**Salvage chemotherapy with gemcitabine, paclitaxel, ifosfamide and cisplatin (Gem-TIP) for relapsed germ cell cancer**

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Conflict of interest

There is no conflict of interest to declare.

**Abstract**

**BACKGROUND:** Metastatic germ cell tumours remain potentially curable when treated with salvage chemotherapy at first relapse. In this phase I/II study, we sought to improve upon the response rate and duration of the TIP regimen by adding gemcitabine.

**METHODS:** Twenty patients were recruited, following failure of first-line cisplatin-containing chemotherapy. Primary objectives were to determine the maximum tolerated dose of gemcitabine when combined with TIP and then to establish the dose intensity of the TIP drugs in this combination. Secondary objectives were response rates, failure-free survival (FFS) and overall survival (OS).

**RESULTS:** The maximum tolerated dose of gemcitabine was 1200mg/m2. The mean relative dose intensity (95% CI) was 95% (90.2, 99.2) for gemcitabine, 96% (92.9, 98.7) for paclitaxel, 92% (84.5, 98.8) for ifosfamide and 94% (89.3, 99.0) for cisplatin. The overall complete response rate was 50%; a further 30% achieved a partial response. One-year FFS and OS rates were 68% (43, 84) and 89.5% (64, 97) respectively.

**CONCLUSIONS:** Gemcitabine can be added to TIP chemotherapy at full dose, with manageable toxicity and no detrimental effect on the dose intensity of the TIP drugs. Response rate and duration are improved on those reported in the MRC TIP trial; further evaluation is warranted.

Keywords: Neoplasms, Germ Cell and Embryonal; Gemcitabine, TIP regimen; Salvage Therapy; Antineoplastic Combined Chemotherapy Protocols

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**Introduction**

Germ cell cancer of the testis (GCT) is the most common malignancy diagnosed in men aged 15-40 years in developed countries, with an age-standardised incidence of 6.7 per 100,000 men in Northern Europe (1). The majority of patients with metastatic disease are cured with first line cisplatin-based combination chemotherapy. The outcome for the 15-20% who experience disease relapse after first line therapy is less certain, although a substantial number are cured with salvage treatment (2).

A number of regimens have been used in this setting, with ifosfamide and cisplatin combined with etoposide (VIP) (3), vinblastine (VeIP) (3) or paclitaxel (TIP) (4, 5). In a Medical Research Council phase II study, TIP produced a response rate of 60%, with one-year progression free survival (PFS) and overall survival (OS) rates of 38% and 70% respectively (5). Using a more intensive regimen with growth factor support, the Memorial Sloan Kettering Cancer Centre achieved greater response rates, albeit in a good prognosis cohort (4). TIP has consequently become one of the most widely used salvage regimens. Efforts have been made to improve upon these figures using high dose and sequential therapies with stem cell rescue, but there remains no consensus on optimal treatment in this setting.

Gemcitabine has documented clinical activity in germ cell cancer as a single agent (6, 7) or in combination (8-10). It has been combined with cisplatin and ifosfamide (GIP), with a two-year OS rate of 73% in the relapsed setting (11). We sought to improve upon the efficacy of TIP by adding gemcitabine to the regimen (Gem-TIP), with the aim of developing a tolerable, highly active, salvage chemotherapy regimen to be used in patients with metastatic germ cell cancer who have failed first line chemotherapy.

**Materials and Methods**

*Study design and treatment*

The Gem-TIP trial was a non-randomised, open-label, multicentre single-arm phase I/II study. The dose of intravenous (IV) gemcitabine was escalated within the phase I trial to determine the maximum tolerated dose (MTD) in combination with the other three drugs. A 3+3 design was used, with three dose levels investigated: 600mg/m2, 900mg/m2 and 1,200mg/m2 day 1. This was used in combination with paclitaxel 175mg mg/m2 IVday 1, cisplatin 20mg mg/m2 IV days 1-5, ifosfamide 1g/m2 IV days 2-6, with peg-filgrastim 6mg subcutaneously on day 7 of a planned 21-day cycle (maximum of four cycles). Subsequent cycles were started on adequate haematological recovery (unsupported neutrophils >0.5 x 109/L and platelets >100 x 109/L) with no planned dose reductions. Patients received a maximum of four cycles.

The trial was approved by the local research ethics committee and authorised by the Medicines and Healthcare Products Regulatory Agency. It was conducted in accordance with the Declaration of Helsinki principals and Good Clinical Practice (GCP) guidelines. All patients gave written informed consent.

*Patients*

Patients were eligible if aged 16 to 60 years old, with a first relapse of metastatic GCT, following failure of treatment with first line cisplatin-containing combination chemotherapy. Patients must have had rising serum tumour markers (AFP, HCG) on sequential measurement, or biopsy proven unresectable GCT. Laboratory criteria included: white cell count >3.5x109/L, platelet count >130x109/L and glomerular filtration rate ≥50mls/minute. Patients were ineligible if they were not fit enough to receive Gem-TIP or if they had primary intracranial tumours, completely resected disease, isolated cerebral metastases or a previous malignancy (excluding non-melanomatous skin cancer or superficial bladder cancer).

*Evaluation and outcomes*

Clinical assessment and tumour markers were performed monthly for four months and then every two months up to 12 months following treatment. A full blood count (FBC) was performed twice weekly on chemotherapy. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 3.0. Chest x-ray and CT head, chest, abdomen and pelvis were performed at baseline, with a further chest x-ray performed prior to each cycle. CT of the chest, abdomen and pelvis (head included if clinically indicated) was performed three weeks after the final cycle. For those patients without a complete response (CR), surgery was considered for non-seminomas. Otherwise the CT and tumour markers were repeated three months later. Patients were defined as having a CR if they had both normal markers and a normal scan, either following chemotherapy alone or chemotherapy with complete resection of teratoma differentiated and/or necrotic tissue. A complete response with surgery (CRs) included those achieving CR following resection of viable cancer but with normal post-operative markers. A partial response (PR) was allocated to those with unresectable residual masses and normal markers. An incomplete response (IR) included patients not achieving a CR or PR, including those with rising serum markers and/or incompletely resected or progressive malignant lesions. Favourable response rate (FRRc) was comprised of those experiencing a CR, CRs and PR.

For patients with a CR no further treatment was recommended. Those with normal markers and PET scan but with residual masses were evaluated for surgery; further chemotherapy was not recommended. Those with a positive PET but normal markers were advised to have a biopsy; chemotherapy was not advised on the basis of a positive PET scan alone. Only those with progressive disease or with incompletely resected active malignancy were recommended for consideration of high dose chemotherapy or alternative further treatment outside of the trial.

*Statistical methods*

The primary endpoint of the phase I trial was the MTD of gemcitabine within the regimen. Once this was reached, a further cohort of 14 patients was to be treated at this dose level. The number of additional patients was determined by the need to estimate, with reasonable accuracy, the relative dose intensity (RDI) of paclitaxel, ifosfamide and cisplatin, when given in combination with gemcitabine. It was calculated that a minimum of 17 patients, including those from the phase I cohort, would be sufficient to ensure that the lower 95% confidence limit for the estimated RDI would be no more than 4% below the mean.

The primary endpoint of the phase II trial was the RDI of paclitaxel, ifosfamide and cisplatin (calculated as the percentage of actual dose intensity relative to the planned dose intensity). Secondary endpoints included the RDI of gemcitabine, response rate, failure-free survival (FFS) and OS. FFS and OS were calculated as time to event variables (from date of initiation of chemotherapy). FFS events included IR, marker-ve relapse after PR/CR and death from any cause. Serious adverse events (SAEs) and toxicity experienced up to 30 days after chemotherapy were safety endpoints.

Statistical analysis was carried out in SAS version 9.3. Survival analyses were summarised with Kaplan-Meier curves. The primary population consists of all evaluable patients, which included all eligible Phase I/II patients but excluded those who had withdrawn due to a non-treatment related event during chemotherapy, as agreed by the data monitoring and ethics committee (DMEC). Safety analyses were analysed on all eligible patients.

**Results**

*Patient characteristics*

At time of completion of the phase I study, six patients received the MTD of 1200mg/m2 of gemcitabine and were deemed evaluable. The patient who was registered but excluded from analysis had a change of treatment plan following additional imaging (requiring high dose chemotherapy), prior to commencing Gem-TIP. Sixteen patients were registered for the phase II trial from March 2010 to August 2012 at a total of five centres. Two of these patients were deemed non-evaluable due to non-compliance during treatment phase, for reasons unrelated to treatment. Therefore, the six patients from the phase I stage and 14 patients from the phase II stage were combined, giving a total evaluable sample size of 20 (see CONSORT diagram; Figure 1). Patient characteristics are summarised in Table 1.

Nineteen of the 20 participants were male with a median age of 32.5 (range 20-61). The most common site of relapse was abdominal (55%). Using the International Prognostic Factors Study Group score (12), eight were defined as low risk, six as intermediate risk and five as high risk (the female patient was excluded as this score is not applicable) (Table 1).

*Treatment*

Of the 20 evaluable patients who commenced treatment with Gem-TIP, 17 received all four cycles of chemotherapy (85%). Treatment was stopped during cycle four for one patient who became unwell with symptoms of an upper respiratory tract infection and later declined to re-start treatment. One patient had treatment stopped after cycle three due to neuropathy and one patient during cycle one due to pulmonary toxicity. Median time between cycles was 21 days (range 19-30). The mean RDI (95% CI) was 95% (90.2, 99.2) for gemcitabine, 96% (92.9, 98.7) for paclitaxel, 92% (89.5, 98.8) for ifosfamide and 94% (89.3, 99.0) for cisplatin (Supplementary Table 1). The proportion of patients receiving >85% RDI for each drug was 85% for gemcitabine, 90% for paclitaxel, 80% for ifosfamide and 85% for cisplatin. Three patients had a dose reduction of gemcitabine: two due to thrombocytopenia and one due to acute renal failure.

*Toxicity*

No dose-limiting toxicities were seen for the 600mg/m2 and 900mg/m2 Phase I cohorts, as reported previously(13). Twenty-two SAEs were reported in nine patients: three were life threatening (two occurrences of thrombocytopenia in the same patient and one episode of respiratory failure secondary to pulmonary toxicity) with the remainder requiring hospitalisation or prolongation of existing hospitalisation*.* Grade 3/4 haematologicaltoxicity was observed in 78.3% (18/23) of patients, with the most common being Grade 3/4 thrombocytopaenia in 65.2% (15/23) and neutropenia in 52.2% (12/23). At least one platelet transfusion was given in 47.8% (11/23) and blood transfusion in 65.2% (15/23) of patients.Grade 3/4 non-haematological toxicity was observed in 43.5% (10/23) of patients, with the most common being sensory neuropathy, raised creatinine and IV line infection. Six patients experienced a septic complication requiring IV antibiotics. No toxic deaths were experienced during Gem-TIP chemotherapy. A summary of haematological toxicities and septic complications is provided in Table 2 and non-haematological toxicities in Supplementary Table 2.

*Response rates and survival*

In total, nine patients out of 20 achieved a CR (45%) with an additional patient achieving a CRs, giving an overall CR rate of 50% (10/20). A further six patients achieved a PR (30%). Therefore the overall FRRc was 80% (16/20). Of those remaining, three patients (15%) had an IR and one (5%) was lost to follow up (Table 3). The one-year FFS rate was 68% (95% CI 43, 84); median FFS was not reached with a median follow up time of 26 months (17, 60)(Figure 2A). The two-year FFS rate was 63.2% (37.9, 80.4). For those classified as good prognosis at screening (n=14), the one-year FFS rate was 77% (44, 92) and for those with poor prognosis (n=6) it was 50% (11, 80) (Figure 2B). For patients with a testis primary (n=15), the one-year FFS rate was 79% (47, 93). Overall, there were seven FFS events; in addition to the three patients who had an IR, four patients relapsed after a CR, CRs or PR. In three patients, the site of relapse was not documented, raised tumour markers only and brain. In the remaining patient, the sites of relapse were abdomen and lungs.

For all 20 evaluable patients, the one-year OS rate from commencement of chemotherapy was 89.5% (95% CI 64, 97); median OS was not reached with median follow-up of 25 months (18, 42) (Figure 3). The one-year OS rate for patients with a testis primary (n=15) was 93% (59, 99). Overall, there were four deaths (20.0%), all related to germ cell cancer, one of which was in the good prognosis group.

*Further treatment*

Post-protocol treatment was at the discretion of the treating physician. Of the seven patients who experienced disease relapse, four subsequently received high dose chemotherapy with peripheral stem cell rescue (HDCT), one had standard dose salvage chemotherapy in addition to radiotherapy, and two patients had radiotherapy alone (to the brain only and to the brain and vertebra). Of the four patients treated with HDCT, one has died, two have active disease and one is disease free, with a median follow up of 18 months. All three patients not treated with HDCT died within one year.

Of the 13 patients without disease relapse, three patients had further treatment outwith the protocol. One patient received standard dose chemotherapy, in addition to consolidation radiotherapy to the abdomen. A second patient had consolidation radiotherapy, in this case to the mediastinum. The third patient had two cycles of back-to-back HDCT, followed by a retroperitoneal lymph node dissection, which revealed teratoma differentiated. Consolidation with high dose therapy in the absence of high-grade residual disease/relapse was not recommended; it was however standard practice in some institutions.

**Discussion**

The optimal treatment regimen for patients in first relapse of metastatic germ cell cancer has not yet been determined. We sought to intensify the established MRC TIP regimen (5) by the addition of gemcitabine.

The majority of patients received >85% RDI for each drug, improving upon the dose intensity previously achieved (5), perhaps in part due to the routine use of growth factors in the current study. Gemcitabine did not therefore have an impact on the deliverable dose of TIP.

We have shown Gem-TIP to have high activity as a second-line treatment for metastatic GCT, with an overall CR rate of 50% and a one-year FFS rate of 68%. These response rates compare favourably with the MRC TIP trial (5) and are broadly comparable to those reported in the MSKCC TIP trial, which produced a 2-year PFS of 65% (4). It should be noted that all patients enrolled on the MSKCC trial had favourable prognostic features, whereas 30% of patients enrolled here were in the poor prognosis category. Higher doses of paclitaxel and ifosfamide were used in the MSKCC regimen; we instead sought to assess the feasibility and safety of adding a fourth agent to the regimen.

It should be noted that three patients without documented disease relapse were given further treatment outwith protocol recommendation. One received two autologous stem cell transplants following high dose chemotherapy. This treatment, beyond what was deemed necessary within the trial, could have had a beneficial effect on the apparent efficacy of Gem-TIP reported here.

The most common toxicity was haematological and moderately severe; Grade 3/4 in 78.3% of patients. Neutropenia was less pronounced compared to TIP, probably secondary to routine use of growth factors in this study, but thrombocytopenia was predictably more pronounced with the addition of gemcitabine. Only two patients required a dose reduction for this reason; however there was a Grade 3/4 per rectum bleed related to low platelets. There were no toxic deaths. Although not insignificant, the toxicity of this regimen was manageable.

In the relapsed setting, metastatic GCTs remain potentially curable. How this is best achieved remains under debate. A randomised phase III trial, TIGER, has commenced, in order to prospectively assess HDCT versus conventional chemotherapy as first salvage treatment(14). There is an absence of data on long-term morbidity following HDCT. Given the median age of 32 in one large retrospective analysis (15), it is clearly important to consider which patients need to receive HDCT intensification in order to spare those who don’t from unnecessary toxicity.

Conclusion

We have established that gemcitabine can be safely added to full dose MRC TIP chemotherapy with manageable toxicity and no detrimental effect on the relative dose intensity of the TIP drugs. The likelihood of evaluating the efficacy of Gem-TIP in a larger randomised setting will depend on the outcome of the TIGER trial.

**Clinical Practice Points**

There is no consensus on the optimum salvage regimen for patients with metastatic germ cell cancer of the testis (GCT) at first relapse. TIP (paclitaxel, ifosfamide and cisplatin) is one of the most widely used, with one- and two- year progression free survival rates of 38% and 65% previously reported(4, 5). By adding gemcitabine to the regimen, we sought to improve its efficacy without compromising safety. There are no previously published reports of this regimen in relapsed GCT.

In combination with the TIP drugs, the maximum tolerated dose of gemcitabine was 1200mg/m2. There was no detrimental effect on the dose intensity of the TIP drugs. The overall complete response rate was 50%, with one-year failure-free survival (FFS) and overall survival rates of 68% (95% CI 43, 84) and 89.5% (64,97) respectively. Haematological toxicity was moderately severe but manageable; Grade 3/4 in 78.3% of patients. There were no toxic deaths. Therefore, we have established that gemcitabine can safely be added to full dose TIP chemotherapy.

This trial presents a novel and viable regimen for the treatment of relapsed metastatic GCT. The likelihood of evaluating the efficacy of Gem-TIP in a larger randomised setting will depend on the outcome of the TIGER trial.

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**Author contributions**

All authors contributed to the interpretation of the results and read, reviewed and approved the final manuscript. GM, RH and MW designed the research. HM wrote the manuscript. MB performed the primary analyses.

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| **Table 1: Patient Characteristics (All evaluable patients, n=20)** |
| **Characteristic** | **No.** |  | **%** |
| ***At primary treatment*** |
| **Primary site** |  |  |  |
| Mediastinum | 1 |  | 5.0 |
| Ovary | 1 |  | 5.0 |
| Retroperitoneum | 2 |  | 10.0 |
| Testis | 15 |  | 75.0 |
| Other | 1 |  | 5.0 |
| **Histology at primary treatment** |  |  |  |
| Seminoma | 6 |  | 30.0 |
| Non-seminoma or mixed tumours | 13 |  | 65.0 |
| Not known (histology not done) | 1 |  | 5.0 |
| **Primary treatment regimen** |  |  |  |
| BEP1 | 12 |  | 60.0 |
| POMB-ACE2 | 3 |  | 15.0 |
| EP3 | 2 |  | 10.0 |
| C-BOP-BEP4 | 2 |  | 10.0 |
| CE-BEP5 | 1 |  | 5.0 |
| **Response to primary treatment** |  |  |  |
| CR | 2 |  | 10.0 |
| CRs | 4 |  | 20.0 |
| PR | 10 |  | 50.0 |
| IR | 4 |  | 20.0 |
| **Progression-free interval (months)6** | 20 |  |  |
| Median |  | 6.7 |  |
| Minimum – Maximum |  | 0.9 - 28.8 |  |
| > 3 | 18 |  | 90.0 |
| < 3  | 2 |  | 10.0 |
| ***At screening*** |
| **Age at screening (years)** |  |  |  |
| Median |  | 32.5 |  |
| Minimum – Maximum |  | 20 - 61 |  |
| Gender - Male | 19 |  | 95.0 |
| **Sites of disease7** |  |  |  |
| Abdominal mass | 11 |  | 55.0 |
| Mediastinal mass | 5 |  | 25.0 |
| Supraclavicular mass | 2 |  | 10.0 |
| Lung | 8 |  | 40.0 |
| Liver  | 4 |  | 20.0 |
| Brain | 4 |  | 20.0 |
| Raised markers | 1 |  | 5.0 |
| Other | 2 |  | 10.0 |
| **International Prognostic Factors Study Group score8** |  |  |  |
| Low risk | 8 |  | 40.0 |
| -1 = Very low risk | 5 |  | 25.0 |
|  0 = Low risk | 3 |  | 15.0 |
| Intermediate risk | 6 |  | 30.0 |
| 1 = Intermediate risk | 6 |  | 30.0 |
| High risk  | 5 |  | 25.0 |
| 2 = High risk | 4 |  | 20.0 |
| 3 = Very high risk | 1 |  | 5.0 |
| Not scored**9** | 1 |  | 5.0 |
| **Memorial prognostic score10** |  |  |  |
| Good prognosis | 14 |  | 70.0 |
| Poor prognosis | 6 |  | 30.0 |
| **Serum tumour markers** |  |  |  |
| βHCGMedianMinimum – Maximum |  | 4.900.99 - 1255 |  |
| AFPMedianMinimum – Maximum |  | 4.001.59 - 2644 |  |
| LDHMedianMinimum – Maximum |  | 464.0147 - 3062 |  |

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| **Table 2: Haematological toxicity and septic complications during chemotherapy, (All eligible patients, n=23)** |
| **Haematological toxicity** | **Any CTCAE grades2** | **CTCAE grade 3 or 4** |
|  | No.1 | %1 | No.1 | %1 |
| Any haematological toxicity | 21 | 91.3 | 18 | 78.3 |
| Low platelets  | 20 | 87.0 | 15 | 65.2 |
| Neutrophils/granulocytes or neutropenia | 15 | 65.2 | 12 | 52.2 |
| Anaemia | 6 | 26.1 | 4 | 17.4 |
| Cellulitis | 2 | 8.7 | 1 | 4.3 |
| Fever | 2 | 8.7 | 0 |  |
| Neutropenic sepsis | 1 | 4.3 | 1 | 4.3 |
| PR bleed related to thrombocytopenia | 1 | 4.3 | 1 | 4.3 |
| Hickman line infection  | 1 | 4.3 | 0 |  |
| Septic complications | No.1 | %1 |  |  |
| Number of patients who experienced a septic complication3 | 6 | 26.1 |  |  |
| Blood culture proven sepsis | 3 | 13.0 |  |  |
| Febrile neutropenia (unknown origin) | 2 | 8.7 |  |  |
| Infection with CTCAE grade 1 or 2 neutrophils | 3 | 13.0 |  |  |

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| **Table 3: Response rates after Gem-TIP chemotherapy (All evaluable patients, n=20)** |
|  | **CR** | **CRs** | **PR**  | **IR** | **Not known** | **FRRc****(CR + CRs + PR-ve)** |
| All patients (n=20) | 9 (45%) | 1 (5%) | 6 (30%) | 3 (15%) | 1 (5%) | 16 (80%) |
| Good prognosis1 (n=14) | 7 (50%) | 0 | 5 (36%) | 1 (7%) | 1 (7%) | 12 (86%) |
| Poor prognosis1 (n=6) | 2 (33%) | 1 (17%) | 1 (17%) | 2 (33%) | 0 | 4 (66%) |
| Non-seminoma (n=14) | 5 (36%) | 1 (7%) | 5 (36%) | 3 (21%) | 0 | 11 (79%) |
| Seminoma (n=6) | 4 (67%) | 0 | 1 (17%) | 0 | 1 (17%) | 5 (83%) |
| Testis primary (n=15) | 7 (47%) | 1 (7%) | 5 (33%) | 1 (7%) | 1 (7%) | 13 (87%) |
| Testis primary, non-seminoma (n=9) | 3 (33%) | 1 (11%) | 4 (44%) | 1 (11%) | 0 | 8 (89%) |
| Testis primary; seminoma (n=6) | 4 (67%) | 0 | 1 (17%) | 0 | 1 (17%) | 5 (83%) |

## Table 1 footnote

1 BEP = Bleomycin, Etoposide, Cisplatin

2 POMB-ACE = Cisplatin, Vincristine, Methotrexate, Bleomycin, Dactinomycin, Cyclophosphamide, Etoposide

3 EP = Etoposide, Cisplatin

4 C-BOP-BEP = Carboplatin, Vincristine, Bleomycin, Etoposide, Cisplatin

5 CE-BEP = Carboplatin, Etoposide, Bleomycin, Etoposide, Cisplatin

6 Progression-free interval = date of diagnosis of this relapse – end date of primary chemotherapy.

7 Patients can be included in more than one category for site of relapse

8 Prognostic score model developed by the International Prognostic Factors Study (12)

9Female patient excluded as cannot be scored using this criteria

10Prognostic score using the Memorial Sloan-Kettering Cancer Centre (MSKCC) criteria (4), where poor prognosis = mediastinal or retroperitoneal primary, and/or incomplete response to first line treatment

**Table 2 footnote**

1 The numbers included in this table relate to the number of patients who have experienced at least one toxicity

2 CTCAE = Common Toxicity Criteria Adverse Event (version 3.0); the worst grade experienced reported if a patient experienced the same toxicity more than once during chemotherapy

3 A septic complication includes the following events: blood culture proven sepsis, febrile neutropenia (unknown origin) and infection with CTCAE grade 1 or 2 neutrophils

**Table 3 footnote**

CR = complete response; CRs = complete response (surgery); PR = partial response (marker -ve); IR = incomplete response; FRRc = favourable response of CR, PR or CRs

1Prognostic score using the Memorial Sloan-Kettering Cancer Centre (MSKCC) criteria (4), where poor prognosis = mediastinal or retroperitoneal primary, and/or incomplete response to first line treatment

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**Titles and legends to figures**

**Figure 1. CONSORT diagram**

## Figure 2. Failure-free survival, A. all evaluable patients (n=20) and B. stratified according to Memorial prognostic score (4).

**Figure 3. Overall survival**, A. all evaluable patients (n=20) and B. stratified according to Memorial prognostic score (4).