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Phase II Study of Dabrafenib and Trametinib in Patients with Tumors with BRAF^{V600E} Mutations: Updated Results From NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol H

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Conflicts of interest: Dr. Salama reports research funding (paid to institution) from: Ascentage, Bristol Myers Squibb, Ideaya, Immunocore, Merck, Olatec Therapeutics, Regeneron, Replimune, Seagen; and has served as scientific advisory board member Bristol Myers Squibb Iovance, Regeneron, Novartis and Pfizer. Dr. Williams reports serving as a consultant to Leidos. Dr. O'Dwyer reports research funding (paid to institution) from: Pfizer, Bristol Myers Squibb, Astra Zeneca, Glaxo Smith Kline, Five Prime, Merck, Syndax, BBI, Novartis, Celgene, Incyte, Lilly/Imclone, Array, h3biomedicine, Taiho, Minneamrata, Pharmacyclics/Abbvie, Mirati. Dr. Flaherty has/had served on the Board of Directors of Clovis Oncology, Strata Oncology, Checkmate Pharmaceuticals, Kinnate Pharmaceuticals and Scorpion Therapeutics; Scientific Advisory Boards of PIC Therapeutics, Apricity, Fog Pharma, Tvardi, xCures, Monopteros, Vibliome, ALX Oncology, Karkinos, Soley Therapeutics, Alterome, IntrECate, and PreDICTA; and as consultant to Novartis, Genentech, Takeda, and Transcode Therapeutics; and received research funding from Novartis.
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Abstract

Purpose: Subprotocol H of the NCI-MATCH trial demonstrated the efficacy of dabrafenib + trametinib in a cohort of patients with *BRAF*^{V600} mutated treatment refractory solid tumors and myeloma. To confirm the longer-term efficacy and safety of this combination in additional patients, an expansion cohort was added.

Methods: Patients with *BRAF*^{V600} mutated malignancies were eligible; patients with cholangiocarcinoma and low-grade serous ovarian cancer were excluded from the expansion cohort. Patients received dabrafenib 150 mg po BID and trametinib 2 mg PO daily. The primary endpoint was to evaluate the objective response rate (ORR); secondary endpoints included progression-free survival (PFS), 6-month PFS, and overall survival (OS).

Results: The expansion cohort enrolled from October 2020-January 2023. In total, 36 patients were included in the primary efficacy analysis for the combined cohort, including 6 patients from the expansion cohort and 30 patients from the original cohort, representing 17 different tumor histologies. 56% of patients were female, with a median age of 60. The ORR was 36.1% (13/36; 90% CI 22.9–51.2%). Median PFS was 11.4 months, and median OS was 28.6 months. 6-month PFS was 67.6% (90% CI 54.5–80.8%). In the 6 molecularly confirmed cases in the expansion cohort, there were 2 responses, including 1 complete response in a patient with a pilocytic astrocytoma; an additional 2 patients without molecular confirmation also had PRs. 3 patients (2 from the original cohort and 1 from the expansion cohort) remain on therapy. The safety profile was consistent with previous reports with dabrafenib and trametinib.

Conclusion: This study confirms the clinical benefit of dabrafenib + trametinib in *BRAF*^{V600} mutated solid tumors, supporting the recent tumor agnostic regulatory approval of this combination.

Trial Registration: clinicaltrials.gov identifier NCT04439292

Introduction

The development of molecularly targeted agents has transformed the treatment landscape in oncology, and comprehensive genomic profiling is now routinely incorporated into standard of care practice. Activating mutations in *BRAF,* of which *BRAF*^{V600} is the most common, are seen in a high percentage of certain malignancies, such as melanoma, and occur at a lower rate in a wide range of other cancers.[1,2] Highly selective BRAF and MEK inhibitors have demonstrated improved clinical outcomes in a number of disease-specific settings,

including *BRAF*^{V600} mutated melanoma and non-small cell lung cancer (NSCLC), among others.[3–6] Benefit was not uniformly seen, however, especially in the setting of *BRAF* mutated colorectal cancer, leading to concerns about the broad applicability of this approach across the spectrum of *BRAF*^{V600} mutated malignancies.[7]

The NCI-MATCH trial was designed as a precision medicine study with distinct tumor agnostic subprotocols in which patients were assigned to receive treatment based on molecular testing results from pre-treatment biopsies. Subprotocol H of the NCI-MATCH trial investigated the efficacy of the selective BRAF + MEK inhibitors dabrafenib and trametinib in *BRAF*^{V600} mutated treatment refractory solid tumors and lymphomas. Previously reported data from 29 patients in the original primary analysis cohort demonstrated an overall response rate (ORR) of 38% and a median overall survival (OS) of 28.6 months.[8] Based on these data, as well as results from the multiple cohort ROAR trial as well as data in pediatric patients with low grade glioma, dabrafenib and trametinib received a tumor agnostic approval from the US Food and Drug Administration (FDA) for the treatment of *BRAF*^{V600} mutated solid tumors.[9,10] This updated analysis reports on longer term follow-up for the original cohort, as well as the inclusion of an expansion cohort.

Methods

Study Design and Patient Population

The Molecular Analysis for Therapy Choice (NCI-MATCH) trial, developed by ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) and the National Cancer Institute (NCI), aimed to find signals of efficacy for treatments targeted to actionable molecular alterations found in any tumor type. Adult patients with any solid tumor, lymphoma, or myeloma who progressed on standard treatment or for whom no standard treatment was available were eligible. Adequate hematopoietic, liver and kidney function, a performance status of ECOG ≤ 1, and submission of fresh biopsy were required. Written informed consent was obtained for all subjects. The study was performed in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was reviewed by institutional review boards at each participating center.

Tumor profiling was accomplished as described in Lih et al.[11] After the end of central testing of 5954 fresh tumor biopsies, patients were accepted if they had eligible molecular alterations identified by molecular profiling done for clinical reasons at one of 26 CLIA accredited laboratories approved to identify NCI-MATCH eligible patients. Patients were assigned using a prospectively defined NCI designed informatics rules algorithm (MATCHBOX), as previously described.[12]

For subprotocol H, patients with melanoma, thyroid or colorectal cancer were excluded; patients with non-small cell lung cancer (NSCLC) were excluded after the FDA approved dabrafenib and trametinib for this indication. With the initiation of the expansion cohort, patients with cholangiocarcinoma and low grade serous ovarian cancer were excluded based on the availability of histology specific data regarding MAPK pathway inhibition in these indications[13 14] Patients were excluded if they had prior exposure to a BRAF or MEK1/2

inhibitor, any history of a *RAS* mutation positive cancer, active brain metastases, or had a left ventricular ejection fraction (LVEF) below the institutional lower limit of normal.

Study treatment and assessments

All subjects received dabrafenib 150 mg twice daily and trametinib 2 mg once daily continuously as part of a 28-day cycle. Patients could continue on therapy until disease progression, intolerable toxicity, or study withdrawal. Response was evaluated every 8 weeks using criteria for solid tumors, lymphoma, glioblastoma multiforme, or multiple myeloma as appropriate.[15–17] Toxicity was evaluated using NCI Common Terminology Criteria for Adverse Events version 4.0.

Statistical Considerations

The primary objective was to evaluate the objective response rate for each subprotocol, as previously reported.[8] Secondary objectives were progression-free survival (PFS6) at 6 months, PFS, toxicity assessment, and evaluation of predictive biomarkers. The original cohort of subprotocol H accrued 35 patients and met the primary endpoint with a 38% response rate, which led to consideration of filing with the FDA for approval of this combination for a tumor agnostic indication. Given this, an expansion cohort was planned to improve the precision of the response rate estimate. The accrual goal for the expansion cohort was the earlier of 50 patients or 21 months of accrual. Due to COVID, the expansion cohort accrued only 8 patients, and the trial was closed to accrual in January 2023. The primary efficacy cohort included patients who were eligible, started protocol treatment and had central molecular confirmation of $BRAF^{V600}$ mutation status. Patients enrolled through designated labs were included in the primary efficacy cohort only if the profiling results were centrally confirmed by the MATCH assay. Toxicity assessment included all patients who started protocol treatment.

Results

Patient characteristics

44 patients with $BRAF^{V600}$ mutations were enrolled on the combined cohort, including both the original and expansion cohorts. 36 patients were included in the primary efficacy analysis for the combined cohort (30 from the original cohort and 6 from the expansion cohort), which included patients who were eligible, began therapy, and had central molecular confirmation of *BRAF* mutation status (Figure 1). One patient included in the previously published primary efficacy analysis of the original cohort was later determined to be ineligible and excluded from the primary efficacy cohort.[8] Two patients from the original cohort with newly confirmed *BRAF* mutations have been included in the primary analysis cohort reported here. Expansion cohort patient characteristics are presented in Table 1. The median age was 52 years, 33% of patients were female, and half had received at least 3 lines of prior therapy. Histology subtypes for the original cohort are noted in eTable 1. In the combined cohort, 17 distinct tumor histologies were represented.

Efficacy and safety

Expansion cohort: Among the 6 patients in the expansion cohort primary analysis group, 2 responses were reported: 1 patient with a pilocytic astrocytoma had a complete response (CR), with a PFS >18 months, and 1 patient with a glioblastoma had a partial response (PR), with a PFS of >12 months. Median PFS was 3.6 months, and median OS was 19.8 months (Figures 2a and 2b). Of note, an additional 2 patients without central molecular confirmation also had PRs, including a patient with pancreatic cancer with a PFS of >7 months, and a patient with ovarian cancer with a PFS of 9 months. Additional details regarding these patients are presented in Table 2. Details regarding PFS and OS for all analyzable patients in the expansion cohort are presented in Figures 3a and 3b.

Combined cohort: For the combined cohort of 36 patients in the primary analysis cohort, the confirmed ORR is 36.1% (90% CI 22.9–51.2%), including one patient with a CR (Figure 4a). Durable responses were seen across a number of histologies (Figure 4b). At the time of data cutoff (Nov 2023) 2 patients in the original cohort and 1 patient in the expansion cohort were still on therapy. The estimated 6-month PFS in the combined cohort is 67.6% (90% CI 54.5–80.8%), and the median OS is 28.6 months (Figures 5a and 5b).

Adverse events: Adverse events (AEs) were previously reported for the original cohort and were similar to established safety profiles of dabrafenib and trametinib. No new safety events were noted in longer term follow-up for the primary or expansion cohort. In the expansion cohort, the most frequently reported AEs that were possibly attributed to therapy in all treated patients (n=8) were nausea and fatigue which occurred in 4/8 patients (50%). Elevations in alkaline phosphatase were noted in 6/8 patients (75%) including 1 grade 3 event, as were elevations in alanine and aspartate aminotransferases, which were each seen in 4/8 patients (50%), including 1 grade 3 event. There were no grade 4 or 5 events in the expansion cohort. Additional details regarding treatment related adverse events for the combined cohort including all treated patients are provided in eTable 2.

Co-occurring genomic alterations: The NCI-MATCH genomic assay was designed to identify prespecified genomic alterations, details of which have been previously published.[11]Co-occurring mutation data was available for all 6 patients in the expansion cohort primary analysis group. In addition to $BRAF^{V600E}$, 4 patients had additional genomic alterations, including 2 patients with a missense mutation in TP53. However, there was substantial heterogeneity, and otherwise no overlapping alterations were identified in the expansion cohort. An updated figure highlighting additional genomic alterations identified in both the original and expansion cohort is shown in eFigure 1. In a prior exploratory analysis, a co-occuring mutation in TP53 appeared to be associated with worse clinical outcomes. In an analysis of the combined cohorts (N=36), patients with wild-type TP53 had a longer PFS compared to those with a mutation HR 0.497 [(95% CI 0.224 – 1.1060, p= 0.087.] (eFigure 2). There additionally continued to be trend in terms of association with TP53 status and objective response: patients with wild-type TP53 had an ORR of 45.8% and those with mutated TP53 had an ORR of 16.7% (p=0.14), though this did not reach statistical significance.

Discussion

This trial met its primary endpoint, with an ORR for the combined cohort of 36.1% (90% CI 22.9–51.2%), a 6-month PFS of 67.6% (90% CI 54.5–80.8%), and a median OS of 28.6 months. These results confirm the potential benefit of therapy with dabrafenib and trametinib across varied tumor types which harbor $BRAF^{V600}$ mutations. Based on these data, as well as those from separately conducted cohort studies, dabrafenib and trametinib received regulatory approval for the treatment of $BRAF^{V600}$ mutated solid tumors in 2022.[8–10]

While the development of secondary resistance to BRAF/MEK inhibitor therapy remains a concern, a number of patients in this study derived durable clinical benefit, as demonstrated by a 6-month PFS rate of nearly 70%, and notably with 3 patients still on active therapy. Consistent with previously reported data in the original cohort, nearly all patients in the expansion cohort demonstrated disease control, with only 1 patient having a best response of PD. The relative rarity of primary resistance to dabrafenib and trametinib has been well documented, though this data is largely derived from front line studies in diseases such as melanoma and non-small cell lung cancer.[3,4] The heterogeneity of the patient population studied in this trial, including the additional patients in the expansion cohort, lends further support to the concept that BRAF targeted therapy can result in meaningful clinical benefit across a varied spectrum of tumor types, even in patients with treatment refractory disease. While tumor agnostic therapeutic approaches have advanced considerably in recent years, at the time of study initiation, sensitivity to BRAF/MEK inhibition across a heterogeneous patient population was largely undefined. Early data reporting on the relative resistance to this approach in $BRAF^{V600}$ mutated colorectal cancer suggested that sensitivity may be histology dependent, further underscoring the need to test this combination in a broad patient population.[7] Longer term results from the ROAR trial, which was a phase 2 basket trial investigating dabrafenib and trametinib in selected patient cohorts with rare tumors, demonstrated response rates that ranged from 0% to nearly 90%.[9] Median PFS and OS were reported by cohort, and ranged from 6.3–9.5 months and 13.5–33.5 months, respectively.[9] The glioma cohort of the ROAR study reported an ORR of 33% [95% CI 20–49] for high grade gliomas; additionally a cohort which included treatment refractory patients with cholangiocarcinoma reported an ORR of 51% [95% CI 36–37].[5,18] As multiple tumor types were represented in this subprotocol, our study was not designed to evaluate the histology specific clinical activity of dabrafenib and trametinib, however, our data is comparable to previously published reports across a range of tumor types. Importantly, the demonstrated high rates of disease control with dabrafenib and trametinib are clinically meaningful, given the treatment refractory nature of the patient population enrolled on this study, who had no standard of care options available at the time of trial enrollment. This has important implications for clinicians in guiding treatment selection, given the low incidence of BRAF mutations overall, histology specific trials are only feasible in selected tumor types, and the cohort reported here fills an important knowledge gap. With additional patients and extended follow-up, the clinical activity and the potential for durable responses supports this combination as a standard in patients with $BRAF^{V600}$ mutated tumors who have progressed on prior therapy.

Co-occurring mutation data was available for all 36 patients in the combined cohort, with TP53 being the most commonly identified additional alteration, a feature that has been seen in other analyses of sequencing data across multiple cancers.[19] The association of mutations in TP53 with potentially poorer outcomes has been reported in numerous other tumor types, but it remains a challenging pathway to successfully target.[20,21]Beyond this, there was significant heterogeneity in additional co-occurring alterations, with minimal overlap, likely reflective of the multiple histologies represented in this study.

While the number of patients enrolled onto the expansion cohort was limited, the benefit seen in this group, including a durable complete response in a patient with a pilocytic astrocytoma, lends further support to using a tumor agnostic approach in selecting targeted therapy for the vast majority of $BRAF^{V600}$ mutated malignancies. These results also further underscore the importance of routine, comprehensive molecular profiling in the management of patients with advanced malignancies. Given the promising benefit seen in this refractory patient population, investigating the role of dabrafenib and trametinib as front-line therapy or in earlier disease stages could be a promising strategy for the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Key objective:

What is the efficacy of dabrafenib and trametinib in *BRAF*^{V600} mutated tumors outside of currently approved FDA indications?

Knowledge generated:

In this single arm phase 2 study of 36 patients with treatment refractory *BRAF*^{V600} mutated solid tumors, dabrafenib and trametinib demonstrated an overall response rate of 36.1%, including a complete response (CR) in a patient with pilocytic astrocytoma. No new safety signals were identified

Relevance:

This study indicates that treatment with dabrafenib and trametinib results in clinically meaningful anti-tumor activity across a number of *BRAF*^{V600} mutated malignancies.

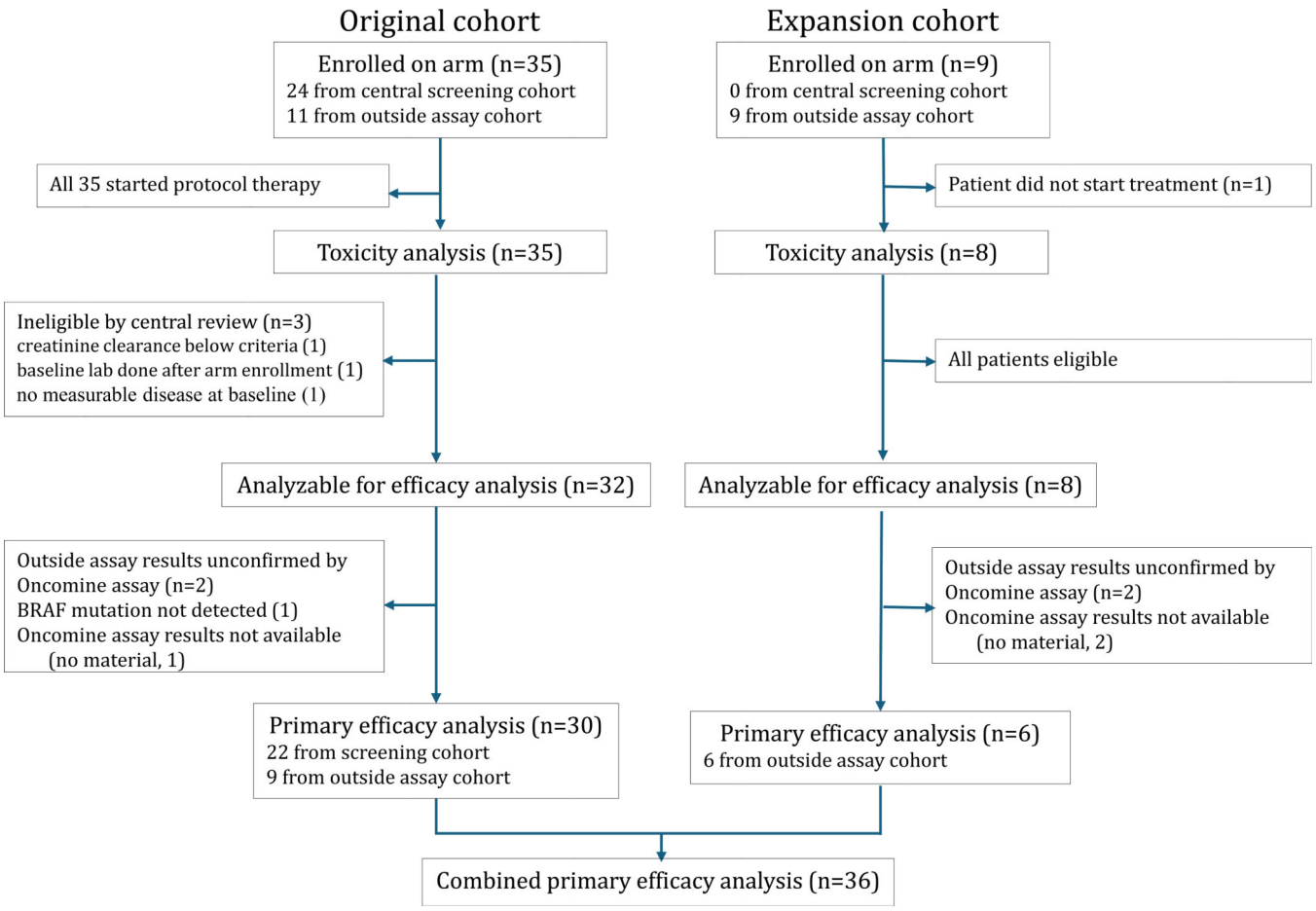

Figure 1:
Patient disposition

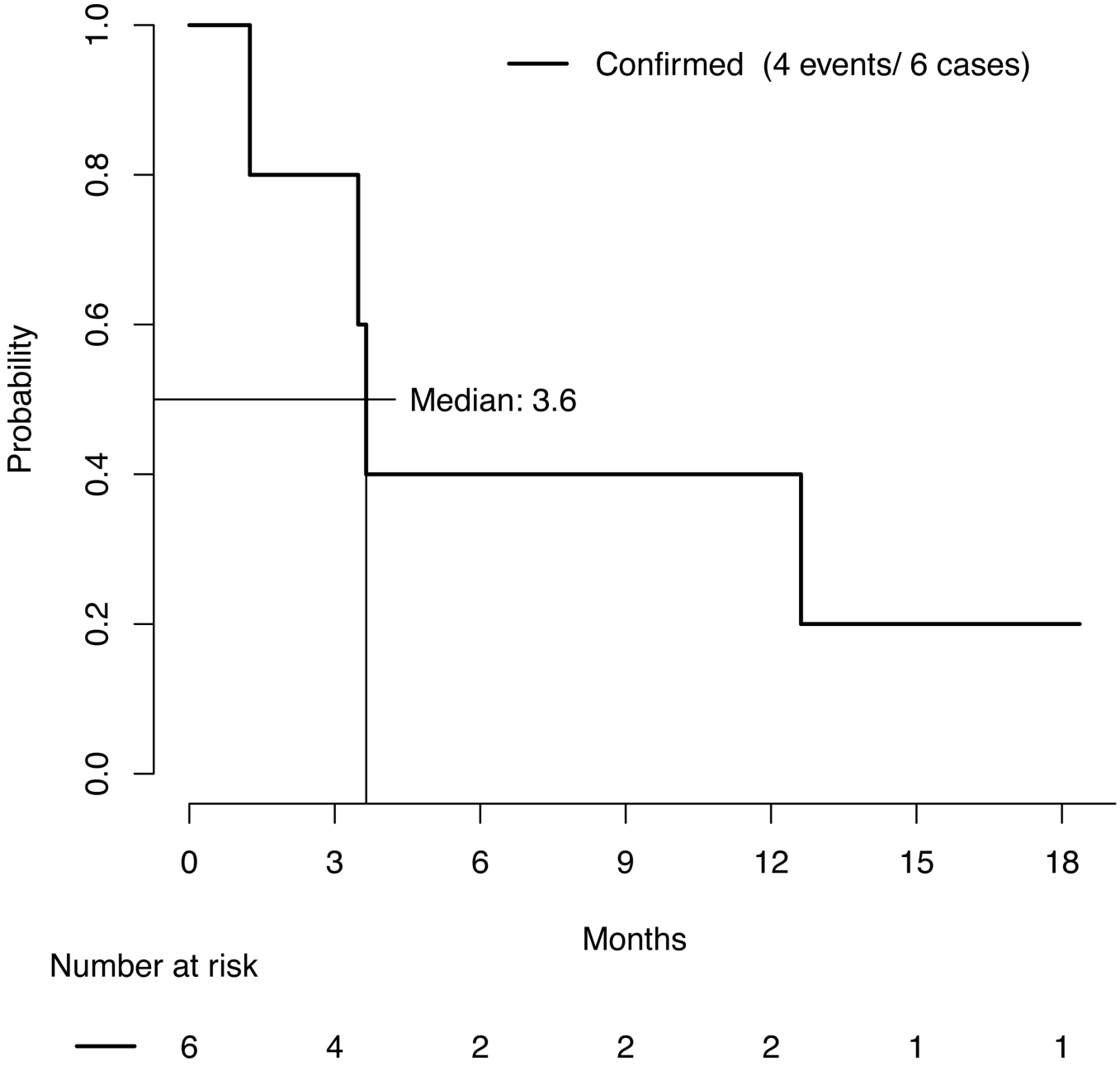

Figure 2a.
Progression-free survival for the primary efficacy analysis in the expansion cohort (N=6).

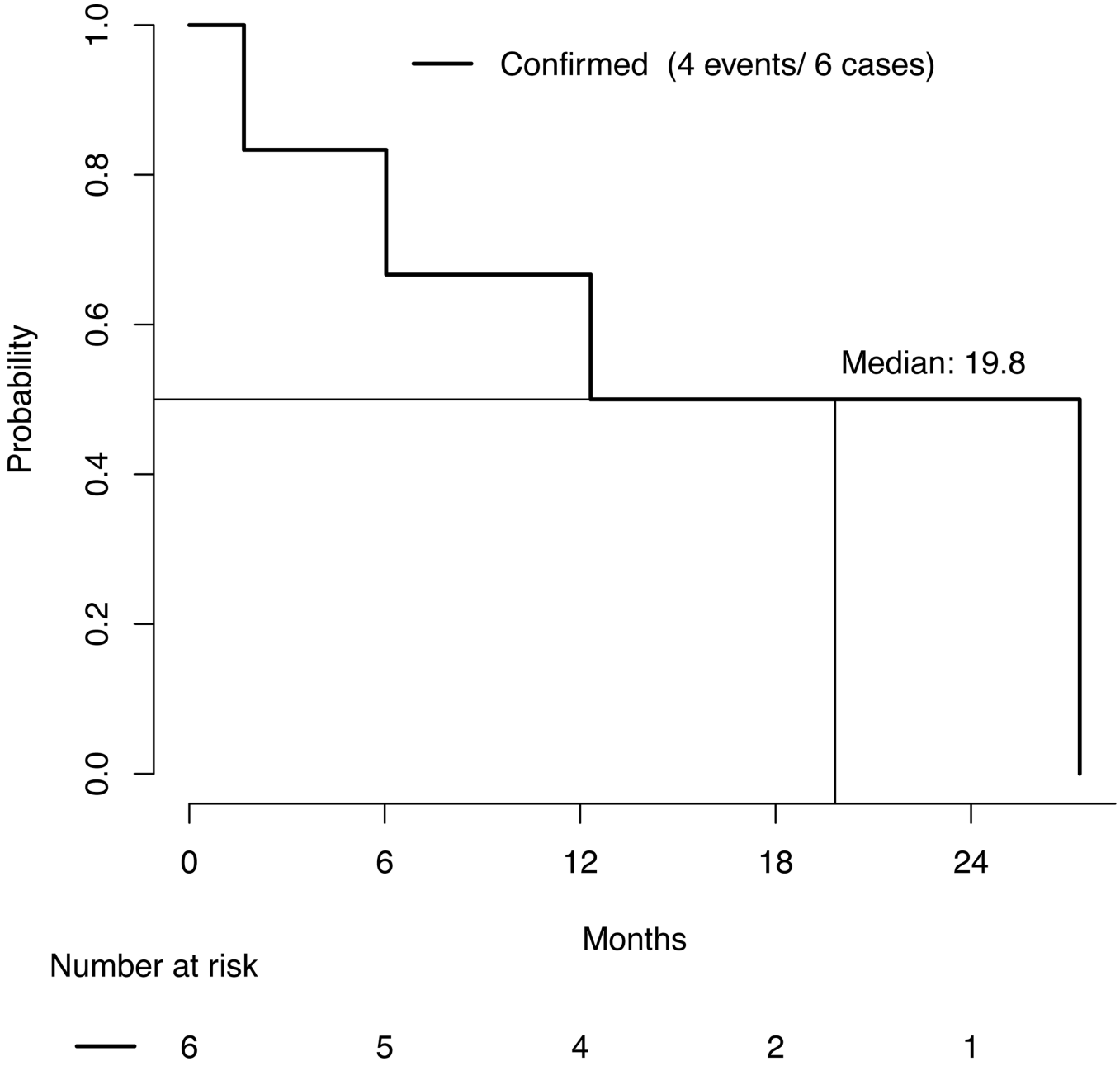

Figure 2b.
Overall survival, for the primary efficacy analysis in the expansion cohort (N=6).

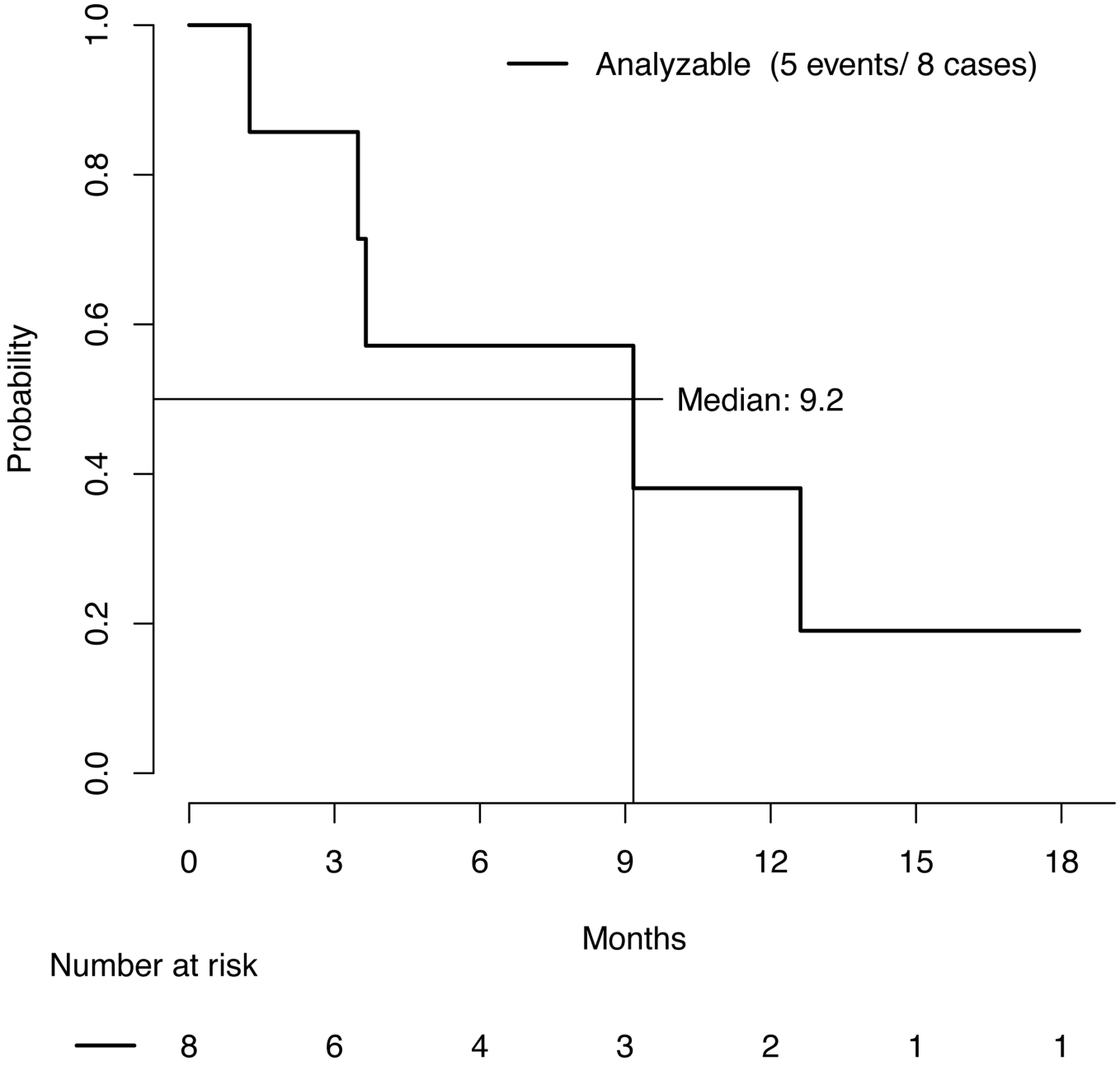

Figure 3a.
Progression-free survival, analyzable cases (expansion cohort).

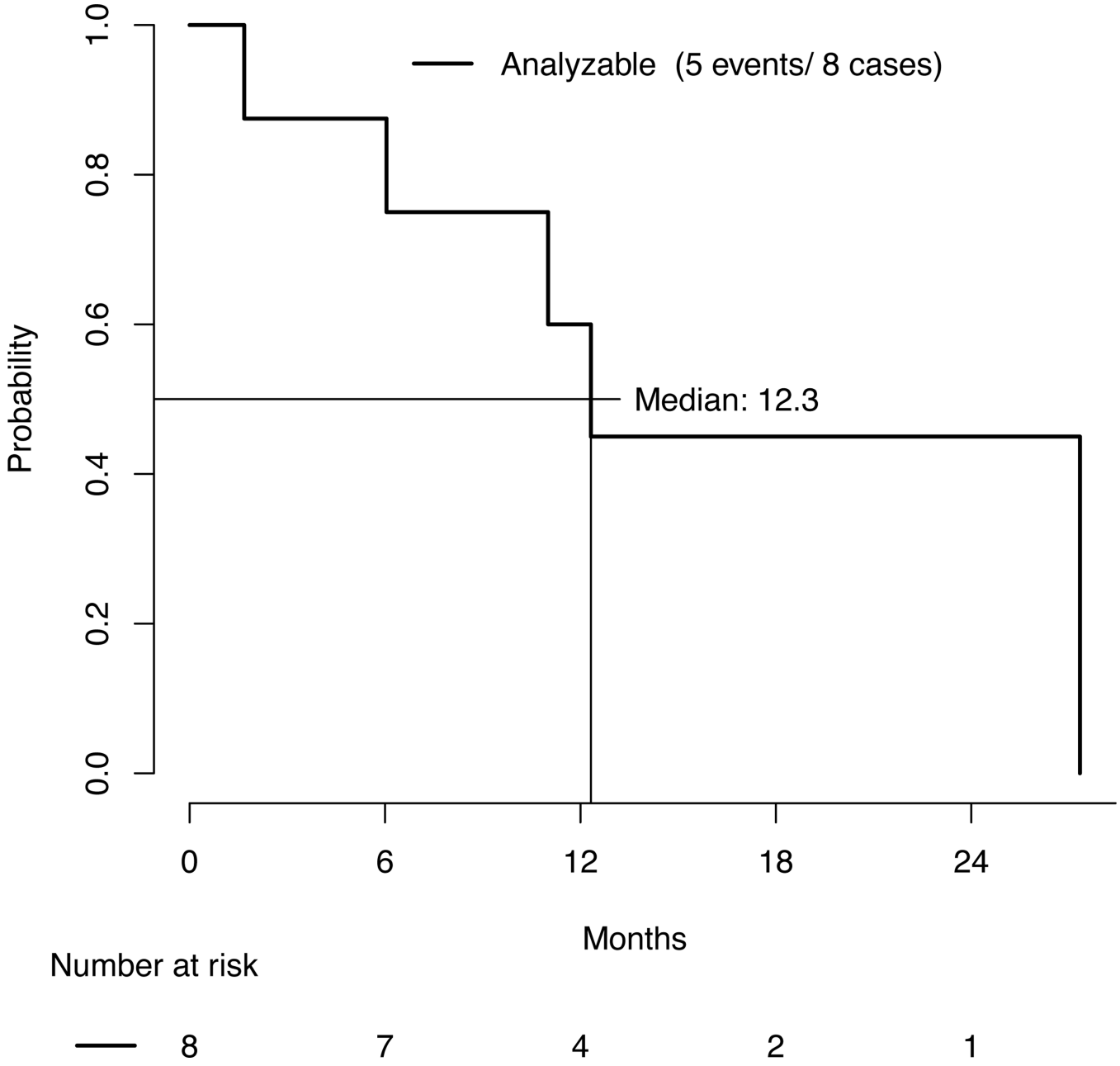

Figure 3b.
Overall survival, analyzable cases (expansion cohort).

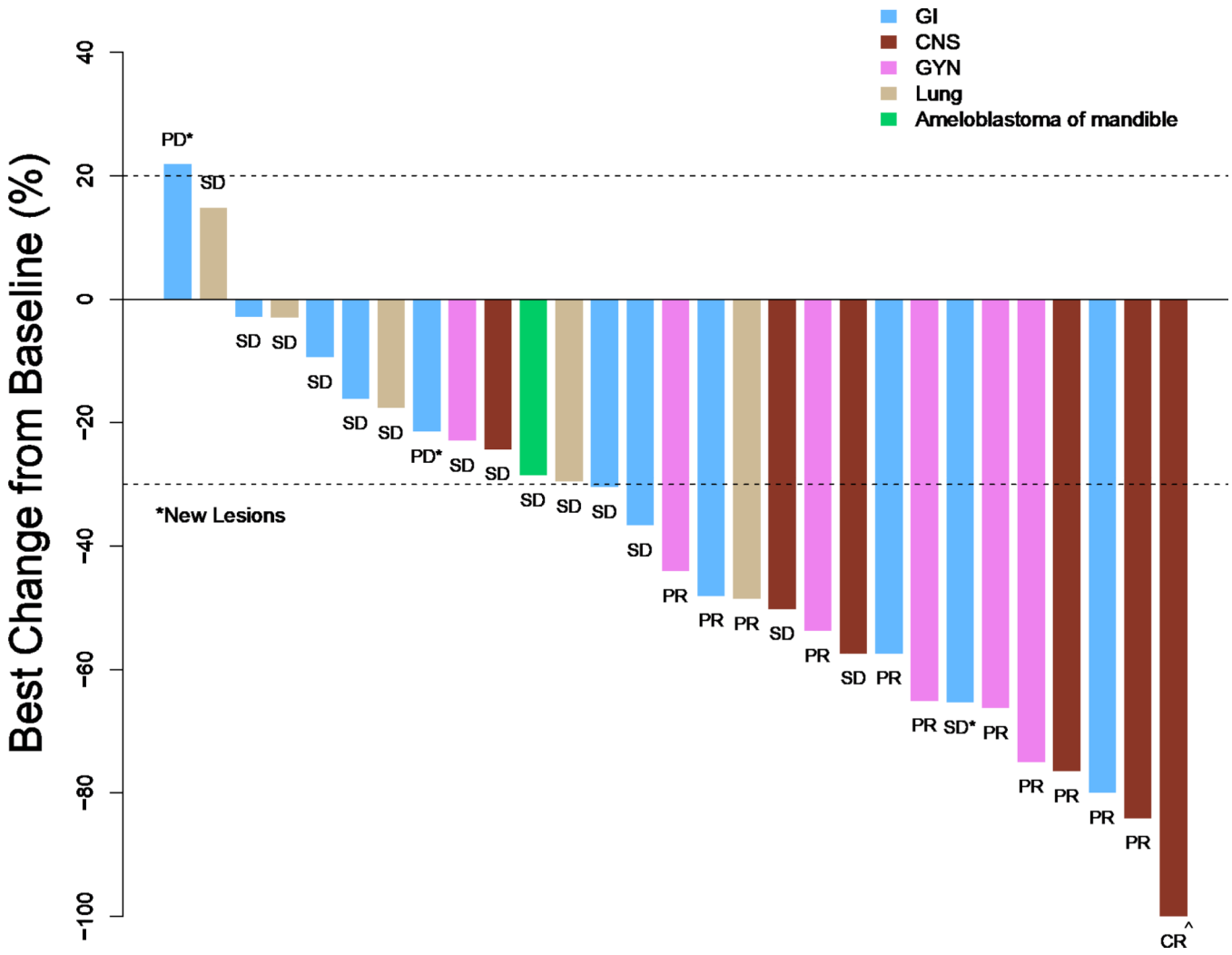

Figure 4a.

Best percentage change in baseline tumor measurements for the combined primary analysis cohort (eligible, treated and molecularly confirmed). Includes 29 patients who were evaluable for response and had baseline and at least one follow-up measurement available. ^ Expansion cohort patient with pilocytic astrocytoma with a complete response.

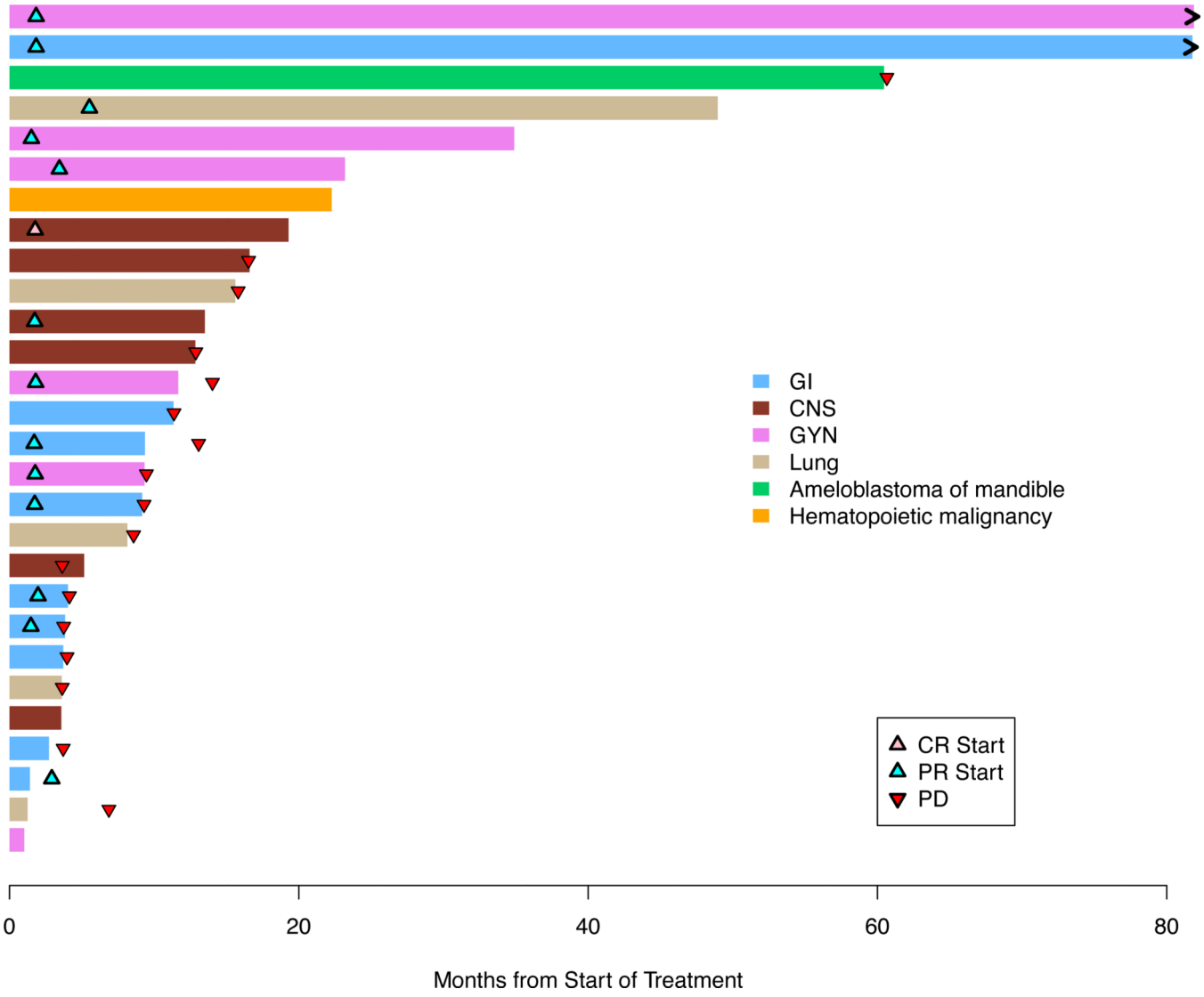

Figure 4b.

Duration of treatment for patients in the combined primary efficacy analysis cohort with best confirmed response of SD, PR or CR. Arrows indicate ongoing therapy at the time of data cutoff. Median duration of treatment was 10.3 months (range 1.0 – 81.9 months).

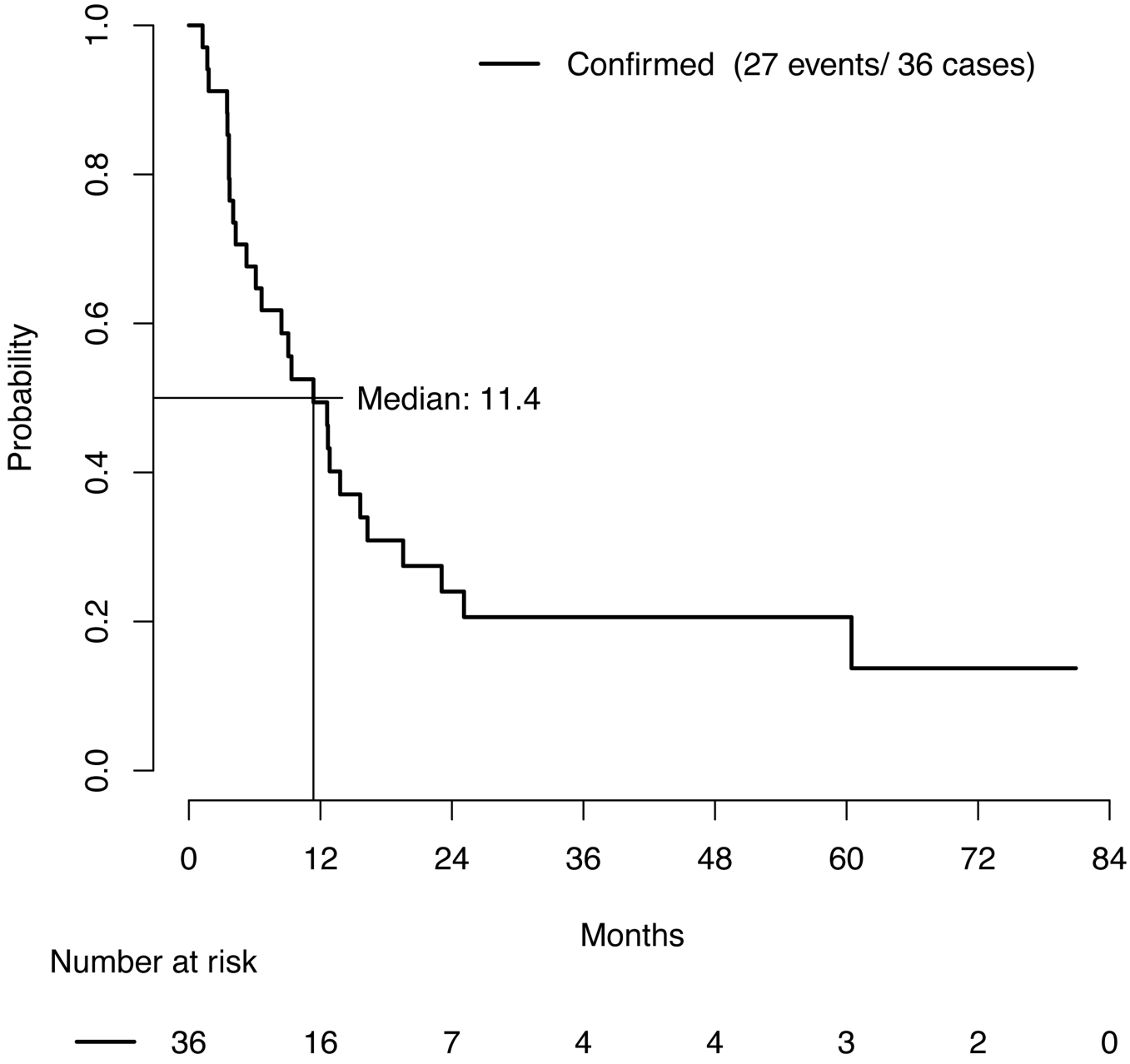

Figure 5a.
Progression-free survival, in the combined primary efficacy analysis cohort (N=36).

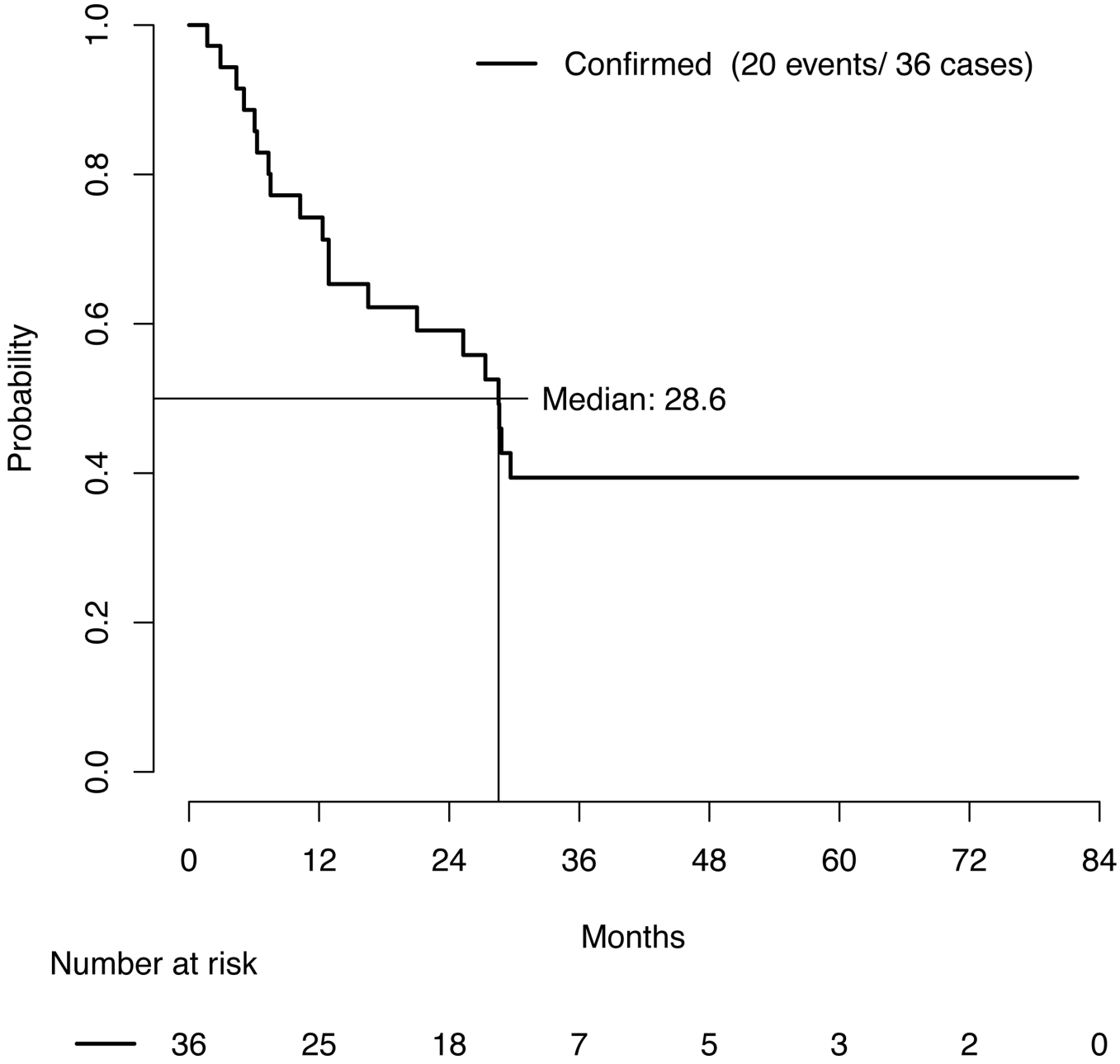

Figure 5b.
Overall survival, in the combined primary efficacy analysis cohort (N=36).

Table 1:

Patient Characteristics: expansion cohort

	Molecularly confirmed (n=6)	Not molecularly confirmed (n=2)	Total N=8
Female	2 (33%)	1 (50%)	3 (38%)
Age (median, yrs)	52	70	60
Race White unknown	 6 (100%)	 1 (50%) 1 (50%)	 7 (88%) 1 (12%)
Hispanic	1 (17%)	1 (50%)	2 (25%)
BRAF mutation type V600E	 6 (100%)	 2 (100%)	 8 (100%)
Performance status 0 1	 2 (33%) 4 (67%)	 0 (0%) 2 (100%)	 2 (25%) 6 (75%)
Prior therapies 1 2 3 ≥4	 1 (17%) 2 (33%) 2 (33%) 1 (17%)	 0 (0%) 0 (0%) 2 (100%) 0 (0%)	 1 (12%) 2 (25%) 4 (50%) 1 (12%)
Gastrointestinal tract Pancreatic cancer* High grade neuroendocrine carcinoma of rectum Large cell neuroendocrine carcinoma of colon	 1 1	1	
Gynecologic Ovarian cancer*		1	
Central nervous system Glioblastoma* Pilocytic astrocytoma	3 1		

* pathology not centrally reviewed (1 case for GBM)

Table 2.

Response details in all analyzable expansion cohort patients with PFS > 168 days

Molecular Assay Status	Best Conf Resp	Best % Reduction	Histology	Cycles	PFS, days
Confirmed	PR	−58%	Glioblastoma	14	384
Confirmed	CR	−100%	Pilocytic astrocytoma	21	559+
Unconfirmed	PR	−69%	Pancreatic cancer (not Islets)	9+	224+
Unconfirmed	PR	−57%	Ovarian cancer, NOS	7	279