LEADING ARTICLE

Drugs 2005; 65 (6): 733-743
0012-6667/05/0006-0733/$39.95/0

Improving Outcomes in Advanced Malignant Melanoma

Update on Systemic Therapy

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Abstract

Malignant melanoma continues to increase in incidence throughout the developed world. Surgery remains the cornerstone of curative treatment and the use of adjuvant systemic therapy has provoked much debate. Metastatic disease is incurable in most patients. While combination chemotherapy or biochemotherapy may be considered in certain circumstances, it is now clear that single-agent chemotherapy remains the mainstay of treatment for the majority of patients.

A number of new agents and novel approaches are under evaluation and show promise. The pro-apoptotic agent oblimersen has shown improved progression-free survival and response rate, although not overall survival, when combined with dacarbazine compared with dacarbazine alone. The BRaf inhibitor sorafenib (BAY 43-9006) has produced encouraging results when administered with chemotherapy and is now being assessed in randomised studies. Thalidomide in combination with chemotherapy is well tolerated and shows a trend towards increased clinical efficacy compared with chemotherapy alone. Other anti-angiogenic drugs, such as bevacizumab, are being investigated in trials. Results with tumour vaccines have been mixed and several large trials are ongoing.

This paper discusses recent pivotal studies and promising new agents in systemic therapy for advanced malignant melanoma.

Malignant melanoma is increasing in incidence in the US, Europe and Australia.[1-4] Surgery remains the cornerstone of treatment for patients with loco-regional disease. However, while a few patients with advanced disease may be cured by surgery, the majority of patients die of their disease.[5,6] In the last 2 years, a number of pivotal randomised trials of newer strategies have been reported. None of these has shown any significant improvement in survival over conventional chemotherapy. However, in the same time frame, a number of new drugs have been developed and entered early phase clinical trials. Many of these are not conventional chemotherapy agents; rather, they target areas outside the cell nucleus. In this review we discuss the lessons learned over the last few years and the most promising new drugs in the treatment of melanoma in 2004/5.

1. Chemotherapy

1.1 Single-Agent Chemotherapy, Combination Chemotherapy or Biochemotherapy?

To date, there has never been a randomised trial comparing chemotherapy with placebo or best sup-

portive care in this patient group. Nevertheless, single-agent dacarbazine has been the standard of care for many years. Response rates of 7–13% have been reported in recent large phase III trials, with a further 15–28% of patients having stable disease.[7,8] However, few responses are longstanding. It is uncertain whether stable disease is a clinically meaningful outcome and there is no good evidence that it is associated with a survival advantage, although conceivably it may correlate with symptom control. Other agents that are active in melanoma include the platinum analogues, vinca alkaloids, nitrosoureas and taxanes; none of these has a higher response rate than dacarbazine.[9]

A number of randomised trials have failed to show a survival advantage for combination therapy over single-agent treatment.[10-12] Combination therapy is associated with an increased response rate, but also significantly increased toxicity resulting in increased numbers of hospital admissions.

Immunotherapy continues to be evaluated in metastatic disease. Response rates of 15% have been reported for interferon (IFN)-α 2b in advanced disease.[13] Response rates for low-dose interleukin (IL)-2 are just 2–3%, but a large proportion of patients have stable disease.[14] High-dose IL-2 has single-agent activity in melanoma with a response rate of 16%. Of particular interest is the fact that 6% of patients achieved a complete response and over half of those remained disease-free at >2 years.[15] However, toxicity with high-dose IL-2 is considerable and has limited the use of this approach to highly selected patients being treated in specialist centres with experience in this area.[16]

Biochemotherapy has been used in the treatment of melanoma for 2 decades. Improvements in response rate, disease-free and overall survival were initially reported.[17] A meta-analysis of five trials comparing single-agent dacarbazine with dacarbazine plus IFN demonstrated a 53% increase in tumour response rate for combination therapy and a nonsignificant trend towards an improvement in overall survival.[18] Kielholz et al.[19] reported 631 patients treated with high-dose IL-2 alone, or in combination with IFN and/or chemotherapy. In this trial, combination biological therapy was superior to IL-2 alone, with no further benefit from adding dacarbazine. Finally, an overview presented at the American Society of Clinical Oncology Annual Meeting in 2003[20] took account of data from three randomised trials of combination therapy versus biochemotherapy presented at that meeting.[21-23] The overview concluded that biochemotherapy does not prolong survival, but may improve time to progression and response rate; however, it is associated with more toxicity and expense, and cannot yet be seen as a standard of care.

The conclusion from these trials is that, for the majority of patients with advanced malignant melanoma requiring systemic therapy, single-agent treatment remains the treatment of choice. However, combination therapy may be warranted in certain circumstances, such as when significant tumour shrinkage is a primary aim.

1.2 Newer Chemotherapy Drugs

Temozolomide is an imidazotetrazine with a mechanism of action similar to dacarbazine. The lead imidazotetrazine was mitozolomide, which showed anticancer activity in tumour model systems. Unlike dacarbazine, which requires metabolic activation, temozolomide is an oral alkylating agent that is spontaneously converted to its active intermediary. A phase I study of temozolomide demonstrated clinical activity in 4 of 23 patients with melanoma[24] and a subsequent phase II trial in patients with progressive melanoma reported a 21% response rate with responders living for 9 months longer than non-responders.[25]

A large phase III randomised control trial of a 3-week cycle of intravenous dacarbazine 250 mg/m^2 on days 1–5 versus a 4-week cycle of oral temozolomide 200 mg/m^2 on days 1–5 as first-line treatment in patients with melanoma demonstrated equivalence for survival, response rate and toxicity, with a trend towards temozolomide being superior for progression free survival and certain quality-of-life domains.[7] As a result of this equivalent outcome there is extensive off-license use for this indication, al-

though temozolomide did not receive a license in advanced melanoma.

The optimum dose and schedule of temozolomide have not yet been defined. We now know that an extended schedule may reduce the effects of DNA repair mechanisms, especially those mediated by O^6-methylguanine-DNA-methyltransferase (MGMT), and so maximise the effects of temozolomide treatment.[26] Long-term, low-dose administration (75 mg/m^2/day for 6 weeks, repeated every 8 weeks) is associated with significant activity and is well tolerated but appears to cause selective CD4+ lymphopenia and an increased risk of opportunistic infection.[27] A randomised phase III trial of extended-schedule temozolomide and dacarbazine is planned by the European Organisation for Research and Treatment of Cancer (EORTC).

Temozolomide may have better blood-brain barrier penetration than dacarbazine and is licensed in Europe, the US and elsewhere for the treatment of refractory high-grade gliomas.[28] The combination of temozolomide and radiotherapy has proven feasible in patients with primary brain tumours.[29,30] Superior CNS penetration is also of particular interest in metastatic melanoma as brain metastases are a common cause of treatment failure.[31] In a retrospective study of 40 patients with melanoma, 2 of 19 patients treated with temozolomide and 8 of 21 receiving dacarbazine subsequently developed brain metastases ($p = 0.0167$).[31] A recently published phase II trial[32] was conducted to assess the effect of temozolomide on brain metastases in patients with malignant melanoma who did not require immediate radiotherapy. Temozolomide 150–200 mg/m^2 for 5 days every 28 days was given to 151 patients. In those patients who were chemotherapy naive, 7% had an objective response, 29% had stable disease and the median survival was 3.5 months. Of the patients who had previously had chemotherapy, 3% (one patient) had a clinical response, 18% of disease was stabilised and the median survival was 2.2 months. Temozolomide clearly has activity in this setting. Evaluation of temozolomide in combination with radiotherapy and with other new drugs is ongoing.

Fotemustine is a chloroethyl nitrosurea which may have a greater ability to cross the blood-brain barrier and induce responses in brain metastases than dacarbazine.[33] A randomised phase III trial of fotemustine versus dacarbazine in 229 patients suggested a nonsignificant trend in terms of overall survival (7.3 vs 5.6 months, $p = 0.067$), response rate (15.2% vs 6.8%, $p = 0.043$) and time to development of brain metastases (22.7 vs 7.2 months, $p = 0.059$) in favour of fotemustine, with no increase in toxicity and no detrimental effect on quality of life.[34]

2. Novel Treatment Approaches

2.1 Drug Resistance Modifiers

Temozolomide exerts its anticancer activity through the methylation of DNA at the O^6 position of guanine residues. The DNA repair protein MGMT is known to be important in tumour resistance to temozolomide. Lomeguatrib [O^6-(4-bromothenyl)guanine][35] and benzylguanine (O^6-benzylguanine)[36] act as pseudosubstrates that exhibit a greater affinity for the active binding site of MGMT than O^6-methylguanine. Pretreatment with either of these agents may reduce resistance to and/or raise the therapeutic index of temozolomide. Both agents are in clinical trials at the present time. In addition, inhibition of poly(adenosine diphosphate-ribose) polymerase DNA repair mechanisms may also sensitise tumours to the effects of temozolomide. This phenomenon has recently been demonstrated in xenograft models[37] and agents directed against this mechanism are also undergoing clinical evaluation.

2.2 Pro-Apoptotic Agents

Oblimersen is an antisense agent targeted to mitochondrial bcl-2. Updated results from a randomised phase III trial[8] comparing dacarbazine combined with oblimersen against dacarbazine alone in 771 patients showed improved progression-free survival of 74 versus 49 days ($p = 0.0003$) and response rates of 13% versus 7% ($p = 0.006$) but no statistical difference in overall survival (9.1 and 8.1 months, respectively). Difficulties with study design made

these results difficult to interpret. There were more long-term survivors in the combination arm and it has been suggested that updated analyses of survival may yield a positive result with increased follow-up.

The inhibitor of apoptosis (IAP) family includes eight family proteins. One of these, X-linked IAP (XIAP), blocks both the endogenous (mitochondrial) and exogenous (death receptor-related) apoptosis pathways and an antisense oligonucleotide directed at XIAP is in clinical evaluation at present.[38] Another apoptosis-directed strategy is to use the proteasome inhibitor, bortezomib which both induces apoptosis and abrogates angiogenesis in human melanoma xenografts, as well as sensitising tumours to temozolomide.[39]

2.3 Anti-Angiogenic Agents

Tumour cells express endothelial markers that do not respond to normal angiogenic control. They recruit other tumour cells by the production of growth factors into the stroma. Melanoma metastases tend to be very vascular and melanoma is a possible candidate for anti-angiogenic therapy.

Thalidomide has anti-angiogenic and immunomodulatory properties, and has been used successfully in the treatment of Kaposi's sarcoma, myeloma and renal cell cancer.[40] The main toxicities are dose-dependent neuropathy, constipation and skin rash. Recent trials in melanoma that added thalidomide to temozolomide have reported a trend towards superior response rates and survival when this combination is compared with temozolomide monotherapy.[41,42] Temozolomide monotherapy was compared with temozolomide-IFN and temozolomide-thalidomide (thalidomide 100 mg/day). Both combination arms showed a trend towards superiority for response rates and overall survival (overall response rates of 9%, 18% and 15% with median survivals of 5.3, 7.7 and 7.3 months for temozolomide monotherapy, temozolomide-IFN and temozolomide-thalidomide, respectively). Grade III/IV myelosuppression was significantly higher in the temozolomide alone and temozolomide-IFN arms than the temozolomide-thalidomide arm. Thus, on the basis of a trend towards improved efficacy with no increase in toxicity, temozolomide-thalidomide was recommended for further study. Hwu et al.[42] treated patients with an extended temozolomide schedule of 75 mg/m^2/day for 6 weeks, followed by a 2-week rest period, and thalidomide up to 400 mg/day. Twelve of 38 patients had a clinical response and the median survival was 9.5 months. The regimen was reasonably well tolerated but 18% of patients required dose reductions or delays because of thalidomide toxicity, reflecting the higher dose of thalidomide used.

Lenalidomide (CC 5013) is a potent analogue of thalidomide that produces T-cell stimulation and has shown single-agent activity in melanoma.[43,44] A large phase III trial of lenalidomide versus placebo as second-line therapy in advanced melanoma has just completed accrual and was stopped in April 2004 on the advice of the Data Monitoring Committee because of inactivity of the study drug in this setting. A first-line study of temozolomide ± lenalidomide is under consideration.

The integrin αVβ3 is up-regulated by a number of growth factors, including vascular endothelial growth factor (VEGF) and β-fibroblast growth factor, and is expressed on a number of tumour cells, including melanoma cells, angiogenic endothelial cells and mature osteoclasts. αVβ3 is involved in angiogenesis, growth and motility, and possibly tumour-induced osteoclastic activity. MEDI-522 is a humanised monoclonal antibody to αVβ3 integrin.[45] A randomised phase II trial of dacarbazine ± MEDI-522 has completed accrual and the results are awaited.

Semaxanib (SU5416) is a selective inhibitor of VEGF receptor-2 (VEFGR-2) and kit receptor tyrosine kinase. A recent phase II study of 31 patients with melanoma showed it to be well tolerated and reported two partial responses.[46] However, significant lymphopenia was described.

Bevacizumab is a monoclonal antibody against VEGF that has shown a significant survival advantage when combined with chemotherapy in advanced colorectal cancer (median survival of 20.3 months with the combination versus 15.6 months with chemotherapy alone, $p < 0.001$).[47] A phase II

trial in melanoma is ongoing and preliminary results described minimal toxicity with tumour responses.[48]

2.4 B-Raf Inhibitors

Raf kinases are serine/threonine protein kinases that function in the Raf/MEK/ERK pathway and are regulated by Ras. The Raf kinase family is composed of three members: ARaf, BRaf and Raf-1 (CRaf). Somatic mutations in the *braf* gene have been reported in 65% of melanomas and, at lower frequencies, in a wide range of human cancers.[49] The V599E mutant form of BRaf activates the Raf/MEK/ERK pathway in human melanoma cells *in vitro*, which leads to cellular proliferation. Casula et al.[50] recently reported that *braf* mutations do not appear to make a big contribution to melanoma susceptibility, that is, very few germ line mutations occur. However, it has been noted that *braf* mutations are more common in melanomas on intermittently exposed skin than elsewhere, but not on chronically exposed skin. This finding suggests that distinct pathways lead to melanoma in different situations.[51] Small-molecule BRaf inhibitors have shown knockdown of BRaf expression causing growth arrest and promoting apoptosis *in vitro* and regression of established pulmonary metastases *in vivo*.[52,53]

Sorafenib (BAY 43-9006) is an orally active small molecule inhibitor of Raf-1, VEGFR-2, wild-type BRaf and the V599E mutant, in addition to a number of other pro-angiogenic receptor tyrosine kinases.[54] Sorafenib is currently in phase I/II trials in a variety of solid tumours, including some that do not have BRaf mutations. Sorafenib has modest activity as a single agent in the treatment of advanced melanoma.[55] A phase II trial of sorafenib combined with carboplatin and paclitaxel in 35 patients with advanced melanoma with predominantly M1c disease (68%), the majority of whom had received previous treatment, reported a response rate of 31%.[56] Randomised phase II studies looking at dacarbazine ± sorafenib and carboplatin plus paclitaxel ± sorafenib are ongoing.

2.5 Other Drugs

The epidermal growth factor receptor (EGFR) family is a complex system with significant inbuilt redundancy. EGFR inhibitors are now being used in the treatment of breast carcinoma and non-small-cell lung carcinoma. EGFR is expressed by both benign and malignant tissue, with increased protein expression in malignant melanoma.[57] There is a low incidence of Her2 over-expression in metastatic melanoma, therefore treatment with trastuzumab is unlikely to provide benefit in these patients.[58] There are no published trials of EGFR antagonists in melanoma.

Imatinib (STI 571) is a well tolerated c-kit tyrosine kinase inhibitor with activity in chronic myeloid leukaemia and gastrointestinal stromal tumours.[59,60] Although c-kit is expressed in more than half of early-stage malignant melanomas,[61] a lack of efficacy with imatinib was associated with significant unexpected toxicity in melanoma patients.[62] A phase II study of imatinib and bevacizumab combination therapy in advanced melanoma is ongoing.

A number of other new drugs are also under evaluation and details of these trials can be found on the National Cancer Institute (NCI) website (www.cancer.gov/search/clinicaltrials).[63]

3. Immune Modulation and Vaccines

3.1 Histamine

Histamine has been demonstrated to protect natural killer cells and T cells from monocyte-/macrophage-induced functional inhibition and apoptosis,[64] and to enhance the antitumour efficacy of IL-2.[65,66] A phase III trial[14] randomised patients with melanoma to histamine dihydrochloride combined with IL-2 versus IL-2 alone in patients with stage IV disease. There was a trend towards an improvement in median survival for the combination therapy (9.1 vs 8.2 months, p-value not significant). A planned subgroup analysis of patients with liver metastases showed a significant improvement in median survival for the IL-2/histamine dihydro-

chloride combination (9.4 vs 5.1 months, p = 0.008). However, a subsequent larger, prospective randomised phase III study comparing IL-2 plus histamine dihydrochloride against IL-2 alone in patients with liver metastases has recently completed accrual and has failed to demonstrate a survival advantage for the combination.[67] A randomised phase III trial comparing IL-2, IFN plus histamine dihydrochloride with standard dacarbazine chemotherapy in 241 patients with stage IV disease found that response rates were similar for both arms (dacarbazine 14%, combination 13%). Survival at 6 months was better for the biological therapy arm but this advantage was not seen at 24 months.[68] Once again, there was a suggestion that patients with liver metastases had an improved outcome with the cytokine combination.

3.2 Vaccines

The last 10 years have seen a dramatic improvement in our understanding of tumour immunology and the complexity therein. The use of vaccines in melanoma has appeared particularly appealing because of the expression of developmental and tumour-specific antigens on tumour tissue, response of patients with advanced disease to cytokine therapy, and lymphocytic infiltration of certain tumours. Vaccine strategies have targeted a number of parts of the immune system, many of which overlap. For ease of explanation, these strategies are set out in table I. The best chance of improving outcome will almost certainly come from use of a number of these in combination; however, the difficulties in evaluating vaccine strategies were recently reviewed.[69] A number of trials are ongoing, both in the adjuvant and the advanced setting. Detailed discussion of these is beyond the scope of this review and a list of ongoing trials can be found on the NCI website.[63] In this review we have concentrated on a representative sample of different approaches; some of these are early phase studies with biological rather than clinical endpoints.

Ganglioside vaccine (GM2) showed an improvement in relapse-free survival in the subset of patients who developed antibodies to the vaccine, when compared with Bacille Calmette-Guerin (BCG).[70] However, the large Intergroup study E1694 comparing GM2 with high-dose IFN in high-risk stage IIB/III patients did not show a clear benefit for the vaccine, although there was no placebo or untreated control arm in this study.[71] Both studies were in the adjuvant setting. A randomised controlled trial is currently being carried out in stage II patients by the EORTC. A number of studies have been carried out using peptide-based antigens (such as melanoma-associated antigen [MAGE], melan A, tyrosinase and glycoprotein [gp] 100) with or without an immune adjuvant (IL-2, granulocyte-macrophage col-

Table I. Vaccine strategies in melanoma

Vaccine
Peptide
developmental (melanoma-associated antigen [MAGE])
melanoma specific (tyrosinase, melan A, glycoprotein [gp]-100)
Ganglioside
Cell lysate
autologous (hsp-96)
cell line (melanoma vaccine Melacine)
Whole cells
autologous
cell lines (Cancervax)
Gene therapy based
peptide
cytokines
Adjuvants/immune modulators
Interleukin-2
Granulocyte-macrophage colony-stimulating factor
CpG motifs
Anti-cytotoxic T lymphocyte antigen-4 antibodies
Accessory cells
Dendritic cells
peptide pulsed
ex vivo expansion
Tumour-infiltrating lymphocytes
Others
Vaccine delivery
Intradermal
Subcutaneous
Intramuscular
Intravenous
Intranodal
Patient conditioning
Non-myeloablative chemotherapy

ony-stimulating factor [GM-CSF]).[72-74] Responses have been recorded in patients with advanced disease. Single peptides do not pose a large 'target' for the immune system. It is hoped that the use of multiple peptides, epitopes or proteins will generate multi-specific cytotoxic T lymphocytes (CTL). A recently completed study by ECOG using multi-epitope vaccine ± GM-CSF and IFNα-2b showed that an immune response to the tyrosinase epitopes appeared to correlate with progression-free survival.[75] Early studies with the cancer testis antigen NY-ESO-1 in protein form have been encouraging.[76] The melanoma vaccine Melacine is derived from the cell lysates of two human melanoma cell lines. A Southwest Oncology Group study[77] of melanoma vaccine Melacine as an adjuvant therapy in patients with intermediate thickness tumours (1.5–4mm) showed no advantage to the vaccine in terms of either relapse-free or overall survival. A confirmatory trial in patients with intermediate-risk melanoma has been approved but not yet begun.[69] Cancervax is a polyvalent allogeneic vaccine derived from three cell lines that has been shown to produce a survival advantage in advanced melanoma when compared with historical controls.[78,79] An international randomised study is currently ongoing. An autologous tumour-derived heat shock protein gp-96 peptide complex has shown activity in a phase II study,[80] a phase III trial has completed accrual and an adjuvant trial is under consideration.

A number of gene therapy-based vaccine strategies are under investigation. A variety of approaches are utilised, most commonly using viral or plasmid DNA delivery systems. Studies looking at *in vitro* transfection of autologous cells with genes encoding GM-CSF[81] and various melanoma-derived CD8+ T-cell epitopes or melanoma-associated antigens,[82] or *in vivo* delivery of single or multiple epitopes have been published.[83]

Dendritic cells are central to immune responses and may be used as adjuvants for tumour vaccine therapy. Dendritic cells can be pulsed *in vitro* with many antigens before being adoptively transferred back into the patient. Vaccines developed in this way tend to generate immunity with acceptable toxicity and some tumour responses.[84,85] A randomised study comparing dacarbazine with autologous dendritic cells pulsed with 19 peptides was stopped after 108 of the target 250 patients had been treated, as analysis indicated that the study goal of an improved response rate with the vaccination could not be achieved. There was no difference in response rate or median overall survival between the two arms.[86] However, this study was the first to show that it is possible to carry out a complex, cell therapy-based clinical trial over a number of centres.

Immunotherapy-based treatment depends on the *in vivo* generation of a large number of anti-tumour T cells that are capable of sustained immunity and not subject to down-regulation. The complexity of in-built redundancy within the immune system serves to frustrate many immunotherapy approaches. The reasons for this are multiple and may include the number of CD4+ cells or adjuvant cytokines required; the need for accessory molecules, such as anti-B7-1 monoclonal antibody; the number of anti-tumour CD8+ cells generated or low avidity of these; and the short lifespan of anti-tumour cells in the circulation. Dudley et al.[87] have approached these problems by using adoptive transfer of highly selective tumour-reactive T cells to self-derived tumour antigens with accessory cells to patients treated with a non-myeloablative fludarabine and cyclophosphamide conditioning regimen. Initial reports of this high-technology approach are very promising.

3.3 Newer Immune Modulators

CTL-associated antigen 4 (CTLA-4) is a critical immunomodulatory molecule. It is expressed on activated T cells and some other regulatory T cells, and is capable of down-regulating T-cell activation. Blockade of CTLA-4 can potentially enhance T-cell-dependent immunity, and so increase response to vaccine therapies and a number of other treatment approaches. MDX-010 is a humanised anti-CTLA-4 monoclonal antibody that is being evaluated in a number of clinical indications. A phase II study of MDX-010 given with a gp100 peptide vaccine reported a response rate of 21% in patients with ad-

vanced melanoma. However, treatment-related toxicity was significant, with 43% grade III/IV autoimmune-mediated manifestations, which appeared to be dose dependent.[88] A subsequent randomised phase II study in 76 patients comparing MDX-010 alone or with dacarbazine suggested potentiated activity in the combination arm. Autoimmune toxicity was significant but appeared manageable in the majority of patients.[89]

Human toll-like receptors (TLRs) are crucial for the recognition of invading pathogens and for the activation of both innate and adaptive immunity. TLRs are preferentially expressed on cells of the innate immune system. Activation of TLRs by bacterial (BCG) and viral (RNA) components has produced anti-tumour effects in preclinical models. There are ten known TLRs in humans and drugs that activate a number of these are under evaluation, including imiquimod, which binds to TCR7 and has been used widely as a topical treatment for viral skin warts and latterly for the treatment of lentigo maligna. A parenteral form is under development. Resiquimod, which binds TLR8, and bacterial CpG, which binds TCR9, are under evaluation in advanced melanoma as vaccine adjuvants and nonspecific immune stimulants.[90]

4. Conclusions

It is hoped that some of the treatment strategies discussed in this review will show promise in malignant melanoma. While negative studies of combination chemotherapy and biochemotherapy are disappointing, we can now focus on other newer, targeted approaches wrought out of smart drug design, and our increasing understanding of the biology of melanoma and its interaction with normal host cells, extracellular matrix and the immune system. Maximising the potential of active new targeted therapies will also pose a number of challenges. We have being taught some important lessons from other solid tumours but have much more to learn.

Acknowledgements

Dr Lorigan has received honoraria from Aventis and from Schering Plough for advisory board work, research support from Genta, and educational grants from Aventis and Schering Plough. Dr Danson has received educational support from Schering Plough. No sources of funding were used to assist in the preparation of this manuscript.

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