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Update on Clinical Trials for Malignant Melanoma

Raffaele Califano¹, Ruth Board², Aidalena Z Abidin¹, Louise Carter¹,
Laura Cove-Smith¹, Bihani Kularatne³ and Paul Lorigan¹

¹*Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester,*

²*Rosemere Cancer Centre, Royal Preston Hospital, Sharoe Green Lane, Preston,*

³*Department of Medical Oncology, Guy's and St Thomas' NHS Trust,
Great Maze Pond, London
United Kingdom*

1. Introduction

After more than 20 years of little improvement in the outcome for patients with malignant melanoma despite a huge international effort spanning basic and clinical research, the last 2 years have shown significant steps forward in treatment options. This year has seen one new drug (Ipilimumab) being licensed and a second (vemurafenib) submitted for approval. This chapter focuses on the key clinical trials in the last 5 years, and gives an indication of the challenges ahead to ensure optimal use of these effective new therapies.

2. Adjuvant treatment

The only agent currently approved in the adjuvant setting for patients with completely resected malignant melanoma is interferon alfa (IFN alfa). A large number of randomised studies evaluating different treatment doses and schedules in a range of American Joint Committee on Cancer (AJCC) stages have been completed.

Despite this, there is still no consensus on the role of IFN as adjuvant treatment and reports have been conflicting in terms of therapeutic efficacy. The majority of studies compared adjuvant IFN to observation alone with a smaller number of studies using vaccines or IFN and chemotherapy as a comparator arm (Kirkwood et al. 2001). This chapter focuses on those studies that have compared interferon to observation only and these are summarised in table 1. Of the 13 published trials, 7 have demonstrated a benefit for IFN over observation in terms of disease free survival (DFS) and 2 have demonstrated an overall survival (OS) benefit (E1684 and DeCOG) (Kirkwood et al. 1996; Garbe et al. 2008)

The Scottish MG trial demonstrated benefits for both DFS and overall survival at 2 years but this diminished with longer follow up and was not statistically significant at 6 years (Cameron et al. 2001).

A meta-analysis of 12 trials was reported in 2003 including 10 trials with IFN compared to observation and 2 studies comparing IFN to a GMK vaccine (Wheatley et al. 2003). This meta-analysis demonstrated a 17% reduction in the risk of recurrence following treatment with IFN compared with control (HR 0.83, $p < 0.001$) but no benefit on overall survival (HR 0.93, $p = 0.1$).

Trial	Stage	IFN regimen	No	Results
NCCTG (Creagan et al. 1995)	IIA-III	IFN-a 20MU/m ² im x3/wk x 12wk	IFN=131 Obs=131	DFS: HR 0.83 (0.61-1.13; ns) OS: HR 0.9 (0.64-1.25; ns)
E1684 (Kirkwood et al. 1996)	IIB-III	IFN-a 20MU/m ² iv x5/wk x4wk then 10MU/ m ² sc x3/wk x48wk	IFN=147 Obs=140	5yr RFS 37% vs 26% (p=0.0023) 5yr OS 46% vs 37% (p=0.0237)
Austrian MMCG (Pehamberger et al. 1998)	II	IFN-a 3MU sc x7/wk x3wk then 3MU sc x3/wk x49wk	IFN=154 Obs=157	RFS 36% vs 24% (p=0.02) OS 13% vs 11% (ns) Median FU 3.4years
French CGM (Grob et al. 1998)	II	IFN-a 3MU sc x3/wk x18mo	IFN=253 Obs=246	DFS: HR 0.75 (0.57-0.98; p=0.035) OS: HR 0.72 (0.51-1.01; p=0.059)
E1690 (Kirkwood et al. 2000)	IIB-III	High: IFN-a 20MU/m ² iv x5/wk x4wk then 10MU/ m ² sc x2/wk x48wk Low: IFN-a 3MU/m ² sc x3/wk x24mo	IFN High=215 Low=215 Obs=212	DFS: High vs obs: HR 1.28 (1.0-1.65; p=0.05); Low vs Obs: HR 1.19 (0.93-1.53; p=0.17) OS: No differences between the 3 groups.
Scottish MG (Cameron et al. 2001)	IIA-III	IFN-a 3MU sc x3/wk x6mo	IFN=47 Obs=49	Median DFS 22 mo vs 9 mo (ns) Median OS 39mo vs 27mo (ns) Statistically different at 2years but not at 6 years FU
WHO (Cascinelli et al. 2001)	III	IFN-a 3MU sc x3/wk x36mo	IFN=225 Obs=219	5yr DFS 28% vs 28% (p=0.5) 5yr OS 35% vs 37% (p=0.72)
UKCCR (AIMHIGH) (Hancock et al. 2004)	IIB-III	IFN-a 3MU sc x3/wk x24mo	IFN=338 Obs=336	DFS: HR 0.94 (0.75-1.18; p=0.6) OS: HR 0.91 (0.75-1.1; p=0.3)
EORTC18871 (Kleeberg et al. 2004)	IIA-III	IFN-a 1MU sc alt days x12mo	IFN=240 Obs=244	DFS: HR 1.04 (0.84-1.3; ns) OS: HR 0.96 (0.76-1.21; ns)

Trial	Stage	IFN regimen	No	Results
EORTC18952 (Eggermont et al. 2005)	IIB-III	1yr: IFN-a 10MU sc x5/wk x4wk then 10MU sc x3/wk x12mo 2yr: IFN-a 10MU sc x5/wk x4wk then 5MU sc x3/wk x24mo	IFN 1 yr=553 2 yr=556 Obs=279	DFS: 2yr vs obs: HR 0.83 (0.66-1.03; ns); 1yr vs Obs: HR 0.93 (0.75- 1.16; ns) OS: No differences between the 3 groups.
DeCOG (Garbe et al. 2008)	III	IFN-a 3MU sc x3/wk x24mo	IFN=148 Obs=148	4yr DFS 59% vs 42% (p=0.0045) 4yr OS 39% vs 27% (p=0.0018)
EORTC18991 (Eggermont et al. 2008)	III	Peg IFN-a 6ug/kg sc x1/wk x8wk then 3mg/kg sc x1/wk x60mo	IFN=627 Obs=629	DFS: HR 0.82 (0.71-0.96; p=0.01) OS: HR 0.98 (0.82-1.16; p=0.78)
Nordic (Mocellin et al. 2010)	IIB-III	1yr: IFN-a 10MU sc x5/wk x4wk then 10MU sc x3/wk x12mo 2yr: IFN-a 10MU sc x5/wk x4wk then 10MU sc x3/wk x24mo	IFN 1 yr=285 2 yr=286 Obs=284	DFS: 2yr vs obs: HR 0.83 (0.68-1.03; p=0.178); 1yr vs Obs: HR 0.77 (0.63-0.96; p=0.034) OS: No differences between the 3 groups.

Abbreviations: IFN-a: interferon alpha; PEG IFN-a: pegylated interferon alpha; DFS, disease free survival; RFS: relapse free survival; OS: overall survival; HR: hazard ratio; wk: week; mo: month; yr: year; sc: subcutaneous; iv: intravenous; im: intramuscular; Obs: observation.

Table 1. Adjuvant studies with Inteferon

An individual patient data (IPD) meta-analysis of 13 trials evaluated efficacy of IFN in high risk melanoma patients (Wheatley 2007). This showed a clear benefit of adjuvant IFN in terms of relapse-free survival (RFS) (HR 0.87, 0.81-0.93; p=0.00004) and an absolute benefit in overall survival of 2% at 10 years (HR 0.9, 0.84-0.97, p=0.008). There was no clear evidence of a difference in outcome by either dose or duration of IFN treatment.

A more recent review and meta-analysis has been published in 2010 and includes 14 trials in total (12 comparing IFN to observation) (Mocellin et al. 2010). This meta-analysis consists of the 12 studies contained in the 2003 report (4 with updated survival data) plus 2 more recent studies (DeCOG and E18991). This demonstrated a relapse-free survival advantage favouring IFN adjuvant treatment (HR 0.82, p<0.001). Original data from 12 of the 14 studies was used to assess overall survival. A statistically significant reduction in risk of death was seen for patients receiving IFN treatment (HR 0.89, p=0.002). No clear differences were identified according to IFN regimen or dose or stage.

Despite the small advantage in OS, the optimal dose and schedule has not been clearly defined. Many of the previous studies used different doses and schedules of IFN and they

varied in the inclusion criteria, particularly by stage of disease. The drug itself can have substantial toxicities especially at high doses and can reduce quality of life for the duration of treatment (Bottomley et al. 2009).

Subgroup analyses of adjuvant studies have attempted to define which group of patients who would be most likely to benefit. EORTC 18952 and EORTC 18991 trials stratified patients according to stage of disease and number of lymph nodes involved (Eggermont et al. 2008; Eggermont et al. 2005). Both these studies suggested that the greatest benefit of IFN is seen in stage II or III-N1 disease with reduced advantage of IFN with macroscopic nodal involvement (stage III-N2 disease)

A subgroup analysis of the meta-analysis published in 2007 (Ives et al. 2007) revealed the effect of IFN did not differ according to age, gender, disease site, stage, number of nodes or Breslow thickness. However, patients with ulcerated tumours appeared to have greatest benefit both in terms of disease-free and overall survival ($p < 0.03$). Combined post hoc analysis of EORTC 18952 and 18991 studies also demonstrated the greatest reductions in disease-free survival and overall survival in patients with ulcerated tumours (Eggermont 2009). This hypothesis will be tested further in the planned EORTC 18081 trial which will compare PEG-IFN α -2b to observation in patients with ulcerated primary melanoma and a Breslow thickness greater than 1mm.

The subsequent meta-analysis of the EORTC 18952 and 18991 studies showed that the benefit for interferon was confined to patients with ulcerated primary tumours. Conversely, unplanned subgroup analysis of the Nordic trial showed most benefit in patients with highest tumour burden before lymph node dissection and no relationship between benefit of IFN and ulceration of the tumour.

Pegylated interferon (PEG Intron) has been approved as an adjuvant therapy in 2010 on the basis of an improvement in DMFS in patients with resected sentinel node positive disease (Eggermont et al. 2008).

Autoimmunity, as defined by the development of serum autoantibodies and/or clinical vitiligo, has been investigated as a potential predictive factor of efficacy for IFN. In one study, patients receiving high dose IFN who developed autoimmunity (about a quarter of the patients) had an improved DFS and overall survival compared to those patients who did not (Gogas et al. 2006). However, other studies have failed to confirm any associations (Bouwhuis et al. 2009).

Vaccine strategies have also been evaluated in clinical trials, but to date the results have not been encouraging. Three studies (Cancervax stage III, Cancervax stage IV resected and EORTC 18961) have shown a survival disadvantage for these vaccines in this situation, and a further study (ECOG 1694) suggested a survival disadvantage for GMK vaccine. Studies with gp100 vaccines in advanced disease have shown no survival disadvantage (Schwartzentruber et al. 2009; Hodi et al. 2010). It is unclear why these adjuvant studies were negative but it encourages caution in employing long term vaccine based immune stimulation as an adjuvant therapy.

The adjuvant treatment of intermediate and high risk melanoma patients still varies greatly from country to country, with greater use of adjuvant interferon in USA and some North European Countries. Participating in a clinical trial remains the preferred option for these patients and most of randomised studies currently ongoing still include an observation arm. The DERMA trial (NCT00796445) is currently randomising MAGE-A3 positive patients with high risk (stage III) melanoma to receive a MAGE peptide vaccine plus adjuvant or placebo. A total of 1300 patients are planned to be enrolled. Prespecified subgroup analysis will

examine whether a previously identified genetic classifier can predict those likely to benefit from treatment (Kruit et al. 2008).

The European Organisation for the Research and Treatment of Cancer (EORTC) Melanoma Group is conducting a randomised double-blind phase III trial (EORTC 18071) evaluating Ipilimumab, a blocking antibody to CTLA4, versus placebo in patients with completely resected stage III disease (NCT00636168). Ipilimumab has recently been approved by the FDA for the treatment of advanced disease. A study comparing ipilimumab to high dose IFN in high risk disease is also planned (NCT01274338).

The AVAST-M study is a large randomised study enrolling across the United Kingdom. Patients with completely resected stage IIB-III melanoma are randomised to receive bevacizumab 7.5 mg/kg every 3 weeks for 1 year or observation. The planned sample is 1320 patients and the study aims to identify an 8% difference in overall survival. Relapse-free survival, quality of life, toxicity and biomarkers are secondary end points.

All 3 studies have nearly completed accrual and results will be available in the next 3-5 years, depending on the mix of risk groups included. The outcomes of these studies, and developments in treatment of advanced disease, will determine the landscape of adjuvant therapy and clinical trials over the next 5-10 years.

3. Advanced disease

The last 20 years have seen a huge body of work trying to improve outcomes for patients with advanced melanoma, with no real benefits. The median survival in recent chemotherapy studies has improved over historical controls, but in the main this has been due to better patient selection and stage migration due to improved imaging techniques. This is now changing very quickly.

Where once we could design clinical trials with an overall survival endpoint, confident that the outcome would not be affected by subsequent treatment, we now have a number of new drugs with either a proven survival benefit, or preliminary data to suggest that this will be the case. Here we review the pivotal clinical trials and their implications for treatment.

3.1 Standard chemotherapy

Single agent dacarbazine (DTIC) became the standard first-line chemotherapy based on a response rate of 10-20% in Phase II studies. No studies have ever been conducted to evaluate single agent chemotherapy against placebo or best supportive care. For this reason, the impact of treatment with DTIC on survival remains unclear.

Temozolamide (TMZ) is an oral alkylating agent and, together with DTIC, a prodrug of the active alkylating agent 5-(3-methyltriazene-1-yl) imidazole-4-carboximide (MTIC). Unlike DTIC, temozolamide spontaneously converts to MTIC.

A large phase III study compared overall survival of 305 chemotherapy-naïve advanced melanoma patients treated with TMZ (200 mg/m²/d for 5 days every 28 days) or intravenous DTIC (250 mg/m²/d for 5 days every 21 days) (Middleton et al. 2000). The trial was designed to detect a 50% increase in survival compared with the 6 months expected with DTIC. Median progression-free survival (PFS) time was improved for temozolamide (1.9 v 1.5 months; HR 1.37; p=0.012). However, objective response was assessed every two cycles and this could explain the longer PFS interval for the temozolamide arm. Patients in the temozolamide arm experienced longer overall survival, which did not reach statistical significance (7.9 vs 5.7 months; p=0.054). There was no difference in response rates between the two arms (CR rate

of 2.6% vs 2.7% and PR rate of 10.9% vs 9.4% for temozolamide and DTIC arm, respectively). Both treatments were well tolerated. Most common grade 3/4 haematological toxicity was thrombocytopenia. Quality of life (QoL) at 12 weeks (QLQ-030 scores) showed a statistically significant difference favouring TMZ for physical functioning, fatigue, and insomnia. This trial demonstrated that TMZ represents an effective alternative to DTIC with potential advantage in QoL. Temozolamide did not receive regulatory approval for use in advanced melanoma, but there is a large use for off-label temozolamide chemotherapy, particularly in patients with brain metastases.

A large study conducted by the European Organization for Research and Treatment of Cancer (EORTC 18032) (Patel et al. 2008), randomized 859 patients with untreated stage IV melanoma, performance status 0-1 and LDH \leq 2x ULN to receive TMZ 150 mg/m² day 1-7 repeated every 14 days ("week on-week off") or DTIC 1000 mg/m² every 3 weeks. Both treatments were given until progression. The extended schedule allowed a 2.1 fold higher cumulative dose than the standard 5-days regimen and was thought to prolong depletion of the DNA repair enzyme MGMT, a known mediator of chemoresistance to temozolamide. Overall survival, did not differ between TMZ and DTIC (9.13 vs 9.36 months, $p=1.0$). There was also no difference in PFS (2.3 vs 2.17 months, $p=0.27$) and response rate (14% vs 10%, $p=0.05$) between the two groups. Thrombocytopenia was higher in the TMZ arm but there were no differences in non-haematological toxicities.

Despite well tolerated, the extended schedule temozolamide regimen confers no survival advantage over standard DTIC.

3.2 Biochemotherapy vs chemotherapy

Several randomized trials have evaluated chemotherapy combined with immunotherapy (IFN \pm IL-2; ie, biochemotherapy) in an attempt to improve both response rates and overall survival (OS) in the advanced setting. A metaanalysis by Ives et al, evaluated the effect of adding interferon- α (IFN α) \pm interleukin-2 (IL-2) to chemotherapy in patients with metastatic melanoma (Ives et al. 2007). Data was extracted from 18 trials with more than 2600 patients. Eleven trials (1395 patients) evaluated chemotherapy \pm IFN and seven trials (1226 patients) evaluated chemotherapy \pm IFN and IL-2.

Patients treated with biochemotherapy had increased PR (odds ratio = 0.66; 95% CI, 0.53 to 0.82; $p=0.0001$), CR (odds ratio = 0.50; 95% CI, 0.35 to 0.73; $p=0.0003$), and overall response rate (odds ratio = 0.59; 95% CI, 0.49 to 0.72; $p<0.00001$). There was a significant increase in overall response rate (ORR) for both the immunotherapy subgroups; IFN (odds ratio = 0.60; 95% CI, 0.46 to 0.79; $p=0.0002$) and IFN+IL-2 (odds ratio = 0.58; 95% CI, 0.44 to 0.77; $p=0.0001$). For PR (test for heterogeneity between subgroups; $p=0.08$) and CR ($p=0.007$) there was some evidence of a difference in treatment effect dependent on the type of immunotherapy used (IFN or IFN + IL-2). Biochemotherapy delayed the time to disease progression (odds ratio = 0.80; 95% CI, 0.71 to 0.89; $p=0.0001$), with no evidence of heterogeneity between individual trials or between the type of immunotherapy used. Despite improvement in response rate and PFS, there was no benefit for biochemotherapy on OS (odds ratio = 0.99; 95% CI, 0.91 to 1.08; $p=0.9$). Toxicity data was available only from 11 trials. Hematological toxicity was higher in the biochemotherapy arm but the treatment-related deaths rate was similar (0.6% vs 0.9%, $p=0.6$) for biochemotherapy group and chemotherapy group, respectively. These data suggest no benefit from adding IL-2 or IFN to chemotherapy.

3.3 Single agent vs combination chemotherapy

A number of combination chemotherapies have been evaluated for advanced melanoma. These regimens seemed promising in II trials, but failed to show survival advantage over DTIC alone when tested in randomized phase III trials.

The two most active combinations are the four-drug combination of cisplatin, DTIC, carmustine (BCNU), and tamoxifen (the Dartmouth regimen) and cisplatin, vinblastine, and DTIC (the CVD regimen).

The Dartmouth regimen was initially evaluated in 42 patients and demonstrated a response rate of 54% and overall survival of 412 days (Lattanzi et al. 1995). The Dartmouth regimen was then evaluated against DTIC in a large (n=240) phase III randomized trial (Chapman et al. 1999). Patients receiving the Dartmouth regimens achieved higher response rates, but the difference was not statistically significant (18.5% vs 10.2%, p=0.09). Median survival time from randomization was 7 months and there was no difference in survival time between the two treatment arms. Bone marrow suppression, nausea/vomiting, and fatigue were significantly more common in the Dartmouth arm. This trial demonstrated that polichemotherapy did not improve survival compared to single agent chemotherapy and crowned DTIC as the standard regimen in advanced Melanoma.

The CVD regimen was evaluated in a phase II trial in 52 patients (Legha et al. 1989). Overall response rate was 40% and median survival was 9 months. The treatment was associated with significant nausea, vomiting and diarrhea. On the basis of these promising results, a phase III trial evaluating CVD vs DTIC was conducted and showed a response rate of 24% and 11%, respectively with no difference in median survival between the two groups (6.7 vs 5.2 months) (Buzaid et al. 1993). (Results of the trials evaluating combination chemotherapy are summarized in table 2)

Because of the lack of improvement in overall survival and the worse toxicity achieved with polichemotherapy regimens, DTIC remains the preferred option as first-line chemotherapy in advanced/metastatic melanoma patients.

Author	Regimen	No	Response rate (%)	OS (mos)
Lattanzi (Lattanzi et al. 1995)	DTIC+C+BCNU	16	25	412 days
	DTIC+C+BCNU+ Tam (Dartmouth)	26	54	412 days
Chapman (Chapman et al. 1999)	Dartmouth	119	18.5	7.7
	DTIC	121	10.2	6.3
Legha (Legha et al. 1989)	CVD	52	40	12
Buzaid (Buzaid et al. 1993)	CVD	46	24	6.7
	DTIC	45	11	5.2

Abbreviations: DTIC: Dacarbazine; C: Cisplatin; BCNU: carmustine; Tam: Tamoxifen; CVD: cisplatin, vinblastine, dacarbazine; Dartmouth: dacarbazine + cisplatin + carmustine + tamoxifen; OS: overall survival; mos: months

Table 2. Phase II-III trials of polichemotherapy for advanced melanoma.

4. Immunotherapy

Melanoma cells can express a number of antigens that excite an immune response, as borne out by the better prognosis seen in patients with evidence of immune activation (vitiligo), the occasional case of spontaneous regression, the better outcome for patients with unknown primary (Chang and Knapper 1982; Lee et al. 2008), the increased incidence of melanoma seen in immunocompromised patients, and the response to immunotherapy agents including interferon alpha and interleukin 2.

4.1 Adoptive cell therapy

The ability to isolate and characterize anti-tumor lymphocyte has enabled the identification and characterization of multiple melanoma-associated antigens that can represent target of immunotherapy. Adoptive cell therapy (ACT) describes an immunotherapy approach in which tumor infiltrating lymphocytes (TIL) are harvested from fresh tumour tissue, expanded *ex vivo* and then reinfused after the patient has been lymphodepleted. Critical components of this complex process include the number, age and type of TILs, the degree of immunosuppression of the host, and the use of IL-2 after reinfusion.

Dudley et al, reported on 3 consecutive trials involving 93 patients in total (Dudley et al. 2008). In the first study, 43 patients received non-myeloablative chemotherapy consisting of cyclophosphamide and fludarabine before the TIL transfer. On the two next trials, patients were treated with 2 days of cyclophosphamide (60 mg/kg) plus 5 days of fludarabine (25 mg/m²) followed by a single fraction of 2 Gy of total body irradiation (TBI) (n=25) or 12 Gy of TBI (n=25). On the day following the final dose of TBI, patients received cell infusion with TIL and started high-dose IL-2 consisting of 720,000 IU/kg intravenously every 8 hours to tolerance. One or 2 days after TIL infusion, cryopreserved CD34+ hematopoietic stem cells were infused intravenously. Thirty seven percent of the patients had received previous chemotherapy and 83% had received previous IL-2. The response rates in these 3 studies were 48.8 %, 52% and 72%, respectively. Response of the marker lesions was seen in all visceral and soft tissue sites, including brain. Ten patients achieved a complete response with no relapses at 31-month follow-up. The median follow-up of these trials was 45, 27 and 10 months, respectively and there was no difference in survival between the groups (p=0.13) bearing in mind that the follow-up of the third trial is quite short. These studies demonstrate that ACT has the potential of improve the outcomes of a highly selected patient population, but its use at present should remains strictly as part of clinical trials.

4.2 Cytotoxic T lymphocyte-associated antigen 4 (CTLA 4) blockade

CTLA 4 is a key molecule in T-cell tolerance that serves as a natural braking mechanism for T-cell activation, allowing a return to homeostasis following an immune response. T-cell activation requires engagement of the T-cell receptor to antigen-bound major histocompatibility complex (MHC) on the antigen-presenting cell (APC) as well as engagement of the costimulatory molecule CD28 on the T-cell surface by members of the B7 family on the APC. Following T-cell activation, CTLA 4 cell-surface receptors are upregulated and compete with CD28 for binding to B7 sending an inhibitory signal that downregulates T-cell activation.

This led to the hypothesis that blocking the CTLA 4-B7 interaction would lead to enhanced and prolonged T-cell activation with subsequent more vigorous antitumor immune response.

Two anti-CTLA 4 blocking antibodies have been evaluated in clinical trials: tremelimumab (formerly CP-675,206 or ticilimumab) and ipilimumab (formerly MDX010)

4.3 Tremelimumab

Tremelimumab is a fully human IgG2 monoclonal antibody specific for human CTLA 4. A Phase II study in 251 previously treated patients with advanced disease reported a median survival of 10 months (Kirkwood et al. 2010)

A phase III trial randomized 655 patients with unresectable stage IIIC and stage IV melanoma without brain metastasis and LDH below twice the upper limit of normal to receive tremelimumab 15 mg/kg every 3 months vs chemotherapy (TMZ 200 mg/m² p.o. d1-5 q28d or DTIC 1,000 mg/m² IV q21d) (Ribas et al. 2008). The study was stopped early by the data safety monitoring committee after the second interim analysis because of futility. The median OS by was 11.8 months (95% CI 10.4, 13.9) in the tremelimumab arm, and 10.7 months (95% CI 9.3, 12.0) in the chemotherapy arm. Subgroup analysis of this trial has suggested that patients with low baseline C-reactive protein had improved survival (median OS: 19.1 vs 12.7 months, $p = 0.0037$) with tremelimumab compared with chemotherapy. (Marshall, Ribas, and Huang 2010)

4.4 Ipilimumab

Ipilimumab is a fully human monoclonal immunoglobulin (IgG1k) specific for CTLA-4 that was investigated in three phase II trials (study 007, 008, and 022), enrolling a total of 487 treatment-naive and pretreated patients with unresectable stage III or stage IV melanoma. Study 007 randomized 115 pretreated and treatment naive patients to receive ipilimumab (10 mg/kg every 3 weeks, for four doses) with prophylactic budesonide/placebo to prevent colitis (Weber et al. 2009) Budesonide did not affect the rate of grade ≥ 2 diarrhea and median survival was 17.7 vs 19.3 months for the budesonide and placebo group, respectively. The one-year survival was greater than 55%.

Study 008 was a single-arm phase II trial investigating ipilimumab at the dose of 10 mg/kg in 155 pretreated patients (O'Day et al. 2010). Best overall response rate (BORR) was 5.8% with a disease control rate (DCR) of 27% and a median overall survival of 10.2 months. The 1-year survival rate was 47.2% and ongoing survival analyses showed 18- and 24-month survival rates of 39.4% and 32.8%, respectively. Most common adverse events (AEs) were immune-related, occurring mainly in the skin (grade 3/4: 3.2%) and gastrointestinal tract (grade 3/4: 8.4%). Study 022 was a randomized, double blind, phase 2 trial that assessed three different doses of ipilimumab (0.3 mg/kg, 3.0 mg/kg, or 10 mg/kg) in 217 pretreated patients (Wolchok et al. 2010). Patients were treated with four 3-weekly doses (induction phase), then patients without PD at week 24 were eligible to continue their assigned dose of ipilimumab every 12 weeks (maintenance phase). Only 20 patients received maintenance therapy. Patients progressing after an initial response or stable disease were allowed to undergo reinduction with ipilimumab at the dose of 10 mg/kg. There was a clear dose response with a statistically significant improvement in best overall response rate with the 10 mg/kg dose (BORR 11.1%). Despite the study was not designed to detect differences in survival, there was a trend for improved overall survival favoring the dose of 10 mg/kg that did not reach statistical significance (8.6 vs 8.7 vs 11.4 months). Most common AEs (skin rash and diarrhea) were immune-related and the frequency rose with increasing dose of ipilimumab. The authors concluded that the dose of 10 mg/kg warranted further evaluation.

Phase II trials of ipilimumab in advanced melanoma are summarized in table 3.

Study	Dose (mg/kg)	Population	No	ORR (%)	DCR (%)	MS (mos)	1y-S (%)
007	10 + budesonide	pre-treated and untreated	58	12	31	17.7	55.9
	10 + placebo		57	16	35	19.3	62.4
008	10	pre-treated	155	5.8	27	10.2	47
022	0.3	pre-treated	73	0	13.7	8.6	39.6
	3	pre-treated	72	4.2	26.4	8.7	39.3
	10	pre-treated	72	11.1	29.2	11.4	48.6

Abbreviations: No: number; ORR: overall response rate; DCR: disease control rate; MS: median survival; mos: months; 1y-s: 1-year survival

Table 3. Phase II trials of ipilimumab in advanced Melanoma

A recently published large phase III trial randomized 676 pretreated HLA-A*0201-positive patients with unresectable stage III or IV melanoma to receive, in a 3:1:1 ratio, ipilimumab plus gp100 (n=403 patients), ipilimumab alone (n=137), or gp100 alone (n=136). (Hodi et al. 2010). Ipilimumab was administered at the dose of 3 mg/kg every three weeks, for four cycles. Patients with stable disease for 3 months after week 12 or a confirmed partial or complete response were offered additional courses of therapy (reinduction) with their assigned treatment regimen, at disease progression. The original primary endpoint was the best overall response rate but this was amended to overall survival. Seventy seven (out of 82) patients had central nervous system metastasis at baseline and received at least one dose of ipilimumab. The median overall survival was 10.0 vs 10.1 vs 6.4 months for the ipilimumab-gp100, ipilimumab alone and gp100 alone arms, respectively.

There was no difference in overall survival between the two ipilimumab groups (HR 1.04; p=0.76). The median progression-free survival was 2.76 months in the ipilimumab-gp100 group, 2.86 months in the ipilimumab-alone group, and 2.76 months in the gp100-alone group. One-year survival and 2-year survival for ipilimumab-plus-gp100 group, the ipilimumab-alone group, and the gp100-alone group were 43.6%, 45.6%, 25.3% and 21.6%, 23.5%, 13.7%, respectively. Consistently with phase 2 data, most common adverse events were immune-related and most affected were skin and gastrointestinal tract. Other serious AEs included hepatitis and endocrinopathies. Grade 3/4 colitis occurred in 3-5% of the patients treated in the ipilimumab-gp100 and ipilimumab-alone arm, respectively. There were 14 treatment-related deaths (2.1%), of which 7 were associated with immune-related adverse events. This study was restricted to patients that were HLA-A2 positive, because the vaccine is presented in a HLA restricted fashion. However, CTLA-4 blockade by ipilimumab is independent of HLA status therefore HLA-typing patients who are suitable to receive ipilimumab is not necessary.

This trial is, so far, the only trial showing a survival advantage in the history of melanoma and has set a new standard of care. On the basis of these results, US Food and Drug Administration (FDA) has recently approved ipilimumab for treatment of unresectable or metastatic melanoma.

Bristol Myers Squibb has also announced that a first-line trial (CA180-024) has met its primary end point demonstrating improvement in overall survival with ipilimumab in combination with dacarbazine vs dacarbazine alone. Data will be presented at the forthcoming ASCO Annual Meeting 2011 and are eagerly awaited.

4.5 Immune-related response criteria

The pattern and duration of responses associated with CTLA 4 blockade differ from those associated with cytotoxic agents. Objective responses to ipilimumab may not occur until the post-induction period of therapy and may occur, in some cases, after PD as defined by WHO or RECIST criteria.

Four patterns of response to ipilimumab have been identified: 1) initial response in baseline lesions, 2) stable disease with subsequent slow and steady decline in total tumor volume, 3) response after increase in total tumor volume, 4) reduction in total tumor burden after the appearance of new lesions.

The apparent increase in tumor burden that sometimes happens before an objective response could be either related to continue tumor growth until a sufficient immune response develops or transient immune cells infiltrate that can cause edema.

In order to provide a more comprehensive assessment of clinical activity of these agents, the immune-related response criteria (IrRC) have been developed as a variation of WHO criteria (Wolchok et al. 2009). Using these criteria, new lesions do not always represent progressive disease, and the criteria for calculating response or progression have been modified. The immune-related response criteria may help to explain why patients with apparent PD by the traditional response criteria go on to experience long-term survival.

5. Targeted agents

The identification of an activating mutation in *braf* in 50-60% of cutaneous melanoma samples (Davies et al. 2002), and the fact that in this was primarily a single codon mutation, resulting in the V600E mutation in the vast majority of cases, opened up the field to the potential for targeted therapy. Since then, it has been shown that approximately 50-70% of cutaneous melanomas have a mutation in the *mAP* kinase pathway, either *BRAF* or *NRAS*, and approximately 20% of acral lentiginous melanomas have a mutation in *c-kit* (Curtin et al. 2005; Curtin et al. 2006). The identification of potential targets resulted in the design of a number of targeted therapies, which have been evaluated in clinical trials.

5.1 Sorafenib

Sorafenib (Nexavar[®], Bayer Healthcare Pharmaceuticals) is a multikinase inhibitor with potent non-selective action against *RAF1*, with additional broad-spectrum activity against *VEGFR-2*, *VEGFR-3*, *PDGFR-β*, the tyrosine kinase *FLT3* and *KIT* receptors. It is one of the first small molecules to be tested in the treatment of melanoma.

Its use as a single agent treatment did not seem to confer any meaningful benefit in melanoma patients (Eisen et al. 2006). A phase II trial investigating the combination of sorafenib/placebo and dacarbazine showed promising results, with an improvement in progression-free survival (21.1 weeks vs 11.7 weeks, HR 0.665; $p=0.068$ for sorafenib and placebo arm, respectively) but no improvement in overall survival (45.6 vs 51.3 weeks HR=1.022; $p=0.927$, for sorafenib and placebo, respectively) for patients receiving dacarbazine/sorafenib combination (McDermott et al. 2008).

Two large phase III trials investigated sorafenib in combination with carboplatin/paclitaxel chemotherapy.

The PRISM study evaluated carboplatin/paclitaxel (CP) with sorafenib/placebo in a phase III randomized study as a second-line treatment for unresectable stage III or stage IV melanoma patients. There was no improvement in either median PFS (17.9 vs 17.4 weeks, HR=0.91; p=0.49, for CP/placebo and CP/sorafenib, respectively) or median OS (42.0 weeks for both arms, p=0.92) (Hauschild et al. 2009). More recently, results from a first-line phase III trial (E2603 intergroup trial) have been reported. This trial randomized 823 previously untreated patients with metastatic melanoma, to receive sorafenib or placebo in combination with CP. The study crossed the futility boundaries and therefore was stopped and unblinded after 75% of the events required for the final analysis were reached. There was no improvement in median OS (11.0 vs 11.3 months in sorafenib and placebo, respectively, p=N/A), and no difference in median PFS (4.9 vs 4.1 months, p=0.48 for sorafenib and placebo, respectively) (Flaherty, Lee et al. 2010).

5.2 BRAF selective inhibitors

Vemurafenib (RG7204, PLX4032), is an orally available inhibitor of mutated BRAF has the most clinical evidence accrued thus far. Preliminary data from the phase I trial of PLX4032 was reported in 2010 in the *New England Journal of Medicine* (Flaherty, Puzanov et al. 2010). The trial enrolled 55 patients, of which 49 diagnosed with melanoma, in a dose escalation phase and further 32 patients harbouring the BRAF V600E mutation enrolled in an extension phase receiving the recommended dose of 960 mg twice daily. Among the 16 patients with melanoma receiving 240 mg twice a day or more the overall response rate was 69%. Five patients with metastatic melanoma without BRAF mutations were treated with no evidence of tumour response. Notably, in the extension phase, 26 out of 32 (81%) patients treated had an objective response. The estimated median progression-free survival in these patients is 7 months and the estimated median overall survival has not yet been reached. The most common grade 2 or 3 adverse events were arthralgia, fatigue and skin-related toxicity including 18 patients with cutaneous squamous cell carcinomas (keratoacanthoma type) treated with excision without interruption of treatment. Of the adverse events observed, 89% were grade 1 and 2.

The exciting results showed in the phase I trial prompted the design of the phase II trial of RG7204 in previously treated patients with metastatic melanoma harbouring a BRAF V600E mutation (BRIM 2 trial). This data was presented by Sosman and colleagues at The Seventh International Melanoma Research Congress of the Society for Melanoma Research, in November 2010 (Sosman et al. 2010). BRIM 2 (NCT00949702) was a single arm, multicentre, open label phase II trial in which 132 patients received RG7204 until progression. Primary endpoint was overall response rate. The presence of the V600E BRAF mutation was confirmed with the cobas® 4800 BRAF V600 mutation test developed by Roche. The ORR was 52% and 30% of patients achieved stable disease. The median PFS was 6.2 months and, as with the phase I trial, median overall survival has not yet been reached. Consistently to what observed in the phase I trial, most common adverse events observed were arthralgia and skin toxicity, including 26% grade 3 cutaneous squamous cell carcinoma. However, fourteen percent of the patients also experienced grade 3 abnormalities in liver function tests and 10% Grade 3 dysphagia and pancreatitis

The confirmation of clinical efficacy from the phase two trial led to the design of BRIM 3 (NCT01006980), a large phase III randomized trial evaluating RG7204 head to head with

dacarbazine in previously untreated patients with metastatic melanoma harbouring BRAF V600E mutation. This study has recently terminated accrual and a recent press release from Roche has showed that RG7204 met its co-primary endpoints. Patients treated with the BRAF selective inhibitor have achieved longer OS and PFS than the chemotherapy arm. Final data will be presented at the ASCO Annual Meeting 2011 (Roche 2011). Since the interim analysis data, the trial protocol has been amended so that patients in the dacarbazine arm who have progressed have now the option to crossover to receive RG7204. Other BRAF selective inhibitors are now in clinical development. GSK2118436 is a potent oral selective ATP competitive BRAF inhibitor. The results from phase I/II dose escalation study of GSK2118436 in melanoma and other solid tumours were reported at ASCO 2010. When reported, maximum tolerated dose had not been reached but clinical activity with minimal toxicity was seen. The most common grade 3/4 toxicities reported were skin changes, headache, nausea, fatigue and vomiting and low grade squamous cell carcinoma in order of reducing frequency. Notably, 79% of patients with BRAF mutation were shown to have exposure-related decrease in FDG-PET metabolic uptake and 60% had a >20% reduction in tumour size by RECIST at initial restaging (Kefford et al. 2010).

A phase III study is ongoing and will compare GSK2118436 to dacarbazine (DTIC) in previously untreated subjects with BRAF V600E mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma. (NCT01227889). Another phase II trial is evaluating GSK2118436 in BRAF Mutant stage IV melanoma with brain metastases (NCT01266967). The RAS/RAF/MEK/ERK pathway is shown in figure 1.

5.3 MEK inhibitors

MEK 1 and 2 belong to a family of dual specificity kinases which are downstream of RAF in the mitogen activated protein kinase signalling cascade (Crews, Alessandrini, and Erikson 1992; Rosen et al. 1994). ERK1/2 is constitutively active in melanoma cells regardless of their BRAF or NRAS status, presenting a potential target for treatment in this population. Phosphorylated ERK is important for melanoma because it plays key roles in cell cycle entry, invasion, and possibly angiogenesis, as well as in resistance to apoptosis (Smalley 2003). AZD6244 is a highly selective allosteric inhibitor of MEK1/2. Treatment with AZD6244 leads to suppression of pERK levels in melanoma in a manner independent of BRAF and NRAS mutation status (Haass et al. 2008). Single agent therapy of melanoma with AZD6244 has been disappointing.

The interim results from a phase 2 study of the safety and efficacy of AZD6244 versus temozolomide in patients with advanced melanoma were reported in 2008. This was an open label randomised multicentre phase 2 study which randomized 200 patients with untreated stage III or IV melanoma to receive AZD6244 or temozolamide. There was no difference in PFS between the two treatment arms in the overall population (HR 1.07; 80% CI 0.86-1.34) or in the BRAF mutant subgroup (HR 0.85; 80% CI 0.58-1.24). Overall survival data are immature (67 deaths) but the interim analysis showed no difference between the two arms in the overall population (HR 1.23; 80% CI 0.88-1.71). Mutation status was assessed in archival tissue and 67 (50%) cutaneous melanoma patients had a BRAF mutation and 24 (18%) patients had a mutation in NRAS. In BRAF mutant patients, the HR estimate for OS favoured AZD6244 (HR 0.68; 80% CI 0.38-1.21) (Dummer et al. 2008).

A randomised phase II study (AZD Study 6, NCRN063) that randomised 91 BRAF V600E mutant patients to receive DTIC + AZD6244/placebo has completed accrual in 2010 and the results are awaited.

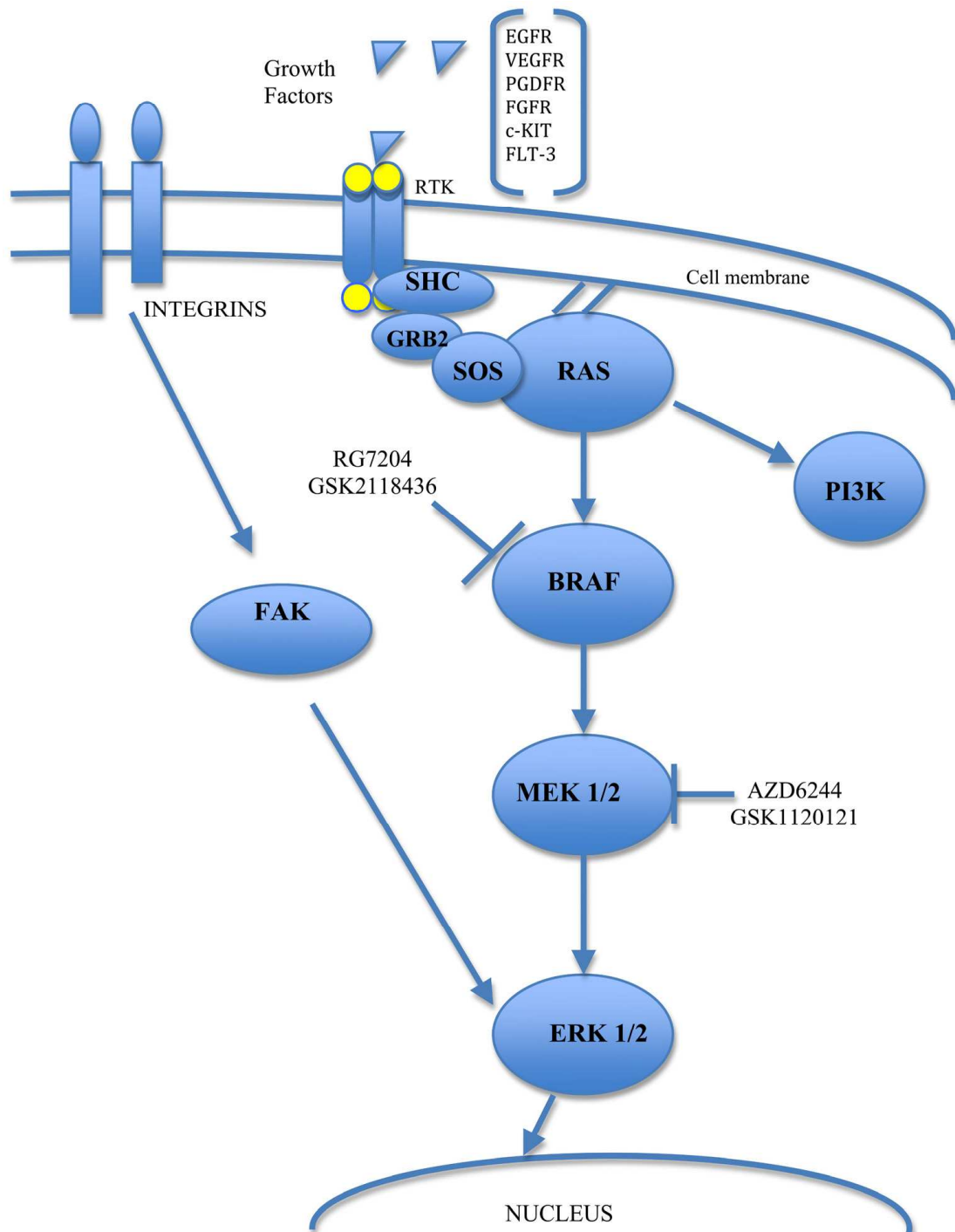


Fig. 1. The RAS/RAF/MEK/ERK pathway

AZD6244 and docetaxel have demonstrated synergy in a variety of animal xenograft models, including melanoma. Furthermore, a patient with wild type BRAF and NRAS treated with AZD6244 showed a response to treatment in the initial study. A phase 1 study of the combination of AZD6244 and docetaxel has been conducted (Astrazeneca study D1532C00004) in 12 patients with melanoma: 1 had a complete response; 1 a partial response; 4 had stable disease beyond 6 cycles of treatment (18+ weeks) indicating clinical activity worthy of further study.

DOC-MEK is a first-line randomised, double-blind placebo controlled phase 2 trial, that randomizes BRAF wild-type stage IV melanoma to receive docetaxel 75mg/m² IV and placebo/AZD6244.

GSK1120212 is a potent and selective allosteric inhibitor of the MEK1/2 enzymes. A three-part phase I trial evaluating GSK1120212 in 84 patients with advanced solid tumors and lymphoma was reported at ASCO 2010 (Infante et al. 2010). This trial included 29 melanoma and 15 pancreatic cancer patients. The maximum tolerated dose was found to be 3 mg OD and recommended phase II dose (RP2D) chosen was 2 mg OD. At doses \geq RP2D (n=77), the most common adverse events were rash (30% G2, 5% G3) and diarrhea (9% G2, 3% G3). In the 20 evaluable melanoma patients with known BRAF status, 5 PR were observed, all having \geq 50% tumor reduction; 3 have stayed \geq 30 weeks on study, the other 2 are ongoing. In the 11 BRAF mutant melanoma patients, 3 PR, 5 SD (including a patient previously treated with the BRAF inhibitor RG7204), and 3 PD were observed. Two of the 3 PD were due to new brain lesions. In 9 BRAF wild-type patients with melanoma, 2 PR, including a patient with a GNAQ mutation, and 3 SD were achieved.

A Phase II open-label, multi-site study to investigate the objective response rate, safety, and pharmacokinetics of GSK1120212 in subjects with BRAF mutation-positive melanoma who were previously treated with or without a BRAF inhibitor has completed accrual and is ongoing.

The recently initiated METRIC Phase 3 study will compare (2:1 randomisation) GSK1120212 vs DTIC (untreated patients) or paclitaxel (previously treated patients) in advanced or metastatic melanoma harbouring BRAF V600 E/K mutation. The primary endpoint is PFS and subjects who have progression on chemotherapy will be offered the option to cross over to receive GSK1120212.

5.4 Bevacizumab

Bevacizumab is a monoclonal antibody that acts indirectly to prevent angiogenesis by binding the VEGF-A receptors, thus preventing the interaction with VEGFR2. Melanoma cells, when exposed to chemotherapy agents, overproduce VEGF thus encouraging the development of chemoresistant tumour phenotypes. There is evidence of increased production of angiogenic factors with more advanced stage of melanoma (Lev et al. 2004; Ugurel et al. 2001). For this reason bevacizumab was investigated as a treatment for melanoma.

A number of phase II trials with bevacizumab in combination with chemotherapy have been reported so far. The BEAM trial randomized (2:1) 214 patients to carboplatin/taxol + bevacizumab or placebo, in the first-line setting. There was an improvement in progression-free survival (primary endpoint) in the bevacizumab arm compared to placebo (5.6 months vs 4.2 months, HR 0.78, p=0.16), which did not reach statistical significance. Notably there was a non statistically significant improvement in OS (secondary endpoint) (12.3 vs 9.2 months, HR=0.79, P=0.19) (O'Day, Sosman, and Peterson 2009)

A phase II trial evaluated the use of bi-weekly bevacizumab in combination with carboplatin and weekly paclitaxel in 53 previously treated patients. The median PFS and OS were 6 and

12 months, respectively. There was a high incidence of haematological toxicities, most common being grade ≥ 3 neutropenia (53%), leukopenia (38%) and thrombocytopenia (11%). There were also 40 episodes of bleeding in 31 patients, including two grade 2 bronchopulmonary haemorrhages and one grade 5 central nervous system hemorrhage (Perez et al. 2009).

A Phase II study of temozolomide 150 mg/m² for 7 days and bevacizumab 10 mg/kg every 2 weeks in 62 patients reported a median PFS of 4.2 months and OS of 9.3 months (Dummer et al. 2010).

5.5 Oblimersen

Oblimersen sodium (Genasense; Genta International Inc, Berkeley Heights, NJ) is a 18-base phosphorothioate antisense oligonucleotide that binds to the first 6 codons of the Bcl-2 mRNA open reading frame (Klasa et al. 2002). Overexpression of Bcl-2 may be partially responsible for the multi drug resistance seen in melanoma (Soengas and Lowe 2003). In a randomised controlled trial reported by Bedikian et al, 771 chemo-naïve advanced melanoma patients were randomised to receive either dacarbazine (1000 mg/m² on day 1) and oblimersen (7 mg/kg/day as a continuous infusion for 5 day) (n=386) or dacarbazine alone (n=385) (Bedikian et al. 2006). There was a trend for longer OS in the oblimersen arm which did not reach the statistical significance (9 vs 7.8 months, HR= 0.87, 95% CI=0.75-1.01, p=0.077). A subgroup analysis for patients with normal LDH showed significantly improved overall survival, PFS and overall response rate in favour of the oblimersen-dacarbazine group. On the basis of these results, a phase III trial (AGENDA trial) has evaluated dacarbazine with or without Genasense in Advanced Melanoma with low LDH level. The initial results showed no impact of the addition of oblimersen to chemotherapy on OS or PFS, but a more mature analysis with longer follow-up is awaited (Genta 2009).

After many years of little or no improvement in outcomes for patients with melanoma, the tides are changing with 2 new agents, either licensed or about to be, showing significant activity in advanced disease. The results of 3 large randomised adjuvant studies will also report in the next few years, hopefully also improving the treatment options for high risk patients. The management algorithm is being rewritten, but is generating more questions than answers. We have little understanding of resistance mechanisms, optimum scheduling, use in combination, long term toxicities etc – these will be the questions addressed in trials over the next 5 years.

Five years ago, we could only have dreamed of being in the position to have to consider these issues. The paradigm of basic scientific research discoveries being explored further in translational studies, then validated in rigorous clinical trials is exemplified by the progress achieved melanoma treatment.

6. References

- Bedikian, A. Y., M. Millward, H. Pehamberger, R. Conry, M. Gore, U. Trefzer, A. C. Pavlick, R. DeConti, E. M. Hersh, P. Hersey, J. M. Kirkwood, and F. G. Haluska. 2006. "Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group." *J Clin Oncol* no. 24 (29):4738-45.

- Bottomley, A., C. Coens, S. Suci, M. Santinami, W. Kruit, A. Testori, J. Marsden, C. Punt, F. Sales, M. Gore, R. Mackie, Z. Kusic, R. Dummer, P. Patel, D. Schadendorf, A. Spatz, U. Keilholz, and A. Eggermont. 2009. "Adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma: a phase III randomized controlled trial of health-related quality of life and symptoms by the European Organisation for Research and Treatment of Cancer Melanoma Group." *J Clin Oncol* no. 27 (18):2916-23.
- Bouwhuis, M. G., S. Suci, S. Collette, S. Aamdal, W. H. Kruit, L. Bastholt, U. Stierner, F. Sales, P. Patel, C. J. Punt, M. Hernberg, A. Spatz, T. L. ten Hagen, J. Hansson, and A. M. Eggermont. 2009. "Autoimmune antibodies and recurrence-free interval in melanoma patients treated with adjuvant interferon." *J Natl Cancer Inst* no. 101 (12):869-77.
- Buzaid A, Legha S, Winn R. 1993. "Cisplatin (C) vinblastine (V), and dacarbazine (D) (CVD) versus dacarbazine alone in metastatic melanoma: preliminary results of a phase III Cancer Community Oncology program (CCOP) trial." *Proc Am Soc Clin Onco* no. 12:389.
- Cameron, D. A., M. C. Cornbleet, R. M. Mackie, J. A. Hunter, M. Gore, B. Hancock, and J. F. Smyth. 2001. "Adjuvant interferon alpha 2b in high risk melanoma - the Scottish study." *Br J Cancer* no. 84 (9):1146-9.
- Chang, P., and W. H. Knapper. 1982. "Metastatic melanoma of unknown primary." *Cancer* no. 49 (6):1106-11.
- Chapman, P. B., L. H. Einhorn, M. L. Meyers, S. Saxman, A. N. Destro, K. S. Panageas, C. B. Begg, S. S. Agarwala, L. M. Schuchter, M. S. Ernstoff, A. N. Houghton, and J. M. Kirkwood. 1999. "Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma." *J Clin Oncol* no. 17 (9):2745-51.
- Crews, C. M., A. Alessandrini, and R. L. Erikson. 1992. "The primary structure of MEK, a protein kinase that phosphorylates the ERK gene product." *Science* no. 258 (5081):478-80.
- Curtin, J. A., K. Busam, D. Pinkel, and B. C. Bastian. 2006. "Somatic activation of KIT in distinct subtypes of melanoma." *J Clin Oncol* no. 24 (26):4340-6.
- Curtin, J. A., J. Fridlyand, T. Kageshita, H. N. Patel, K. J. Busam, H. Kutzner, K. H. Cho, S. Aiba, E. B. Brocker, P. E. LeBoit, D. Pinkel, and B. C. Bastian. 2005. "Distinct sets of genetic alterations in melanoma." *N Engl J Med* no. 353 (20):2135-47.
- Davies, H., G. R. Bignell, C. Cox, P. Stephens, S. Edkins, S. Clegg, J. Teague, H. Woffendin, M. J. Garnett, W. Bottomley, N. Davis, E. Dicks, R. Ewing, Y. Floyd, K. Gray, S. Hall, R. Hawes, J. Hughes, V. Kosmidou, A. Menzies, C. Mould, A. Parker, C. Stevens, S. Watt, S. Hooper, R. Wilson, H. Jayatilake, B. A. Gusterson, C. Cooper, J. Shipley, D. Hargrave, K. Pritchard-Jones, N. Maitland, G. Chenevix-Trench, G. J. Riggins, D. D. Bigner, G. Palmieri, A. Cossu, A. Flanagan, A. Nicholson, J. W. Ho, S. Y. Leung, S. T. Yuen, B. L. Weber, H. F. Seigler, T. L. Darrow, H. Paterson, R. Marais, C. J. Marshall, R. Wooster, M. R. Stratton, and P. A. Futreal. 2002. "Mutations of the BRAF gene in human cancer." *Nature* no. 417 (6892):949-54. doi: 10.1038/nature00766 nature00766 [pii].
- Dudley, M. E., J. C. Yang, R. Sherry, M. S. Hughes, R. Royal, U. Kammula, P. F. Robbins, J. Huang, D. E. Citrin, S. F. Leitman, J. Wunderlich, N. P. Restifo, A. Thomasian, S. G.

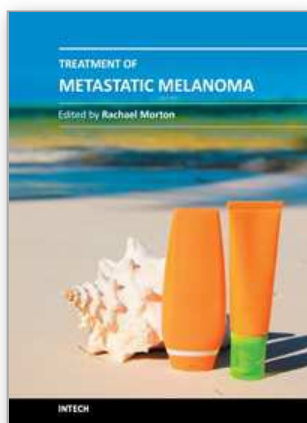
- Downey, F. O. Smith, J. Klapper, K. Morton, C. Laurencot, D. E. White, and S. A. Rosenberg. 2008. "Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens." *J Clin Oncol* no. 26 (32):5233-9.
- Dummer, R., O. Michielin, B. Seifert, A. F. Ochsenbein, R. Cathomas, M. R. Schlaepfli, M. Simcock, S. Gillessen, S. M. Goldinger, R. von Moos, and Swiss Group for Clinical Cancer Research 2010. "First-line temozolomide (TEM) combined with bevacizumab (BEV) in metastatic melanoma (MM): A multicenter phase II trial (SAKK 50/07)." *ASCO Meeting Abstracts* no. 28 (15_suppl):8521.
- Dummer, R., C. Robert, P. B. Chapman, J. A. Sosman, M. Middleton, L. Bastholt, K. Kemsley, M. V. Cantarini, C. Morris, and J. M. Kirkwood. 2008. "AZD6244 (ARRY-142886) vs temozolomide (TMZ) in patients (pts) with advanced melanoma: An open-label, randomized, multicenter, phase II study." *ASCO Meeting Abstracts* no. 26 (15_suppl):9033.
- Eggermont, A. M., S. Suci, R. MacKie, W. Ruka, A. Testori, W. Kruit, C. J. Punt, M. Delauney, F. Sales, G. Groenewegen, D. J. Ruiter, I. Jagiello, K. Stoitchkov, U. Keilholz, and D. Lienard. 2005. "Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomised controlled trial." *Lancet* no. 366 (9492):1189-96.
- Eggermont, A. M., S. Suci, M. Santinami, A. Testori, W. H. Kruit, J. Marsden, C. J. Punt, F. Sales, M. Gore, R. Mackie, Z. Kusic, R. Dummer, A. Hauschild, E. Musat, A. Spatz, and U. Keilholz. 2008. "Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial." *Lancet* no. 372 (9633):117-26.
- Eggermont, A., S. Suci, A. Testori, P. Patel, A. Spatz. 2009. "Ulceration of primary melanoma and responsiveness to adjuvant interferon therapy: Analysis of the adjuvant trials EORTC18952 and EORTC18991 in 2,644 patients." *J Clin Oncol* no. 27:15s (suppl; abstr 9007).
- Eisen, T., T. Ahmad, K. T. Flaherty, M. Gore, S. Kaye, R. Marais, I. Gibbens, S. Hackett, M. James, L. M. Schuchter, K. L. Nathanson, C. Xia, R. Simantov, B. Schwartz, M. Poulin-Costello, P. J. O'Dwyer, and M. J. Ratain. 2006. "Sorafenib in advanced melanoma: a Phase II randomised discontinuation trial analysis." *Br J Cancer* no. 95 (5):581-6.
- Flaherty, K. T., S. J. Lee, L. M. Schuchter, L. E. Flaherty, J. J. Wright, P. D. Leming, and J. M. Kirkwood. 2010. "Final results of E2603: A double-blind, randomized phase III trial comparing carboplatin (C)/paclitaxel (P) with or without sorafenib (S) in metastatic melanoma." *ASCO Meeting Abstracts* no. 28 (15_suppl):8511.
- Flaherty, K. T., I. Puzanov, K. B. Kim, A. Ribas, G. A. McArthur, J. A. Sosman, P. J. O'Dwyer, R. J. Lee, J. F. Grippo, K. Nolop, and P. B. Chapman. 2010. "Inhibition of mutated, activated BRAF in metastatic melanoma." *N Engl J Med* no. 363 (9):809-19.
- Garbe, C., P. Radny, R. Linse, R. Dummer, R. Gutzmer, J. Ulrich, R. Stadler, M. Weichenthal, T. Eigentler, U. Ellwanger, and A. Hauschild. 2008. "Adjuvant low-dose interferon {alpha}2a with or without dacarbazine compared with surgery alone: a prospective-randomized phase III DeCOG trial in melanoma patients with regional lymph node metastasis." *Ann Oncol* no. 19 (6):1195-201.

- Genta. 2009. New Publication Confirms Critical Link of LDH Biomarker in Genasense® Trials to Overall Survival in Advanced Melanoma, http://www.genta.com/Press_Releases/2009/New_Publication_Confirms_Critical_Link_of_LDH_Biomarker_in_Genasense®_Trials_to_Overall_Survival_in_Advanced_Melanoma.html.
- Gogas, H., J. Ioannovich, U. Dafni, C. Stavropoulou-Giokas, K. Frangia, D. Tsoutsos, P. Panagiotou, A. Polyzos, O. Papadopoulos, A. Stratigos, C. Markopoulos, D. Bafaloukos, D. Pectasides, G. Fountzilias, and J. M. Kirkwood. 2006. "Prognostic significance of autoimmunity during treatment of melanoma with interferon." *N Engl J Med* no. 354 (7):709-18.
- Haass, N. K., K. Sproesser, T. K. Nguyen, R. Contractor, C. A. Medina, K. L. Nathanson, M. Herlyn, and K. S. Smalley. 2008. "The mitogen-activated protein/extracellular signal-regulated kinase kinase inhibitor AZD6244 (ARRY-142886) induces growth arrest in melanoma cells and tumor regression when combined with docetaxel." *Clin Cancer Res* no. 14 (1):230-9.
- Hauschild, A., S. S. Agarwala, U. Trefzer, D. Hogg, C. Robert, P. Hersey, A. Eggermont, S. Grabbe, R. Gonzalez, J. Gille, C. Peschel, D. Schadendorf, C. Garbe, S. O'Day, A. Daud, J. M. White, C. Xia, K. Patel, J. M. Kirkwood, and U. Keilholz. 2009. "Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma." *J Clin Oncol* no. 27 (17):2823-30.
- Hodi, F. S., S. J. O'Day, D. F. McDermott, R. W. Weber, J. A. Sosman, J. B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J. C. Hassel, W. Akerley, A. J. van den Eertwegh, J. Lutzky, P. Lorigan, J. M. Vaubel, G. P. Linette, D. Hogg, C. H. Ottensmeier, C. Lebbe, C. Peschel, I. Quirt, J. I. Clark, J. D. Wolchok, J. S. Weber, J. Tian, M. J. Yellin, G. M. Nichol, A. Hoos, and W. J. Urban. 2010. "Improved survival with ipilimumab in patients with metastatic melanoma." *N Engl J Med* no. 363 (8):711-23.
- Infante, J.R., L. A. Fecher, S. Nallapareddy, M. S. Gordon, K. T. Flaherty, D. S. Cox, D. J. DeMarini, S. R. Morris, H. A. Burris, W. A. Messersmith; Sarah Cannon 2010. "Safety and efficacy results from the first-in-human study of the oral MEK 1/2 inhibitor GSK1120212." *J Clin Oncol* no. 28 (suppl; abstr 2503).
- Ives, N. J., R. L. Stowe, P. Lorigan, and K. Wheatley. 2007. "Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients." *J Clin Oncol* no. 25 (34):5426-34.
- Kefford, R., H. Arkenau, M. P. Brown, M. Millward, J. R. Infante, G. V. Long, D. Ouellet, M. Curtis, P. F. Lebowitz, and G. S. Falchook. 2010. "Phase I/II study of GSK2118436, a selective inhibitor of oncogenic mutant BRAF kinase, in patients with metastatic melanoma and other solid tumors." *ASCO Meeting Abstracts* no. 28 (15_suppl):8503.
- Kirkwood, J. M., J. G. Ibrahim, J. A. Sosman, V. K. Sondak, S. S. Agarwala, M. S. Ernstoff, and U. Rao. 2001. "High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801." *J Clin Oncol* no. 19 (9):2370-80.
- Kirkwood, J. M., P. Lorigan, P. Hersey, A. Hauschild, C. Robert, D. McDermott, M. A. Marshall, J. Gomez-Navarro, J. Q. Liang, and C. A. Bulanhagui. 2010. "Phase II trial

- of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma." *Clin Cancer Res* no. 16 (3):1042-8.
- Kirkwood, J. M., M. H. Strawderman, M. S. Ernstoff, T. J. Smith, E. C. Borden, and R. H. Blum. 1996. "Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684." *J Clin Oncol* no. 14 (1):7-17.
- Klasa, R. J., A. M. Gillum, R. E. Klem, and S. R. Frankel. 2002. "Oblimersen Bcl-2 antisense: facilitating apoptosis in anticancer treatment." *Antisense Nucleic Acid Drug Dev* no. 12 (3):193-213.
- Kruit, W. H., S. Suci, B. Dreno, V. Chiarion-Sileni, L. Mortier, C. Robert, M. Maio, V. G. Brichard, F. Lehmann, and U. Keilholz. 2008. "Immunization with recombinant MAGE-A3 protein combined with adjuvant systems AS15 or AS02B in patients with unresectable and progressive metastatic cutaneous melanoma: A randomized open-label phase II study of the EORTC Melanoma Group (16032- 18031)." *ASCO Meeting Abstracts* no. 26 (15_suppl):9065.
- Lattanzi, S. C., T. Tosteson, J. Chertoff, L. H. Maurer, J. O'Donnell, P. J. LeMarbre, L. Mott, S. A. DelPrete, R. J. Forcier, and M. S. Ernstoff. 1995. "Dacarbazine, cisplatin and carmustine, with or without tamoxifen, for metastatic melanoma: 5-year follow-up." *Melanoma Res* no. 5 (5):365-9.
- Lee, C. C., M. B. Faries, L. A. Wanek, and D. L. Morton. 2008. "Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma." *J Clin Oncol* no. 26 (4):535-41.
- Legha, S. S., S. Ring, N. Papadopoulos, C. Plager, S. Chawla, and R. Benjamin. 1989. "A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma." *Cancer* no. 64 (10):2024-9.
- Lev, D. C., A. Onn, V. O. Melinkova, C. Miller, V. Stone, M. Ruiz, E. C. McGary, H. N. Ananthaswamy, J. E. Price, and M. Bar-Eli. 2004. "Exposure of melanoma cells to dacarbazine results in enhanced tumor growth and metastasis in vivo." *J Clin Oncol* no. 22 (11):2092-100.
- Marshall, M. A., A. Ribas, and B. Huang. 2010. "Evaluation of baseline serum C-reactive protein (CRP) and benefit from tremelimumab compared to chemotherapy in first-line melanoma." *ASCO Meeting Abstracts* no. 28 (15_suppl):2609.
- McDermott, D. F., J. A. Sosman, R. Gonzalez, F. S. Hodi, G. P. Linette, J. Richards, J. W. Jakub, M. Beeram, S. Tarantolo, S. Agarwala, G. Frenette, I. Puzanov, L. Cranmer, K. Lewis, J. Kirkwood, J. M. White, C. Xia, K. Patel, and E. Hersh. 2008. "Double-blind randomized phase II study of the combination of sorafenib and dacarbazine in patients with advanced melanoma: a report from the 11715 Study Group." *J Clin Oncol* no. 26 (13):2178-85.
- Middleton, M. R., J. J. Grob, N. Aaronson, G. Fierlbeck, W. Tilgen, S. Seiter, M. Gore, S. Aamdal, J. Cebon, A. Coates, B. Dreno, M. Henz, D. Schadendorf, A. Kapp, J. Weiss, U. Fraass, P. Statkevich, M. Muller, and N. Thatcher. 2000. "Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma." *J Clin Oncol* no. 18 (1):158-66.
- Mocellin, S., S. Pasquali, C. R. Rossi, and D. Nitti. 2010. "Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis." *J Natl Cancer Inst* no. 102 (7):493-501.

- O'Day, S. J., M. Maio, V. Chiarion-Sileni, T. F. Gajewski, H. Pehamberger, I. N. Bondarenko, P. Queirolo, L. Lundgren, S. Mikhailov, L. Roman, C. Verschraegen, R. Humphrey, R. Ibrahim, V. de Pril, A. Hoos, and J. D. Wolchok. 2010. "Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: a multicenter single-arm phase II study." *Ann Oncol* no. 21 (8):1712-7.
- O'Day, S.J., J.A. Sosman, and A.C. Peterson. 2009. "BEAM: A randomized phase II study evaluating the activity of Bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated Advanced Melanoma." *Eur J Cancer Supplements* no. 7 (3):13.
- Patel P, S. S., Mortier L. 2008. Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV malignant melanoma: Final results of the randomised phase III study EORTC 18032. Paper read at 33rd European Society of Medical Oncology (ESMO) Congress.
- Perez, D. G., V. J. Suman, T. R. Fitch, T. Amatruda, 3rd, R. F. Morton, S. Z. Jilani, C. L. Constantinou, J. R. Egner, L. A. Kottschade, and S. N. Markovic. 2009. "Phase 2 trial of carboplatin, weekly paclitaxel, and biweekly bevacizumab in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group study, N047A." *Cancer* no. 115 (1):119-27.
- Ribas, A., A. Hauschild, R. Kefford, J. Gomez-Navarro, D. Pavlov, and M. A. Marshall. 2008. "Phase III, open-label, randomized, comparative study of tremelimumab (CP-675,206) and chemotherapy (temozolomide [TMZ] or dacarbazine [DTIC]) in patients with advanced melanoma." *ASCO Meeting Abstracts* no. 26 (15_suppl):LBA9011.
- Roche. 2011. Roche Media Release "Roche Personalised investigational medicine shows survival benefit in advanced skin cancer." http://www.roche.com/media/media_releases/med-cor-2011-01-19.htm
- Rosen, L. B., D. D. Ginty, M. J. Weber, and M. E. Greenberg. 1994. "Membrane depolarization and calcium influx stimulate MEK and MAP kinase via activation of Ras." *Neuron* no. 12 (6):1207-21.
- Schwartzentruber, D. J., D. Lawson, J. Richards, R. M. Conry, D. Miller, J. Triesman, F. Gailani, L. B. Riley, D. Vena, and P. Hwu. 2009. "A phase III multi-institutional randomized study of immunization with the gp100: 209-217(210M) peptide followed by high-dose IL-2 compared with high-dose IL-2 alone in patients with metastatic melanoma." *ASCO Meeting Abstracts* no. 27 (18S):CRA9011.
- Smalley, K. S. 2003. "A pivotal role for ERK in the oncogenic behaviour of malignant melanoma?" *Int J Cancer* no. 104 (5):527-32.
- Soengas, M. S., and S. W. Lowe. 2003. "Apoptosis and melanoma chemoresistance." *Oncogene* no. 22 (20):3138-51.
- Sosman, J., K. Kim, L. Schuchter, R. Gonzalez, A. Pavlick, J. Weber, G.T. McArthur 2010. An open-label, multicentre phase 2 study of continuous oral dosing of RG7204 (PLX4032) in previously treated patients with BRAF V600E mutation- positive metastatic melanoma. Paper read at The Seventh International Melanoma Research Congress of the Society for Melanoma Research at Sydney Australia.
- Ugurel, S., G. Rapp, W. Tilgen, and U. Reinhold. 2001. "Increased serum concentration of angiogenic factors in malignant melanoma patients correlates with tumor progression and survival." *J Clin Oncol* no. 19 (2):577-83.

- Weber, J., J. A. Thompson, O. Hamid, D. Minor, A. Amin, I. Ron, R. Ridolfi, H. Assi, A. Maraveyas, D. Berman, J. Siegel, and S. J. O'Day. 2009. "A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma." *Clin Cancer Res* no. 15 (17):5591-8.
- Wheatley, K. , N. Ives, A. Eggermont, J. Kirkwood, N. Cascinelli, S. N. Markovic, B. Hancock, S. Lee, S. Suci. 2007. "Interferon- as adjuvant therapy for melanoma: An individual patient data meta-analysis of randomised trials." *J Clin Oncol (Meeting Abstracts)* no. 25:18s (June 20 suppl; abstr 8526).
- Wheatley, K., N. Ives, B. Hancock, M. Gore, A. Eggermont, and S. Suci. 2003. "Does adjuvant interferon-alpha for high-risk melanoma provide a worthwhile benefit? A meta-analysis of the randomised trials." *Cancer Treat Rev* no. 29 (4):241-52.
- Wolchok, J. D., A. Hoos, S. O'Day, J. S. Weber, O. Hamid, C. Lebbe, M. Maio, M. Binder, O. Bohnsack, G. Nichol, R. Humphrey, and F. S. Hodi. 2009. "Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria." *Clin Cancer Res* no. 15 (23):7412-20.
- Wolchok, J. D., B. Neyns, G. Linette, S. Negrier, J. Lutzky, L. Thomas, W. Waterfield, D. Schadendorf, M. Smylie, T. Guthrie, Jr., J. J. Grob, J. Chesney, K. Chin, K. Chen, A. Hoos, S. J. O'Day, and C. Lebbe. 2010. "Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study." *Lancet Oncol* no. 11 (2):155-64.



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Surgery continues to be the mainstay treatment for melanoma localized to the primary tumor and/or lymph nodes. Results from randomized controlled trials indicate that sentinel node biopsy for the treatment of cutaneous melanoma of intermediate thickness has a beneficial effect on recurrence rates, and adjuvant radiotherapy to regional lymph node fields following surgical resection reduces loco-regional recurrence in patients at high risk of relapse. Isolated limb perfusion, electrochemotherapy, and photodynamic therapy continue to be evaluated for treatment of stage IV disease. However, the greatest excitement in new treatment has been with targeted therapies for genetic mutations. In particular, the promising results of partial and complete tumor response in stage IV disease from early phase trials of the B-RAF kinase inhibitors. This book provides a contemporary insight into the therapeutic treatment options for patients with metastatic melanoma and is relevant to clinicians and researchers worldwide. In addition, an update on current clinical trials for melanoma treatment has been included, and two chapters have been reserved to discuss the treatment of oral and uveal melanoma.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821