

AFP, AFP-L3% and DCP levels in patients with advanced hepatocellular carcinoma treated with sorafenib

JOHANNES
GUTENBERG
UNIVERSITÄT
MAINZ

Henning Schulze-Bergkamen¹, Arndt Weinmann¹, Marcus A. Wörns¹, Pia R. Spies, Andreas Teufel¹, Christoph Düber², Gerd Otto³, Annette Shresta¹, Binje Vick¹, Robert Küper⁴, Josef Schurek⁵, Peter R. Galle¹, Marcus Schuchmann¹, Martin Volkmann⁵

¹Medizinische Klinik und Poliklinik, Universität Mainz, ²Klinik und Poliklinik für Radiologie, Universität Mainz, ³Transplantationschirurgie und Chirurgie von Leber, Gallenwegen, Pankreas, Universität Mainz, ⁴Wako Pure Chemical Industries, Ltd., Neuss, ⁵Labor Prof. Seelig und Kollegen, Karlsruhe

Background and aims

The multikinase inhibitor sorafenib (Nexavar®) was approved for the therapy of advanced hepatocellular carcinoma (HCC) in 2008. Within the SHARP study a life-extension of 2,8 months with an acceptable profile of side-effects could be demonstrated for patients with Child-Pugh A liver cirrhosis.¹

AFP-L3 (in %) is the fraction of *Lens culinaris* agglutinin-reactive AFP to total AFP and is also like **DCP** (des-gamma-carboxyprothrombin) useful for early detection and prognosis assessment of HCC.^{2,3}

Considering the shortcomings of RECIST criteria in the age of targeted therapy we have investigated in this study serum levels of AFP, AFP-L3 and DCP as potential markers for monitoring of the response to sorafenib therapy.

Patients and methods

In 32 patients, who were treated between January 2007 and December 2008 with the standard dose of sorafenib in the case of advanced HCC (2x400mg/day), AFP, AFP-L3 and DCP were determined (AFP-L3 and DCP were measured by the Liquid-phase Binding Assay System™, Wako Chemicals GmbH). In 17 patients at least one additional determination of the markers was carried out 3-6 months after the initiation of the therapy. 3-4 months after initiation of the therapy a radiological staging (CT or MRT) was performed.

| | |
|---------------------------------------|-----------|
| Total number of patients | 32 |
| Sex | |
| Male | 29 |
| Female | 3 |
| Age (Years) | |
| Median | 65 |
| Range | 48-81 |
| ECOG performance status | 12/13/5/2 |
| Aetiology of the liver disease | |
| Nutritive-toxic | 9 |
| Hepatitis B | 4 |
| Hepatitis C | 6 |
| Haemochromatosis | 2 |
| NASH | 4 |
| No liver disease | 4 |
| cryogenic cirrhosis | 3 |
| Child-Pugh stage | |
| No liver cirrhosis | 10 |
| A/B/C | 4/16/2 |
| BCLC score | |
| B/C/D | 8/20/4 |
| Initial therapy | |
| RFA/PEI | 3 |
| surgical resection | 11 |
| Liver transplantation | 3 |
| TACE | 14 |
| Systemic chemotherapy | 3 |

Table 1: Patient characteristics at therapy initiation with sorafenib.

Results

In 14/32 patients (44%) all 3 markers (AFP, AFP-L3 and DCP) were elevated significantly, in only 1/32 patient no marker was elevated (Fig. 1).

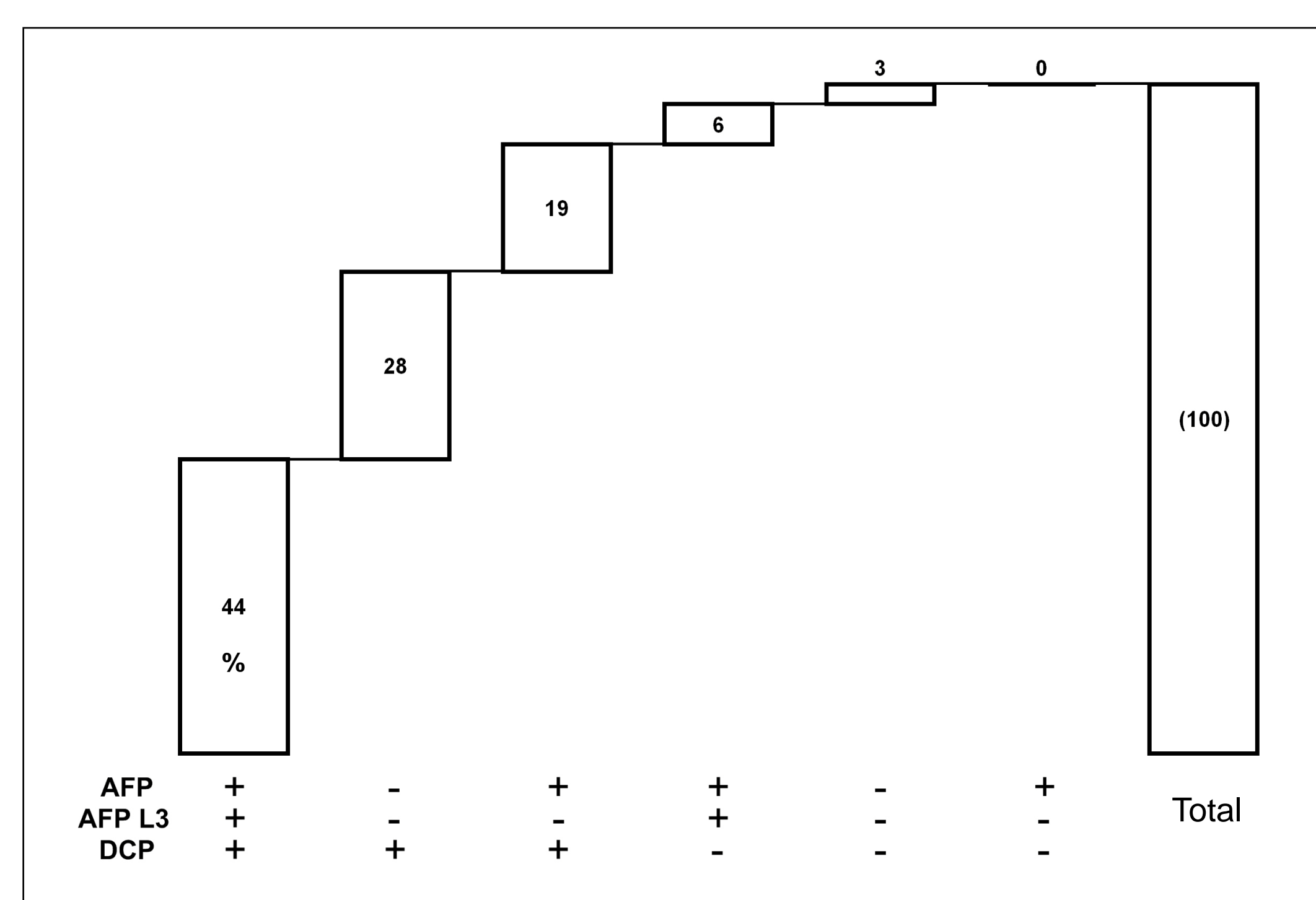


Fig. 1: Serum marker results in 32 patients with advanced HCC before sorafenib-therapie (data in %).

A positive DCP result (>7,5ng/ml) was found in 29/32 patienten (91%). In the tumour stage UICC III-IV all patients showed an elevated DCP (Fig. 2). AFP was elevated in 22/32 patients. Of the patients with positive AFP (>10ng/ml) 16/22 showed an elevated L3 fraction (>10%). In a control cohort of 55 patients with liver cirrhosis an elevated AFP was detected in 2/55, elevated AFP-L3% in 0/55 and an elevated DCP in 7/55 patients.

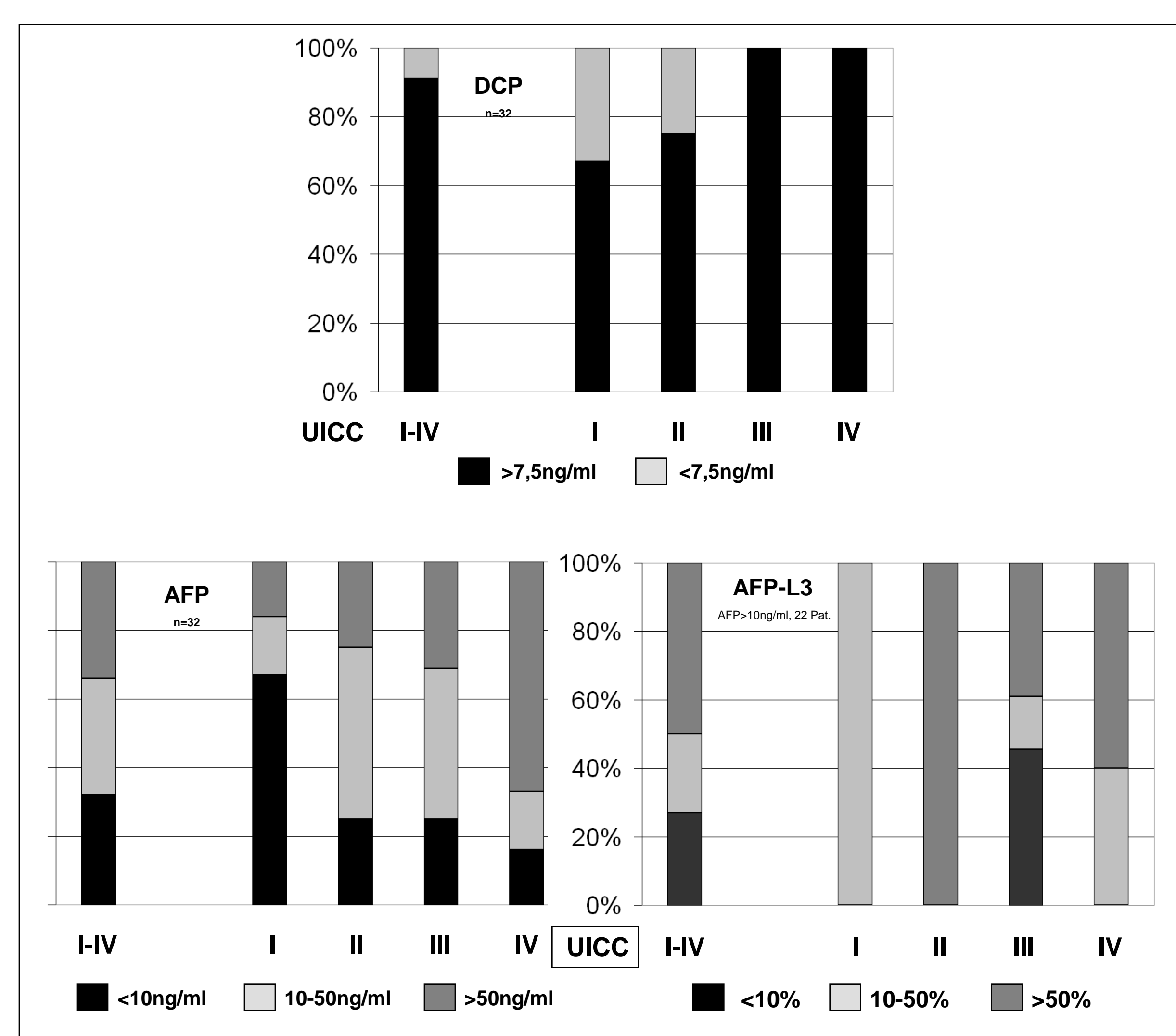


Fig. 2: Serum marker results in relation to the UICC stage before initiation of the sorafenib therapy (n=32).

Subsequently a correlation of the serum marker course with the response to sorafenib was investigated (Fig. 3). In the total cohort (n=17) after 3-4 months of therapy a Disease Control Rate (DCR) of 35% was observed. In patients without AFP increase the DCR was 38%, in those without DCP or AFP-L3% increase 67% and in those without DCP and AFP-L3 increase 100%.

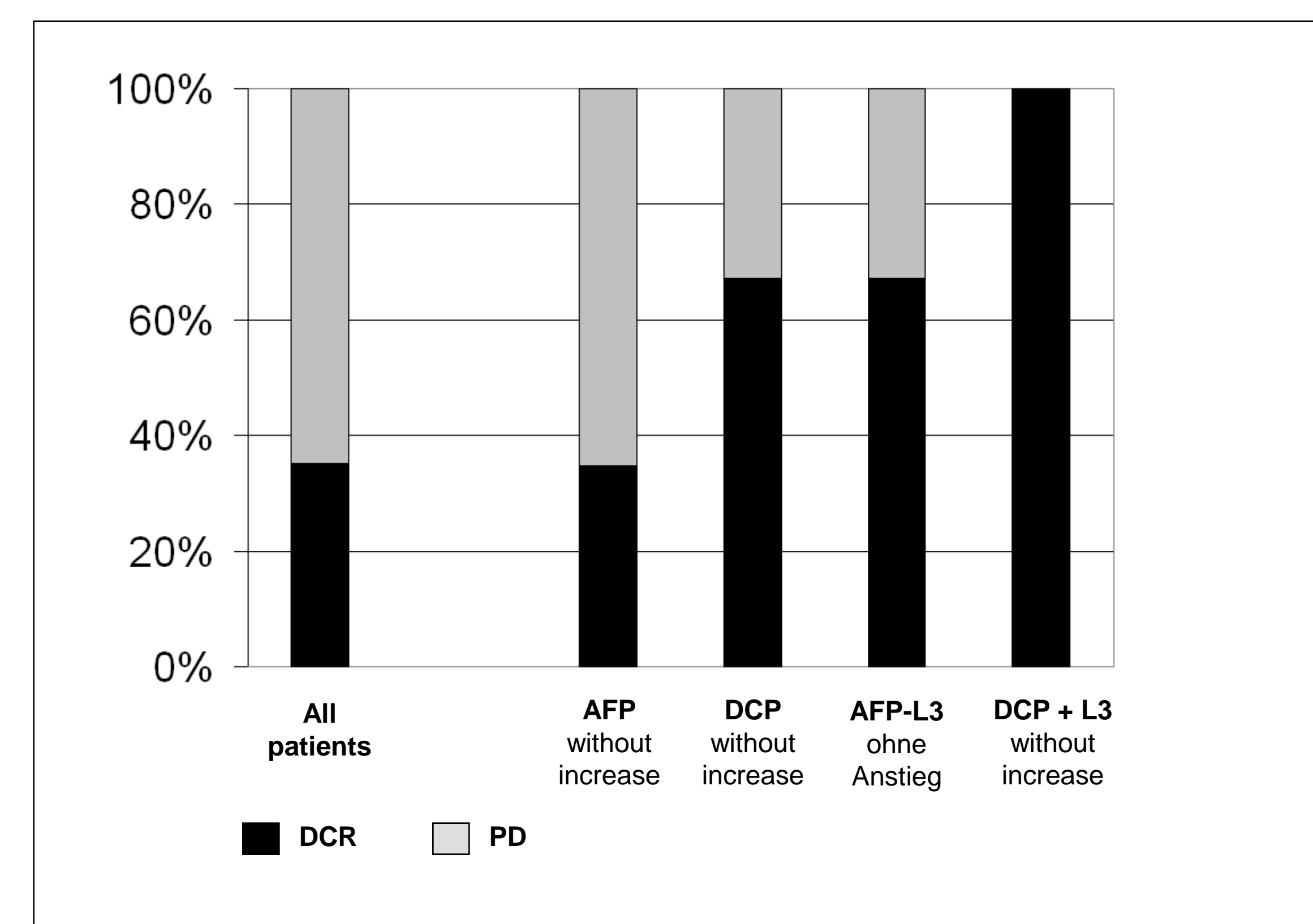


Fig. 3: Serum marker course in 17 patients with advanced HCC under sorafenib therapy (staging 3-4 months after initiation of the therapy). DCR, Disease Control Rate, PD, Progressive Disease.

Patients with increasing DCP value survived shorter than those with constant or decreasing DCP value (p=0.2) (median survival time 233 days in the case of increasing DCP; median survival in the case of constant or decreasing DCP not achieved) (Fig. 4).

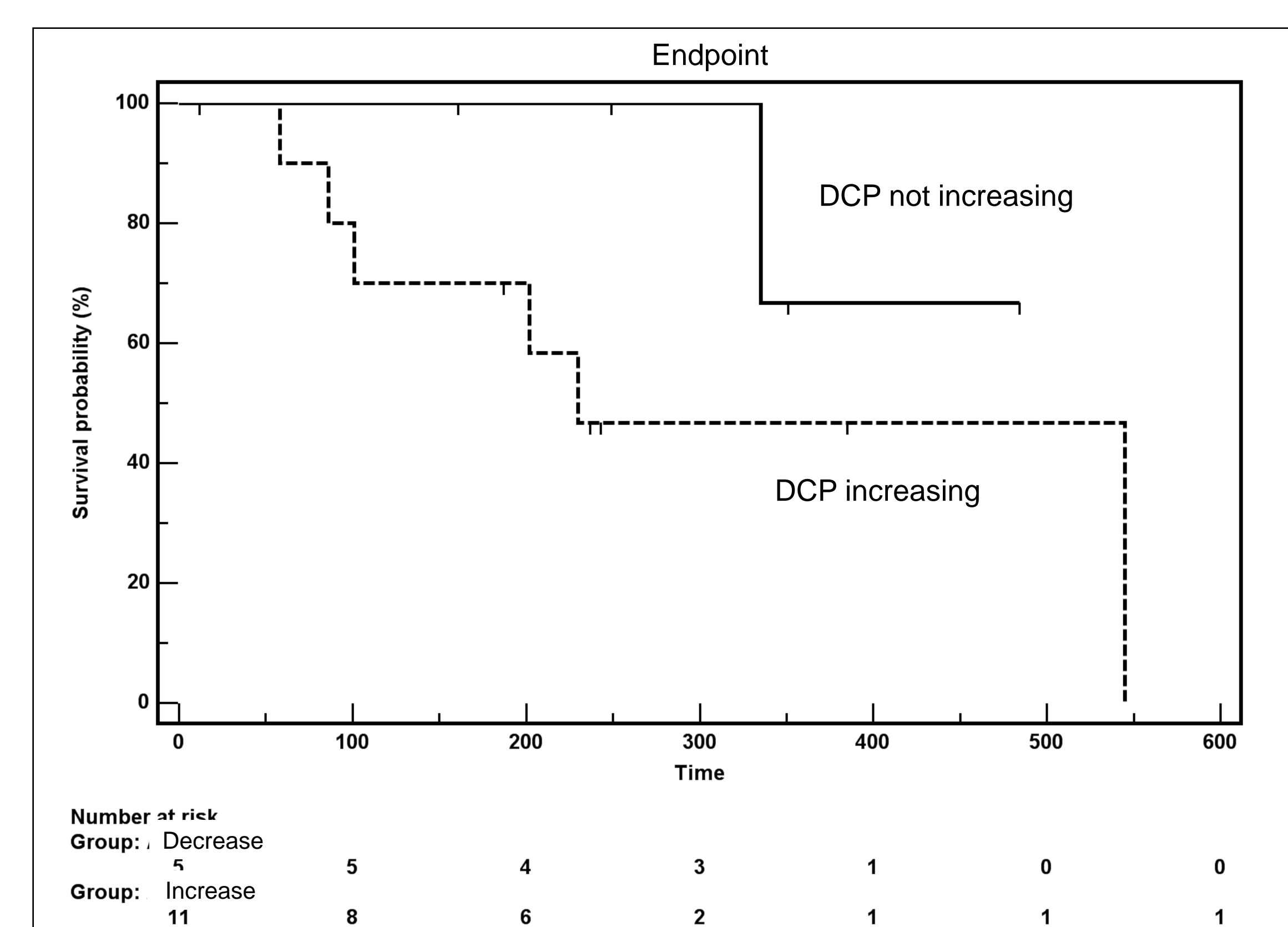


Fig. 4: Kaplan Meier curve: Survival against DCP serum marker course under therapy with sorafenib.

Conclusion

Monitoring of AFP, AFP-L3% and DCP in serum may provide a readily available marker combination to assess response to sorafenib in patients with advanced hepatocellular carcinoma.

¹Llovet JM *et al.*, N Engl J Med 2008; 359:378-90

²Hayashi K *et al.*, Am J Gastroenterol 1999;94:3028-33.

³Durazo FA *et al.*, J Gastroenterol Hepatol 2008; *Epub ahead of print*