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Novel Therapies for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

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Abstract

The most common type of non-Hodgkin lymphoma in adults is diffuse large B-cell (DLBCL). There is a historical unmet need for more effective therapies in the 2nd and 3rd line setting. Emerging immunochemotherapies have shown activity in small studies of heavily pre-treated patients with prolonged remissions achieved in some patients. Anti-CD19 CAR (chimeric antigen receptor) T cells are potentially curative in the 3rd line and beyond setting and are under investigation in earlier lines of therapy.[1] Antibody-drug conjugates (ADC's) such as polatuzumab vedotin targeting the pan-B-cell marker CD79b has proven effectiveness in multiply-relapsed DLBCL patients. Tafasitamab (MOR208) is an anti-CD19 monoclonal antibody producing prolonged remissions when combined with Lenalidomide in patients who were not candidates for salvage chemotherapy or autologous stem cell transplant. Selinexor, an oral, small-molecule selective inhibitor of XPO1-mediated nuclear export (SINE), demonstrated prolonged activity against heavily-pretreated DLBCL without cumulative toxicity and is being investigated as part of an oral, chemotherapy-free regimen for relapsed aggressive lymphoma. This article reviews current strategies and novel therapies for relapsed/refractory DLBCL.

Keywords: Relapsed or Refractory Diffuse Large B Cell Lymphoma, DLBLC, immunotherapy, chemotherapy-free regimen

Introduction

Diffuse large B-Cell Lymphoma (DLBCL) is an aggressive subtype accounting for 25-30% of Non-Hodgkin lymphoma (NHL) with an incidence of 5.6 per 100,000 persons per year.[2, 3] DLBCL is usually symptomatic at presentation with either nodal or extranodal disease. Diagnosis is made when large, transformed B cells (CD19+, CD20+, CD79+) with prominent nucleoli, diffuse growth pattern, and a high proliferation fraction are seen on tissue biopsy.[2] The World Health Organization (WHO) schema classifies by cell of origin (COO) classification including germinal B-cell (GCB) subtype or activated B cell (ABC) subtype. GCB cases have a better overall survival than ABC cases; possibly due to lower incidence of coexpression of MYC/BCL2 even without oncogene translocation.[4, 5] Despite multiple studies attempting to improve upon outcomes, R-CHOP remains first line treatment for DLBCL regardless of IPI score, COO, or gene expression profile except for DHL. In the 2017 revision of WHO classifications, DLBCL with translocations of MYC and BCL2 and/or BCL6 – double-hit (DHL) or triple-hit (THL) – are reclassified as Diffuse Aggressive B-Cell Lymphomas, with more intense therapeutic regimen such as DA-EPOCH-R with CNS prophylaxis in the first line setting had a 4 hour overall survival of 76%.[6]

DLBCL cases that don't fit a specific subtype have an overall survival rate of 65% when treated with standard R-CHOP (Rituximab, Cyclosporine, Vincristine, Prednisone) therapy.[2] The Standard International Prognostic Index (IPI) is widely used for risk stratification with aggressive B-cell lymphoma,

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and has been validated with continued prediction of risk in the Rituximab era.[7] Pts with high IPI score have poor prognosis with OS as low as 20-25%. [61] In the future, upfront treatment for DLBCL may be based on COO and molecular markers. Certain mutations and pathways are common in GCB subtype such as EZH2, BCL2 and PI3K. In ABC subtype, NF-KB activation, MYD88 mutations and JAK-STAT pathways are more common. [63]

While most patients respond, 30-40% of patients with DLBCL relapse or are unable to achieve remission with first-line treatment. In these cases the prognosis is poor.[3] Approximately 50% of patients with relapsed or refractory (R/R) DLBCL have a response to second-line chemotherapy; up to 50% of these patients proceed to undergo autologous hematopoietic stem-cell transplantation in some settings, and of these, approximately 30 to 40% remain progression-free 3 years after transplantation.[8] [9-12] Median survival for primary and secondary refractory DLBCL is 5-7 months.[12]

Patients who progress after receiving R-CHOP receive combination salvage chemotherapy. Commonly used regimens R-ICE, R-DHAP, R-GDP, R-GemOx, O-DHAP, O-ICE, and DR-ICE have similar treatment effect.[13, 14] However, analysis of real-world data from 126 community-based hematology/oncology practices in the US between 2010-2016 demonstrated that only 13% of patients who received salvage regimens intended for ASCT eventually underwent ASCT.[15]

The unmet need for more effective regimens is highlighted by the wide heterogeneity in regimens used in clinical practice with consistently poor outcomes.[13] Pts that are not ASCT or CAR-T candidates have poor outcomes with salvage chemotherapy regimens. Response rate comparisons between studies are unreliable due different rates of enrollment of primary refractory disease. In the phase III CORAL trial (n=396) comparing R-ICE and R-DHAP followed by autologous hematopoietic cell transplant (HCT) for chemosensitive patients, the overall response was 63% and three year overall survival 47%. Median overall survival of R/R DLBCL who failed second-line regimens in CORAL was 4.4 months.[12] The LY.12 trial (n=619) compared the platinum-containing regimens R-GDP and R-DHAP followed by autologous HCT and had response rate 45%.[11] SCHOLAR-1 is the most comprehensive analysis of pooled outcomes from several large studies of relapsed and refractory DLBCL (*n* = 636) treated with various standard of care chemotherapy regimens, and the ORR was 26%, CR rate of 7%, and median overall survival was 6.2 months.[16, 17]

Lenalidomide (LEN) is an immunomodulatory drug that has shown single agent activity in R/R DLBCL with response rates of 20-30%.[18] In a phase 2 trial, LEN was combined with rituximab for treatment of R/R DLBCL and other NHL, ORR was 28% and CR was 22%.[19] Ibrutinib is a Bruton's tyrosine kinase inhibitor that has shown activity in R/R DLBCL, especially ABC subtype with ORR of 37%.[20] However in a phase 1b/2 study, the combination of LEN, Ibrutinib and rituximab demonstrated an ORR of 38% and CR of 7% among all R/R DLBCL.[21] Since ABC subtype have poor prognosis compared to GBC subtype, Ibrutinib and LEN have been studied in upfront setting with R-CHOP. The Phoenix trial, a phase 3 randomized trial comparing RCHOP +/- Ibrutinib in untreated ABC subtype DLBCL; failed to meet its primary endpoint of disease-free survival.[22] ROBUST is a large phase 3 clinical trial (n=570) that compared LEN with RCHOP vs RCHOP in first line treatment of ABC subtype DLBCL, and LEN+RCHOP failed to demonstrate a PFS benefit over RCHOP.[23] Based on this data, RCHOP remains standard treatment for upfront DLBCL therapy; but LEN and Ibrutinib in combination with immunotherapy have activity in R/R DLBCL.

Cost-effectiveness analysis of DLBCL regimens from the Truven database with claims data from US government and private payers highlighted the direct costs associated with the 2/3 of patients with

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DLBCL who received subsequent 2nd-line regimen after completing R-CHOP.[24] More effective treatment options for this resource intensive condition has the potential to both decrease mortality and reduce the costs of subsequent lines of therapy including ASCT.[24, 25] Innovative targeted treatment modalities have emerged over the past few years, with higher rates of prolonged immune-mediated remissions (Table 1).

Table 1 – Novel Regimens with FDA Approval

Agent	Year of FDA Approval	Regimen	Population	Relapse <1 yr of DLBCL diagnosis	Refractory to last regimen	DHL/THL	Efficacy Outcomes
Polatuzumab vedotin[26]	2019	Pola + BR	R/R DLBCL Ineligible for ASCT	53%	75%	0 %	CMR 40% mOS 12.4 mos
Selinexor[27]	2020	Selinexor 60mg po on days 1 and 3 of each week	R/R DLBCL	33% §§	72%	4 %	ORR 28% CR 12% mOS 9.1 mos
Tafasitamab[28]	2020	Tafa + LEN 25 mg	R/R DLBCL Ineligible for ASCT	19% §	44%	0 %	ORR 58% CR 33% mOS 22 mos
Lenalidomide[19]	2005	R2: Ritux + LEN 20 mg	R/R DLBCL	NR	NR	NR	ORR 28% CR 22% mOS 10.2 mos

FDA: United States Food and Drug Administration; Pola: Polatuzumab vedotin; BR: Bendamustin and Rituximab; Ritux: Rituximab; LEN: Lenalidomide; Tafa: Tafasitamab; dx: diagnosis; DHL: Double Hit Lymphoma; THL: Triple Hit Lymphoma; R/R DLBCL: Relapsed or Refractory Diffuse Large B Cell Lymphoma; ORR: Overall Response Rate; CR: Complete Response; mOS: Median Overall Survival; mos: months CMR: Complete Metabolic Response; PR: Partial Response; po: by mouth; NR: Not Reported

§ Excluded if received anti-CD20 therapy within 6 months.
§§ Excluded if not in PR or CR and received therapy within 14 weeks.

Tafasitamab

Tafasitamab (MOR208) is an Fc-enhanced, humanized, anti-CD19 monoclonal antibody that has shown preclinical and single-agent activity in patients with relapsed or refractory B-cell malignancies.[29] It has been engineered to have better antibody directed cellular cytotoxicity (ADCC) than a native antibody LEN enhances natural killer cell-meditated, antibody-dependent cellular cytotoxicity with tafasitamab in vitro.[30] A recently published analysis confirmed synergistic effects of combining tafasitamab with LEN by comparing the L-MIND study (combination) to RE-MIND (LEN monotherapy).[31] L-MIND is an open-label, single-arm, phase II clinical trial of tafasitamab plus lenalidomide in patients with relapsed or refractory DLBCL who were ineligible for high-dose chemotherapy with autologous stem-cell transplantation due to factors such as advanced age, refusal, or comorbidities.[28] Double-hit (simultaneous detection of *MYC* with *BCL2* or *BCL6* translocation) and primary refractory patients who relapsed within 6 months of anti-CD20 therapy were excluded (in the first 6 months of recruitment the exclusion was only 3 months to be primary refractory). Of the 80 patients who received the dual therapy, 43% experienced complete responses and 18% exhibited partial responses, and the median duration of these responses was 21.7 months. In contrast to LEN monotherapy in similar patients, where only 13.2% experienced complete response.[31] And in contrast to the R2 regimen of LEN and Rituximab for R/R DLBCL, where only 13.3% experienced complete response.[19] All Tafasitamab+LEN patients experienced treatment-emergent adverse events, with neutropenia being the most common adverse event. Nonhematologic adverse events were most often grade 1 or 2 and included diarrhea and rash.[28] Notably, 12% of patients discontinued study treatment because of adverse events, and four patients died of treatment-emergent adverse events, although none of these deaths were deemed by

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the investigators to be due to the study treatment.[32] However, cytopenias are likely related to LEN use. Now in a phase 1b study, MOR 208 is being studied in combination with R-CHOP and lenalidomide for frontline DLBCL treatment.[59]

Polatuzumab Vedotin

Polatuzumab vedotin is an antibody–drug conjugate (ADC) consisting of a humanized anti-CD79b monoclonal antibody and the anti-mitotic agent, mono-methyl auristatin E (MMAE).[33] This Polatuzumab vedotin's antibody recognizes the CD79b protein that is associated with the B-cell receptor. After the antibody binds to CD79b, the ADC's toxic payload (MMAE) enters the B cell and then kills it by preventing tubulin polymerization. Targeting the pan-B marker CD79b is ideal since it will not select for resistance to CD19 regimens for patients who may later require CAR T cell therapy directed against CD19.[34] Given as a parenteral triplet polatuzumab-vedotin plus bendamustine and rituximab, it is approved for third-line therapy use after demonstrating a median overall survival of 12.4 months compared with 4.7 months for patients receiving a current standard salvage regimen of bendamustine and ritixumab.[26] Patients were excluded if history grade $\geq$2 peripheral neuropathy or prior HSCT. Primary-refractory nor double/triple-hit lymphomas were excluded. Adverse reactions led to dose reduction in 18%, dose interruption in 51%, and permanent discontinuation of all treatment in 31%. The most common adverse reactions leading to treatment discontinuation were thrombocytopenia and/or neutropenia.[35] In early phase studies and clinical practice, experts suggest Polatuzumab has significant single agent activity and it can be given without bendamustine. The POLARGO study is a currently enrolling multicenter phase III randomized controlled trial of pola-R-GemOx vs R-GemOx alone in R/R DLBCL.[36] Pt with relapsed disease who need a bridge to either CAR-T or ASCT, polatuzumab has proven to be active regimen used in this situation. Since polatuzumab has been so effective and well tolerated, currently there is an ongoing trial, POLARIX using it in upfront therapy with RCHOP

Selinexor

Selinexor, an oral selective inhibitor of XPO1-mediated nuclear export (SINE), has a broad potential mechanism of action. It induces the expected nuclear accumulation and activation of tumor suppressor proteins and reduces Bcl2, Bcl-X_L, and c-Myc oncoprotein concentrations.[27] It received accelerated FDA approval in 2019 for relapsed or refractory DLBCL after 2 lines of systemic therapy in addition to approval for relapsed Multiple Myeloma.[37] The multicenter, open-label, phase 2b SADAL study, 127 patients with DLBCL who had received two to five lines of previous therapies, and progressed after or were not candidates for autologous stem-cell transplantation were given selinexor orally at the fixed dose of 60 mg on day 1 and day 3 weekly, until disease progression or manifested unacceptable toxicity.[38] The primary endpoint of overall response rate was 28% (36/127) with median duration of response 23 months. Complete response was achieved in 12% with a median duration of 23.0 months. In subgroup analysis of those with low c-myc expression by immunohistochemistry, overall response rate was 42%.[27] Selinexor caused adverse events that were reversible with standard supportive care and dose modification to 40 mg dosing. Without apparent cumulative toxicity, there is currently no maximum duration of treatment; the longest duration of treatment in the SADAL study with selinexor is >3.5 years**.[27]** Two experimental studies (NCT02303392 and NCT03955783) in aggressive lymphoma, testing the combinations of selinexor with ibrutinib or venetoclax are active and recruiting. Results of the studies might clarify if a totally oral and chemotherapy free treatment should be an option for patients with relapsed or refractory DLBCL.

CAR T Cells

Anti-CD19 CAR T cell therapy has transformed the approach to multiple-relapsed/refractory aggressive B-cell lymphomas. Three anti-CD19 CAR T cell products have demonstrated efficacy in relapsed DLBCL

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with remarkably long duration of effect in patients who achieve a complete response. Second generation receptors, dual target CD19/CD22, novel dose escalation protocols, and addition of PD-1 blockade are in ongoing studies for improved efficacy and/or reduced toxicity.[39] The indications for use may expand in the future as the collection and manufacturing process becomes more streamlined and more centers develop experience managing its toxicities.[8, 40-42] Currently axicabtagene ciloleucel (axi-cel) and Tisagenlecleucel (tisa-cel) are approved by the US Food and Drug Administration in adults with relapsed or refractory DLBCL after two or more lines of systemic therapy. The ZUMA study (n=101) of axi-cel reported a 58% CR and 24 month survival rate of 50.5%. The cohort of patients age ≥65 years (n=81) had a 44% rate of grade ≥3 neurologic toxicity. The JULIET study (n=93) of tisagenlecleucel had a 40% CR and 12 month overall survival rate of 49%. The TRANSCEND study (n=344) of lisocabtagene maraleucel reported CR 53% and estimated 12 month overall survival rate 58%.[43] Multiple randomized trials are currently enrolling patients with primary refractory or early relapsed aggressive B-cell lymphomas comparing anti-CD19 CAR T cell therapy with traditional salvage therapy and ASCT (TRANSFORM, NCT03575351; BELINDA, NCT03570892; and ZUMA-7, NCT03391466).[1] A key limitation of CAR-T therapies is limitations in access and the time that lapses between collecting and infusing cells that often require 6 weeks to engineer.

Table 2 - Novel Regimens Under Investigation for Relapsed or Refractory Diffuse Large B Cell Lymphoma

Bispecific Abs					
	Epcoritamab (CD3/CD20) Flat dose Subcutaneous weekly Escalation study	Hutchings, et al[44] NCT03625037	Phase 1/2 R/R DLBCL	N= 41	Enrolling Median f/u 4.7 mo ORR 56% CR 44% No dose limiting toxicities
Monoclonal Abs					
	Tafasitamab (anti-CD19) (Fc-enhanced, humanized) + Lenolidomide	Nowakowski, et al[31] Maddocks, et al[45] NCT02399085	Phase 1/2 R/R DLBCL Ineligible for ASCT Excluded double-hit	N=81	Enrolling phase 3 ORR 58% CR 33% Median OS 22 mos (95% CI: 18.6 – NR)
	Magrolimab (5F9) (anti-CD47, promote phagocytosis) +Rituximab	Advani, et al[46] NCT02953509	Phase 1b/2 R/R DLBCL	N=15	Enrolling, Preliminary results ORR 40% CR 27% On-target anemia primarily 1st dose
Anti-PD-L1 Containing Regimens					
	Atezolizumab (anti-PDL1) +Obinituzumab (anti-CD20) +Venetoclax (BCL2 inhibitor)	Herbaux, et al[47] NCT03276468	Phase 2 R/R DLBCL	N=58	Interim Results ORR 23.6% CMR 18%
	Mogamulizumab (anti-CCR4) + Pembrolizumab	Joffe, et al NCT03309878	Phase 1b/2 R/R DLBCL Ineligible for ASCT		Enrolling
	Avelumab (anti-PD-L1) +/- Utomilumab (4-1BB agonist) +/- Rituximab +/- Bendamustine or Azacitidine	Chen, et al[48] NCT02951156	Phase 1b/3 R/R DLBCL Ineligible for ASCT ECOG≤1		Enrolling
Bispecific CAR T Cell Therapies					
	AUTO3 (CD19/CD22) Dual targeted + Pembrolizumab	Osborne, et al NCT03287817	Phase 1/2 R/R DLBCL	N=11	 ORR 64% CRR 55%
	LV20.19CAR (CD19/CD20) Dual targeted Lentiviral	Shah, et al[49] NCT03019055	Phase 1 R/R NHL 45% DLBCL		Enrolling in expansion phase ORR 82% CR 54.5% No grade 3-4 CRS or NTX in first 11 pts.
Antibody-Drug Conjugates					
	Polatuzumab vedotin (anti-CD79b/MMAE) added to BR	Sehn et al[26] Lu et al[33] NCT02257567	Phase 2 R/R DLBCL Ineligible for ASCT	N=80	CMR 40% Median OS 12.4 mos
	Polatuzumab vedotin	Haioun, et al[36]	Phase 3		Enrolling

	(anti-CD79b/MMAE) added to GemOx	NCT04182204	R/R DLBCL		
Engineered Toxin Bodies					
	MT-3724 (CD20 / SLT-I A1)	Fanale, et al[50] Duque, et al[51] NCT02361346	Phase 1 Relapsed B-NHL after anti-CD20 and CT	N=100	Safety and efficacy assessment of 50 mcg/kg/dose ongoing.
Selective Inhibitor of XPO-1-mediated Nuclear Export (SINE)					
	Selinexor 60mg po on days 1 and 3	Chiappella, et al[38] NCT02227251	Phase 2b R/R DLBCL	N=127	Interim Results ORR 28% CR 12%
PI3K Inhibitor					
	Parsaclisib 20 mg po daily	Coleman, et al[52, 53] NCT02998476	Phase 2 R/R DLBCL	N=60	Interim Results ORR 25% CMR 12.5%
	Buparlisib 80 mg po daily + Ibrutinib	Batlevi, et al[54] NCT02756247	Phase 1/2 R/R DLBCL, Mantle Cell, Follicular	N=37	Interim Results ORR 31% CMR 23%
BTK Inhibitors					
	Acalabrutinib 100mg po BID +Pembrolizumab	Witzig, et al[18] NCT02362035	Phase 1/2 R/R DLBCL	N=61	ORR 26% CR 7%
	Zanubrutinib 160mg po BID	Yang, et al[55] NCT03145064	Phase 2 R/R Non-GBC DLBCL Ineligible for ASCT	N=41	ORR 29.3% CR 17.1% Median OS 8.4 mos
Immunomodulators					
	R2-GDP Lenalidomide 10mg po d1-14 + R-GDP	Merino, et al[56] EudraCT 2014-001620-29	Phase 2 R/R DLBCL Ineligible for ASCT	N=79	Enrolling ORR 59% CR 32% Median OS 12 mos
	R2-ICE Lenalidomide 20mg po d1-14 + RICE	Guerra-Bauman, et al[57] NCT02628405	Phase 1/2 R/R DLBCL Candidates for ASCT		Enrolling

mAb = Monoclonal Antibody; PO = by mouth; BID = twice daily; Mo(s) = month(s); ORR = Overall Response Rate; CR=Complete Response; CMR=Complete Metabolic Response by Positron Emission Testing (PET); Dur.= Duration; CT = Chemotherapy; ATE+OBI+VEN (Atezulizumab+Obinituzumab+Venetoclax); BR = Bendamustin/Rituximab; Gem-Ox = Gemcitabine/Oxaliplatin; AE Trmt DC Ac/Pem =Adverse Events causing Treatment Discontinuation due to Acalabrutinib/Pembrolizumab; SLT-I A1=Shiga-like toxin-I A1; R2-GDP (Lenalidomide, Rituximab, Gemcitabine, Dexamethasone, Cisplatin); R2-IMED (Lenalidomide, Rituximab, Methotrexate, Etoposide, and Dexamethasone); R2-ICE (Lenalidomide, Rituximab, Ifosfamide, Carboplatin, Etoposide);

Future of DLBCL and immunotherapy

There are many other immunotherapy based regimens under early clinical trials aside from ones mentioned above (Table 2). MT-3724 is a novel Engineered Toxic Body (ETB) comprised of a proprietarily engineered form of Shiga-like Toxin A subunit (SLT-A) genetically fused to an antibody-like binding domain that binds CD20. ETB's work though a novel mechanism of action whereby internalization of the fragment when bound to CD20 delivers the toxin intracellularly where ribosomal inactivation leads to targeted cell death.[50, 51] MT-3724 is currently being studied in three ongoing Phase 2 studies for relapsed and refractory DLBCL.[51] Loncastuximab tesirine, ADCT-402 is an n antibody-drug conjugate composed of a humanized monoclonal antibody against CD19 and conjugated to a pyrrolobenzodiazepine dimer cytotoxin. In phase 2 trials, ADCT-402, 145 pts with relapsed or refractory DLBCL were enrolled and ORR was 45%. [64] The common side effect were cytopenias requiring dose adjustments, otherwise well tolerated. Hu5F9-G4, a humanized monoclonal antibody is a macrophage immune checkpoint inhibitor blocking CD47 that induces tumor-cell phagocytosis. A phase 1B study, 22 pts with relapsed NHL were treated with Hu5F9-G4 in combination with rituximab. [65] The ORR in DLBCL subset was 40% with CR of 33%. Most common AEs were infusion reaction, fever and chills. Immune checkpoint inhibitors have gained recognition in multiple solid tumor and demonstrate durable responses. PD-1 and PDL-1 are expressed in many hematologic malignancies and have recently been approved for second line HL. In a phase 1 trial of relapsed DLBCL patients, nivolumab showed an ORR of 36%, but these responses were not durable. [66] There are a few trials in DLBCL being completed with

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immune checkpoint inhibitors in combination with anti-CD-20 antibodies (NCT03401853) and immunomodulators and targeted agents like LEN (NCT03015896) and Copanlisib (NCT03484819). Table 1 includes a list early clinical trials involving immunotherapy for treatment of relapsed/refractory DLBCL.

Conclusions

Novel agents are changing treatment strategies in relapsed or refractory DLBCL after failure of cytotoxic chemoimmunotherapy. Harnessing the surveillance of the patient's T cell immunity has produced prolonged responses in studies of heavily pre-treated patients. The inclusion of immunotherapies like CAR T cells, bispecific antibodies, ADCs, and other immunomodulatory drugs to the treatment algorithms for DLBCL is filling the unmet need for agents with activity in the multiply relapsed setting. A recurring theme in the development of noncytotoxic regimens is that chemotherapy free does not equal toxicity-free.[1] Distinct adverse effects seen with immunotherapies are part of these treatment decisions, and ongoing studies are informing the physical toxicities expected in broader populations. Learning which patients reap the most benefit from these agents enables more accurate calculation of financial toxicities.

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