A Multicenter Phase 2 Study of Risk-adjusted Salvage Chemotherapy Incorporating Vinorelbine and Gemcitabine for Relapsed and Refractory Lymphoma

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BACKGROUND. Administration of salvage chemotherapy to patients with relapsed or refractory lymphoma is associated with significant toxicity. Vinorelbine and gemcitabine are novel chemotherapeutic agents with minimal overlapping toxicity. We present a phase 2 study of vinorelbine and gemcitabine with or without ifosfamide administered in an ambulatory care setting for relapsed or refractory lymphoma.

METHODS. Ninety patients were enrolled. Group 1 comprised patients with "good" risk disease, Group 2 comprised patients with "high" risk disease, and Group 3 comprised patients relapsing after prior stem cell transplant. Patients in Group 1 and Group 3 received vinorelbine and gemcitabine with filgrastim support (VGF); those in Group 2 received the above regimen with ifosfamide (FGIV). We incorporated a standardized interim evaluation with dose escalation for patients with suboptimal response after 2 cycles.

RESULTS. Toxicities were acceptable. Febrile neutropenia was uncommon: 7% after VGF (7 of 107 cycles) and 19% for FGIV (26 of 148 cycles). Unplanned admissions occurred in 23 of 107 cycles (21%) after VGF and 50 of 148 (34%) after FGIV. Overall response for Groups 1, 2 and 3, respectively was 76%, 39% and 50%, with median overall survival of 28, 9 and 30 months.

CONCLUSIONS. Vinorelbine-based and gemcitabine-based chemotherapy is effective in the salvage setting against lymphoma and can be administered in an ambulatory setting. ***Cancer* 2008;113:3192–8.** © *2008 American Cancer Society.*

KEYWORDS: lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, vinorelbine, gemcitabine.

The prevalence of lymphoma is rapidly increasing in the industrialized world and it has been estimated that by 2020, the incidence will approach that of non–small cell lung cancer.[1,2] Although many patients achieve excellent long-term outcomes after treatment with established first-line regimens, a significant proportion are refractory to primary therapy, or relapse after initial response, and have a poorer prognosis.[3-5] Despite the finding that many patients retain sensitivity to alternative salvage chemotherapy regimens, survival using these therapies alone for high-grade non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) is below 10% and 20%,

Informed consent was sought and received from all patients before enrollment in this study. The consent forms, plain English statements, and the trial itself were reviewed by ethics committees at all participating institutions before enrollment of any subjects.

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respectively, at 5 years.[6] As such, for patients with ongoing chemosensitivity, high-dose chemotherapy conditioned autologous stem cell transplantation (ASCT) as a consolidative approach is currently regarded as the optimal strategy and is curative in a significant proportion of patients.[7,8] In patients planned for ASCT, it is therefore important to try to avoid excessive prior toxicity, similarly, for patients unsuitable for ASCT, where salvage therapy alone is unlikely to be curative,[9,10] it is preferable to avoid hospitalization and regimen-related toxicities.

Vinorelbine and gemcitabine have been shown, as single agents, to have efficacy in the treatment of patients with heavily pretreated lymphoma.[11,12] Vinorelbine is a semisynthetic *Vinca* alkaloid which inhibits microtubule synthesis,[13] whereas gemcitabine is a nucleoside analog of deoxycytidine which undergoes intracellular activation.[14] The agents have differing mechanisms for activity and little overlapping toxicity, and can both be administered in the outpatient setting via short intravenous infusions. Preliminary evidence of single-agent efficacy and satisfactory tolerability for gemcitabine against relapsed and refractory lymphoma has seen it incorporated into treatment combinations.[15,16] Combination therapy with vinorelbine and gemcitabine has been found to be effective in the management of advanced nonsmall cell lung cancer,[17] and we have previously shown that the combination of vinorelbine and gemcitabine is an effective and tolerable salvage approach for both NHL and HL with overall response rates of 70%, and 47%, for patients in first relapse or with more advanced disease, respectively.[18] Combinations of gemcitabine and vinorelbine with liposomal doxorubicin (GND) have been used successfully for the salvage of Hodgkin disease.[19] Ifosfamide is an alkylating agent, with established efficacy in combination chemotherapy regimens for lymphoma.[20] Outpatient administration of ifosfamide, gemcitabine, and vinorelbine (IGEV) has been found to be an effective salvage approach in a series of 91 patients with relapsed/refractory Hodgkin lymphoma, with an overall response rate of 83.3%, with few treatment-related toxicities and effective facilitation of stem cell mobilization.[21]

We present the results of a multicenter, phase 2 prospective study, conducted between December 2002 and December 2004, evaluating the performance in an ambulatory care setting of vinorelbine and gemcitabine incorporating a risk-adapted strategy, rigorous mid-treatment evaluation, and early dose escalation for patients who fail to achieve satisfactory interim responses.

TABLE 1
Initial Treatment Regimens*

	VGF (Groups 1 and 3)		FGIV (Group 2)	
Day	Drug	Dose	Drug	Dose
1	Vinorelbine	25 mg/m^2 IV	Vinorelbine	25 mg/m^2 IV
	Dexamethasone	16 mg/m^2 IV	Dexamethasone	16 mg/m^2 IV
	Gemcitabine	1000 mg/m^2 IV	Gemcitabine	1000 mg/m^2 IV
	—	—	Ifosfamide*	3000 mg/m^2 IV
8	Vinorelbine	25 mg/m^2 IV	Vinorelbine	25 mg/m^2 IV
	Dexamethasone	16 mg/m^2 IV	Dexamethasone	16 mg/m^2 IV
	Gemcitabine	1000 mg/m^2 IV	Gemcitabine	1000 mg/m^2 IV
9	Pegfilgrastim	6 mg sec	Pegfilgrastim	6 mg sec

*Patients were prehydrated, given Mesna 600 mg/m^2 in 100 mL normal saline over 15 minutes, and discharged with oral Mesna 1.2 g/m^2 to be taken at 2 and 6 hours after completion of ifosfamide.

MATERIALS AND METHODS

Patients

Patients were eligible if they were older than 17 years, had relapsed or primary refractory HL or NHL, and an Eastern Cooperative Oncology Group performance status of 0, 1, or 2. Patients with impaired renal (serum creatinine greater than twice the upper limit of normal), hepatic (bilirubin greater than twice the upper limit of normal), or hemopoietic (neutrophil count below 0.5×10^9/L and/or platelets below 50×10^9/L) function were excluded unless the impairment was considered directly due to lymphoma. Those who had relapsed within 6 months of a stem cell transplant procedure were also excluded.

Patients were stratified into 3 groups. Group 1 comprised "good risk" patients in first relapse, after a durable first complete remission, defined as a remission longer than 12 months for follicular (FL) NHL,[22] or beyond 6 months for all other subtypes of NHL and HL. Group 2 comprised patients with "poor risk" disease, who were either primary refractory, or had relapsed within 12 months (for FL NHL) or 6 months (for all other NHL subtypes and HL) of initial therapy,[23] or were in second or subsequent relapse and had not previously undergone any form of transplantation procedure. Group 3 comprised post-transplant patients who had relapsed at least 6 months after prior ASCT.

Treatment Schedule

All 3 regimens were administered as 21-day cycles, using a central venous device when available. Table 1 outlines the VGF (vinorelbine, gemcitabine, filgrastim) and FGIV (addition of ifosfamide to VGF) regimens. Treatment was administered in outpatient chemotherapy facilities unless therapy was initiated during an inpatient admission. Four cycles of treatment were planned. Patients in Groups 1 and 3 com-

menced therapy with the less aggressive VGF regimen. It was anticipated that some patients in Group 1 would respond to the gentler regimen alone. Patients in Group 2 commenced with the more intensive FGIV regimen, to attempt rapid control of their highly aggressive disease. Patients in Group 3 received the less aggressive VGF regimen to minimize excess toxicity given their prior history of ASCT.

Interim response assessments and escalation

After 2 cycles, all patients underwent re-evaluation with complete physical examination as well as repeat of previously positive imaging-computerized tomography of the chest, abdomen, and pelvis, as well as functional imaging (gallium or positron emission tomography) if undertaken at baseline. Patients were considered to have achieved a satisfactory interim response if they had at least a 50% reduction in tumor bulk at all previous sites of measurable disease and negative functional imaging at previously avid sites. Those with a satisfactory response continued the current regimen to a total of 4 cycles, whereas those with inadequate response (ie, <50% reduction in disease burden or residual positive functional imaging) were escalated (VGF to FGIV or FGIV to IVAC). (IVAC required inpatient administration: Day 1-5: etoposide 60 mg/m^2; ifosfamide 1.5 g/m^2. Day 1-2: cytarabine 2 g/m^2 12 hourly [4 doses]. Day 6: Pegfilgrastim 6 mg subcutaneously.[24]) After 4 cycles of therapy, patients were restaged and final response was classified according to current international guidelines for assessing lymphoma response.[25] Patients were able to exit the study after the second cycle to undergo ASCT at the discretion of their attending physician, and any patients found to have stable disease (SD) or progressive disease (PD) were also removed from the study.

Toxicity assessment

Hematologic and nonhematologic toxic effects of therapy were graded after each cycle of treatment according to the adapted World Health Organization grading system.[26] Dose reduction was permitted on the basis of clinical and laboratory parameters before Day 1 treatment; dose reduction was not permitted on the basis of Day 8 hematological parameters. Treatment was withheld if the neutrophil count was below 0.5 $\times$ 10^9/L or platelet count below 50 $\times$ 10^9/L, and treatment was reduced by 25% if these values were between 0.5 $\times$ 10^9/L to 1.0 $\times$ 10^9/L or 50 $\times$ 10^9/L 100 $\times$ 10^9/L, respectively.

Statistical Methodology

Sample size was calculated based on an α of 0.05, a power of 0.90, and a postulated proportion of desired response of 35% against a hypothetical of 20%. All adverse events were graded according to the adapted World Health Organization recommendations.[26] Key data (demographics and disease history) were collected for all patients. For continuous variables, summary measures included the mean, standard deviation, median, minimum, and maximum; for categorical variables, frequency tables were generated; for time-to-event variables, progression-free survival (PFS) and overall survival (OS), Kaplan-Meier survival was calculated, including estimates of 4-year survival. Survival estimates were summarized by prognostic and disease groups, as well as between transplanted and nontransplanted cohorts. An exploratory comparison of survival between patients with positive and negative functional imaging at interim evaluation was planned. All analyses were on an intention-to-treat basis.

TABLE 2
Characteristics of Patients by Prognostic Group

Characteristic	Group 1	Group 2	Group 3	Total
No. of patients	26	52*	12	90
Age, y (range)	57 (33-78)	59 (17-75)	54 (24-67)	58 (17-78)
Prior therapies (range)	1	3 (1-14)	5 (2-9)	2 (1-14)
ECOG performance status				
0	18	26	4	48
1	4	17	6	27
2	4	9	2	15
LDH >normal	18	41	11	70
sIPI				
Low	9	8	2	19
Low/Int	7	22	6	35
High/Int	5	11	2	18
Diagnoses				
DLBCL	13	24	6	43
FL	0	15	3	18
HL	9	5	2	16
PTCL	1	5	0	6
Other	3	3	1	7

ECOG, Eastern Cooperative Oncology Group system; LDH, lactate dehydrogenase; sIPI, second-line International Prognostic Index; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; PTCL, primary T-cell lymphoma; Other, diagnoses were mantle-cell lymphoma (2); marginal-zone lymphoma (2); mucosa-associated lymphoid tissue (MALT) lymphoma (2); Burkitt lymphoma (1).
*The number of patients in Group 2 with primarily refractory disease was 10.

Ethics Considerations

The trial was approved by the Ethics Committee or equivalent at each participating center, and each patient provided written informed consent.

RESULTS

Ninety patients were enrolled between December 2002 and December 2004, through 10 centers around Australia. The baseline characteristics of these patients are described in Table 2. There were 49 males

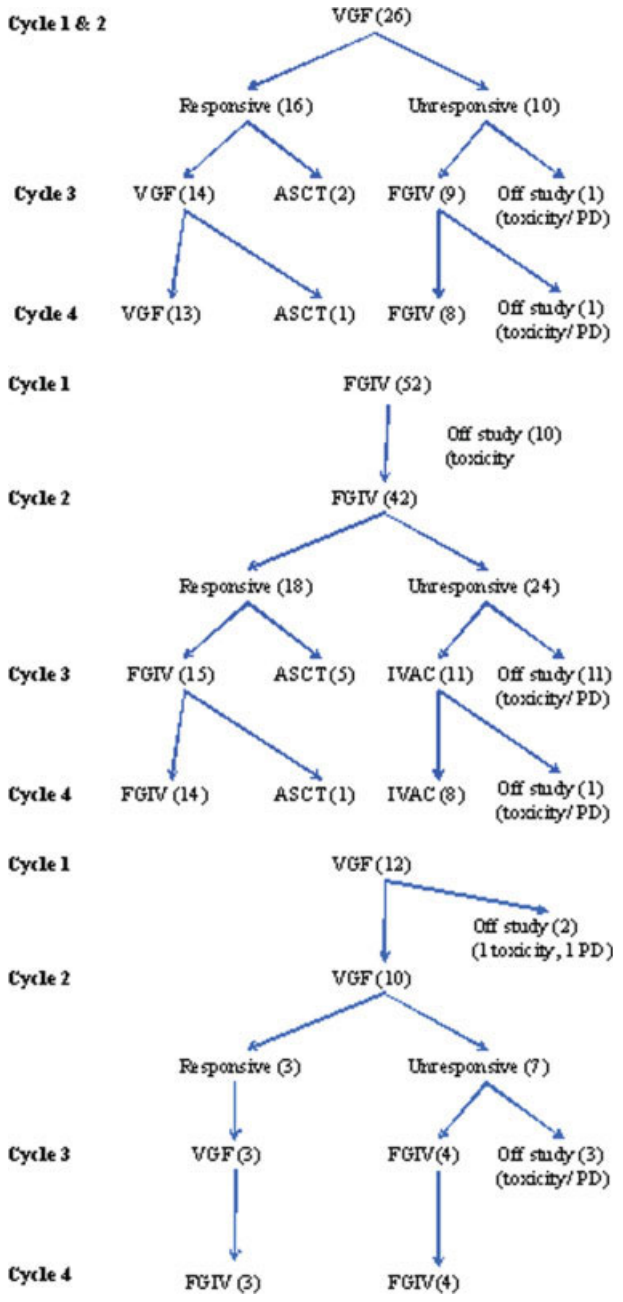


FIGURE 1. This illustration outlines the course and response of the enrolled patients.

and 41 females in the cohort. Figure 1 outlines the course and response of the enrolled patients. In Group 1, at final restaging overall response rate was 77% (complete response 42% and partial response 35%). In Group 2, the overall response rate at restaging was 39% (complete response 21% and partial response 18%). This was a heavily pretreated group (median previous therapies = 3) and removal from study because of toxicity or progressive disease was frequent (n = 30). In Group 3, 12 patients commenced VGF. At restaging, the overall response rate seen was 50% (complete response 8% and partial response 42%).

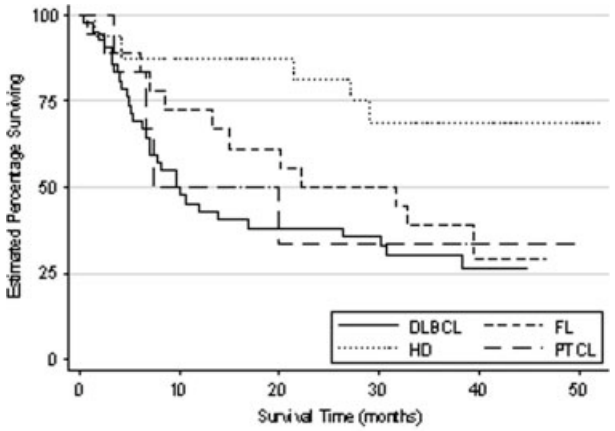
TABLE 3
Toxicities of VGF and FGIV Regimens

	VGF	FGIV
Characteristic	**No (%)**	**No (%)**
No. of patients	107	148
Febrile neutropenia	7 (6)	26 (19)
Unplanned admission	23 (21)	50 (34)
Treatment delays	7 (6)	15 (9)
25% dose reductions	2 (2)	10 (7)
Grade 3 nonhematologic toxicities	35 (33)*	87 (59)†
Grade 4 nonhematologic toxicities	3 (3)	12 (9)
Hemoglobin 6.5-7.9 g/dL	7 (7)	30 (20)
Platelets 25-50 $\times 10^9$/L	12 (11)	25 (17)
Neutrophils 0.5-0.9 $\times 10^9$/L	13 (12)	21 (14)
Hemoglobin <6.5 g/dL	1 (1)	4 (3)
Platelets <25 $\times 10^9$/L	19 (18)	53 (36)
Neutrophils <0.5 $\times 10^9$/L	19 (18)	68 (46)

*Gastrointestinal toxicity occurred in 10 patients (6 abnormal LFTs; 3 had nausea and vomiting; 1 had diarrhea); 7 had infection; 4 had pulmonary toxicity.
†Gastrointestinal toxicity occurred in 22 patients (8 had nausea and vomiting; 7 had diarrhea; 7 had abnormal LFTs); infection occurred in 19 patients and alopecia in 13 patients.

Of the 43 patients with a diagnosis of diffuse large B cell lymphoma (DLBCL), response, as evaluated after cycle 4 was seen in 12 patients (complete response in 7, partial response in 5). Of the 13 patients in Group 1 with DLBCL, response was seen in 5 patients (complete response in 4, partial response in 1). Of 24 patients with DLBCL in Group 2, response was seen after cycle 4 in 4 patients (complete response in 2, partial response in 2). Of the 6 patients with DLBCL in Group 3, 3 achieved response (complete response in 1, partial response in 2). Among the 18 patients with follicular lymphoma, response was seen after 4 cycles of therapy in 7 patients (complete response in 2, partial response in 5). Of the 16 patients with HL, response was seen in 9 patients (complete response in 7, partial response in 2): all patients achieving a complete response with this diagnosis were in Group 1. There was no significant difference in response rates in each risk group between histologic subtypes (P = 1.0, 0.84, and 0.07 for Groups 1, 2, and 3, respectively, by Fisher exact test).

Toxicities associated with VGF and FGIV are shown in Table 3. The VGF regimen was well tolerated, with few unplanned hospital admissions and with grade 3 of 4 hematologic toxicities occurring in fewer than one-third of patients. The addition of ifosfamide to the VGF regimen (FGIV) increased both hematologic and nonhematologic toxicities. In parti-



Diagnosis	N	Survival (%) [95% CI]
DLBCL	43	26.4 [13.7-41.1]
FL	18	29.2 [9.3-52.8]
HL	16	68.8 [40.5-85.6]
PTCL	6	33.3 [4.6-67.6]
Other	7	16.7 [0.8-51.7]

FIGURE 2. Overall 4-year survival for each lymphoma subtype is depicted.

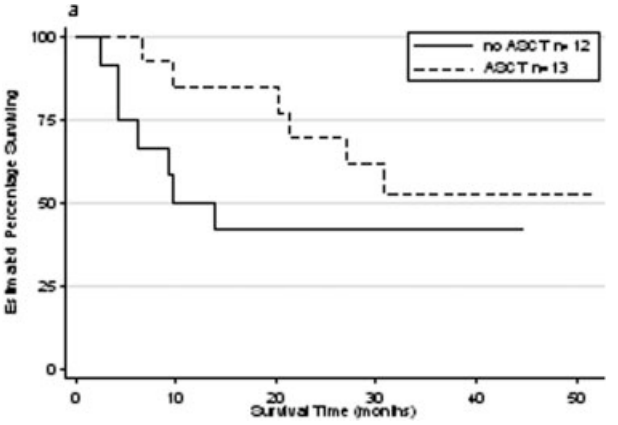


FIGURE 3. Among Group 1 patients, the difference in overall survival between patients with and without ASCT was not significant (overall survival at 24 months for ASCT 69.2% [37.3-87.2] vs 41.7% [15.3-66.5], $P = .255$), although the number of patients in this group was smaller.

cular, grade 4 neutropenia and thrombocytopenia was seen in 46% and 36% of patients, respectively. For both regimens, treatment delays and requirements for dose reduction were uncommon.

Median progression-free survival was 21 months (range, 2-52), 5 months (range, 1-47), and 4 months (range, 1-38) and overall survival 28 months (range, 3-52), 9 months (range, 1-47), and 30 months (range, 4-48) for Groups 1, 2, and 3, respectively. Estimated 4-year overall survival was 49%, 28%, and 31% for Groups 1, 2, and 3, respectively. Overall 4-year survival for each lymphoma subtype is depicted in Figure 2. Patients with HL had a significantly superior 4-year overall survival (68.8% [40.5-85.6]) when compared with patients with DLBCL (26.4 [13.7-41.1]), $P < .05$.

An improved response was seen in 9 of 22 patients for whom treatment was escalated, but improvements in overall survival for those responding compared with those who did not respond did not reach statistical significance (overall survival escalation response 50.0%, 95% confidence interval, 18.4-75.3 vs overall survival no escalation response 36.6%, 95% confidence interval, 12.5-62.0, $P = .306$). Patients with HL were more likely to achieve a final response (either complete or partial) if they had negative functional imaging at interim evaluation than if imaging remained positive, even if computed tomographic imaging otherwise indicated satisfactory response (87.5% vs 0%, $P < .03$, by Fisher exact test).

A total of 30 patients from Groups 1 and 2 underwent autologous stem cell transplantation either during the course of treatment or subsequently. Patients who underwent ASCT had improved progression-free survival and overall survival compared with those who did not (progression-free survival at 24 months for ASCT 40.0% [95% confidence interval, 22.8-56.7] vs 18.3% [8.2-31.7] for non-ASCT, $P < 0.005$; overall survival at 24 months for ASCT 73.3% [53.7-85.7] vs 24.4 [13.2-37.6] for non-ASCT, $P < .0001$). The improved survival associated with ASCT was most striking among Group 2 patients (overall survival at 24 months for ASCT 76.5% [48.8-90.5] vs 18.2% [7.4-32.8] for non-ASCT, $P < .0001$). Among Group 1 patients, the difference in overall survival between those with ASCT and those without ASCT was not significant (overall survival at 24 months for ASCT 69.2% [37.3-87.2] vs 41.7% [15.3-66.5], $P = .255$), although the number of patients in this group was smaller (Fig. 3).

There was a trend toward improved overall survival at 24 months for patients with DLBCL receiving ASCT in Group 1 (44.4% [13.6-71.9] for those without ASCT compared with 75%[12.8-96.1]) for those with ASCT and in Group 2 (20% [6.2-39.3] for those patients without ASCT, compared with 66.7% [5.4-94.5] for those with ASCT), although significance was not achieved, most likely because of small sample sizes. There was a clear benefit in overall 24-month survival by transplanting patients with FL in Group 2 (22.2% [3.4-51.3] for patients without ASCT compared with 83.3% [27.3-97.5] in patients with ASCT, $P < .04$).

DISCUSSION

Our results confirm that outpatient administration of vinorelbine-based and gemcitabine-based chemotherapy is feasible and efficacious for the salvage ther-

apy of relapsed or refractory Hodgkin and non-Hodgkin lymphoma, and can be administered in a multicenter context. Our outcomes with VGF and FGIV appear to be comparable to other established salvage regimens requiring inpatient management, although variations in patient populations and study design clearly limit the validity of any direct comparison.[10,22]

The application of interim treatment escalation during therapy in a salvage setting was a unique aspect of our study. Published data show that patients with residual positron emission tomography positivity after 2 to 3 cycles of primary therapy have a poorer outcome compared with those with negative imaging.[27,28] We purposefully set a "low" threshold for escalation, incorporating functional imaging into the assessment. Our results indicate that escalation improves responses in some patients who were "failing" therapy. However, the lack of improvement in survival among escalated patients achieving an improved response compared with those who do not achieve an improved response warrants further investigation; these patients must have a more refractory illness with a poorer outcome. The significant adverse impact with respect to final overall response rate of positive functional imaging at the interim evaluation within the HL group also implies that these refractory patients have a more high-risk disease.

That differences between outcomes for patients in Group 1 who did or did not proceed to ASCT failed to achieve statistical significance raises the possibility that patients who have had durable first remissions may achieve further durable responses with salvage therapeutic approaches without the necessity for ASCT. This may be particularly relevant for patients with CD20+ disease, where VGF and FGIV would present a relatively low-toxicity platform for the incorporation of immunotherapeutic agents (such as anti-CD20 antibody).

We conclude that VGF and FGIV are effective and well-tolerated salvage approaches that can be delivered in an ambulatory care setting. The exploratory analysis of interim disease evaluation suggests that disease outcomes may be improved with escalation of therapy in selected patients and justifies further study. Finally, both VGF and FGIV represent attractive targets for combination with available immunotherapeutics.

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