Title

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Gene expression profiling identifies responsive patients with cancer of unknown primary treated with carboplatin, paclitaxel, and everolimus: NCCTG N0871 (alliance)†

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Background: Carboplatin (C) and paclitaxel (P) are standard treatments for carcinoma of unknown primary (CUP). Everolimus, an mTOR inhibitor, exhibits activity in diverse cancer types. We did a phase II trial combining everolimus with CP for CUP. We also evaluated whether a gene expression profiling (GEP) test that predicts tissue of origin (TOO) could identify responsive patients.

Patients and methods: A tumor biopsy was required for central confirmation of CUP and GEP. Patients with metastatic, untreated CUP received everolimus (30 mg weekly) with P (200 mg/m^2) and C (area under the curve 6) every 3 weeks. The primary end point was response rate (RR), with 22% needed for success. The GEP test categorized patients into two groups: those having a TOO where CP is versus is not considered standard therapy.

Results: Of 45 assessable patients, the RR was 36% (95% confidence interval 22% to 51%), which met criteria for success. Grade ≥3 toxicities were predominantly hematologic (80%). Adequate tissue for GEP was available in 38 patients and predicted 10 different TOOs. Patients with a TOO where platinum/taxane is a standard ($n = 19$) tended to have higher RR (53% versus 26%) and significantly longer PFS (6.4 versus 3.5 months) and OS (17.8 versus 8.3 months, $P = 0.005$), compared with patients ($n = 19$) with a TOO where platinum/taxane is not standard.

Conclusions: Everolimus combined with CP demonstrated promising antitumor activity and an acceptable side-effect profile. A tumor biomarker identifying TOO may be useful to select CUP patients for specific antitumor regimens.

ClinicalTrials.gov: NCT00936702.

Key words: cancer of unknown primary, tissue of origin, everolimus, platinum chemotherapy, taxane chemotherapy, expression profile

introduction

Cancer of unknown primary site (CUP) is a heterogeneous group of cancers where the site of origin remains occult after detailed investigations. CUP is generally treated with empiric platinum/taxane or platinum/gemcitabine which yields tumor response rates (RR) of 15%–20% and a survival of ∼9 months [1–7]. Accurate identification of the tissue of origin (TOO) via molecular profiling and subsequent site-specific therapy may improve outcomes. Gene expression profiling (GEP) has accurately identified the TOO in ∼85% of patients in patients with known primary [8–12]. In retrospective studies, molecular profiling rendered a prediction in the majority of CUP patients that was consistent with clinical and pathologic features [10, 13]. In CUP patients whose primary was detected later, molecular

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testing predicted the primary in 75% of cases [14]. However, data are limited on whether site-specific (versus empiric) therapy based on molecular TOO improves outcomes (supplementary Table S1, available at *Annals of Oncology* online) [13, 15, 16]. To date, no prospective studies have evaluated whether a specific molecular profile is associated with differential clinical outcomes among CUP patients treated with uniform chemotherapy.

Even with new TOO assays, novel therapies are needed. Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase involved in cell proliferation, growth, differentiation, migration, and survival [17]. Everolimus, an mTOR inhibitor, has shown preclinical/clinical antitumor activity, alone and combined with chemotherapy, in multiple cancer types.

We assessed the activity of everolimus in combination with carboplatin and paclitaxel in untreated patients with CUP. We also performed tumor GEP using a clinically available assay to assess TOO, and determined clinical outcomes according to the predicted TOO.

patients and methods

This prospective, phase II trial was conducted across 24 sites in the North Central Cancer Treatment Group (now Alliance for Clinical Trials in Oncology) (NCT00936702). Sites obtained institutional review board approval, and patients provided written informed consent.

patient selection

Eligible patients had newly diagnosed CUP after the following procedures were unrevealing of a primary site: medical history, physical examination, blood counts, chemistry profile, computed tomography (CT) scan of the chest, abdomen/pelvis, directed evaluation of all symptomatic areas, mammography in women, and colonoscopy in patients with liver metastasis or an elevated carcinoembryonic antigen (CEA) (see supplementary Methods, available at *Annals of Oncology* online, for details).

protocol interventions

All patients were assigned to receive everolimus (30 mg once per week) combined with carboplatin [area under the curve (AUC) 6] and paclitaxel (200 mg/m^2) once every 21 days [18]. Tumor assessments were conducted with CT scans every 6 weeks. Protocol treatment continued until disease progression (RECIST) or unacceptable toxicities.

Weekly monitoring reports were established to monitor adverse events (AEs) throughout the trial. In the first 10 patients assessable for AEs, 5 patients experienced at least one grade 4 hematologic toxicity at least possibly related to study treatment (4 patients with grade 4 neutropenia, including 1 with grade 4 anemia; 1 with grade 4 thrombocytopenia). There were no grade 4 nonhematologic toxicities. The per-protocol stopping rule boundary, focused on grade 4 or higher nonhematologic AEs, was never crossed. However, due to higher than anticipated myelosuppression, the protocol was amended to reduce the starting dose [carboplatin (AUC 5), paclitaxel 175 mg/m^2].

expression profiling

Of 46 specimens sent for processing (Pathwork Diagnostics, now Response Genetics, Los Angeles, CA), which included microdissection and RNA extraction, as described [11], 8 were disqualified (decalcified [1]; insufficient tumor [6]; inadequate RNA [1]). The remaining 38 specimens were analyzed using the ResponseDX Tissue of Origin™ Test, a 2000-gene expression microarray-based assay that quantifies the similarity to the 15 tissues on the panel as a Similarity Score (range 0–100) summing to 100 across all 15 tissues [11, 19].

statistics

The primary objective was to estimate the confirmed RR. A two-stage phase II Simon optimal design was used to determine whether the confirmed RR was at least 30% versus at most 15%. Interim analysis was to be performed after the first 20 assessable patients, with further accrual abandoned if ≤3 responses were observed. If the study continued to full accrual, as occurred, ≥11 responses in the first 50 assessable patients (22%) was considered worthy of further study. Fifty patients provided 85% power to detect a confirmed RR of 30% (1-sided α 0.10). Secondary end points include progression-free survival (PFS), overall survival (OS), duration of response (DOR), and safety and tolerability. Predefined secondary analysis included evaluation of OS and PFS by TOO. (See supplementary Methods, available at *Annals of Oncology* online, for further details.)

results

baseline characteristics

Between October 2009 and October 2012, 46 patients with centrally confirmed CUP were enrolled (supplementary Figure S1, available at *Annals of Oncology* online). The trial closed before the target sample size ($n = 50$) was reached, because a sufficient number of confirmed responses had occurred to meet the primary end point. Baseline patient characteristics are summarized in Table 1. The majority of patients had distant metastases to the liver, lung, or bone (68%), with tumors exhibiting poor/anaplastic differentiation (80%) (Table 1).

Table 1. Baseline characteristics ($N = 46$)

Variable	*n* (%)
Age, years	
Median (range)	61 (32–79)
Gender	
Female	28 (61)
Male	18 (39)
Performance score	
0	25 (54)
1	15 (33)
2	6 (13)
Histologic diagnosis	
Adenocarcinoma	36 (78)
Poorly differentiated nonsmall-cell carcinoma	5 (11)
Poorly differentiated squamous carcinoma	1 (2)
Other	4 (9)
Histologic grade	
Well	1 (2)
Moderate	8 (18)
Poor	28 (62)
Undifferentiated, anaplastic	8 (18)
Predominant location of disease	
Liver	18 (39)
Lung	10 (22)
Soft tissue	9 (20)
Bone	3 (7)
Other	6 (13)

Table 2. Patient outcomes ($N = 45$ assessable patients)

Variable	*n* (%)
Best clinical response	
Complete response	0
Partial response	16 (36)
Stable disease	15 (33)
Progression	13 (29)
Not assessed	1 (2)
Confirmed response rate	
Responders, *n*	16
Evaluable, *n*	45
Rate, %	36% (95% CI 22% to 51%)
Overall survival	
Median, months	10.1 (95% CI 7.3–14.8)
Progression-free survival	
Median, months	4.1 (95% CI 2.8–5.7)

CI, confidence interval.

outcome

Forty-five patients were assessable for tumor response, OS, and PFS (Table 2). One patient was deemed ineligible (treated prior to registration). There were 16 confirmed partial responses, yielding a RR of 36% [95% confidence interval (CI) 22% to 51%], which met the predefined criteria for success for the primary end point.

Median DOR was 5.8 (95% CI 2.5–6.8) months. With a median follow-up of 34.1 months (range 19.0–36.0 months), 12 of the 16 patients with a confirmed response subsequently progressed. Median OS was 10.1 (95% CI 7.3–14.8) months, and median PFS was 4.1 (95% CI 2.8–5.7) months (supplementary Figure S2 and S3, available at *Annals of Oncology* online).

treatment received

A median of 4.5 cycles (range 1–50) of therapy were administered across all 46 patients. Treatment was discontinued for the following reasons: disease progression ($n = 34$, 74%), AEs ($n = 8$, 17%), patient refusal ($n = 2$, 4%), alternative treatment ($n = 1$, 2%), and other ($n = 1$, 2%).

toxicity

All 46 patients were assessable for toxicity. Table 3 shows all >grade 3 AEs regardless of relatedness occurring more than once or that were ≥grade 4. Forty patients (87%) had at least one grade 3/4 AE. Myelosuppression was frequent as expected with carboplatin/paclitaxel. Two patients (4%) had febrile neutropenia. There were 21 patients with at least one grade 4 or higher AE, which were almost entirely hematologic [95% (20/21)].

The most common grade 3/4 nonhematologic toxicities included hypersensitivity (13%), alkaline phosphatase (9%), fatigue (9%), hyponatremia (9%), neuropathy (9%), and abdominal pain (9%). Two patients developed pneumonitis (grade 3, probably related; grade 4, unlikely related), and two patients had grade 3 dyspnea (possibly and unlikely related). There was one grade 5 sepsis event considered unrelated to study treatment.

Table 3. Serious adverse events regardless of relatedness to therapy ($N = 46$)[a]

n (%)	Grade 3	Grade 4
Hematology		
Neutropenia	14 (30)	17 (37)
Leukopenia	21 (46)	4 (9)
Thrombocytopenia	8 (17)	5 (11)
Anemia	5 (11)	2 (4)
Lymphopenia	2 (4)	0
Nonhematologic		
Hypersensitivity	6 (13)	0
Alkaline phosphatase increased	3 (7)	1 (2)
Fatigue	4 (9)	0
Hyponatremia	4 (9)	0
Peripheral sensory neuropathy	4 (9)	0
Abdominal pain	4 (9)	0
Dehydration	3 (7)	0
Thrombosis	1 (2)	1 (2)
Ascites	2 (4)	0
Diarrhea	2 (4)	0
Nausea	2 (4)	0
Febrile neutropenia	2 (4)	0
Aspartate aminotransferase increased	2 (4)	0
Pneumonitis	1 (2)	1 (2)
Dyspnea	2 (4)	0
Hyperkalemia	2 (4)	0
Back pain	2 (4)	0
Pain not otherwise specified	2 (4)	0

There was one grade 5 sepsis event deemed unlikely to be related to treatment.

Table 4. Predicted tissue of origin ($N = 38$)

Predicted tissue	*n* (%)	Platinum/taxane standard?
Nonsmall-cell lung	8 (21)	Yes
Ovarian	7 (18)	
Bladder	2 (5)	
Breast	2 (5)	
Subtotal	**19 (50)**	
Colorectal	7 (18)	No
Pancreas	6 (16)	
Hepatocellular	3 (8)	
Kidney	1 (3)	
Gastric	1 (3)	
Sarcoma	1 (3)	
Subtotal	**19 (50)**	

tumor profiling

Among 38 patients with assessable expression profiling data (see Patients and Methods), 10 different TOOs were predicted (Table 4). The most common sites of origin were nonsmall-cell lung, ovarian, colorectal, and pancreas, which together accounted for 73% (28/38) of cases.

Expression profiles in 50% (19/38) of cases showed a TOO in which platinum/taxane therapy is standardly used, whereas the

other half showed sites of origin where platinum/taxane is not standardly used (Table 4). A trend toward a higher confirmed RR (53% versus 26%, $P = 0.097$) and DOR (median 6.6 versus 2.8 months; $P = 0.10$), and significantly longer PFS [median 6.4 versus 3.5 months, $P = 0.026$; HR 0.47 (95% CI 0.24–0.93)] and OS [median 17.8 versus 8.3 months, $P = 0.0052$; HR 0.37 (95% CI 0.18–0.76)] were observed in patients with a predicted TOO in which platinum/taxane is standardly used versus not used, respectively (Figure 1).

discussion

We evaluated the tolerability and activity of everolimus in combination with carboplatin and paclitaxel in previously untreated patients with poor-prognosis CUP. Our results demonstrate that this regimen was reasonably well tolerated with a toxicity profile as expected from these agents [18, 20]. The primary end point of a confirmed RR (36%) was achieved, which was higher than the RR (15%) observed in the poor-prognosis group of the largest CUP trial to date utilizing a carboplatin/paclitaxel doublet [1]. Additionally, these results were superior to the RR (12%) observed in an NCCTG phase II trial evaluating gemcitabine plus irinotecan [21] and the carboplatin/paclitaxel arm of another trial [7]. Unlike prior CUP trials, mammograms (in women), and colonoscopy (in those with liver metastasis or elevated CEA) were required, possibly decreasing the frequency of good prognosis breast and colorectal tumor profiles (see below) [13, 15, 16, 22]. Though our trial was not powered for OS, the median observed OS (10.1 months) was generally similar to prior randomized trials [3–5, 7]. Based on this encouraging antitumor activity, a randomized phase III trial comparing the antitumor activity of a platinum/taxane regimen that includes everolimus is certainly warranted. However, a conventional randomized trial may be difficult to complete in a timely manner. Instead, innovative trials designs that integrate IHC, TOO profiling, and driver mutations may be preferable [23].

The role of gene expression profiles in the management of CUP has not been defined in prospective trials utilizing uniform therapy. In this regard, we examined patient tumors utilizing an array-based CUP profile that previously showed strong accuracy in identifying the TOO [10, 11]. A total of 83% of tumors were evaluable, comparable with the performance of other CUP assays [9, 13, 15]. Half (19/38) of the tumors identified through expression profiling were predicted to have a TOO where platinum/taxane therapy would be considered a standard regimen (i.e. 'platinum/taxane-sensitive'), whereas the other half had cancer types where platinum/taxane therapy is not standard (i.e. 'platinum/taxane-resistant'). Patients with an assay-predicted

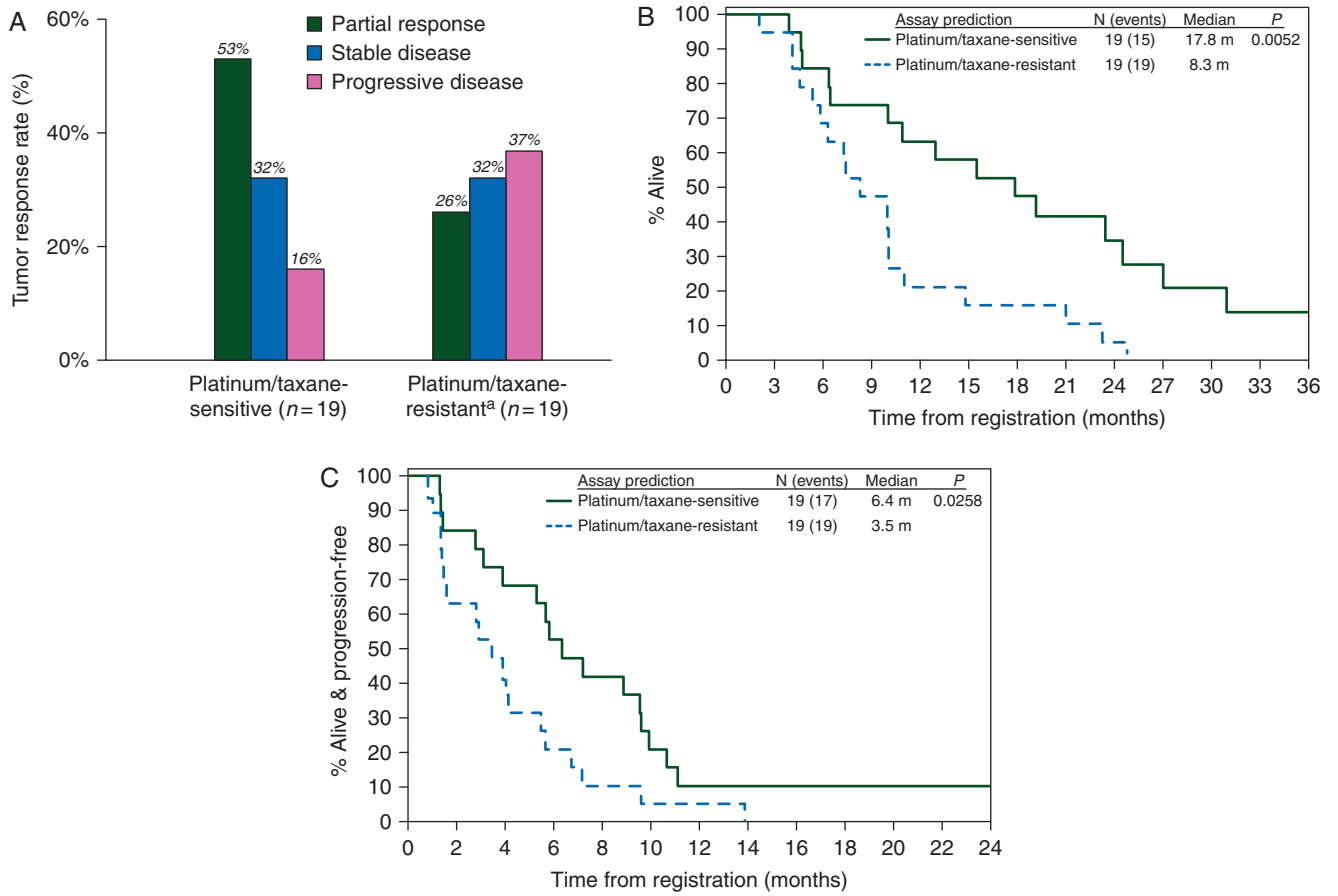

Figure 1. Tumor response rates (A), overall survival (B), and progression-free survival (C) in patients with metastatic carcinoma of unknown primary treated with everolimus, carboplatin, and paclitaxel therapy in the N0871/Alliance trial are shown, according to whether gene expression analysis predicted a platinum/taxane-sensitive *v*-resistant tumor profile. [a]Excludes one case where tumor response was not assessed.

platinum/taxane-sensitive tumor tended to have higher confirmed RR (53% versus 26%), and exhibited both statistically and clinically significantly longer PFS (6.4 versus 3.5 months) and OS (17.8 versus 8.3 months), compared with those with assay-predicted platinum/taxane-resistant tumors. To our knowledge, these are the first data to show that a TOO test is associated with tumor response and survival in patients prospectively treated with uniform platinum/taxane-based therapy.

Our findings complement data from the largest prospective evaluation of TOO tests and patient outcomes, which suggested that the assignment of therapy based on the results of TOO may improve outcomes in at least some patients [15]. A key novelty of our study is that all patients received platinum/taxane therapy regardless of the TOO result, when compared with TOO-directed therapies in the prior study. In the prior study, patients with a NSCLC, ovary, or breast profile, who thus predominantly received platinum/taxane therapy, exhibited a longer median OS than other CUP subtypes; and their outcomes are comparable with the platinum/taxane-sensitive group in our study (supplementary Table S1, available at *Annals of Oncology* online). While we designated breast, lung, and ovarian profiles as platinum/taxane-sensitive, it is important to note that subsequent lines of therapy can differ between these tumors as a result of TOO testing and identification of a targetable lesion (e.g. *HER2* in breast, *ALK* in NSCLC). In addition, retrospective data indicate that CUP patients with a CRC profile who received site-specific therapy have an RR and OS that is higher than expected for empirically treated CUP [24, 25], although this finding was not prospectively confirmed [15].

Caution must be utilized in interpreting these results. Published studies, to date, including ours, share the limitation that improved outcomes compared with historical controls may result from lead-time bias. The only unequivocal way to assess the clinical utility of these assays would be a prospective trial with randomization to either empiric or assay-directed therapy. However, such a trial is unlikely to be feasible due to the large sample size required, partly because a substantial portion of CUP patients, as shown in the current study, as well as previously [15], have cancer profiles where standard profile-directed therapy does not differ dramatically from empiric CUP therapy (e.g. ovarian, breast, NSCLC). For CUP patients with cancer types where profile-directed therapy differs from empiric therapy, the random assignment would likely be met with physician and patient reluctance and would take years to complete, as noted by others [15].

Our findings have relevance for research efforts. Specifically, CUP patients whose TOO predicts a low clinical benefit from a platinum/taxane-based regimen should be considered for prospective trials in which alternative regimens are studied. In our study, most cancer types in this group were CRC, pancreatic, and hepatocellular (HCC), and their observed survival (8.3 months) fell within the expected range for patients with known pancreatic and HCC primaries, but was shorter than expected for known CRC. We suggest incorporating sequence-based strategies to identify key oncogenic alterations and to select patients for clinical trials testing agents which target these alterations. Recent genomic sequencing data of 236 cancer-related genes in 200 CUP tumors showed one or more targetable genomic alterations in 85% of tumors [26]. The low frequency of an anomaly in any particular pathway makes it challenging to randomize patients at the level of each druggable alteration. Therefore, piggybacking on established early trials (e.g. M-PACT), initiating innovative small trials, or performing randomized trials in international consortiums may be feasible approaches until further characterization of CUPs is available [23].

Our study has several strengths, including central pathologic review, the participation of multiple centers in a cooperative group, and meticulous prospective collection of outcomes. Limitations include the relatively modest sample size, which reflects the uncommon incidence of CUP in the United States.

In conclusion, we found that everolimus combined with carboplatin and paclitaxel demonstrated promising antitumor activity and was reasonably tolerated in patients with untreated metastatic CUP. A TOO assay identified patients clinically responsive to everolimus plus platinum/taxane and may be useful to select CUP patients for specific antitumor regimens.

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disclosure

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references

1. Briasoulis E, Kalofonos H, Bafaloukos D et al. Carboplatin plus paclitaxel in unknown primary carcinoma: a phase II Hellenic Cooperative Oncology Group Study. J Clin Oncol 2000; 18: 3101–3107.
2. Greco FA, Burris HA III, Litchy S et al. Gemcitabine, carboplatin, and paclitaxel for patients with carcinoma of unknown primary site: a Minnie Pearl Cancer Research Network study. J Clin Oncol 2002; 20: 1651–1656.
3. Culine S, Lortholary A, Voigt JJ et al. Cisplatin in combination with either gemcitabine or irinotecan in carcinomas of unknown primary site: results of a randomized phase II study–trial for the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01). J Clin Oncol 2003; 21: 3479–3482.
4. Hainsworth JD, Spigel DR, Clark BL et al. Paclitaxel/carboplatin/etoposide versus gemcitabine/irinotecan in the first-line treatment of patients with carcinoma of unknown primary site: a randomized, phase III Sarah Cannon Oncology Research Consortium Trial. Cancer 2010; 16: 70–75.
5. Gross-Goupil M, Fourcade A, Blot E et al. Cisplatin alone or combined with gemcitabine in carcinomas of unknown primary: results of the randomised GEFCAPI 02 trial. Eur J Cancer 2012; 48: 721–727.
6. Varadhachary GR, Raber MN. Cancer of unknown primary site. N Engl J Med 2014; 371: 757–765.
7. Hainsworth JD, Daugaard G, Lesimple T et al. Paclitaxel/carboplatin with or without belinostat as empiric first-line treatment for patients with carcinoma of unknown primary site: a randomized, phase 2 trial. Cancer 2015; 4: 673–681.

8. Erlander MG, Ma XJ, Kesty NC et al. Performance and clinical evaluation of the 92-gene real-time PCR assay for tumor classification. J Mol Diagnostics 2011; 13: 493–503.
9. Kerr SE, Schnabel CA, Sullivan PS et al. Multisite validation study to determine performance characteristics of a 92-gene molecular cancer classifier. Clin Cancer Res 2012; 18: 3952–3960.
10. Horlings HM, van Laar RK, Kerst JM et al. Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinomas of unknown primary. J Clin Oncol 2008; 26: 4435–4441.
11. Pillai R, Deeter R, Rigl CT et al. Validation and reproducibility of a microarray-based gene expression test for tumor identification in formalin-fixed, paraffin-embedded specimens. J Mol Diagn 2011; 13: 48–56.
12. Monzon FA, Lyons-Weiler M, Buturovic LJ et al. Multicenter validation of a 1,550-gene expression profile for identification of tumor tissue of origin. J Clin Oncol 2009; 27: 2503–2508.
13. Varadhachary GR, Talantov D, Raber MN et al. Molecular profiling of carcinoma of unknown primary and correlation with clinical evaluation. J Clin Oncol 2008; 26: 4442–4448.
14. Greco FA, Lennington WJ, Spigel DR, Hainsworth JD. Molecular profiling diagnosis in unknown primary cancer: accuracy and ability to complement standard pathology. J Natl Cancer Inst 2013; 105: 782–790.
15. Hainsworth JD, Rubin MS, Spigel DR et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon research institute. J Clin Oncol 2013; 31: 217–223.
16. Hainsworth JD, Schnabel CA, Erlander MG et al. A retrospective study of treatment outcomes in patients with carcinoma of unknown primary site and a colorectal cancer molecular profile. Clin Colorectal Cancer 2012; 11: 112–118.
17. Hidalgo M, Rowinsky EK. The rapamycin-sensitive signal transduction pathway as a target for cancer therapy. Oncogene 2000; 19: 6680–6686.
18. Eberhardt WE, Mitchell P, Schiller JH et al. Feasibility of adding everolimus to carboplatin and paclitaxel, with or without bevacizumab, for treatment-naive, advanced non-small cell lung cancer. Invest New Drugs 2014; 32: 123–134.
19. Dumur CI, Lyons-Weiler M, Sciulli C et al. Interlaboratory performance of a microarray-based gene expression test to determine tissue of origin in poorly differentiated and undifferentiated cancers. J Mol Diagn 2008; 10: 67–77.
20. Hauke RJ, Infante JR, Rubin MS et al. Everolimus in combination with paclitaxel and carboplatin in patients with metastatic melanoma: a phase II trial of the Sarah Cannon Research Institute Oncology Research Consortium. Melanoma Res 2013; 23: 468–473.
21. Holtan SG, Steen PD, Foster NR et al. Gemcitabine and irinotecan as first-line therapy for carcinoma of unknown primary: results of a multicenter phase II trial. PLoS One 2012; 7: e39285.
22. Varadhachary GR, Raber MN, Matamoros A, Abbruzzese JL. Carcinoma of unknown primary with a colon-cancer profile-changing paradigm and emerging definitions. Lancet Oncol 2008; 9: 596–599.
23. Varadhachary G. Carcinoma of unknown primary site: the poster child for personalized medicine? JAMA Oncol 2015; 1: 19–21.
24. Greco FA, Lennington WJ, Spigel DR et al. Carcinoma of unknown primary site: outcomes in patients with a colorectal molecular profile treated with site specific chemotherapy. J Cancer Ther 2012; 3: 37–43.
25. Varadhachary GR, Karanth S, Qiao W et al. Carcinoma of unknown primary with gastrointestinal profile: immunohistochemistry and survival data for this favorable subset. Int J Clin Oncol 2014; 19: 479–484.
26. Ross JS, Wang K, Gay L et al. Comprehensive genomic profiling of carcinoma of unknown primary site: new routes to targeted therapies. JAMA Oncol 2015; 1: 40–49.

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Seeking the driver in tumours with apparent normal molecular profile on comparative genomic hybridization and targeted gene panel sequencing: what is the added value of whole exome sequencing?

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Background: Molecular tumour profiling technologies have become increasingly important in the era of precision medicine, but their routine use is limited by their accessibility, cost, and tumour material availability. It is therefore crucial to assess their relative added value to optimize the sequence and combination of such technologies.

Patients and methods: Within the MOSCATO-01 trial, we investigated the added value of whole exome sequencing (WES) in patients that did not present any molecular abnormality on array comparative genomic hybridization (aCGH) and

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