Relapse in teenage and young adult (TYA) patients treated on a paediatric minimal residual disease (MRD) stratified ALL treatment protocol is associated with a poor outcome: Results from UKALL2003

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Abstract:

Outcomes for teenage and young adult (TYA) patients with acute lymphoblastic leukaemia (ALL) who relapse on contemporary risk-adapted paediatric protocols are largely unknown and there is no consensus on optimal salvage strategies. We assessed the treatment and outcome of TYA patients (aged 16-24 years), recruited to the UKALL2003 trial, who relapsed following attainment of complete morphological remission. Forty-two of 223 patients (18.8%) relapsed, the majority (n=26, 62%) on treatment. Thirty-eight (90%) patients received salvage treatment with 22 (59%) achieving second remission (CR2) consolidated with an allogeneic haematopoietic cell transplant (alloHSCT) in 21. Post-relapse outcomes were poor with a 5-year overall survival (OS) of 23% (95% CI;11-37%). Outcomes for patients relapsing on active treatment were inferior to those relapsing after completing treatment (5-year OS 9% v 52% log-rank P=0.001). No patient with B-cell ALL relapsing on treatment was alive at the end of the study period. TYA patients with ALL who relapse on the UK paediatric protocol, UKALL2003, are largely unsalvageable with conventional approaches aimed at achieving CR2 followed by alloHSCT. Future efforts should be aimed at identifying those patients who are destined to relapse and exploring novel treatment approaches for this high-risk group and for those who do relapse.

Introduction

Over the last decade, it has been demonstrated that teenage and young adult (TYA) patients with acute lymphoblastic leukaemia (ALL), have superior outcomes if treated according to paediatric chemotherapy-based protocols rather than transplant-focused adult protocols. In an analysis of the UK Medical Research Council (MRC) ALL97/99 paediatric protocol, the 5-year event-free survival for TYA patients was 16% higher than that seen for TYA patients treated on the contemporaneous adult protocol, UKALL-XII/E2993 (65% vs 49% respectively). The superiority of paediatric approaches for the TYA population has now been seen in multiple retrospective analyses with higher CR rates, higher EFS, lower relapse risk, and with comparable rates of non-relapse mortality (NRM) (Boissel *et al*, 2003; de Bont *et al*, 2004; Hallbook *et al*, 2006; Ramanujachar *et al*, 2007; Lopez-Hernandez *et al*, 2008; Ribera *et al*, 2008; Stock *et al*, 2008; Usvasalo *et al*, 2008; Huguet *et al*, 2009; Hough *et al*, 2016).

Despite these improvements, the outcomes for TYA patients remain inferior to the excellent sustained remission (CR) rates of approximately 90% seen in the paediatric patient population. This is a consequence of multiple factors including inferior rates of recruitment to clinical trials and increased susceptibility to treatment related toxicity. In addition, TYA patients have evidence for a leukaemia biology that is intrinsically treatment resistant (Roberts *et al*, 2012), as well as suboptimal compliance with prescribed regimens, two factors that may contribute to the increased relapse rates seen in TYA patients compared to younger cohorts (Hough *et al*, 2016).

Studies of adult patients with ALL have demonstrated that overall survival (OS) following relapse is poor (Fielding *et al*, 2007; Tavernier *et al*, 2007; Oriol *et al*, 2010; Gokbuget *et al*, 2012). These studies included TYA patients and poor outcomes were also seen in the youngest cohorts. However, these trials followed 'adult style' protocols that employ lower cumulative doses of immunosuppressive drugs, less frequent use of intrathecal methotrexate, greater exposure to myelotoxic drugs, and an emphasis on alloHSCT in first CR (Goldstone *et al*, 2008; Ram *et al*, 2012). The outcome for TYA patients who relapse following a paediatric inspired regimen is unclear. Crucially there is also limited information on which salvage regimens are effective in this context, such that no clear recommendations on best treatment in the event of relapse can be made in the TYA population.

UKALL2003 was a prospective, multicentre, randomised controlled trial using risk-adapted treatment and included the investigation of treatment modification according to MRD status at the end of induction in consecutively diagnosed children and young people with *BCR-ABL* negative ALL recruited between October 2003 and June 2011. Here we report the treatments and outcome for TYA patients (aged 16-24 years) recruited to this trial who subsequently relapsed.

Study Design

From 1st October 2003 to 30th June 2011 the MRC UKALL2003 trial recruited children and TYA patients with a new diagnosis of ALL at 45 centres in the UK and Ireland. The upper age limit was extended from the 18th to the 20th birthday in April 2006, and to the 25th birthday in September 2007. Patients with mature B ALL were not eligible and patients with Philadelphia chromosome were treated on alternative protocols. Details of the whole trial have been published previously and the specific treatment regimens for TYA patients treated on UKALL2003 have also been described (Hough *et al*, 2016).

In brief, all TYA patients received regimen B induction chemotherapy. Patients with high-risk cytogenetics at presentation [*KMT2A* (*MLL*) rearrangements, near haploidy (<30 chromosomes), low hypodiploidy (30-39 chromosomes), t(17;19)(q23;p13), intrachromosomal amplification of chromosome 21 (iAMP21) or t(9;22)(q34:q11)/*BCR-ABL1*] were assigned to receive regimen C. Further details of the regimens and overall treatment protocols are provided in supplementary material.

CR was defined as marrow blasts <5% at day 29 of induction. MRD assessment of immunoglobulin and T-cell receptor antigen rearrangements was performed by real-time quantitative polymerase chain reaction in four laboratories in the UK and with central review of all results. MRD low-risk patients continued on regimen B and were randomly assigned (1:1) to receive one or two delayed intensifications (DI). MRD high-risk patients were randomly assigned (1:1) to continue with Regimen B with 2 DI or to transfer to the intensive Regimen C. Patients with high-risk disease and those not in CR at 29 of induction were not eligible for MRD stratification and randomization. Patients with bone marrow blast count ≥25% at day 29 or patients with high-risk cytogenetics with ≥5% blasts were eligible for an

allogeneic transplant (alloHSCT) in first CR. Treatment of relapse was at the discretion of the local treatment centre.

The UKALL 2003 trial protocol was approved by the Scottish Multi-Centre Research Ethics Committee and was registered with the International Standard Randomized Controlled Trial Number (ISRCTN) registry, number ISRCTN07355119.

Identification of relapsed patients

All patients who relapsed before 1st April 2015 after initial attainment of CR were identified using the central trial database, which also provided data regarding prognostic factors at presentation, MRD risk-group, treatment allocation, site of and time to relapse, and overall outcome. Individual treatment centres were then contacted and provided follow-up information subsequent to relapse. Clinical information gathered included salvage chemotherapy used, the response to salvage therapy, use of alloHSCT, overall outcome, last follow up, and where relevant, cause of death. The same definition of CR was used to define the response to salvage treatment. Data on patients relapsing before 1st April 2015 was censored at last follow-up prior to August 1st 2015.

Statistical analysis

Differences between groups were assessed using Fisher's exact test. Survival outcomes were analysed using the Kaplan-Meier method and log-rank test with P<0.05 considered significant.

Results

Demographics

UKALL 2003 registered 3126 patients eligible for analysis. Of these, 229 patients were TYA (aged 16-24 years at diagnosis) representing 7.3% of the total trial accrual. Six patients died within 35 days or never remitted and were deemed induction failures. Of the 223 patients achieving CR, 42 (18.8%) were identified from the central trial database as having relapsed. The outcome of these 42 TYA patients with ALL in first relapse is the focus of this study. The

median follow up from trial entry for the 9 patients alive at the end of the study period was 71 months (range 49 - 111), and the median follow-up from relapse was 50 months (range 11-69).

Time to relapse and overall survival according to clinical features at presentation and initial therapy received.

The median time from the initiation of chemotherapy to relapse was 17 months (range 2-68), with no difference between patients treated on regimen B or C (median 17 and 14 months respectively, P = 0.1)(Figure 1). This remained the case when the 3 patients receiving transplant in CR1 were excluded (median 18 and 15 months respectively, P = 0.1). Next we examined whether any of the known prognostic characteristics at presentation including sex, cytogenetics, immunophenotype, or the MRD risk group were related to the time to relapse and OS following relapse (Table I.) Only one patient who relapsed had had CNS disease at presentation meaning there were insufficient numbers for analysis. This patient with high-risk cytogenetics and high-risk MRD had an isolated BM relapse after 8 months but died less than one month post relapse having been refractory to salvage therapy.

There was no impact of sex on time to relapse. Patients with a higher white count at presentation or T cell disease relapsed earlier. This shorter time to relapse may be driven by the higher number of patients with T cell disease with higher WCC counts with 7 of 12 (58%) patients with T cell disease having WCC >50, compared to 8 of 30 (27%) with B cell disease although this did note reach statistical significance (P=0.08). Patients with good-risk CGN and low-risk MRD had a non-significant trend towards later relapse although the small numbers with such favourable disease profiles who ultimately relapsed limits the power of the analysis.

The median OS from relapse was 6.5 months with a 5-year OS of 23% (95% CI; 11-37%). The initial therapy received, sex, presenting WCC, and immunophenotype did not have an impact on OS (Table II). Patients with good-risk cytogenetics appeared to have longer OS following relapse that did not reach statistical significance. Median OS following relapse for good, intermediate, high, T-cell, and unknown cytogenetics were 39, 1, 7, 4.5, and 7 months respectively (P=0.3). There was a trend for patients with low risk MRD at the end of the first cycle of treatment to have longer OS following relapse. If the patients with indeterminate MRD

are excluded the median OS for high versus low MRD is 6 months v undefined respectively, HR 3.49 (0.95 - 12.85), P=0.06.

Clinical features and overall survival according to timing of relapse

Three patients relapsed following alloHSCT. Of the remaining 39 patients, 23 (59%) relapsed on active treatment, the majority of whom (17/23, 74%) relapsed during maintenance therapy. Of those relapsing following completion of therapy 8/13 (62%) relapsed within 6 months of the end of treatment date.

Response to salvage therapy

Salvage chemotherapy with curative intent was attempted in 38 of 42 patients (90%), with 20 (53%) attaining CR2 after one salvage treatment (Table II). Eight patients who failed to achieve a CR2 following first salvage received further treatment but only 2 additional remissions were achieved (overall CR2 22/38, 58%). Patients were more likely to achieve CR2 if relapse occurred following completion of chemotherapy rather than during therapy including maintenance (85% vs 42%, p=0.02)(Table III).

Twenty-one of the 22 patients achieving CR proceded to alloHCT, whilst 1 patient was treated according to the UK paediatric relapse regimen (ALL R3 protocol (Parker *et al*, 2010)) and remains in remission without transplant. Nine of these 22 patients remain alive with median follow up following relapse of 50 months (range 11-69 months); 8 in remission and 1 undergoing active treatment for further relapse. Five (24%) patients died of transplant related mortality (infection or graft versus host disease) and 9 (42.9%) patients relapsed post-transplant.

Survival following relapse

Patients relapsing on treatment had a significantly poorer survival than patients relapsing off treatment with a median survival of 5 months compared to a median not reached at the end of the study period (P=0.001 log-rank, HR 3.8 (1.7 to 8.4)), with OS at 3 years of 9% and 52% respectively (Fig 2A). The median survival for patients with precursor B phenotype relapsing on and off treatment was 5.5 months compared to a median not reached (*P*=.0002) log-rank

HR 5.0 (2.7-17.9) with 3-year OS of 0% and 57% respectively (Fig 2B). When only the patients achieving CR2 are assessed, patients who relapse on treatment still have inferior outcomes (median 10.5 months v median not reached, P=0.002), 3 year OS 10% v 54% (Fig 2C). There was no difference between the groups in the numbers of patients who attained CR2 subsequently receiving alloHCT 80% v 91%, P=0.6. The inferior outcomes for patients relapsing on treatment therefore result from both a failure to attain a CR2 and also a failure to survive following attainment of CR2, including post alloHCT.

Response to salvage an overall survival according to salvage regimen employed

The most commonly used first salvage regimens were the R3 protocol (n = 8), and protocols based on fludarabine and cytarabine (n = 17) (Table III). Both regimens were employed as a means of achieving a CR2 prior to alloHSCT with both regimens having equivalent efficacy (Table IV, Figure 3).

Discussion

This is the largest study of TYA patients with ALL relapsing following treatment on a paediatric risk-adapted protocol. Outcomes for TYA patients with ALL have undoubtedly improved with the wider use of paediatric inspired chemotherapy protocols which achieve a lower overall incidence of relapse (Boissel *et al*, 2003; de Bont *et al*, 2004; Hallbook *et al*, 2006; Ramanujachar *et al*, 2007; Lopez-Hernandez *et al*, 2008; Ribera *et al*, 2008; Stock *et al*, 2008; Usvasalo *et al*, 2008; Huguet *et al*, 2009; Hough *et al*, 2016). However, we demonstrate that if relapse occurs in this setting, the outcome is extremely poor, even though the majority of patients still have chemosensitive disease at relapse with a second CR achieved in 58% patients.

The outcome following relapse is similar to the smaller ALL-96 study in which 7 of the relapsed patients remained alive in CR2 (30.4%), 12 of 23 patients (52%) relapsed on treatment and only one of these patients attained a durable second remission (Ribera *et al*, 2008). However the age, cytogenetic risk, and immunophenotype of these patients is not reported, nor is the number in whom true salvage followed by alloHSCT was attempted or which salvage regimens were used. In the MRC UKALL12/ECOG 2993 adult study, the 5 year OS for relapsed patients aged <20 years was 12%(CI 6-18%) and for those aged 20-34 years

was 7% (CI 4-11%)(Fielding *et al*, 2007). In 229 adult patients aged 18-63 years, who relapsed on the GRAALL 2003/5 studies, 53% of patients achieved a CR2, but the overall survival at 2 and 5 years was only 19.3% and 13.3% respectively (Desjonqueres *et al*, 2016). As with our study, cure was more likely in those with a longer CR1 and in those who were able to proceed to transplant in CR2.

Together these data demonstrate that relapse in TYA patients treated with contemporary paediatric inspired ALL protocols is associated with an extremely poor prognosis, akin to that reported in adults. Although around 60% patients have chemosensitive disease at relapse, only a small proportion of patients will have a durable remission; primarily those with an off treatment relapse whose second CR is consolidated with an alloHSCT. Improving survival for the majority of patients will demand a) improving early detection of those destined to relapse and intervening with novel or escalated conventional therapy early to prevent relapse and b) improving therapy for those patients who do relapse, for example with the use of antibody based therapies or chimeric antigen receptor (CAR)-T cells with or without alloHCT.

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Authorship contributions

RH and RS designed the study and analysed the data

AV was the chief investigator of UKALL2003 and RH and CR were the national coordinators of this trial for the TYA age group

NG and CM were co-investigators for UKALL2003

AM analysed and provided cytogenetic data for UKALL2003 and this study

All authors evaluated the data and contributed to the preparation of the manuscript

Conflicts of interest

The authors declare no competing conflicts of interest.

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TABLE I. Characteristics of patients relapsing on and off active treatment (the 3 patients transplanted in CR1 are excluded)

Relapse Group		On treatment (n=26)	Off treatment (n=13)	Overall (n=39)
Sex	Female	6	6	12
	Male	20	7	27
White count	<50x10^9/l	15	11	26
	>50x10^9/l	11	2	13
CNS disease	Yes	1	0	1
	No	25	13	38
CGN risk group	Good	0	4	4
	Intermediate	10	3	13
	High	3	1	4
	T	9	1	10
	Unknown	3	4	7
Immunophenotype	B	16	12	28
	T	10	1	11
MRD risk group	Low	2	0	2
	Intermediate	8	3	11
	High	16	10	26
Regimen received	Regimen B	18	10	28
	Regimen C	8	3	11

First Relapse

		On treatment	Off treatment	
Treatment stage	Induction	0	NA	
	Consolidation	1	NA	
	IM1	1	NA	
	DI1	2	NA	
	IM2	3	NA	
	DI2	2	NA	
	Maintenance	17	NA	
Site of relapse	Isolated marrow	21	8	29
	Isolated extramedullary	3	3	6
	Combined	2	2	4

TABLE II. Time to relapse and OS following relapse according to presenting clinical features and initial treatment

Presenting Feature		No,	Time to relapse Median (range)	OS from relapse (months) Median (HR, 95% CI)
Sex	Female	14	12 (3 - 68)	8
	Male	28	17 (2 - 53) P=0.97	6 (0.76, 0.36 - 1.61) P=0.48
White count	<50x10^9/l	27	18 (2 - 68)	7
	>50x10^9/l	15	13 (7- 42) P=0.034	5 (0.78, 0.37 - 1.64) P=0.51
CGN risk group	Good	4	42 (30 - 47)	39
	Intermediate	6	12.5 (5 - 53)	1
	High	13	17 (2 - 68)	7
	T	12	14 (6 - 41)	4.5
	Unknown	7	28 (10 - 45) P=0.1	7 P=0.3
Immunophenotype	B	30	17.5 (2 - 68)	7
	T	12	14 (6 - 41) P=0.032	4.5 (0.74, 0.33- 1.67) P= 0.47
MRD risk group	Low	2	17.5 (12 - 13)	Undefined
	Indeterminate	12	11.5 (2 -53)	4.5
	High	28	12.5 (3 - 68) P=0.49	6 P=0.16
Regimen received	Regimen B	29	17 (3 - 68)	7
	Regimen C	13	14 (2 -41) P=0.098	6 (0.97, 0.45- 2.10) P=0.94

TABLE III. Salvage treatments employed following relapse and overall response

Relapse Group		On treatment (n=26)	Off treatment (n=13)
1st Salvage given	R3	7	1
	Flu/Ara-C based	12	5
	Clo/Cyclo/Etop	1	2
	Nelarabine based	1	1
	Other ⭘	3	4
	None	2	0
Response to 1st	CR2	10	9
	Refractory	10	4
	NRM	3	0
	Unknown ⊙	1	0
2nd salvage given	R3	0	1
	Flu/Ara-C based	2	2
	Cyclo/Etop based	1	1
	Nelarabine based	1	0
	None	6	0
	NA	14	9
Response to 2nd	CR2	0	1
	Refractory	3	2
	NRM	0	0
	Unknown	1	1
CR2 ever		10	11
Allograft post salvage*		11	10

⭘ Other includes 1 patient treated with single agent Clofarabine,, 1 MARALL study receiving Veltuzumab and Epratuzumab, 1 Blinatumamb, 1 intrathecal + high-dose methotrexate, 1 UKALL2011 induction, 1 UKALL12 induction, and 1 HyperCVAD).

⊙Unknown response to salvage treatment includes one patient whose disease was never reassessed, and 2 patients that had empty marrows on assessment but with no evidence of disease but with no normal haematopoiesis or count recovery.

*Three patients who achieved CR2 did not receive a transplant, one because this was a post-transplant relapse, one because there were concerns of toxicity (trisomy 21 without a sibling donor), and one because of disseminated tuberculosis. Two patients went into transplant pancytopenic without definitive CR2.

Abbreviations: IM1, interim maintenance 1; IM2, interim maintenance 2; DI1, delayed intensification 1; DI2, delayed intensification 2; R3, R3 protocol containing either idarubicin or mitoxantrone described previously(Parker *et al*, 2010); Flu, fludarabine; Ara-C, cytosine arabinoside; Clo, Ccofarabine; Cyclo, Cyclophosphamide, Etop, etoposide; CGN, cytogenetic; MRD, minimal residual disease; CR, second complete remission; NRM, non-relapse mortality.

TABLE IV. Comparison of R3 and fludarabine/cytarabine based regimens

	R3	Fludarabine/Cytarabine	
<u>All relapsed patients</u>	(n=8*)	(n=17)	
CR after first salvage	4 (50%)	7 (41%)	
Allogeneic transplant received	3(38%)	8 (47%)	
Alive at end of study period	1 (13%)	5 (29%)	
Median OS from relapse	5.5 months	7 months	P=0.4
<u>Patients relapsing on treatment only</u>	(n=7)	(n=12)	
CR after first salvage	3 (43%)	5 (42%)	
Allogeneic transplant received	3 (43%)	5 (42%)	
Alive at end of study period	1 (14%)	1 (8%)	
Median OS from relapse	5 months	3 months	P=0.9

* Excludes one patient transplanted in CR1 and who died of progressive disease
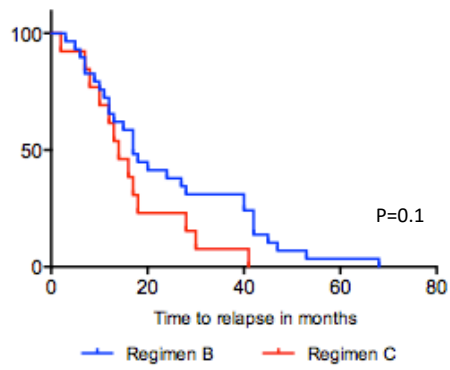
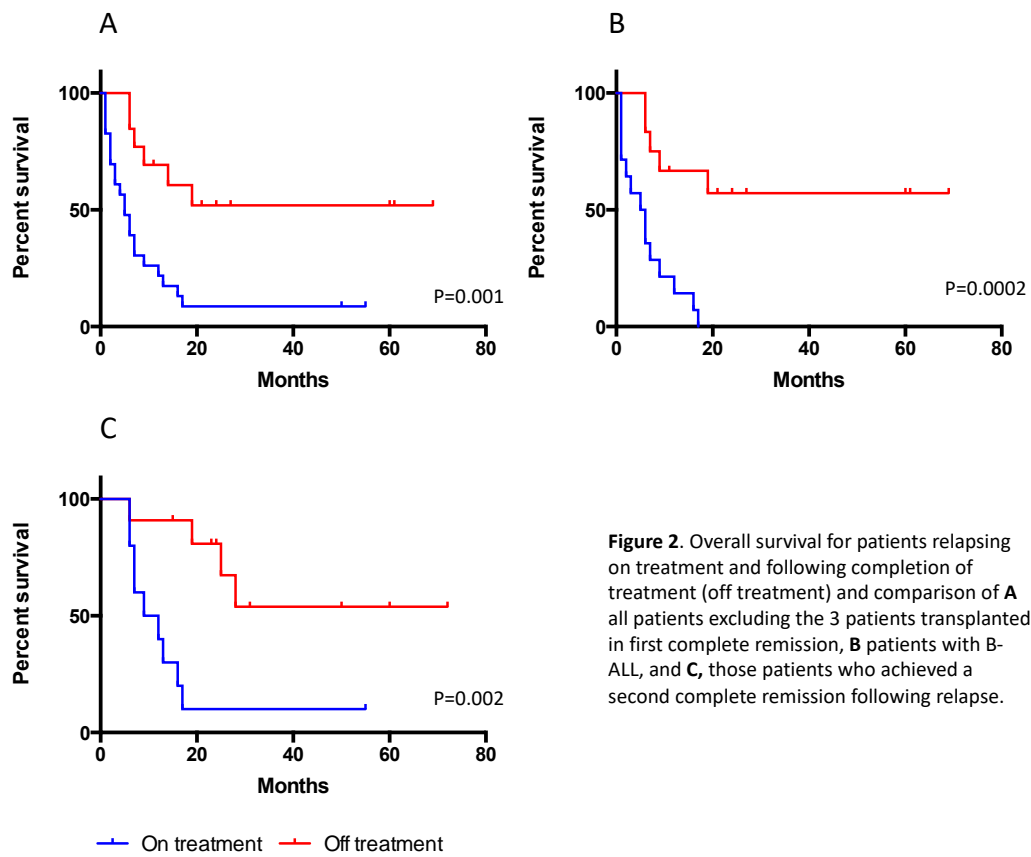**Figure 1**. Time to relapse according to treatment regimen received

A

B

C

Figure 2. Overall survival for patients relapsing on treatment and following completion of treatment (off treatment) and comparison of **A** all patients excluding the 3 patients transplanted in first complete remission, **B** patients with B-ALL, and **C,** those patients who achieved a second complete remission following relapse.
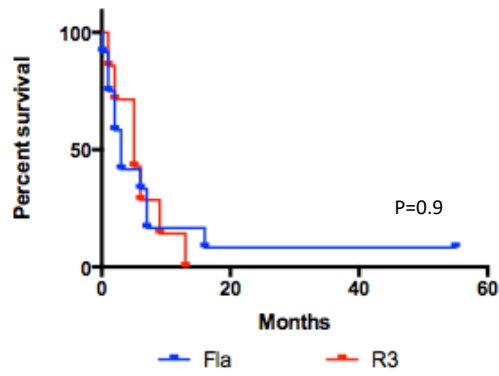
On treatment   Off treatment

18

Figure 3. Overall survival for patients relapsing on treatment and following completion of treatment (off treatment) according to initial salvage regimen received, fludarabine/cytarabine (Fla) or R3.