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# Predictive biomarkers to chemotherapy in patients with advanced melanoma receiving the combination of cisplatin--vinblastine--temozolomide (PVT) as first-line treatment: a study of the Hellenic Cooperative Oncology Group (HECOG).

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## Abstract

### BACKGROUND/AIM:

Recent progress with BRAF and immune checkpoint inhibitors has dramatically changed the treatment landscape of metastatic melanoma (MM). The limited duration of responses to new agents, however, justifies the, still important, role of chemotherapy in the management of MM. This study prospectively explored biomarkers to first-line temozolomide-based chemotherapy.

### MATERIALS AND METHODS:

Tumor samples from patients with advanced MM who received first-line therapy with the PVT combination (cisplatin-vinblastine-temozolomide), i.e. cisplatin (CDDP) 30 mg/m2 (days 1-3) i.v., vinblastine (CVT) 2 mg/m2 (days 1-3) i.v., temozolomide (TMZ) 150 mg/m2 (days 1-5) orally, every 21 days, were collected. Biomarkers (MGMT, ERCC1, p16), were evaluated by immunohistochemistry and BRAF mutations by PCR/sequencing.

### RESULTS:

Out of 35 patients included in this clinical phase II study, 12 objective response rates were achieved (ORR; 34%) including 1 complete response CR; 9 disease stabilisations (SD; 26%), with overall clinical benefit rate (CR+PR+SD) 60%, median response duration 6 months (95% confidence interval (CI)=2-16), median PFS 4 months (95% CI=2-6), median OS 12 months (95% CI=6-25) and 1-year survival rate 52%. From 24 tumor samples evaluated for biomarkers, 13 (54%) were BRAF mutated and 11 (46%) wild-type (wt). Patients with BRAF-mutated tumors showed better response rates compared to BRAF wild-type (39% vs. 27%) and improved PFS/OS. Sub-analyses, according to BRAF status, did not reveal any significant correlations with excision repair cross-complementation group 1 enzyme (ERCC1), however, in patients with BRAF-mutated tumors, low O6-methylguanine-DNA methyltransferase (MGMT) nuclear expression correlated with better PFS, p=0.0384.

### CONCLUSION:

First-line PVT chemotherapy for MM is efficacious and well-tolerated. Interesting 'hypothesis-generating' results show that candidate predictive biomarkers could identify subgroups of patients, i.e. tumors with BRAF mutation and low MGMT expression, with better outcomes following TMZ-based chemotherapy, thus warranting further evaluation in larger cohorts.