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REVIEW

Axicabtagene Ciloleucel in the Management of Follicular Lymphoma: Current Perspectives on Clinical Utility, Patient Selection and Reported Outcomes

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Abstract: Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor T-cell therapy (CAR-T) that has shown efficacy in B-cell non-Hodgkin's lymphoma. It has shown high efficacy in relapsed/refractory follicular lymphoma (FL) even in the presence of high risk features (early relapse, heavily pretreated patients and bulky disease). Treatment options for R/R follicular lymphoma do not offer long-term remissions, especially in the third-line setting. Axi-cel was studied in R/R FL in the ZUMA-5 study, which showed high response rates with durable remissions. Axi-cel was associated with anticipated but manageable toxicities. Long-term follow up may be able to inform the potential for cure of FL. Axi-cel should be part of the standard of care options for R/R FL beyond second line.

Keywords: axicabtagene ciloleucel, follicular lymphoma, immunotherapy, cellular therapy

Introduction

Follicular lymphoma (FL) is the second most common lymphoma diagnosed in the Western hemisphere.[1,2] It accounts for approximately one-third of all non-Hodgkin lymphomas and over two-thirds of the indolent ones.[2] The disease is characterized by a heterogeneous clinical course, with some patients having a very indolent clinical presentation without requiring treatment for a relatively long time and others having a more aggressive clinical presentation requiring more immediate treatment for disease control. FL generally presents with clinically enlarged lymph node(s), which could be symptomatic or even asymptomatic; at times, it is incidentally found on radiologic imaging performed for other purposes. A large proportion of patients have advanced disease at initial diagnosis, with the bone marrow being commonly involved. In fact, less than 10% of FL cases have stage 1–2 disease at the time of presentation. FL cells overexpress BCL-2 protein, owing to t(14;18) in almost all cases.[3,4]

Treatment is not necessarily required if patients are clinically asymptomatic, and close clinical surveillance is considered acceptable. Once symptoms ensue, whether due to symptomatic nodal disease, impaired organ function, and/or symptomatic cytopenias, among other reasons, treatment becomes indicated. In that case, the most commonly prescribed regimen consists of a combination of bendamustine plus rituximab (BR).[2,5] Other chemoimmunotherapy options such as the combination of cyclophosphamide, vincristine, and prednisone (CVP) plus rituximab or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus rituximab are also acceptable.[2,6] The majority of patients obtain long-term remissions with frontline regimens.

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Patients relapsing after first-line chemoimmunotherapy are offered several treatment options depending on the clinical presentation; for example, if relapse occurred at a single site (in which radiation therapy is an acceptable option) or if it is systemic. High-dose therapy and autologous (auto) or allogeneic (allo) hematopoietic cell transplantation (HCT) are also part of the treatment algorithm for relapsed FL. Furthermore, patients failing two or more lines of therapy are nowadays offered chimeric antigen receptor T-cell (CAR T) therapy. Two products are currently approved by the United States Food and Drug Administration (FDA), namely, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, based on results of ZUMA-5 and ELARA studies, respectively.[7,8]

Below, we provide a comprehensive review of axi-cel in FL and discuss the role of other cell therapies, allo-HCT, and other immune-based therapies for the treatment of FL.

Axicabtagene Ciloleucel: Structure, Mechanism of Action, and Manufacturing Process

The CAR concept was initially developed by Eshhar et al, using single chain variable fragment antibody domain (svFC) with single signal without costimulation, known as first-generation CAR, which promoted cytotoxic activity but limited clinical efficacy.[9,10] A major improvement in CAR-T cell design was the addition of a costimulatory signal (CD28, 4–1BB, etc), which represented a major development that led to better CAR-T cell signaling, expansion, persistence and clinical efficacy[11–14]. Axi-cel (previously known as KTE-C19) has three components: an extracellular portion with the svFC domain that targets CD19; a transmembrane or hinge portion and an intracellular (signaling) portion composed of a CD3zeta activation domain coupled with the costimulatory molecule, CD28 (CD19-CD28-CD3zeta).[15]

The antitumor response in a normal immune system is mainly elicited by the cytotoxic effect mediated by T-cell activation of the T-cell receptor (TCR), a process that includes the presentation of tumor peptides/antigens by the major histocompatibility complex (MHC). Several mechanisms affect this immunologic process, such as MHC downregulation, T-cell exhaustion, T-cell senescence, etc. CAR-T cell therapy overcomes these resistance mechanisms by targeting tumor antigens in an MHC independent fashion.[15,16]

A key role for CAR-T expansion and activation is provided by conditioning chemotherapy. In the case of axi-cel, the optimal conditioning regimen is the combination of fludarabine and cyclophosphamide. The rationale for prescribing a conditioning regimen, also known as lymphodepletion, eliminates regulatory and inhibitory T-cells and likely suppressive myeloid cells. It also promotes the production of cytokines, such as interleukin (IL)-15 that favors the proliferation, activation and homing of CAR-T cells.[16]

Axi-cel was approved in March 2021 based on the results of the ZUMA-5 trial and tisagenlecleucel was approved in May 2022 based on the results of the ELARA trial.[7,8]

Rationale for Axi-Cel in R/R Follicular Lymphoma

Targeting CD19 with CAR-T cell therapy has been mostly studied in R/R diffuse large B-cell lymphoma (DLBCL) and subtypes with excellent results, as reported in various pivotal studies.[17–19] As CD19 is widely expressed in B-cell malignancies, assessing the efficacy in FL was clearly the logical next step. The initial studies with anti-CD19 CAR-T cell therapy included small numbers of indolent NHL but the results were compelling enough to launch pivotal studies in FL. In fact, the first reported successful treatment with CAR-T in NHL was a patient with R/R FL at the National Cancer Institute (NCI).[20] Pivotal NCI studies in the NCI included eight patients with iNHL (FL=5, MZL=1, indolent mantle cell lymphoma=1 and unspecified indolent B-cell NHL=1) and showed ORR and CR rates of 100% and 67%, respectively, with half of the patients still in remission at 55 month follow up.[21,22]

Other CAR constructs were also studied in indolent B-cell NHLs. Using the anti-CD19 CAR-T cell CAR-T on a 1:1 ratio of CD4+/CD8+ T-cells and the costimulatory molecule 4–1BB, the Fred Hutchinson Cancer Research Center (FHCRC) reported the data in FL.[23,24] This Phase I/II study included only two patients with heavily pretreated FL, including prior auto-HCT and prior anthracycline exposure. At the CAR-T cell target dose of 2×106 CAR cells/kg (and with prior Flu/Cy as conditioning chemotherapy), the therapy was highly effective with an ORR and CR of 100% and 88%, respectively. At the last follow up, the median progression-free survival (PFS) and OS were not reached.[24]

The University of Pennsylvania (UPenn) also reported its data in FL using CTL019 (which will became tisagenlecleucel) anti-CD19 CAR-CD3zeta- CD137(4–1BB) lentiviral gene-vector transfer in 15 R/R FL patients after multiple

lines of therapy. In this study the ORR and CR rates were 79% and 71%, respectively.[25] The most recent update reported a five-year PFS of 43% in infused patients.[26]

The ZUMA-5 Clinical Trial: Axi-Cel in Refractory/Relapsed Follicular Lymphoma

The ZUMA-5, single-arm, Phase II trial included 148 patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (NHL), FL (n=124) and marginal zone lymphoma (MZL) (n=24) treated with axi-cel.[7] The primary endpoint was overall response rate (ORR). Patients with FL had bulky disease (52%), stage IV (85%), most of them (63%) were heavily pretreated with more than three lines of therapy, had a progression of disease within 24 months of receiving frontline chemoimmunotherapy (POD24) (55%), and had received and failed previous autologous stem cell transplant (auto-HCT) (24%). Bridging therapy was given to 4% of all patients (4/124 patients with follicular lymphoma). The median time from leukapheresis to CAR T product delivery was 17 days. Patients received standard conditioning chemotherapy as described for DLBCL in the ZUMA-1. With a median follow up, for FL patients, of 30.9 months, the ORR following axi-cel for patients with FL was high, at 92%, with 76% of the patients achieving complete remission (CR). High response rates translated into durable responses with a duration of response (DOR) in FL patients of 38.6 months, and 57% of eligible patients were in ongoing response at data cut-off.[7] The estimated median PFS and overall survival (OS) were 39.6 months and not reached for patients with FL, respectively.[27] Long-term PFS rates were consistent among key subgroups, namely, high-tumor burden, >4 lines of prior therapy. In terms of toxicity, the cytokine release syndrome (CRS) and neurologic event (NE) rates were relatively high (for FL, CRS=78% and NE=56%). Higher grade >3 CRS and NE were 6% and 15%, respectively. The most common grade >3 NE was encephalopathy (8%). In terms of cytopenias, 24%, 10%, 4% had grade >3 anemia, neutropenia and decrease in white blood cells (WBC), respectively. See Table 1 for a summary of the ZUMA-5 highlights.

Other Cell Therapies for R/R Follicular Lymphoma

Based on the earlier results reported by the UPenn group, the pivotal ELARA study was launched to study the role of tisa-cel in R/R FL. The ELARA trial included 97 infused patients, with a median age of 57 years, median prior therapies of 4 (27.8% >4 lines), bulky disease in 63.9%, stage III–IV in 85.6%, POD24 in 62.9%, and 36.1% with prior autologous HCT.

Table 1 ZUMA-5 Summary of the Trial

Product	Axicabtagene Ciloleucel (axi-cel): • Autologous anti-CD19 CAR T cell • Antibody fragment derived targeting CD19 • CD3-zeta and CD28 costimulatory intracellular domains • Viral vector: retrovirus
Patients	Enrolled/leukapheresed: 151; Infused: 146 (FL: 124, MZL: 22) Median follow up: FL (30.9 months), MZL (23.8 months)
Key inclusion/exclusion criteria	Inclusion (patient population): • Relapse/refractory FL (grades 1–3a) and MZL to at least 2 lines of therapy. Must have progressed within 1 year from last therapy. • Must have had an anti-CD20 antibody and an alkylating agent. Exclusion: • Pts with SLL, WM, splenic MZL, FL grade 3B or any prior transformation to DLBCL. • Prior allogeneic HCT.
Manufacturing	Median time from apheresis to CAR T infusion: 17 days Manufacturing success: 100%
Conditioning regimen and dose of axi-cel	Fludarabine 30 mg/m2 and cyclophosphamide 500 mg/m2 x 3 days IV Axi-cel target dose: 2×10^6 CAR-T cells/kg

(*Continued*)

Table 1 (Continued).

Key population characteristics	Median age: 61 years (34–79) FLIPI >3: 47% Bulky disease: 49% Median prior therapies: 3 (1–10) POD24: 55% Prior HCT: 23% Prior lenalidomide: 31%; prior Pi3K inhibitor: 29%
Efficacy	ORR: 92% (FL: 94%, MZL: 85%) CR: 76% (FL: 80%, MZL: 60%) DoR: 38.6 months (FL: 38.6, MZL: NR months) PFS: 39.6 months (FL: 39.6 months, MZL: 17.3 months)
Toxicity	CRS • Any grade: 82%, grade > 3: 7% • Time to onset: 4 days (1–15) NT • Any grade: 60%, grade >3: 19% • Median time to onset: 7 (1–177)

Abbreviations: FL, follicular lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenstrom macroglobulinemia; DLBCL, diffuse large B-cell lymphoma; HCT, hematopoietic cell transplantation; POD24, progressive disease within 24 months; ORR, overall response rate; CR, complete response; DoR, duration of response; NR, not reached; CRS, cytokine release syndrome; NT, neurotoxicity.

Bridging therapy was needed in 45% of cases. The median time from enrollment to infusion was 46 days. At a median follow up of 9.9 months, the ORR and CR rates were 91.8 and 75.3%, respectively. The one-year PFS rates for all patients and patients achieving CR were 67% and 85.5%, respectively. The one-year PFS was lower in patients with POD24 (60.8% vs 77.9%), high baseline total metabolic tumor volume (TMTV) >510 cm3 (54.5% vs 68.5%), and >5 lines of therapy (59.6% vs 69.7%).[8] Median OS was not reached. The 9-month DOR was 86.5%. CAR T-related toxicities were also reported with grade 1–2 CRS of 48.5% (no grade >3 CRS) and all grades NE and grade >3 of 37.1 and 3.1%, respectively. Cytopenias were also seen: 32% had grade >3 neutropenia, anemia and leukopenia in 32%, 13.4% and 12.4%, respectively. By 12-months, 92.3%, 100% and 100% recovered their WBC, hemoglobin, and neutrophils, respectively.[8]

ALLO-501, an allogeneic CAR T product, which uses TALEN ® gene editing to disrupt the T-cell receptor alpha constant gene and the CD52 gene, has also been studied in 23 patients with R/R FL and showed ORR and CR rates of 82.6% and 52.2%, respectively. The responses appeared to be short-lived, with a six-month CR rate of 36.4%.[28]

Both trials showed high response rates with the use of their respective CAR T cell therapies for FL. While the CRand ORR rates with tisa-cel in the ELARA trial appear to be numerically lower than those with axi-cel, this needs to be interpreted with caution because of the difference in patient, disease, and treatments characteristics between the two studies (Table 2).[7,8] The ELARA study included more patients with advanced, bulky, and refractory disease. The median lines of previous therapy were 3 (2–4) in ZUMA-5 compared to 4 (2–13) in ELARA. A higher proportion of patients had POD24 in the ELARA compared to the ZUMA-5 trial (62.9% vs 55%, respectively). Moreover, 45% of ELARA trial patients required bridging therapy, perhaps suggesting that these patients may have had more symptoms from their disease. Yet, this could also be explained by longer cell manufacturing time with tisa-cel compared to axi-cel, increasing the wait time for patients and, consequently, the need for bridging therapy. In a "Matched adjusted indirect comparison of tisa-cel and axi-cel", similar ORR (89.77% with tisa-cel vs 94.5% with axi-cel, SD=−4.28%, in sensitivity analysis after weighing), CR rates (75.05% with tisa-cel vs 79.76% with axi-cel, SD=−4.71%), and PFS (hazard ratio [HR]=1.13, 95% CI 0.60–2.15, p=0.70).[9] Tisa-cel was associated with a better safety profile compared to axi-cel (Grade >3 CRS, 0.08% vs 6.45%, SD=−6.37%, grade >3 NE, 0.97% vs 15.32%, SD=−14.35%).[29] While such comparison has inherent biases, it suggests that using either of those CAR T products could possibly lead to similar outcomes. In contrast, axi-cel is associated with higher toxicities, comparable to those reported when used as treatment for large B-cell lymphoma (LBCL). To our knowledge, no study has evaluated to date the prognostic predictors of toxicities in patients with FL

Table 2 Comparison Between ZUMA-5 and ELARA Trials

Characteristic	ZUMA-5 (n=124)	ELARA (n=97)
Median age (range), years	60 (34–79)	57 (23–77)
Stage III–IV disease, n (%)	85%	83.4%
≥3 FLIPI, n (%)	44%	59.8%
High tumor bulk (GELF criteria), n (%)[a]	64 (52)	NA
Median no. of prior therapies (range)	3 (1–10)[b]	4 (2–13)
Prior PI3Ki therapy, n (%)	27%	20.6%
Refractory disease, n (%)[c]	68%	77.3%
POD24, n (%)[d]	55%	59.8%
Prior autologous HCT, n (%)	24%	36.4%
Efficacy		
ORR	92%	86.2%
CR	76%	69.1%
PFS	39.6 months	29.5 months
Safety (in FL cohort)		
CRS (all/G >3)	78%/6%	48.5%/0
NT (all grades/G >3)	56%/15%	9.3%/1%

Abbreviations: FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; PI3Ki, phosphatidyl inositol-3 kinase inhibitor; POD24, progressive disease within 24 months; HCT, hematopoietic cell transplantation; ORR, overall response rate; CR, complete response; PFS, progression free survival; CRS, cytokine release syndrome; NT, neurotoxicity; G, grade.

receiving CAR T cell therapy. While tumor burden could predict toxicity in patients with LBCL undergoing CAR T cell therapy,[30] this may not be necessarily true for patients with indolent NHLs. Hence, selection of tisa-cel vs axi-cel as the preferred therapy is presently based on physician discretion and/or familiarity with a specific product. Table 2 compares the two studies: ELARA and ZUMA-5.

Adoptive Immunotherapy with Allo-HCT and/or Donor Lymphocyte Infusion (DLI)

Allo-HCT represents an acceptable treatment option for patients with chemosensitive relapsed FL that can lead to long-term remissions and even cure. The majority of published studies in FL have evaluated reduced intensity conditioning (RIC) regimens due to the fact that patients with FL are generally of advanced age and may have associated comorbidities rendering them less fit. RIC and non-myeloablative (NMA) regimens rely primarily on the bona fide graft-versus-lymphoma (GVL) effect mediated by the donor T cells for disease control.[31] The efficacy of DLI in inducing a disease response has been described in various hematologic malignancies, including FL and other lymphoma histologies.[32] The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) conducted a multicenter Phase II trial evaluating an RIC regimen combining fludarabine, cyclophosphamide, and high-dose rituximab (FCR) in 65 patients with a median age of 55 (29–74) years.[33] The majority of patients (77%) had received 3 or more prior regimens. The overall response rate after HCT, in 62 evaluable cases, was 94% (CR=90%).[33] With a median follow up of 47 (30–73) months, the authors reported three-year PFS and OS rates of 71% and 82%, respectively.[33] A single institution study also using FCR reported estimated PFS and OS rates of 83% and 85%, respectively, at a median follow up of 60 months.[34] While there may still be a cytoreductive benefit from chemotherapy and/or radiotherapy, this is undoubtedly less pronounced compared to myeloablative conditioning (MAC) regimens. One limitation of allo-HCT remains the resulting incidence of graft-versus-host disease and resulting comorbidities.[31,34]

Other Immune-Based Therapies

T-cell engager antibodies or bispecific antibodies (BiAbs) have emerged as potential and promising treatment options for R/R FL. Several Fc-based BiAbs have been studied in B-cell NHL to date. The first in class is mosunetuzumab, a CD20/CD3 BiAbs, which showed promising efficacy in heavily pretreated R/R FL. The initial Phase I portion of the study showed ORR and CR rates of 66.2% and 48.5%, respectively, with a median PFS of 11.8 months.[35] The pivotal Phase II study in R/R FL with two or more prior lines of therapy and at the recommended phase 2 dose, included 90 patients with high risk factors such as POD24 (52%), prior HCT (21%), and three median lines of therapy. In this study, the ORR and CR rates were 80% and 60%, respectively, with a median PFS of 17.9 months.[36] Mosunetuzumab is currently approved by the EMA for the treatment of R/R FL after at least two lines of prior therapy and may be approved soon in the US.

Other bispecific antibodies have shown promising efficacy but their follow up is short and a small number of patients are involved. Odronextamab, glofimatab and epcoritamab have elicited an ORR of 78%, 80%, and 90%, respectively, in the third-line setting.[37–39]

There are inherent advantages of BiAbs, such as rapid availability, logistics, and administration. However, it is still too early to establish long-term efficacy.

Other immunotherapy-based regimens are currently being investigated (such as loncastuximab, lenalidomide, and tafasitamab), which may further change the landscape treatment of FL (NCT 04680052 and NCT 04998669).

Patient Selection

Given its high efficacy and potential life-threatening toxicities, a key aspect is to determine which patients are fit for axi-cel therapy. Early referral to a CAR T center is of paramount importance as the CAR T teams will be able to determine whether a patient is an appropriate candidate for CAR-cell therapy. Patients with early relapse (POD24) are particularly at high risk of early death and should be considered for early referral despite not yet meeting the FDA label criteria.[40] Potential factors that may affect CAR T eligibility include comorbidities, logistics, need of caregiver, and manufacturing time. Insurance approval delays may also affect patient access to CAR T. As opposed to aggressive NHLs, patients with indolent NHLs follow a less rapid course of disease progression, therefore manufacturing time may be a less critical factor to some extent. Prior therapies, especially consideration of bendamustine in the relapse setting, should be discussed carefully as it may affect the quality of the T-cells that are essential for CAR T manufacturing.

In the third-line (3L) setting, especially for those double refractory (refractory to alkylating agent and anti-CD20 monoclonal antibody) and early relapse patients, CAR T therapy should be considered as part of the standard of care landscape, given the high efficacy and prolonged remissions when compared to other therapies. Mosunetuzumab will certainly be part of the treatment landscape in the 3L setting, complicating treatment choices and sequencing. The CAR T product selection is more challenging, given the high efficacy of either axi-cel or tisagenlecleucel. Manufacturing time and longer-follow up data appears to favor axi-cel, whereas a lower toxicity profile is a noted advantage for tisagenlecleucel.

Discussion

In the third-line setting, the treatment patterns for R/R FL are highly heterogenous, reflecting the lack of a definitive standard approach. In addition, response duration is short, with increased mortality, especially for those patients refractory to alkylating-based regimens.[41] Standard treatments for patients with R/R FL after third line and beyond include conventional therapy using phosphoinositide-3 kinase inhibitors (PI3Ki), EZH2 inhibitors, auto-HCT or allo-HCT and, more recently, CAR T cell therapy. Although response rates with PI3K and EZH2 inhibitors range between 60–70%, the CR rate is very low (12% with copanlisib [PI3Ki] and 13% with EZH2 inhibitors).[42–44] In addition, with the withdrawal of most of PI3Ki for R/R FL (due to concerns regarding toxicities and increased mortality) from the market, there has been growing interest in developing effective strategies for R/R FL.[45] CAR T cell therapy is associated with higher ORR (axi-cel 94% and tisa-cel 91.8%) and CR rates (axi-cel 79% and tisa-cel 75.3%). As discussed above, axi-cel was associated with higher rates of CRS and NE but faster manufacturing time. Longer follow up is needed to confirm those findings, determine the durability of response, and assess survival.

To date, no prospective data is available comparing CAR T versus other available standard options. The SCHOLAR-5 study attempted to answer this question in a propensity scoring, analysis using relevant prognostic factors such as POD24, refractoriness to last therapy, number of prior lines of therapy, disease burden, and prior exposure to anti-CD20 antibody/alkylating agent. After matching for these factors, ZUMA-5 had significantly higher PFS and OS response rates.[46]

The outcomes of patients with POD24 remain poor, even with CAR T cell therapy. Strategies to improve outcomes of these patients could include combination therapies with CAR T cell therapy to enhance CAR T expansion and improve persistence. A study combining acalabrutinib and axi-cel in patients with R/R B-cell lymphoma, including patients with FL, is ongoing (NCT04257578). The ZUMA-22 study will assess the efficacy of axi-cel in comparison with standard of care therapies for R/R FL after at least one line of therapy if POD24 or after two lines (NCT05371093). An ongoing Phase I/II trial is currently evaluating CD20 CAR T cell for patients with B-cell lymphoma (NCT03277729) and another trial is assessing the used of dual-target anti-CD20/19 CAR T cell therapy (NCT04186520). Allogeneic CAR T cells are being explored in FL offering an off-the-shelf option, especially for patients in rapid need of treatment (NCT03939026).

The outcome of patients receiving check-point inhibitors after CAR T cell therapy is as yet unknown. A study is currently evaluating nivolumab for patients relapsing after CAR T cell therapy in patients with B-cell lymphoma (NCT04205409).

In our opinion, allo-HCT remains a valid option in patients with R/R FL using RIC. However, owing to the higher anticipated treatment-related mortality with allo-HCT (vs CAR T therapy), we believe that the future role of allo-HCT would be relegated to a later stage of the therapeutic algorithm of FL; for example, in patients who fail to achieve a CR with CAR T therapy and are fit enough to tolerate an allo-HCT.

Conclusion

Axi-cel and other CAR T cell therapies represent a welcome addition to the treatment armamentarium of FL, yielding impressive responses in heavily pretreated cases and with relatively well tolerated side effects. Future efforts should focus on making this treatment available to all patients for whom this treatment is indicated, as its current cost makes it prohibitive and unaffordable in developing countries.

Disclosure

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