Dose-Dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin With or Without Panitumumab in Patients With Advanced Urothelial Carcinoma: Multicenter, Randomized, French Unicancer GETUG/AFU 19 Study

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Original article

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Abstract

This study looked at whether the EGFR inhibition by monoclonal antibody panitumumab could increase the efficacy of standard chemotherapy in advanced urothelial cancer. Results were disappointing with higher toxicity and no improvement in efficacy in the combination arm.

Background: Epidermal growth factor receptor (EGFR) overexpression is frequent and associated with poor outcome in urothelial carcinoma (UC). EGFR inhibition could improve antitumor activity of chemotherapy.

Patients and Methods: Patients with advanced, treatment-naïve, histologically confirmed advanced UC and no *HRAS* or *KRAS* mutation in the primary tumor received dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) without or with anti-EGFR monoclonal antibody panitumumab (Pmab). A randomized (1:2) phase II design was used with progression-free survival (PFS) as primary endpoint.

Results: Ninety-seven eligible patients were randomized; 96 patients were evaluable for toxicity and 87 for efficacy. The median PFS were 6.8 months (95% CI = 6.3-9.2) for dd-MVAC and 5.7 months (95% CI = 4.6-6.4 months) for dd-MVAC+Pmab. For both immunohistochemical and molecular definition of basal/squamous phenotype (BASQ) tumors, no difference was observed in objective response rates and PFS between the two arms in BASQ and non-BASQ tumors.

Conclusion: dd-MVAC+Pmab was associated with more serious adverse events and no improvement in efficacy outcomes.

Key words: Epidermal growth factor receptor; monoclonal antibody; chemotherapy; cisplatin; transitional cell carcinoma

Introduction

In patients with clinically localized muscle-invasive urothelial carcinoma (UC), multimodal treatment including perioperative chemotherapy and surgery represent the cornerstone of therapy. However, up to 50 % of patients develop metastases and ultimately succumb to their disease. Cisplatin-based first-line chemotherapies including standard or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) or gemcitabine plus cisplatin (GC) lead to response rates (RR) of about 50-60% with different toxicity profiles. Median progression-free survival (PFS) and median overall survival (OS) are usually of about 8-9 months and 14-15 months, respectively.[1,2] Additionally, a proportion of patients with metastatic UC (up to 50%) cannot be offered first-line cisplatin-based combination chemotherapy because of underlying conditions. In this population of "unfit" patients, gemcitabine and carboplatin is the most widely used chemotherapy regimen, leading to less favorable median OS of about 8-9 months.[3]

Novel approaches are clearly needed to improve quality of life, disease stabilization, and/or OS for patients with advanced UC. Panitumumab (Pmab) is an IgG_2 fully human monoclonal antibody that targets the extracellular, ligand-binding domain of the epidermal growth factor receptor (EGFR) and inhibits its signalling pathway. EGFR overexpression is a frequent event which has been associated with higher tumor grade, stage and shorter survival in UC.[4] Preclinical data as well as recent molecular classifications have suggested that activation of the EGFR pathway could a prominent feature associated with a subset of particularly aggressive UC called squamous cell carcinoma-like or basal-like transcriptional (BASQ) subtype.[5-7]

In 2009, we designed a randomized study to assess the efficacy and toxicity of Pmab in combination with dd-MVAC in the first-line treatment of patients with advanced disease. As the benefit of EGFR inhibition in colon cancer is restricted to tumors expressing the wild-type

form of the *KRAS* and *NRAS* genes,[8] patients with mutations in the *KRAS* or *HRAS* genes were excluded from the present study. Considering the potential role of the EGFR pathway in BASQ tumors, exploratory analyses were conducted in this subset of patients.

Patients and Methods

Patient selection

The GETUG/AFU 19 trial was conducted in 19 centers of the French GEnito-urinary TUmour Group from September 2010 to November 2015 after the approval by the Board for the Protection of Persons subjected to Biomedical Research (EudraCT number: 2009-011882-10). All patients signed a written informed consent form. Eligibility criteria included an age over 18 years; primary tumor of the bladder or upper urinary tract with pathological diagnosis of UC (pure or mixed histology except for any small cell component); no *HRAS* or *KRAS* mutation; advanced disease defined by a locally advanced stage (T4b or T any N2-3) ineligible for surgical resection or a metastatic stage; measurable disease on imaging as per RECIST (version 1.1); Eastern Cooperative Oncology Group (ECOG) performance status < 2; adequate organ functions (absolute neutrophil count ≥ 1500/µL, platelet count ≥ 100.000/µL, serum creatinine clearance ≥ 60 ml/min, normal liver tests, left ventricular ejection fraction ≥ 50%); absence of previous chemotherapy for advanced disease (prior neoadjuvant or adjuvant chemotherapy with gemcitabine and platinum salt was allowed if ended more than a year ago); no prior exposure to Pmab.

Treatment plan

Patients were randomized 1:2 to receive a combination of dd-MVAC (methotrexate 30 mg/m^2 on day 1, vinblastine 3 mg/m^2, doxorubicin 30 mg/m^2, and cisplatin 70 mg/m^2 on day 2 every 2 weeks) without (chemotherapy alone, C arm) or with Pmab 6 mg/kg on day 2 (CP arm) with

prophylactic GCSF for 7 days, starting 24 hours after the last dose of cytotoxic drug. Chemotherapy was stopped in both arm after 6 cycles. In CP arm, patients without disease progression at the end of chemotherapy continued on Pmab until progression or unacceptable toxicity. Patients in either arm with locally advanced disease were offered local therapy as deemed medically appropriate.

Patient evaluation

The baseline evaluation included a complete history, physical examination, assessment of performance status, complete blood count, and chemistry studies. Imaging included chest, abdominal and pelvic computed tomography, and a radionucleotide bone scan. During therapy, patients were assessed for toxicity at the beginning of each 2-week cycle. Complete blood counts and chemistry studies were monitored weekly. Imaging was repeated every 6 weeks while patients were on study therapy. Investigator assessments were used to determined response rates and PFS according to RECIST. Adverse events were graded by using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Biological studies

Extraction of DNA was centralized (department of pathology, hôpital Henri Mondor, Créteil, France) and performed from 5 to 10 µm sections of pre-selected areas (using QIAGEN EZ1 IVD labelled system). *K-RAS* codon 12 and 13 mutations was determined with Taqman assays and *H-RAS* mutations on codons 12, 13 and 61 was determined by capillary sequencing of PCR products.

For the patients with a signed consent for ancillary study and available FFPE tumour blocks, the basal/squamous (BASQ) molecular subtype was determined through two different

methods. First, a dual immunostaining CK5/6-GATA3 was used and tumors with a predominant high CK5/6 – low GATA3 pattern were defined as BASQ and others as non-BASQ tumors.[5] Second, RNAs were extracted from FFPE blocks and analyzed using a NanoString code set of 29 genes differentially expressed between BASQ and non-BASQ tumors.

Statistical considerations

The primary endpoint of the study was PFS at 9 months. The number of patients was determined from the 9-month median PFS rate reported with dd-MVAC in the randomized comparison with standard MVAC.[2] Using a one stage Fleming design, dd-MVAC+Pmab treatment was considered active and potentially evaluable in further studies if at least 37 patients among 62 did not show tumor progression at 9 months. This decision took into account the observed PFS rate in the control arm. Treatment was considered insufficiently active if 26 patients or more experience progression in the 9 months following treatment initiation (p0=0.50, p1=0.70, alpha=0.08, and beta=0.03). No formal statistical comparisons were planned between the two treatment arms due to the small sample size of this trial.

Results

Patient characteristics

Between September 2010 and November 2015, 170 patients were selected in 19 French institutions (Figure 1). Fifteen (9%) were excluded because of *HRAS* or *KRAS* mutations in the tissue biopsies. Follow-up continued until data cutoff in September 2016. Among 113 randomized patients, 16 were deemed ineligible. Another patient died of disease before starting therapy and was replaced. Initial characteristics of 97 eligible patients were well balanced (Table 1). Eighty-seven patients (90%) had metastatic disease, of whom 12 (14%)

had lymph node metastases only. Twenty-patients (23%) patients were assigned into the low risk prognostic group (ECOG < 2 and no visceral metastases).[9] Five patients (5%) had previously received perioperative chemotherapy with gemcitabine and cisplatin. One patient with peritoneal carcinomatosis rapidly died of bowel obstruction after the first cycle of ddMVAC+Pmab. Ninety-six and 87 patients were evaluable for safety and efficacy, respectively.

Treatment delivery and toxicity

The median number of cycles was 6 in both arms (Table 2). Seventy-nine percent and 68% of patients received 6 cycles of dd-MVAC in C arm and CP arm, respectively. The median relative dose intensities of methotrexate, vinblastine and doxorubicin per cycle were similar in both arms. A trend towards a lower median relative dose intensity of cisplatin was observed in C arm. In CP arm, 3 patients continued on Pmab maintenance after the end of dd-MVAC for a median duration of 9.6 months (range, 2-22). Adverse events are reported in Table 3. Severe adverse events (SAE, grade ≥3) occurred in 79% and 76% of patients in C and CP arm, respectively. The most common SAE in both arms (≥ 10% of patients) were myelosuppression, mucositis, diarrhea, acneiform rash, asthenia and hypomagnesemia. Grade 3/4 mucositis, diarrhea, acneiform rash, kidney injury and hypomagnesemia were more common in CP arm. Additionally, more episodes of febrile neutropenia were observed in CP arm. No toxic death was registered.

Efficacy

Objective response rates were 69.7% in C arm and 47.6% in CP arm, with overlapping 95% confidence intervals. A complete response was reported in 2 and 1 patients, respectively. Survival curves are depicted in Figures 2 and 3. PFS at 9 months was 37% (95% CI, 21-54) and

17% (95% CI, 8-27) in C and CP arm, respectively. The median PFS was 6.8 months (95% CI, 6.3-9.2) in C arm and 5.7 months (95% CI, 4.6-6.4) in CP arm (Hazard ratio [HR], 1.6; 95% CI, 1.0-2.5). With a median follow-up of 27 months (range, 0.7-34.4), the median overall survival was 20.2 months (95% CI, 14.7-27.8) in C arm and 12.5 months (95% CI, 9.5-17.3 months) in CP arm (HR, 1.81; 95% CI, 1.1-3.0). Ten patients remained free of disease progression, 6 in the C arm and 4 in CP arm.

Exploratory analyses

Using the dual CK5/6-GATA3 immunostaining, the basal/squamous phenotype was available for 73/88 patients: 2 (9%) in C Arm and 8 (16%) in CP arm were classified BASQ. The RNA based NanoString classification was available for 50/88 cases: 5 (36%) in C arm and 9 (26%) in CP arm were classified BASQ. For both immunohistochemical and molecular definition of BASQ tumors, no difference was observed in objective response rates and PFS between the two arms in BASQ and non-BASQ tumors.

Discussion

To our knowledge, we report here the first study assessing the efficacy of panitumumab in patients with advanced UC. The results are clearly disappointing since the combination of dd-MVAC and Pmab was associated with more serious adverse events and no improvement in efficacy outcomes as compared to dd-MVAC alone. In 2009, the choice of dd-MVAC as standard arm was based on a higher complete response rate and borderline relative reduction in the risk of progression and death compared to standard MVAC.[2] The lower rate of complete responses observed in the present study could be explained by the higher proportion of patients assigned into the favourable prognostic group in the EORTC trial (65% versus 23%).

Two previous trials have evaluated the potential role of EGFR blockade in advanced UC using cetuximab, a recombinant, human/murine-chimeric monoclonal antibody.[10,11] The first was a randomized, multicenter study of cetuximab alone or in combination with paclitaxel in patients who had received one line of platinum-based chemotherapy in the perioperative or metastatic setting. The cetuximab arm closed early after the inclusion of 11 patients since it reached the futility threshold, with a median PFS less than 8 weeks. In the combination arm, objective responses were observed in 25% of 28 patients and the median PFS was 16 weeks, suggesting a potential interest for the combination.[10] A second cetuximab trial included 88 patients in first-line treatment for advanced UC. Patients were randomized 1:2 to gemcitabine plus cisplatin (GC) without or with cetuximab. The objective response rates were 57% and 61%, respectively. There were no differences in survival secondary endpoints. Additionally, a higher rate of SAE was reported in the combination arm, including and thromboembolic events (TEE) and toxic deaths.[11] A meta-analysis of prospective randomized trials conducted with anti-EGFR agents, especially cetuximab, have confirmed the higher risk of TEE.[12] As compared to the GC +/- cetuximab study, the French trial used a similar randomized 1:2 design to treat patients with a four-drug, potentially more toxic cisplatin-based regimen and a fully human monoclonal antibody targeting EGFR. Broadly similar SAE rates of 80% were reported. More frequent acneiform rash and hypomagnesemia in anti-EGFR treatment arms were seen in both studies. However, TEE occurred in only 10% of patients with no difference between the two arms while no toxic death was observed in our study. Conversely, mucositis, diarrhea, kidney injury and febrile neutropenia events turned out to arise more frequently in the CP arm, suggesting a synergistic toxic effect between Pmab and dd-MVAC.

From a biological perspective, possible reasons for the lack of increased efficacy of chemotherapy with Pmab include either alterations in the pathway downstream the EGFR leading to ligand-independent activation of this pathway or a lack of enrichment for patients

whose tumors are truly driven by EGFR alterations. Both cetuximab studies did not exclude patients with tumors harboring *RAS* mutations. Cetuximab is approved in metastatic colorectal cancer since it provides additional benefit when combined with chemotherapy. However, it has been shown that this benefit is restricted to patients with tumors expressing the wild-type form of the *KRAS* and *NRAS* genes.[8] Given that mutations in the *KRAS* or *HRAS* genes have been reported to occur in approximately 10% to 15% of UC,[13] this lack of biological selection could have altered the results of cetuximab studies. In the present study, such mutations were observed in the tumor samples of 15 out of 170 (9%) patients who were therefore not randomized. Considering the disappointing results of our study, it can be concluded that the low efficacy of monoclonal antibodies targeting EGFR is not explained by concomitant *RAS* mutations.

Recent whole genome characterizations of UC revealed molecular subtypes associated with different survival outcomes and responses to treatments in retrospective studies. Among them, a consensus was reached regarding a subgroup of so-called basal/squamous-like tumors (BASQ) with a predominant high CK5/6 – low GATA3 pattern.[5] BASQ tumors have been shown to present an activation of the EGFR pathway linked to frequent EGFR gains and activation of an EGFR autocrine loop. In a chemically induced model of BASQ bladder cancer, tumor cells were sensitive to anti-EGFR treatment.[6] However, after both immunohistochemical and molecular selection of BASQ tumors in the present study, no difference was observed in objective response rates and PFS between the two arms in BASQ and non-BASQ tumors. The low number of patients preclude to draw firm conclusion.

Conclusion

Targeting the EGFR pathway does not improve clinical outcomes in advanced UC despite encouraging preclinical data. Future advances in the development of targeted therapies for

advanced UC are expected to come from fibroblast growth factor (FGFR) inhibitors,[14] along with immune checkpoint inhibitors.

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Disclosure
SC has served in an advisory role and provided lectures for Astellas, Bayer, Janssen, Takeda, has undertaken clinical trials for Amgen, AstraZeneca, Bayer, MSD, Roche, Sotio and has received travel/accommodation/expenses from Ipsen and Janssen.
YL received honoraria for speaker, consultancy or advisory role from Astellas, AstraZeneca, BMS, Ipsen, Janssen, MSD, Pfizer, Roche, Sanofi, Seattle Genetics.
JPS received honoraria for speaker, consultancy or advisory role from AstraZeneca, Biogaran, BMS, Gilead, Leopharma, Lilly, MSD, Mylan, Novartis, Pfizer, Roche.
All remaining authors have declared no conflicts of interest.

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Figure 1 – CONSORT flow diagram

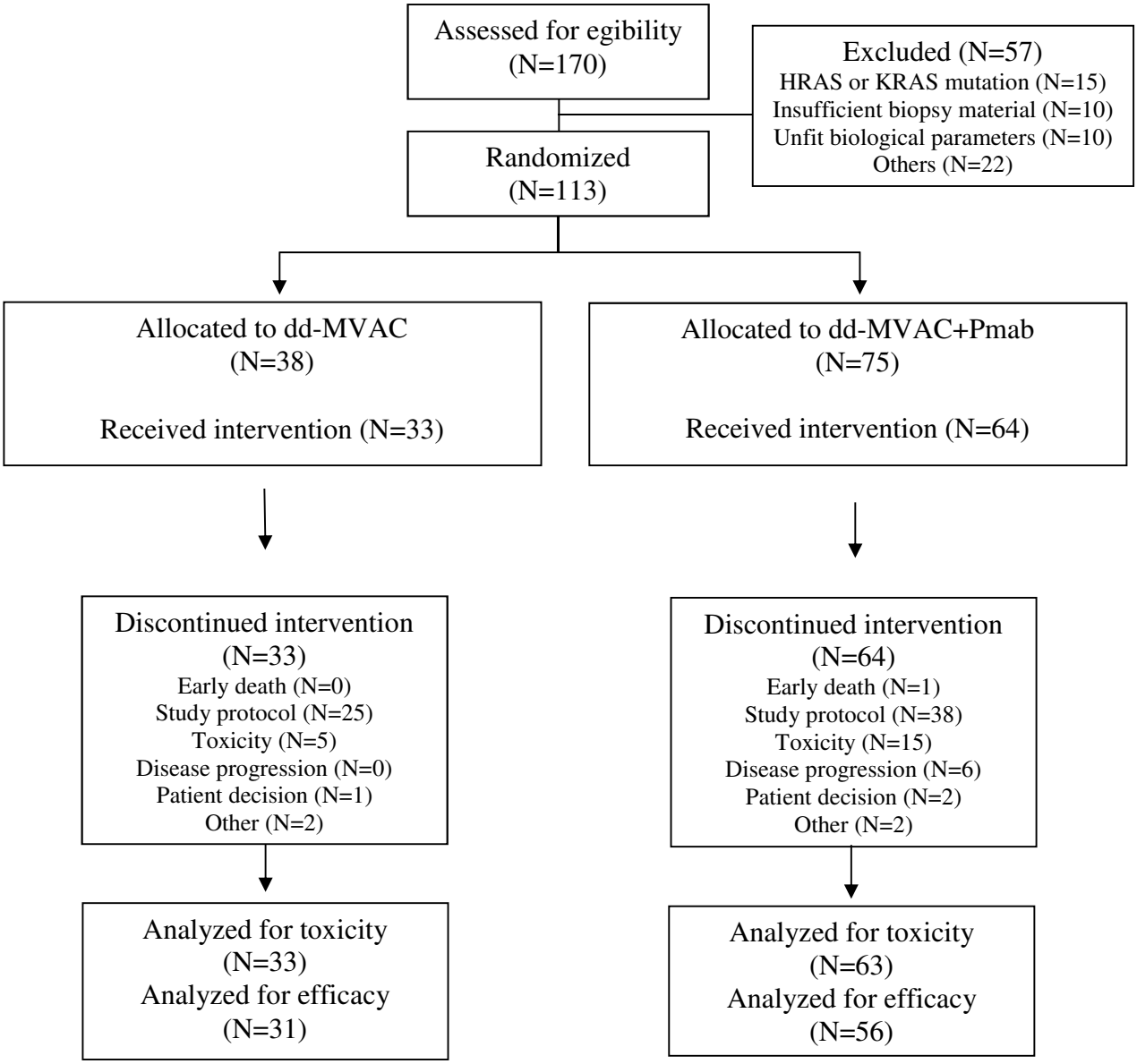

Table 1. Initial characteristics of eligible patients

Characteristic	dd-MVAC (N=33)	dd-MVAC+Pmab (N=64)
Age (years)		
Median (range)	65 (40-75)	64 (35-74)
Primary site		
Bladder	22 (67)	46 (72)
Upper tract	6 (18)	15 (23)
Both	5 (15)	3 (5)
Histological variant		
None (pure urothelial)	27 (82)	56 (87)
Squamous	3 (9)	1 (2)
Glandular	0	1 (2)
Unknown	3 (9)	6 (9)
ECOG performance status (%)		
0	13 (39)	25 (39)
1	17 (52)	30 (47)
2	0 (0)	1 (2)
Unknown	3 (9)	8 (12)
Disease stage (%)		
Locally advanced	4 (12)	6 (9)
Metastatic	29 (88)	58 (91)
Metastatic sites		
Lymph nodes only	3 (9)	9 (14)
Lymph nodes	7 (21)	14 (22)
Lung	18 (55)	26 (41)
Liver	11 (33)	15 (23)
Bone	10 (30)	22 (34)
Bajorin risk group		
Favorable	7 (21)	15 (23)
Intermediate	23 (70)	40 (62)
Poor	0	1 (2)
Unkown	3 (9)	8 (12)
Previous treatments		
Radiotherapy	3 (9)	5 (8)
Chemotherapy	1 (3)	3 (5)
Chemoradiotherapy	0 (0)	1 (2)

ECOG: Eastern Cooperative Oncology Group

Table 2. Treatment delivery

Parameter	dd-MVAC (N=33)	dd-MVAC+Pmab (N=63)
Number of chemotherapy cycles		
Median (range)	6 (1-6)	6 (1-6)
< 4	4	14
4	1	3
5	2	3
6	26	43
Total doses (mg), median (range)		
Methotrexate	331 (55-376)	301 (57-390)
Vinblastine	33 (5-38)	30 (6-40)
Doxorubicine	321 (54-377)	302 (57-396)
Cisplatin	700 (128-879)	661 (133-924)
Panitumumab	NA	2256 (440-3300)
Relative dose intensity (%), median (range)		
Methotrexate	92 (64-105)	93 (41-105)
Vinblastine	92 (57-104)	93 (39-105)
Doxorubicin	90 (64-104)	93 (41-105)
Cisplatin	86 (51-104)	92 (32-105)
Panitumumab	NA	90 (14-108)
Number of patients with relative dose intensity ≥ 80% (%)		
Methotrexate	24 (77)	46 (77)
Vinblastine	25 (76)	48 (76)
Doxorubicin	25 (76)	49 (78)
Cisplatin	20 (61)	44 (70)
Panitumumab	NA	38 (60)
Number of delay or dose reduction/cycle (%)		
None	128 (71)	198 (63)
Delay	24 (13)	32 (10)
Dose reduction	13 (7)	58 (18)
Both	14 (8)	26 (8)
Number of delay or dose reduction/patient (%)		
None	10 (30)	14 (22)
Delay	3 (9)	13 (21)
Dose reduction	7 (21)	11 (17)
Both	13 (39)	25 (40)

Table 3. Adverse events

Adverse event	dd-MVAC (N=33)	dd-MVAC+Pmab (N=63)
Nausea (%)		
Grade < 3	30 (91)	60 (95)
Grade 3-4	3 (9)	3 (5)
Vomiting (%)		
Grade < 3	32 (97)	60 (95)
Grade 3-4	1 (3)	3 (5)
Mucositis		
Grade < 3	29(88)	48 (76)
Grade 3-4	4 (12)	15 (24)
Diarrhea		
Grade < 3	32 (97)	56 (89)
Grade 3-4	1 (3)	7 (11)
Acneiform rash (%)		
Grade < 3	33 (100)	56 (89)
Grade 3	0 (0)	7 (11)
Neutropenia (%)		
Grade < 3	21 (64)	42 (67)
Grade 3-4	12 (36)	21 (33)
Febrile neutropenia (%)	2 (6)	11 (17)
Thromboembolic events (%)	3 (9)	7 (11)
Thrombocytopenia (%)		
Grade < 3	26 (79)	52 (83)
Grade 3-4	7 (21)	11 (17)
Anemia (%)		
Grade < 3	21 (64)	47 (75)
Grade 3-4	12 (36)	16 (25)
Kidney injury (%)		
Grade < 3	33 (100)	59 (94)
Grade 3-4	0 (0)	4 (6)
Hypokaliemia (%)		
Grade < 3	30 (91)	60 (95)
Grade 3-4	3 (9)	3 (5)
Hypomagnesemia (%)		
Grade < 3	33 (100)	56 (89)
Grade 3-4	0 (0)	7 (11)

Table 4. Efficacy outcomes

Endpoint	dd-MVAC (N=33)	dd-MVAC+Pmab (N=63)
Overall response rate (%)*	69.7 (51-84)	47.6 (35-61)
Complete response, n (%)	2 (6.1)	1 (1.6)
Partial response, n (%)	21 (63.6)	29 (46.0)
Stable disease	7 (21.2)	19 (30.2)
Median progression-free survival (months)*	6.8 (6.3-9.2)	5.7 (4.6-6.4)
Median overall survival (months)*	20.2 (14.7-27.8)	12.5 (9.5-17.3)

(*) 95% confidence intervals

Figure 2. Progression-free survival

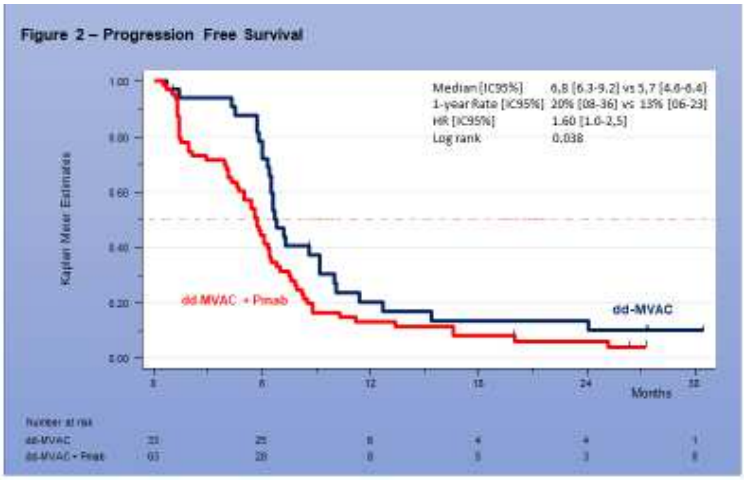

Figure 3. Overall survival