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Journal

Cancer, 122(16)

ISSN

1097-0142

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Publication Date

2016-08-15

DOI

10.1002/cncr.30069

Peer reviewed

HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2018 May 31.

Published in final edited form as:

Cancer. 2016 August 15; 122(16): 2505–2511. doi:10.1002/cncr.30069.

Outcomes of patients with CLL treated with first line idelalisib plus rituximab after cessation of treatment for toxicity

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Abstract

Background—More active therapies are needed for older and unfit patients with CLL who are not eligible for chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab. The PI3Kδ inhibitor idelalisib is effective in treatment-naïve and relapsed/refractory patients with CLL as monotherapy and in combination with rituximab, but can be associated with treatment-limiting adverse events, particularly diarrhea/colitis. The outcomes for patients ceasing treatment for adverse events have not been previously described.

Methods—We analyzed long-term follow-up data on 40 patients treated at MD Anderson Cancer Center on a phase II study of idelalisib plus rituximab for treatment-naïve patients ≥65 years of age.

Results—In patients permanently ceasing treatment due to toxicity, time to subsequent disease progression to treatment according to baseline characteristics was analyzed. Fifteen patients permanently ceased therapy due to toxicity (PCT_{TOX}), most commonly diarrhea/colitis (n=7), at a median time of 11 months after commencing treatment. PCT_{TOX} was associated with a higher risk of subsequent disease progression [HR 6.61 (1.77–16.15)] relative to that seen in patients who remained on therapy. Ten patients subsequently progressed and 7 required salvage therapy; 5 patients remain progression-free at a median of 23.3mo (range 8.5–28.6mo). Patients who were ZAP70 positive showed more rapid disease progression post-treatment cessation (p=0.048). There were no CLL-related deaths.

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Disclosures:

JAB has received Honoraria, served as a consultant and received research funding from Gilead Sciences. SMO has served as a consultant and received research funding from Gilead Sciences and Genentech. WGW has received honoraria, served as a consultant and received research funding from Gilead Sciences and Genentech.

Author contributions:

PAT provided clinical care to patients, developed critical themes, collected and analyzed data and wrote the paper; FS performed statistical analysis and co-wrote the paper; MJK, AF, JAB, WGW and TMK provided clinical care to patients, developed critical themes and co-wrote the paper; SOB designed and analyzed the clinical trial, provided clinical care to patients, developed critical themes and wrote the paper.

Conclusions—PCT_{TOX} is the major determinant of PFS in patients receiving first-line idelalisib-based treatment; However, a subgroup of patients with favorable biologic characteristics have prolonged PFS, even after PCT_{TOX}. The absence of CLL-related deaths indicates that salvage treatment is generally successful after PCT_{TOX}.

Keywords

Idelalisib; rituximab; toxicity; disease-free survival; remission; CLL

Introduction

More active therapies are needed for older and unfit patients with chronic lymphocytic leukemia (CLL). The combination of fludarabine, cyclophosphamide and rituximab (FCR) improved response rates and survival in younger, fitter patients,[1] but is poorly tolerated by older patients and those with co-morbidities. Obinutuzumab plus chlorambucil was the first treatment which improved survival, compared to chlorambucil monotherapy, in older and unfit patients; however, the median progression-free survival (PFS) was still relatively short at 29 months.[2]

Phosphyotidylinositol-3-kinase delta (PI3Kδ) expression is found only within hematopoietic cells and plays a critical role in regulation of B cell homeostasis and function, transducing signals from the B cell receptor (BCR) and CD40 ligand.[3] Sustained activation of the (PI3Kδ)-Akt pathway is essential for CLL cell survival. Mice with inactivating PI3Kδ mutations have reduced numbers of B cells, reduced immunoglobulin levels, and immune dysregulation. They demonstrate hypoactive responses to immunization, defective BCR and CD40 signaling and can develop inflammatory bowel disease.[3–5] The PI3Kδ inhibitor idelalisib (CAL101, GS-1101) inhibits PI3Kδ signaling *in vivo*, abrogates proliferation in response to IgM crosslinking, and reduces proliferation in response to anti-CD40, IL-4 and LPS.[4]

Idelalisib is effective in treating relapsed/refractory CLL as monotherapy[6] and in combination with rituximab.[7] In the relapsed/refractory (R/R) setting, therapy is well tolerated, with treatment cessation due to adverse events (AEs) in <10% of patients. A pivotal phase III study in relapsed/refractory CLL compared rituximab plus idelalisib 150mg BID to rituximab plus placebo and demonstrated a survival advantage for the patients receiving idelalisib. The most frequent events leading to treatment cessation in the idelalisib arm were rash and diarrhea (+/− colitis), but overall treatment cessation due to AEs was no more frequent than in the rituximab monotherapy comparator arm.[7]

Given the excellent efficacy and tolerability of idelalisib in R/R CLL, the combination of idelalisib plus rituximab was evaluated in a 64 patient phase II study for previously untreated patients over 65 years of age. The results of this study were previously reported.[8] Forty patients were treated at our center and our experience suggested that treatment cessation due to adverse events (AEs), particularly late-onset diarrhea/colitis, was more frequent than reported in the R/R population. Recent data from a first line study using idelalisib monotherapy for two months followed by the addition of atumumab have also shown a very high rate of early-onset hepatitis, as well as other presumed immunologic AEs, such as

colitis and pneumonitis.[9] The mechanisms underlying the adverse events are not well characterized, but T-cell infiltrates are seen in affected organs; this, combined with responses to corticosteroids +/− immunosuppressive therapy[8, 9] argues for a probable immunologic mechanism underlying the hepatitis, colitis and pneumonitis seen in patients treated with idelalisib-based regimens. We reviewed our experience to characterize the frequency and nature of AEs leading to treatment cessation and subsequent outcomes of patients who permanently ceased therapy due to toxicity (PCT_{TOX}), with a particular emphasis on PFS after PCT_{TOX}.

Methods

Full study eligibility criteria were previously outlined.[8] Briefly, patients were eligible for this study if they were treatment-naïve, had an indication for treatment according to IWCLL 2008 criteria,[10] were aged ≥65 years, had a WHO performance status ≤2 and adequate organ function. All patients gave informed consent and the study was conducted according to the Declaration of Helsinki.

We reviewed study records and the electronic medical records of the 40 patients treated at UT MD Anderson Cancer Center to determine response rates, reason for study cessation, progression-free survival (PFS), overall survival (OS) and TTP after PCT_{TOX}. Responses were assessed according to IWCLL criteria.[10] PFS was defined as the time from study initiation to documented disease progression as defined by IWCLL 2008 criteria,[10] initiation of alternative salvage treatment, or death from any cause. Progressive disease was defined according to IWCLL 2008 criteria and PFS after PCT_{TX} was defined as time from cessation of idelalisib to death from any cause, disease progression according to IWCLL 2008 criteria, or initiation of alternative salvage treatment.

Statistical analyses were performed using R version 3.0.3 and SPSS version 22 (IBM Corp, Armonk, New York). Descriptive statistics were used to summarize patient characteristics. Univariable survival analyses were performed using the method of Kaplan and Meier[11] and difference between groups for each variable assessed using the log-rank test.[12] A multi-stage model with three stages (treatment, PCT_{TOX} and disease progression) was implemented to study disease progression and the intermediate effect of early PCT_{TOX}. Transition-specific hazards were modeled with proportional hazard Cox models. Cumulative baseline hazard curves are shown for all three possible transitions (baseline-to- PCT_{TOX}, baseline-to-progression, PCT_{TOX}-to-progression). Given the small sample size and the small number of events, no multivariable analysis was performed. Additionally, given the small numbers of events, we did not attempt to identify baseline disease or patient-specific factors associated with greater likelihood of PCT_{TOX}, or PFS. However, we did evaluate the relationship between baseline immunologic parameters and PCT_{TOX} using linear regression analysis.

Results

40 patients were enrolled between March 2011 and February 2012. Baseline characteristics are shown in Table 1.

Response rate, PFS and survival

Median follow-up for surviving patients from the start of idelalisib therapy is 36 months (18–43mo). Median PFS for the entire cohort has not been reached. Seventeen of 40 patients remain on therapy and 23 of 40 are currently progression-free (Figure 1). The reason for permanent cessation of therapy (PCT) was toxicity in 15 patients, death in remission in 4, progressive disease in 2, primary refractory disease in 1 and transfusion-dependent pure red cell aplasia in 1. Only 2 patients developed progressive disease while remaining on treatment at 28.3 and 37.5 months of treatment. Ten of 15 patients who experienced PCT_{TOX} subsequently progressed or received salvage therapy.

The overall response rate (ORR) for the 40 treated patients was 95%; the complete remission (CR) rate was 14.7%. Median PFS and OS have not been reached in surviving patients (Figure 1). There was a trend toward a lower CR rate in patients with Rai stage III-IV disease (p=0.064), but there were no significant associations between other baseline prognostic characteristics and ORR or CR rate. Median PFS and OS have not been reached in surviving patients (Figure 1). Among the total cohort, there was a trend toward inferior PFS in those patients with unmutated immunoglobulin heavy chain variable gene (*IGHV*) compared to those with mutated *IGHV* (median 24.9mo vs not-reached (NR), p=0.077). There was no association between the presence of del(17p) or del(11q), age >70, Rai stage III-IV disease, ZAP70 expression or bulky lymphadenopathy and PFS or OS.

Adverse events leading to permanent cessation of treatment

Sixteen of 40 patients permanently ceased study treatment due to AEs, including 1 patient who died from pneumonitis. AEs leading to PCT_{TOX} were as follows: diarrhea/colitis (n=7), pneumonitis (n=4, 1 case fatal), abnormal liver function tests (n=1), rash (n=1), abdominal pain (n=1), fatigue (n=1) and recurrent infections (n=1) Median time to PCT_{TOX} was 11mo (0.9–22.1). The patient that developed fatal pneumonitis after 3 months of treatment could not be assessed for time-to-progression post-treatment cessation. Diarrhea/colitis was predominantly a late event with a median time to PCT_{TOX} for colitis of 11.3mo (7.3–22.1). Five of 7 patients who permanently ceased treatment for diarrhea had a colonoscopy with biopsies performed. Macroscopic evidence of pancolitis was seen in 4 of 5 patients. Colonic biopsies in these 4 patients showed lymphocytic infiltration in the epithelium, colonic glands and the lamina propria. Immunohistochemistry was performed in 3 of 4 cases to evaluate the lymphoid infiltrate and in all cases the lymphocytes were CD3-positive T cells.

All five deaths that occurred during the study were in patients in at least partial remission (sepsis in 2 patients, myocardial infarction in one and pneumonitis in one); the pneumonitis-related death was thought to be treatment-related. One patient with numerous co-morbidities stopped idelalisib and rituximab due to severe fatigue after only 3 months of treatment. He died suddenly from unknown causes 2 years after PCT_{TOX}; he was being treated with ibrutinib (PCI 32765) plus rituximab at the time of his death and had achieved a durable partial response with this therapy.

Given the possible immunologic mechanism underlying the observed toxicity, we evaluated immunologic parameters at baseline to see whether there was any correlation between these

and PCT_{TOX}. 14 patients had quantitation of T-cell subsets at baseline; this was not mandated per protocol and was performed according to individual investigator practice. There was a wide range of baseline T-cell counts [median CD4 count 2206/microL (range 466–8797), median CD8 count 1530 (range 222–11053)]. Only 3 patients who had T-cell subsets quantitated developed PCT_{TOX}, so conclusions regarding the relationship between these numbers and PCT_{TOX} cannot be drawn. Immunoglobulin levels also varied widely at baseline: median IgG was 833mg/dL (range 380–3840); median IgA 101mg/dL (range 6–527); median IgM 44mg/dL (range 4–405). There was no association between IgG levels (R^2 0.03, p=0.84), IgA levels (R^2 0.05, p=0.73) and IgM levels (R^2 0.10, p=0.78) and likelihood of PCT_{TOX}.

Time-to-progression and survival outcomes after permanent treatment cessation for toxicity

Median time-to-progression (TTP) after PCT_{TOX} was 17.2mo (figure 1); 5 patients remain progression-free at a median of 23.3mo (range 8.5–28.6mo). Of these patients, 1 was in CR and 4 in PR; 3 patients with PR had persistent marrow and nodal disease and 1 did not have a bone marrow biopsy for response assessment due to early treatment cessation at 3 months. All patients had an absolute lymphocyte count <5000/microL, with peripheral blood MRD of 1–10%, and normalization of hemoglobin, platelets and neutrophil counts. Of these 5 patients, 4 had PFS of >23 months (1 only 8.5 months); all 4 of these patients with prolonged follow-up and highly-durable responses post-PCT_{TOX} received ≤12 months of treatment. In all 4 patients, the CLL cells were ZAP70 negative and 3 of 4 had a mutated *IGHV*; all had Rai stage I or II disease and none had bulky lymphadenopathy (≥5cm) at baseline; none had del(11q) or del(17p) on FISH. ZAP70 positivity was associated with an increased risk of progression after PCT_{TOX} (p=0.048); unmutated *IGHV* gene was associated with a trend toward increased risk of progression (p=0.09), figure 2. No other pre-treatment variables were associated with risk of progression post-PCT_{TOX}. Multivariable analysis could not be performed due to small numbers. There was also no difference in TTP according whether PCT_{TOX} related to presumed immune-mediated toxicity (defined as colitis, pneumonitis or hepatitis) or to other causes (figure 2D). The duration of treatment prior to PCT_{TOX} (<11mo vs ≥11mo) did not impact PFS after cessation (p=0.169, data not shown). The cumulative baseline hazard curves for PFS and OS, with 95% confidence intervals, are shown in Figure 1.

A multi-stage model (Figure 1) was used to understand whether early treatment termination due to toxicity had an effect on PFS. This effect was measured by a coefficient associated with a time-dependent covariate in a Cox proportional hazards model. The cumulative hazard of progression after PCT_{TOX} was compared to the cumulative hazard of progression in patients continuing idelalisib. Early PCT_{TOX} resulted in a statistically significantly (p<0.001) higher risk [HR=6.61 (1.77–16.15)] of developing disease progression relative to that seen in patients receiving continuous idelalisib therapy. Given the small number of deaths in the study, no analysis of the effect of early treatment cessation on survival could be made.

Subsequent treatment and response

Seven of 15 patients have had subsequent salvage therapy after PCT_{TOX}. Subsequent treatment and responses are shown in Table 2. Treatment was heterogenous and follow-up limited. Eight of the 15 patients remain treatment-free, at a median of 19.7mo after PCT_{TOX} (range 8.5–28.6mo); of these, five are progression-free.

Discussion

Idelalisib and rituximab is a highly efficacious regimen for older, treatment-naïve patients with CLL and is associated with an ORR of 95% and favorable PFS and OS. Our results are notable for a higher rate of PCT_{TOX} than in the relapsed/refractory setting; 16/40 (40%) of patients permanently ceased therapy due to AEs, compared to 8–12.9% in the relapsed/refractory patients.[7, 13] Particularly noteworthy is that 7 of 40 patients in this study permanently ceased treatment due to diarrhea/colitis and an additional 3 patients due to presumed treatment-related pneumonitis, which was fatal in 1 patient. Pan-colitis with lymphocytic infiltration of the colonic mucosa and glands was demonstrated in 4 of 5 patients who had a colonoscopy for investigation of non-infectious diarrhea/colitis. The lymphocytes were shown to be predominantly T cells in all 3 patients where immunohistochemistry was performed. The mechanism for colitis and pneumonitis in idelalisib-treated patients is not well-characterized and is an important area for research. However, the delayed onset, presence of a T cell infiltrate in colitis, and the response to corticosteroids in both colitis and pneumonitis suggests an immunologic mechanism. Additionally, the increased frequency of presumed immunologic adverse events in the first line setting may be due to the patients in this setting having more intact cellular immunity, although this remains speculative.

We were interested in characterizing the durability of responses after PCT_{TOX}. Patients with PCT_{TOX} had a higher risk of disease progression. Nonetheless, a subset of patients had durable remissions after early PCT_{TOX}; 8 of 15 patients with PCT_{TOX} have yet to require salvage therapy, at a median time of 17.2 mo post-PCT_{TOX}, and 4 patients remain progression-free 22.2–28.6 months after PCT_{TOX}. It appeared the major influence on TTP after PCT_{TOX} was the underlying biological characteristics of the disease rather than duration of therapy. Statistical power was limited, given small numbers; however, patients with durable treatment-free intervals appeared to generally have low-risk features (*IGHV* unmutated, ZAP70 negative, Rai stage I or II disease). There was no difference in response rate according to baseline characteristics (data not shown); thus it seems most likely that the reason for prolonged treatment-free interval after PCT_{TOX} in patients with low-risk biological features relates to a slower lymphocyte doubling time in these patients rather than deeper initial responses. These findings will require confirmation in larger groups of patients. Subsequent therapy at progression after PCT_{TOX} was highly heterogenous and conclusions regarding the most effective treatment in this setting will require systematic investigation in larger groups of patients.

Our data differ somewhat from those presented by Lampson et al.[9] That study was noteworthy for a very high rate of early grade ≥3 hepatitis (57% of patients), presumably immune-mediated, but with a lower rate of colitis (14%) than in our study. Twenty-three

percent of patients in the published idelalisib plus rituximab first line study developed grade ≥3 transaminitis.[8] However, most of these patients were successfully re-challenged with idelalisib and therefore did not appear in our analysis, which focused on outcomes of patients who permanently ceased idelaisib for toxicity. The study presented by Lampson et al had a short median follow-up of only 8 months; colitis is a late AE (median time to onset of 11.3 months in our data). Thus, differences in follow-up duration may be responsible for the apparent differences in observed toxicity; however, we cannot exclude that the specific schedule of administration (idealisib monotherapy for two months, followed by addition of ofatumumab in the study from Lampson et al vs concurrent idelalisib and rituximab administration in our study) may have contributed to the observed differences in AE frequencies.

PCT_{TOX} was the single most important determinant of duration of response in this study, rather than the development of disease resistance during therapy, which was rare; patients who developed toxicity leading to permanent treatment cessation had a higher risk of subsequent disease progression than those remaining on therapy. Immunologic toxicity associated with idelalisib in the front line setting thus appears to be the major barrier to durable remission, rather than development of refractory disease. However, despite the importance of PCT_{TOX} in determining subsequent PFS, a number of patients, generally those with favorable biological characteristics, achieved prolonged remission duration with subsequent therapy. In addition, there were no disease-related deaths in the patients permanently ceasing treatment due to toxicity who subsequently progressed, indicating that such patients are generally able to successfully receive salvage therapy. Developing appropriate strategies to predict and/or manage therapy-related toxicity is essential to maximize the therapeutic potential of this combination. Athough toxicity is thought to be immune-mediated, the mechanisms for toxicity are poorly defined and may not be the same for each type of toxicity. Better characterization of these mechanisms may both allow more specific management of toxicity to allow better selection of patients for such therapy and/or management of toxicity in order to allow patients to remain on therapy longer.

Acknowledgments

The authors would like to thank Ms. Susan Smith for her assistance with data management.

Funding:

PAT received funding from CLL Global Research Foundation and the Haematology Society of Australia and New Zealand.

This work was funded, in part, by the M.D. by the MD Anderson Cancer Center Support Grant P30 CA016672.

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Key Points

1. Toxicity, likely immunologically-mediated, is the major limitation to achieving long-term remission during first line treatment with idelalisib plus ritixumab for CLL.
2. Overall survival is favorable, despite the high rate of treatment cessation due to toxicity.

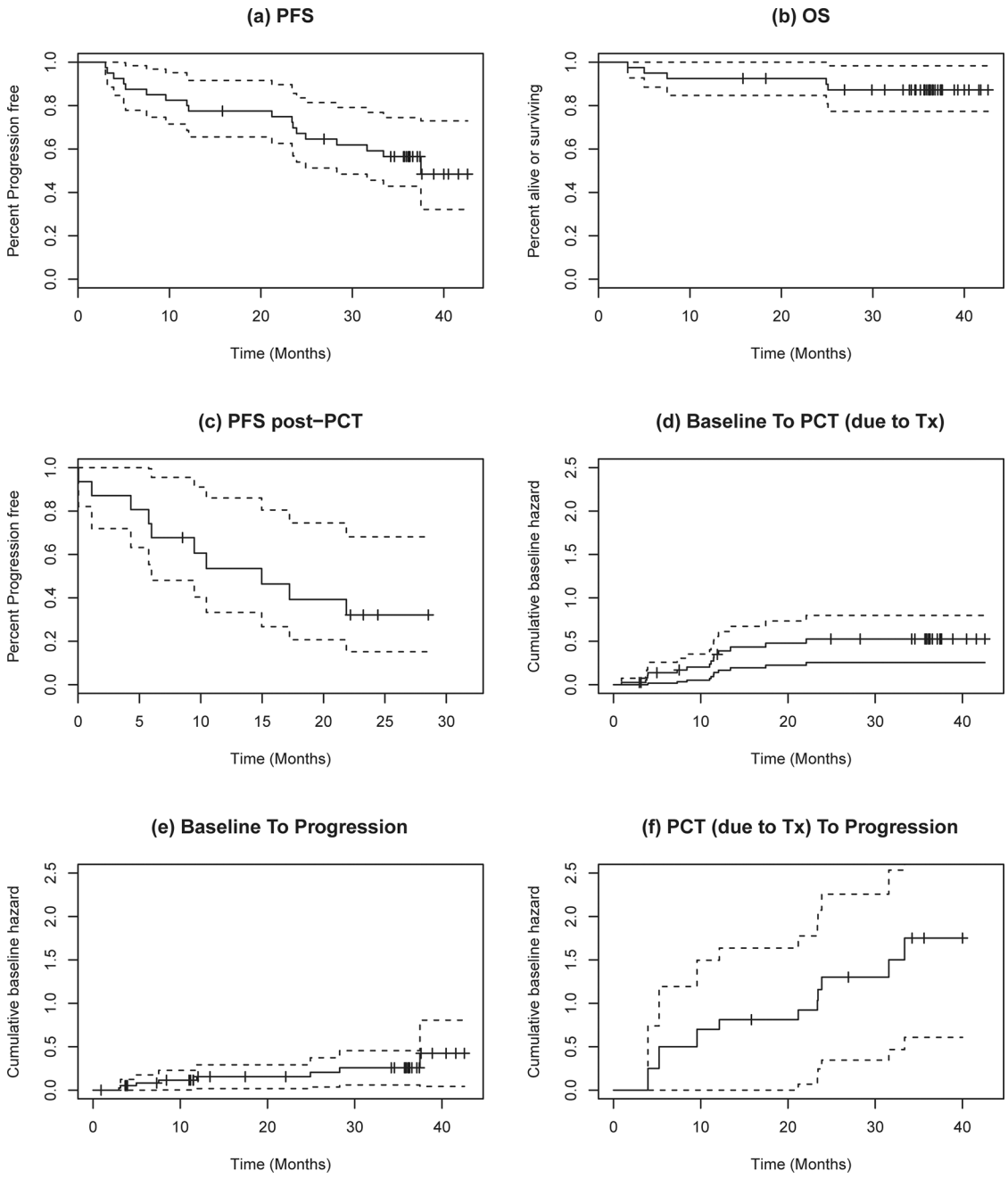

Figure 1.

A. Progression-free survival (PFS) and 95% confidence interval for the 40 patient cohort. B. Overall survival (OS) and 95% confidence interval for the 40 patient cohort. C. Time-to-progression (TTP) after permanent treatment cessation for toxicity (PCT_{TX}). D. Cumulative hazard for $PCT_{TX.}$ E. Cumulative hazard for progression in the absence of PCT_{TX}. F. Cumulative hazard for progression following PCT_{TX} relative to patients who remained on idelalisib.

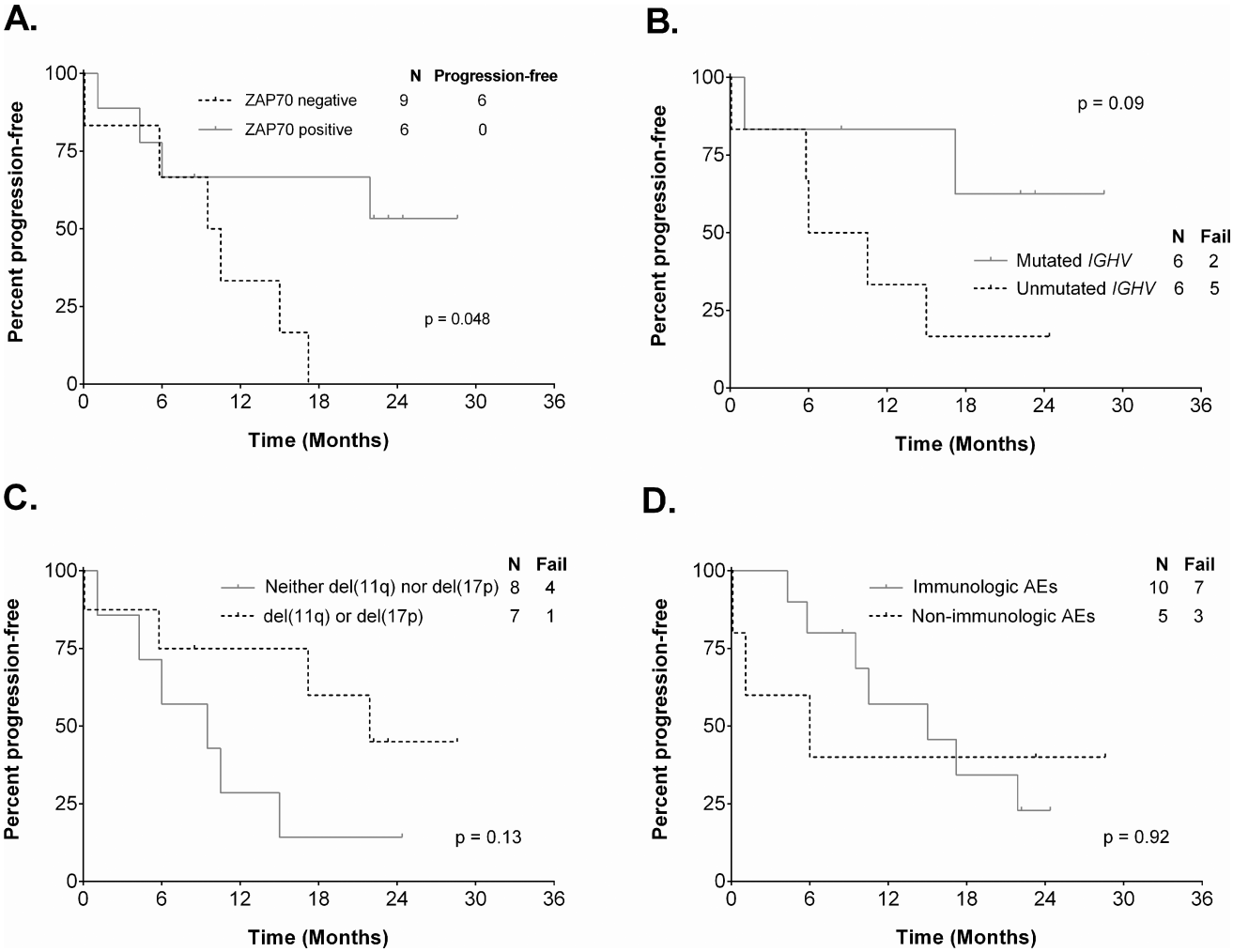

Figure 2.

A. Time-to-progression (TTP) after permanent treatment cessation for toxicity (PCT_{TOX}) according to ZAP70 positivity vs negativity. B. TTP after $PCT_{TOX,}$ according to *IGHV* mutation status. C. TTP after PCT_{TOX} according to high-risk cytogenetics vs not. D. TTP after PCT_{TOX} according to whether the toxicity that led to treatment cessation was immunologic or not.

Table 1

Baseline characteristics.

Variable (N=40 unless stated)	Number (%)
Male gender	28 (70)
Age, median (range)	70 (65–90)
Rai stage III–IV disease	15 (37.5)
β_2-microglobulin mg/L, median (range), n=39	3.7 (2.0–7.4)
B2M ≥4.0, n=39	14 (35.9)
ZAP70) positive	24 (60.0)
FISH, n=39	
del(13q)	7 (18)
Negative	8 (21)
Trisomy 12	10 (26)
Del(11q)	8 (21)
Del(17p)	6 (15)
Complex metaphase karyotype, n=27	3 (11.1)
Unmutated *IGHV*, n=34	20 (58.8)
Bulky lymphadenopathy ≥5cm	4 (10)

Abbreviations: *IGHV*, immunoglobulin heavily chain variable; FISH, fluorescence *in situ* hybridization; ZAP-70, Zeta-associated protein-70.

Table 2

Subsequent treatment and response.

Treatment	Number of patients	Responses
Rituximab monotherapy	2	NR*, NR
TRU16 + rituximab	1	NR
Ibrutinib + rituximab	1	PR
Ibrutinib monotherapy	1	PR with lymphocytosis
Fludarabine + rituximab – 6 cycles	1	Unknown
Fludarabine, bendamustine and rituximab - 3 cycles	1	CR, MRD negative.

Abbreviations: CR, complete response; MRD, minimal residual disease; NR, No response; PR, partial response.