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Personalised chemotherapy based on tumour marker decline in poor-prognosis germ-cell tumours: results of the GETUG 13 phase III trial

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Contributors

KF, CL, and SC contributed to the study concept and design. KF was the principal investigator. KF, LP, AF, JM, LG, PK, CC, RD, FR, CT, GR, GG, JCE, JPM, CL, MR, CL, and SC recruited and treated patients; all authors participated in evaluation and interpretation of the data; AL and FJ were responsible for statistical analysis; all authors contributed to the content of the manuscript and reviewed manuscript drafts. All authors reviewed and approved the final manuscript prior to submission. The authors take full responsibility for the scope, direction, and content of the manuscript.

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Abstract

Background—Poor-prognosis germ-cell tumours (GCT) are associated with only a 50% cure rate. Our hypothesis was that treatment intensification based on an early tumour marker decline will improve progression-free survival (PFS).

Methods—In this phase III, multicentre, international trial (NCT00104676 ; EU-20502), after patients with poor-prognosis GCT defined according to the International Germ-Cell Cancer Consensus Group (IGCCCG) had received one cycle of cisplatin (20 mg/m^2/day × 5 days), etoposide (100 mg/m^2/day × 5 days), and bleomycin (30 mg/week) (BEP), AFP and hCG were assessed between day 18 and 21: 1) patients with a favourable decline continued BEP (Fav-BEP); 2) patients with an unfavourable decline were randomised to receive either BEP (Unfav-BEP) or a dose-dense regimen (Unfav-dose-dense), consisting of paclitaxel (175 mg/ m^2 day 1)-BEP plus oxaliplatin (130 mg/ m^2 day 10) (2 cycles), followed by cisplatin (100 mg/ m^2 day 1), ifosfamide (2 g/ m^2 on days 10, 12, 14 + mesna), and bleomycin (25 units/day, by continuous infusion × 5 days on day 10 to 14) (2 cycles), with G-CSF support. Centrally blocked randomisation stratified by centre was used. The primary endpoint was PFS and the efficacy analysis was conducted on an intention-to-treat basis i.e. it included all randomised patients. The planned trial accrual was completed in May 2012 and follow-up is ongoing.

Results—263 patients were enrolled and 203 had an unfavourable tumour marker decline (randomised: 105 Unfav-dose-dense arm, 98 Unfav-BEP arm). The 3-year PFS rate was 59% [95% Confidence Interval (CI): 49–68] in the Unfav-dose-dense arm versus 48% [95% CI: 38–59] in the Unfav-BEP arm (p=0.05; HR: 0.66 [95% CI: 0.44–1.00]). The 3-year PFS rate was 70% [95% CI: 57%–81%] for patients in the Fav-BEP arm (p=0.01 for PFS compared with the Unfav-BEP arm). More grade 3–4 neurotoxicity (7 [7%] vs 1 [1%]) and greater haematotoxicity occurred in the dose-dense arm, with no excess febrile neutropenia (18 [17%] vs 18 [18%]) or toxic deaths (1 each arm). Salvage high-dose chemotherapy + a stem-cell transplant were required in 6 [6%] in the Unfav-dose-dense arm and 16 [16%] patients in the Unfav-BEP arm (p=0.015).

Conclusion—Personalising treatment with chemotherapy intensification reduces the risk of progression or death in patients with poor-prognosis GCT and an unfavourable tumour marker decline.

Introduction

Approximately 80% of disseminated non-seminomatous germ-cell tumours (NSGCT) have been cured with cisplatin-based chemotherapy and surgery (1). In the International Germ-Cell Cancer Consensus Group (IGCCCG) classification, a poor-risk group is defined with a progression-free survival (PFS) rate of only 41% (2). Four cycles of cisplatin, bleomycin and etoposide (BEP) became the standard regimen for this group after a trial found that survival was improved (3). All attempts to improve the results of BEP focusing on increasing the peak dose-intensity (4,5), high-dose chemotherapy with stem cell support (6–

8), incorporating ifosfamide (9), and developing alternating regimens (10,11), have failed, perhaps partly because the planned accrual could not be completed in some trials.

Although the unique chemosensitivity of GCT is a strong rationale for testing high-dose chemotherapy, this approach has been hampered by early deaths, in part due to toxicity (7,12). An alternative approach is to shorten the interval between courses of chemotherapy rather than increase the doses (the concept of dose-density) (13). Although the results were encouraging, toxicity was significant (14), indicating a need for better selection. Investigators have studied whether a slow decline in hCG and AFP could identify patients likely to fail conventional therapy (7,15,16). A subgroup of patients with poor-prognosis NSGCT with a better outcome was identified based on a tumour marker decline assessed 3 weeks after the start of chemotherapy: patients with an unfavourable decrease and those with a favourable decrease had a 3-year PFS rate of 46% and 73%, (p= 0.01) and an overall survival (OS) rate of 59% and 81% (p= 0.02), respectively (17). In recent years, paclitaxel (18) and oxaliplatin (19) were shown to be active in refractory NSGCT. We hypothesised that incorporating new drugs into a dose-dense regimen will improve current therapeutic results in patients with slowly decreasing tumour markers.

Patients and methods

Patients had to be older than 16 years and they had to exhibit evidence of testicular, retroperitoneal, or mediastinal NSGCT based on histologic findings or on clinical evidence and highly elevated serum hCG or AFP levels, with IGCCCG poor prognosis criteria: a primary mediastinal NSGCT, or non-pulmonary visceral metastases, and/or high serum tumour markers (hCG > 50,000 UI/l, AFP > 10,000 ng/ml, or LDH > 10-fold the upper normal value). No prior chemotherapy was allowed nor any previous malignancy, except for basal-cell carcinoma. No exclusion was based on the performance status, life expectancy, site of metastases, lung function, or ureteral compression. Human Immunodeficiency Virus (HIV) infection was the only exclusion co-morbidity. All patients provided a signed informed consent and the trial was approved by the Institutional Review Boards. This was a multicentre, international randomised trial sponsored by Unicancer, and co-sponsored by the University of Texas MD Anderson Cancer centre for the US. Pretreatment evaluation is detailed in the web extra material.

Chemotherapy

After registration, patients began the first cycle of BEP (cisplatin 20 mg/m^2/day IV × 5 days, etoposide 100 mg/m^2/day IV × 5 days, bleomycin 30 mg/d IV or IM day 1, 8, and 15) (4). Tumour markers were reassessed between day 18 and 21, and decline kinetics was centrally calculated for hCG and AFP. The methodology used for tumour marker decline calculation was previously published (17) and is summarized in the web appendix. Briefly, baseline and day 18–21 tumour marker values are introduced in a logarithmic formula, which defines a favourable and an unfavourable pattern of decrease in the serum tumour markers. A decline is defined as favourable only if both AFP and hCG declines are considered favourable by the formula. The calculator tool is available online at http://www.gustaveroussy.fr/calculation-tumor/NSGCT.html. Patients with a favourable decline rate (including those with normal

tumour marker values at baseline and at day 18–21 and those whose tumour markers had normalized) received 3 subsequent cycles of BEP (Fav-BEP arm). Patients with an unfavourable decline were randomised to receive either 3 additional cycles of BEP (Unfav-BEP arm) or a sequential dose-dense regimen (Unfav-dose-dense arm) comprising two cycles of T-BEP-Oxaliplatin: paclitaxel 175 mg/ m^2 IV over 3 h on day 1, before BEP as described above, oxaliplatin 130 mg/ m^2 IV over 3 hours, given on day 10, G-CSF 263 g/day SC, to be started one day after chemotherapy and stopped one day before the next scheduled chemotherapy cycle (d6–7, d9, d11–14, d16–20). After two cycles of T-BEP-oxaliplatin (recycled every 21 days), patients received 2 cycles of cisplatin, bleomycin, and ifosfamide: cisplatin 100 mg/ m^2 IV over 2 hours on day 1, bleomycin 25 units/day, by continuous IV infusion over 24 hours for 5 days on day 10 to 14, ifosfamide 2 g/ m^2 IV over 3 hours on days 10, 12, 14, mesna 500 mg/m^2 IV at time 0, 3, 7 and 11 hour (s) on the days when ifosfamide was administered (mesna could also be given orally), G-CSF 263 g/day SC on days 2–9 and days 16 to 20 (Figure S1).

Criteria for starting and recycling chemotherapy

Each cycle of the dose-dense regimen was started if the clinical status and biological data (granulocyte count > 1000/mm^3, platelets 100,000 mm^3) allowed it. These criteria were also applicable for the administration of oxaliplatin and ifosfamide. If chemotherapy could not be reinitiated, it was delayed until the limiting toxicity had resolved. If oxaliplatin was delayed by more than 2 days due to limiting toxicity, it was omitted from that cycle. Lung function was to be assessed by spirometry and CO diffusion before the initiation of cycles 4 and 5. Criteria for administering bleomycin included no clinical lung toxicity and no drop in forced vital capacity 10% over the baseline. Bleomycin was not administered if the respiratory test showed CO diffusion (DLCO/VA report) <65%. Bleomycin was administered in the BEP and the T-BEP regimens even when haematological criteria for recycling chemotherapy were not fulfilled. After the first cycle of chemotherapy, patients scheduled for treatment with BEP but who could not receive bleomycin due to lung dysfunction were able to receive ifosfamide (VIP) instead. If creatinine clearance was less than 60 ml/min, the dose of cisplatin and ifosfamide could be reduced, and bleomycin could be discontinued. In case of moderate to severe peripheral neurotoxicity or ototoxicity, dose reduction of cisplatin, paclitaxel, and oxaliplatin was discussed on a case-by-case basis with the trial chair.

Particular medical settings requiring specific management like major cancer spread to the lungs (20), ureteral compression, brain metastases, and patients with a poor performance status at baseline, are detailed in the web extra material.

Guidelines for treatment after completion of chemotherapy

Tumour markers were obtained every 3 weeks and a CT scan of the abdomen, pelvis and thorax was performed after completion of chemotherapy. Patients with a complete response and normal tumour markers after chemotherapy were followed up without additional therapy. Patients with radiographically detectable residual masses and normal serum tumour markers underwent exploratory surgery to remove any residual masses. Patients found to have viable carcinoma in completely resected masses were managed either with immediate post-operative chemotherapy or surveillance alone with chemotherapy at relapse (21,22).

Patients with brain metastases and residual masses after chemotherapy were managed either with surveillance or treated with neurosurgery or radiotherapy. Patients with evidence of a growing teratoma syndrome (23) were scheduled for a complete resection. Patients with evidence of tumour progression were managed at the investigator's discretion.

Surveillance schedule after completion of therapy

Patients were to be followed for at least 3 years according to the following schedule: once every 2 months for 2 years, once every 4 months in the 3rd year, once every 6 months in the 4th year, once every year after the 4th year. Surveillance included: a clinical examination, serum hCG, AFP, LDH, creatinine, blood count, a CT-scan of the initially involved sites every 4 months for 2 years, and then, once yearly in the next 3 years.

Endpoints

Patients with normal tumour markers and no clinical or radiologic evidence of disease were classified as having achieved a complete response to chemotherapy (cCR). Patients with normal tumour markers and completely resected residual masses containing only necrosis or teratoma were classified as having achieved a pathologic complete response (pCR). Patients with normal tumour markers and completely resected masses containing viable cancer were classified as having achieved a surgical complete response (sCR). All other responses were considered incomplete. Progressive disease (PD) was defined as rising tumour markers confirmed at least twice, an increase in tumour size on imaging, or the appearance of new lesions (no central review of response by imaging was performed).

PFS and OS were calculated from the randomisation date to the event date (or the last follow-up date in case of censored data). PFS events included tumour marker progression, radiological progression, a growing teratoma syndrome, and death (all causes). OS events were death (all causes). The detailed surveillance protocol is provided as web extra material.

Statistical analysis

A previous analysis (17) suggested that 3-year PFS of patients with poor-prognosis NSGCT and an unfavourable tumour marker decline is 46%. To detect a 20% difference in PFS (with a statistical power of 80% and a type one error of 5%, two-sided logrank test) between the BEP arm and the dose-dense arm with the possibility that 80 events may be observed during this period, a total of 196 patients had to be enrolled (98 per group). As 80% of the patients with poor-prognosis NSGCT were expected to have an unfavourable decline in tumour markers, a total of 240 patients were needed in this trial.

An interim analysis to test for efficacy was planned once 40 events were observed, with a nominal significance level of 0.005. The objective of this interim analysis was to allow the Independent Data Monitoring Committee's (IDMC) to review the data and make a recommendation of trial discontinuation if needed. The IDMC kept the interim analysis confidential until the final analysis was released.The nominal significance level for the final analysis was 0.048 (24).

PFS was compared by a logrank test adjusted on the only stratification factor (centres). Hazard Ratios (HR) are the risk of an event in the dose-dense arm as compared to the BEP arm. HR and survival rates are presented with their 95% confidence interval. The HR and 95% confidence intervals (95%CI) were estimated by a multivariate Cox regression model. p values were calculated with the Wald test. SAS version 9.3 was used for statistical analyses.

All patients evaluable for tumor markers after cycle 1 were considered assessable. The primary endpoint efficacy analysis was conducted on an intention-to-treat basis i.e. it included all randomised patients.

A tumour marker validation analysis was pre-planned. An exploratory sensitivity analysis based on known prognostic factors was also performed.

The protocol is accessible on the web at: http://www.gustaveroussy.fr/service.php?p_m=download&p_file=soins/prostate/getug13-protocol-amended-09-28-05.pdf. The case report form (CRF) was very simple in order to minimize missing data. A patient alive with no news since January 1, 2012 was defined as a patient lost to follow-up.

Randomisation and masking

Patients were enrolled by the investigators. Eligible patients were centrally registered before their first BEP cycle and their baseline tumour markers (HCG and AFP) were recorded. Three weeks later, tumour markers were reassessed centrally to determine the marker decline pattern (favourable vs unfavourable) in each patient. Patients with an unfavourable tumour marker decline were randomly assigned in a 1/1 ratio to continue BEP or to start dose-dense chemotherapy. Centrally blocked randomisation stratified by centre was used. The marker decline pattern and the allocated treatment arm were sent by the registration office to each investigator by fax or e-mail. The trial was unblinded.

This study is registered with ClinicalTrials.gov, number NCT00104676; EU-20502.

Amendments

Based on the IDMC's recommendations, several amendments were applied:

- In September 2005, Oxaliplatin was withdrawn from cycle 4–5 of the original dose-dense regimen when excess peripheral neuropathy (3 of 12 patients) was observed;
- In September 2005, G-CSF also became mandatory for patients treated with BEP, due to an unexpected excess rate of neutropenic fever;
- In March 2009, as 25% of patients with available data had a favourable tumour marker decline (as compared to an expected 20%), the total number of patients to be included in the trial was increased to 260, to ensure randomisation of at least 196.

Roles of authors and funders—Prof Fizazi had access to all the data and was responsible for the decision to submit the manuscript, based on a recommendation from the

IDMC. The sponsors were in charge of administrative and regulatory issues, data collection, and pharmacovigilance of the trial. The analysis, interpretation, writing of the manuscript and the decision to submit were independent of the trial sponsors.

Results

From November 28, 2003 to May 16, 2012, 263 patients from France (20 centres), USA (1 centre) and Slovakia (1 centre) were enrolled. The analysis was conducted in an intent-to-treat fashion for all patients (n=254) evaluable for tumour marker decline after their first cycle (Figure 1): 51 patients had a favourable decline and 203 patients had an unfavourable decline and were randomised to continue BEP (n=98) or to receive the dose-dense regimen (n=105). All patients had at least one criterion for IGCCCG poor-prognosis NSGCT: 102/254 (40%), 26/254 (10%), and 23/254 (9%) had liver, brain, and bone metastases respectively (Table 1). Prognostic factors were well-balanced between the randomisation arms and brain metastases were present in 10/98 (10%) and 12/105 (11%) patients respectively in the Unfav-BEP and in the Unfav-dose-dense arm.

Treatment received

During the first cycle, the received dose was reduced by ≥20% in only 10/253 (4%), 12/253 (5%), and 29/253 (12%) patients for cisplatin, etoposide, and bleomycin, respectively (details on received doses at cycle 1 are missing for 1 patient).

The doses and timing of the drug infusion were mostly adhered to in both arms (Table S1). In the Unfav-BEP arm, the median received dose of cisplatin and etoposide was 100 mg/m^2 and 500 mg/m^2 at each cycle. The median received dose of bleomycin was 90 mg at all cycles, with only 8/97 (8%), 5/94 (5%), and 14/91 (15%) of the patients receiving less than the three planned 30 mg injections at cycle 2, 3, and 4, respectively.

Of the 105 patients randomised to the dose-dense arm, 2 patients (2%) eventually refused to receive dose-dense chemotherapy: they did not receive it at all and continued with the BEP regimen. Of the 103 remaining patients, all received the dose-dense regimen for cycles 2–4, and 91 (87%) received the last cycle. The median received dose was as planned for all drugs in all cycles of the dose-dense regimen. The received dose of bleomycin was reduced by 20% or greater in 7/103 (7%), 12/103 (12%), 39/103 (38%) and 41/91 (45%) in cycles 2–5. The first 12 patients received oxaliplatin for four cycles, before it was deleted from cycle 4 and 5 due to excess neurotoxicity for the subsequent 93 patients by an amendment dated September 2005.

Post-chemotherapy resection of residual masses was performed in 64/98 (65%), 73/105 (70%), and 37/51 (73%) patients in the Unfav-BEP, Unfav-Dose-dense, and Fav-BEP arms respectively.

Response to treatment

A CR was achieved in 42/105 (40%) patients treated in the Unfav-dose-dense arm and in 29/98 (30%) in the Unfav-BEP arms (p=0.12). The CR rate was 45% (23/51) in the Fav-BEP arm. Six and 0 patients in the Unfav-dose-dense and the Unfav-BEP arms respectively

achieved a CR with chemotherapy alone (Table S2). Post-chemotherapy complete necrosis was observed in 29/64 (45%) and 40/72 (56%) patients in the Unfav-BEP arm and the Unfav-dose-dense arm, respectively. Viable cancer was still present in resected masses in 11/64 (17%) and 5/72 (7%) patients, respectively.

Progression-free survival and overall survival

At the cut-off date of March 15, 2013, the median follow-up was 4.1 years (range: 0.3–8.8 years). Respectively 63 and 46 patients in the Unfav-dose-dense arm and in the Unfav-BEP arm were continuously progression-free, 7 and 4 patients being lost to follow-up. Of the 42 and 52 events observed in the Unfav-dose-dense arm and in the Unfav-BEP arm respectively, the first event was death in 5 and 8 cases. PFS favoured the Unfav-dose-dense arm versus the Unfav-BEP arm (HR=0.66 [95% CI: 0.44–1.00]; p=0.05). The 3-year PFS rates were 59% [95% CI: 49–68] and 48% [95% CI: 38–59] (figures 2 and 3). No significant interaction was found between prognostic factors qualifying for poor-risk NSGCT and PFS. Patients with a testis or retroperitoneal primary and those with non-pulmonary visceral metastases benefited more numerically (figure 3).

Six out of 105 patients (6%) in the Unfav-dose-dense arm and 16/98 (16%) patients in the Unfav-BEP arm required salvage high-dose chemotherapy with an autologous stem cell transplant (p=0.015).

At the last follow-up, respectively 78 and 66 patients in the Unfav-dose-dense and the Unfav-BEP arms were alive. The 3-year OS rate was 73% [95% CI: 64–81] and 65% [95% CI: 55–75] (HR= 0.78 (0.46–1.31), p=0.34) (Figure 2 and Figure 3). Two patients in the Unfav-BEP arm died of progressive NSGCT after 5 years.

Toxicity

The incidence of neutropenic fever (17% in each arm) was similar in the Unfav-dose-dense and the Unfav-BEP arms (Table 2). Patients in the Unfav-dose-dense arm experienced anaemia and thrombocytopenia, mucositis, nausea/vomiting, diarrhoea, and fatigue more frequently. They also experienced grade 3–4 peripheral motor or sensory neuropathy more often (7% vs 1%). Severe neuropathy tended to increase during the first year and then began to improve with time: 13% vs 0% at 1 year; 0% vs 0% at 2 years, respectively.

Although patients in the Unfav-dose-dense arm received a higher cumulative dose of bleomycin, they did not report more grade 3–4 dyspnoea than those in the Unfav-BEP arm (9% and 11%, respectively).

Six (6%) and 1 (1%) randomized patient(s) did not receive the last cycle of dose-dense or BEP chemotherapy due to toxicity.

Two patients (one in each arm) died of chemotherapy toxicity and two other patients (one in each arm) died post-operatively after excision of residual masses. Six patients (Unfav-BEP arm: 4, Unfav-Dose-dense arm: 2), all with a primary mediastinal NSGCT, developed a second malignancy: acute leukaemia in 5 and melanoma in 1.

Validation of tumour marker kinetics

To prospectively validate the method that we used to calculate tumour marker decline (24), the outcome of patients treated with BEP was compared (Figure 4): 3-year PFS rates were 70% [95% CI: 57%; 81%] and 48% [95% CI: 38%; 59%] in the Fav-BEP and Unfav-BEP groups (HR= 0.66 [95% CI: 0.49–0.88]; p=0.01 for PFS). The 3-year OS rates were 84% [95% CI: 71%; 92%] and 65% [95% CI: 55%; 75%], respectively (HR= 0.65 [95% CI: 0.45–0.95]; p=0.024 for OS).

Discussion

In contrast to previous trials that attempted and failed to improve the results obtained with BEP in patients with poor-risk NSGCT (4–11), this trial selected patients based on a tumour marker decline after one cycle of chemotherapy. The primary endpoint, PFS in patients with an unfavourable tumour marker decline receiving dose-dense chemotherapy was improved: 59% [95% CI: 49–68] versus 48% [95% CI: 38–59] (p=0.05; HR: 0.66 [95% CI: 0.44–1.00]). This 34% reduction in the risk of death or progression is clinically meaningful. Indeed, in this population of young adults with poor-risk testicular cancer, being rendered free of progression signifies that cure is achieved in most cases. The prognostic value of a tumour marker decline was prospectively confirmed for both PFS and OS. Tumour marker decline assessment was experimental before this trial: the results now support its routine use.

The dose-dense regimen used in this trial was designed to improve the results obtained with BEP by different means: using six drugs, using continuous infusion bleomycin for 2 cycles and individual bleomycin adjustment based on lung function assessment to prevent lung toxicity, increased dose-density, increased platin exposure (cisplatin and oxaliplatin), limiting the cumulative dose of etoposide to try to prevent secondary leukaemia, and the selection of patients considered unlikely to achieve cure according to a tumour marker decline. Whether only one or a combination of these changes contributed to the results is unknown. The BEP control arm was not disadvantaged in this trial: the doses and timing were adhered to and more than 90% of the patients received the planned dose of bleomycin. As the recommended doses for all agents used in the dose-dense regimen and data on combinations were already available (9,25), we decided to design the trial as a phase III rather than conduct a formal phase I-II trial. The side effects in the dose-dense arm were assessed early and regularly discussed with the IDMC. This decision allowed us to save time and to limit undue side effects (two injections of oxaliplatin were withdrawn from the original protocol after three patients experienced severe peripheral neuropathy). The modest numerical difference in the incidence of post-chemotherapy surgery use (Unfav-dose-dense arm: 73/105 (70%) versus Unfav-BEP arm: 64/98 (65%)), is likely related to the fact that more patients in the Unfav-BEP arm experienced early cancer progression or death (figure 2) while on chemotherapy, thus indirectly supporting greater efficacy with the treatment intensification strategy: patients experiencing early progression were typically managed with salvage chemotherapy rather than post-chemotherapy surgery. No significant interaction was found between prognostic factors qualifying for poor-risk NSGCT and PFS, although patients with a non-mediastinal primary and those with non-pulmonary visceral metastases may benefit more. Although caution should be exercised when interpreting these results

because of the limited number of patients, we cannot affirm that patients with a primary mediastinal NSGCT benefit from the dose-dense regimen, which would be consistent with findings indicating that this tumour is a distinct biological entity (26).

The incidence of neutropenic fever (17% in each arm) and that of toxicity-related deaths (1% in each arm) was similar, although the dose-dense regimen was associated with more non-neutropenia side effects, especially peripheral neuropathy and auditory toxicity. Patients tended to recover from peripheral neuropathy at 2 years. We intend to collect long-term data concerning survival and toxicity in the future. The rigorous use of lung function assessment in this trial made it possible to continue bleomycin beyond the classic 300 mg cumulative dose in selected patients randomised to the dose-dense arm, without an increased incidence of lung failure, and this may have contributed to treatment efficacy. This emphasises the need for centralisation of care in expert centres for optimal management of patients with poor-risk NSGCT (27). Importantly, fewer patients in the dose-dense arm required salvage high-dose chemotherapy (HDCT) plus a stem cell transplant (6% vs 16%; p=0.015). Attempting to cure patients with poor-risk disease with first-line treatment is exceedingly relevant given the well-known high toxicity of salvage therapies, including toxic deaths (12). When this trial was conducted and until now, salvage HDCT has not been proven beneficial neither for PFS nor for survival in randomised trials (28), when compared to standard-dose salvage therapy. This is why investigators were free to use the salvage treatment they considered the most appropriate.

This trial also provides a prospective validation of the prognostic role of a tumour marker decline in patients with poor-risk NSGCT: 70% [95% CI: 57%; 81%] vs 48% [95% CI: 38%; 59%] for 3-year PFS (p=0.01), and 84% [95% CI: 71%; 92%] vs 65% [95% CI: 55%; 75%], for OS (p=0.02). The method used for the calculation of a tumour marker decline is based on only two values (at baseline and at 3 weeks), which allows physicians to switch patients to more active therapies early during the course of treatment, unlike other methods (7,8,16). On the other hand, only approximately 20% of poor-risk patients were spared treatment intensification. Similar findings were reported in the salvage GCT setting and for other cancers (29–31). A post-hoc analysis of a previous study suggested a better outcome for patients with an unfavourable decline treated with intensive chemotherapy, although treatment was not allocated according to tumour marker decline and patients with intermediate prognosis GCT were also included (8). Data from the non-randomized SWENOTECA study also demonstrated that assessing tumour marker decline and allocating treatment accordingly is feasible at country level (16). The exclusion of a number of early deaths where a 3-week marker evaluation was not possible affects the comparability of results to those of other similar trials.

Research in context

Systematic review—Before starting this trial, we searched PubMed and Medline in 2003 using the words “germ-cell tumours”, “poor prognosis” or “poor risk”. As recently reviewed (1), all attempts to improve the results of BEP in patients with poor-risk NSGCT have failed in the last 25 years (4–11).

Interpretation—Using dose-dense chemotherapy in an algorithm based on tumour marker decline assessed after one cycle of chemotherapy reduces the relative risk of progression or death by 34%. The overall chance of curing patients with poor-risk NSGCT managed according to this algorithm (BEP for patients with a favourable decline and dose-dense chemotherapy for patients with an unfavourable decline) exceeds 75%. We believe that the results of GETUG 13 are practice-changing and that patients with poor-risk GCT should benefit from treatment intensification in case of unfavourable tumour marker kinetics on BEP. On the other hand, whether this dose-dense regimen is optimal or should be challenged by another one could definitely be the subject of a new trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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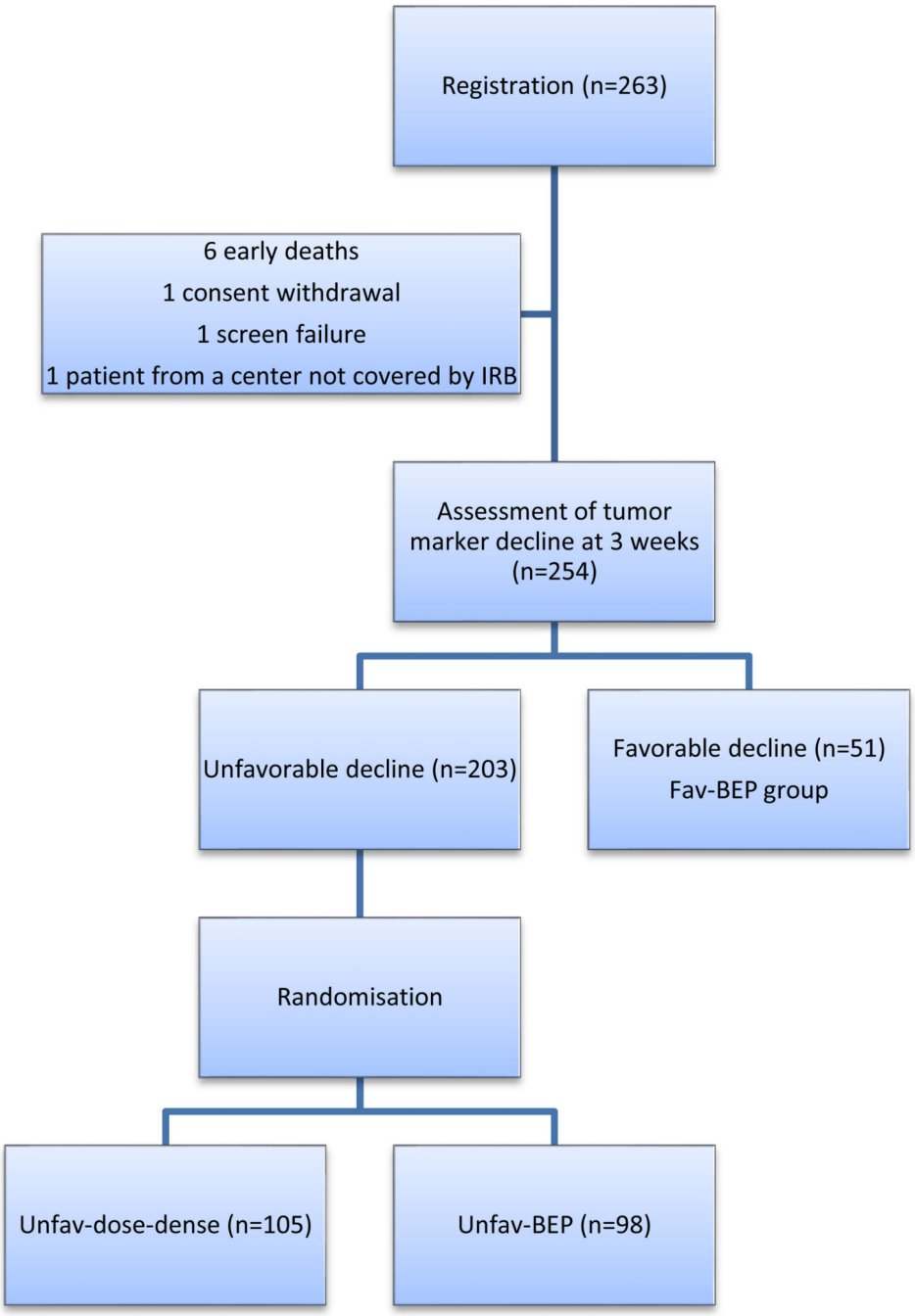
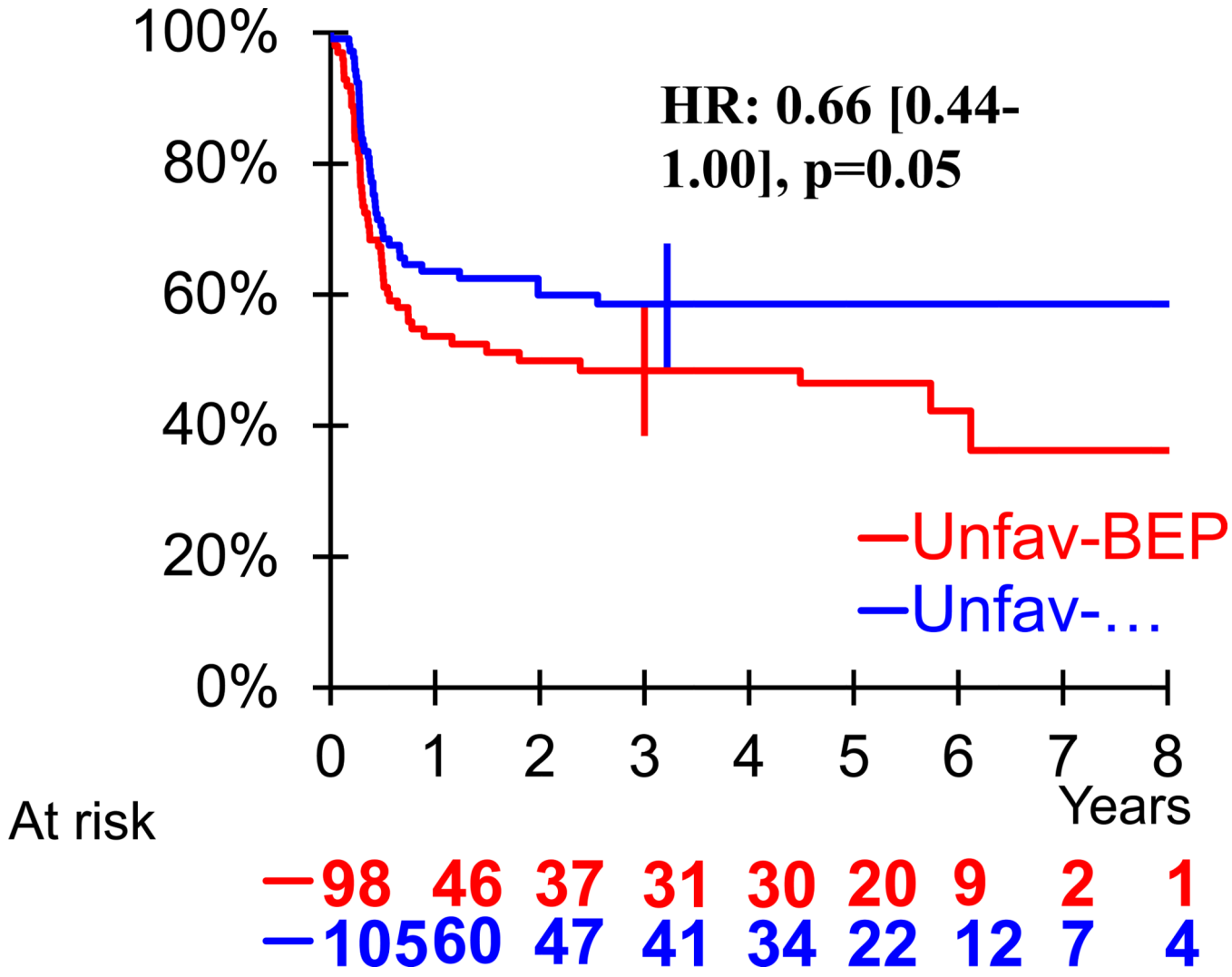


Figure 1.
Consort diagram



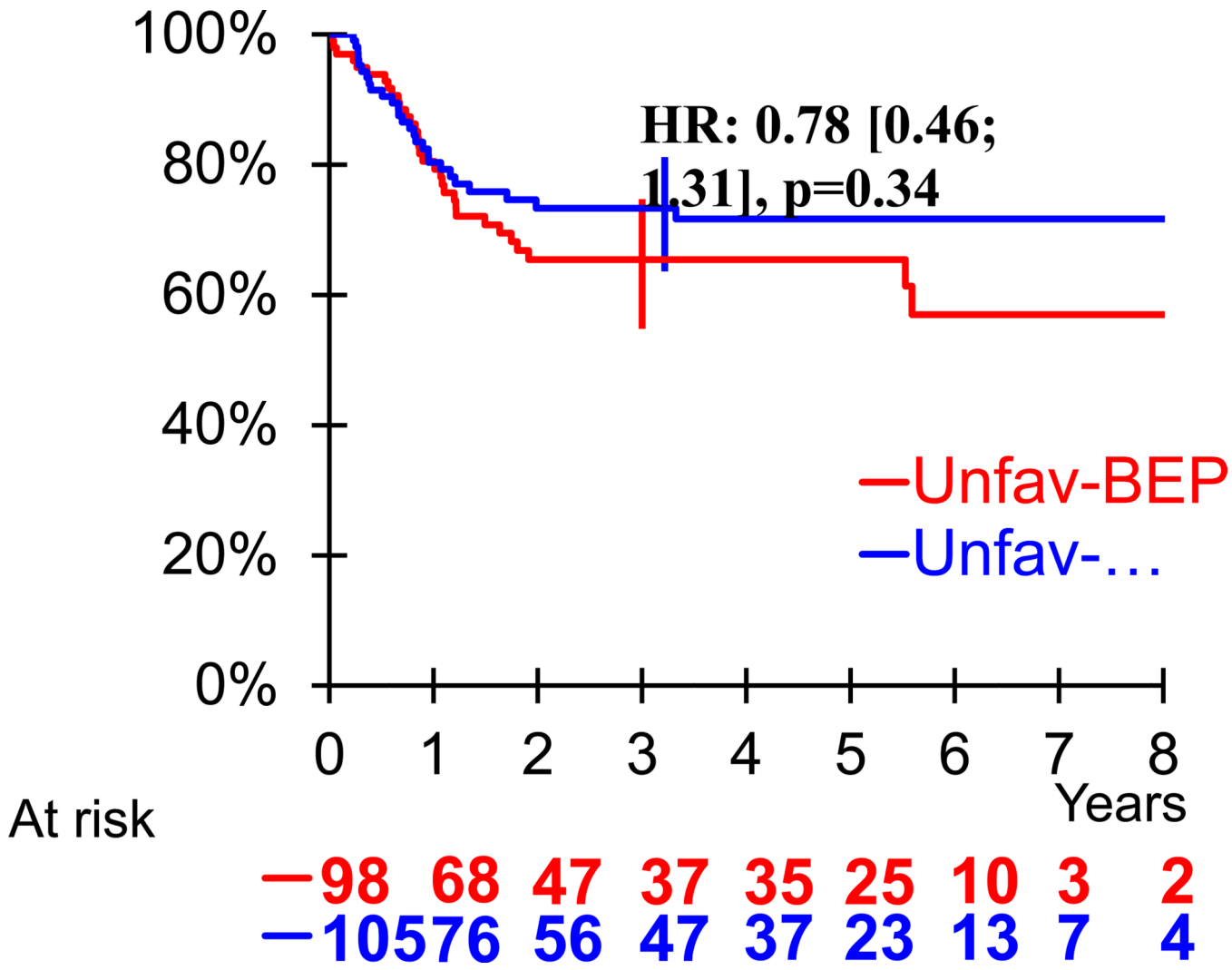


Figure 2.
PFS (2A) and OS (2B) in randomised patients with an unfavourable tumour marker decline.

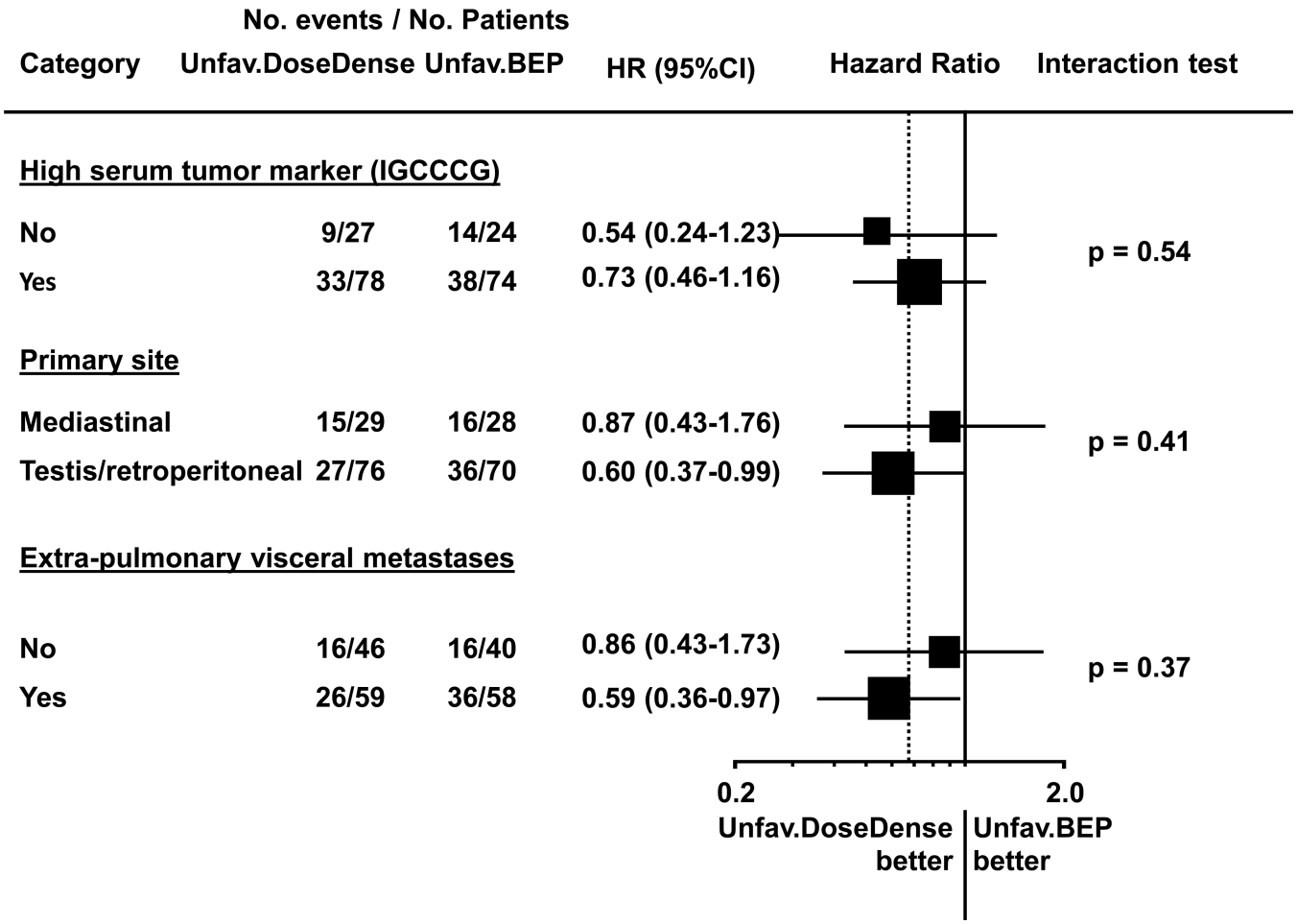
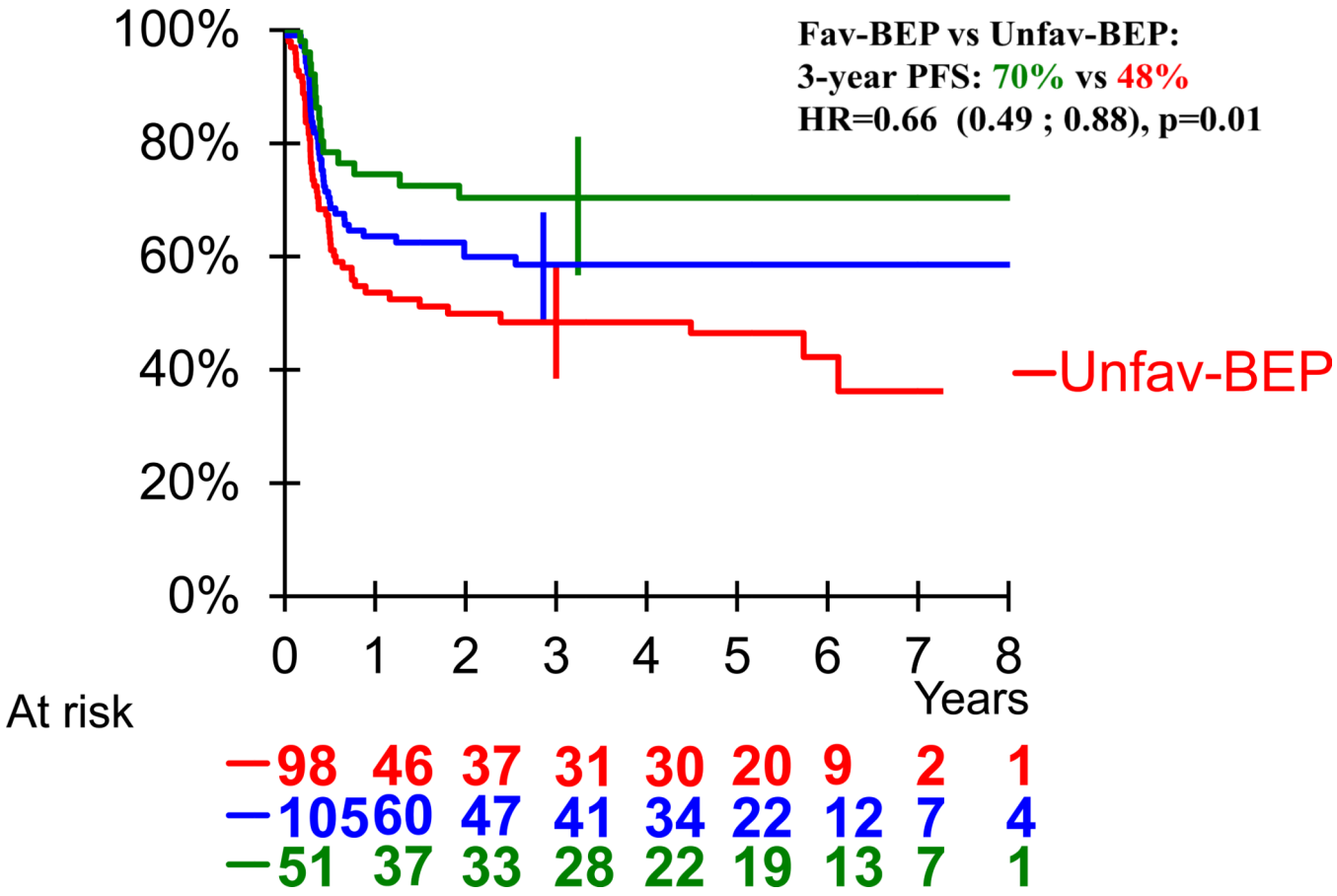


Figure 3.
Sensitivity analysis of PFS



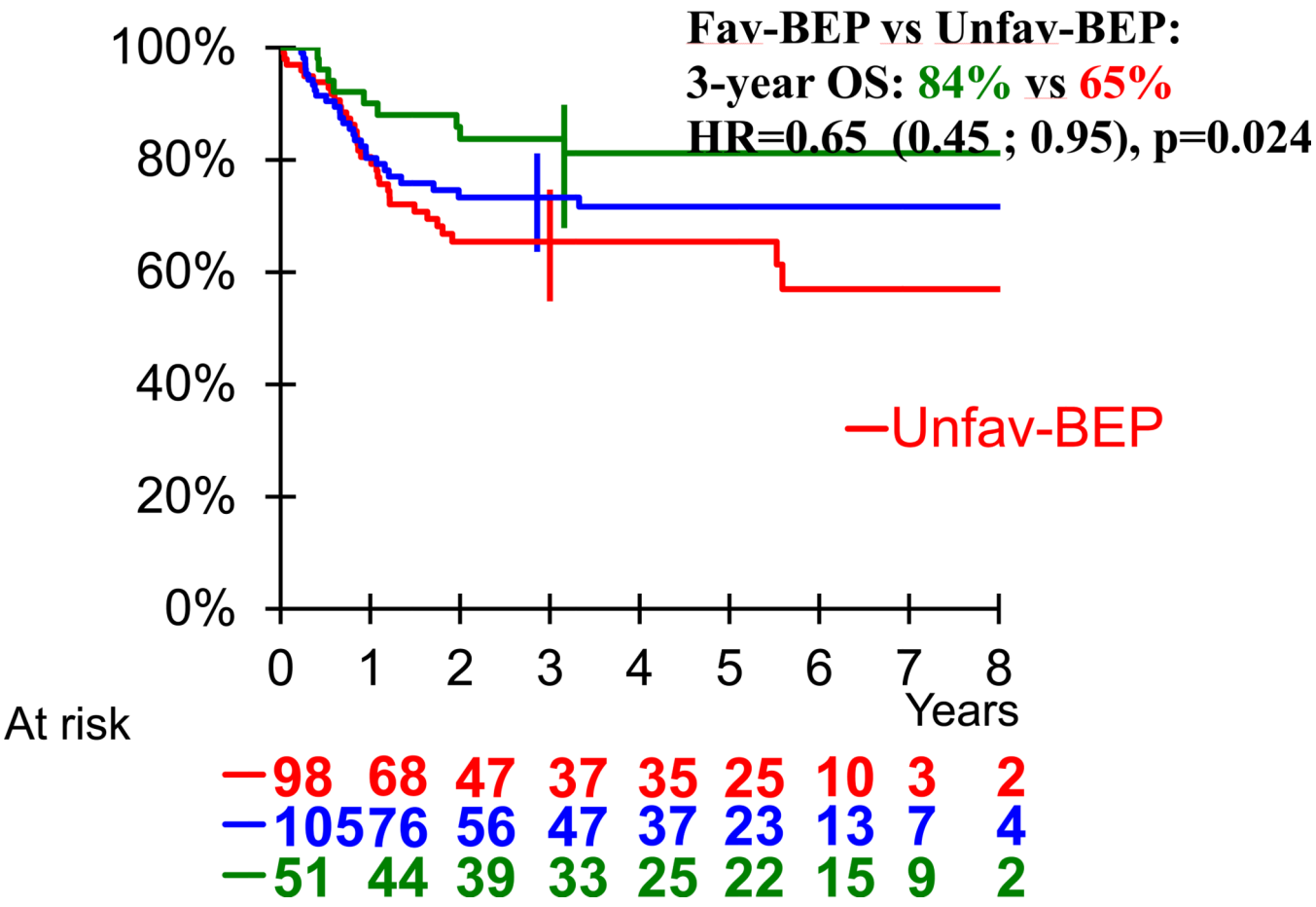


Figure 4.
PFS (4A) and OS (4B) in patients with a favourable and unfavourable tumour marker decline

Table 1

Patient characteristics

	Unfav-BEP (n=98)	Unfav-DoseDense (n=105)	Fav-BEP (n=51)
Age: median, years (range)	**27 (17–72)**	**29 (16–51)**	**27 (19–54)**
IGCCCG criteria			
Tumour markers			
• hCG>50 000 UI/l	45 (46%)	38 (36%)	16 (31%)
• AFP>10 000 ng/ml	25 (26%)	40 (38%)	4 (8%)
• LDH>10 × ULV	17 (17%)	9 (9%)	9 (18%)
hCG>50 000 and/or AFP>10 000			
And/or LDH>10 × ULV	75 (77%)	80 (76%)	28 (55%)
Extra-pulmonary visceral metastases	58 (59%)	59 (56%)	32 (63%)
Primary mediastinal NSGCT	28 (29%)	29 (28%)	9 (18%)
ECOG performance status			
0	30 (33%)	35 (35%)	19 (40%)
1	38 (41%)	43 (43%)	23 (48%)
2–4	24 (26%)	21 (21%)	6 (13%)

ULV: Upper Limit Value

Table 2

Toxicity

	Unfav-BEP (n=98)		Unfav-Dose Dense (n=105)		Fav-BEP (n=51)	
	n	**%**	**n**	**%**	**n**	**%**
Rash						
Grade 1–2	18	18%	27	26%	16	31%
Grade 3–4	0	0%	0	0%	0	0%
Nausea/vomiting						
Grade 1–2	70	71%	66	63%	36	71%
Grade 3	2	2%	24	23%	1	2%
Diarrhoea						
Grade 1–2	19	19%	45	43%	12	23%
Grade 3	1	1%	6	6%	1	2%
Mucositis						
Grade 1–2	18	18%	36	34%	13	25%
Grade 3	0	0%	7	7%	3	6%
Grade 4	0	0%	1	1%	0	0%
Liver						
Grade 1–2	40	41%	31	30%	15	29%
Grade 3	3	3%	5	5%	0	0%
Motor neuropathy						
Grade 1–2	1	1%	6	6%	1	2%
Grade 3	0	0%	2	2%	0	0%
Sensory neuropathy						
Grade 1–2	20	20%	73	70%	13	25%
Grade 3	1	1%	6	6%	0	0%
Auditory						
Grade 1–2	28	29%	48	46%	10	20%
Grade 3	0	0%	2	2%	0	0%

	Unfav-BEP (n=98)		Unfav-Dose Dense (n=105)		Fav-BEP (n=51)	
	n	%	n	%	n	%
Dyspnoea						
Grade 1–2	23	23%	34	32%	4	8%
Grade 3	5	5%	9	9%	0	0%
Grade 4	6	6%	0	0%	1	2%
Renal						
Grade 1–2	9	9%	27	26%	3	6%
Grade 3	0	0%	2	2%	0	0%
Fatigue						
Grade 1–2	69	70%	71	68%	35	69%
Grade 3	7	7%	19	18%	1	2%
Infection						
Grade 1–2	14	14%	23	22%	12	24%
Grade 3	8	8%	9	9%	3	6%
Grade 4	1	1%	1	1%	0	0%
Haemoglobin						
Grade 1–2	71	72%	58	55%	39	76%
Grade 3	18	18%	36	34%	8	16%
Grade 4	8	8%	11	10%	2	4%
Neutropenia						
Grade 1–2	16	16%	21	20%	10	20%
Grade 3	17	17%	18	17%	13	25%
Grade 4	45	46%	45	43%	18	35%
Platelets						
Grade 1–2	55	56%	56	53%	35	69%
Grade 3	15	15%	27	26%	4	8%
Grade 4	1	1%	5	5%	0	0%
Febrile neutropenia	18	18%	18	17%	7	14%

	Unfav-BEP (n=98)		Unfav-Dose Dense (n=105)		Fav-BEP (n=51)	
	n	%	n	%	n	%
Transfusion	31	32%	55	52%	6	12%
Platelet transfusion	6	6%	16	15%	2	4%

Infection= Infectious event without neutropenic fever