

Idelalisib at the Crossroads of B-Cell Lymphoproliferative Disorders

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ABSTRACT

Phosphatidylinositol 3-kinases (PI3Ks) are considered as lipid kinases that are very active in the pathobiology of lymphoproliferative disorders (LPDs). Idelalisib, a selective inhibitor of the delta isoform of PI3K, provides significant clinical efficacy and has an acceptable side-effect profile in the treatment of B-LPDs. The aim of this review is to outline the pharmacobiological basis of idelalisib that is located at the crossroads of B-LPDs. The PI3K signaling pathway with downstream targets including Akt is involved in hematologic malignancies and lymphomas. Idelalisib has been most widely studied in chronic lymphoid leukemia (CLL) and B-lymphoma. The activity of idelalisib in high-risk FL with early relapse following front line immunochemotherapy was recently shown. The unique immunological toxicity pattern of idelalisib was also described in this review. Further clinical investigations will help for the better selection of the subsets of the patients with B-LPD that would be best candidates for the clinical utilization of idelalisib. Other indications such as marginal zone lymphoma, mantle cell lymphoma, Waldenström's Macroglobulinemia and other B-cell disorders could likely to be expanded. Future clinical and experimental data combined with the next-generation genomics strategies and personalized medicine for the treatment of malignant disorders will enlightened us for better placement of idelalisib in the treatment algorithm of the patients.

Keywords: Idelalisib, B-cell, Lymphoproliferative disorders

ÖZET

B-Hücreli Lenfoproliferatif Hastalıkların Dönüm Noktası İdelalisib

Fosfatidilinositol 3-kinaz (PI3K)'lar lenfoproliferatif hastalıklar (LPH)'in patobiyojisinde oldukça aktif olan lipid kinazlardandır. PI3K'nin delta izoformunun selektif bir inhibitörü olan İdelalisib, B-LPH'in tedavisinde önemli klinik etkinlikle beraber kabul edilebilir bir yan etki profiline sahiptir. Bu derlemede, B-LPH'in dönüm noktasında yer alan İdelalisib'in farmakobiyolojik temeli vurgulanmaya çalışılmıştır. Hematolojik malignansi ve lenfomalarda, Akt'yi de içeren PI3K yolağındaki hedefler rol almaktadır. İdelalisib yaygın olarak kronik lenfositik lösemi ve B-lenfoma çalışmalarında araştırılmıştır. İdelalisib'in ilk sıra immünokemoterapi ardından erken relaps olan yüksek riskli foliküler lenfoma hastalarındaki etkinliği son zamanlarda ortaya konmuştur. Bu derlemede ayrıca İdelalisib'in benzersiz immünolojik toksite paterni de ele alınmıştır. İlerdeki klinik araştırmalar, İdelalisib'in klinikteki kullanımı için aday olacak B-LPH hastalarının seçiminde yardımcı olacaktır. İdelalisib'in genişletilmiş endikasyonları arasında marjinal zon lenfoma, mantle hücreli lenfoma, Waldenström Makroglobinemi ve diğer B-hücreli hastalıklar sayılabilir. Gelecekteki klinik ve deneysel verilerin yeni nesil genomik stratejileri ile birleştirilmesi ve malign hastalıkların tedavisinde kişiselleştirilmiş ilaçların gelişimi, İdelalisib'in hastaların tedavi algoritmasındaki yerinin belirlenmesini sağlayacaktır.

Anahtar Kelimeler: İdelalisib, B-hücre, Lenfoproliferatif hastalıklar

INTRODUCTION

Phosphatidylinositol 3-kinases (PI3Ks) are considered as lipid kinases that are very active in the pathobiology of lymphoproliferative disorders (LPDs).¹ PI3Ks regulate diverse cellular processes including proliferation, adhesion, survival, and motility in LPDs. Thus, dysregulated PI3K pathway signaling occurs in the majority of the LPDs (1). Idelalisib, a selective inhibitor of the delta isoform of PI3K, provides significant clinical efficacy and has an acceptable side-effect profile in the treatment of B-LPDs.² The aim of this review is to outline the pharmacobiological basis of idelalisib that is located at the crossroads of B-LPDs. Targeted therapy of B-LPDs promise a chemotherapy-free future for the patients based on the results for the current clinical trials.^{3,4} Idelalisib will shape the future clinical landscape of B-cell malignancies.⁵ The recently approved small molecule kinase inhibitors are effective treatment options for elderly LPD patients with decreased tolerance for aggressive regimens and in patients with poor prognostic features who do not benefit from conventional chemoimmunotherapy regimens.⁶

Idelalisib, PI3Ks and B-lymphoproliferative Disorders

The PI3K signaling pathway with downstream targets including Akt is involved in hematologic malignancies and lymphomas. The development of PI3K inhibitors, particularly idelalisib, directed toward this pathway with confirmed clinical efficacy.⁷ The importance of the PI3K signaling pathway, main location for idelalisib, in B-LPDs is depicted in Figure 1.

Idelalisib in Chronic Lymphoid Leukemia

Idelalisib has been most widely studied in chronic lymphoid leukemia (CLL) and B-lymphoma in numerous clinical trials.^{5,6,8-17} Recently published mature results of the initial treatment of CLL with idelalisib plus rituximab demonstrated that the combination is extremely effective with manageable toxicity in older CLL patients.^{15,18}

O'Brien et al presented the first clinical trial of idelalisib with rituximab for the initial therapy of CLL in patients with a median age of 71 years, 42% of whom had advanced-stage disease.¹⁵ The overall

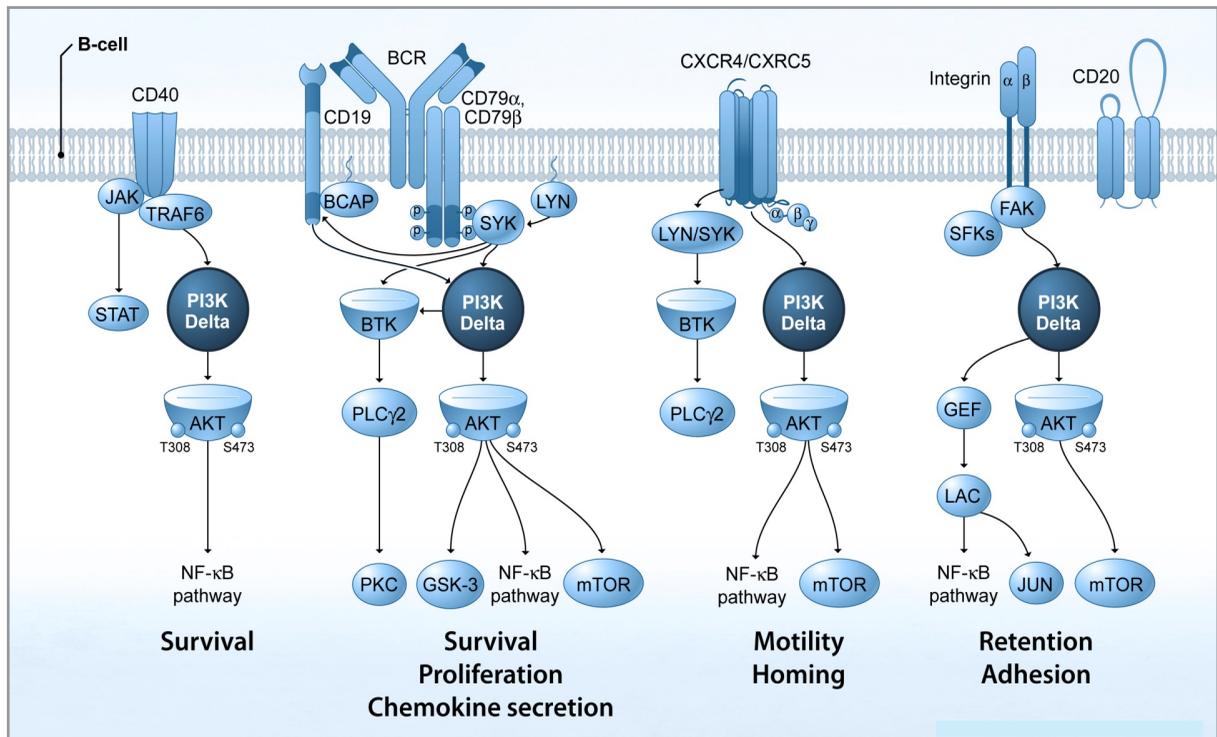


Figure 1. The importance of the PI3K signaling pathway in B- lymphoproliferative disorders

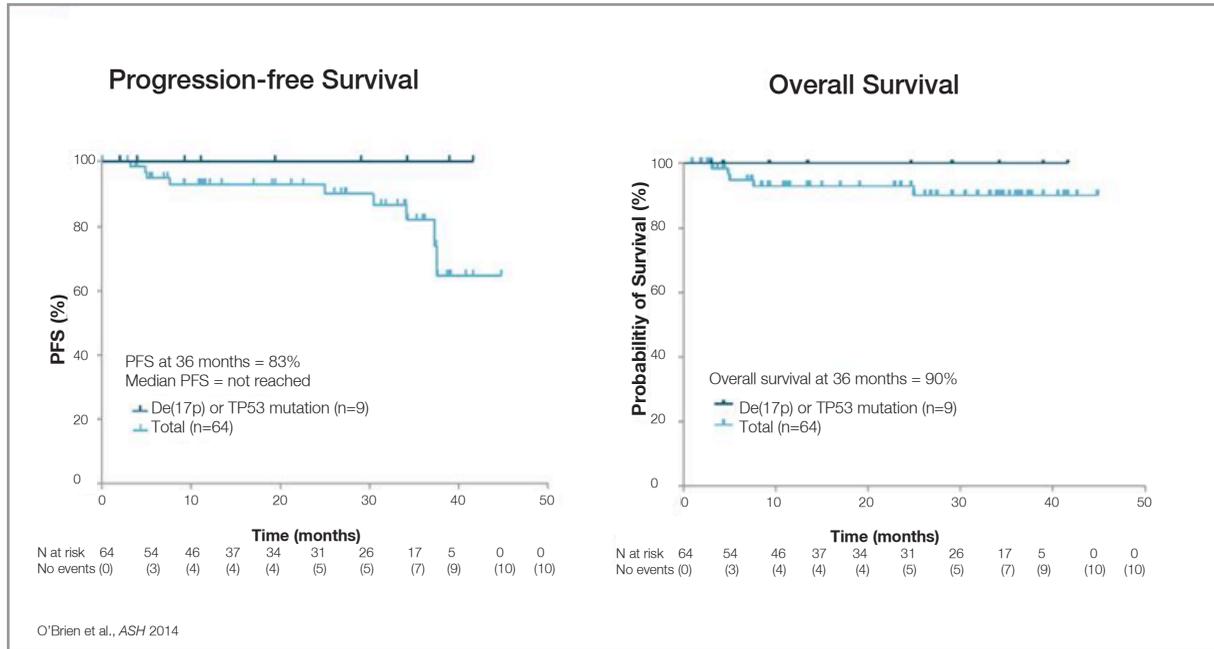


Figure 2. The progression-free survival (PFS) is 83% at 36 months with idelalisib in the front-line study of chronic lymphoid leukemia (CLL).

response rate is 97%, with 19% being complete responders. The progression-free survival (PFS) is an impressive 83% at 36 months, with only 4 events of disease progression, despite only 23 of 64 patients currently continuing on idelalisib.^{15,18} The effectiveness of idelalisib is particularly striking in patients with high-risk cytogenetic abnormalities like 17p deletion and in older CLL patients in whom chemoimmunotherapy is apparently less well-tolerated. Among the highest-risk TP53-mutated patients (n= 9), the overall response rate is 100% and none have progressed, consistent with the known excellent activity of idelalisib in relapsed patients in this high risk group (Figure 2).

On the other hand in the patients with heavily pre-treated high-risk relapsed CLL not suitable for chemotherapy, idelalisib added to Rituximab improved PFS including patients with del(17p)/TP53 mutation or IGHV mutational status “unmutated”.^{17, 19-26} The idelalisib plus rituximab combination had improved overall response rate and lymph node response, improved overall survival (OS) and quality of life (QoL) independent of poor prognostic factors of CLL at the same study an acceptable safety profile. The most impressive find-

ing was that idelalisib and rituximab treatment had similar efficacy regardless of the presence of 17p deletion or IGHV mutational status. OS is higher for patients on idelalisib+rituximab despite cross-over in extension design. Favorable benefit/risk ratio is maintained during the longer follow-up of the study.^{17,19-26} Figure 3 illustrates the superiority of idelalisib+rituximab combination versus the control arm in terms of PFS.

Idelalisib in combination with bendamustine+ rituximab (BR) is superior to BR alone, reducing the risk of both disease progression and death, increasing PFS and OS, and with a safety profile consistent with prior reported studies. Median PFS of IDELA + BR vs BR + placebo: 23 mo vs 11 mo (HR=0.33; p<0.0001), median OS of IDELA + BR vs BR + placebo not reached for either arm (HR= 0.55; p= 0.008). Rai stage III/IV 46%; median time since completion of last prior therapy 16 months; patients with del(17p)/p53mut 32.9%, patients with unmutated IGHV 83.2%, patients with refractory disease 29.8%, median number of prior therapies: 2 (range: 1-13). Those results were consistent across pts with high-risk features. The addition of idelalisib to BR was also beneficial in patients

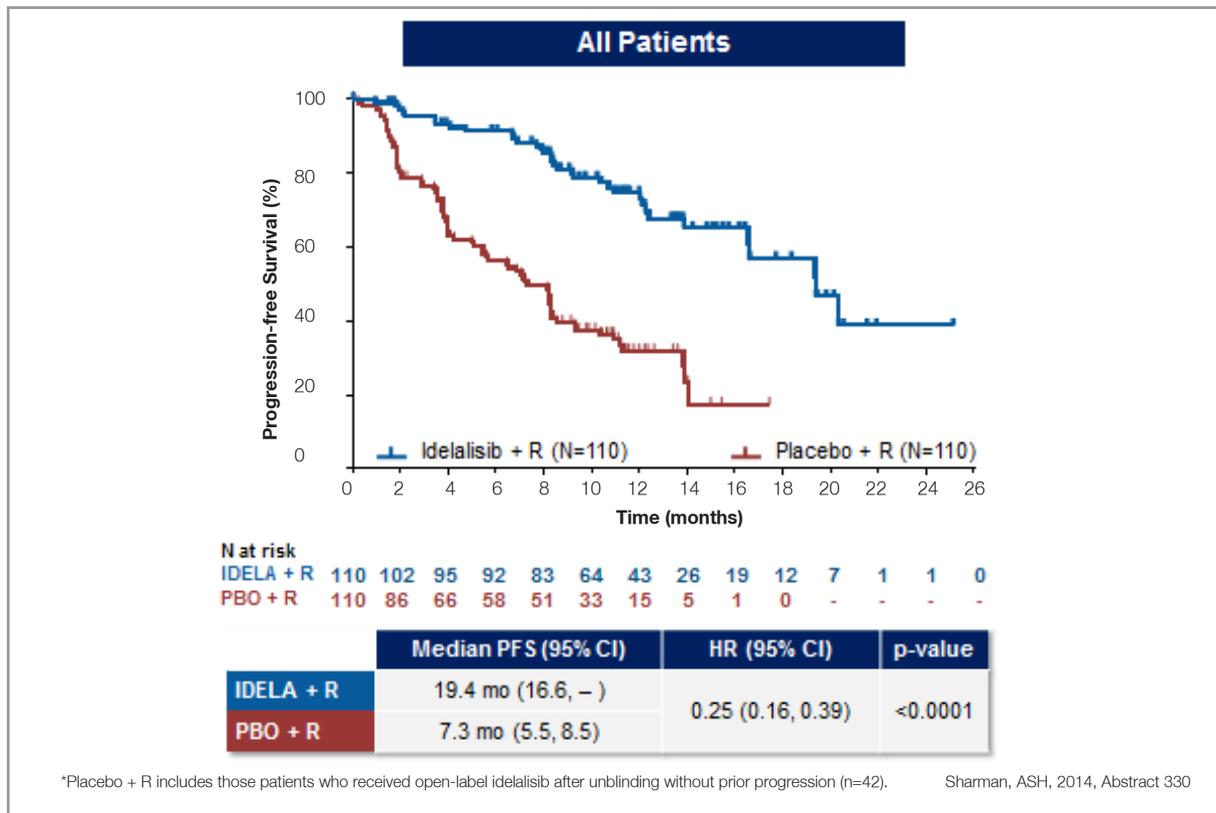


Figure 3. The progression-free survival (PFS) of idelalisib+rituximab combination is superior versus the control arm in heavily pre-treated high-risk relapsed chronic lymphoid leukemia (CLL) not suitable for chemotherapy.

without del(17p)/TP53mut. This kind of idelalisib regimen represents an important new option for the patients with relapsed and resistant CLL.¹⁶

The complexity of CLL with respect to different chromosomal aberrations, lack of a common aberrant signaling pathway activation, and associated immune suppression of the disease seems to be challenging for the targeted therapies.²⁷ Current CLL trials of idelalisib^{17,19-26} appear to be overcoming this obstacle. The possibility of a chemotherapy-free treatment approach may be possible not only for CLL but also other B-LPDs.³

Idelalisib in B-lymphoma

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) with a heterogeneous natural history of disease and a median survival of 8 to 12 years. The activity of idelalisib in high-risk FL with early relapse following front line immunochemotherapy was recently shown.¹⁰

The study subgroup of 46 patients with FL and having received first-line immunochemotherapy, of which 37 experienced early disease progression, defined as starting second-line treatment within 24 months of initial first-line treatment. PFS and OS following initiation of immunochemotherapy and idelalisib were assessed in this small subset study.¹⁰ Best responses included 5 (13.5%) patients with CR, 16 (43.2%) with PR, 2 (5.4%) with SD, and 1 (2.7%) with PD. Estimated probabilities of survival and progression-free status at 2 years following initiation of idelalisib were 79%±7% and 29%±10%, respectively. Thus, idelalisib may have significant clinical activity in high-risk and doubly-refractive FL following early relapse status post first-line immunochemotherapy.¹⁰

Mature follow-up data from a phase 2 study of idelalisib in patients with double (rituximab and alkylating agent)-refractory indolent B-NHL (R/R iNHL) were established. Patients had received a median of 4 prior regimens (range, 2 to 12), with

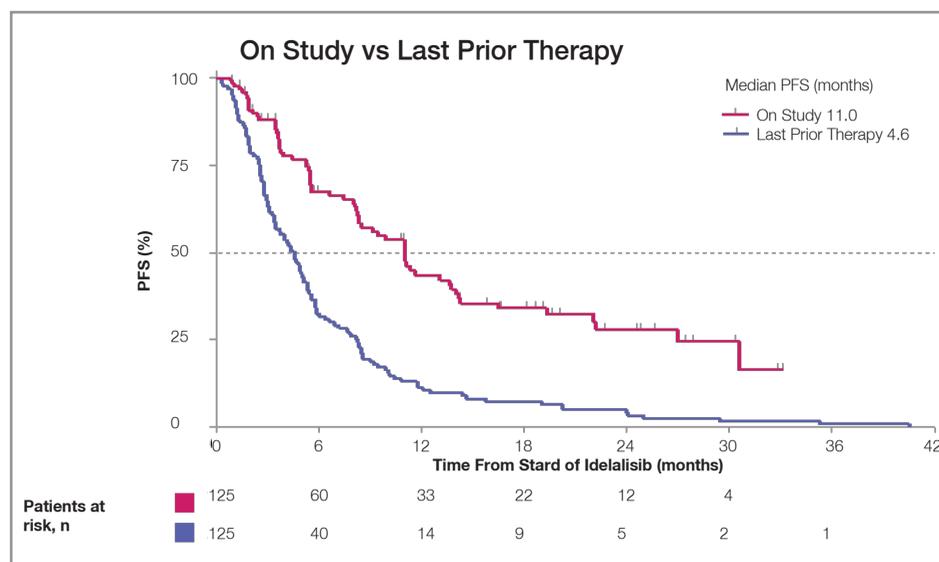


Figure 4. The safety profile of Idelalisib on continuous therapy was manageable with effective response in lymphoma

73 patients (58%) having received 4 or more prior regimens.²⁸ Idelalisib demonstrated high response rates (ORR 58%) in patients with R/R iNHL. Response durations were prolonged (median 12.5 months). With a median 9.7 months follow-up; the median progression-free survival was 11.0 months (wh, with 47% of the patients remaining progression free at 48 weeks). The median overall survival was 20.3 months, and overall survival at 1 year was estimated to be 80%. The safety profile of idelalisib in these patients on continuous therapy was manageable (Figure 4).²⁸

Likewise, durable responses following the treatment with idelalisib in combination with rituximab, bendamustine, or both, in recurrent iNHL were also reported in phase I/II trials.²⁹ Idelalisib in combination therapy for patients with R/R iNHL resulted in high response rates (ORR of 81%), durable response (median PFS of 37 months and DOR at 36 months of 55%), manageable safety profile with treatment >3 years, with no unexpected toxicities. This data provides strong support for Phase 3 trials of idelalisib in combination with rituximab or bendamustine/rituximab for the treatment of patients with R/R iNHL.²⁹

The Unique Immunological Toxicity Pattern of Idelalisib

In the clinical idelalisib trials performed in the R/R setting, the ORR was 70-80%, while the frequency of significant toxicity was easily manageable (grade ≥ 3 transaminitis 14%, pneumonitis 3%, grade ≥ 3 diarrhea 14%).³⁰ However, the use of idelalisib as first-line therapy in CLL results in more frequent and severe toxicities than its use in the R/R setting. Idelalisib toxicity has an immune-mediated mechanism. The delayed time to onset, the immune cell infiltrate in biopsies of affected organs (such as the colonic mucosa) and abatement of toxicity with immunosuppressants have all supported the unique immunological toxicity pattern of idelalisib.³¹ Affected CLL patients had depressed Treg functionality at baseline and lost marker of Treg activation after idelalisib therapy.³¹ On the other hand, previous studies³² disclosed that CD4+CD25+ T cells were elevated in inflammatory bowel disease (IBD) suggesting a partial role of activated T cell response in the disease pathophysiology. Thus, the conclusion that CD4+CD25+ regulatory T cells may play a key role in the immunopathogenesis of IBD³² shall be further searched for the immunity-mediated colitis associated with the idelalisib as well.³³ Non-immune toxicity profile of idelalisib is expected and usually easier to manage.^{8,30,34-45}

Expanding Spectrum of Idelalisib and PI3K Pathway in B-lymphoproliferative Disorders

In USA/FDA; Idelalisib is indicated in combination with rituximab for patients with relapsed chronic lymphocytic leukemia (CLL) for whom rituximab alone would be considered appropriate therapy and as monotherapy for patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) and small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies.

In Europe/EMA; Idelalisib has been approved for use in combination with rituximab for patients who have received at least one prior therapy; or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemotherapy for the treatment of CLL. For the treatment of FL, Idelalisib has been approved as a monotherapy in patients who are refractory to two prior lines of treatment.^{14,46,47} Further clinical investigations will help for the better selection of the subsets of the patients with B-LPD that would be best candidates for the clinical utilization of idelalisib. Other indications such as marginal zone lymphoma¹³, mantle cell lymphoma⁴⁸, Waldenstrom's Macroglobulinemia^{49,50}, and other B-cell disorders⁵¹ could likely to be expanded. Future clinical and experimental data combined with the next-generation genomics strategies and personalized medicine for the treatment of malignant disorders will enlightened us for better placement of idelalisib in the treatment algorithm of the patients.

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