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(54) Title: GENERAL PROGNOSTIC PARAMETERS FOR TUMOUR PATIENTS

(57) **Abrégé/Abstract:**

Described is a method for identifying the prognosis for improved clinical benefit of an individual suffering from a tumor comprising providing a blood sample of said individual, (a1) determining the number of lymphocytes in the blood of said individual, and/or (a2) determining the number of neutrophils in the blood of said individual, and (b1) identifying the individual as having a good prognosis for improved clinical benefit, if the number of lymphocytes is above a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially above 1.6×10^9 per liter blood; or (b2) identifying the individual as having a good prognosis for improved clinical benefit, if the number of neutrophils is below or equal to a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially below or equal to 5.0×10^9 neutrophils per liter blood; or (b3) identifying the individual as having a bad prognosis for improved clinical benefit, if the number of lymphocytes is below or equal to a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood and the number of neutrophils is above a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood.



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GENERAL PROGNOSTIC PARAMETERS FOR TUMOUR PATIENTS

The present invention relates to the determination of parameters which allow a prognosis of clinical benefit of a tumor patient.

There is increasing evidence that the immune system already plays a critical role in controlling early events in the recognition and destruction of first malignant cells, but importantly a proper function is also very important in later stages of the disease to control and stabilise progression (at least for a certain time). It is, however, well known that the immune system of cancer patients is often impaired due to the disease and also due to immunosuppressive therapies. Cancer immunotherapies, such as therapies involving cancer vaccines, rely on a proper function of the immune system as one of the key requisites for a possible clinical efficacy.

A white cell blood count enumerating various types of white blood cells as one parameter of the status of the immune system is always measured in the course of a cancer therapy. Thus, the number of neutrophils or the number of lymphocytes is always determined in tumor patients undergoing clinical trials. These data have been correlated by some groups with the success of the cancer therapy and prognosis in a few cancer indications.

For example, Fumagalli et al. (J Immunother. 2003 Sep-Oct;26(5): 394-402) reported that lymphocyte counts independently predicted overall survival in advanced cancer patients as a biomarker for IL-2 immunotherapy. In this study it was retrospectively evaluated whether lymphocytosis, in addition to clinical characteristics at baseline and to tumor objective response, might predict overall survival in metastatic renal cell carcinoma patients who received IL-2 subcutaneously (s.c.). Overall survival, clinical characteristics, tumor response, and total lymphocyte count at baseline and during the first treatment cycle of 266 advanced renal cell cancer patients, being treated with 1 of 4 different first-line s.c. IL-2-based protocols, were studied using the Cox multivariate analysis. A two-step bootstrapping procedure confirmed such predictive performance. Lymphocyte count monitoring was regarded to represent a biomarker of the

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host response to subcutaneous IL-2 treatment useful for multimodal clinical assessment, as it predicts overall survival in advanced cancer patients independently from tumor response and from main clinical characteristics.

Ownby et al. (Cancer. 1983 Jul 1;52(1):126-30) have published that peripheral lymphocyte and eosinophil counts could be used as indicators of prognosis in primary breast cancer. As a part of a major study on the pathophysiologic indices for recurrence of human breast cancer, preoperative eosinophil and lymphocyte counts were determined on 419 and 581 primary breast cancer patients, respectively. Patients with lymphocyte counts less than or equal to 1500/mm³ and/or eosinophil counts of less than 55/mm³ had significantly higher risk of recurrent disease than those patients who had normal or high levels of eosinophils and/or lymphocytes. These findings were reported to possibly indicate that the immunologic activities of eosinophils and lymphocytes enhance the patients' ability to respond against disease.

The purpose of the study of Atzpodien et al. (Br J Cancer. 2003 Feb 10;88(3):348-53) was to identify a comprehensive prognostic system of pretreatment clinical parameters in 425 patients (pts) with metastatic renal-cell carcinoma treated with different subcutaneous (s.c.) recombinant cytokine-based home therapies in consecutive trials. Treatment consisted of (A) s.c. interferon-alpha 2a (INF-alpha), s.c. interleukin-2 (IL-2) (n=102 pts), (B) s.c. IFN-alpha 2a, s.c. IL-2, and i.v. 5-fluorouracil (5-FU) (n=235 pts) or (C) s.c. IFN-alpha 2a, s.c. IL-2, and i.v. 5-FU combined with p.o. 13-cis-retinoic acid (13cRA) (n=88 pts). Kaplan-Meier survival analysis, log-rank statistics, and Cox regression analysis were employed to identify risk factors and to create a multiple risk factor model. The following pretreatment risk factors were identified by univariate analysis: (1) three and more metastatic sites, (2) presence of liver, lymph node or bone metastases, (3) neutrophil count $\geq$ 6500 cells microl⁻¹, (4) serum lactate dehydrogenase level (LDH) $\geq$ 220 U l⁻¹, and (5) serum C-reactive protein level (CRP) $\geq$ 11 mg l⁻¹. Cox regression analysis with forward stepwise variable selection identified neutrophil counts as the major prognostic factor (hazard ratio = 1.9, P<0.001), while serum levels

of LDH and CRP, time between diagnosis of tumor and onset of metastatic disease, number of metastatic sites, and bone metastases were significant but somewhat less important prognostic variables within the multiple risk factor model (hazard ratio $< \text{or} = 1.5$).

The total and differential leucocyte counts were determined by Luc et al. (Sysmex J Int 8 : 38-40, 1998) in 81 patients with newly diagnosed early stage breast cancer, classified as clinical stage 0, I or II and compared with the same counts in 39 age matched healthy women and 67 patients with a benign breast lesion. None of the patients selected for this study had any other medical disorder that could influence these counts. Significantly lower lymphocyte, basophil and eosinophil counts were found in the patients with early stage breast cancer, when compared with the healthy age matched control group. The neutrophil counts were significantly higher in patients with a benign or malignant lesion of the breast in comparison with the control group. There were no significant alterations in the total leucocyte counts in the three groups.

Zahorec (Bratisl Lek Listy 2001; 102 (1): 5.14) investigated the ratio of neutrophil to lymphocyte counts as a rapid and simple parameter of systemic inflammation and stress in critically ill. Rapid serial changes in white blood cell populations were observed in 90 ICU oncological patients as a response of the immune system to surgical stress, systemic inflammation or sepsis. Preliminary results showed a correlation between the severity of clinical course and the grade of neutrophilia and lymphocytopenia. The ratio of neutrophil and lymphocyte counts (in absolute and/or relative % values) was suggested to be an easily measurable parameter which may express the severity of affliction. The ratio of neutrophil to lymphocyte counts (neutrophil-lymphocyte stress factor) was suggested to be routinely used in clinical ICU practice in intervals of 6-12 and 24 hours. The prognostic value of neutrophil-lymphocyte stress factor was proposed to be evaluated in further studies.

Paesmans et al. (J Clin Oncol. 1995 May;13(5):1221-30 and Cancer. 2000 Aug 1;89(3):523-33) described prognostic factors for

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survival in advanced non-small-cell lung cancer. It was attempted to determine the prognostic value for survival of various pretreatment characteristics in patients with nonresectable non-small-cell lung cancer in the context of more than 10 years of experience of a European Cooperative Group. 23 variables were prospectively collected and analysed by univariate and multivariate methods. However, the long term prognosis associated with small cell lung carcinoma is poor. The well-known prognostic values of disease extent and Karnofsky performance status were confirmed, but the authors also identified age and gender (which are more controversial) as independent characteristics, in addition to citing the role of complete response in the attainment of long term survival. The independent role of neutrophils observed by the authors was reported as having to be validated by further studies.

It is becoming clearer and clearer that inflammation plays a crucial role in cancer development. Inflammation is a critical component of tumor progression. Many cancers arise from sites of infection, chronic irritation and inflammation. It is now becoming clear that the tumor microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, survival and migration. In addition, tumor cells have co-opted some of the signalling molecules of the innate immune system, such as selectins, chemokines and their receptors for invasion, migration and metastasis. These insights are fostering new anti-inflammatory therapeutic approaches to cancer development (Cousens et al. (Nature 240 (2002))).

McMillan et al. (Nutr Cancer. 2001;41(1-2):64-9) reported that measurement of the systemic inflammatory response predicted cancer-specific and non-cancer survival in patients with cancer. Patients with a diagnosis of colorectal (n = 182), gastric (n = 87), breast (n = 99), or bronchogenic (n = 404) cancer and who had measurements of C-reactive protein and albumin were identified. Median survival, from the time of sampling, ranged from 478 days in the colorectal cancer patients to 60 days in patients with bronchogenic cancer. On univariate analysis, there was, in each tumor type, a significant relationship between the

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duration of survival and both log10 C-reactive protein and albumin concentrations ($P \leq 0.0002$). On multivariate analysis, in each tumor type, log10 C-reactive protein remained a significant independent predictor of survival ($P \leq 0.0002$). When all four groups of cancer patients were analysed ($n = 772$), the hazard ratio for a 10-fold increase in C-reactive protein concentration in cancer-specific survival was 2.21 (95% confidence interval = 1.92-2.56, $P < 0.0001$) and the corresponding hazard ratio for non-cancer survival was 5.48 (95% confidence interval = 3.55-8.46, $P < 0.0001$). The results of this study indicated that in advanced cancer patients the presence of a systemic inflammatory response and the magnitude of that response predicted the duration of cancer-specific and non-cancer survival.

Nozoe et al. (American Journal of Clinical Oncology. 23(3): 263-266, June 2000) reported the significance of a preoperative elevation of serum C-reactive protein (CRP) as an indicator of the malignant potential and prognosis in colorectal cancer. The reduction of circulating lymphocytes was said to reflect the immunosuppressive conditions of patients with neoplasms. It was shown that preoperative elevation of serum CRP was significantly related to the reduction of lymphocyte percentages in peripheral blood, and that it could be an indicator of impaired immunity in the patients with colorectal cancer.

Schmidt et al. (Brit.J.Cancer 93 (2005), 273-278) report that elevated neutrophil and monocyte counts in peripheral blood are associated with poor survival in patients with metastatic melanoma receiving IL-2-based immunotherapy.

It is an object of the present invention to provide objective immunological parameters measured at baseline (for clinical trials: preferably before first treatment of enrolled patients) that have a prognostic impact on the overall clinical benefit that a patient might enjoy, especially a prognostic parameter for overall survival (OS). These parameters should be easily detectable and manageable.

Therefore, the present invention provides a method for identifying the prognosis for improved clinical benefit of an individual

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suffering from a tumor comprising

- providing a blood sample of said individual,
- (a1) determining the number of lymphocytes in the blood of said individual and/or
- (a2) determining the number of neutrophils in the blood of said individual, and
- (b1) identifying the individual as having a good prognosis for improved clinical benefit, if the number of lymphocytes is above a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially above 1.6×10^9 per liter blood; or
- (b2) identifying the individual as having a good prognosis for improved clinical benefit, if the number of neutrophils is below or equal to a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially below or equal to 5.0×10^9 neutrophils per liter blood; or
- (b3) identifying the individual as having a bad prognosis for improved clinical benefit, if the number of lymphocytes is below or equal to a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood and the number of neutrophils is above a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood.

According to the present invention, it was surprisingly determined that neutrophil numbers and lymphocyte numbers in individuals could be efficient prognosis markers for clinical benefits of tumor patients, if baselines were considered which are usually within the "normal" values of individuals. It is clear that tumor patients which already have a lymphocyte or neutrophil number within pathological ranges have a bad prognosis in general. However, the present invention makes use of a significant difference in prognosis within the physiological range of neutrophil numbers and lymphocyte numbers or combinations of these numbers (especially the difference of lymphocytes and neutrophils).

Usually, neutrophil numbers within 1.7 and 7.5×10^9 per liter blood, lymphocyte numbers within 1.2 and 4.5×10^9 per liter

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blood, or leukocyte numbers within 4 and 10×10^9 per liter blood, are regarded as physiological ("normal"). Pathological values differ from source to source, e.g. neutropenia is reported to be associated with less than 1×10^9 neutrophils; severe neutropenia is associated with less than 0.5×10^9 neutrophils. Lymphopenia is associated with less than 1×10^9 lymphocytes per liter blood; leukopenia with less than 4×10^9 leukocytes per liter blood. According to the present invention, individuals with a number of lymphocytes or neutrophils within the physiological range are contemplated, i.e. with at least 0.5×10^9 lymphocytes or neutrophils per liter blood, preferably with at least 1×10^9 lymphocytes or neutrophils per liter blood. This does not exclude transiently artificially reduced levels of lymphocytes or neutrophils within the course of the present invention to be excluded from the preferred embodiments of this invention.

Within the present invention certain critical baselines for lymphocytes or neutrophils numbers (which are within the physiological range) are contemplated, for example to define a low neutrophil number or a high lymphocyte number, or combinations of these values, such as the difference between neutrophil count and lymphocyte count (neutrophils minus lymphocytes; NML) or neutrophils or lymphocytes low high (NOL-LH).

Specifically the parameter NOL-LH (low neutrophils or high lymphocytes for a good prognosis) is a surprising result, because although it is in principle beneficial to have a high lymphocyte number, but even if lymphocytes are low, good prognosis is even possible when the neutrophil count is low. On the other hand, it is beneficial to have a low neutrophil number, however, even if neutrophil numbers are high, prognosis is still good, if the lymphocyte numbers are high. Only if the lymphocyte numbers are low and neutrophil numbers are high, a very bad prognosis is given. Since neutrophils represent usually around 70 % of total leukocytes, the subject matter of the present invention also relates to methods as disclosed herein, where instead of neutrophils total leukocytes are contemplated, optionally with a correction factor of (around) 70 %, e.g. instead of 4.0 to 6.0, especially 5.0×10^9 neutrophils per liter blood, one could also use 6.5 to 8.5, especially 7.5×10^9 leukocytes per liter blood.

However, there is a likelihood that a certain amount of significance is lost, if one relies on the total leukocyte number instead of neutrophil counts.

The present invention allows a statistically significant prognosis of the progression of the tumor disease. The clinical benefit according to the present invention may be defined in various established ways in tumor medicine. For example, definition is proper if based on time-to-event measurements (against a control group):

- Improvement in overall survival (fully accepted by all oncologists and regulatory authorities)
- Improvement in relapse-free survival (when no clinically evident tumor mass is present; i.e. after surgery; = adjuvant setting)
- Improvement in progression-free survival (time until disease is progressing, based on defined measurable increase in tumor mass).

Benefit also is often also claimed in case of an improved response rate (based on defined shrinking of a tumor mass for a certain time period). However, clinical response in terms of tumor shrinking does not necessarily improve survival parameters. According to a preferred embodiment, the improved clinical benefit is an improved overall survival time.

As already stated above, the method according to the present invention is preferably performed only with individuals having a number of neutrophils or lymphocytes within "normal" ranges, i.e. usually above 1.0×10^9 of each cell type per liter blood. Preferably the number of lymphocytes is from above 1.6×10^9 to 5.0×10^9 per liter blood for a good prognosis, especially from 1.6×10^9 to 4.5×10^9 per liter blood. According to a preferred embodiment, the number of neutrophils for a good prognosis is from 1.0×10^9 to 5.0×10^9 per liter blood, especially from 1.7×10^9 to 5.0×10^9 per liter blood.

According to another aspect, the present invention also relates to a method for identifying the prognosis for improved clinical benefit of an individual suffering from a tumor comprising

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- providing a blood sample of said individual,
- (a1) determining the number of lymphocytes in the blood of said individual and/or
- (a2) determining the number of neutrophils in the blood of said individual and
- (b1) identifying the individual as having a good prognosis for improved clinical benefit, if the number of lymphocytes is above a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially above 1.6×10^9 per liter blood; or
- (b2) identifying the individual as having a good prognosis for improved clinical benefit, if the number of neutrophils is below or equal to a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially below or equal to 5.0×10^9 neutrophils per liter blood; or
- (b3) identifying the individual as having a bad prognosis for improved clinical benefit, if the number of lymphocytes is below or equal to a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood and the number of neutrophils is above a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood.

The methods according to the present invention are generally applicable for all types of tumor patients, specifically for tumor patients undergoing tumor therapy. The present invention is therefore specifically suited for solid tumors, especially for tumors of the colorectal system. The present method is surprisingly suitable for tumors which are non-immunogenic tumors (i.e. tumors with low frequency of spontaneous remission; in contrast to immunogenic tumors, such as melanoma or renal cell carcinoma). Preferred tumors for the method according to the present invention are tumors which are non-immunogenic tumors (and therefore do not have a direct correlation to white blood cells), especially epithelial tumors. These preferred tumors have an extremely low likelihood for spontaneous remission mainly, because these tumors are more "hidden" to the immune system. Examples of preferred tumors according to the present invention are breast cancer, lung cancer, especially Non-Small-

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Cell-Lung-Cancer (NSCLC), cancer in the stomach, pancreas carcinoma, prostate cancer, ovarian carcinoma and colorectal cancer. The present method is preferably applied for patients with colorectal cancer.

Preferably, the prognosis is made of a tumor patient in stage III or IV of said tumor, classified according to the American Joint Committee on Cancer Manual for Staging Cancer, 6th Edition (2002), especially a tumor patient in stage IV.

The neutrophil or lymphocyte number may also be adjusted to a level for good prognosis, if the original level of the individual does not indicate good prognosis. Therefore, the cancer patient individual is an individual who had received a neutrophil reduction treatment, preferably selected from one or more of neutrophil reducing apheresis, radiation therapy or administration of neutrophil reducing agents, especially of chemotherapeutic drugs, monoclonal antibodies against neutrophil markers, immunomodulatory drugs, cytokines or mixtures thereof. With such suitable methods, it is possible to modulate neutrophil values in peripheral blood e.g. to or below or equal to 5.0×10^9 per liter blood, respectively. Such a transient modulation of the WBC counts of cancer patients could e.g. be done immediately before start of cancer therapy, especially before cancer immunotherapy (against all common understanding of the problems caused by a damaged immune system for cancer vaccination) and may then lead to a survival benefit. As stated above, this could be achieved by several means:

- Apheresis techniques to transiently reduce neutrophil counts
- Radiation therapies to transiently reduce neutrophil counts
- Pre-treatment with agents that reduce the number of neutrophils, such as chemotherapeutic drugs, monoclonal antibodies against lymphocyte markers (e.g. OKT-3, anti- CD25 Mabs), immunomodulatory drugs, cytokines or mixtures thereof in an amount to effectively bring the neutrophil number to the desired level for good prognosis.

Alternatively, the cell number, especially the number of lymphocytes may be raised by suitable methods. It may therefore be preferred if the individual is an individual who had received a

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lymphocyte number enhancement treatment, preferably IL-2 administration or lymphocyte administration.

In a preferred embodiment according to the present invention, a method for identifying the prognosis for improved clinical benefit of an individual suffering from a tumor is provided which comprises

- providing a blood sample of said individual,
- (a1) determining the number of lymphocytes in the blood of said individual, and
- (a2) determining the number of neutrophils in the blood of said individual and
- (b1) identifying the individual as having a good prognosis for improved clinical benefit, if the number of lymphocytes is above a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially above 1.6×10^9 per liter blood (even if the number of neutrophils is above 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood); or
- (b2) identifying the individual as having a good prognosis for improved clinical benefit, if the number of neutrophils is below or equal to a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially below or equal to 5.0×10^9 neutrophils per liter blood (even if the number of lymphocytes is below or equal to 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood); or
- (b3) identifying the individual as having a bad prognosis for improved clinical benefit, if the number of lymphocytes is below or equal to a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood and the number of neutrophils is above a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood.

A preferred parameter within the scope of the present invention is a composite parameter based on the difference of the neutrophil number and the lymphocyte number. This parameter has proven to have a very good prognosis efficacy. Accordingly, it is pre-

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ferred that the difference of the neutrophil number and the lymphocyte number (neutrophils minus lymphocytes; NML) is determined and

- (b4) identifying the individual as having a good prognosis for improved clinical benefit, if the NML is below or equal to an NML baseline level of from $2,4$ to $4,4 \times 10^9$ cells per liter blood, especially below or equal to $3,4 \times 10^9$ cells per liter blood; or
- (b5) identifying the individual as having a bad prognosis for improved clinical benefit, if the NML is above an NML baseline level of from $2,4$ to $4,4 \times 10^9$ cells per liter blood, especially above $3,4 \times 10^9$ cells per liter blood.

The present method is specifically suitable for designing and evaluating clinical trials for proving efficacy of a given tumor treatment by grouping of individuals in specific groups selected and determined according to the parameters at baseline according to the present invention. This results in an efficient grouping which is not based on an unknown and therefore unconsidered prognosis factor of a group which would otherwise make a proper evaluation of the cancer treatment difficult. This grouping can be done also retrospectively, because lymphocyte numbers and neutrophil numbers are measured on a routine basis in all clinical trials involving tumor patients. Results of controlled clinical trials may be corrected for possible imbalances regarding the here described prognostic factors using statistical methods such as Cox' regression analysis. According to a specific aspect, the present invention therefore also relates to a method for conducting clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a lymphocyte number above a lymphocyte baseline level and a group which has a lymphocyte number below or equal to a lymphocyte baseline level, said lymphocyte baseline level being a value from 1.4 to 1.8×10^9 lymphocytes per liter blood, especially 1.6×10^9 per liter blood.

The invention, consequently, also relates to a method for conducting clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a neutrophil number above a neutrophil baseline level and a group which has a

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neutrophil number below or equal to a neutrophil baseline level, said neutrophil baseline level being a value from $4,0$ to $6,0 \times 10^9$ neutrophils per liter blood, especially $5,0 \times 10^9$ per liter blood.

The invention also contemplates on a method for conducting clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a lymphocyte number above a lymphocyte baseline level, said lymphocyte baseline level being a value from 1.4 to 1.8×10^9 lymphocytes per liter blood, especially 1.6×10^9 per liter blood and a neutrophil number below or equal to a neutrophil baseline level, said neutrophil baseline level being a value from 4.0 to 6.0×10^9 neutrophils per liter blood, especially 5.0×10^9 per liter blood.

According to the present invention, also a method for conducting clinical trials for a tumor treatment is provided which comprises the grouping of individuals into a group which has an NML below or equal to an NML baseline level of from 2.4 to 4.4×10^9 cells per liter blood, especially below or equal to 3.4×10^9 cells per liter blood and a group which has an NML above an NML baseline level of from 2.4 to 4.4×10^9 cells per liter blood, especially above 3.4×10^9 cells per liter blood.

The present invention also relates to a method for conducting clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a number of lymphocytes below or equal to a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood and a number of neutrophils above a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood.

According to another aspect, the present invention also relates to a method for re-analysing the results of clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a lymphocyte number below or equal to a lymphocyte baseline level and a group which has a lymphocyte number above a lymphocyte baseline level, said lymphocyte baseline level being a value from 1.4 to 1.8×10^9 lymphocytes per liter

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blood, especially 1.6×10^9 per liter blood and re-evaluating the efficacy of the clinical trial based on this grouping based on lymphocyte number.

The invention also relates to a method for re-analysing the results of clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a neutrophil number above a neutrophil baseline level and a group which has a neutrophil number below or equal to a neutrophil baseline level, said neutrophil baseline level being a value from 4.0 to 6.0×10^9 neutrophils per liter blood, especially 5.0×10^9 per liter blood and re-evaluating the efficacy of the clinical trial based on this grouping based on neutrophil number.

A specific method for re-analysing the results of clinical trials for a tumor treatment according to the present invention comprises the grouping of individuals into a group which has an NML below or equal to an NML baseline level of from 2.4 to 4.4×10^9 cells per liter blood, especially below or equal to 3.4×10^9 cells per liter blood and a group which has an NML above an NML baseline level of from 2.4 to 4.4×10^9 cells per liter blood, especially above 3.4×10^9 cells per liter blood.

Another specific method for re-analysing the results of clinical trials for a tumor treatment according to the present invention comprises the grouping of individuals into a group which has a number of lymphocytes below or equal to a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood and a number of neutrophils above a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood.

These methods for conducting or re-analysing clinical trials have been proven to be effective in colorectal cancer trials, but are in principle applicable for all cancer trials, especially those cancers which do not primarily involve the immune system itself (malignancies of the hemopoietic system, such as e.g. in leukemias). Preferably, the tumor patients are human tumor patients in stage III or IV of said tumor, classified ac-

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according to the American Joint Committee on Cancer Manual for Staging Cancer, 6th Edition (2002), especially a tumor patient in stage IV. However, also prognosis for early stages (e.g. Ib, II or IIIa, etc.) is possible according to the present invention (as shown in the example section for NSCLC).

The conduct or re-analysis of clinical trials is often performed with the assistance of professional firms having computerised data bases or systems for such clinical trials offered to their customers. Examples of such data bases or systems are disclosed e.g. in US 2002/0143577 A1, US 6,820,235 B1, US 6,904,434 B1, and many of the documents cited in these documents. The present invention therefore also relates to such data storage means used and offered in connection with clinical trials comprising a grouping of individuals as defined according to the present invention (as well as the computers on which these data storage means are running or are operatable).

According to another aspect, the present invention relates to a method for identifying an individual suffering from a tumor as having a good prognosis for improved overall survival time comprising

- providing a blood sample of said individual,
- determining the number of neutrophils and the number of lymphocytes in the blood of said individual, and
- identifying the individual as having a good prognosis for improved overall survival time, if the difference of the number of neutrophils and the number of lymphocytes is below or equal to a neutrophil-minus-lymphocyte baseline level of from 3.0 to 4.0×10^9 per liter blood, especially below or equal to 3.4×10^9 per liter blood.

As already mentioned above, this method is preferred in patients having colorectal cancer. This method is specifically suited for patients in later stages of the disease, for example tumor patients in stage III or IV of said tumor, classified according to the American Joint Committee on Cancer Manual for Staging Cancer, 6th Edition (2002), especially a tumor patient in stage IV.

The present invention is further described in the following ex-

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amples and figures, yet without being restricted thereto.

Fig.1 shows the influence of baseline neutrophil counts on overall survival for all placebo patients;

Fig.2 shows the influence of baseline neutrophil counts on overall survival for all stage IV placebo patients;

Fig.3 shows the influence of baseline neutrophil counts on overall survival for all stage IV placebo patients with colorectal carcinoma;

Fig.4 shows the influence of baseline lymphocyte counts on overall survival for all placebo patients;

Fig.5 shows the influence of baseline lymphocyte counts on overall survival for all stage IV placebo patients;

Fig.6 shows the influence of baseline lymphocyte counts on overall survival for all stage IV placebo patients with colorectal carcinoma;

Fig.7 shows the influence of baseline neutrophil minus lymphocyte counts on overall survival for placebo patients;

Fig.8 shows the influence of baseline neutrophil minus lymphocyte counts on overall survival for all stage IV placebo patients;

Fig.9 shows the influence of baseline neutrophil minus lymphocyte counts on overall survival for all stage IV placebo patients with colorectal carcinoma;

Fig.10 shows shows the influence of baseline neutrophil or lymphocyte counts on overall survival for placebo patients;

Fig.11 shows the influence of baseline neutrophil or lymphocyte counts on overall survival for all stage IV placebo patients;

Fig.12 shows the influence of baseline neutrophil or lymphocyte

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counts on overall survival for all stage IV placebo patients with colorectal carcinoma;

Fig. 13 shows the influence of neutrophil counts at relapse on overall survival for all relapsed patients with NSCLC;

Fig. 14 shows the influence of lymphocyte counts at relapse on overall survival for all relapsed patients with NSCLC;

Fig. 15 shows the influence of neutrophil minus lymphocyte counts at relapse on overall survival for all relapsed patients with NSCLC;

Fig. 16 shows the influence of neutrophil counts at baseline on relapse-free survival for all patients with NSCLC stages Ib, II and IIIa;

Fig. 17 shows the influence of neutrophil counts at baseline on overall survival for all patients with NSCLC stages Ib, II and IIIa;

Fig. 18 shows the influence of neutrophil minus lymphocyte counts at baseline on relapse-free survival for all patients with NSCLC stages Ib, II and IIIa; and

Fig. 19 shows the influence of neutrophil minus lymphocyte counts at baseline on overall survival for all patients with NSCLC stages Ib, II and IIIa.

Examples:

The present investigations are based on a data set accumulated in the context of a finished and thus opened double-blind placebo controlled Phase IIb trial with the cancer vaccine IGN101 (Himmeler et al., Proceedings ASCO 2005, Abstract # 2555, "A randomized placebo-controlled phase II study with the cancer vaccine candidate IGN101 in patients with epithelial cancers") in patients with epithelial cancers. For the present analyses, only data of patients randomised to placebo were used in order to rule out any possible influence of the tested vaccine IGN101

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on the further disease course. Therefore, the results are assumed to be representative. As for the induction of an immune response white blood cells are crucially important, the investigations described in this example utilise standard white blood cell counts, in particular lymphocyte and neutrophil counts.

Methods:

For the phase IIb, placebo-controlled trial to evaluate the efficacy, safety, tolerability and immunogenicity of multiple doses of IGN101, the present values for the leukocyte, neutrophil and lymphocyte counts were analysed. In general, analyses are based on the Intention To Treat (ITT) population. The actually used number of patients is always mentioned in the respective section. These numbers may differ to a minor extent from the ITT population as defined in the official study report, since (very few) patients with missing baseline parameters or death date information had to be omitted.

For the calculations and plotting of figures the following software programmes were used:

- Tables: MS Excel
- Kaplan Meier survival curves: GraphPad Prism 4
- Cox' regression analysis: Internet:

<http://members.aol.com/johnp71/prophaz2.html>

Results:

Analysis of parameters with possible prognostic value for OS

1. All placebo patients: Neutrophil counts at baseline

The majority of leukocytes in peripheral blood are neutrophils. Patients were separated into two groups with a threshold of $5,0 \times 10^9 / L$ neutrophils measured at baseline. The respective Kaplan-Meier results for all placebo patients are shown in Fig. 1.

The observed difference of the survival curves is highly statistically significant ($P = 0,0018$ log-rank; median survival 253 vs 717 days). Stage III patients (who in general have a longer

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OS than stage IV patients) predominantly are in the group with lower neutrophil numbers. The distribution of patients in the two analysed groups is as follows:

	< 5		> 5	
Stage III:	43	36.4 %	11	9.3 %
colon:	18		5	
rectum:	12		1	
NSCLC:	5		5	
gastric:	6		0	
other:	2		0	
Stage IV:	30	25.4 %	34	28.8 %
colon:	17		8	
rectum:	8		13	
NSCLC:	1		8	
gastric:	3		4	
other:	1		1	

In Cox' regression analysis with KPS, neutrophil count at baseline and stage (III or IV) as parameters, the neutrophil count is a statistically significant independent predictor for OS. Lower neutrophil counts at baseline are associated with improved survival:

Var	Coeff.	StdErr	p	Lo95%	Hi95%
Neutrophils	0.1133	0.0514	0.0276	0.0130	0.2135
KPS	-0.0887	0.0232	0.0001	-0.1340	-0.0433
Stage	1.3042	0.3056	0.0000	0.7083	1.9002

2. Placebo patients stage IV: Neutrophil counts at baseline

Next, the influence of the neutrophil count at baseline on OS of the stage IV patients only was evaluated, using the same principles as described in 1. The Kaplan-Meier results are shown in Figure 2.

The difference of the survival curves is close to statistical

significance ($P = 0.0851$ log-rank; median survival 227 vs 365 days). In Cox' regression analysis, however, with KPS and neutrophil count at baseline as parameters in order to correct for the influence of KPS on OS, the neutrophil count turns out to be a highly statistically independent predictor for OS. Lower neutrophil counts at baseline are associated with improved survival:

Var	Coeff.	StdErr	p	Lo95%	Hi95%
Neutrophils	0.1599	0.0586	0.0064	0.0456	0.2742
KPS	-0.0783	0.0265	0.0032	-0.1300	-0.0266

3. Placebo patients with colo-rectal cancer stage IV: Neutrophil counts at baseline

The influence of the neutrophil count at baseline on OS of the colo-rectal cancer patients stage IV patients was evaluated as well, using the same principles as described in 1. The respective Kaplan-Meier results are shown in Figure 3.

According to this Kaplan-Meier analysis, the observed minor differences of the survival curves are not significant. However, when the data are corrected for a possible influence of KPS on OS by Cox' regression analysis with neutrophil counts at baseline and KPS as descriptors, the neutrophil count again appears as a significant independent predictor of OS. Lower neutrophil numbers relate to better OS:

Var	Coeff.	StdErr	p	Lo95%	Hi95%
Neutrophils	0.1961	0.0799	0.0141	0.0403	0.3520
KPS	-0.0644	0.0298	0.0307	-0.1225	-0.0063

4. All placebo patients: Lymphocyte counts at baseline

The leukocytes of the peripheral blood in general consist of neutrophils (usually the largest fraction), monocytes and lymphocytes. Since the lymphocytes (in particular B cells and T cells) are especially important for the establishment of an immune response and to maintain immunity, a set of analyses as described in the previous section was also done with the lymphocyte counts at baseline. For this, patients were separated into two groups with a threshold of 1.6×10^9 / L lymphocytes measured

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at baseline. The respective Kaplan-Meier results for all placebo patients are shown in Fig. 4.

The difference of the survival curves is almost statistically significant. In contrast to the results obtained with neutrophils and leukocytes, where lower cell counts at baseline were associated with longer OS, according to this analysis patients apparently have a longer OS when presenting with higher lymphocyte counts at baseline. The distribution of patients in the two analysed groups is as follows:

	< 1.6		> 1.6	
Stage III:	18	15.3 %	36	30.5 %
colon:	7		16	
rectum:	6		7	
NSCLC:	3		7	
gastric:	2		4	
other:	0		2	
Stage IV:	27	22.9 %	37	31.4 %
colon:	5		20	
rectum:	12		9	
NSCLC:	6		3	
gastric:	4		3	
other:	0		2	

However, in Cox' regression analysis with KPS, lymphocyte count at baseline and stage (III or IV) as parameters, the lymphocyte count does not appear as significant independent predictor for OS, only KPS and stage are independent predictors. Likely, a lower lymphocyte count is associated with a lower KPS:

Var	Coeff.	StdErr	p	Lo95%	Hi95%
Lymphocytes	-0.1267	0.1662	0.4457	-0.4508	0.1973
KPS	-0.0922	0.0233	0.0001	-0.1377	-0.0468
Stage	1.3371	0.3061	0.0000	0.7402	1.9340

5. Placebo patients stage IV: Lymphocyte counts at baseline

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A similar analysis was done in the more homogeneous group of all stage IV patients of the placebo group. The Kaplan-Meier results are shown in Fig. 5.

The observed differences of the survival curves are significant. However, In Cox' regression analysis with KPS and lymphocyte count at baseline as parameters, the lymphocyte count does not appear as significant independent predictor for OS, a trend is still seen. Obviously, KPS and lymphocyte count have a correlation:

Var	Coeff.	StdErr	p	Lo95%	Hi95%
1	-0.0809	0.0264	0.0022	-0.1324	-0.0294
2	-0.2702	0.1967	0.1695	-0.6537	0.1134

6. Placebo patients with colo-rectal cancer stage IV: Lymphocyte counts at baseline

The Kaplan-Meier results of the analysis of the CRC IV patients as most homogeneous group are shown in Fig. 6.

The observed difference of the survival curves is not significant. Also in Cox' regression analysis with KPS and lymphocyte count at baseline as parameters, the lymphocyte count does not appear as significant independent predictor for OS, a trend, however, is still seen.

Var	Coeff.	StdErr	p	Lo95%	Hi95%
KPS	-0.0656	0.0311	0.0350	-0.1263	-0.0049
lympho	-0.3323	0.2358	0.1589	-0.7922	0.1276

7. All placebo patients: Baseline neutrophil minus lymphocyte counts

According to the results described so far, both the neutrophil count and the lymphocyte count have a certain prognostic value, lower neutrophil counts and higher lymphocyte counts relate to improved OS. An also observed prognostic value of the summary leukocyte count (lower leukocyte counts relate to improved OS) therefore is mostly determined by the neutrophil count.

In order to use the lymphocyte and neutrophil results optimally in one parameter, the difference of the neutrophil count and the lymphocyte count as new parameter is introduced (abbreviation NML for Neutrophils Minus Lymphocytes). Although NML probably has no direct biological correlate, it should strengthen the prognostic potential, as a low values for neutrophils and high values for lymphocytes are required for better OS. The threshold of $3.4 \times 10^9/\text{L}$ used for NML was derived from the thresholds used for the single analyses $[(5.0 - 1.6) \times 10^9/\text{L}]$.

The Kaplan-Meier results for all placebo patients, using baseline NML as prognostic parameter, are shown in Figure 7.

As expected, this parameter led to a pronounced differences in OS. Similarly, high significance was also found in Cox' regression. Lower values of NML are strongly correlated with improved OS.

Var	Coeff.	StdErr	p	Lo95%	Hi95%
KPS	-0.0861	0.0234	0.0002	-0.1317	-0.0404
NML	0.1245	0.0516	0.0158	0.0239	0.2250
stage	1.2894	0.3059	0.0000	0.6930	1.8859

8. Placebo patients stage IV: NML counts at baseline

A similar analysis as described in 7. was also performed for the stage IV patients of the placebo group. The Kaplan-Meier results are shown in Figure 8.

The results are highly significant. Similarly, in Cox' regression analysis with KPS and NML as predictors, NML retained as significant independent prognostic parameter. Lower values are associated with improved survival:

Var	Coeff.	StdErr	p	Lo95%	Hi95%
KPS	-0.0756	0.0268	0.0048	-0.1278	-0.0233
NML	0.1715	0.0568	0.0025	0.0608	0.2823

9. Placebo patients with colo-rectal cancer stage IV: NML

counts at baseline

Analysis of the CRC IV patients of the placebo group regarding the prognostic value of NML led to very similar results as described above. The Kaplan-Meier survival curves are shown in Fig. 9.

The results again are highly significant. In the group with lower NML, the median survival time is more than doubled (395 d versus 188 d, hazard ratio 0.4162). Also the 1-year survival is more than doubled: 55.2% versus 17.6%. The slope of the two survival curves is different (as seen also in Figures 7 and 8), indicating a higher proportion of long-term survivors in the group with lower NML.

In Cox' regression analysis with KPS and NML as predictors, also for CRC IV patients NML retained as strongly significant independent prognostic parameter. Lower values are associated with improved survival:

Var	Coeff.	StdErr	p	Lo95%	Hi95%
KPS	-0.0625	0.0302	0.0386	-0.1214	-0.0036
NML	0.2048	0.0762	0.0072	0.0563	0.3533

10. All placebo patients: Combination of low neutrophil or high lymphocyte counts at baseline

Another way of combining the prognostic values of low neutrophil and high lymphocyte counts at baseline is a combination as follows: Placebo patients were grouped according to a baseline lymphocyte count of $> 1.6 \times 10^9/L$ or a baseline neutrophil count of $\leq 5.0 \times 10^9/L$. In consequence, the remaining patients have a baseline lymphocyte count $\leq 1.6 \times 10^9/L$ and a baseline neutrophil count $> 5.0 \times 10^9/L$. This novel composite parameter is named NOL-LH (Neutrophils Or Lymphocytes-Low High).

The respective Kaplan Meier result based on NOL-LH is shown in Fig. 10.

The difference of the survival curves is highly significant. Re-

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markably, more than 80% of the patients are in the group with improved survival. The use of NOL-LH seemingly leads to a precise selection of patients with substantially worse prognosis. The distribution of patients is as follows:

	≤ 5 or > 1.6		> 5 and ≤ 1.6	
Stage III:	51	43.2 %	3	2.9 %
colon:	22		1	
rectum:	13		0	
NSCLC:	8		2	
gastric:	6		0	
other:	2		0	
Stage IV:	46	39.0 %	18	15.3 %
colon:	23		2	
rectum:	13		8	
NSCLC:	4		5	
gastric:	4		3	
other:	2		0	

In stage III, 51 of 54 patients (94.4%) belong to the group with good prognosis. This is in agreement with the generally better prognosis of stage III patients and indicates the power of the composite parameter NOL-LH to discriminate between patients with good and bad prognosis, and even "recognise" tumor stages with favorable prognosis, only based on the information of a certain pattern of the white blood cell counts regarding neutrophils and lymphocytes.

11. Placebo patients stage IV: Combination of low neutrophil or high lymphocyte counts at baseline

A similar analysis as described in 10 was also done for the placebo stage IV patients only. The Kaplan-Meier results are shown in Figure 11.

The results show a highly significant survival difference and are very similar to those described in 10. More than 70% of patients are in the group with better prognosis, again indicating

the power of NOL-LH to select patients with bad prognosis.

12. Placebo patients with colo-rectal cancer stage IV: Combination of low neutrophil or high lymphocyte counts at baseline

Finally, this kind of analysis was applied for the placebo CRC IV patients. The Kaplan Meier results are shown in Figure 12: The use of the composite parameter NOL-LH for selection of CRC IV patients again leads to a highly significant difference of the survival curves. In the group with improved prognosis the median survival is doubled (365 days vs 184 days), and the 1-year survival is 5-times higher (50% vs 10%). More than 75% of all CRCIV patients are in the group with improved survival, again indicating the power of NOL-LH to precisely identify CRC IV patients with bad prognosis.

13. Summary of results regarding prognostic parameters

The following table summarises the P values (Kaplan-Meier curves; log-rank) obtained with leukocyte-, neutrophil-, lymphocyte-, NML-, and NOL-LH counts at baseline regarding their ability to define patient groups with different overall survival.

	threshold (x10E9/L)	P values		
		all placebo pts (n=118)	placebo stage IV (n=64)	placebo CRC IV (n=46)
leukocytes	7.5	0.0311	0.1297	0.5694
neutrophils	5	0.0018	0.0851	0.4008
lymphocytes	1.6	0.0561	0.0377	0.247
NML	3.4	<0.0001	0.0007	0.0057
NOL-LH	5 or 1.6	<0.0001	<0.0001	0.0032

NOL-LH is the best parameter to prospectively define patient groups with substantially different prognosis for overall survival, with high statistical significance in all tested patient groups, closely followed by NML. Both NOL-LH and NML are composite parameters regarding neutrophil and lymphocyte counts, reflecting the results obtained with each of the single parameters (lower neutrophil counts and higher lymphocyte counts relate to improved OS).

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14. Placebo-controlled clinical trial in patients with NSCLC, stages Ib, II and IIIa

Furthermore, a placebo-controlled double blind clinical trial with the cancer vaccine IGN101 in 762 patients with Non-Small-Cell-Lung-Cancer (NSCLC) stages Ib, II and IIIa was used to analyze above described prognostic parameters. As the study was still blinded, all patients (regardless of placebo or vaccine treatment) were used. At the time of analysis the study had included all patients and was ongoing for approx. 5 years. As in this study patients are included directly after R0-resection of their lung cancer, both relapse-free and overall survival (RFS and OS) is evaluated. In consequence, the prognostic parameters were both assessed regarding their prognostic value for RFS and OS. Neutrophil counts and lymphocyte counts were measured at entry for all patients and at the time of relapse for relapsed patients.

As shown in Figures 13-15, neutrophil counts, lymphocyte counts and NML at relapse have a similar prognostic value for overall survival as described above: Higher neutrophil counts and lower lymphocyte counts are indicators of bad prognosis. Higher NML also is a sign of bad prognosis.

Strikingly, neutrophil counts and NML measured at entry of the NSCLC patients, i.e. directly after surgery, in the early stages Ib, II and IIa, also have a substantial prognostic value, both for RFS and OS. This is shown in Figures 16-19. Higher neutrophil counts and higher NML are signs of bad prognosis regarding RFS and OS. It is especially surprising that white blood cell counts directly after surgery of early stage NSCLC patients already have prognostic value for overall survival, as death of these patients due to lung cancer usually occurs several years after surgery (median in this study approx. 3 years after surgery) and usually after a relapse.

Claims:

1.: A method for identifying the prognosis for improved clinical benefit of an individual suffering from a tumor comprising

- providing a blood sample of said individual,
- (a1) determining the number of lymphocytes in the blood of said individual, and/or
- (a2) determining the number of neutrophils in the blood of said individual, and
- (b1) identifying the individual as having a good prognosis for improved clinical benefit, if the number of lymphocytes is above a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially above 1.6×10^9 per liter blood; or
- (b2) identifying the individual as having a good prognosis for improved clinical benefit, if the number of neutrophils is below or equal to a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially below or equal to 5.0×10^9 neutrophils per liter blood; or
- (b3) identifying the individual as having a bad prognosis for improved clinical benefit, if the number of lymphocytes is below or equal to a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood and the number of neutrophils is above a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood.

2.: A method according to claim 1, characterised in that the improved clinical benefit is an improved overall survival time.

3.: A method according to claim 1 or 2, characterised in that the number of lymphocytes is from 1.6×10^9 to 5.0×10^9 per liter blood.

4.: A method according to any one of claims 1 to 3, characterised in that the number of lymphocytes is from 1.6×10^9 to 4.5×10^9 per liter blood.

5.: A method according to any one of claims 1 to 4, character-

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ised in that the number of neutrophils is from 1.0×10^9 to 5.0×10^9 per liter blood.

6.: A method according to any one of claims 1 to 5, characterised in that the number of neutrophils is from 1.7×10^9 to 5.0×10^9 per liter blood.

7.: A method for identifying the prognosis for improved clinical benefit of an individual suffering from a tumor comprising

- providing a blood sample of said individual,
- (a1) determining the number of lymphocytes in the blood of said individual, and/or
- (a2) determining the number of neutrophils in the blood of said individual, and
- (b1) identifying the individual as having a good prognosis for improved clinical benefit, if the number of lymphocytes is above a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially above 1.6×10^9 per liter blood; or
- (b2) identifying the individual as having a good prognosis for improved clinical benefit, if the number of neutrophils is below or equal to a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially below or equal to 5.0×10^9 neutrophils per liter blood; or
- (b3) identifying the individual as having a bad prognosis for improved clinical benefit, if the number of lymphocytes is below or equal to a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood and the number of neutrophils is above a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood.

8.: A method according to any one of claims 1 to 7, characterised in that said tumor is an epithelial tumor, preferably breast cancer, lung cancer, especially Non-Small-Cell-Lung-Cancer (NSCLC), cancer in the stomach, pancreas carcinoma, prostate cancer, ovarian carcinoma or colorectal cancer, especially colorectal cancer.

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9.: A method according to any one of claims 1 to 8, characterised in that said individual is a tumor patient in stage III or IV of said tumor, classified according to the American Joint Committee on Cancer Manual for Staging Cancer, 6th Edition (2002), especially a tumor patient in stage IV.

10.: A method according to any one of claims 1 to 9, characterised in that said individual is an individual who had received a neutrophil reduction treatment, preferably selected from one or more of neutrophil reducing apheresis, radiation therapy or administration of neutrophil reducing agents, especially of chemotherapeutic drugs, monoclonal antibodies against neutrophil markers, immunomodulatory drugs, cytokines or mixtures thereof.

11.: A method according to any one of claims 1 to 10, characterised in that said individual is an individual who had received a lymphocyte number enhancement treatment, preferably IL-2 administration or lymphocyte administration.

12.: A method according to any one of claims 1 to 10, characterised in that the difference of the neutrophil number and the lymphocyte number (neutrophils minus lymphocytes; NML) is determined and

- (b4) identifying the individual as having a good prognosis for improved clinical benefit, if the NML is below or equal to an NML baseline level of from 2.4 to 4.4×10^9 cells per liter blood, especially below or equal to 3.4×10^9 cells per liter blood; or
- (b5) identifying the individual as having a bad prognosis for improved clinical benefit, if the NML is above an NML baseline level of from 2.4 to 4.4×10^9 cells per liter blood, especially above 3.4×10^9 cells per liter blood.

13.: Method for conducting clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a lymphocyte number above a lymphocyte baseline level and a group which has a lymphocyte number below or equal to a lymphocyte baseline level, said lymphocyte baseline level being a value from 1.4 to 1.8×10^9 lymphocytes per liter blood, especially 1.6×10^9 per liter blood.

14.: Method for conducting clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a neutrophil number above a neutrophil baseline level and a group which has a neutrophil number below or equal to a neutrophil baseline level, said neutrophil baseline level being a value from 4.0 to 6.0×10^9 neutrophils per liter blood, especially 5.0×10^9 per liter blood.

15.: Method for conducting clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a lymphocyte number above a lymphocyte baseline level, said lymphocyte baseline level being a value from 1.4 to 1.8×10^9 lymphocytes per liter blood, especially 1.6×10^9 per liter blood and a neutrophil number below or equal to a neutrophil baseline level, said neutrophil baseline level being a value from 4.0 to 6.0×10^9 neutrophils per liter blood, especially 5.0×10^9 per liter blood.

16.: Method for conducting clinical trials for a tumor treatment comprising the grouping of individuals into a group which has an NML below or equal to an NML baseline level of from 2.4 to 4.4×10^9 cells per liter blood, especially below or equal to 3.4×10^9 cells per liter blood and a group which has an NML above an NML baseline level of from 2.4 to 4.4×10^9 cells per liter blood, especially above 3.4×10^9 cells per liter blood.

17.: Method for conducting clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a number of lymphocytes below or equal to a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood and a number of neutrophils above a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood.

18.: Method for re-analysing the results of clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a lymphocyte number below or equal to a lymphocyte baseline level and a group which has a lymphocyte number

above a lymphocyte baseline level, said lymphocyte baseline level being a value from 1.4 to 1.8×10^9 lymphocytes per liter blood, especially 1.6×10^9 per liter blood and re-evaluating the efficacy of the clinical trial based on this grouping based on lymphocyte number.

19.: Method for re-analysing the results of clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a neutrophil number above a neutrophil baseline level and a group which has a neutrophil number below or equal to a neutrophil baseline level, said neutrophil baseline level being a value from 4.0 to 6.0×10^9 neutrophils per liter blood, especially 5.0×10^9 per liter blood and re-evaluating the efficacy of the clinical trial based on this grouping based on neutrophil number.

20.: Method for re-analysing the results of clinical trials for a tumor treatment comprising the grouping of individuals into a group which has an NML below or equal to an NML baseline level of from 2.4 to 4.4×10^9 cells per liter blood, especially below or equal to 3.4×10^9 cells per liter blood and a group which has an NML above an NML baseline level of from 2.4 to 4.4×10^9 cells per liter blood, especially above 3.4×10^9 cells per liter blood.

21.: Method for re-analysing the results of clinical trials for a tumor treatment comprising the grouping of individuals into a group which has a number of lymphocytes below or equal to a lymphocyte baseline level of 1.4 to 1.8×10^9 per liter blood, especially below or equal to 1.6×10^9 per liter blood and a number of neutrophils above a neutrophil baseline level of from 4.0 to 6.0×10^9 per liter blood, especially above 5.0×10^9 neutrophils per liter blood.

22.: Method according to any one of claims 13 to 21, characterised in that said tumor is an epithelial tumor, preferably breast cancer, lung cancer, cancer in the stomach, pancreas carcinoma, prostate cancer, ovarian carcinoma or colorectal cancer, especially colorectal cancer.

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23.: A method according to any one of claims 13 to 22, characterised in that said patients are tumor patients in stage III or IV of said tumor, classified according to the American Joint Committee on Cancer Manual for Staging Cancer, 6th Edition (2002), especially a tumor patient in stage IV.

24.: Data storage means comprising a grouping of individuals as defined in any one of claims 13 to 23.

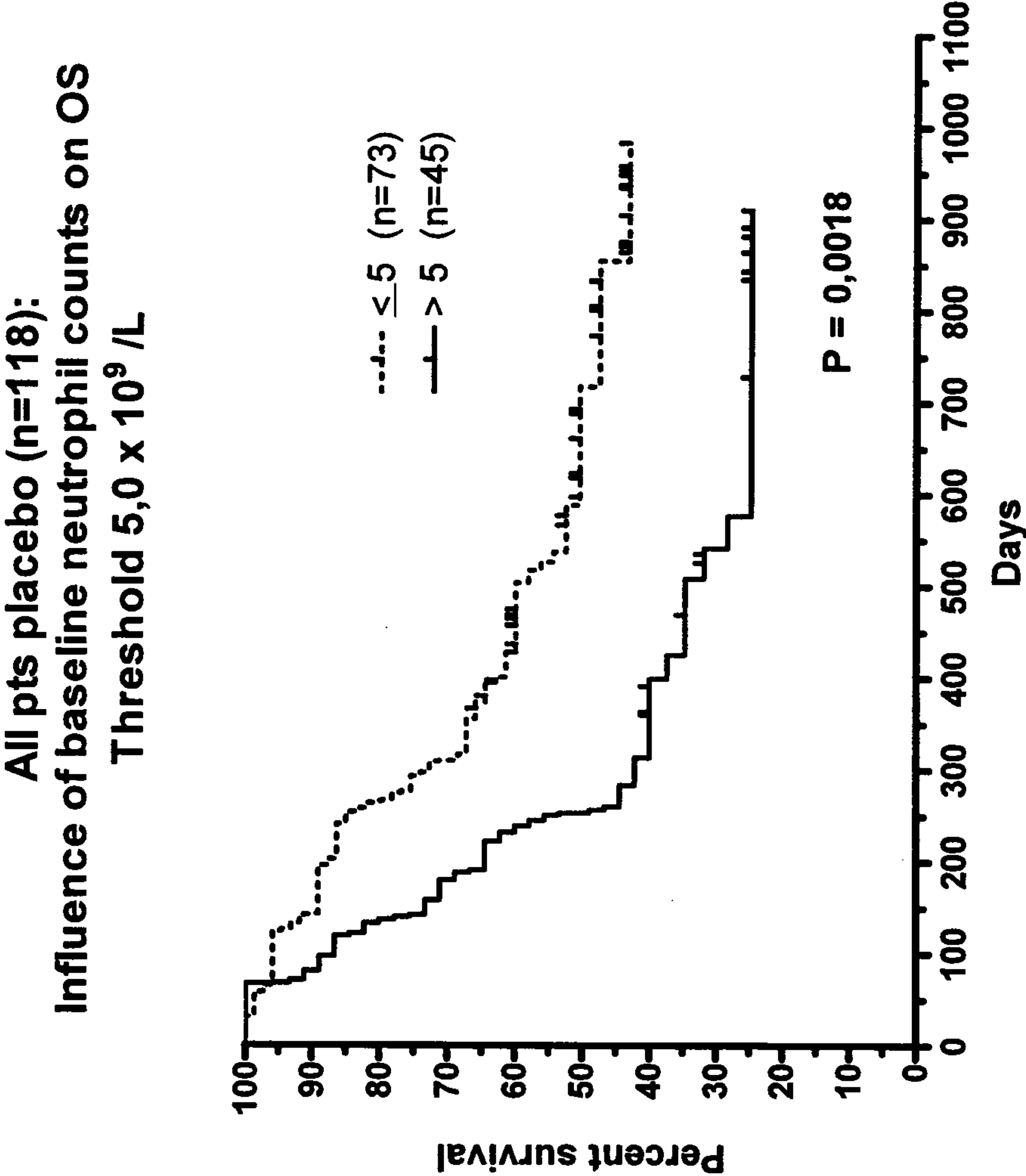
25.: A method for identifying an individual suffering from a tumor as having a good prognosis for improved overall survival time comprising

- providing a blood sample of said individual,
- determining the number of neutrophils and the number of lymphocytes in the blood of said individual and
- identifying the individual as having a good prognosis for improved overall survival time, if the difference of the number of neutrophils and the number of lymphocytes is below or equal to a neutrophil-minus-lymphocyte baseline level of from 3.0 to 4.0×10^9 per liter blood, especially below or equal to 3.4×10^9 per liter blood.

26.: A method according to claim 25, characterised in that said tumor is colorectal cancer.

27.: A method according to claim 25 or 26, characterised in that said patients are tumor patients in stage III or IV of said tumor, classified according to the American Joint Committee on Cancer Manual for Staging Cancer, 6th Edition (2002), especially a tumor patient in stage IV.

Fig. 1



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Fig. 2

Stage IV pts placebo (n=64):
Influence of baseline neutrophil counts on OS
Threshold $5,0 \times 10^9 /L$

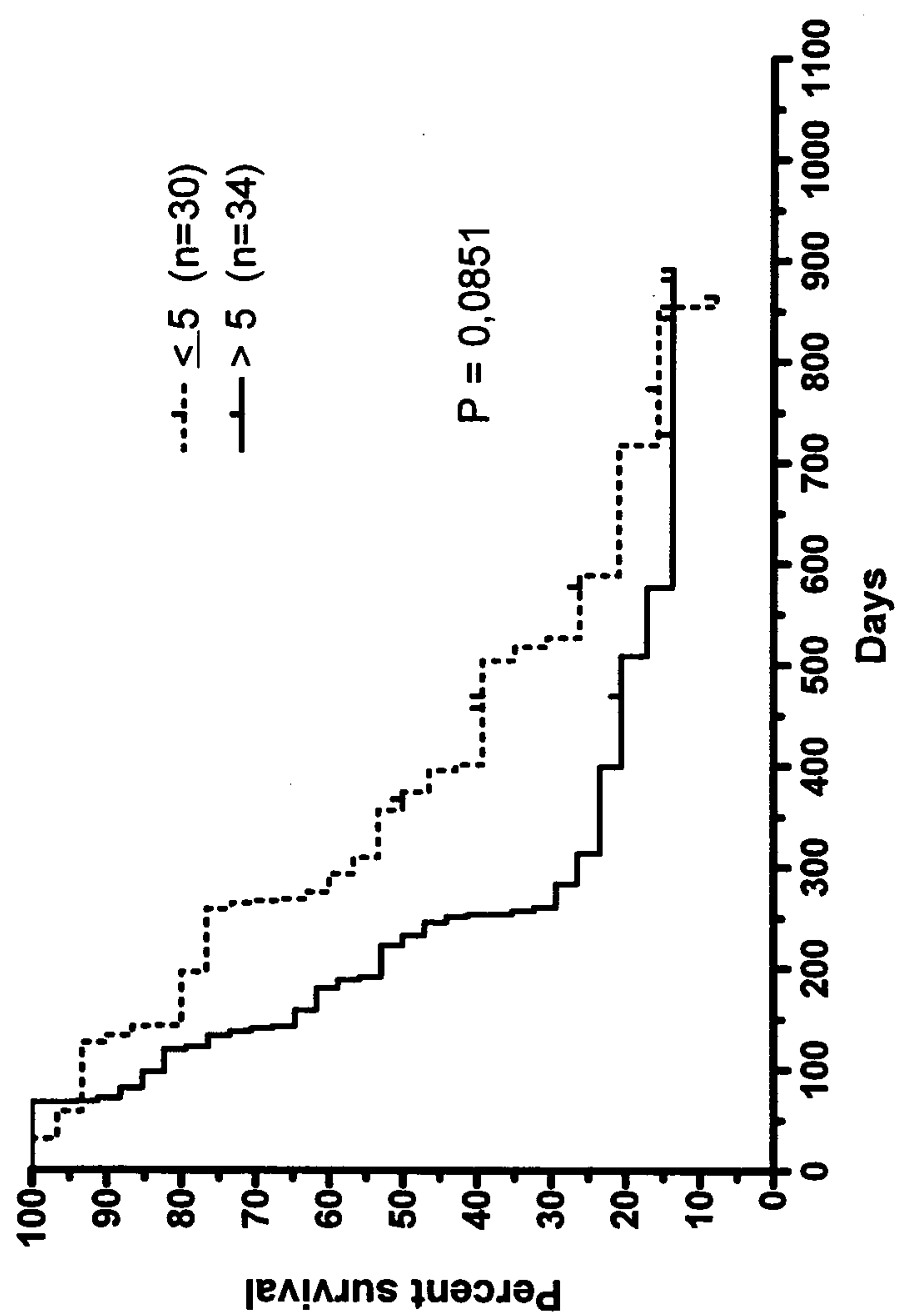


Fig. 3

CRC IV pts placebo (n=46):
Influence of baseline neutrophil counts on OS
Threshold $5,0 \times 10^9 /L$

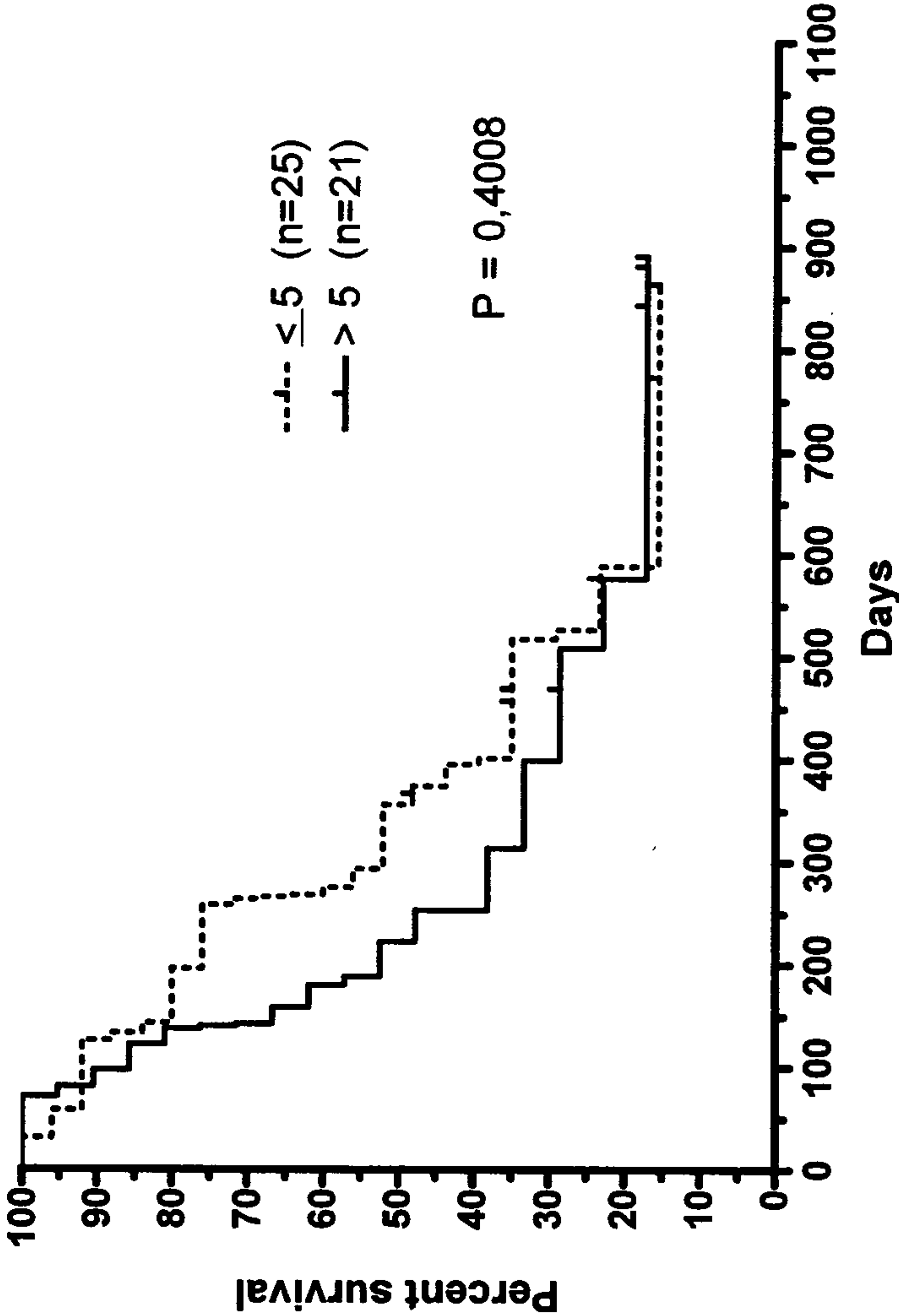
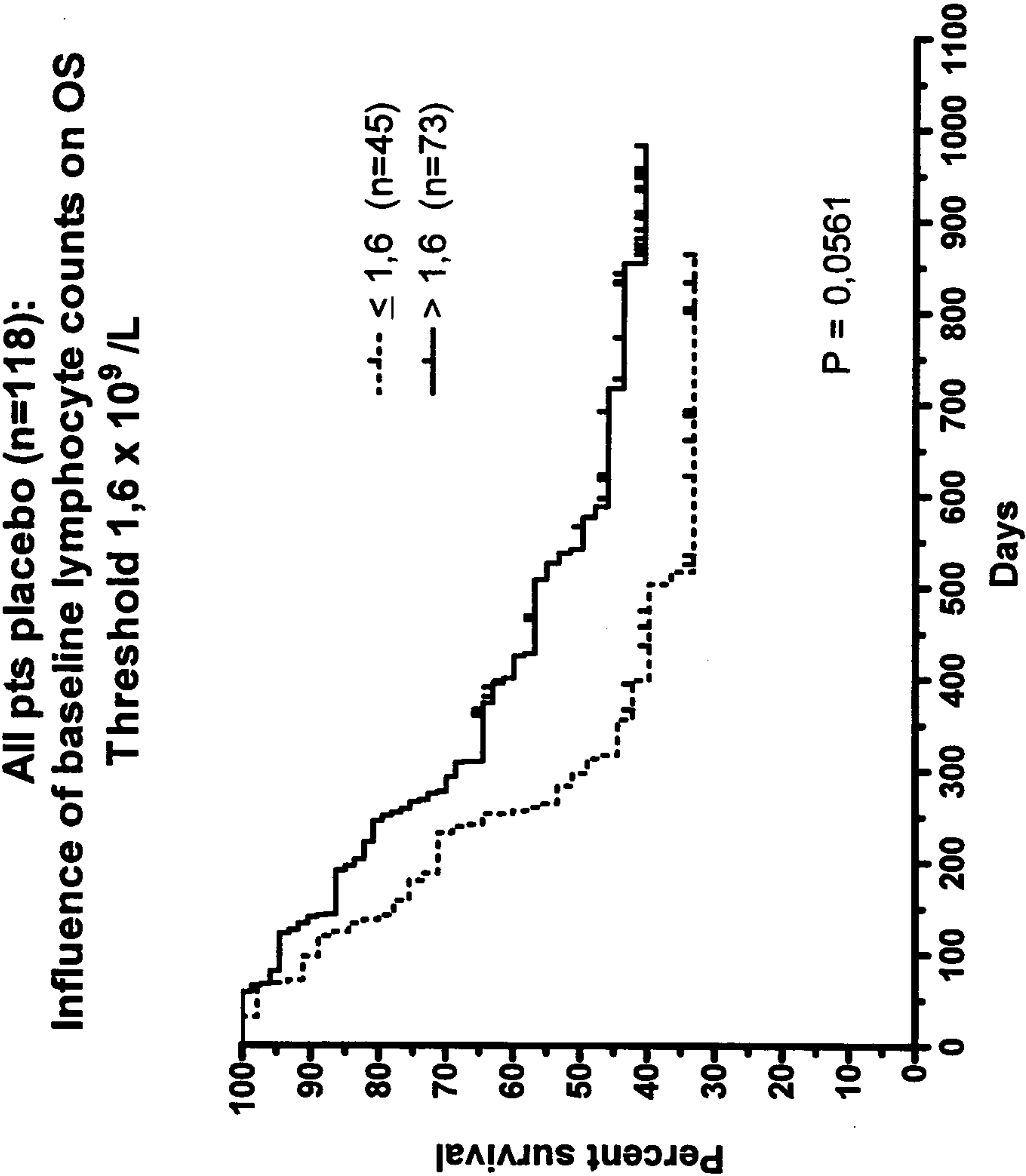


Fig. 4



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Fig. 5

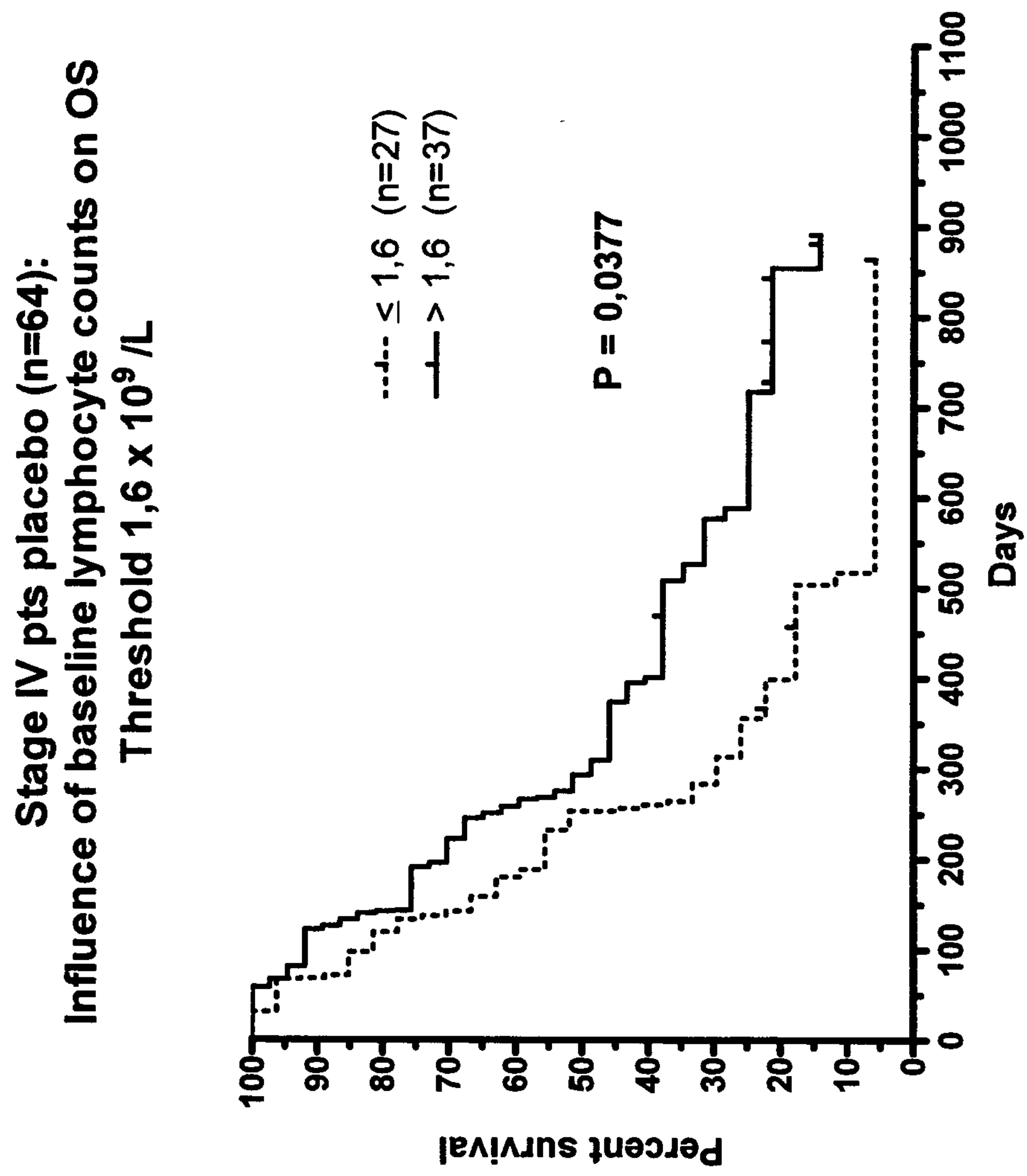
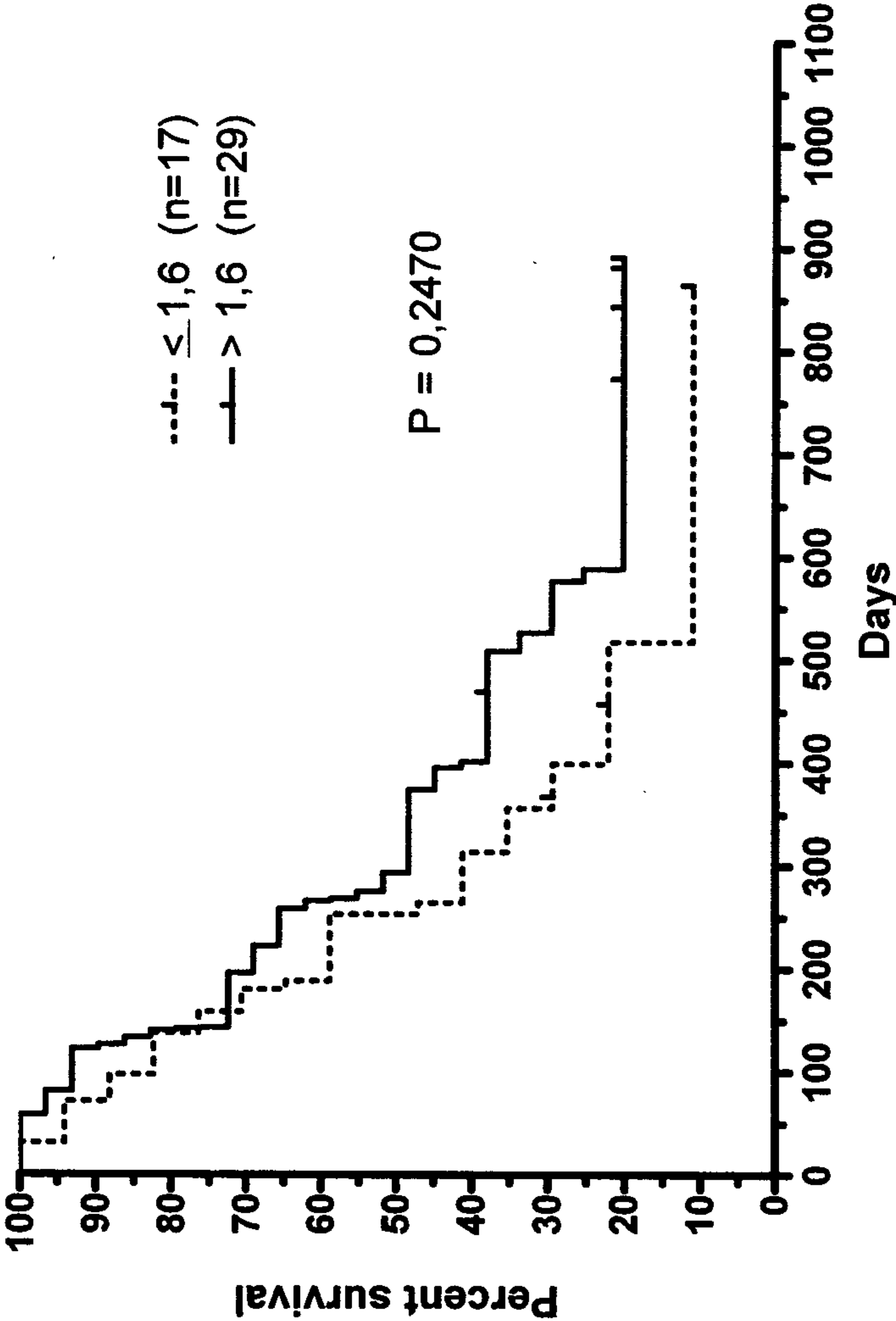


Fig. 6

CRC IV pts placebo (n=46):
Influence of baseline lymphocyte counts on OS
Threshold $1,6 \times 10^9 /L$



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Fig. 7

all pts placebo (n=181):
Influence of baseline neutrophil minus lymphocyte counts on OS
Threshold $3,4 \times 10^9 /L$

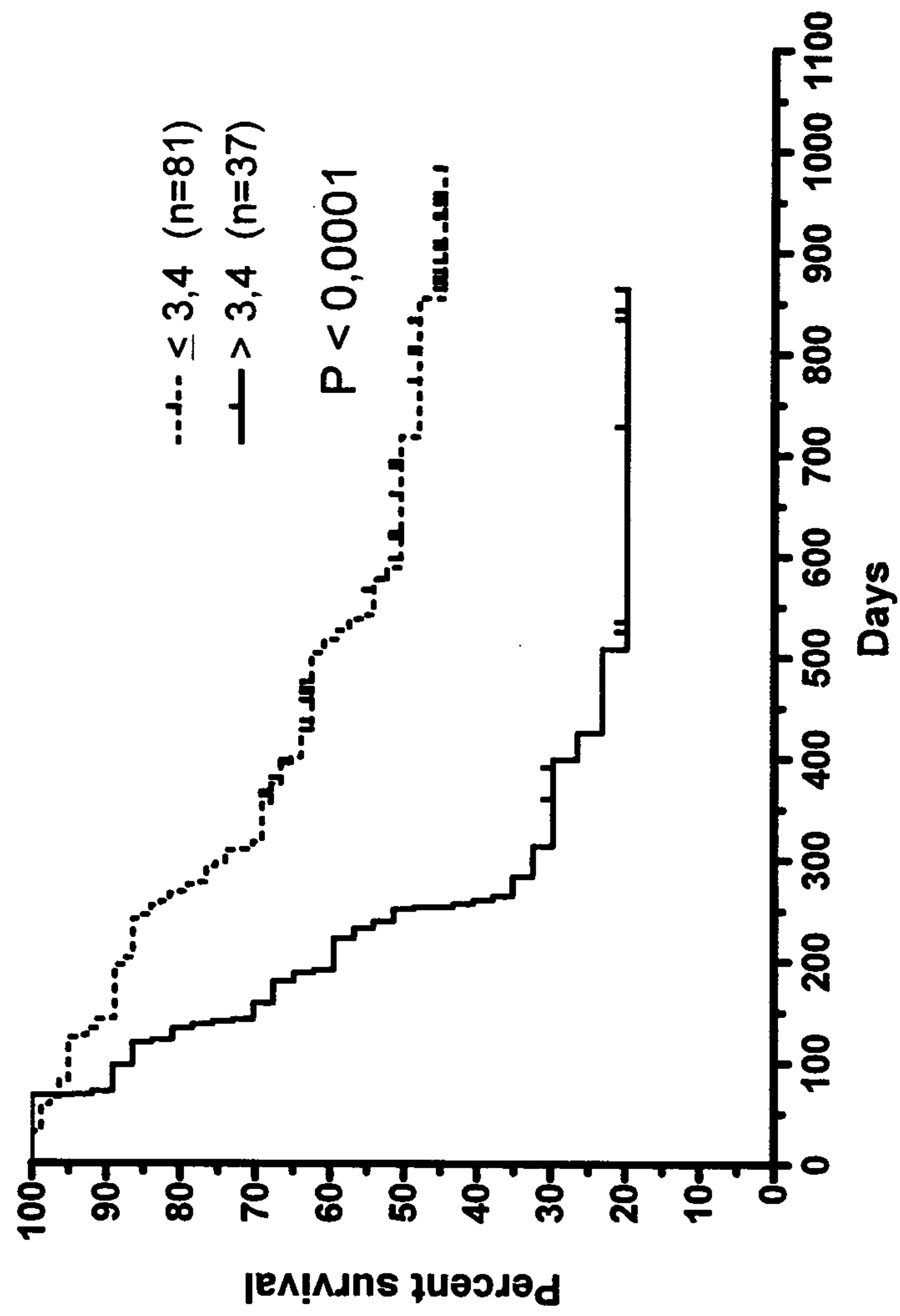


Fig. 8

stage IV pts placebo (n=64):
Influence of baseline neutrophil minus lymphocyte counts on OS
Threshold $3,4 \times 10^9 /L$

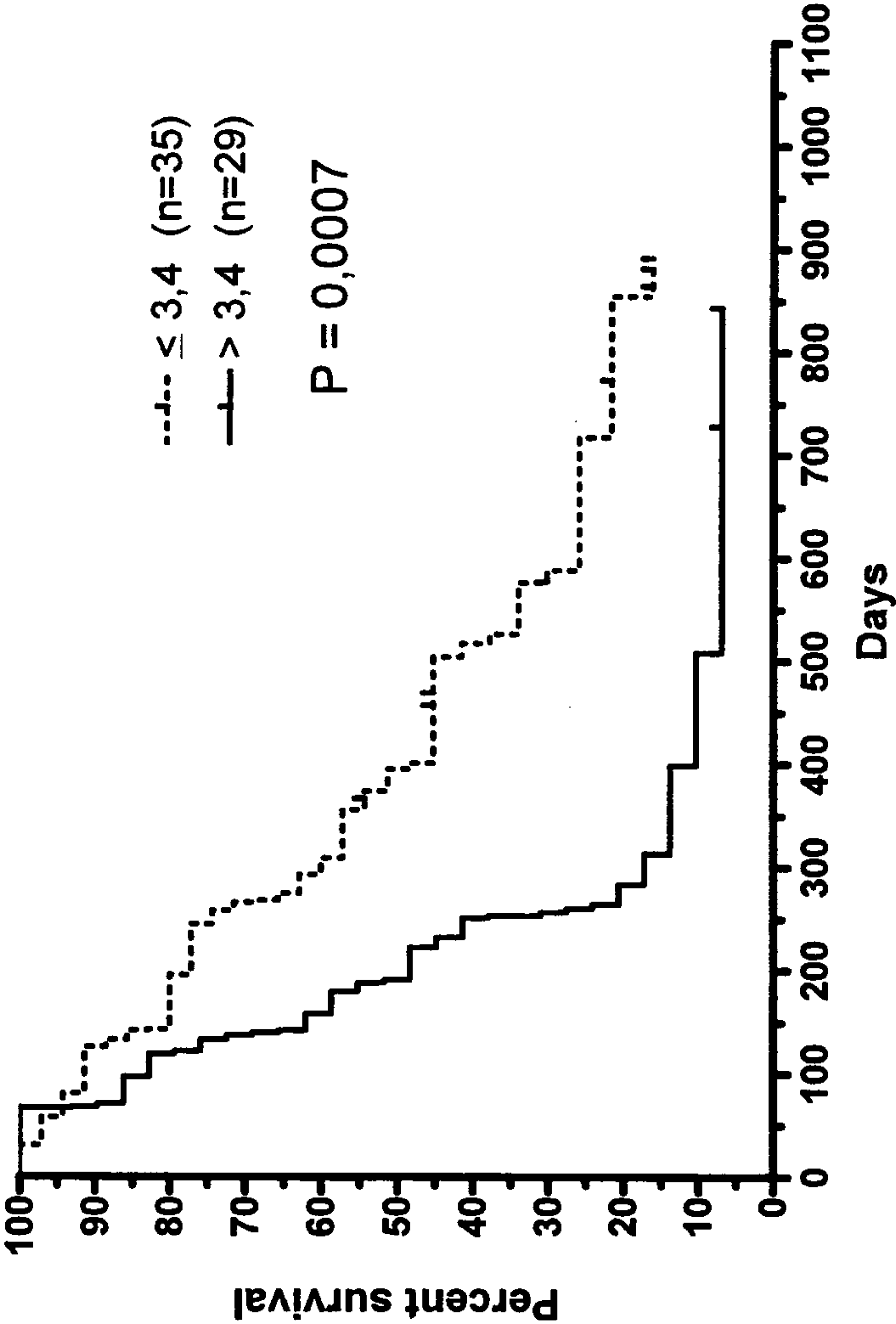
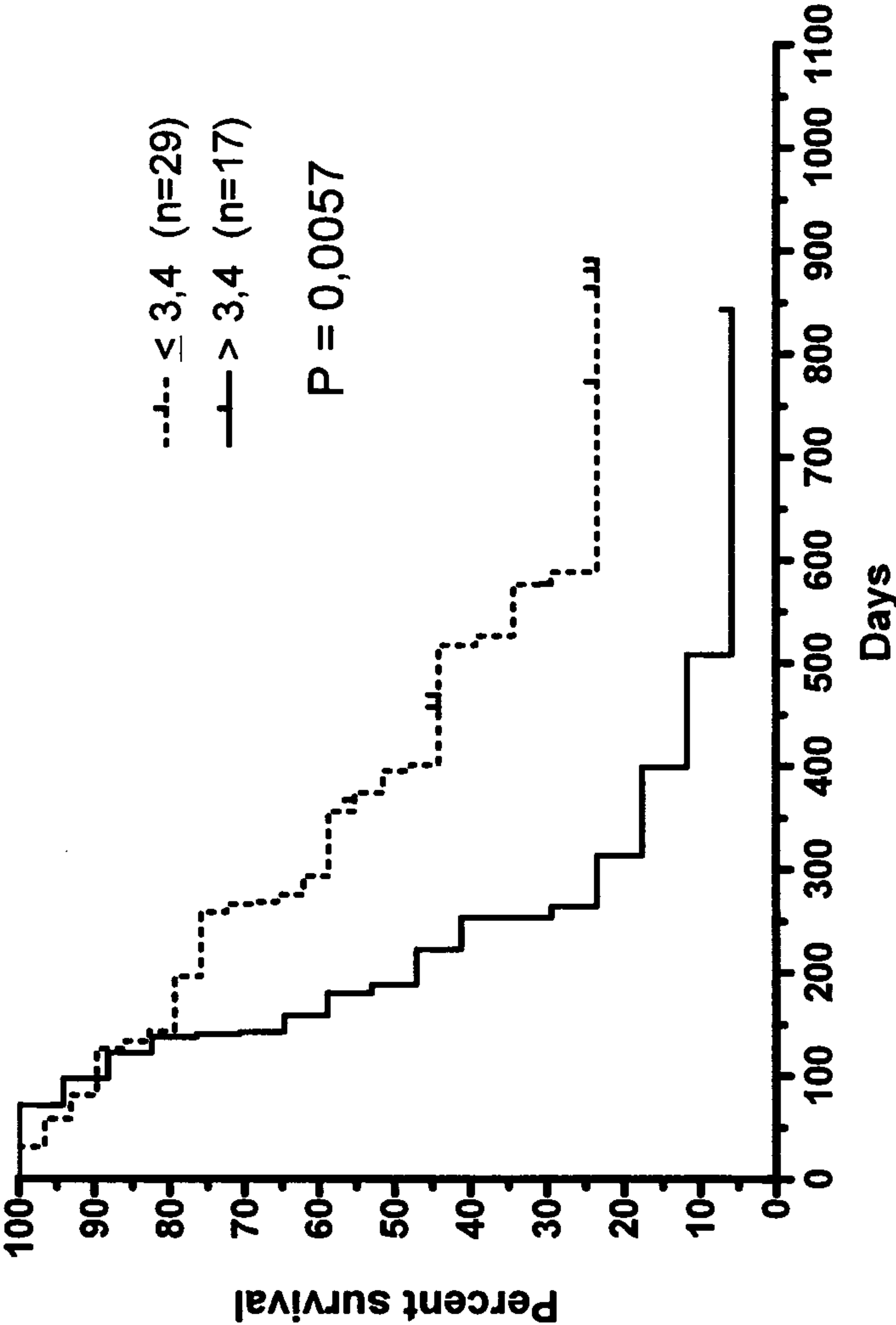


Fig. 9

CRC IV pts placebo (n=46):

Influence of baseline neutrophil minus lymphocyte counts on OS

Threshold $3,4 \times 10^9 /L$



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Fig. 10

all pts placebo (n=118):
Influence of baseline neutrophil counts $\leq 5,0 \times 10^9 /L$
or lymphocyte counts $> 1,6 \times 10^9 /L$ on OS

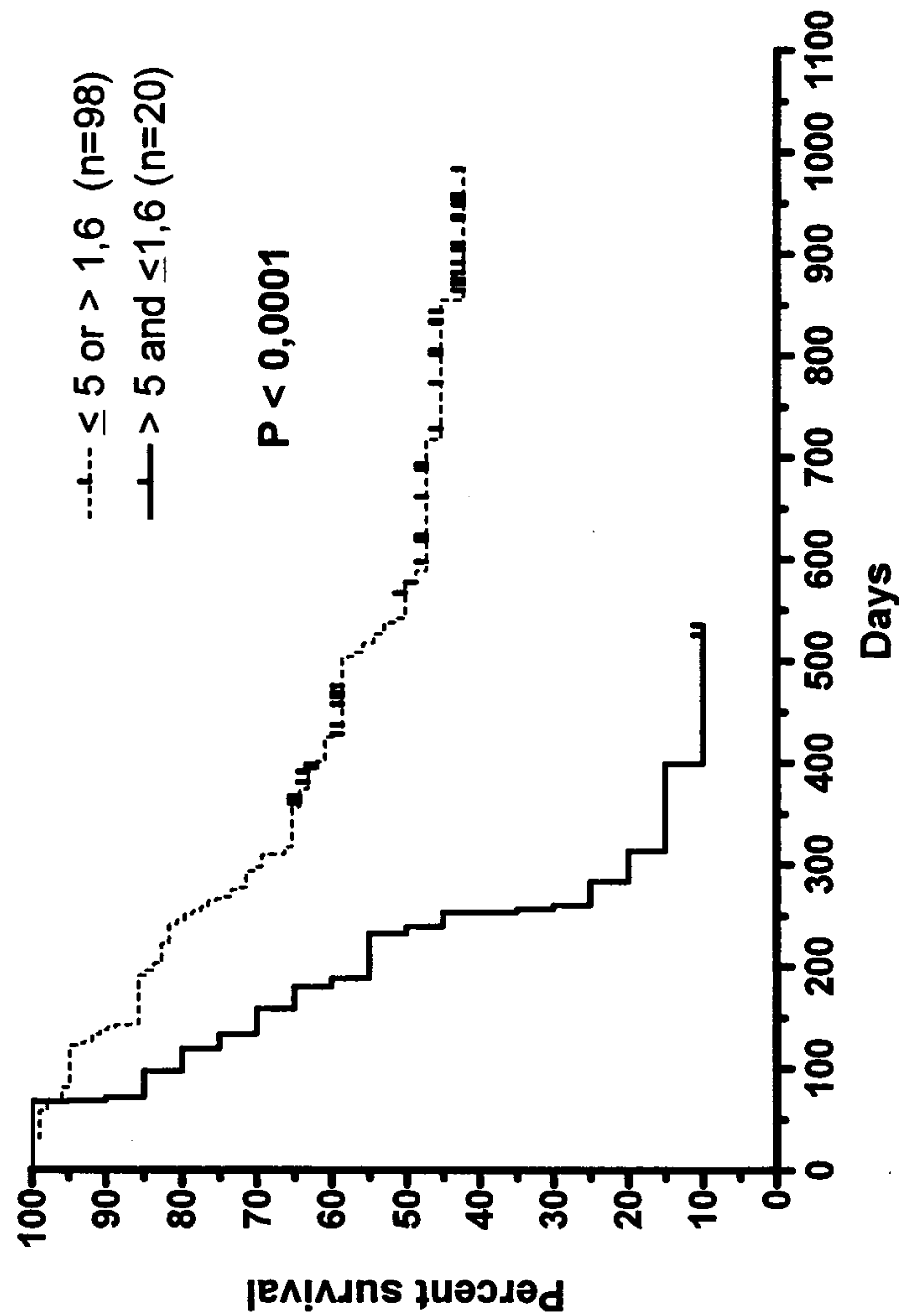


Fig. 11

All stage IV placebo (n=64):
Influence of baseline neutrophil counts $\leq 5,0 \times 10^9 /L$
or lymphocyte counts $> 1,6 \times 10^9 /L$ on OS

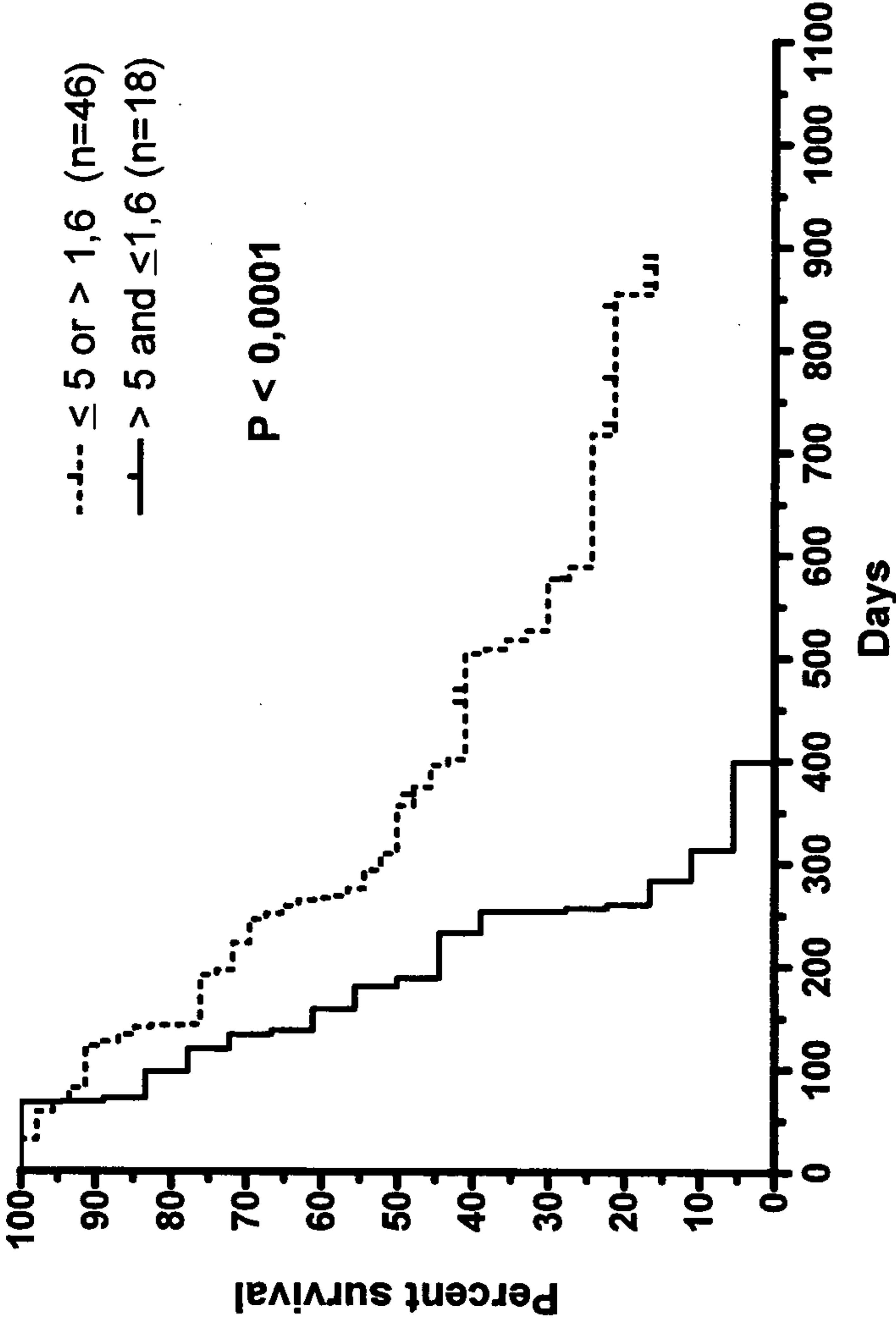


Fig. 12

CRC IV placebo (n=46):

**Influence of baseline neutrophil counts $\leq 5,0 \times 10^9 /L$
or lymphocyte counts $> 1,6 \times 10^9 /L$ on OS**

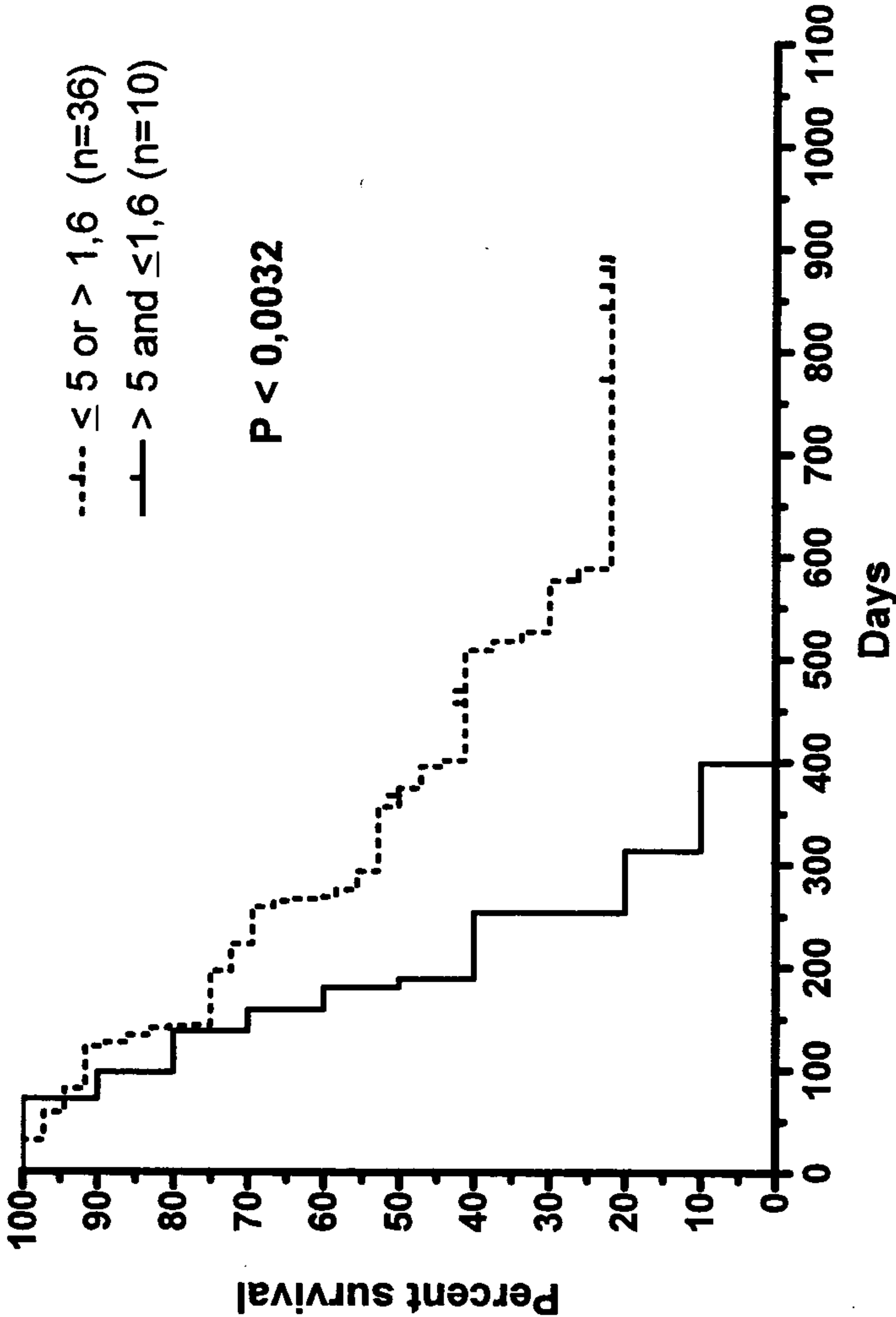


Fig. 13

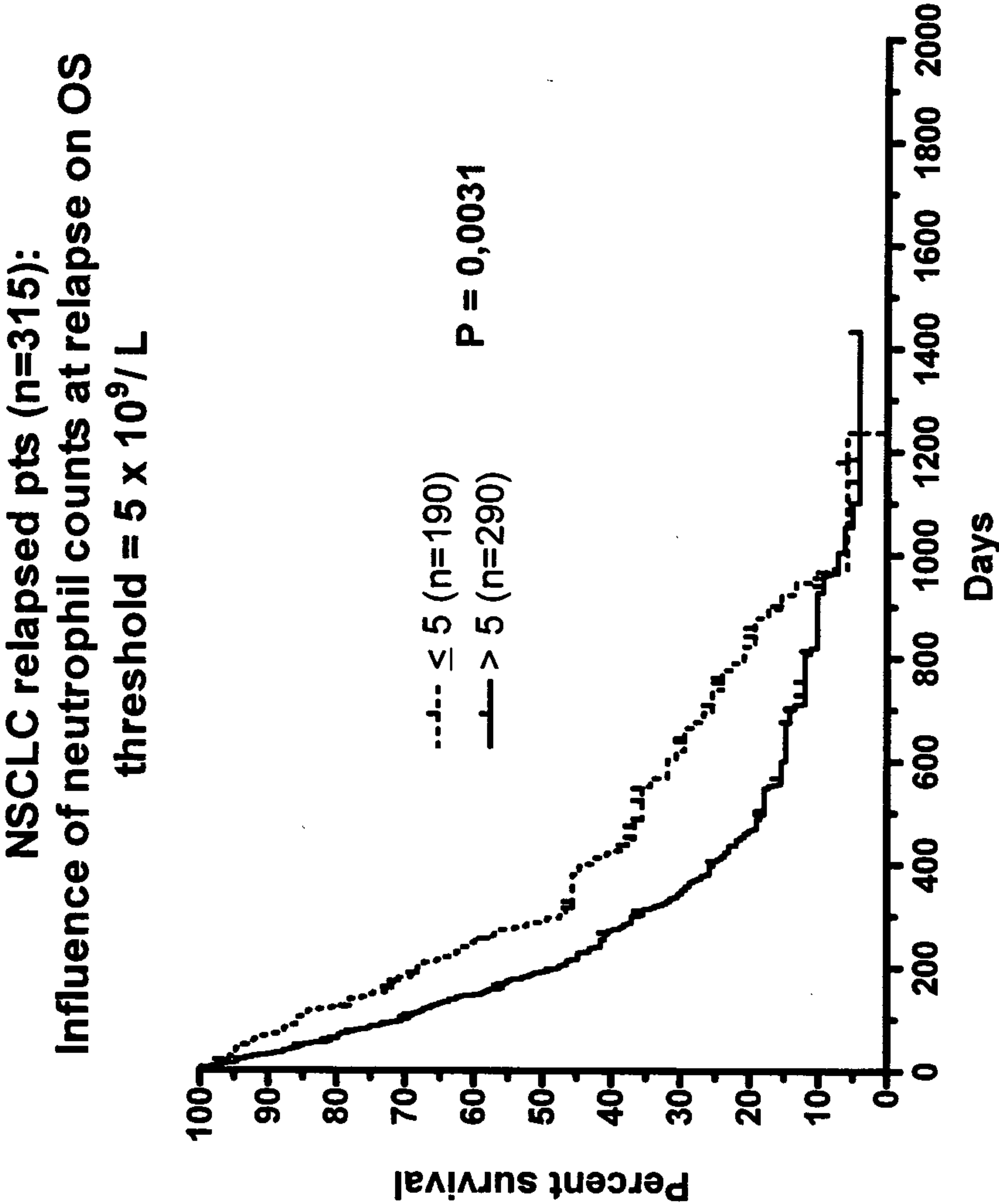


Fig. 14

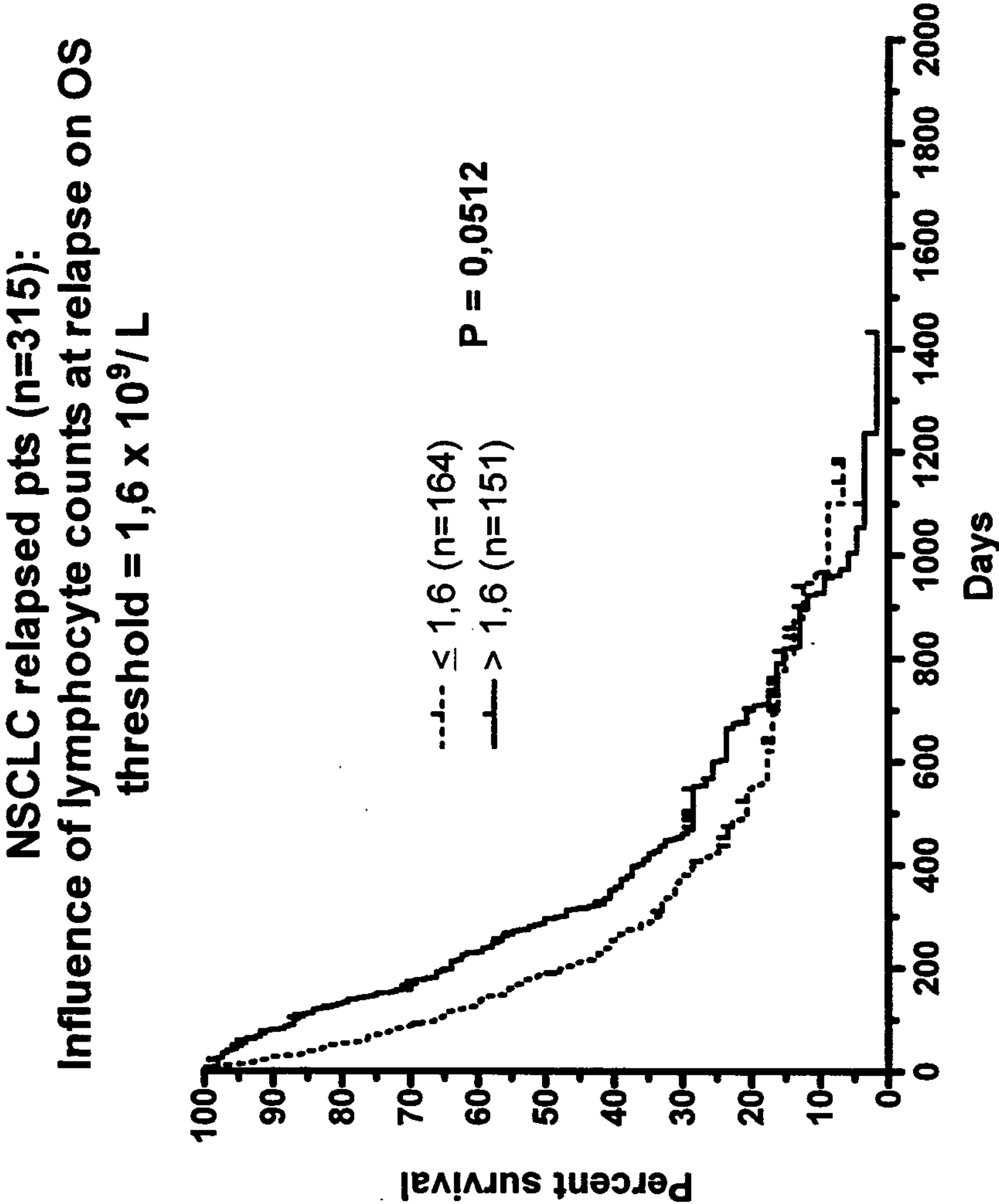
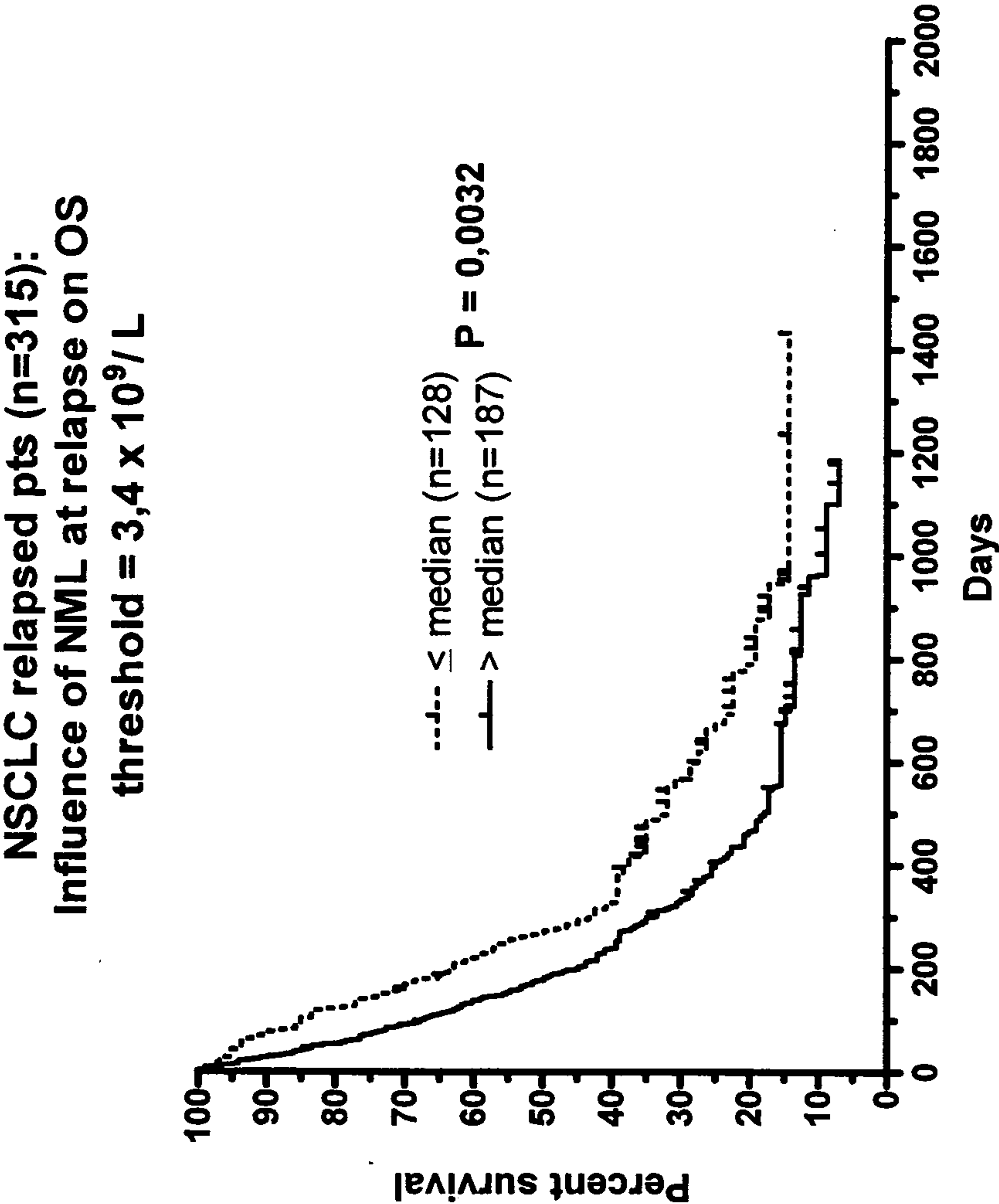
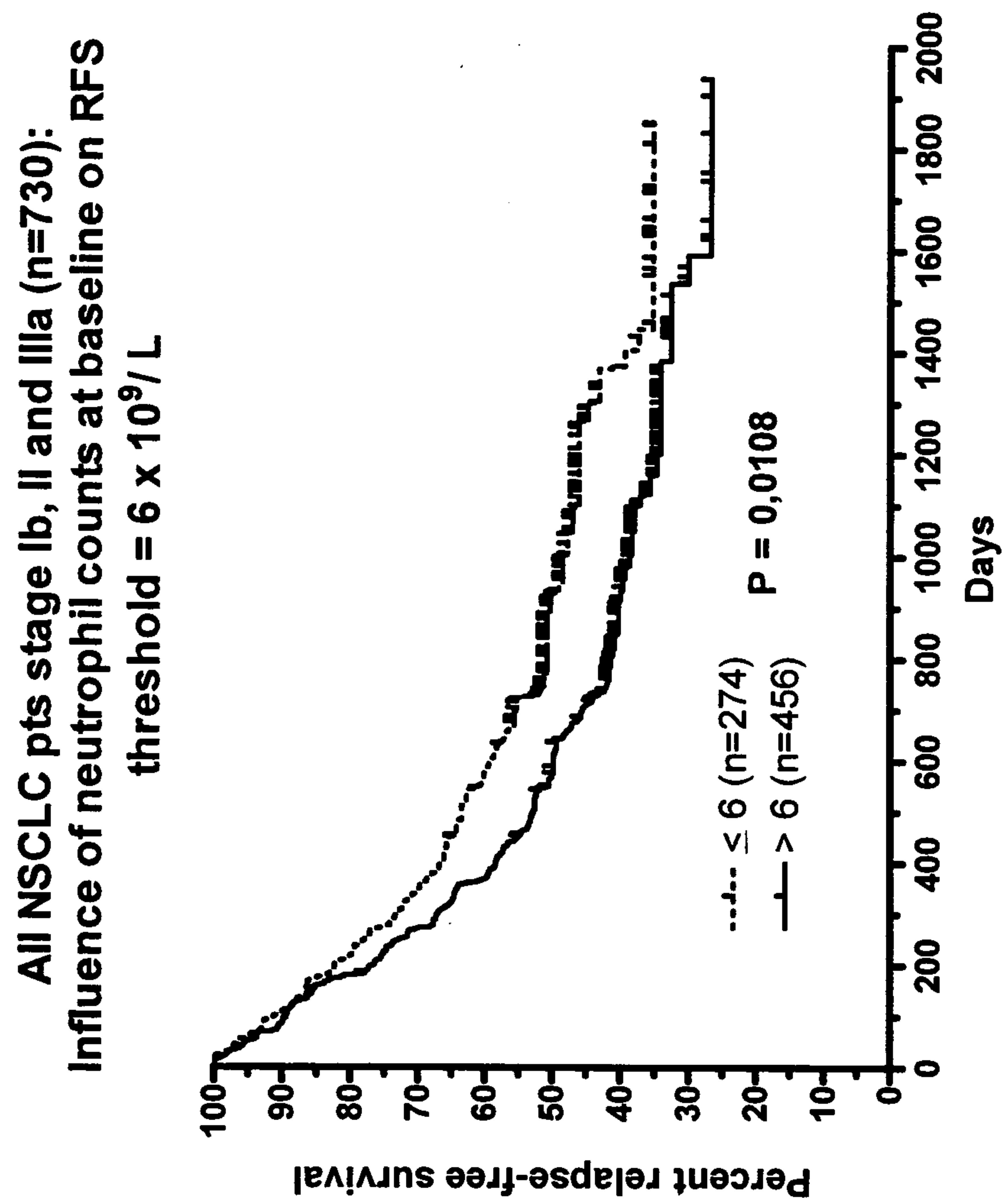


Fig. 15



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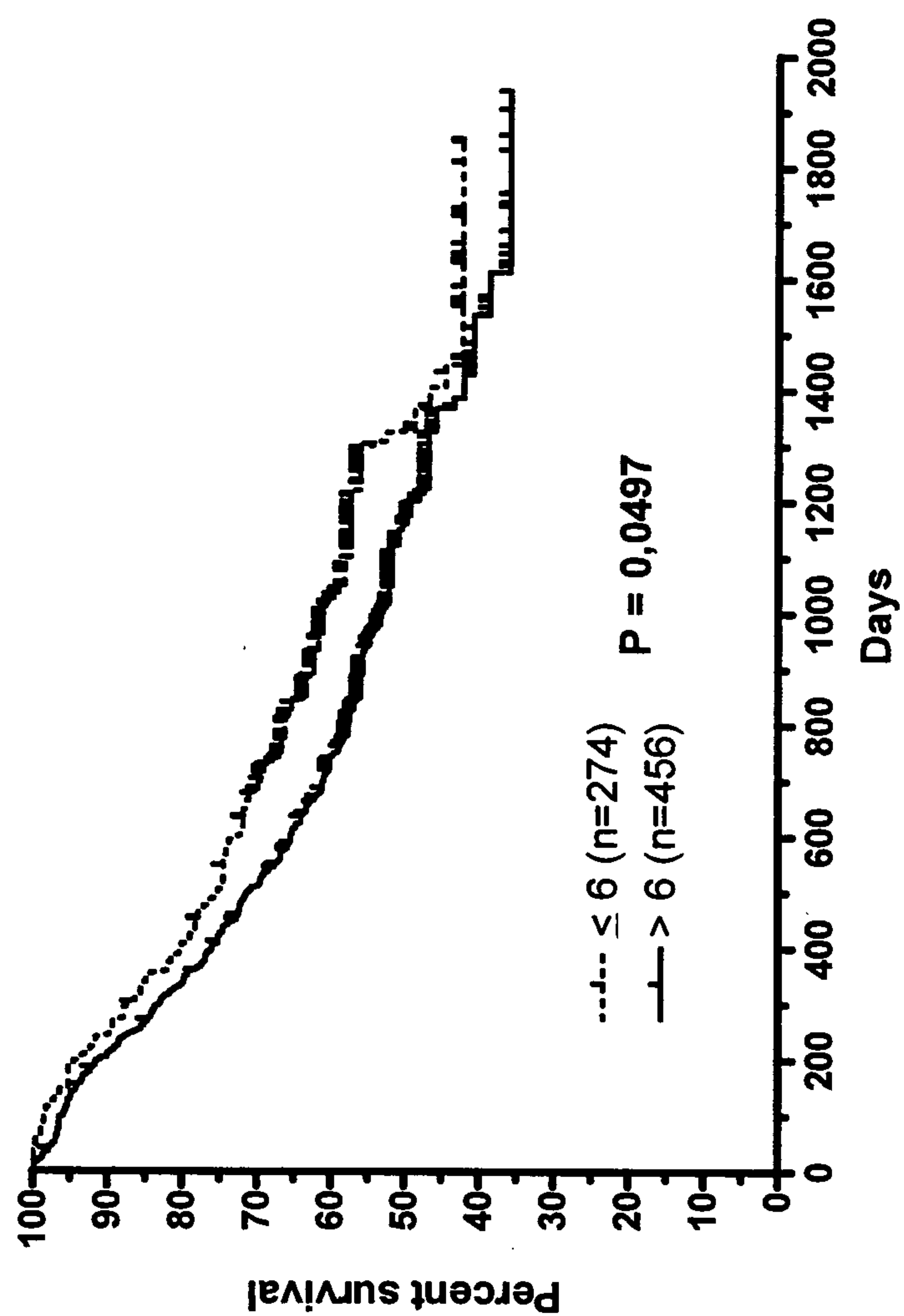
Fig. 16



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Fig. 17

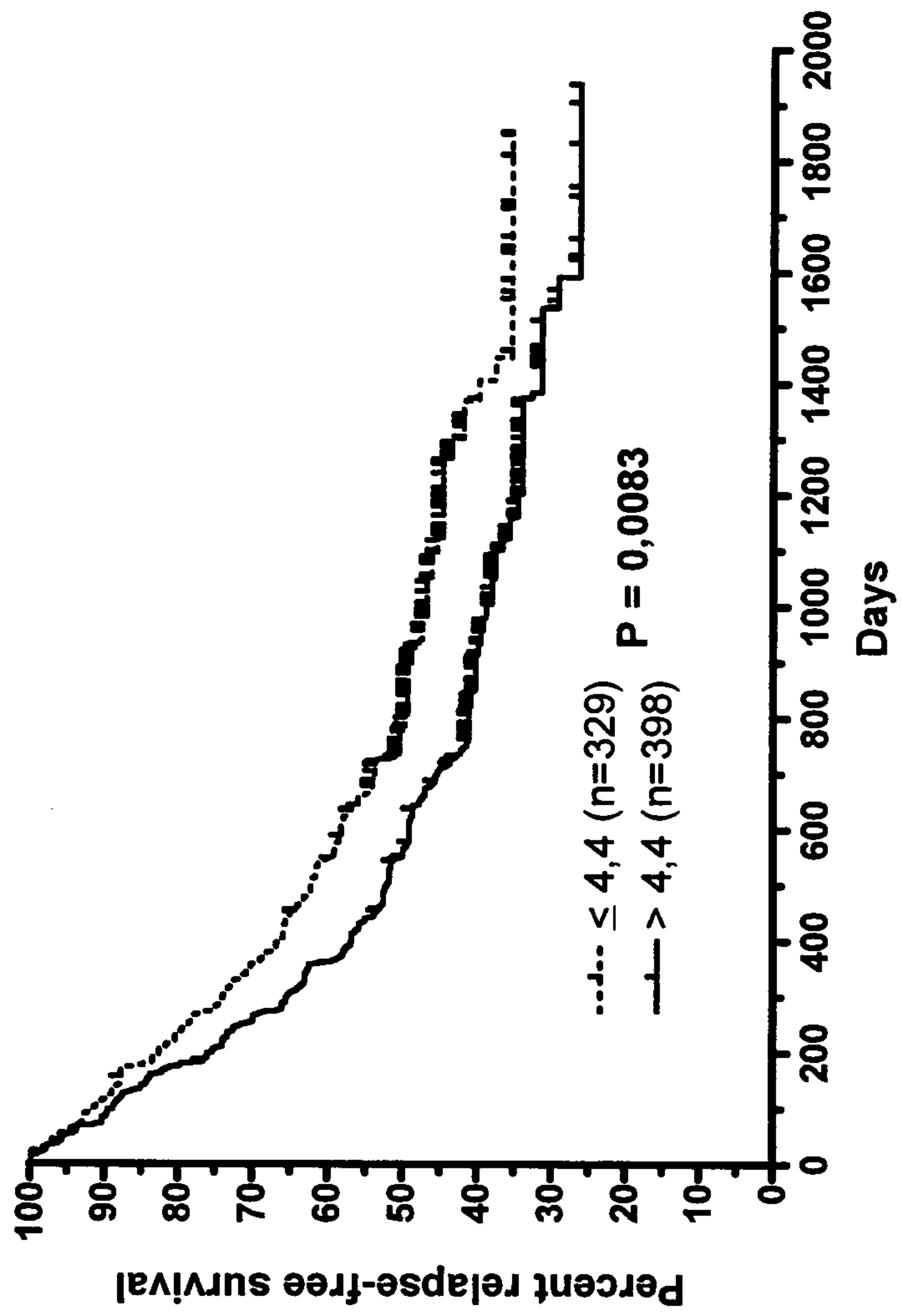
All NSCLC pts stage Ib, II and IIIa (n=730):
Influence of neutrophil counts at baseline on OS
threshold = $6 \times 10^9/L$



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Fig. 18

All NSCLC pts stage Ib, II and IIIa (n=727):
Influence of NML at baseline on RFS
threshold = $4,4 \times 10^9/L$



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Fig. 19

