REVIEW ARTICLE

Prospects for non-immunological molecular therapeutics in melanoma

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Summary

In 2006 there were 60,000 new cases of cutaneous melanoma in the European Union and 13,000 deaths (www.europeancancerleagues.org). Currently available systemic treatment options for metastatic melanoma, including both cytotoxic and immunologic therapies, produce low rates of response and have modest survival impact. Therefore, there is an urgent need for effective novel therapies. Molecularly targeted treatments have demonstrated efficacy in certain cancers e.g. in HER2-positive breast cancer and in chronic myeloid leukaemia.

Several pathways are currently being investigated as potential molecular targets in melanoma. The best studied is BRAF which is frequently mutated in melanoma. A multi tyrosine kinase inhibitor, sorafenib, which targets BRAF, has shown promising activity in preclinical studies and is currently being tested in combination with chemotherapy in patients with metastatic disease.

In addition to BRAF, therapies which target other components of the Raf/Ras/MAPK pathway are being investigated. Other novel targets currently being investigated include the PI3/AKT pathway, tyrosine kinases, angiogenesis, poly (ADP ribose) polymerases, survivin and heat shock protein 90. Progress on preclinical and clinical evaluation of these novel targets in melanoma will be reviewed.

Key words: angiogenesis,BRAF,HSP90,PARP,PI3K/AKT,tyrosine kinase

Introduction

The incidence of melanoma has been increasing continuously over the last four decades, with current incidence rates varying between 15-60 per 100,000 [1]. Early-stage melanoma is potentially curable with wide local excision, however, for patients who develop disseminated disease the 5-year survival rate is less than 10% [2]. This poor prognosis is due both to the aggressiveness of malignant melanoma and the inherent resistance of the disease to conventional cytotoxic agents. The standard chemotherapy treatments, single-agent dacarbazine, or temozolomide, produce low response rates of 15-20% [3]. Combinations of dacarbazine or temozolomide with other cytotoxic therapies have not significantly improved patient survival **[2]**. Adjuvant immunotherapy with interferon alpha offers some benefit in terms of recurrence-free and overall survival. Adding immunomodulators (e.g. interferon alpha or interleukin-2) to chemotherapy increases the response rates (and the toxicity) in patients with metastatic disease, but has not been shown to produce superior survival compared to chemotherapy alone in random assignment trials [4]. There is therefore an urgent need for new systemic therapies for metastatic melanoma.

Our increasing knowledge of the molecular alterations associated with melanoma progression provides potential druggable targets for development of novel therapeutic strategies, including alterations in key intracellular signalling pathways and growth factor receptors.

While several new molecular immunotherapy approaches are being explored [5], the focus of this review is on novel non-immunologic molecularly targeted therapies for melanoma.

Targeting the Ras/Raf/MAPK pathway in melanoma

Activation of the Ras/Raf/MAPK pathway is a frequent and early event in melanoma **[6]**. BRAF, a key component in the pathway, is mutated in 60-70 % of melanoma cases [7]. The mutation valine-600-glutamic acid (V600E) accounts for approximately 80 % of BRAF mutations [8]. Analysis of BRAF mutation status showed that the presence of the mutated BRAF in primary tumours (n=114) did not impact on prognosis or survival but was associated with a significantly poorer prognosis (n=86) when detected in metastatic melanomas [9].

A number of BRAF inhibitors are in clinical development (Table 1). Sorafenib (BAY43-9006, Bayer) is a bi-aryl urea small molecule inhibitor of vascular endothelial growth factor receptor (VEGFR) and Raf kinase, which also has activity against C-Kit and platelet-derived growth factor receptor beta (PDGFR-β). Preclinical studies demonstrated that sorafenib can inhibit BRAF in melanoma cell lines resulting in inhibition of MAPK activity and melanoma cell growth *in vitro* and *in vivo* [10]. Sorafenib also exerts antiangiogenic effects by blocking Ras/Raf/MAPK signalling in endothelial cells [11]. Sorafenib showed no significant antitumour activity as a single agent in advanced melanoma [12], however, in a recent randomised phase II study, sorafenib in combination with dacarbazine produced significantly improved progression free survival (21.1 weeks vs. 11.7 weeks, hazard ratio [HR], 0.619) compared to dacarbazine alone. There was no improvement in overall survival [13]. The addition of sorafenib to paclitaxel and carboplatin as second line treatment for advanced melanoma did not improve progression-free survival or overall response rates [14]. This regimen is currently being evaluated in a phase III trial in chemotherapy-naïve advanced melanoma. Several phase II trials of sorafenib in combination with chemotherapy or with other targeted agents are currently ongoing (www.clinicaltrials.gov).

Two specific mutant BRAF inhibitors, PLX-4032 and PLX-4720 (Plexxikon Inc.) have been developed and are being tested in melanoma. PLX-4720, a 7-azaindole derivative, reduced MAPK activation in V600E mutated melanoma cell lines but did not alter MAPK activation in BRAF wild type cell lines, suggesting that PLX-4720 has the ability to specifically target cancer cells with mutant BRAF. *In vivo* studies confirmed the inhibition of melanoma cell growth and no toxicity was reported [15]. RAF-265 (Novartis) is a potent inhibitor of Raf and VEGFR. Preclinical research has shown that RAF-265 inhibits all 3 isoforms of Raf, as well as mutant B-Raf (www.novartisoncology.com). Both PLX-4032 and RAF-265 are currently recruiting patients for phase I trials in metastatic melanoma.

MEK (MAPK/ERK kinase), downstream of BRAF may be a potential target in melanoma. BRAF-induced hyperactivation of MEK has been implicated in melanoma [16]. A number of MEK inhibitors are being investigated in solid tumours, including RO5126766 (Hoffman-La Roche), and AZD6244 (AstraZeneca) which has been shown to be cytostatic as monotherapy and cytotoxic in combination with docetaxel in preclinical evaluation in melanoma [6]. AZD6244 is currently undergoing evaluation in phase I-II trials in melanoma.

Targeting the PI3/AKT pathway in melanoma

Constitutive activation of the phosphatidylinositol-3-kinase (PI3K)/AKT pathway (Figure 1) has been implicated in chemoresistance in many human cancers, including melanoma [17]. Although PI3K itself is rarely mutated [18] or overexpressed [19] in melanoma, activation of downstream signalling components, e.g. AKT, have been implicated in melanoma progression [20]. In one study, phosphorylated AKT was detected in 17, 43, 49, and 77% of normal nevi (n=12), dysplastic nevi (n=58), primary melanoma (n=170) and melanoma

metastases (n=52), and strong p-AKT staining correlated inversely with overall and 5-year survival of patients with primary melanoma ($p < 0.05$) [21].

Increased AKT activation can be caused by mutation or loss of phosphatase and tensin homolog (PTEN), a tumour suppressor which can downregulate the AKT pathway [22]. Loss of PTEN reduces apoptosis and promotes cell survival and thereby promotes melanoma tumour development, and has been reported in 20-40% of melanomas [23,24]. Increased mTOR (mammalian target of rapamycin) activation has also been implicated in melanoma cell growth. Proliferation of melanoma cells lines was blocked by the mTOR inhibitor rapamycin [25]. mTOR is a downstream target of the PI3K/AKT kinase signalling pathway and regulates cancer cell growth and metabolism [26,27].

Rapamycin (sirolimus) and its analogs, temsirolimus (CCI-779, Wyeth Pharmaceuticals), everolimus (RAD-001, Novartis) and deforolimus (AP23573, ARIAD Pharmaceuticals, Inc. and Merck & Co., Inc.), which inhibit mTOR have shown promising activity in several cancers [28]. Rapamycin has been shown to inhibit melanoma cell growth *in vitro* and *in vivo*, and synergistically enhances apoptosis and chemosensitivity in melanoma cells [29-32]. Temsirolimus also inhibits growth and enhances response to dacarbazine and cisplatin in melanoma cell lines and mouse models of melanoma [33]. Temsirolimus did not demonstrate any clinical benefit as a single agent in the treatment of metastatic melanoma [34]. Phase II trials of temsirolimus and everolimus in combination with chemotherapy or other targeted agents in melanoma, are currently recruiting patients (www.clinicaltrials.gov).

The pan-PI3K inhibitor, LY294002, which has been restricted to preclinical studies , showed antitumour activity in preclinical models of melanoma [35,36], demonstrating the potential

benefits of targeting the PI3K/AKT pathway in melanoma. Although specific PI3K inhibitors have not yet been tested in melanoma patients, a number of inhibitors are undergoing trials in other solid tumours and may be potential therapies for melanoma. For example NVP-BEZ 235, a dual PI3K/mTOR inhibitor, has shown antiproliferative effects in glioblastoma, multiple myeloma and breast cancer cell lines [37-39], and is currently in phase I/II trials in solid tumours and breast cancer (www.clinicaltrials.gov). Several other PI3K inhibitors are also in phase I trials, including SF1126 (Semofore), XL765 and XL147 (Exelixis Inc.) and GDC-0941 (Genentech).

Perifosine (AOI Pharma Inc. and Keryx Biopharmaceuticals), an alkylphosphocholine (APC) analogue, inhibits phosphorylation of AKT by blocking membrane translocation [28]. A phase II trial of single-agent perifosine as first line treatment in metastatic melanoma patients produced no objective responses [40]. Further trials of perifosine in combination with chemotherapy and targeted agents in other solid tumours are ongoing.

Targeting either the MAPK or AKT pathway individually may be beneficial, but there is substantial preclinical evidence to support targeting both pathways simultaneously [32,41]. Indeed, Cheung et al. showed that AKT3 and mutant BRAF cooperate to promote melanoma development [15]. Dual inhibition of MAPK and PI3K/AKT/mTOR has shown antitumour activity in melanoma cell lines [32,41,42]. The combination of MAPK and AKT inhibitors completely suppressed invasive growth of melanoma cells in regenerated human skin **[43]**. A phase I/II trial of combined BRAF and mTOR inhibition by sorafenib and temsirolimus, is currently recruiting melanoma patients (www.clinicaltrials.gov).

Novel tyrosine kinase targets in melanoma

C-Kit receptor

Stimulation of the C-Kit receptor tyrosine kinase by its ligand, stem cell factor (SCF), leads to activation of intracellular signalling pathways including Ras/Raf/MAPK, SRC and PI3K/AKT signalling [44]. It is expressed at high levels in normal melanocytes [45] and is essential for normal melanocyte development and homeostasis [46]. Until recently it was believed that c-Kit expression was lost with melanoma progression [47]. However, recent studies have shown that c-Kit is overexpressed in a small percentage of melanoma patients [45,48-50]. The c-Kit overexpressing patients are generally not BRAF-mutated and are defined as being mucosal, acral or chronic sun damaged [51-53].

Imatinib mesylate (Gleevec, Novartis), which targets c-Kit in addition to BCR-Abl, inhibited proliferation in melanoma cell lines due to cell cycle arrest in the G_2M phase [54]. Imatinib has been tested in phase II trials in metastatic melanoma patients without success [55]. However, trials which target acral melanoma patients who have c-Kit over expression, exclusive of BRAF mutation, are underway [52].

SRC kinase

Members of the SRC kinase family have been implicated in melanoma progression **[56-60]** and both SRC and Yes are reported to be elevated in melanoma cells compared to normal melanocytes [56,61]. The many functions of SRC kinase may be attributable to its relationships with several oncogenes such as the non receptor tyrosine kinase, focal adhesion kinase (FAK) and Stat3 [62]. SRC kinase regulates Stat3 which is active in melanoma but not normal or benign melanocytes [63]. Blocking SRC kinase leads to inhibition of Stat3, and as a result, induction of apoptosis in melanoma cells [64].

Dasatinib, a multitarget tyrosine kinase inhibitor, which targets BCR-Abl, SRC kinases, C-Kit, PDGFR and ephrin-A receptor kinases, is the most potent SRC kinase inhibitor currently in clinical development with an IC_{50} of 0.5 nM for SRC kinase (IC_{50} of < 30 nM for the other targets) [65]. In melanoma cell lines, dasatinib has shown antiproliferative effects and significantly reduced tumour cell migration and invasion [66]. Dasatinib has also shown preclinical activity in prostate cancer [67], triple-negative breast cancer [68] and colon cancer cells [69]. Dasatinib is currently being tested in phase I and II trials in metastatic melanoma.

AZD0530 (AstraZeneca), a selective SRC kinase inhibitor, reduced tumour formation in a skin carcinogenesis model [69], and reduced tumour growth in a SRC-transfected 3T3-fibroblast xenograft model [70]. A phase II clinical trial of AZD0530, as a single agent, is currently recruiting patients with stage III/IV melanoma. SKI-606, a SRC/Abl kinase inhibitor has shown antitumour effects in breast cancer *in vitro* and *in vivo* [71], but has not yet been tested in melanoma.

c-Met

The c-Met receptor tyrosine kinase is involved in cell growth, invasion, metastasis, and angiogenesis. Binding of its ligand, hepatocyte growth factor (HGF), to c-Met results in activation of c-Met and subsequent activation of signal transducers such as PI-3-kinase, PLC-γ, STATs, ERK 1 and 2, and FAK [72]. Through increased paracrine or autocrine signalling, this pathway can enhance tumour cell proliferation, survival, motility, and invasion [73] and is implicated in a variety of human malignancies including melanoma. c-Met is overexpressed and associated with the metastatic potential of melanoma and patient survival [74-77].

c-Met is expressed on normal epithelial cells and melanocytes. HGF is normally produced mainly by mesenchymal cells and interacts with its receptor in a paracrine manner [78]. Most melanoma cells, but not normal melanocytes, produce HGF, which can induce sustained activation of its receptor. Also, prolonged HGF stimulation induces downregulation of the intracellular adhesive molecule E-cadherin that is implicated in the control of melanocyte proliferation [79]. In transgenic mice that ubiquitously expressed HGF, ectopic localisation of melanocytes and hyperpigmentation in skin were observed, melanoma arose spontaneously and UV radiation-induced carcinogensis was accelerated [80]. Hence, an autocrine HGF/c-Met signalling loop may be involved in the development of melanomas [81].

Puri et al. [81] showed that a small molecule tyrosine kinase inhibitor of c-Met, SU11274, inhibited growth of melanoma cells by causing apoptosis and inducing differentiation. c-Met was detected in 88% of melanomas (n=40) and in only 15% of nevi (n=20) examined. Mutations in the juxtamembrane domain of c-Met were also identified in melanoma cell lines and in tumour tissue [81].

Thus the c-Met/HGF pathway may be a rational target for therapeutic intervention in melanoma. Several c-Met and HGF inhibitors are in phase I clinical trials at present and the dual c-Met/VEGFR inhibitor, GSK1363089 (GlaxoSmithKline and Exelexis) is being tested in phase II trials in a number of solid tumours.

Targeting angiogenesis in melanoma

Similar to other cancers, angiogenesis is a critical step in the development of melanoma [for review see 82]. Melanoma cells produce several proangiogenic factors, including vascular

endothelial growth factor (VEGF), platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and interleukin 8. In addition to targeting BRAF, sorafenib targets the VEGF and PDGF receptors on endothelial cells, and has demonstrated antiangiogenic activity in tumour xenograft models [83,94]. Several other antiangiogenic therapies are being tested in melanoma including the VEGF monoclonal antibody bevacizumab (Avastin, Hoffman-La Roche) and the small molecule inhibitors sunitinib (Sutent, Pfizer), axitinib (AG 013736, Pfizer) and cediranib (AZD2171, AstraZeneca). A phase II trial of carboplatin, paclitaxel, and bevacizumab recently reported clinical benefit in patients with unresectable stage IV melanoma [85]. Nine out of 53 patients (17%) achieved partial remission, and 30 (57%) achieved stable disease for at least 8 weeks. Median progression-free survival and median overall survival were 6 and 12 months, respectively. Axitinib, which targets VEGF receptors and FGF receptor [86,87], has demonstrated single-agent activity in patients with metastatic melanoma, with an overall response rate of 15.6% [88].

Other potential targets in melanoma

Poly (ADP ribose) polymerases (PARP)

Poly (ADP ribose) polymerases (PARP) are a family of 17 members which are found in nearly all eukaryotic cells [89] and act as DNA nick sensors which can signal the presence of DNA damage, e.g. caused by methylating agents, and facilitate its repair [90,91] . PARP inhibitors have been developed to potentiate the effect of DNA damaging agents, such as temozolomide and dacarbazine [92]. In melanoma, overexpression of PARP in radial and vertical growth phase has been associated with recurrence [93].

In preclinical studies, systemic administration of a PARP inhibitor GPI-15427 (Guilford Pharmaceutical Inc.) potentiated temozolomide activity in an intracranial melanoma model [94]. ABT-888 (Abbott), a PARP-1/PARP-2 inhibitor, also potentiates temozolomide activity

[95] and achieved a reduction in PARP-1 levels in patients, including one melanoma patient [96]. Preliminary data from a phase I trial of the PARP inhibitor INO-1001 (Inotek Pharmaceuticals), an isoindolinone derivative, in combination with temozolomide in patients with stage IV unresectable melanoma, reported that of the 3 evaluable patients, one had an objective response, one had stable disease, and the third patient had progressed [97].

As most chemotherapy agents are used at the maximum tolerated dose, it is unclear whether combination of PARP inhibitors and chemotherapy will exacerbate the dose-limiting effects of chemotherapy [98]. Despite these concerns, PARP inhibitors are currently one of the most promising therapeutic strategies for melanoma.

Survivin

Apoptosis or programmed cell death is commonly dysregulated in cancer [99], including melanoma [100]. Survivin, a member of the inhibitor of apoptosis (IAP) family, has been implicated in inhibition of apoptosis and regulation of cell division [101]. Expression of survivin in tumours is associated with increased aggressiveness and decreased survival [102,103] and several studies have identified high levels of survivin expression in metastatic melanoma [103-105]. Interestingly, the localisation of survivin alters as melanoma progresses. Survivin expression has been identified in the cytoplasm in a spectrum of melanocytic lesions, however in metastatic melanoma its localisation changes to the nucleus [106], suggesting that nuclear survivin may be associated with poor prognosis. Studies in other solid tumours have also reported an association between nuclear survivin and poor prognosis [107,108].Grossman et al. showed that targeting survivin in melanoma cells resulted in increased apoptosis [105].

Several novel molecules have been developed which can suppress the activity of survivin (Table 1). The small molecule survivin inhibitor, YM155, targets survivin and induces apoptosis in prostate cancer cell lines. In xenograft studies YM155 induced significant tumour regression. Interestingly, the tumour concentration of YM155 has been found to be 20 times greater than the plasma concentration, demonstrating the cancer-specific nature of this compound [109]. A phase II trial of YM155 in metastatic melanoma demonstrated that the drug was well tolerated and one patient out of the 34 treated had an objective response and a second patient a minor response [110]. The first survivin antisense molecule, LY2181308 (Lilly and Co., and ISIS Pharmaceuticals) is currently in phase II trials in a number of solid tumours. A novel antisense molecule, SPC3042 (Santaris Pharma), which is a 16-mer locked nucleic acid oligonucleotide, has an IC_{50} < 5 nM for downregulation of survivin mRNA and protein. SPC3042 induces cell cycle arrest and apoptosis *in vitro* and also sensitised prostate cancer cells to paclitaxel treatment [111].

Heat shock protein 90

Heat shock protein 90 (HSP90) is an essential molecular chaperone that regulates the stabilisation, activation, and degradation of client proteins [112], such as BCR-ABL, EGFR, CRAF, BRAF, VEGFR, and MET [113]. Inhibition of HSP90 leads to targeted degradation of the client proteins by the proteasome, resulting in inhibition of growth and induction of apoptosis [112,114].

Mutated BRAF (V600E) is a client protein of HSP90, and HSP90 inhibition results in preferentially degradation of mutant BRAF over wild-type BRAF [115,116]. Furthermore, in a recent tissue microarray study, HSP90 expression was significantly higher in melanomas (n=468) than in nevi (n=414) and in metastatic (n=270) vs. primary specimens (n=198). In

primary melanomas, high HSP90 expression was associated with the adverse histologic features of a higher Clark level and increased Breslow depth [117]. Thus, HSP90 may be a good target for melanoma treatment.

Several HSP90 inhibitors are in preclinical or clinical development. Early attempts focussed on geldanamycin and radicicol analogues but more recent compounds being studied include synthetic small molecule inhibitors such as AUY922 (Novartis), BIIB021 (Conforma Therapeutics), and SNX2112 (Serenex Inc.) [113].

A phase I study of tanespimycin (17-allylamino, 17-demethoxygeldanamycin (17-AAG)) (Kosan Biosciences Inc.), a geldanamycin derivative, in patients with advanced malignancies included 6 patients with metastatic malignant melanoma. No patient had a complete or partial response. Four of the melanoma patients progressed within 2 months, while 2 melanoma patients had prolonged stable disease at 15 and 49 months [118]. The patient who had stable disease at 15 months had a (V600E)BRAF mutation and wild-type NRAS, while the patient who had stable disease at 49 months had a (G13D)NRAS mutation and wild-type BRAF, suggesting that mutations in BRAF or NRAS may be predictive of response to HSP90 inhibition in melanoma [119]. However, a recently published phase II trial of 17-AAG in patients with metastatic melanoma was disappointing as no objective antimelanoma response was seen. Although an increase in HSP70 and a decrease in cyclin D1 were observed post-treatment, RAF levels were not altered. The authors concluded that further trials in melanoma should focus on a more potent HSP90 inhibitor or a formulation that can be administered chronically for a more prolonged suppression of the MAPK pathway [120].

Conclusions

At this point in time no non-immunologic molecular targeted treatment can be considered as standard therapy for metastatic melanoma. Several agents have shown promising preliminary activity. The very poor results which are obtained with conventional chemotherapy and immunotherapy provide a powerful ethical justification for studying candidate molecular agents in the first-line therapy of appropriately selected patients with metastatic disease.

One of the challenges of molecular therapeutics is the development of appropriate drug development processes for novel agents. The methodologies used in the development of conventional cytotoxics, for example large-scale sequential safety and efficacy studies conducted in patients with histologically determined eligibility criteria, may not be optimal. Many molecular agents have produced very modest results in trials of this type conducted in other solid tumours. Molecular eligibility, as used in the development of trastuzumab, has resulted in a greater impact. Thus, every effort should be made to ensure that all therapeutic trials of novel molecular agents in melanoma and other cancers have mandatory tissue collection and translational components.

Table 1. Molecularly targeted agents currently being evaluated in malignant melanoma

Drug name	*Targets*	*Clinical trials status*[a]
Sorafenib	B-Raf, VEGF, PDGFR, c-Kit,	Phase III
RAF-265	Raf, VEGFR	Phase I
PLX-4032	Mutant B-Raf	Phase I
RO5126766	MEK	Phase I/II
Perifosine	AKT	Phase II
Rapamycin	mTOR	Phase II
Temsirolimus	mTOR	Phase II
Everolimus	mTOR	Phase II
Deforolimus	mTOR	Phase I
Imatinib mesylate	c-Kit, BCR-Abl, PDGFR	Phase II
Bevacizumab	VEGF	Phase II
Sunitinib	VEGFR, PDGFR, c-Kit, FLT3, CSF-1R, RET	Phase II
Axitinib	VEGFR, PDGFR	Phase II
Cediranib	VEGFR, PDGFR, FGFR, c-Kit	Phase II
KU-0059436	PARP	Phase I
ABT-888	PARP	Phase I
INO-1001	PARP	Phase I
Dasatinib	BCR-Abl, Src, c-KIT, PDGFR, Ephrin-A receptors	Phase I/II
AZD0530	Src, Abl	Phase II
YM-115	Survivin	Phase II
LY2181308	Survivin	Phase II
17-AAG	HSP90	Phase II

[a] Clinical trial status obtained from www.clinicaltrials.gov.

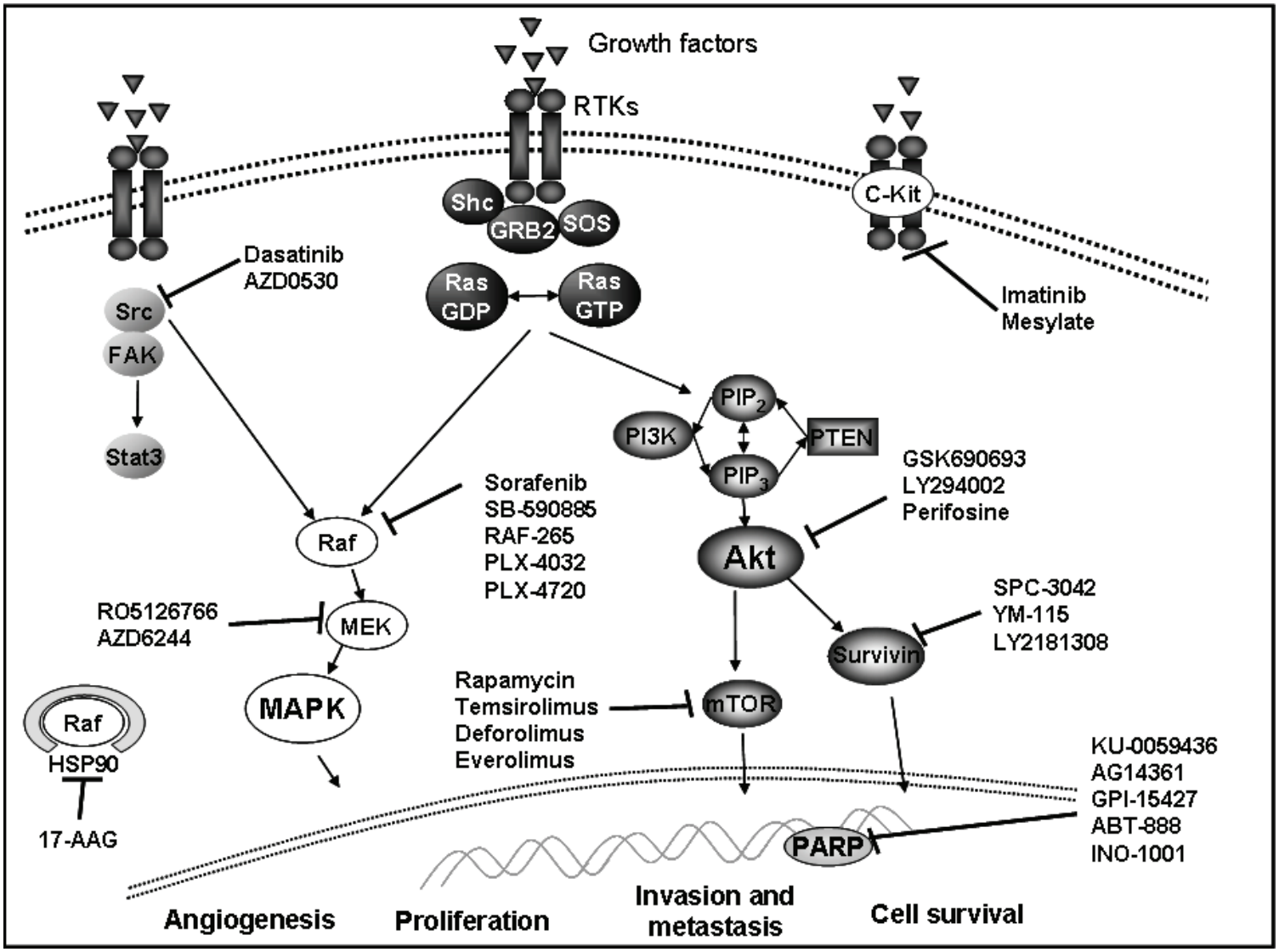

Figure 1. Signalling pathways and molecules that are potential targets for melanoma therapy.

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