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Chemoimmunotherapy of Advanced Malignant Melanoma: Sequential Administration of Subcutaneous Interleukin-2 and Interferon-α After Intravenous Dacarbazine and Carboplatin or Intravenous Dacarbazine, Cisplatin, Carmustine and Tamoxifen

J. Atzpodien, E. Lopez Hänninen, H. Kirchner, A. Franzke, A. Körfer, M. Volkenandt, S. Duensing, A. Schomburg, S. Chaitchik and H. Poliwoda

Both chemotherapy and interleukin-2 and/or interferon-α produce objective responses in a proportion of advanced malignant melanoma patients. While duration of response to chemotherapy is short, i.e. usually below 4 months, immunotherapy has resulted in a small number of long-lasting remissions in patients with metastatic melanoma. In two consecutive phase II trials in a total of 67 patients, we assessed the potential synergism between both modalities, i.e. chemo- and immunotherapy. Treatment consisted of intravenous (i.v.) carboplatin (CBDCA, 400 mg/m^2) and dacarbazine (DTIC, 750 mg/m^2) given twice (i.v. bolus over 30 min) at 3-week intervals, or 4 cycles of DTIC (220 mg/m^2 i.v. 3 days), cisplatin (DDP, 35 mg/m^2 i.v. 3 days), carmustine (BCNU, 150 mg/m^2 i.v. cycles 1 and 3) and tamoxifen (TAM, 20 mg oral/daily) at 3-week intervals. Chemotherapy was followed by immunotherapy with combined subcutaneous (s.c.) interleukin-2 (rIL-2) and SC interferon-α2 (rIFN-α). Among 40 patients who received a full cycle of chemotherapy with CBDCA/DTIC and sequential immunotherapy, there were 3 (7.5%) complete remissions (CRs) with a median duration of 19 months (range 13–26+). Partial remissions (PRs) were noted in 11 (27.5%) patients with a median response duration of 8 (range 5–14) months. Among 27 patients who received DTIC/DDP/BCNU/TAM and rIL-2/rIFN-α, there were 3 (11%) complete remissions and 12 (44.5%) partial remissions. Duration of complete and partial remissions ranged from 9+ to 13+ (median, 11+), and 5 to 15+ (median, 7+) months, respectively. Chemotherapy produced mostly moderate toxicity. Thrombocytopenia was common with the nadir after a median time of 18 days following start of CBDCA/DTIC and DTIC/DDP/BCNU, respectively. 10 patients required transfusion of thrombocytes. Nausea and vomiting due to chemotherapy were well tolerated using concomitant ondansetrone (8 mg i.v.). Immunotherapy was self-administered at home with mild to moderate side effects; malaise, fever, chills, nausea/vomiting, diarrhoea, anorexia and arthralgias were most frequent, but were spontaneously reversible after ending rIL-2/IFN-α. A mean 87 and 88% of the projected doses of rIL-2 and rIFN-α were administered on either protocol. There were no life-threatening complications and no treatment-related deaths. The sequential combination of chemotherapy and rIL-2 plus rIFN-α had at least additive therapeutic activity against metastatic malignant melanoma. The schedules produced long-lasting remissions and were tolerated well overall. These trials substantiate a potential role for low to intermediate dose immunotherapy in maintaining and consolidating therapeutic effects of chemotherapy in metastatic melanoma.

Key words: malignant melanoma, interleukin-2, interferon-α, dacarbazine, carboplatin, cisplatin, carmustine, tamoxifen

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INTRODUCTION

THE USE of various chemotherapeutic agents has shown activity against metastatic malignant melanoma. Single agent chemotherapy employing dacarbazine (DTIC), cisplatin (DDP), or carmustine (BCNU) produces objective remissions in 10 to 20% of patients with advanced melanoma [1–4]; carboplatin (CBDCA) at doses of 400 mg/m^2 yields a remission rate of up to 19% [5, 6]. Reported remission durations have been short, with a median of less than 4 months. Previous combination chemotherapy regimens using DTIC, DDP, BCNU and tamoxifen (TAM) have demonstrated response rates of 55% in metastatic melanoma patients [7].

Inpatient high dose intravenous (i.v.) interleukin-2 (rIL-2) in combination with subcutaneous (s.c.) interferon-α2 (rIFN-α) has resulted in an overall response rate of 33%; complete remissions (CRs) were reported in 8% of advanced melanoma patients and continued for more than 9 months after initiation of therapy [8]. Home therapy employing low to intermediate doses of SC rIL-2 in combination with rIFN-α has produced objective tumour regressions in 14% of patients with metastatic melanoma [9].

In this study, we report two consecutive sequential chemoimmunotherapy phase II trials consisting of outpatient SC rIL-2/rIFN-α combined with CBDCA/DTIC, or DTIC/DDP/BCNU/TAM. Alternating chemotherapy and immunotherapy was given to assess the sequential and potentially synergistic effects of each phase of therapy. Previous studies demonstrated that platinum based chemotherapy does not significantly impair rIL-2 induced generation of killer lymphocytes [10, 11]. Thus, in the present investigation, we added rIL-2/rIFN-α to chemotherapy regimens in an effort to maintain and/or consolidate responses after i.v. chemotherapy in metastatic malignant melanoma.

PATIENTS AND METHODS

Patients

All patients had histologically confirmed metastatic malignant melanoma, and presented with clinically progressive disease as demonstrated by standard radiographic procedures. Patients were treated with one of two sequential chemoimmunotherapy regimens. Patient characteristics for each protocol group are given in Table 1.

This study was approved by the institutional review board at Medizinische Hochschule Hannover; written informed consent was obtained from all patients prior to entry into this study.

Treatment plan and patient evaluation

Treatment was conducted as outlined in Table 2. Patients received chemotherapy with CBDCA/DTIC and DTIC/DDP/BCNU in the outpatient clinic and on the ward, respectively, while immunotherapy was administered on an outpatient basis.

Subcutaneous rIL-2 (EuroCetus, Division of Chiron Corp., Emeryville, CA, U.S.A.) and rIFN-α (Hoffmann-La Roche, Basel, Switzerland) were self-administered at home. The rIL-2 used had a specific activity of 18 000 000 international units (IU) per mg protein; the rIFN-α had a biological activity of 1 000 000 IU per 6 μg protein. Patient inclusion criteria are given in Table 3. Criteria for each response category are defined in Table 4.

*Table 1. Characteristics of 67 patients**

	DTIC, CBDCA rIL-2, rIFN-α	DTIC, DDP, BCNU, TAM rIL-2, rIFN-α
Sex		
Male	27	18
Female	13	9
Age (years)		
Median	52	56
Range	23–73	21–71
Performance status (Karnofsky)		
≥ 90%	22	17
80%	14	7
70%	4	3
Histology†		
Cutaneous	21	22
Nodular	9	9
Amelanotic	7	5
Spindle cell	3	3
Superficial spreading	2	5
Choroidal	6	1
Unknown	13	4
Pretreatment		
Chemotherapy	11	7
Radiotherapy	6	2
Immunotherapy‡	8	4

*67 patients were evaluated in this study, all of whom completed chemotherapy and received at least one dose of immunotherapy. †In 17 patients, location of the primary tumour was unknown; in these patients, histology was documented in metastatic lesions. ‡Interferon-α and/or interleukin-2 was given to 6 patients.

Statistical analyses

Statistical significance was assessed using *t*-test, paired *t*-test and Wilcoxon analyses wherever appropriate.

RESULTS

Patient characteristics and treatment

Patient characteristics are summarised in Table 1. Between February 1990 and September 1991, a total of 40 patients were entered on a phase II trial employing CBDCA/DTIC/rIL-2/rIFN-α. Patients (27 males/13 females; median age of 52 years, range 23–73 years) received a total of 83 courses of CBDCA, DTIC, rIL-2 and rIFN-α, and were all evaluable for treatment response and toxicity. Between November 1991 and June 1993, 27 patients were treated with a combination of DTIC/DDP/BCNU/TAM/rIL-2/rIFN-α (18 males/9 females, median age of 56 years, range 21–71 years).

Among all patients, there were 39 with an Karnofsky index of ≥ 90%, 21 patients and 7 patients had a Karnofsky index of 80% and 70% before therapy, respectively. In 17 patients, location of primary tumours was unknown; in these patients histology was confirmed in metastatic lesions; 7 patients had primary choroidal melanoma, and 43 patients had cutaneous melanoma (18 nodular, 12 amelanotic, 6 spindle cell, and 7 superficial spreading melanomas). Previous cancer therapy included surgery (n = 36), radiotherapy (n = 8), chemotherapy (n = 18; 10 patients DTIC, 5 melphalan, 2 DTIC/cisplatin/vindesine, 1 mitomy-

Correspondence to J. Atzpodien.
J. Atzpodien, E. Lopez Hänninen, H. Kirchner, A. Franzke, A. Körfer, S. Duensing, A. Schomburg and H. Poliwoda are at the Medizinische Hochschule, D-30623 Hannover, Germany; M. Volkenandt is at the Memorial Sloan-Kettering Cancer Center, New York, U.S.A.; and S. Chaitchik is at the Tel-Aviv Medical Center, Israel.
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Table 2. Two treatment schedules

DTIC, CBDCA, rIL-2, rIFN-α*†§		
Dacarbazine	750 mg/m²	i.v. over 30 min, wk 1 and 4
Carboplatin	400 mg/m²	i.v. over 30 min, wk 1 and 4
Interleukin-2	4.8 million IU/m²	s.c. three times daily, day 1, wk 7 and 10
		twice daily, day 2, wk 7 and 10
	2.4 million IU/m²	s.c. twice daily, days 3–5, wk 7 and 10
		s.c. twice daily, day 1–5, wk 8, 9, 11, 12
Interferon-α	3 million U/m²	s.c. days 3 and 5, wk 7 and 10
	6 million U/m²	s.c. days 1, 3, 5, wk 8, 9, 11, 12
DTIC, DDP, BCNU, TAM, rIL-2, rIFN-α‡§		
Dacarbazine	220 mg/m²	i.v. over 30 min, days 1–3, wk 2, 5, 8, 11
Cisplatin	35 mg/m²	i.v. over 30 min, days 1–3, wk 2, 5, 8, 11
Carmustine	150 mg/m²	i.v. over 30 min, day 1, wk 2 and 8
Tamoxifen	20 mg/d	oral throughout chemotherapy
Interleukin-2	20 million IU/m²	s.c. days 3–5, wk 14 and 17
	5 million IU/m²	s.c. days 1, 3, 5, wk 1, 15, 16, 18 and 19
Interferon-α	6 million U/m²	s.c. day 1, wk 14 and 17;
		days 1, 3, 5, wk 1, 15, 16, 18, and 19

*Patients received chemotherapy in the outpatient clinic, while cytokine therapy was administered at home; treatment cycles were repeated unless disease progression occurred. †Further therapy was postponed at weekly intervals unless patients had reached the nadir of peripheral thrombocytes and leucocytes, respectively. ‡Patients received chemotherapy on the ward, while cytokine therapy was administered at home. §Upon immunotherapy, WHO grade 4 toxicity led to treatment discontinuation; in the case of WHO grade 3, a 50% dose reduction was performed until symptoms improved.

Table 3. Patient inclusion criteria

Histologically confirmed and evaluable progressive malignant melanoma
Age between 18 and 75 years
Expected survival of more than 3 months
Karnofsky performance status ≥ 70%
Adequate organ function as defined by
  WBC ≥ 3 500/μl
  Platelets ≥ 100 000/μl
  HCT ≥ 28%
  Creatinine clearance ≥ 60 ml/min
  Forced expiratory volume > 2 litres in 1 s or ≥ 75% of predicted for height and age
No clinical evidence of congestive heart failure, severe coronary artery disease, or cardiac arrhythmias
No clinical evidence of CNS metastases, or significant central nervous disorders
No evidence of serious active infections (including HIV or infectious hepatitis)
No chemotherapy or immunomodulatory treatment during the previous 4 weeks
No simultaneous use of prostaglandin E2 synthesis inhibitors or corticosteroids
Signed informed consent

cin/5-FU) and immunotherapy (n = 12; patients rIFN-α, 4 rIL-2/rIFN-α, 2 other).

Response

The tumour response of 40 evaluable patients upon CBDCA/DTIC/rIL-2/rIFN-α is given in Table 5. The overall objective response rate was 35% (95% confidence interval, 21–52%) with 7.5% complete remissions, and 27.5% partial remissions. In all responding patients, tumour regression occurred during the first treatment course. 6 patients (15%) responded to the initial chemotherapy phase. In all other responding patients, objective tumour regression developed after one full course of CBDCA/DTIC/rIL-2/rIFN-α. 2 patients with an initial minor remission achieved a partial remission (PR) after the second treatment course, and except for 2 patients, all responders received a total of three consecutive treatment courses. All 3 patients achieved a CR during the third course of therapy. Of all CR patients, upon start of therapy, 1 patient had more than 50 cm² and 2 patients had more than 20 cm² total tumour area, respectively. Complete responses were seen in the lung (n = 2), liver (n = 1), soft tissue (n = 1), spleen metastases (n = 1) and peripheral lymph nodes (n = 2). Partial tumour responses occurred in lung (n = 8), liver (n = 2), subcutaneous metastases (n = 2) and in abdominal (n = 4), mediastinal (n = 4) and peripheral (n = 1) lymph nodes, respectively. Response durations for complete responders were 13–26+ months (median, 19 months); PRs had a median duration of 8 months (range 5–14 months). Among the 14 treatment responders, there were 4 patients who had progressed upon previous chemotherapy (DTIC, n = 3), and 1 complete responder who had failed prior therapy with rIFN-α.

*Table 4. Grading system for therapeutic responses**

Complete response (CR)
Disappearance of all signs of disease for a minimum of 8 weeks
Partial response (PR)
≥ 50% reduction in sum of products of the greatest perpendicular diameters of measurable lesions
No increase in lesion size
No new lesions
Stable disease
Less than a PR with no disease progression for at least 8 weeks
Progressive disease
≥ 25% increase in sum of the products in the longest perpendicular diameters of measurable lesions
Development of new lesions

*Patients who went off study due to progressive disease were included for evaluation of therapeutic response. Duration of CRs was measured from time of best response; duration of PRs was measured from start of therapy.

Table 5. Response of patients receiving dacarbazine, carboplatin, recombinant human interleukin-2 and recombinant human interferon-α (n = 40)

	Response				
Tumour site*	CR	PR	SD	PD	Total
Lung	2	8	7	4	21
Liver	1	2	10	4	17
Local relapse	—	—	2	1	3
Lymph nodes	2	9	6	6	23
Skin/subcutaneous	—	2	3	3	8
Soft tissue	1	—	—	1	2
Bone	—	—	2	1	3
Other	1†	—	2‡	2	5
Total	3 (7.5%)	11 (27.5%)	16 (40%)	10 (25%)	40

Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.
*Patients may have had more than one site. †Spleen metastasis. ‡Adrenal and pleural metastasis.

Table 6. Response of patients receiving dacarbazine, cisplatin, carmustine, tamoxifen, recombinant human interleukin-2 and recombinant human interferon-α (n = 27)

	Response				
Tumour site	CR	PR	SD	PD	Total
Lung	1	7	1	5	14
Liver	1	5	1	3	10
Lymph nodes	2	6	1	6	15
Skin/subcutaneous	1	1	1	3	6
Soft tissue	1	—	—	1	2
Bone	—	2	—	1	3
Other	—	3*	1†	1‡	5
Total	3 (11%)	12 (44.5%)	2 (7.5%)	10 (37%)	27

Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.
*Diffuse intra-abdominal and adrenal metastases. †Bone marrow infiltration. ‡Local relapse of choroidal melanoma.

Upon DTIC/DDP/BCNU/TAM/rIL-2/rIFN-α (n = 27), 3 patients (11%) reached CR and 12 patients (44%) had PR, with an overall objective response rate of 55.5% (95% confidence interval, 35–75%). In 13 patients (48%), tumour regressions occurred after the initial chemotherapy phase and in 2 patients, tumour regressions were seen after additional immunotherapy. Of all CR patients, upon start of therapy, 2 patients had more than 50 cm^2 and 1 patient had more than 20 cm^2 total tumour area. Tumour regressions were seen in the lung (n = 8), liver (n = 6), lymph nodes (n = 8), skin/subcutaneous metastases (n = 2), soft tissue (n = 1), bone (n = 2), diffuse intra-abdominal metastases (n = 2), and adrenal metastasis (n = 1). Median response durations for CR and PR patients were 11+ (range, 9+–13+), and 7+ (range, 5+–15+) months, respectively (Table 6).

Adverse effects

All courses were evaluated for treatment-related adverse effects. Overall, systemic toxicity of this combination regimen was moderate. Patients received CBDCA/DTIC and DTIC/DDP/BCNU in the outpatient clinic and on the ward, respectively, while rIL-2 and rIFN-α were self-administered at home. No life-threatening complications nor toxic deaths occurred.

Chemotherapy with CBDCA/DTIC and DTIC/DDP/BCNU produced significant haematologic toxicity in 51 and 97% of all treatment courses, respectively; thrombocytopenia was most common (Table 7) with the thrombocyte nadir reached after a median of 18 days (range, 14–35 days) upon CBDCA/DTIC and DTIC/DDP/BCNU, respectively. 3 and 5 patients required a 25 and 50% dose reduction, respectively, upon CBDCA/DTIC and of these, 5 received transfusion of thrombocytes. While leucopenia after CBDCA/DTIC was usually limited to grade 1/2 (2 and 5% grade 3 and 4 leucopenia), with DTIC/DDP/BCNU, the majority of patients experienced WHO grade 2–4 leucopenia (99% of treatment courses).

Both chemotherapy and rIL-2/rIFN-α caused nausea and vomiting (CBDCA/DTIC, 71% of treatment courses; DTIC/DDP/BCNU, 73% of treatment courses); gastrointestinal side effects of chemotherapy were well tolerated using concomitant ondansetrone (8 mg i.v.). In addition, rIL-2 and rIFN-α immunotherapy regimens caused anorexia (77 and 79% of

*Table 7. Systemic toxicity of dacarbazine, carboplatin, recombinant human interleukin-2, and recombinant human interferon-α or dacarbazine, cisplatin, carmustine, tamoxifen, recombinant human interleukin-2 and recombinant human interferon-α**

Side effect†	WHO Grade	Percent of treatment cycles: CBDCA,DTIC,rIL-2,rIFN-α 1	2	3	4	DTIC,DDP,BCNU,TAM,rIL-2,rIFN-α 1	2	3	4
Thrombocytopenia‡		20	8	11	12	17	16	39	25
Anaemia		28	12	—	—	45	21	—	—
Leucopenia		24	6	2	5	—	26	47	26
Nausea/vomiting		41	24	6	—	39	30	4	—
Anorexia		29	24	18	6	31	27	13	8
Diarrhoea		47	6	6	—	38	10	5	—
Fever		25	56	8	—	23	48	5	—
Malaise		5	43	15	4	9	38	18	3
Chills		29	24	12	—	32	21	8	—
Dyspnoea		15	18	2	—	17	15	—	—
Hypotension		24	6	—	—	20	5	—	—
Dermatologic toxicity		18	32	—	—	14	23	—	—
Mucositis		24	6	—	—	21	9	—	—
Alopecia		12	—	—	—	10	5	—	—
Arthralgia		6	4	14	—	7	9	—	—

*All patients who received a single dose of drug were evaluated for toxicity; no life-threatening complications and no toxic deaths occurred. †Toxicity grades based on World Health Organization criteria. ‡The thrombocyte nadir was reached after a median time of 18 days (range 14–35 days) upon CBDCA/DTIC and DTIC/DDP/BCNU, respectively; 10 patients required thrombocyte transfusions.

treatment courses, respectively) and diarrhoea (59 and 53% of treatment courses, respectively). Subsequent weight loss of more than 5 and 10% was noted in 18 and 6% of treatment courses, respectively, but was reversible when therapy ended. Chills, fevers and malaise due to rIL-2/rIFN-α were also frequent (up to 89% of treatment courses); general malaise of WHO grade 3 and 4 developed in up to 18% and 4% of courses respectively, and required dose reduction. Mild WHO grade 1/2, dyspnoea and hypotension were observed in up to 33% of treatment courses; patients never developed severe pulmonary oedema and hypotension related to capillary leak. Skin dryness, inflammation at the rIL-2 injection sites and mucositis were common (up to 50% of treatment courses), but were always limited to grade 1/2 and resolved after cessation of therapy. Transient arthralgias occurred in 24% of treatment courses (14% grade 3) and were most frequent after administration of rIL-2.

Immunotherapy never resulted in significant renal dysfunction or electrolyte imbalance. Overall, rIL-2 and rIFN-α related adverse effects were managable in an outpatient setting. A mean of 87 and 88% of the projected doses of rIL-2/rIFN-α were administered on either protocol.

DISCUSSION

In the present study, we combined CBDCA/DTIC or DTIC/DDP/BCNU with rIL-2 and rIFN-α in an effort to assess the potentially additive or synergistic effects of sequential chemo- and immunotherapy in the treatment of metastatic melanoma.

Previously, all six agents demonstrated therapeutic activity against malignant melanoma when used alone or in combination [1–6, 12–14]. In addition, there was no clinical evidence of crossresistance between cytotoxic and biologic therapy; neither did platinum and/or dacarbazine based chemotherapy abrogate the immunoactivation of cytokine induced cytotoxic lymphocytes in human [10, 11].

The present results showed that the combination of i.v. chemotherapy and s.c. immunotherapy was active in metastatic melanoma with an overall objective response rate of 35% (CBDCA/DTIC/rIL-2/rIFN-α) and 55% (DTIC/DDP/BCNU/TAM/rIL-2/rIFN-α), respectively. Responses were seen in a broad spectrum of metastatic sites including lung, liver, spleen, lymph nodes, skin, subcutaneous and soft tissue. However, there were no objective responses in patients with choroidal primaries.

The sequential administration of chemotherapy and immunotherapy on these trials allowed for evaluation of response to each phase of treatment. The initial chemotherapy with CBDCA/DTIC produced objective remissions (PR) in 15% (95% CI, 6–30%) of patients; responses occurred in lung, lymph nodes and skin lesions. The response rate to DTIC and CBDCA in this study was similar to other reported DTIC and/or platinum based chemotherapies [1–4, 15, 16]. With DTIC/DDP/BCNU/TAM/rIL-2/rIFN-α, the initial chemotherapy phase produced remissions in 48% (95% CI, 29–68%) of all patients and at a rate similar to previous results [7]; the hypothesised role of tamoxifen as a modulator of multidrug resistance gene expression remains unclear.

With CBDCA/DTIC and DTIC/DDP/BCNU, an additional 6 and 2 patients who did not respond to initial chemotherapy achieved a PR after the first cycle of rIL-2 and rIFN-α, respectively. This indicated that rIL-2 and rIFN-α based immunotherapy was active after initial chemotherapy. Chemotherapy did not abrogate response to subsequent rIL-2 and rIFN-α based immunotherapy. It should be noted that objective responses to combination chemoimmunotherapy in this study also included liver, subcutaneous and soft tissue, sites which were unresponsive to the initial chemotherapy.

Our outpatient regimen of CBDCA/DTIC/rIL-2/rIFN-α was at least as effective in the treatment of metastatic malignant

melanoma as the most aggressive chemotherapy regimen reported [15–18]. While median response durations of 2–4 months were noted with chemotherapy alone [1, 2, 17, 18], CRs and PRs with CBDCA/DTIC/rIL-2/rIFN-α had median response durations of 19 and 8 months, respectively; with DTIC/DDP/BCNU/TAM/rIL-2/rIFNα, CRs and PRs had median durations of 11+ and 7+ months, respectively.

Recent studies combining DTIC, platinum derivates and rIL-2 with or without rIFN-α yielded similar response rates and response durations in melanoma [19–21]. However, rIL-2 was used as i.v. inpatient bolus or continuous infusion at doses 10-fold higher than in the present regimen.

In our study, treatment-related adverse effects of SC rIL-2 and rIFN-α were limited mostly to WHO grade 1 and 2 malaise, fever, nausea and diarrhoea. Except for fatigue and anorexia, few patients suffered dose-limiting grade 3 or 4 toxicity. It is important to note that rIL-2 induced capillary leak, interstitial oedema, and serious hypotension did not occur and therefore, patients always received immunotherapy at home.

In summary, it appears that the present chemoimmunotherapy regimens induce long-lasting tumour regressions in advanced melanoma. While our data suggest at least an additive activity against melanoma of both cytotoxic and biological agents, they cannot provide conclusive evidence. For this purpose, we have initiated a randomised trial at our institutions comparing combination chemoimmunotherapy versus chemotherapy alone in patients with metastatic malignant melanoma.

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