JNCI Cancer Spectrum (2018) 2(4): pky038

doi: 10.1093/jncics/pky038
Article

ARTICLE

Strategy for Assessing New Drug Value in Orphan Diseases: An International Case Match Control Analysis of the PROPEL Study

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Abstract

Background: Although randomized studies are designed to assess overall survival (OS) benefit, the conduct of regulatory studies in patients with orphan diseases can be timely and costly without offering the same commercial return on the investment. The peripheral T-cell lymphomas (PTCL) represent a rare group of heterogeneous lymphoid malignancies with very poor prognosis. PROPEL was a pivotal phase II study that led to the accelerated approval of pralatrexate for patients with relapsed or refractory PTCL.
Methods: An international database of 859 patients was assembled from four institutions with an interest in PTCL, of which 386 were considered eligible for matching against the PROPEL criteria. Using a rigorous propensity score matching algorithm, a unique 1:1 case match of 80 patients was performed.
Results: The analysis demonstrated an OS benefit for the PROPEL population with a median OS of 4.07 and 15.24 months (hazard ratio = 0.432, 95% confidence interval = 0.298 to 0.626), respectively, for the control and PROPEL populations. Highly statistically significant improvements in OS were noted for the PROPEL population about the subtype of PTCL (save anaplastic large cell lymphoma) and all age groups, including the elderly (>65 years of age). For patients on PROPEL, there was a statistically significant prolongation in progression free survival compared with the line of prior therapy, including those with refractory disease.
Conclusion: In the context of this case-match-control study, patients treated on PROPEL experienced an OS advantage compared with an international database of historical controls. This information can help inform critical decision-making regarding clinical studies in PTCL.

Regulatory approval of new drugs in rare and orphan diseases represents a challenge for investigators seeking to broaden treatment options and improve the standard of care for these patients. Increasing regulatory pressure to conduct randomized clinical studies in cancer drug development, coupled with the increasing splitting of diseases based on molecular phenotyping, is increasing the challenges and delaying further the time to regulatory approval. Although the US Food and Drug Administration has been receptive to approving drugs in rare entities based on reasonably sized single arm multicenter phase II studies, many other regulatory bodies insist on randomized studies irrespective of the disease rarity.

The peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphomas with over 29 distinct entities (1). Several new agents have been approved over the past 5 years (2,3). PTCL have the poorest outcomes relative to all other forms of non-Hodgkin lymphoma. Important barriers to improve the outcome of these patients include: 1) their rarity, 2) the increasing splitting of subtypes based on molecular phenotyping, and 3) the marked geographic variability. In the United States, the

Received: February 28, 2018; **Revised:** June 14, 2018; **Accepted:** July 11, 2018

PTCL account for only 10% to 15% of all cases of non-Hodgkin lymphoma, with an annual incidence of about 6000 to 10 000 cases (4). Although advances in our biological understanding of the disease are compelling investigators to consider trials in smaller and smaller subsets of one disease entity, the practicality remains a deterrent (5,6,7).

PROPEL was a single arm, phase II study of pralatrexate in patients who relapsed or were refractory to systemic chemotherapy (8,9). PROPEL reported an overall response rate (ORR) of 29% based on independent central review and 39% based on investigator assess responses. These data led to an accelerated approval of pralatrexate in 2009, making it the first drug approved in this setting. Although a randomized study would unequivocally establish the clinical benefit relative to other standards of care, it would also increase the length of time and cost required to conduct the study. As a result, sponsors of new drugs in rare diseases are faced with the conundrum of having to decide whether to pursue the single arm study, hoping the results are worthy enough for an accelerated approval and a postmarketing commitment study (by definition a randomized study), or to conduct a randomized study from the beginning.

One strategy that could gauge the merits of an orphan drug would be to assess its activity relative to a well-annotated historical control in a case-match-control study (CMCA). Statistically, case match control data are more robust than single arm data and could provide regulatory authorities with a metric to evaluate the merits of a drug in comparison with "conventional standards" (10). This specific analysis would not be intended to circumnavigate the need to conduct confirmatory randomized phase III studies but rather guide sponsors and regulatory authorities in their decision-making processes.

The challenge in conducting CMCAs is obtaining access to large annotated databases. In addition, given the continuous emergence of new molecular data, the maintenance of such databases would require ongoing support and updating to be useful. We identified four academic groups on three continents that had invested internal resources to start and maintain such databases on patients with relapsed or refractory PTCL. Based on these data, we conducted a CMCA of the PROPEL study population.

Materials and Methods

PROPEL Study Conduct

PROPEL was an international, multicenter, single arm phase II trial of pralatrexate in 109 patients with relapsed or refractory PTCL, described in detail elsewhere (8). In 2009 pralatrexate received accelerated approval by the US Food and Drug Administration.

Description of Databases

Survival outcome (overall survival [OS]) data from four centers with prospectively collecting data on patients with PTCL in the United States, Europe, and Korea were acquired. Data were collected from 1) Memorial Sloan Kettering Cancer Center (MSKCC) for 171 patients who were treated at their institution between June 1997 to July 2011, 2) University of Nebraska Medical Center (UNMC) provided data for 67 patients diagnosed between July 1, 1984 and May 17, 2010 who were part of the Nebraska Lymphoma Study Group, 3) Groupe d'Etude des Lymphomes de l'Adulte (GELA) provided information on 117 patients whose first-line treatment was administered under the four clinical trials conducted between December 1997 and April 2008, and 4) The Samsung Medical Center (SMC) in South Korea provided data on 504 patients based on a retrospectively characterized databased collected between 1995 and 2007 and a prospectively maintained database initiated in 2008. In total, data from 859 patients were collected from the four sites.

A total of 386 patients (including 69, 44, 110, and 163 patients collected from MSKCC, UNMC, GELA, and SMC databases, respectively) were identified from these four databases based on the following specific selection criteria: 1) histologies consistent with the inclusion criteria of PROPEL; 2) patients who received at least two lines of prior therapy (ie, the second line of therapy would match with patients receiving pralatrexate on PROPEL, which required one line of prior therapy); and 3) patients who had not received pralatrexate. The efficacy data were not part of the criteria to select patients for inclusion in the historical database.

Propensity Score Matching

Survival data were provided from all the databases but were not used as the part of the criteria for matching patients. Hence, survival times are objective and were consistently measured across all databases. Because response rates and progression free survival (PFS) data were not collected according to a consistent methodology across the databases and were not available for all patients in the historical databases, all efficacy comparisons were made based on OS data only, the regulatory standard of interest.

Survival analyses were conducted based on propensity score matching. The propensity score is the probability of treatment assignment conditional on observed baseline characteristics. The propensity score is a measure of the likelihood that a person would have been treated (case or control) using only their covariate scores (11). The propensity score allows for the design and analysis on an observational (nonrandomized) study so that it mimics some of the particular characteristics of a randomized controlled trial. In particular, the propensity score is a balancing score conditional on the distribution of observed baseline covariates that will be similar between case and control patients.

The propensity score for each patient in the dataset was calculated accordingly to previously published methods (12). In brief, multivariable logistic regression was performed using the following terms in the model: histology, number of previous treatments received, age at diagnosis (with 65+ years interval), and sex. Based on this, the probability of the dependent variable of a patient in case or control was used to calculate the propensity score for each patient in the dataset (12). This single score (between 0 and 1) represents the relationship between multiple characteristics and the dependent variable as a single characteristic. Matching on this score balances the demographic and baseline characteristics in case and control groups (13).

With the predicted probability, we used the algorithm, which makes "best" matches first and "next-best" matches next in a hierarchical sequence until no more matches can be made. Best matches are those with the highest digit match on propensity score. First, case patients are matched to control patients on eight digits of the propensity score. For those that do not match, cases are then matched to controls on seven digits of the

Table 1. Demographic features of historical and PROPEL population*

Characteristics	MSKCC (n = 69)	UNMC (n = 44)	GELA (n = 110)	SMC (n = 163)	PROPEL (n = 109)
Age at diagnosis, y					
Mean	54.1	48.4	55.9	50.8	55.5
SD	17.44	13.09	14.02	13.83	14.36
Min–max	12–89	17–70	15–79	17–76	19–85
Sex, No. (%)					
Male	47 (68.1)	27 (61.4)	73 (66.4)	114 (69.9)	74 (67.9)
Female	22 (31.9)	17 (38.6)	37 (33.6)	49 (30.1)	35 (32.1)
Number of regimens No. (%) (including pralatrexate for PDX-008)					
2	37 (53.6)	21 (47.7)	55 (50.0)	76 (46.6)	23 (21.1)
3–4	24 (34.8)	21 (47.7)	49 (44.5)	87 (53.4)	52 (47.7)
≥5	8 (11.6)	2 (4.5)	6 (5.5)	0 (0.0)	34 (31.2)
Median	2.0	3.0	2.5	3.0	4.0
Min–max	2–7	2–15	2–5	2–4	2–12
Time from diagnosis to pralatrexate or last comparator therapy, months					
Median	11.0	7.5	15.2	7.3	15.5
Min–max	0.033–104	1.774–130.9	0.953–132.5	-23.1–99.42	0.854-322.4
N missing	0	1	0	0	0
Histology as per 2008 WHO classification, No. (%)					
Adult T-cell leukemia/lymphoma (HTLV 1+)	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.9)
Anaplastic large cell lymphoma, primary systemic type	18 (26.1)	12 (27.3)	2 (1.8)	18 (11.0)	17 (15.6)
Angioimmunoblastic T-cell lymphoma	15 (21.7)	2 (4.5)	55 (50.0)	20 (12.3)	13 (11.9)
Blastic NK lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.7)
Enteropathy-type intestinal lymphoma	0 (0.0)	0 (0.0)	5 (4.5)	0 (0.0)	0 (0.0)
Extranodal peripheral T/NK-cell lymphoma unspecified	0 (0.0)	0 (0.0)	8 (7.3)	0 (0.0)	1 (0.9)
Hepatosplenic T-cell lymphoma	5 (7.2)	2 (4.5)	1 (0.9)	0 (0.0)	0 (0.0)
PTCL-unspecified	24 (34.8)	28 (63.6)	38 (34.5)	56 (34.4)	59 (54.1)
Subcutaneous panniculitis T-cell lymphoma	1 (1.4)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
T/NK-cell lymphoma nasal	3 (4.3)	0 (0.0)	0 (0.0)	68 (41.7)	2 (1.8)
Transformed mycosis fungoides	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	12 (11.0)
Histology classification (2008 WHO), No. (%)					
Cutaneous	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	12 (11.0)
Extranodal	9 (13.0)	2 (4.5)	15 (13.6)	68 (41.7)	7 (6.4)
Leukemic	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.9)
Nodal	57 (82.6)	42 (95.5)	95 (86.4)	94 (57.7)	89 (81.7)
Age at initiation of pralatrexate or last comparator therapy, y					
Mean	55.4	49.9	57.8	51.8	58.0
SD	17.40	13.66	14.45	14.10	14.19
Min–max	13–90	18–72	17–83	17–78	21–85
N missing	0	1	0	0	0
Response to any therapy, No. (%)					
No	7 (10.1)	6 (13.6)	19 (17.3)	79 (48.5)	21 (19.3)
Yes	62 (89.9)	38 (86.4)	91 (82.7)	84 (51.5)	88 (80.7)
Response to 2nd last therapy, No. (%)					
No	32 (46.4)	20 (45.5)	44 (40.0)	108 (66.3)	68 (62.4)
Yes	37 (53.6)	24 (54.5)	66 (60.0)	55 (33.7)	41 (37.6)

*GELA = Groupe d'Etude des Lymphomes de l'Adulte; MSKCC = Memorial Sloan Kettering Cancer Center; SMC = Samsung Medical Center; UNMC = University of Nebraska Medical Center; HTLV = Human T-cell Leukemia-Lymphoma Virus; NK = Natural Killer; WHO = World Health Organization; PTCL = peripheral T-cell lymphomas.

propensity score. The algorithm proceeds sequentially to the lowest digit match on propensity score (1 digit). This is referred to as the 8 to 1 Digit Match (14).

Progressive Resistance and PFS Analysis

Among the patients evaluable for efficacy in PROPEL, three analysis sets were identified to investigate the overall response rate (ORR), complete remission (CR), PFS, and duration of response (DOR) based on the number of prior line of treatment, including 1) patients (n = 23) who had received one prior systemic therapy, 2) patients (n = 29) who had received two prior systemic therapies, and 3) patients (n = 57) who had received at least three prior systemic therapies.

The von Hoff analysis (10,15,16), compares the PFS on the study treatment to the PFS on the line of therapy before. The analysis is predicated on the idea that successive lines of therapy almost never produce a benefit greater than the lines of treatment before. Thus, the statistics of the analysis are defined as PFS on the experimental drug / PFS for the line of therapy just before, with a ratio greater than 1.3 being considered statistically significant, where the hypothesis would miss up to 15% for PFS ratio more than 1.3. The Von Hoff analysis was performed

on the subset of patients with refractory disease (n = 68) that responded to pralatrexate treatment (n = 16).

Results

Characterization of Historical and PROPEL Study Populations

Details regarding the PROPEL study are presented in detail elsewhere (8). Table 1 compares the demographic characteristics for both the historical and PROPEL study populations. The data across all the site databases and PROPEL study population are highly concordant. The age and sex distribution roughly approximates the median age for the disease. The means range from age 48.4 to 55.9 years. The median number of prior therapies was also very consistent, with a range of two to three lines of prior therapy. Among these study populations, the PROPEL population is very heavily treated given the mean age of the population, which is a little higher than that noted for the UNMC data. The study populations are also similar with regard to the number of lines of prior therapy received. The median number of lines of prior treatment ranged from two to three, which closely matched the three lines seen in the PROPEL study population. The time from diagnosis was also similar, ranging from 7.3 to 15.5 months, being greatest for the PROPEL study population. Given the dynamic state of PTCL classification, not every subtype treated in PROPEL was captured in the historical database, owing to their rarity. Nonetheless, all the major subtypes treated were identified. We also acknowledge that, although cases in the PROPEL cohort were centrally reviewed, such central review was not possible in the historical cohort. However, the four institutions representing the historical cohort are well-renown institutions for their expertise in PTCL. What is intriguing and consistent with what has been reported by the British Columbia Cancer Agency (17) is that, in general, less than 20% of patients respond to any therapy, and more than 50% of patients failed to respond to their last line of therapy. Table 2 presents a summary of matched variables between historical controls and PROPEL cases. These data confirm high-level matching on all the major eligibility criteria. Prior stem cell transplant was not a variable for matching, but, of note, the matched patient populations included patients who received prior autologous or allogeneic transplantation. Specifically, 6 of 80 patients in the historical cohort and 15 of 80 patients in the PROPEL cohort received prior stem cell transplant, suggesting that the PROPEL cohort represented a more heavily pretreated patient population compared with the historical cohort. Supplemental Table 1 (available online) shares the patients excluded from the analysis and the reason. Overall, most patients excluded were from the MSKCC and SMC, where many patients were excluded based on either a prior exposure to pralatrexate or they received only one line of prior therapy. Histologies not included in the PROPEL eligibility accounted for very few exclusions. Supplemental Tables 2, 3, 4, and 5 (available online) reveal the remarkable heterogeneity when it comes to the line of therapy patients received prior to pralatrexate or its matched treatment. By far, etoposide-containing regimens were the most commonly used, typically in the form of ICE chemotherapy. In fact, more than 60 different treatment regimens were used for essentially the same study population across four sites and three continents. This profound heterogeneity in treatment seen among centers with experience in managing the disease reflects a complete lack of any consensus or acknowledged standard of care for patients with relapsed or refractory disease.

Table 2. Summary of matched variables between historical controls and PROPEL cohort (by age increment 10 years)*

Matched variables	Control n = 80	PROPEL n = 80
Histology, No. (%)		
Adult T-cell leukemia/lymphoma (HTLV-1+)	0 (0.0)	1 (1.3)
Anaplastic large cell lymphoma, primary systemic type	12 (15.0)	13 (16.3)
Angioimmunoblastic T-cell lymphoma	12 (15.0)	12 (15.0)
Extranodal peripheral T/NK-cell lymphoma unspecified	0 (0.0)	1 (1.3)
PTCL-unspecified	52 (65.0)	49 (61.3)
T/NK-cell lymphoma nasal	2 (2.5)	2 (2.5)
Transformed mycosis fungoides	2 (2.5)	2 (2.5)
Sex, No. (%)		
Male	52 (65.0)	52 (65.0)
Female	28 (35.0)	28 (35.0)
Prior therapy, No. (%)		
1	19 (23.8)	20 (25.0)
2–3	47 (58.8)	46 (57.5)
≥4	14 (17.5)	14 (17.5)
Age at initiation of PROPEL or last comparator therapy		
Mean, y	55.8	58.2
Time from diagnosis to PROPEL or last comparator therapy		
Median, months	11.5	13.7

*HTLV = Human T-cell Leukemia-Lymphoma Virus; NK = Natural Killer; PTCL = peripheral T-cell lymphomas.

Prognostic Features of the PROPEL Study Population

Table 3 shares the outcome of patients on PROPEL as a function of line of prior therapy. The PROPEL population was the most

Table 3. Outcome of patients on PROPEL as a function of time at prior therapy (by central review and by investigator review)*

	One prior therapy n = 23		Two prior therapies n = 29		Three or more prior therapies n = 57	
Efficacy assessment	Central review	Investigator review	Central review	Investigator review	Central review	Investigator review
Overall response rate, No. (%)	8 (34.8)	10 (43.5)	7 (24.1)	11 (37.9)	17 (29.8)	23 (40.4)
Complete response, No. (%)	4 (17.4)	6 (26.1)	3 (10.3)	4 (13.8)	4 (7.0)	9 (15.8)
Progression free survival, mo	8	5.3	3.2	3.2	1.7	4.4
Duration of response, mo	NR	12.5	10	4.7	3.4	8.2

*NR = not reached.

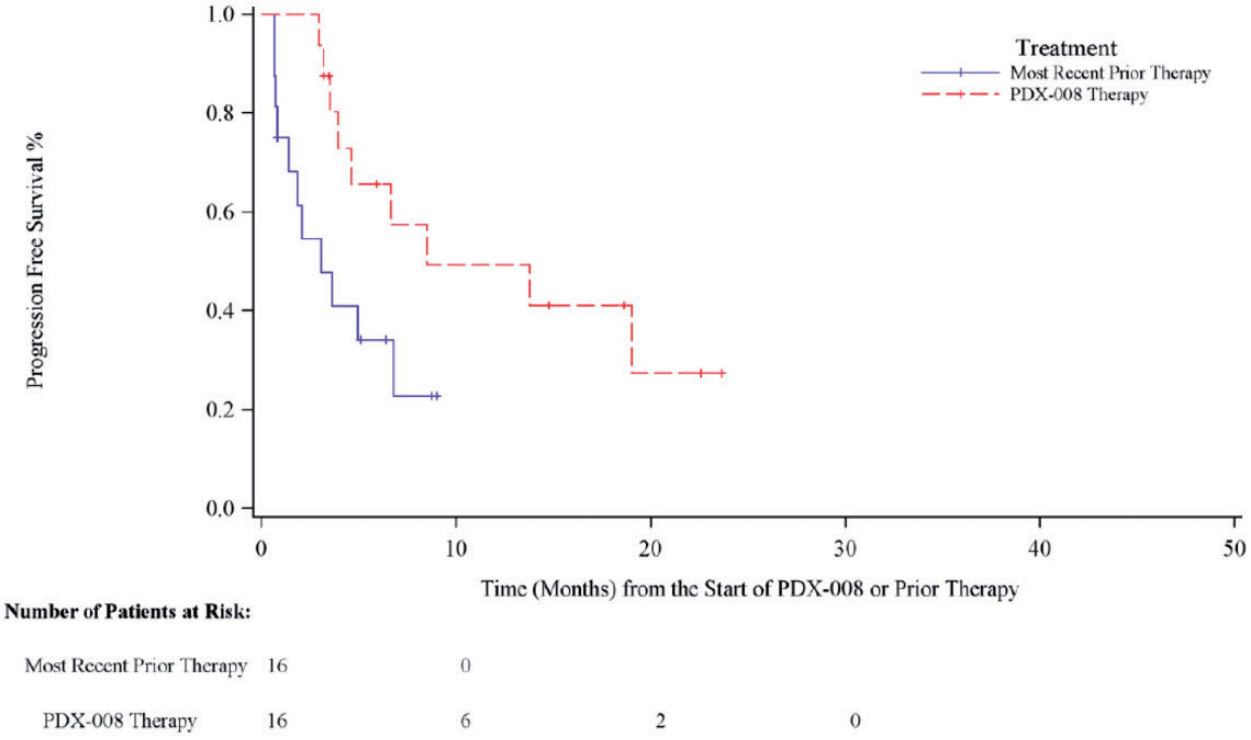

Figure 1. Progression-free survival from central review between PROPEL (PDX-008) and most recent prior line of therapy in patients with refractory disease.

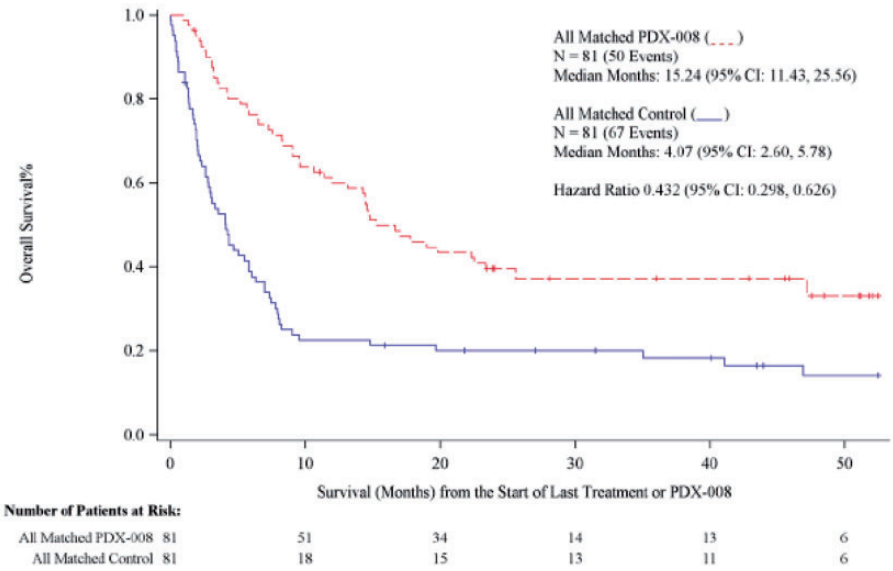

Figure 2. Overall survival for pralatrexate-treated vs unique 1:1 control-matched patients by sex, number of treatments, age at diagnosis in every 10 years, and WHO histology.

diverse in its inclusion of poor prognostic histologies and with regard to how heavily treated these patients were (median number was three, with 20% of patients having more than four lines of prior therapy). There is a trend towards increasing clinical benefit as pralatrexate moves up in the lines of treatment. For example, the ORR, CR, median PFS, and DOR for the general population were 29.8%, 7%, 1.7 months, and 3.4 months, respectively, while for patients with two lines of prior therapy the results were 24.1%, 10.3%, 3.2 months, and 10 months, respectively. For those patients who had only one line of prior therapy, the same results were 34.8%, 17.4%, 8 months, and not reached at 2 years. These data reveal strong trends toward improvement in the CR rate, PFS, and DOR as use moves up in line of treatment. In addition, we identified 68 patients with refractory disease, defined as progression of disease or stable disease to the line of treatment prior to PROPEL enrollment. The Von Hoff analysis was performed on the subset of patients with refractory disease (n = 16) who responded to pralatrexate treatment. The PFS ratio

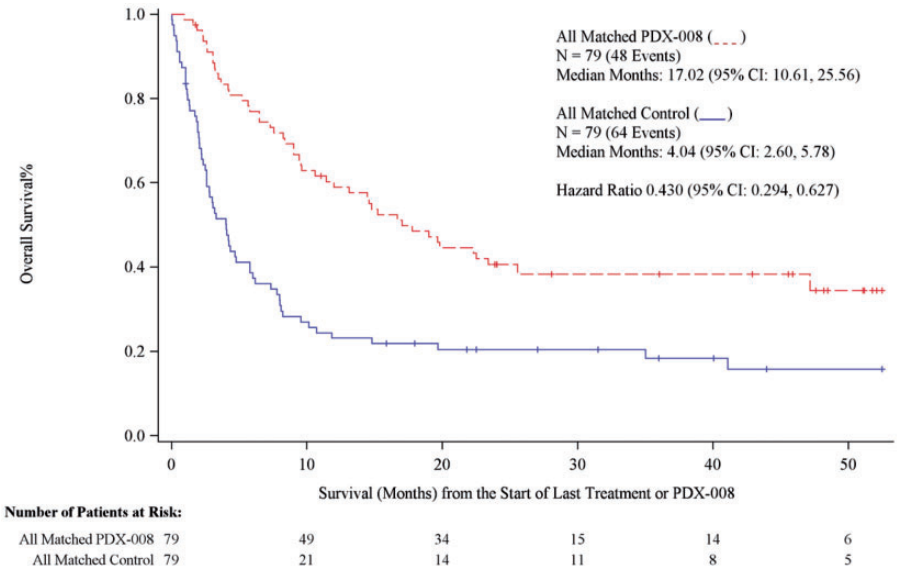

Figure 3. Overall survival for pralatrexate-treated vs unique 1:1 control-matched patients by sex, number of treatments, age at diagnosis 65+ years, and WHO histology.

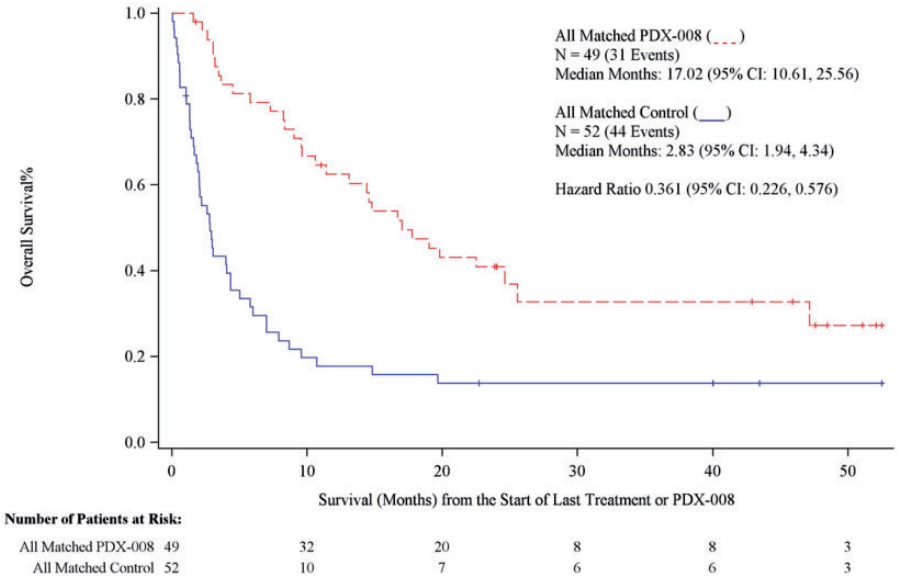

Figure 4. Overall survival for pralatrexate-treated vs unique 1:1 control-matched patients by sex, number of treatments, and age at diagnosis in every 10 years (histology: PTCL-Unspecified).

for this subset of patients was 4.63, which was statistically significant. Figure 1 depicts the PFS curves for this population. These data support the notion that the clinical benefit is greater the earlier pralatrexate is administered in the line of treatment.

OS Analyses

A comparison of the OS estimates for the PROPEL and matched control populations (Supplemental Figure 1, available online) reveals some similarity and is consistent with what has been reported in the literature. The median OS among the MSK, UNMC, GELA, and SMC databases was 6.1, 8.7, 4.2, and 3.7 months, respectively, in contrast to 14.7 months for the PROPEL study population. The OS curves for the pralatrexate-treated vs the unique 1:1 control-matched PTCL patients, as shown in Figure 2, demonstrate a statistically significant OS estimate for the PROPEL study population compared with the control-matched population. In fact, for the matched population of 81 patients, the median survival was 4.07 months (95% CI = 2.6 to 5.78 months) in contrast to 15.2 months (95% CI = 11.43 to 25.56 months) for the pralatrexate-treated patient population, with a hazard ratio (HR) of 0.432 (95% CI = 0.298 to 0.626), supporting a statistically significant benefit for the pralatrexate-treated PROPEL population. These differences held up within the analysis when explored in elderly patients older than 65 years (HR = 0.43; 95% CI = 0.294 to 0.627) (Figure 3). Figures 4 and 5 depict similar curves for specific subtypes of PTCL, in particular

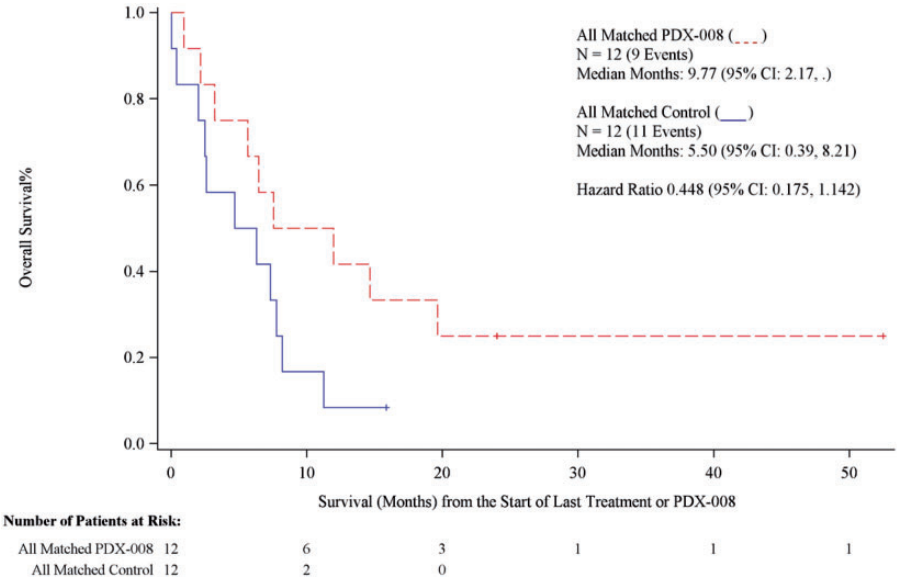

Figure 5. Overall survival for pralatrexate-treated vs unique 1:1 control-matched patients by sex, number of treatments, age at diagnosis in every 10 years (histology: angioimmunoblastic T-cell lymphoma).

PTCL-NOS and angioimmunoblastic T-cell lymphoma (AITL). For patients with PTCL-NOS, these data depict an OS for historical and PROPEL populations of 2.83 months (95% CI = 1.94 to 4.34 months) and 17.02 months (95% CI = 10.61 to 25.56 months), respectively, with an HR of 0.361 (95% CI = 0.226 to 0.576) (Figure 4), while for patients with AITL the OS estimates were 5.5 months (95% CI = 0.39 to 8.21 months) and 9.77 months (95% CI = 2.17 to 10.2 months, with an HR of 0.448 (95% CI = 0.1756 to 1.142) (Figure 5), respectively. Interestingly, the OS curves for control and PROPEL patients with anaplastic large T-cell lymphoma (ALCL) were superimposable, suggesting that pralatrexate was as good as any conventional standard of care (Supplemental Figure 2, available online).

Discussion

The gold-standard metric for clinical benefit in interventional trials in oncology is OS, and the gold-standard metric for determining OS benefit is through appropriately powered randomized clinical trials. For orphan diseases, randomized studies are costly and timely and complicated further by the likely diminished commercial return on investment. Althouh single arm, phase II studies can be used for regulatory submissions, they usually require a randomized phase IV postmarketing commitment, which by definition is a randomized study. Strategies intermediate between single arm, phase II studies and a randomized study could provide insights into a possible survival advantage and inform decision-making. Although CMCA have statistical strengths and limitations, short of randomized studies, they are the only other way to assess OS.

The databases across the variables described are remarkably concordant, and even the OS curves of the populations are similar to that described from other international registries (17,18). First, the data confirm that those patients receiving pralatrexate earlier exhibit superior benefit as measured by ORR, CR, DOR, and PFS. Although not surprising, it debunks the notion that the more lines of therapy patients receive, the "better" that population. This is enforced by the comparison of PFS on study vs the line of therapy immediately prior to study drug. Sometimes referred to as the von Hoff analysis, this metric assumes that clinical benefit with any drug for a patient with cancer diminishes with each successive line of therapy. The attractiveness of the analysis is that it uses each patient as his/her own control. These findings revealed a PFS ratio of 4.8 for patients refractory to the line of chemotherapy prior to PROPEL treatment. These data demonstrated that pralatrexate reversed the trend toward progressive resistance and produced a PFS superior to the line of therapy just prior, irrespective of histology and the number of lines of prior therapy.

Irrespective of the subset, OS was superior for patients treated on PROPEL compared with the historical controls, and these differences were statistically significant. In each case, the historical control curves are nearly identical to those reported from other international registries, confirming consistency. For the entire PROPEL population, those older than age 65 years, and the two PTCL subtypes PTCL-NOS and AITL, the survival advantage holds up. In patients with ALCL, there was no difference, implying that single agent pralatrexate was as good as any conventional treatment these patients received prior to PROPEL-based therapy. The lack of demonstrable differences in ALCL probably reflects the more chemotherapy-sensitive features of the disease, even in the relapsed setting. Another intriguing aspect of these data, as shown in Supplemental Tables 3 to 5 (available online), is that patients on PROPEL received single agent therapy compared with the typically multi-agent chemotherapy approaches seen with the line of therapy before, challenging the notion these patients require combination chemotherapy to attain disease control. We also emphasize that the process of matching patients, based on the propensity score, was applied to balance as much as possible the PROPEL and historical cohort, but there are absolutely no prognostic criteria that have been identified in the multiple relapsed setting that would allow to define a more favorable and/or unfavorable cohort of patients.

Every trial design has its strengths and limitations. The goal of course is to assimilate as much meaningful data as possible

to inform the decision-making process. We believe the use of case-match-control analyses represents yet another tool. These findings suggest that a focus on collecting data on rare diseases on a larger collaborative basis can create a valuable resource for investigators conducting clinical research in these diseases and should be a funding priority. Similarly, the coalescence of national and international efforts can provide a synergy with regard to providing insights on how new therapeutic strategies might influence the natural history of challenging orphan malignancies.

Notes

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Dr Owen O'Connor has received a laboratory and clinical research grant from Spectrum.

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