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Clinical Trial Results

Melatonin and Metformin Failed to Modify the Effect of Dacarbazine in Melanoma

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Key Words. Melanoma • Melatonin • Metformin • Dacarbazine

Trial Information

- **ClinicalTrials.gov Identifier**: NCT02190838
- **Sponsor**: N.N. Petrov National Medical Research Center of Oncology
- **Principal Investigator**: Aleksei Novik
- **IRB Approved**: Yes

Lessons Learned

- Melatonin did not increase the efficacy of systemic chemotherapy in melanoma.
- Metformin did not increase the efficacy of systemic chemotherapy in melanoma.

Abstract

Background. Current data support the possibility of antitumor activity of melatonin and metformin.

Methods. From March 2014 to December 2016, 57 patients with disseminated melanoma received dacarbazine (DTIC) 1,000 mg/m^2 on day 1 of a 28-day cycle, either as monotherapy (first group) or in combination with melatonin 3 mg p.o. daily (second group) or metformin 850 mg two times a day p.o. daily (third group) as the first-line of chemotherapy. The primary endpoint was objective response rate (ORR). Secondary endpoints were time to progression (TTP), overall survival (OS), immunologic biomarkers, and quality of life.

Results. ORR was 7% and did not differ among the treatment groups. Median TTP was 57, 57, and 47 days, respectively, in the first, second, and third groups (p = .362). Median OS was 236, 422, and 419 days, respectively (p = .712). Two patients from the combinations groups showed delayed response to therapy. The increase of $CD3^+CD4^+HLA\text{-}DR^+$ lymphocytes (p = .003), $CD3^+CD8^+HLA\text{-}DR^+$ (p = .045), $CD3^+CD8^+$ lymphocytes (p = .012), $CD4^+CD25^{high}CD127^{low}$ lymphocytes (p = .029), and overall quantity of lymphocytes (p = .021) was observed in patients with clinical benefit.

Conclusion. No benefit was found in either combination over DTIC monotherapy. Delayed responses in melatonin and metformin combination groups were registered. The increase of lymphocyte subpopulations responsible for antitumor immune response demonstrates the immune system's potential involvement in clinical activity. ***The Oncologist*** 2021;26:364–e734

Discussion

At present, a significant breakthrough has been reached in the treatment of disseminated cutaneous melanoma [1]. Chemotherapy is now not considered an option for selection of therapy. Nevertheless, patients whose disease progresses on modern therapy modalities or those who have no access to the expensive therapies could still be treated with chemotherapy. So there is still an unmet medical need for the enhancement of DTIC activity by inexpensive tools.

The studies of the role of melatonin in circadian rhythms, aging, and carcinogenesis regulation showed that its synthesis disturbances often accompany the development of malignant tumors [2]. Several studies have shown that melatonin

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 http://dx.doi.org/10.1002/onco.13761

participates in circadian rhythm regulation and is relevant for immune system regulation processes.

Metformin can decrease glucose level, its higher consumption by malignant cells, and reduce the well-known Warburg effect [3,4]. The influence of metformin includes the suppression of mTOR function, and it is similar to the impact of registered target medications [5]. Metformin is also known to inhibit the unfolded protein response (UPR), activate the immune response, and possibly target cancer cells [6,7].

Our study did not meet its primary endpoint of an improvement in ORR. Two delayed responses in melatonin and metformin combination groups were registered. The ORR was 5.3% in the first and second groups, respectively (p = .57). Median TTP was 57, 57, and 47 days, respectively, in the first, second, and third groups (p = .362). The study was preliminarily closed because of the inefficacy of conducted therapy. Patients' significant life duration in all treatment groups could be due to holding the new treatment methods in patients who completed participation in the trial, which influenced the life expectancy that had been already proved. Thus, three patients received ipilimumab, five patients received PD-L1 inhibitors, and eight patients received targeted therapy.

The inclusion of 96 patients was planned (32 in each group) to confirm a 30% improvement in response rate. No interim analysis was planned at the study beginning. The trial was stopped due to the low response rate and appearance of the new effective therapies.

During treatment, one patient who received melatonin and dacarbazine developed complete regression after the 12th cycle of the therapy, which has been maintained for 32+ months now. Another patient who had received metformin with dacarbazine developed a partial response, which made up six months. Nevertheless, after discontinuing the treatment within the study, the patient continued the therapy with the metformin, which led to stabilization for five months more. Now this patient is alive and currently receiving the 9th line of treatment.

Trial Information	
Disease	Melanoma
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study	Phase II, randomized
Primary Endpoint	Overall response rate
Secondary Endpoints	Time to progression Overall survival Toxicity Correlative endpoint Quality of life

Additional Details of Endpoints or Study Design

Patients were randomized into three groups in a 1:1:1 ratio. The block randomization method was used. Patients were stratified by the American Joint Committee on Cancer 7 M1 stage, presence of subclinical glucose intolerance, or mild sleep disorders.

Kaplan-Maier method was used for survival assessment, χ^2 was used for response and life quality assessment, and Mann-Whitney U was used for immunological assessments.

A 5% α level was used as a significance cutoff.

Response rate was assessed by Response Evaluation System for Solid Tumors (RECIST) v. 1.1 [8]. Toxicity was assesed using Common Terminology Criteria for Adverse events (CTC AE) [9].

The inclusion of 96 patients was planned (32 in each group) to confirm a 30% improvement in response rate. No interim analysis was planned at the study beginning. The trial was stopped because of the low response rate and appearance of the new effective therapies.

Investigator's Analysis	Inactive because results did not meet primary endpoint

Drug Information: DTIC	
Generic/Working Name	DTIC
Drug Type	Cytotoxic
Drug Class	Alkylating agent
Dose	1,000 mg/m^2
Route	IV
Schedule of Administration	Day 1 every 28 days

Drug Information: DTIC + Metformin	
DTIC	
Generic/Working name	DTIC
Drug Type	Cytotoxic
Drug Class	Alkylating agent
Dose	1,000 mg/m^2
Route	IV
Schedule of Administration	Day 1 every 28 days
Metformin	
Generic/Working Name	Metformin
Drug Type	Targeted
Drug Class	biguanides
Dose	850 mg per flat dose
Route	oral (p.o.)
Schedule of Administration	Two times a day (after breakfast and supper)

Drug Information: DTIC + Melatonin	
DTIC	
Generic/Working Name	DTIC
Drug Type	Cytotoxic
Drug Class	Alkylating agent
Dose	1,000 mg/m^2
Route	IV
Schedule of Administration	Day 1 every 28 days
Melatonin	
Generic/Working Name	Melatonin
Drug Type	Hormones
Drug Class	Hormones
Dose	3 mg per flat dose
Route	oral (p.o.)
Schedule of Administration	1 time a day (at night before bed)

Drug Information for Phase II Overall	
DTIC	
Generic/Working Name	DTIC
Drug Type	Other
Drug Class	Alkylating agent
Dose	1,000 mg/m^2
Route	IV
Schedule of Administration	Day 1 every 28 days
Melatonin	
Generic/Working Name	Melatonin
Trade Name	Melaxen
Drug Type	Hormones
Drug Class	Hormones
Dose	3 mg per flat dose
Route	oral (p.o.)
Schedule of Administration	One time a day (at night before bed)

Metformin	
Generic/Working Name	Metformin
Drug Type	Targeted
Drug Class	Biguanid
Dose	850 mg per flat dose
Route	oral (p.o.)
Schedule of Administration	Two times a day (after breakfast and supper)

Patient Characteristics: Control	
Number of Patients, Male	9
Number of Patients, Female	10
Stage	Stage III inoperable - 3 (16%) Stage IV - 16 (84%)
Age	Median (range): 61 (27–78) years
Number of prior systemic therapies	0
Performance Status: ECOG	0 — 13 1 — 6 2 — 0 3 — 0 Unknown — 0
Other	Patients with known diabetes were excluded from the study. Molecular analysis: mutated BRAF- 7 (37%); wild BRAF - 7 (37%); unknown BRAF - 5 (26%)

Patient Characteristics: DTIC + Metformin	
Number of Patients, Male	7
Number of Patients, Female	11
Stage	IV - 18 (100%) Mutated BRAF- 9 (50%%) Wild BRAF - 4 (22%) Unknown BRAF - 5 (28%)
Age	Median (range): 52.5 (27—65) years
Number of prior systemic therapies	0
Performance Status: ECOG	0 — 10 1 — 8 2 — 0 3 — 0 Unknown — 0
Other	Patients with known diabetes were excluded from the study.

Patient Characteristics: DTIC + Melatonin	
Number of Patients, Male	10
Number of Patients, Female	10
Stage	Stage - IV 10 (100%) Mutated BRAF- 11 (55%)

	Wild BRAF - 4 (20%) unknown BRAF - 5 (25%)
Age	Median (range): 56 (33–69) years
Number of prior systemic therapies	0
Performance Status: ECOG	0 — 9 1 — 11 2 — 0 3 — 0 Unknown — 0
Other	Patients with known diabetes were excluded from the study.

Patient Characteristics: Overall	
Number of Patients, Male	26
Number of Patients, Female	31
Stage	Stage III inoperable - 3 (5%) Stage IV - 54 (95%) Mutated BRAF- 27 (47%) Wild BRAF - 15 (26%) Unknown BRAF - 15 (26%)
Performance Status: ECOG	0 — 32 1 — 25 2 — 0 3 — 0 Unknown — 0
Other	Patients with known diabetes were excluded from the study.

Primary Assessment Method: Control	
Title	Efficacy assessment
Number of Patients Screened	19
Number of Patients Enrolled	19
Number of Patients Evaluable for Toxicity	19
Number of Patients Evaluated for Efficacy	19
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 2 (11%)
Response Assessment SD	*n* = 5 (26%)
Response Assessment PD	*n* = 11 (58%)
Response Assessment OTHER	*n* = 1 (5%)
(Median) Duration Assessments TTP	57 days, CI: 50–63
(Median) Duration Assessments OS	236 days, CI: 71–401

Secondary Assessment Method: Control	
Title	Quality of Life
Number of Patients Screened	19
Number of Patients Enrolled	19

Number of Patients Evaluable for Toxicity	19
Number of Patients Evaluated for Efficacy	19
Evaluation Method	QLQ30

Secondary Assessment Methods: Control - Outcome Notes			
Scale	**Baseline**	**On therapy**	**At progression**
Anorexia	0	0	0
Pain	50	50	50
Diarrhea	0	0	0
Constipation	0	0	0
Cognitive functions	100	91.5	100
Sleep disorders	33	50	100
General health status	58	54	25
Social activity	100	83.5	67
Shortness of breath	0	16.5	0
Role activity	83	58.5	17
Weakness	33	22	33
Sleeping	20.5	21	20
Vomiting and nausea	0	0	0
Physical activity	87	735	60
Financial difficulties	33	33.5	67
Emotional status	83	96	92

Primary Assessment Method: DTIC+Metformin	
Title	Efficacy assessment
Number of Patients Screened	18
Number of Patients Enrolled	18
Number of Patients Evaluable for Toxicity	18
Number of Patients Evaluated for Efficacy	18
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 1 (5%)
Response Assessment SD	*n* = 1 (5%)
Response Assessment PD	*n* = 16 (90%)
Response Assessment OTHER	*n* = 0 (0%)
(Median) Duration Assessments PFS	
(Median) Duration Assessments TTP	47 days, CI: 41–53
(Median) Duration Assessments OS	419 days, CI: 80–758

Secondary Assessment Method: DTIC + Metformin	
Title	Quality of Life
Number of Patients Screened	18
Number of Patients Enrolled	18
Number of Patients Evaluable for Toxicity	18
Number of Patients Evaluated for Efficacy	18
Evaluation Method	QLQ30

Outcome Notes			
Scale	**Baseline**	**On therapy**	**At progression**
Anorexia	33	0	0
Pain	50	50	50
Diarrhea	0	0	0
Constipation	0	0	0
Cognitive functions	83	98.1	91.5
Sleep disorders	16.5	11	33.5
General health status	62.5	50	75
Social activity	100	100	66.5
Shortness of breath	33	0	33.5
Role activity	67	89	66.5
Weakness	33	24.4	39
Sleeping	20	23	23
Vomiting and nausea	4.25	9.4	0
Physical activity	73	87	70
Financial difficulties	50	18.5	50
Emotional status	75	86	71

Primary Assessment Method: DTIC + Melatonin	
Title	Efficacy assessment
Number of Patients Screened	20
Number of Patients Enrolled	20
Number of Patients Evaluable for Toxicity	20
Number of Patients Evaluated for Efficacy	20
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 1 (5%)
Response Assessment PR	*n* = 0 (0%)
Response Assessment SD	*n* = 5 (25%)
Response Assessment PD	*n* = 13 (65%)
Response Assessment OTHER	*n* = 1 (5%)
(Median) Duration Assessments PFS	
(Median) Duration Assessments TTP	57 days, CI: 51–63
(Median) Duration Assessments OS	422 days, CI: 344–499

Secondary Assessment Method: DTIC+Melatonin	
Title	Quality of life
Number of Patients Screened	20
Number of Patients Enrolled	20
Number of Patients Evaluable for Toxicity	0
Number of Patients Evaluated for Efficacy	20

Secondary Assessment Method: DTIC+Melatonin - Outcome Notes			
Scale	**Baseline**	**On therapy**	**At progression**
Anorexia	0	0	0
Pain	67	50	58.5

Diarrhea	0	0	16.5
Constipation	0	0	0
Cognitive functions	83	100	100
Sleep disorders	33	0	16.5
General health status	33	67	66.5
Social activity	100	100	83.5
Shortness of breath	0	0	0
Role activity	83	100	100
Weakness	22	22	22
Sleeping	19	21	24
Vomiting and nausea	0	0	0
Physical activity	73	80	90
Financial difficulties	0	0	0
Emotional status	83	75	83.5

Primary Assessment Method: Overall	
Title	Efficacy assessment
Number of Patients Screened	61
Number of Patients Enrolled	57
Number of Patients Evaluable for Toxicity	57
Number of Patients Evaluated for Efficacy	56
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 2 (1%)
Response Assessment PR	*n* = 5 (3%)
Response Assessment SD	*n* = 19 (11%)
Response Assessment PD	*n* = 70 (40%)
Response Assessment OTHER	*n* = 4 (2%)
(Median) Duration Assessments PFS	
(Median) Duration Assessments TTP	56 days, CI: 48–64
(Median) Duration Assessments OS	406 days, CI: 270–541
(Median) Duration Assessments Response Duration	

Secondary Assessment Method: Overall	
Title	Immunologic biomarkers
Number of Patients Screened	57
Number of Patients Enrolled	57
Number of Patients Evaluable for Toxicity	57
Number of Patients Evaluated for Efficacy	57
Evaluation Method	Tumor marker
Response Assessment CR	*n* = 1 (2%)
Response Assessment PR	*n* = 3 (5%)
Response Assessment SD	*n* = 11 (19%)
Response Assessment PD	*n* = 40 (70%)
Response Assessment OTHER	*n* = 2 (4%)
(Median) Duration Assessments TTP	56 days, CI: 48–64
(Median) Duration Assessments OS	406 days, CI: 270–541

Secondary Assessment Methods: Overall - Outcome Notes				
Test	**Timepoint**	**Clinical benefit (median)**	**Disease progression (median)**	***p***
$CD3^+$ $CD8^+$	Baseline	0.64	0.40	.003
HLA-DR activated CTLs, %	Baseline	22.79	15.64	.003
$CD3^+CD4^+$HLA-DR^+, % from Th	Baseline	13.24	7.39	.013
$CD3^+CD4^+CD25^+$, % from Th	Baseline	11.16	17.25	.014
$CD3^+CD4^+CD25^+$	Baseline	0.12	0.08	.009
$CD3^+CD4^+CD25^+$, % from Ly	Baseline	8.28	4.85	.004
Lymphocytes	On therapy	2.40	1.43	.021
Lymphocytes, %	On therapy	37.40	24.80	.004
$CD3^+CD19^-$	On therapy	0.1335	0.088	.027
$CD3^+CD8^+$	On therapy	0.51	0.31	.012
HLA-DR activated CTLs	On therapy	012	0.05	.045
$CD3^+CD4^+CD25^{high}CD127^{low}$	On therapy	0.06	0.04	.029
$CD3^+CD4^-CD8^-$	On therapy	0.06	0.02	.037

Abbreviations: CTL, cytotoxic lymphocytes; Th, T-helper.

Adverse Events: Control							
All Cycles							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Febrile neutropenia	89%	5%	0%	5%	0%	0%	11%
Neutrophil count decreased	95%	0%	0%	5%	0%	0%	5%
Peripheral sensory neuropathy	100%	0%	0%	0%	0%	0%	0%
Respiratory failure	100%	0%	0%	0%	0%	0%	0%
Phlebitis	100%	0%	0%	0%	0%	0%	0%
Anemia	95%	5%	0%	0%	0%	0%	5%
Anorexia	100%	0%	0%	0%	0%	0%	0%
Diarrhea	95%	5%	0%	0%	0%	0%	5%
Alanine aminotransferase increased	89%	11%	0%	0%	0%	0%	11%
Vomiting	100%	0%	0%	0%	0%	0%	0%
Weight loss	100%	0%	0%	0%	0%	0%	0%
Nausea	100%	0%	0%	0%	0%	0%	0%
Hypoalbuminemia	100%	0%	0%	0%	0%	0%	0%
Neutrophil count decreased	95%	5%	0%	0%	0%	0%	5%
Rash maculo-papular	89%	5%	0%	5%	0%	0%	11%
Death NOS	89%	0%	0%	0%	0%	11%	11%
Platelet count decreased	89%	5%	0%	5%	0%	0%	11%
Lymphocyte count decreased	95%	5%	0%	0%	0%	0%	5%
Lymphocyte count decreased	95%	5%	0%	0%	0%	0%	5%
White blood cell decreased	89%	5%	0%	5%	0%	0%	11%
Fever	95%	5%	0%	0%	0%	0%	5%
Edema limbs	100%	0%	0%	0%	0%	0%	0%
Myalgia	100%	0%	0%	0%	0%	0%	0%
Creatinine increased	89%	11%	0%	0%	0%	0%	11%
Constipation	100%	0%	0%	0%	0%	0%	0%
Headache	95%	5%	0%	0%	0%	0%	5%
Generalized muscle weakness	79%	21%	0%	0%	0%	0%	21%

Toxicities were recorded for all cycles of therapy Patients received 162 cycles of therapy in all groups. Average cycle number was 2.9, range from 1 to 14.
Abbreviation: NC/NA, no change from baseline/no adverse events; NOS, not otherwise specified.

Adverse Events: DTIC+Metformin							
All Cycles							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Weight loss	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fever	0%	100%	0%	0%	0%	0%	100%
Peripheral sensory neuropathy	0%	100%	0%	0%	0%	0%	100%
Respiratory failure	0%	50%	0%	50%	0%	0%	100%
Pneumonitis	0%	67%	0%	33%	0%	0%	100%
Phlebitis	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Anemia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Anorexia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Diarrhea	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Alanine aminotransferase increased	0%	100%	0%	0%	0%	0%	100%
Vomiting	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nausea	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Edema limbs	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lymphocyte count decreased	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lymphocyte count decreased	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Neutrophil count decreased	0%	50%	0%	50%	0%	0%	100%
Platelet count decreased	N/A	N/A	N/A	N/A	N/A	N/A	N/A
White blood cell decreased	0%	100%	0%	0%	0%	0%	100%
Arthralgia	0%	100%	0%	0%	0%	0%	100%
Myalgia	0%	100%	0%	0%	0%	0%	100%
Constipation	0%	100%	0%	0%	0%	0%	100%
Creatinine increased	0%	100%	0%	0%	0%	0%	100%
Death NOS	0%	0%	0%	0%	0%	100%	100%
Rash maculo-papular	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vomiting	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Generalized muscle weakness	0%	25%	75%	0%	0%	0%	100%

Abbreviations: N/A, not applicable; NC/NA, no change from baseline/no adverse events; NOS, not otherwise specified.

Adverse Events: DTIC + Melatonin							
All Cycles							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Rash maculo-papular	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Anemia	0%	67%	0%	33%	0%	0%	100%
Anorexia	0%	100%	0%	0%	0%	0%	100%
Arthralgia	0%	100%	0%	0%	0%	0%	100%
Generalized muscle weakness	0%	100%	0%	0%	0%	0%	100%
Diarrhea	0%	100%	0%	0%	0%	0%	100%
Respiratory failure	0%	100%	0%	0%	0%	0%	100%
Constipation	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hypoalbuminemia	0%	0%	0%	100%	0%	0%	100%
Headache	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Diarrhea	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Neutrophil count decreased	0%	67%	0%	33%	0%	0%	100%
Lymphocyte count decreased	0%	100%	0%	0%	0%	0%	100%
Platelet count decreased	N/A	N/A	N/A	N/A	N/A	N/A	N/A
White blood cell decreased	0%	100%	0%	0%	0%	0%	100%
Edema limbs	0%	50%	0%	50%	0%	0%	100%

Alanine aminotransferase increased	0%	100%	0%	0%	0%	0%	100%
Vomiting	0%	100%	0%	0%	0%	0%	100%
Weight loss	0%	100%	0%	0%	0%	0%	100%
Nausea	0%	100%	0%	0%	0%	0%	100%

Abbreviations: N/A, not applicable; NC/NA, no change from baseline/no adverse events.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Investigator's Assessment	Inactive because results did not meet primary endpoint

Preclinical and clinical data support the possibility of anticancer action for both melatonin and metformin in solid tumors [2,3,5-7,10-21]. Few studies have analyzed their activity in melanoma [22-25]. High doses of melatonin were used in all studies. We have used low doses instead according to the registered one in the drug label. We aimed to find the net effect of melatonin or metformin in melanoma patients with no indications for their use. Our study failed to show any differences in response rate (RR), time to progression (TTP), or survival between studied groups. We found no differences in quality of life assessment except for sleep quality that improved in the melatonin arm. No new safety signals were found. This study confirmed the low efficacy of all treatment arms. We have stopped the trial because of a lack of therapy efficacy and the appearance of new effective drugs in melanoma.

Currently, dacarbazine (DTIC) is considered an ineffective and old drug for melanoma treatment [1]. BRAF inhibitors combined with MEK inhibitors or immune checkpoint inhibitors (ICIs) are now a standard of care. Yet different ICIs have shown their activity in combination with DTIC in randomized trials. This supports the absence of a negative DTIC influence on effective treatment. We have shown significant improvement in sleep quality in the melatonin group. This confirms the main action of the drug was not affected by DTIC. We can conclude that the negative trial result was related to the absence of melatonin and metformin antitumor efficacy in low doses in combination with DTIC.

Trials with similar designs conducted in our center for breast cancer patients have shown that only patients with HER2-positive breast cancer obtained benefit from the addition of melatonin or metformin to neoadjuvant chemotherapy [26]. Patients with other molecular subtypes receiving neoadjuvant chemotherapy or hormonal therapy do not receive any benefit. So, we can speculate that specific biological properties of a tumor may be essential for the development of anticancer action of either melatonin or metformin.

We made an immunologic assessment in the overall population due to low patients numbers and the absence of differences in efficacy. Patients with clinical effect had higher levels of effector cells (lymphocytes, cytotoxic T-lymphocytes) which were chronically activated and suppressed by T-helper and T-regulatory cells. Probably, DTIC action helped to release this suppressor activity from immune cells in selected patients. This is why some long-lasting effects were observed, including one complete response lasting without therapy for more than 3 years.

We have found no new safety issues in our trial. Both combinations were safe with no significant increase in toxicity.

Quality of life measurements showed a trend toward improvement in sleep scales in the melatonin group, which was lost at disease progression. Other scales have no significant differences between groups.

The addition of melatonin or metformin to dacarbazine is safe and does not significantly increase the incidence of adverse events. The addition of melatonin or metformin to DTIC has not shown additional toxicity. Biomarker findings propose an immune component of therapy action in patients with clinical benefit.

Disclosures
The authors indicated no financial relationships.

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