to repair the lesion without inserting any deletion or mutations [30]. PARP1 is one of the first proteins recruited at the DSB and once there it regulates both early phases of the repair by PARylation of upstream kinases [31], [32], and late phases by limiting DNA processing and avoiding extensive resection [33], [34].

PARP1 also plays an important role in preventing the accumulation of DNA damage due to arrested replication forks. DNA replication machinery collision with a DNA lesion leads to replication arrest. If the replication machinery remains stalled for an extensive time due to the persistence of the damage, the fork collapses with the formation of a DSB. PARP1 activity is essential to avoid this detrimental situation by binding the arrested fork and promoting a fork reversal process, which consists in the annealing of the two newly replicated strands into a regressed arm at the fork [35], [36]. The generation of this four-way junction favors fork stabilization and limits the activity of proteins involved in its degradation, ultimately providing cells enough time to repair the lesion [36].

It is important to mention that, in addition to the proteins involved in DDR, PARP1 parylates Tumor protein p53 (TP53) as well. This modification increases ‘s ability to bind the DNA of target genes and, therefore, contributes to strengthening the p53-dependent cellular response after DNA damage [37]. Furthermore, in the context of DNA damage induced by ionizing radiations, PARP1 activates p53 indirectly by activating ATM serine/threonine kinase (ATM) [38]. In turn, p53 partner ribonucleotide reductase regulatory TP53 inducible subunit M2B (RRM2B) avoids a disproportionate activation of PARylation at the replication fork, protecting DNA from degradation [39].

1.4 Role of PARP1 in RNA metabolism

PARP1 cellular activity is not restricted to the recognition and repair of DNA damage and spans many other cellular processes. An increasing amount of data shows that PARP1 is involved in RNA metabolism at different levels, by regulating transcription, splicing, mobility, turnover, and translation [36] **Fig.1b**.

PARP1 indirectly promotes transcription initiation by PARylating histones and opening the chromatin structure to allow binding of the transcriptional machinery [40]. However, it can also directly regulate transcription by modulating RNA polymerase II pausing during the RNA elongation phase [41].

In addition, PARP1 directly interacts with the spliceosome complex and regulates splice factors. Specifically, PARP1 directly regulates splicing by interacting with the U2 subunit of the spliceosome complex [42], while it regulates splice factors by PARylating them and triggering or limiting their functionality by reducing their RNA/DNA binding ability [43], [44]. Another level of splicing regulation is through the PAR binding ability that some splicing factors harbor. Particularly, there is a competition between RNA and PAR for binding to these proteins. This ultimately leads to alteration in RNA-protein complexes and different outcomes in terms of alternative splicing [45], [46].

PARP1 is also involved in RNA transport and stability. It binds and PARylates the human antigen R (HuR**)** protein, favoring its nucleocytoplasmic translocation [47] and, in turn, influencing mRNA transport. PARP1-HuR interaction is also important for mRNA stability, since the enhanced shuttling of HuR to the cytoplasm, caused by PARylation, determines an increased HuR interaction with target mRNAs, promoting their stability and favoring protein expression [48].

RNA regulatory functions are mainly mediated by PARP1's parylase activity, however, it has recently been reported that cytoplasmic PARP1 can directly bind to RNA through its zinc finger domains, making it also a *de facto* RNA-binding protein [49]. This function increases the complexity of the role that PARP1 plays within the cell and opens the way to new areas of investigation. In melanoma, we have recently reported that PARP1, through its RNA binding activity, regulates the translation of *BRAF-X1* mRNA (*ENST00000496384.7/BRAF-204*) and thus controls the signaling of the highly oncogenic MAPK pathway in a PARylation-independent manner [50].

1.5 Role of PARP1 in cell metabolism and cell death

NAD+ is an essential cofactor involved in most reductive-oxidative metabolic pathways. It is reduced to NADH through glycolysis and the citric acid cycle. In turn, in the electron transport chain, NADH is oxidized to NAD+ so that ATP can be produced [51]. NAD+ is also the donor of ADP-ribose used

by PARP1 to perform its PARylation activity. Activation of PARP1 due to DNA damage leads to a strong depletion of cellular NAD+ [52], which is usually transient and triggers a metabolic shift to oxidative phosphorylation over glycolysis to enhance ATP production and replenish the NAD+ reservoir **Fig.1b** [53]. However, prolonged activation of PARP1 due to the persistence of DNA damage can impair the energetic balance, leading to ATP depletion and cell death [54]. In general, a slow rate of ATP depletion triggers apoptosis by activating the Caspase-3 (CASP3) axis, conversely, rapid ATP depletion determines loss of plasma membrane homeostasis and ultimately leads to necrosis [55]. For example, the overactivation of PARP1 caused by DNA-alkylating agents such as 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) causes rapid ATP depletion and necrosis. Particularly, this caspase-independent cell death is triggered by the release of Apoptosis inducing factor mitochondria associated 1 (AIFM1) from mitochondria into the cytoplasm. Here, AIFM1 forms a degrading complex with H2A.X variant histone (H2AX) and Peptidylprolyl isomerase A (PPIA), and promotes DNA fragmentation [56]. It should also be noted that PARP1 is a substrate for CASP3 cleavage and that cleaved-PARP1 has no enzymatic activity. In a situation in which cells die without caspase activation, PARP1 activity determines futile consumption of NAD+ and ATP, contributing to energetic crisis and necrosis, rather than controlled cell death [57].

The overactivation of PARP1 caused by oxidative stress leads to PARthanatos. This peculiar cell death mechanism is characterized by the accumulation of PAR polymers on the mitochondria membrane, so that AIFM1 release is triggered [58], [59]. In addition, cleaved PARP1 undergoes auto-PARylation and translocates in the cytoplasm, where it favors AIFM1 release from mitochondria **Fig.1b** [60].

Cell death is also triggered by PARP1 downregulation or inhibition. In general terms, the absence of PARP1-mediated DNA repair activities causes an accumulation of genetic mutations and chromosomal aberrations. The latter ultimately lead to incorrect cell entry into mitosis and trigger cell death via a mechanism called mitotic catastrophe, which is characterized by the missegregation of chromosomes [61], [62].

In addition, PARP1 inhibition has been recently linked to pyroptosis, a cell death tightly associated with inflammation [63]. Pyroptosis is characterized by the release of inflammatory molecules due to the presence of pores in the cellular membrane. In turn, these pores are formed by oligomerized fragments produced by CASP3-dependent cleavage of a member of the gasdermin protein family, particularly Gasdermin E (GSDME) [64]. PARP1 trapping on DNA caused by Talazoparib (see below) triggers this pathway by activating CASP3 and promoting GSDME cleavage [65].

Finally, PARP1 pharmacological inhibition or genetic deletion has been linked to ferroptosis, a recently identified form of regulated cell death driven by iron-dependent lipid peroxidation. PARP1 inactivation causes the p53-dependent downregulation of cystine transporter Solute carrier family 7 member 11 (SLC7A11), which leads to reduced glutathione biosynthesis so that iron-dependent lipid peroxidation cannot be counteracted **Fig.1b** [66].

2. Pharmacological targeting of PARP1 with PARP inhibitors

2.1 Rationale for PARP inhibitors and synthetic lethality

Drugs targeting proteins involved in DNA repair have proven effective in cancer therapy [67]. Cancer cells are deficient in DNA repair and rely on few functional pathways that allow them to proliferate without accumulating excessive genome instability. Based on this assumption, it is not surprising that inhibition of PARP1 is a strategy exploited to treat cancer.

PARP inhibitors (PARPi) have proven to be particularly effective in breast and ovarian cancers deficient in the HR pathway due to mutations in *BRCA1* or *2 DNA repair associated* (*BRCA1* or *BRCA2*) genes [68]. Recently, their usage has expanded to prostate and pancreatic cancer, and in some instances, they proved to be useful even in the absence of BRCA deficiency [69], [70].

PARPi act as NAD+ mimetics, binding to the catalytic domain of PARP1 and blocking PARylation reaction. In cells deficient for BRCA1 or BRCA2, the DSBs cannot be repaired with the error-free mechanism HR, forcing cells to resort to the error-prone NHEJ mechanism. In the end, PARPi cause an excessive accumulation of mutations, promoting gross chromosomal rearrangements and genomic instability, leading to cell death. This phenotype in which a combination of two viable

mutations causes cell death is called synthetic lethality and several anti-cancer therapies are designed to take advantage of this effect [71].
It has been recently proposed that PARPi efficacy mainly depends on their ability to cause PARP1 steady binding to DNA (trapping). This results in DNA damage by two distinct mechanisms: by impending binding of downstream DNA repair effectors at the DNA lesion and by the accumulation of DSBs due to replication fork collapse, when the DNA replication machinery collides with PARP1 trapped on DNA [72]. To date, four PARP inhibitors have been approved by the Food and Drug Administration (FDA): Olaparib, Rucaparib, Niraparib, and Talazoparib. Each inhibitor has a different PARP1 trapping efficiency with Talazoparib having the highest [73]. Combination of these drugs with other agents causing DNA damage or targeting other genes involved in DDR is common in therapy, to minimize dosage requirements and to increase drug efficiency [74].

2.2 Mechanisms of resistance to PARPi

Despite promising results and improved clinical outcomes, PARPi are no exception and acquired resistance is a frequent occurrence.
One of the main causes of acquired resistance is the restoration of HR functionality, either by secondary mutations on *BRCA1* or *BRCA2* genes or by disruption of genes involved in NHEJ. In the first case, secondary mutations in *BRCA1/2* open reading frame can restore their expression and compensate for the initial deleterious mutation, leading to restoration of the HR pathway and reduced PARPi efficiency [75], [76]. In the latter case, mutations in genes involved in NHEJ, such as *tumor protein p53 binding protein 1* (*TP53BP1*), *mitotic arrest deficient 2 like 2* (*MAD2L2*), or the shielding complex [77], [78], promote HR functionality, even in the absence of BRCA1/2, thus reducing PARPi effectiveness [79], [80].
Another determinant of acquired resistance to PARPi is an increased drug efflux. In ovarian cancer, the overexpression of ATP binding cassette subfamily B member 1 and 2 (ABCB1 and 2) (ABCB1 and 2) determines resistance to PARPi due to an increase in their extrusion from cells [81].
More recently, two additional mechanisms of acquired resistance have been proposed: stabilization of the replication fork and downregulation of PAR degrading enzymes. As mentioned above, PARP1 inhibition determines DNA damage by replication fork collapse, therefore the downregulation of genes involved in the degradation of arrested forks is linked to increased resistance to PARPi. Particularly, this has been shown by depleting PAX interacting protein 1 (PAXIP1) and MUS81 structure-specific endonuclease subunit (MUS81), which are factors that promote the recruitment of downstream effectors involved in fork degradation [82], [83]. Finally, depletion of PAR degrading enzymes, such as PARG, is a common occurrence in PARPi-resistant BRCA2-deficient mouse mammary tumor models. Indeed, inactivation of PARG enables PAR accumulation to maintain adequate PARP function. However, further studies are required to determine if this is a relevant mechanism of resistance in human cancer as well [84].
Although several mechanisms have been described, many resistance cases remain unexplained. For this reason, several groups are searching PARP1 interaction networks for novel genes to target in combination with PARPi. The final aim is to enhance efficacy and at the same time to prevent resistance development [85], [86], [87].

3. Combined treatment with PARPi

3.1 DNA damage and the innate immune response

Increasing evidence has pointed to the crucial interaction between the DNA damage response and the immune system in oncology, particularly during cancer treatment [88].
Most standard cancer therapies are based on chemotherapeutic agents that induce various types of DNA damage. In turn, the generation of DNA damage promotes the activation of different immunological responses related to the recognition of cytoplasmic DNA. For instance, chemotherapeutic agents such as Topoisomerase I and II inhibitors or 5-Fluorouracil induce DNA breaks, causing the generation of micronuclei - small membrane-bound compartments with a DNA content encapsulated by a nuclear envelope and spatially separated from the nucleus - that release free nuclear DNA into the cytoplasm [89]. Additionally, many chemotherapeutics express their

cytotoxicity by generating reactive oxygen species (ROS) and promoting, consequently, mitochondrial stress. In this case, mitochondrial DNA is released into the cytoplasm [90].
An intracellular specialized pathway, named cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway, senses cytosolic DNA and activates an immunological response. Briefly, upon recognition of cytosolic DNA, cGAS produces the second messenger cyclic GMP–AMP (cGAMP), which activates STING signaling. As a consequence, type-I interferons (IFNs) and pro-inflammatory cytokines are produced [91], [92]. The cGAS-STING pathway plays a critical role not only in protecting normal cells from a variety of pathogens but also within the innate immune response against cancer cells upon treatment with radiotherapy and chemotherapy [93], [94]. For example, in melanoma cells, carboplatin and carbon ion irradiation have been shown to induce apoptosis both *in vitro* and *in vivo*, by promoting cGAS-STING activation [95], [96].
This interplay between DDR and innate immune response has been confirmed by a gene expression-based molecular subtype of breast cancer in which double-strand break repair-deficient tumors (enriched for BRCA1/2 mutations) show activation of the innate immune response [97]. Further studies have confirmed that the loss of DNA repair genes like *BRCA1/2* activates an innate immune response characterized by the upregulation of IFN-regulated genes, such as *C-X-C motif chemokine ligand 10* (*CXCL10*), *C-C motif chemokine ligand 5* (*CCL5*), and *interferon beta 1* (*IFNB1*), independently of immune infiltration or neoantigen production [98].

3.2 Rationale for combining PARPi with Immune Checkpoint Inhibitors (ICIs)

In the intricate landscape of cancer therapy, the inhibition of PARP1 emerges as a multifaceted strategy with far-reaching implications, not limited to DNA damage repair but extending into the realm of the immune response against cancer cells.
The inhibition of PARP1 results in the accumulation of DNA damage, including fragmented DNA molecules which serve as potent danger signals, alerting the immune system to the presence of aberrant genetic material. In this scenario, the inhibition of PARP1 can activate the cGAS-STING pathway in cancer cells. Recent studies have evaluated the efficacy of combining PARP inhibitors with STING agonists in BRCA-deficient breast cancer [99], [100].
However, the intricate connections between PARP1 inhibition and the immune response transcend the activation of the STING pathway. Indeed, Ding and colleagues revealed that PARP1 inhibition elicits a potent antitumor immune response in the context of BRCA1-deficient ovarian tumors [101]. Remarkably, the study highlighted the crucial role of antigen-presenting cells (APCs), such as dendritic cells, in orchestrating this immune response. They found that, following PARP1 inhibition, APCs sense double-stranded DNA (dsDNA) fragments originating from the enhanced genomic instability of the BRCA1-deficient cancer cells. Building on these data, PARPi have been extensively tested to strengthen the antitumor immune response and increase the efficacy of ICIs [102].
The rationale for PARP inhibitors in combination with ICIs mainly involves the following aspects: (1) neoantigen production and (2) upregulation of CD274 molecule, also known as Programmed cell death 1 ligand 1 (PD-L1). Neoantigens are mutated proteins expressed exclusively by the tumor, rendering it highly immunogenic and a key target for immunotherapy. Immune cell response to neoantigens is of particular interest because it is not affected by central T-cell tolerance, and it is not expected to result in autoimmune toxicity. PARP1 inhibition, by increasing the intrinsic genetic instability in cancer cells, results in tumor cell death and the subsequent release of tumor-associated neoantigens [103]. PD-L1, an inhibitory ligand found on the surface of tumor cells, antagonizes T-cell activation, proliferation, and secretion of cytotoxic molecules. It has been shown that PARP inhibitors up-regulate the expression of PD-L1 on cancer cells. This is due to multiple mechanisms, such as the cGAS-STING-dependent production of IFNs, the activation of the ATM-ATR serine/threonine kinase (ATR)-Checkpoint kinase 1 (CHEK1) pathway, and the inhibition of Glycogen synthase kinase 3 beta (GSK3B) [104], [105]. This heightened PD-L1 expression is of particular significance because it indicates the tumor's vulnerability to immune-mediated attack, making it an attractive target for ICIs [106]. For example, in breast cancer, PARPi upregulate PD-L1 expression through the inhibition of GSK3B and enhance cancer-associated immunosuppression in preclinical models [87]. Today more than 35 clinical trials are evaluating the efficacy of combining PARP inhibitors with immunotherapies in different solid tumors, including melanoma (NCT04633902 and NCT04187833, see below).

4. PARP1 in melanoma

4.1 *PARP1* alterations and SNPs in melanoma

PARP1 is increasingly studied in melanoma, and there is growing evidence that it plays a role in melanoma genesis and progression.

Cutaneous melanoma ranks third for *PARP1* alterations among the tumors of the TCGA Pan-Cancer dataset [107]. Such alterations are mostly mutations. They are present in nearly 4% of cases [107] **Fig.2a** and their association with melanoma risk/prognosis has been demonstrated in several clinical studies. For example, a GWAS study of an Australian cohort identified a melanoma risk locus on chromosome 1, including several genes among which *PARP1* was found [108].

Additionally, several polymorphisms within the *PARP1* gene have been associated with risk, prognosis, and response to chemotherapy in melanoma patients. The SNP rs3219125 was found to be significantly associated with melanoma risk in a set of 585 melanoma cases and 585 controls [109]. An opposite role has been observed for the SNP rs3219090, which has a protective effect [110]. Davies et al. [111] studied the genetic variant rs2249844, which is significantly associated with an increased risk of death. They also showed that the T allele of rs3219090 is associated with reduced melanoma risk but poor survival, as later confirmed in the study by Law et al. [112]. The SNP rs144361550, located in a *PARP1* intron, is a functional melanoma risk variant and can influence PARP1 expression [113]. The SNP rs1805407 is associated with response to chemotherapy and increases sensitivity to PARPi in melanoma and other cancer cells [114].

4.2 *PARP1* expression levels in melanoma

Alterations and SNPs have revealed a link between the *PARP1* gene and melanoma. This association appears even more meaningful when the expression of this gene is considered at both mRNA and protein levels.

PARP1 mRNA expression is lower in normal melanocytes than in melanoma [107], [115] and increases in high-stage melanoma compared to low-stage melanoma [115], [116] **Fig.2b**. Consistently, several clinical studies show that PARP1 expression is a prognostic marker for melanoma survival. High PARP1 expression (mRNA and protein) is associated with poor patient prognosis [116], [117], [118], [119] both in primary and metastatic melanoma patients [115] **Fig.2c**. PARP1 expression levels are also associated with adverse histopathological parameters, including tumor ulceration regardless of Breslow thickness classification [111]. Finally, PARP1 protein belongs to a signature capable of stratifying stage III melanoma patients into prognostic subgroups [119].

Interestingly, Kupczyk et al. [116] showed a significant correlation between PARP1 expression and primary tumor location: PARP1 is higher in head and neck melanomas compared to those belonging to the trunk and extremities. Furthermore, Staibano et al. [118] observed that in head and neck lesions PARP1 expression is associated with the transition from radial to vertical tumor growth, another important histopathological indicator of tumor aggressiveness. These data suggest a specific involvement of PARP1 in melanomas that develop at sites with high sun exposure.

4.3 Molecular role of PARP1 in melanoma cells

Considering that PARP1 is a DNA repair enzyme [4] and is actively involved in removing UV-induced DNA photolesions, it is not surprising that many *in vitro* and *in vivo* preclinical studies have unveiled the molecular role played by PARP1 in melanoma genesis and progression.

Choi et al. reported a pro-proliferative effect of PARP1 in melanocytes and melanoma [113]. They observed that ectopic expression of PARP1 leads to increased melanocyte proliferation, both in the presence and absence of the mutated version of BRAF. BRAFV600E is present in most melanocytic nevi [120], however, melanocytes are generally dormant and non-proliferative due to a phenomenon called oncogene-induced senescence (OIS) [121]. Interestingly, elevated PARP1 levels can reverse cell senescence, leading to a tumorigenic phenotype. Moreover, in the same study, it is shown that PARP1 activates Melanocyte inducing transcription factor (MITF) expression in a PARylation-independent manner. These results suggest that PARP1 promotes melanoma genesis in BRAFV600E melanocytic nevi.

We showed that PARP1 directly regulates the MAPK pathway by modulating BRAF protein levels [50]. In brief, PARP1 directly binds to the 3'UTR of the long coding transcript of *BRAF* (*BRAF-X1*)

[122] via its zinc finger domains (in a PARylation-independent manner) and interferes with protein translation. In this way, PARP1 can downregulate the BRAF-X1 isoform, leading to a decrease in total BRAF levels and consequently in MAPK signaling. The same correlation was observed in melanoma patients of the TCGA dataset: PARP1 protein levels are inversely correlated with BRAF protein levels. We propose that this mechanism may work in concert with the one described by Choi et al. to promote the malignant transformation of melanocytes. Specifically, BRAFV600E expression in melanocytes generates oncogene-induced senescence [120], while its downregulation mediated by PARP1 may contribute to the escape from OIS described by Choi et al [113].
In addition, PARP1 plays a role in melanoma progression and metastasis. Stable PARP1 knockdown (KD) has been reported to impair the tumorigenic potential of melanoma cells *in vivo* [123]. PARP1 KD melanoma cells did not show growth differences compared to parental cells (with native PARP1 levels). However, when xenografted into mice, PARP1 KD cells showed delayed tumor formation and reduced tumor size. In the same study, animals injected intracranially with PARP1-deficient cells showed increased survival. At the molecular level, tumors belonging to the PARP1 KD melanoma transplants showed reduced expression of the angiogenesis marker Platelet and endothelial cell adhesion molecule 1 (PECAM1) and the pro-inflammatory mediators Tumor necrosis factor (TNF) and TNF receptor superfamily member 18 (TNFRSF18). PARP1 is also a modulator of the expression of Vimentin (VIM), a tumor-specific angiogenesis marker and a key regulator of the epithelial-mesenchymal transition (EMT) [124]. In the study by Rodriguez et al. [125] PARP1, through regulation of VIM, is shown to promote vasculogenic mimicry and EMT. In turn, targeting PARP1 strongly reduces metastatic dissemination of melanoma cells in an *in vivo* model.
These results show a pivotal role of PARP1 in melanoma onset and progression and provide the rationale to investigate PARP inhibitor treatments.

5. PARP inhibitors in melanoma therapy

In the past years, the management of melanoma patients has been revolutionized by the development of MAPK inhibitors (MAPKi) and ICIs. Despite promising initial success, most patients treated with BRAF/MEK inhibitors relapse after 6-9 months due to the development of drug resistance [126], while 40-60% of melanoma patients harbor *de novo* or acquired resistance to ICIs with consequent disease progression. Furthermore, the duration of ICIs administration can be limited due to immune-related adverse events [127], [128]. Therefore, the treatment of targeted therapy or immunotherapy relapsed melanoma patients is a challenge and requires new therapeutic approaches.
As mentioned above, homologous recombination deficiency (HRD, such as mutations in *BRCA1, BRCA2*, or other key HR genes (*ATM*, *RAD51 recombinase* (*RAD51*), and *partner and localizer of BRCA2* (*PALB2*); epigenetic alterations like DNA hypermethylation) is associated with increased sensitivity to PARPi [129]. Alterations in HR genes are frequent in melanoma (their incidence ranges from 18.1% to 57.1 % [8], [130], [131]). Hence, at least a subset of patients may benefit from PARP inhibition.

5.1 Preclinical evidence of PARPi efficacy in melanoma

In the absence of HR alterations, PARPi monotherapy reduces the viability of melanoma cells *in vitro* inducing apoptosis, irrespective of their *BRAF* or *NRAS proto-oncogene, GTPase* (*NRAS*) mutation status [132], [133]. PARPi also reduce the ability of melanoma cells to migrate and invade *in vitro* and to disseminate *in vivo* [125], [132]. However, PARPi show even stronger effects in melanoma cells harboring HR or DNA repair defects. For instance, Olaparib alone, and combined with Dacarbazine, is effective in DNA ligase 4 (LIG4)-deficient melanoma cells [134]). LIG4 is a gene involved in DSB repair and is often downregulated in melanoma compared to normal melanocytes. In these cell lines, using a synthetic lethality approach, the authors observed that treatment with Olaparib, with or without the alkylating agent Dacarbazine, could reduce tumor cell proliferation *in vitro*, while the combination reduced tumor size in mouse xenografts.
Several preclinical studies demonstrate the efficacy of the combination of PARPi with radiotherapy or chemotherapy. PARPi exert a radiosensitizing effect on melanoma cell lines, increasing G2/M cell cycle arrest and cell death [135], [136]. In addition, dual inhibition of PARP1 and MET proto-

oncogene, receptor tyrosine kinase (MET) in combination with radiotherapy causes a strong reduction of viability in BRAF wild-type melanoma cells *in vitro* and a significant tumor growth inhibition in a melanoma xenograft *in vivo* [137]. Coadministration of PARPi with chemotherapy, such as Temozolomide, Cisplatin, or Dacarbazine, promotes cell death increasing DNA-damaging and cytotoxic effects of the alkylating agents [138], [139], [140]. A recent study suggested the addition of the histone deacetylases (HDAC) inhibitor Valproic Acid (VPA) to the combination of Talazoparib with Dacarbazine, as VPA enhances the cytotoxicity of the other two drugs increasing the DNA damage levels, likely through the downregulation of FA complementation group D2 (FANCD2) and RAD51 [141].

Several preclinical studies support the use of PARPi in the context of targeted therapy with MAPKi [142], [143]. Interestingly, the PARPi Veliparib promotes cell death and inhibits migration and invasion in A375 melanoma cells both sensitive and resistant to Dabrafenib [132]. In addition, another recent work pointed out that melanoma cells resistant to MAPKi are significantly more sensitive to PARP1 inhibition due to reduced ATM expression. The reduction of ATM levels associated with MAPKi resistance was also confirmed by immunohistochemistry in tissue samples from a patient before and after the onset of BRAFi resistance, and by the analysis of mRNA sequencing data of melanoma samples before and after BRAFi resistance or BRAFi/MEKi double resistance.

Finally, preclinical evidence about the efficacy of PARP1 in combination with ICIs starts to be reported. In the BRCA-proficient SK6005 skin syngeneic transplant mouse model the coadministration of Niraparib and an anti-Programmed cell death 1 (PDCD1, also known as PD-1) antibody results in 44% tumor growth reduction, while the effect of single agents is milder (16% and 11% tumor growth reduction, respectively) [144].

Taken together these data support further clinical testing of PARPi on melanoma patients, either alone or in combination.

5.2 Response of melanomas to PARPi

The clinical benefit of PARPi in HR-deficient melanomas has also been demonstrated in patients. Multiple case reports describe patients with mutations in HR genes or genome-wide LOH (gLOH) who benefit from PARPi as monotherapy [145], [146], [147], or in combination with chemotherapy [148]. Furthermore, two immunotherapy-relapsed melanomas with HR defects, one with 28.4% gLOH and multiple mutations in DNA repair genes, and the other with 32.9% gLOH in the absence of HR gene mutations, were treated with Nivolumab and Olaparib. They achieved an almost complete radiological response and a total clearance of the previously detected mutations [145], [149]. Interestingly, Phillipps and colleagues recently reported a promising case series of three advanced melanoma patients who progressed on immunotherapy and/or BRAF/MEK inhibitors. All patients harbor MAPK-activating mutations and two of them also carry a mutation in an HR gene (ATM and WRN RecQ like helicase (WRN)). Adding Olaparib to the therapy regimen produced a complete clinical response with ctDNA clearance in one patient and a partial response with marked ctDNA reduction in the other two. These studies confirm the preclinical evidence of a possible synergistic interaction between ICIs, BRAFi/MEKi, and PARPi in melanoma [150].

In clinical trials, PARPi have been combined with chemotherapy to overcome chemoresistance in advanced metastatic melanoma. One of the first studies identified the optimal tolerated dose of Olaparib in combination with Dacarbazine but did not observe a clinical advantage of the combination over Dacarbazine monotherapy [151]. Two more trials evaluated the combination of PARPi with Temozolomide [152], [153]. The results showed an improvement in progression-free survival (PFS) although without reaching statistical significance, likely because patients were not stratified based on their HR status. Furthermore, both trials showed enhanced bone marrow suppression which required an 80% dose reduction for the safe coadministration of the drugs. A still active study is investigating the combination of Veliparib, Carboplatin, and Paclitaxel in solid tumors including melanoma (NCT01366144), but the outcome is not available yet.

Since HRD is a promising biomarker of PARPi response in melanoma, most of the ongoing studies are enrolling patients based on their HR status. A completed phase II trial investigated the effect of Niraparib in several metastatic solid tumors (including melanoma) carrying a mutation in *BRCA1 associated deubiquitinase 1* (*BAP1*) or other DNA repair genes. Niraparib was tolerated but the predetermined efficacy of the overall response rate (ORR) was not reached. Nevertheless, 78% of

patients harboring a mutation in *BAP1* benefited from Niraparib treatment [154]. To date three studies with PARPi as monotherapy are active: the first evaluates the effect of Olaparib in patients with unresectable melanoma harboring mutations in *BRCA1/2* (NCT05482074), the other two assess Niraparib in advanced melanoma with HR alterations (NCT03925350), or in solid tumors (including melanoma) with confirmed *PALB2* mutations (NCT05169437).
Since numerous preclinical and clinical evidence indicate that PARPi can synergize with immunotherapy, multiple trials investigate the efficacy of the combination of PARPi with ICIs in melanoma patients carrying HR defects (NCT05983237, NCT04633902, NCT04187833). Moreover, one active study evaluates the combined effect of Olaparib and Pembrolizumab in uveal melanoma without stratifying patients according to their HR status (NCT05524935). The safety of these combinations is still under evaluation. Trials of similar combinations performed in other types of cancer indicate that the same adverse events (AEs) observed with the single agent are likely to occur with the combination. These AEs include nausea, fatigue, constipation, hematologic-related toxicities (such as lymphopenia, anemia, leukopenia, and thrombocytopenia), commonly observed with PARPi monotherapy, and the immune-related adverse effects (irAEs) observed with ICIs [103]. As far as melanoma is concerned, AEs experienced by patients treated with PARPi and ICIs are available through case reports. Among them, only one describes a melanoma patient treated with Nivolumab and Olaparib who developed grade III hepatitis [149].
A list of PARPi currently undergoing clinical trials in melanoma is reported in **Table 1**.

5.3 Challenges of melanoma patient selection for treatment with PARPi

PARP inhibition may be a successful therapeutic strategy for melanoma, even in targeted therapy- or immunotherapy-refractory cases, but patient selection is challenging.
Targeted sequencing is relatively limited in melanoma due to the impact of *BRAF* analysis on the decision about the therapeutic approach. In addition, the search for loss of function mutations in HR genes through direct gene testing is likely insufficient to predict the response to PARPi. It would be preferable to determine the HRD status, a complex score that considers not only point mutations or epigenetic changes, but also HRD signatures, such as gLOH, telomeric allelic imbalance (TAI), and large-scale genomic transitions (LST) [155], [156]. However, there are some challenges to be overcome.
Firstly, genomic profiling is technically complex and highly expensive, even though commercially available targeted NGS panels have incorporated quantification of HRD based on surrogate genomic scars [138], [157].
Secondly, we lack a unified HRD scoring and a reliable cut-off value to identify sensitivity to PARP1 inhibition. The recommended HRD cut-off for PARPi-sensitive tumors is ≥25% for ovarian cancer, ≥29% for breast cancer, ≥28% for pancreatic cancer, and ≥33% for all other cancers [146]. However, melanoma-specific cut-offs have not been established yet.
Alternatively, several studies demonstrated that the assessment of RAD51 nuclear foci by immunofluorescence is an accurate HRD biomarker to predict PARPi response in other types of cancer [158], [159], [160]. This histology-based assay is technically simpler and less expensive than NGS methods and could be used as a first-line screening for HRD melanoma patients.
In addition, gLOH measurement has been reported as a good biomarker to predict PARPi efficacy in melanoma [145], [149]. In line with this, a recent case report described four melanoma patients with gLOH ≥25% who had a positive response to PARPi even without HR gene mutations [146]. Of these four cases, one was a primary mucosal melanoma (gLOH 43.9%) and three were metastatic melanomas (gLOH 57.7%, 32.9%, 28%) [146]. These promising results highlight the necessity to establish a reliable gLOH cut-off to distinguish those patients who will likely respond to PARPi from those who will not, as mentioned above for HRD status.
The expression level of PARP1 could be used as a predictive biomarker of PARPi response as well. As aforementioned, PARP1 level is higher in melanoma cells than in normal melanocytes. Furthermore, in melanoma patients high PARP1 expression correlates with worse prognosis and PARP1 has been shown to promote the tumorigenic properties of melanoma cells. Based on this evidence, Frohlich and colleagues suggested that metastasized melanoma patients (stage III-IV) with high PARP1 expression would benefit from PARPi administration due to higher cytotoxicity caused by PARP1 trapping. Moreover, PARPi treatment should not affect the low PARP1-expressing non-malignant skin cells, resulting in limited side effects. Therefore, to evaluate the eligibility for

PARPi treatment melanoma patients should be tested not only for HRD status but also for PARP1 expression.

Additional “non-HRD” biomarkers of response to PARP1 have been identified in lung cancer and should be further investigated in melanoma. PI3K/AKT/mTOR pathway activation has been reported as a marker of PARPi resistance [161], [162], while high expression of Cadherin 1 (CDH1) is a predictor of PARPi sensitivity [163]. Protein kinase, DNA-activated, catalytic subunit (PRKDC) and a 5-gene panel (*glutaminase* (*GLS*), *ubiquitin conjugating enzyme E2 C* (*UBE2C*), *2-hydroxyacyl-CoA lyase 1* (*HACL1*), *musashi RNA binding protein 2* (*MSI2*), and *LOC100129585*) predict sensitivity to Veliparib [164]. Schlafen family member 11 (SLFN11) predicts response to Talazoparib [163], [165], [166], [167]. Interstingly, SLFN11 appears as a predictive biomarker of PARPi response across the NCI-60 collection of cell lines [168], which include melanoma. Finally, we mention MET, the receptor tyrosine kinase of Hepatocyte growth factor (HGF). MET phosphorylates PARP1 at Y907 residue. This phosphorylation prevents PARPi binding to PARP1 and makes cancer cells resistant to inhibitors [169], [170], [171], [172]. Since HGF signaling is often upregulated in melanoma [173], [174], MET hyperactivation and PARP1 phosphorylation on Y907 residue could predict patient resistance to PARPi.

CONCLUSIONS AND FUTURE PERSPECTIVES

A growing body of evidence supports the role of PARP1 in melanoma genesis and progression. This aspect could be successfully exploited to respond to the new challenges in the field of melanoma including *de novo* and acquired resistance to targeted therapies and ICIs.
However, some considerations and speculations should be made from both a basic and a translational point of view.

From a basic research perspective, the role of PARP1 in melanoma should be further elucidated using *in vitro* and *in vivo* models. *In vitro*, PARP1 expression can be modulated in well-established melanoma models, refining its contribution to melanoma initiation and progression. Many *in vivo* models [175] are now widely used and closely resemble the events that lead to human melanoma. We mention a genetically engineered zebrafish model, in which the overexpression of the BRAFV600E oncogene and the loss of function of p53 in the melanocytic lineage lead to the formation of nevi that progress to melanoma (*Tg(mitfa:BRAFV600E-Myc);p53(lf)*) [176]. We also mention *Tyr::CreER^{T2};Pten$^{LoxP/LoxP}$;Braf$^{CA/+-}$* mice that, upon induction using tamoxifen, rapidly develop melanoma tumors with a high tendency to metastasize to lymph nodes and lungs [177], [178]. However, we point out that PARP1 needs to be investigated in *in vitro* and *in vivo* models of melanoma driven by other mutations as well, including those in NRAS and Neurofibromin 1 (NF1).

From a clinical point of view, the association of PARP1 alteration/SNP/expression with histopathological and genetic features should be further investigated. For example, in head and neck melanomas PARP1 shows increased expression levels and is associated with the transition from radial to vertical tumor growth. Head and neck melanomas are also characterized by a prevalence of NRAS mutation [179]. Therefore, it would be interesting to investigate whether these features are functionally linked.
In more general terms, a systematic analysis of PARP1 alteration/SNP/expression across the different histopathological (cutaneous (CM), acral (AM), uveal (UV), and mucosal (MM)) and genetic (BRAF mutated, NRAS mutated, NF1 mutated, and triple wt) subgroups of melanoma should be undertaken. Kim and colleagues reported that more than 20% of melanoma patients have at least one mutation in a gene involved in DNA repair mechanisms, and concurrent mutations of DDR genes were found in 39% BRAF, 22% NRAS, and 39% NF1 mutated samples. However, PARP1 mutations were not investigated [8].
Another unanswered question is whether PARP1 plays a role in melanoma brain metastases and whether PARP1 mutation/expression has a prognostic value in this context. We suggest that publicly available high-throughput NGS data should be systematically interrogated to establish whether PARP1 alteration/SNP/expression differ among primary melanomas, melanoma brain metastases, and metastases to other body sites. This knowledge would be crucial to address a tremendous clinical issue.

From a therapeutic perspective, many points remain to be clarified.
First, the feasibility of combining PARPi and targeted therapy/ICIs requires further investigation *in vitro* and *in vivo*.
Regarding PARPi and targeted therapy, on one side PARP1 impairs BRAF expression, and this mechanism is not affected by the administration of Olaparib, which indicates that it does not rely on PARP1 catalytic activity. On the other side, Veliparib administration inhibits viability, migration, and invasion in A375 melanoma cells, both sensitive and resistant to dabrafenib. Analogously, Talazoparib inhibits cell viability and xenograft tumor growth of A375 cells resistant to vemurafenib, suggesting a possible therapeutic purpose for patients who develop targeted therapy resistance. BRAFi/MEKi and PARPi showed a synergistic effect in patients as well. However large clinical trials are needed to confirm it.
Based on current knowledge, PARP inhibitors might be even more effective in combination with ICIs than in combination with targeted therapy because they activate the STING pathway and potentiate host immune response against cancer cells through neoantigen production and upregulation of PD-L1. However, further *in vivo* evidence is crucial to ultimately establish their therapeutic potential.
Second, the selection of melanoma patients who may benefit from PARPi remains a challenge. More prospective clinical trials with large cohorts of metastatic melanoma patients are needed to correlate

HRD status with PARPi response. HRD status displays a high degree of variability across patients and, as mentioned above for PARP1 alteration/SNP/expression, it remains to be established whether it differs across histopathological and/or genetic subgroups of melanoma
It is equally crucial to establish which HRD assessment method is the most reliable. Additionally, it should be clarified whether the expression level of PARP1 itself, as well as that of other “non-HRD” biomarkers, needs to be considered. In this scenario, it could be helpful to use synthetic data from real patients generated by artificial intelligence (AI) tools [180]. They do not contain any personal information and are obtained by using an algorithm trained to learn the characteristics of a real source dataset. Synthetic data have been validated as similar to real data and can be widely used to accelerate research in life sciences [180]. Soon, these technologies could be successfully used to evaluate the benefit of PARPi administration in melanoma patients, thus accelerating the progress in the field. All this information together will make it possible to identify melanoma patients who can benefit from treatment with PARP inhibitors (alone or in combination), thereby further improving the survival of these patients **Fig.3**.

In conclusion, PARP1 represents a new major player in melanoma biology, and a better understanding of its role, coupled with more translational studies, may represent a new way to address the current unresolved challenges in melanoma treatment.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions
A.M. conceived the project. A.G.L.R., B.S., and L.P. supervised the project. A.M., L.M., and S.L. gathered the information. All authors contributed to writing and editing the text.

Declaration of generative AI and AI-assisted technologies in the writing process
The authors declare that they have not used AI and AI-assisted technologies in the writing process.

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FIGURE LEGENDS

Figure 1. Schematic representation of PARP1 structure and its intracellular functions.

a) PARP1 is composed of 3 functional domains: the DNA/RNA binding domain (Zn1, Zn2, and Zn3, in green), which is formed by 3 zinc finger motifs; the auto-modification domain (BRCT and WGR, in gray), which contains important autoregulatory elements; and the catalytic domain (CAT, in blue), which is responsible for catalytic activity. PARylation is the reaction carried out by the catalytic domain and consists in attaching a negatively charged single ADP-ribose (MAR) or numerous long and branched chains of poly(ADP-ribose) (PAR) on target proteins. PARP1 uses the oxidized form of nicotinamide adenine dinucleotide (NAD+) as a substrate.

b) PARP1 is involved in a plethora of intracellular processes such as DNA repair, RNA metabolism, cell metabolism, and cell death.

Figure 2. PARP1 in melanoma.

a) PARP1 is altered in nearly 4% of melanoma patients [107].

b) PARP1 expression increases along with melanoma progression [181].

c) PARP1 expression has a prognostic value in melanoma [107].

Figure 3. Hypothesis for stratifying patients with melanoma who are likely to benefit from treatment with PARP inhibitors.

Based on HRD status and/or PARP1 alteration/SNP/expression, it might be possible to predict which patients will benefit from PARPi treatment alone or in combination with other therapies. The goal is to increase therapeutic options available for these patients and enhance their efficacy.

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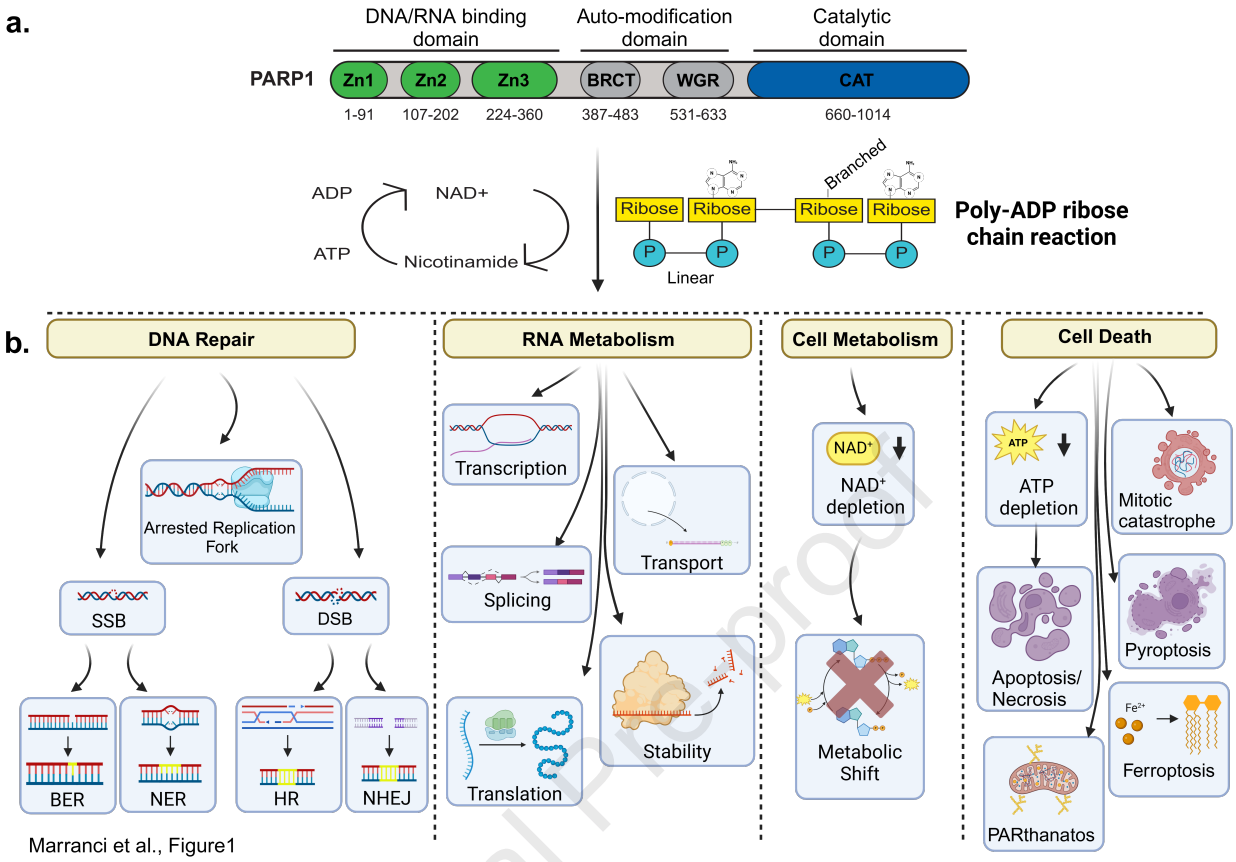
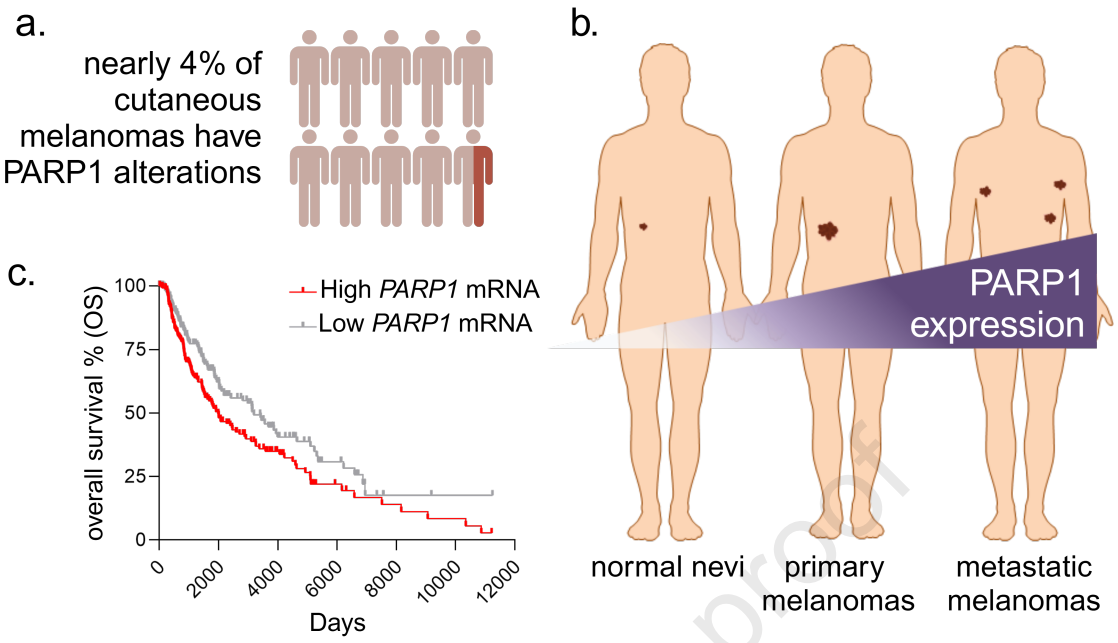
Table 1

PARPi currently undergoing clinical trials in melanoma

Trial ID	Agents	HR status	Phase
NCT03925350	Niraparib	HR mutations	II
NCT03207347	Niraparib*	*BAP1* mutations and DDR-deficiency	II
NCT05169437	Niraparib	*PALB2* mutations	II
NCT05482074	Olaparib	*BRCA1/2* mutations	II
NCT00516802	Olaparib + Dacarbazine	Not tested	I
NCT00526617	Veliparib + Temozolomide	Not tested	I
NCT00804908	Veliparib + Temozolomide*	Not tested	II
NCT01618136	Stenoparib + Temozolomide / Stenoparib + Carboplatin + Paclitaxel	Not tested	I/II
NCT01366144	Veliparib + Paclitaxel + Carboplatin	Not tested	I
NCT01605162	E7016 + Temozolomide	Not tested	II
NCT00804908	Veliparib + Temozolomide*	Not tested	II
NCT05983237	Fluzoparib + Camrelizumab + Temozolomide	HR mutations	I/II
NCT05524935	Olaparib + Pembrolizumab	Not tested	II
NCT04633902	Olaparib + Pembrolizumab	HR mutations	II
NCT04187833	Nivolumab + Talazoparib	*BRCA* mutations or BRCAness phenotype	II

*Completed.
Clinicaltrial.gov accessed on January 16th 2025.





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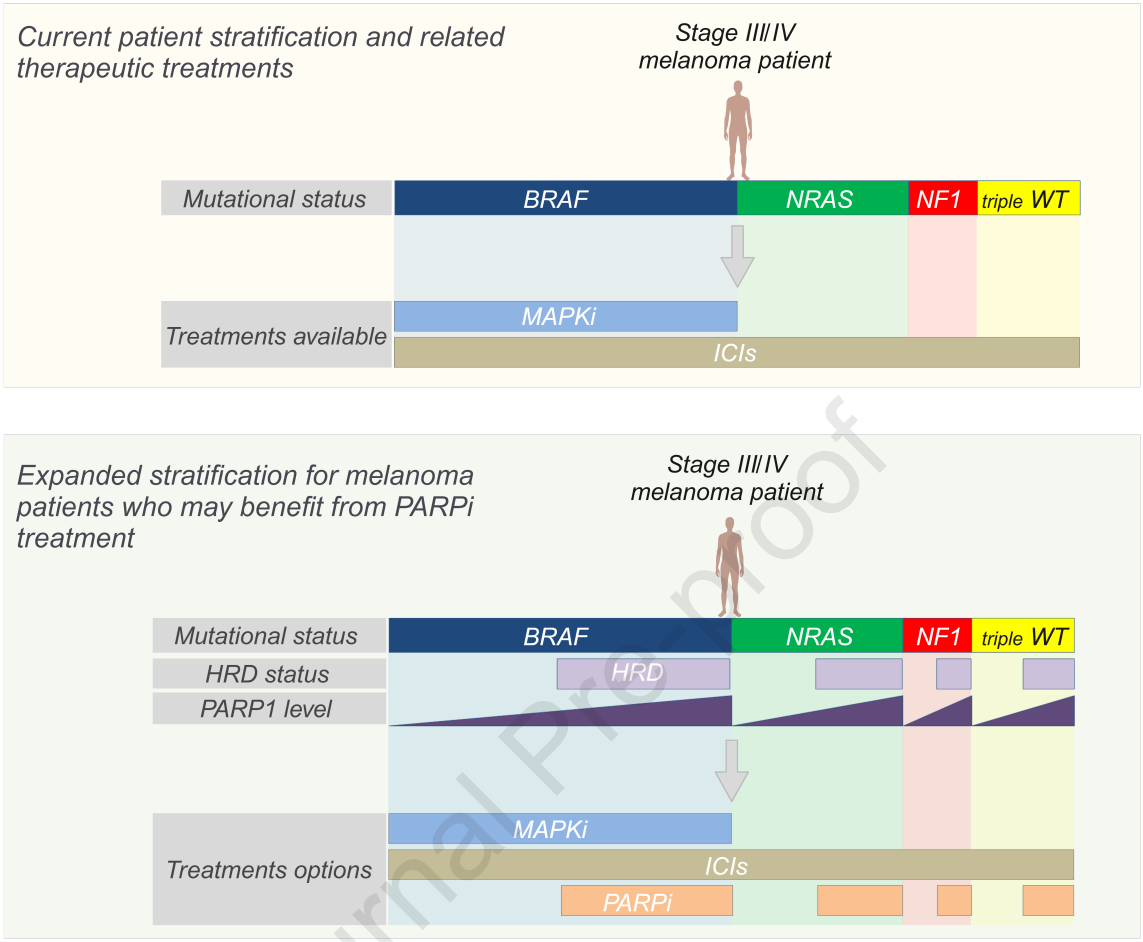

Marranci et al., Figure 3

HIGHLIGHTS

- PARP1 has multiple pro-oncogenic roles in melanoma cells
- PARP1 is a prognostic marker for melanoma patients
- PARP inhibition is effective after failure of BRAFi/MEKi or immunotherapy
- Proper stratification of melanoma patients might enhance PARPi efficacy

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: