Research Article

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Journal of **Comparative Effectiveness Research**

Comparative effectiveness of glasdegib versus venetoclax combined with low-dose cytarabine in acute myeloid leukemia

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Background: Two combination therapies recently approved and recommended for use in combination with low-dose cytarabine (LDAC) in acute myeloid leukemia patients unfit for intensive chemotherapy are glasdegib+LDAC and venetoclax+LDAC. **Materials & methods:** An indirect treatment comparison used median overall survival, overall survival hazard ratios, complete remission (CR), CR+CR with incomplete blood count recovery and transfusion independence to assess comparative effectiveness, and a simulated treatment comparison accounted for differences in patient characteristics between trials. **Results:** Differences in efficacy between glasdegib+LDAC and venetoclax+LDAC were suggestive and not statistically significant. **Conclusion:** With no significant differences in comparative effectiveness, considerations such as safety profiles, burden of administration and patient preference are likely to guide treatment decisions.

First draft submitted: 10 December 2020; Accepted for publication: 22 February 2021; Published online: 18 March 2021

Keywords: AML • comparative effectiveness • glasdegib • indirect treatment comparison • low-dose cytarabine • nonintensive chemotherapy • simulated treatment comparison • venetoclax

Acute myeloid leukemia (AML) is an aggressive hematologic cancer caused by clonal proliferation of malignant myeloid stem cells in peripheral blood, bone marrow and other tissues [1]. AML accounts for nearly a third (29–32%) of annual leukemia diagnoses in the USA [2]. The American Cancer Society estimates 19,940 new cases of AML and 11,180 deaths due to AML in 2020 [3]. The median age of diagnosis in the USA is 68 years, and death rates from AML are higher among those aged 65 years and older [4]. Although overall 5-year survival rates have improved steadily since the 1970s, the estimated 5-year survival rate remains low, at 25% in 2018 [3]. Age is an important prognostic factor for AML outcomes, and older patients face poorer outcomes and have fewer treatment options [4,5]. Nonintensive chemotherapy (NIC) is often preferred for older patients and those with comorbidities, unfavorable cytogenetic markers and lower performance status.

There is no standard treatment regimen for patients with AML who are not candidates for IC [6]. In late 2018, the US FDA approved glasdegib (GLAS) in combination with low-dose cytarabine (LDAC) to treat newly diagnosed AML in patients aged 75 years and older, and in those who have comorbidities that preclude the use of intensive induction chemotherapy [7]. GLAS binds to and inhibits smoothened, a transmembrane protein involved in hedgehog signal transduction, and in a rodent model, the combination of GLAS+LDAC showed synergy, reducing the percentage of $CD45^{+}/CD33^{+}$ blasts in the marrow more than either agent alone [8]. GLAS+LDAC was approved by the EMA in 2020 for adult patients with AML who are not candidates for standard induction chemotherapy [9]. Treatment with GLAS+LDAC was approved following the results of the BRIGHT AML 1003 randomized controlled trial, which demonstrated improved clinical response and overall survival (OS) compared with LDAC alone [10]. Venetoclax (VEN), a small-molecule inhibitor of the anti-apoptotic protein BCL-2, displaces pro-apoptotic proteins and triggers mitochondrial outer membrane permeabilization and the activation of programmed cell death [11]. For patients aged 75 years and older or who have comorbidities that preclude the use of intensive induction chemotherapy, VEN gained FDA approval in 2018 in combination with

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azacytidine (AZA), decitabine (DEC) or LDAC, and a recent Phase III trial showed treatment with VEN+LDAC resulted in higher rates of clinical response and increased OS in unplanned analyses versus LDAC alone [11,12]. Both treatment regimens are recommended in the National Comprehensive Cancer Network 2020 guidelines for patients ≥60 years who are not candidates for IC [13].

Because these two regimens have not been compared in a head-to-head trial, indirect treatment comparisons (ITCs) are necessary for assessing comparative effectiveness. Both trials used a comparator arm of LDAC alone, and that common anchor allows for indirect comparison of treatment efficacy through relative treatment effects compared with control [14–18]. This methodology is more robust than comparisons of absolute event rates, but differences in patient populations between trials may limit the validity of the comparison [19]. A simulated treatment comparison (STC) adjusts for differences in patient baseline characteristics between trials before performing the ITC to provide population-adjusted estimates of comparative effectiveness [19,20]. The anchored STC approach can account for within- and between-trial differences in patient populations to compare GLAS+LDAC versus VEN+LDAC despite a lack of head-to-head trial data. In this study, both 'unadjusted' ITC (i.e., unadjusted for between-trial differences) and anchored STC (which adjusts for between-trial differences) were used to assess the comparative effectiveness of GLAS+LDAC and VEN+LDAC with respect to OS, clinical response and transfusion independence.

Materials & methods

Data sources

To compare GLAS+LDAC to VEN+LDAC, we leveraged the analysis of individual patient data (IPD) from the BRIGHT AML 1003 GLAS+LDAC, a Phase II randomized clinical trial, and published results were extracted from the VIALE-C VEN+LDAC trial. The trials were selected for the STC as they represent the most up-to-date clinical trial results for both comparators.

Cortes *et al.* present the BRIGHT AML 1003 trial; this publication was used in combination with IPD made available as a part of GLAS clinical study report (CSR) B1371003 of Pfizer (NY, USA) based on the January 2017 data extraction [21,22]. Reporting of baseline characteristics and outcomes in the primary publication pools both AML and myelodysplastic syndrome patients; thus, for this report, the Pfizer IPD were extracted for the AML patients only (n = 116) [22]. To confirm validity of the dataset, point estimates generated from the Pfizer IPD were confirmed to match the CSR. However, the CSR presented outcomes with 80% CIs. To compare results with other selected studies, we recalculated the IPD-derived results with 95% CIs.

Efficacy data for VEN came from the Phase III VIALE-C randomized controlled trial of VEN+LDAC versus LDAC (n = 211) [12]. Derived results are associated with clinicaltrials.gov protocol NCT03069352 [23]. The VIALE-C study reported OS outcomes based on the initial planned analyses and unplanned analyses, using an additional 6-month follow-up. The STC was performed using the results of the unplanned analyses, and STC of the initial analysis results was considered a sensitivity analysis (results not presented in this publication). The unplanned analysis demonstrated a significant treatment benefit with respect to OS; therefore, STC comparing these results was considered a conservative approach for comparative effectiveness.

The validity of ITC and STC rely on three main assumptions: transitivity, homogeneity and consistency, which ensure indirect measures of treatment effect that are not biased by differences in study characteristics. To assess the appropriateness of comparative effectiveness analyses with respect to these assumptions, study designs, populations and inclusion/exclusion criteria were compared between BRIGHT AML 1003 and VIALE-C. The major differences between trial designs were that VIALE-C was double blind and stratified by AML status, age and region, whereas BRIGHT AML 1003 was open label and stratified by cytogenic risk factor. In BRIGHT AML 1003, patients were randomized 2:1 to GLAS+LDAC or LDAC alone. AML patients receiving GLAS (n = 78) received 100-mg daily, plus 20-mg LDAC, administered subcutaneously twice a day on days 1–10 of 28-day cycles. The control group (n = 38) received LDAC alone. In VIALE-C, 143 patients treated with oral VEN 600-mg per day were given LDAC 20-mg/m^2 per day administered subcutaneously the first 10 days of each cycle, and the control group was given LDAC alone (n = 68). The study designs, populations and inclusion criteria were clinically and statistically comparable enough between trials for ITC and STC to be considered appropriate (Table 1). Unadjusted ITC is subject to biases associated with between-trial differences in patient baseline covariates, which motivates the use of STC to provide population-adjusted estimates. Patient characteristics of BRIGHT AML 1003 and VIALE-C were evaluated to identify potential effect modifiers and prognostic variables to be incorporated into the STC models (see Table 2 for baseline characteristics).

Table 1. Characteristics of included studies.

Study (year)	Study type	Intervention	Population	Inclusion criteria	Ref.
BRIGHT AML 1003: Cortes (2019)	Open-label, Phase II RCT	GLAS+LDAC vs LDAC	Older patients with previously untreated AML or high-risk MDS, who are unfit for intensive chemotherapy	One or more of the following: • Age ≥75 years • ECOG PS 2 • Serum creatinine >1.3 mg/dl • Severe cardiac disease (left ventricular ejection fraction <45%)	[21,22]
VIALE-C: Wei (2020)	Double-blind, Phase III RCT	VEN+LDAC vs LDAC	Older patients with previously untreated AML, who are unfit for intensive chemotherapy because of comorbidity or other factors	• Age ≥18 years with previously untreated AML (except for hydroxyurea) • Age ≥75 years or one or more of the following: • ECOG PS of 2 or 3 • Cardiac history of congestive heart failure requiring treatment or ejection fraction ≤50% or chronic stable angina • Diffusion capacity of the lung for carbon monoxide ≤65% or first second of forced expiration ≤65% • Creatinine clearance ≥30–<45 ml/min • Moderate hepatic impairment with total bilirubin >1.5–≤3.0 × upper limit of normal • Any other comorbidity that was physician judged to be incompatible with conventional intensive chemotherapy	[12]

AML: Acute myeloid leukemia; ECOG PS: Eastern Cooperative Oncology Group performance status; GLAS: Glasdegib; LDAC: Low-dose cytarabine; MDS: Myelodysplastic syndrome; RCT: Randomized controlled trial; VEN: Venetoclax.

Table 2. Patient baseline characteristics of included studies.

Characteristic	BRIGHT AML 1003 CSR; AML patients only		VIALE-C publication, Wei (2020)	
	GLAS+LDAC	LDAC	VEN+LDAC	LDAC
Age, years; median (range)	77	76	76	76
Male n (%)†	59 (76%)	23 (61%)	78 (55%)	39 (57%)
AML type				
– *De novo*	38 (49%)	18 (47%)	85 (59%)	45 (66%)
– Secondary	40 (51%)	20 (53%)	58 (41%)	23 (34%)
ECOG PS 0 or 1 n (%)†	37 (47%)	20 (53%)	74 (51%)	34 (50%)
Bone marrow blast count (%)				
– Median (range)	41% (16–100%)	46% (13–95%)	–	–
– <30% blasts	18 (23%)	10 (27%)	42 (29%)	18 (27%)
– 30%–<50% blasts	24 (31%)	9 (24%)	36 (25%)	22 (32%)
– ≥50% blasts	35 (45%)	18 (49%)	65 (46%)	28 (41%)
Poor cytogenetic risk category†	29 (37%)	17 (45%)	47 (33%)	20 (29%)

† Key differences.
AML: Acute myeloid leukemia; CSR: Clinical study report; ECOG PS: Eastern Cooperative Oncology Group performance status; GLAS: Glasdegib; LDAC: Low-dose cytarabine; VEN: Venetoclax.

Statistical analysis

Comparative OS was assessed using two end points: indirect OS hazard ratio (HR) of GLAS+LDAC versus VEN+LDAC and mean difference (MD) in relative median OS (mOS) gain, both based on the unplanned analysis of VIALE-C with additional 6 months of follow-up. Sensitivity analyses were performed using the initial planned OS results. For STC of OS outcomes, six parametric survival models were specified and applied – exponential, Weibull, Gompertz, lognormal, log-logistic and generalized gamma – to generate adjusted estimates of the BRIGHT AML 1003 OS in the VIALE-C population. Results of optimal-fitting models based on visual inspection and fit statistics were obtained. Binary outcomes such as clinical response, defined complete remission (CR) and CR+CR with incomplete blood count recovery (CRi), and transfusion independence (defined as eight consecutive weeks without transfusion after baseline) were compared using risk ratios (RRs) with 95% CIs. Logistic regression models were used to estimate the adjusted RR of the BRIGHT AML 1003 trial in the VIALE-C population according to previously published methodology [20,24]. Each end point was compared via unadjusted ITC and adjusted STC.

Table 3. Trial end points: glasdegib+low-dose cytarabine vs venetoclax+low-dose cytarabine.

End point	BRIGHT AML 1003 CSR; AML patients only†		VIALE-C publication, Wei (2020)			
	GLAS+LDAC	LDAC	Planned analyses		Additional follow-up	
			VEN+LDAC	LDAC	VEN+LDAC	LDAC
Remission						
CR	18%	2.6%	27%	7%	Not Applicable	
CRi	6%	2.6%	21%	6%		
Overall response (CR+CRi)	24%	5.3%	48%	13%		
Overall survival						
Median OS, months (95% CI)	8.3 (4.7–12.2)	4.3 (2.9–4.9)	7.2 (5.6–10.1)	4.1 (3.1–8.8)	8.4 (5.9–10.1)	4.1 (3.1–8.1)
OS HR (95% CI)	0.46 (0.30–0.72)		0.75 (0.52–1.07)		0.70 (0.50–0.98)	
Transfusion independence (any time after day 0)						
Independence from both red blood cells and platelets	42% (33/78)	21% (8/38)	37%	16%	Not Reported	

†Derived full analysis set as reported in CSR.
AML: Acute myeloid leukemia; CR: Complete remission; CRi: CR with incomplete blood count recovery; CSR: Clinical study report; GLAS: Glasdegib; HR: Hazard ratio; LDAC: Low-dose cytarabine; OS: Overall survival; VEN: Venetoclax.

Potential covariates considered for STC adjustment models were the following mutually available patient baseline characteristics: age, sex, AML type (*de novo* or not *de novo*), Eastern Cooperative Oncology Group performance status, bone marrow blast percentage (≥50 vs <50%) and cytogenetic risk. Per the NIH and Care Excellence Decision Support Unit guidance, anchored ITC/STC characteristics, deemed to potentially modify treatment effects or influence prognosis, are recommended for inclusion in adjusted models [25–27]. Furthermore, included covariates should be imbalanced between trial populations. Subject matter literature review suggests each available baseline characteristic is a potentially important effect modifier. Full models included all mutually available covariates, while stepwise models were based on a backwards elimination approach using a retention p-value of 0.05 for prognostic variables and 0.1 for effect modifiers.

Results

Table 2 includes the set of mutually available patient characteristics from both trials. Based on a comparison of the covariate values, the BRIGHT AML 1003 trial had a higher proportion of males (particularly in the GLAS+LDAC group), had a higher proportion of secondary AML patients and had higher proportions of patients with poor cytogenetic risk compared with VIALE-C, considered the most important effect modifiers. These differences, per decision support unit recommendations, supported the use of STC, which adjusts for baseline differences [25].

Table 3 lists the mOS and OS HR, as well as the clinical response and transfusion independence end points extracted from each study. Figure 1 includes forest plots for different comparative effectiveness end points measured in this study following ITC and anchored STC.

OS HRs

Table 4 presents the estimated HRs of GLAS+LDAC versus LDAC and VEN+LDAC versus LDAC and the final ITC to derive the GLAS+LDAC versus VEN+LDAC HRs. An HR <1 indicates relatively higher survival throughout follow-up. The unadjusted HR was obtained using the reported Cox-proportional hazards model HRs from each publication without covariate adjustment. Results from the best fitting full and stepwise models are presented.

The results of the STC are consistent with the findings of the initial data regardless of variable selection and parameterization. GLAS+LDAC is numerically or directionally favored over VEN+LDAC (unadjusted ITC OS HR: 0.66; 95% CI: 0.38–1.15 and exponential STC OS HR: 0.56; 95% CI: 0.24–1.32). However, the differences are nonsignificant regardless of adjustment and parameterization. A forest plot of the final OS HR ITC/STC results is presented in Figure 1A. The figure demonstrates the numerical superiority of GLAS+LDAC over VEN+LDAC with respect OS as each estimate falls on the left side of the reference line (HR = 1); however, the result is not statistically significant as the CIs overlap the reference line.

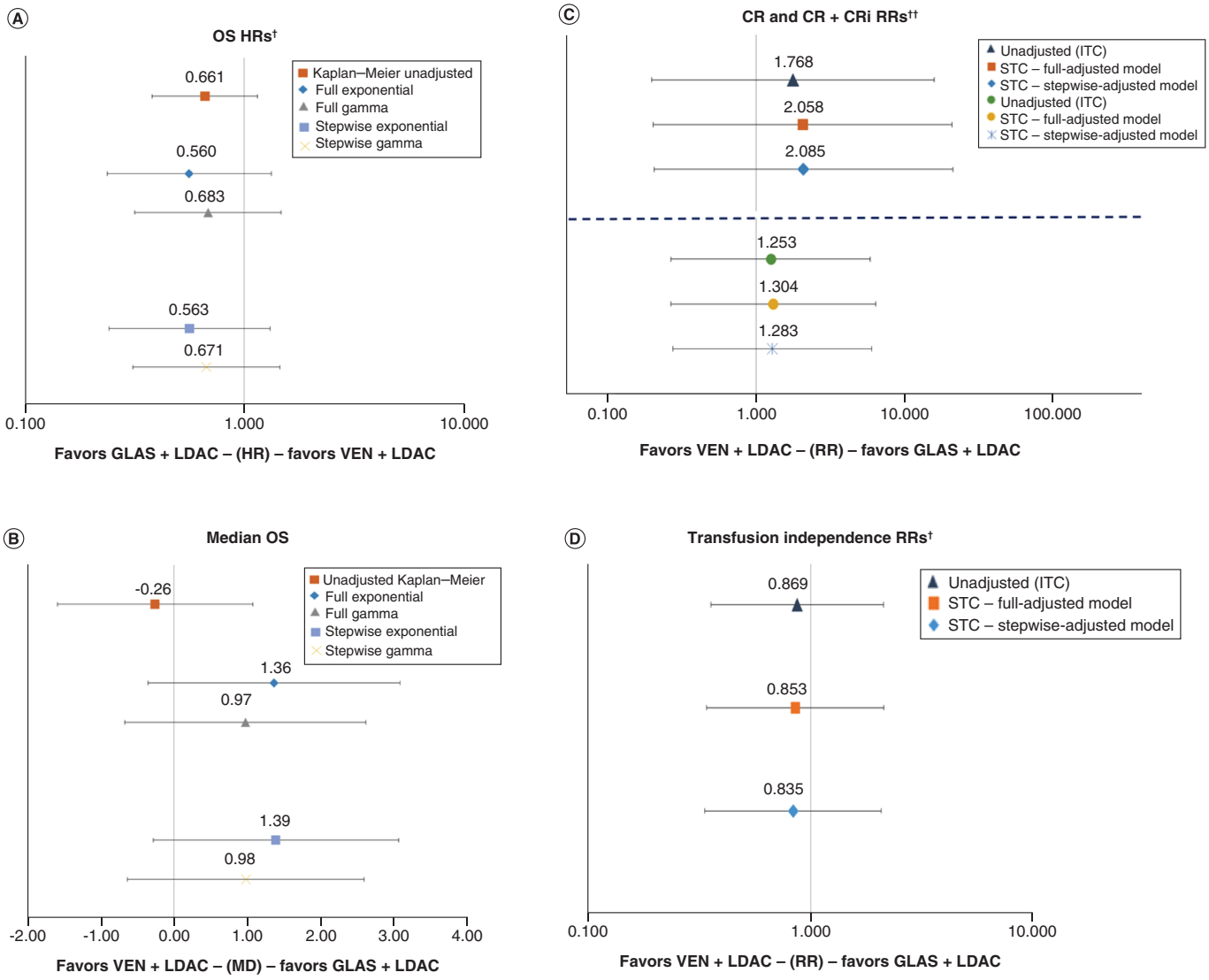

Figure 1. Forest plots of comparative effectiveness using unplanned additional venetoclax overall survival follow-up data.
†The log-scale is used to present the x-axis.
‡CR is above dotted line, CR + CRi is below dotted line.
Bars represent 95% CIs.
HR: Hazard ratio; ITC: Indirect treatment comparison; MD: Mean difference; RR: Risk ratio; STC: Simulated treatment comparison.

Table 4. Overall survival hazard ratio indirect treatment comparison and simulated treatment comparison results.

Characteristics	GLAS+LDAC trial			VEN trial (comparator)			Final ITC/STC result		
	GLAS+LDAC vs LDAC			VEN+LDAC vs LDAC			GLAS+LDAC vs VEN+LDAC		
	OS HR	CI-	CI+	OS HR	CI-	CI+	OS HR	CI-	CI+
Standard unadjusted Kaplan–Meier (ITC)	0.46	0.30	0.72	0.70	0.50	0.98	**0.66**†	**0.38**	**1.15**
Full exponential (STC)	0.39	0.18	0.87	0.70	0.50	0.98	**0.56**†	**0.24**	**1.32**
Full gamma (STC)	0.48	0.23	0.91	0.70	0.50	0.98	**0.68**†	**0.32**	**1.47**
Stepwise exponential (STC)	0.39	0.18	0.85	0.70	0.50	0.98	**0.56**†	**0.24**	**1.31**
Stepwise gamma (STC)	0.47	0.23	0.90	0.70	0.50	0.98	**0.67**†	**0.31**	**1.45**

The last three columns list the final indirect comparison results.
†GLAS+LDAC favored.
CI-: Lower bound of the 95% CI; CI+: Upper bound of the 95% CI; GLAS: Glasdegib; HR: Hazard ratio; ITC: Indirect treatment comparison; LDAC: Low-dose cytarabine; OS: Overall survival; STC: Simulated treatment comparison; VEN: Venetoclax.

Table 5. Median overall survival differences (in months) indirect treatment comparison/simulated treatment comparison results.

Characteristics	BRIGHT AML 1003 trial			VIALE-C trial (comparator)			Final ITC/STC result		
	GLAS+LDAC vs LDAC			VEN+LDAC vs LDAC			GLAS+LDAC vs VEN+LDAC		
	Δ mOS (months)	CI-	CI+	Δ mOS (months)	CI-	CI+	MD (months)	CI-	CI+
Standard unadjusted Kaplan–Meier (ITC)	4.04	1.94	6.15	4.30	2.67	5.93	**-0.26**‡	**-1.59**	**1.07**
Full exponential (STC)	5.66	2.64	8.68	4.30	2.67	5.93	**1.36**†	**-0.36**	**3.08**
Full gamma (STC)	5.27	2.43	8.11	4.30	2.67	5.93	**0.97**†	**-0.67**	**2.61**
Stepwise exponential (STC)	5.69	2.77	8.60	4.30	2.67	5.93	**1.39**†	**-0.28**	**3.06**
Stepwise gamma (STC)	5.28	2.50	8.06	4.30	2.67	5.93	**0.98**†	**-0.63**	**2.59**

The last three columns list the final indirect comparison results.
†GLAS+LDAC favored.
‡VEN+LDAC favored.
Δ mOS: Difference in median OS between trial arms; CI-: Lower bound of the 95% CI; CI+: Upper bound of the 95% CI; GLAS: Glasdegib; ITC: Indirect treatment comparison; LDAC: Low-dose cytarabine; MD: Mean difference; OS: Overall survival; STC: Simulated treatment comparison; VEN: Venetoclax.

Table 6. Complete remission, complete remission with incomplete blood count recovery, and transfusion independence risk ratio indirect treatment comparison and simulated treatment comparison results.

Complete remission	GLAS+LDAC trial			VEN trial (comparator)			Final ITC/STC result		
	GLAS+LDAC vs LDAC			VEN+LDAC vs LDAC			GLAS+LDAC vs VEN+LDAC		
	RR	CI-	CI+	RR	CI-	CI+	RR	CI-	CI+
Standard unadjusted (ITC)	6.82	0.93	49.97	3.86	1.56	9.56	1.77†	0.20	15.77
Full model (STC)	7.94	0.95	66.60	3.86	1.56	9.56	2.06†	0.20	20.78
Stepwise model (STC)	8.04	0.96	67.54	3.86	1.56	9.56	2.08†	0.21	21.08
CR+CRi									
Standard unadjusted (ITC)	4.63	1.14	18.85	3.69	1.95	6.99	1.25†	0.27	5.86
Full model (STC)	4.81	1.13	20.58	3.69	1.95	6.99	1.30†	0.27	6.37
Stepwise model (STC)	4.74	1.17	19.23	3.69	1.95	6.99	1.28†	0.28	5.98
Transfusion independence									
Standard unadjusted (ITC)	2.01	1.03	3.92	2.31	1.29	4.15	0.87‡	0.36	2.11
Full model (STC)	1.97	0.98	3.98	2.31	1.29	4.15	0.85‡	0.34	2.13
Stepwise model (STC)	1.93	0.96	3.87	2.31	1.29	4.15	0.84‡	0.34	2.07

†GLAS+LDAC favored
‡VEN+LDAC favored.
CI-: Lower bound of the 95% CI; CI+: Upper bound of the 95% CI; CR: Complete remission; CRi: Complete remission with incomplete blood count recovery; GLAS: Glasdegib; HR: Hazard ratio; ITC: Indirect treatment comparison; LDAC: Low-dose cytarabine; RR: Risk ratio; STC: Simulated treatment comparison; VEN: Venetoclax.

Median OS

The unadjusted mOS was estimated using the difference in Kaplan–Meier estimates for each study. Results of an analysis using the unplanned revised analysis from 6-month VEN follow-up of OS are presented in Table 5 & Figure 1B.

The analysis reported a higher mOS in the VEN trial arm (difference in mOS between trial arms: 4.30 months; 95% CI: 2.67–5.93). The results show VEN+LDAC is numerically favored based on standard unadjusted ITC (MD: -0.026 months); however, following STC, GLAS+LDAC is numerically favored (MD: 0.97–1.39 months). The differences are nonsignificant regardless of adjustment and parameterization (exponential vs gamma).

CR & CRi

Table 6 reports the results of the unadjusted and STC-adjusted ITC for CR, CR+CRi and transfusion independence. GLAS+LDAC and VEN+LDAC demonstrated higher rates of CR compared with LDAC alone in their respective trials [12,22]. Furthermore, VEN+LDAC demonstrated higher absolute rates of CR (27 vs 18%) and CR+CRi (48 vs 24%) (Table 3); however, the estimates presented in Table 6 are relative to each trial's respective control arm. In the last three columns, RRs >1 demonstrate that GLAS+LDAC was numerically favored compared with

VEN+LDAC following anchored analysis. The unadjusted ITC compares the original proportion of GLAS+LDAC patients reaching CR against VEN+LDAC patients reaching CR using unadjusted ITC. Table 6 also presents STC results with either full or stepwise adjustments for VEN+LDAC patient covariate values. Both ITC and STC found GLAS+LDAC to be numerically superior to VEN+LDAC (unadjusted ITC CR RR: 1.77; 95% CI: 0.2–15.77 and full STC CR RR: 2.06; 95% CI: 0.20–20.78), but, as the estimated CIs cross RR = 1 (Figure 1C), none of the differences were statistically significant.

CR+CRi results are similar to the findings for CR alone (Table 6). However, while directionally still favoring GLAS+LDAC, the difference in effectiveness between GLAS+LDAC and VEN+LDAC is attenuated relative to CR findings. Unadjusted ITC and adjusted STC showed that GLAS+LDAC was nonsignificantly numerically favored with respect to CR+CRi RR (unadjusted ITC CR+CRi RR: 1.250; 95% CI: 0.27–5.86 and full STC CR+CRi RR: 1.30; 95% CI: 0.27–6.37). Results were consistent regardless of variable selection. Figure 1C is a forest plot conveying the results from the clinical response analyses. The plot demonstrates the numeric superiority of GLAS+LDAC regardless of adjustment and end point, but the results are nonsignificant.

Transfusion independence

The unadjusted ITC and adjusted STC both found VEN+LDAC and GLAS+LDAC to be similar with respect to transfusion independence RR, and both demonstrated higher rates of transfusion independence versus LDAC alone. VEN+LDAC is numerically favored over GLAS+LDAC for transfusion independence in both unadjusted and adjusted models (unadjusted ITC TI RR: 0.87; 95%CI: 0.36–2.11 and full STC TI RR: 0.85; 95%CI: 0.34–2.13) (Table 6). While the results are consistent regardless of variable selection, they are not statistically significant (Figure 1D).

Discussion

In this study, ITC and STC analyses demonstrated consistently that GLAS+LDAC was numerically favored over VEN+LDAC with respect to OS and clinical response. VEN+LDAC was numerically favored with respect to transfusion independence. A sensitivity analysis of data from the VEN 6-month follow-up was used as a conservative estimate of OS comparative effectiveness. The similarity in clinical outcomes for GLAS+LDAC and VEN+LDAC in the BRIGHT AML 1003 and VIALE-C trials suggests that the choice of therapy between these two regimens for AML patients not suitable for IC may be guided by a range of additional factors including differences in safety profiles, burden of administration and patient preferences.

In terms of safety profiles as reported in the US prescribing information, ≥20% patients in either the GLAS+LDAC arm of BRIGHT AML 1003 or the VEN+LDAC arm of VIALE-C experienced thrombocytopenia, anemia, fatigue, febrile neutropenia, nausea, hemorrhage and musculoskeletal pain. Moreover ≥10% patients in either the GLAS+LDAC arm of BRIGHT AML 1003 or the VEN+LDAC arm of VIALE-C experienced grade 3/4 thrombocytopenia, febrile neutropenia, anemia, pneumonia and lymphopenia. Key safety differences are that in BRIGHT AML 1003, ≥20% of patients experienced edema, dyspnea, decreased appetite, dysgeusia, mucositis, constipation and rash, and ≥10% of patients experienced grade 3/4 fatigue and dyspnea. In VIALE-C, ≥20% of patients experienced neutropenia, lymphopenia, diarrhea, vomiting and pneumonia, and ≥10% of patients experienced grade 3/4 neutropenia [11,28]. Based on the findings of this STC, GLAS and VEN have comparable efficacy when used in combination with LDAC; thus, patient factors relating to safety may be a consideration in selecting a treatment.

While both regimens include both oral and subcutaneous components administered in 28-day cycles, they have some key differences. Administration of GLAS+LDAC involves one 100-mg oral tablet of GLAS once daily on days 1–28 in combination with LDAC 20-mg subcutaneously twice daily on days 1–10 [28]. Administration of VEN+LDAC involves 600-mg oral VEN once daily (six 100-mg tablets) on days 1–28 with LDAC 20-mg/m^2 per day administered subcutaneously once daily on days 1–10 [11]. Patients and physicians may prefer one treatment regimen over the other based on burden of administration.

While the efficacy of the two regimens was largely similar in this STC, GLAS+LDAC showed a general trend toward improved response and survival versus VEN+LDAC. These results are in line with a published STC for GLAS+LDAC versus AZA and versus DEC, demonstrating that the GLAS+LDAC regimen may provide survival benefits over several other regimens available for NIC in AML [29].

STC methods rely on mutually reported patient characteristics across studies to match patient populations, and results are susceptible to residual confounding if patient characteristics are unbalanced with respect to unmeasured

treatment effect modifiers. Small sample sizes may reduce the power of the analysis to detect significant differences between treatments. For example, an STC could not be performed to compare likelihood of CRi alone between GLAS+LDAC and VEN+LDAC, as there were so few patients achieving CRi in the GLAS+LDAC treatment arm (n = 5). In addition, survival by clinical response subgroup was not reported in the VEN+LDAC trial, so comparisons of OS assume homogeneity across the strata of clinical response. If such end points become available, future analyses could incorporate strata-specific ITC/STC comparisons of OS to further strengthen the comparative effectiveness analyses.

It is possible that certain patients may have a better response to GLAS+LDAC or VEN+LDAC based on cytogenetic subtypes or molecular features of the cancer cells that make them more susceptible to inhibition of smoothened or BCL-2. The data available for the two trials did not permit comparisons by biologic subtype, but as clinical data in AML evolve, it may be valuable to conduct ITCs or STCs by biologic subtype.

The GLAS+LDAC trial was open label and the VEN+LDAC trial was blinded, which may account for the different LDAC control-arm response rates between trials, and may in turn may cause an overcorrection and overestimate of GLAS+LDAC response rates versus LDAC alone. IPD were only available for BRIGHT AML1003. LDAC dosing was different between trials, with a flat dose of 20-mg twice a day in BRIGHT AML 1003 and a dose of 20-mg/m^2 once daily in VIALE-C. Both trials were relatively small and had different sample sizes and trial sites. Furthermore, indirect comparison of landmark end points such as response and transfusion independence may be biased by differences in length of follow-up. STC of medians is not conducted on the log scale, which is considered optimal for ITC; however, the results of the OS HR ITC/STC agree with the mOS ITC/STC, which suggests validity of the comparison. This approach is more appropriate than a naive comparison of trials that does not account for differences in patient population. While the best available evidence on this topic is provided and evaluated here, studies with larger sample sizes and numbers of events would more effectively discern possible underlying treatment differences.

Conclusion

Overall findings suggest that GLAS+LDAC is directionally favored over VEN+LDAC with respect to OS and clinical response, but not transfusion independence. Nonetheless, no differences were significant, which suggests that the comparative effectiveness evidence is inconclusive. In the realm of NIC, the standard of care has shifted away from monotherapy with hypomethylating agents such as AZA and DEC and toward combination therapies. Combinations include LDAC in combination with NIC such as GLAS or VEN, or VEN+hypomethylating agent. As the evidence based on these options grows, patient needs are likely to play a significant role in treatment choices. For example, GLAS and VEN have different safety profiles with comparable efficacy when used in combination with LDAC, based on the findings of our STC. Other considerations, including dosing regimens and patient preference are also likely to influence treatment decisions.

Summary points

- Both, glasdegib (GLAS) combined with low-dose cytarabine (LDAC) and venetoclax (VEN) combined with LDAC, are approved in the USA to treat patients who are not candidates for standard chemotherapy.
- Unadjusted indirect treatment comparison and anchored simulated treatment comparison were completed to compare treatment effectiveness of GLAS+LDAC versus VEN+LDAC using patient-level data and results from the GLAS+LDAC trial and published aggregated trial data from the VEN+LDAC trial.
- Analyses showed that, while GLAS+LDAC was numerically more effective in terms of median overall survival and clinical response and VEN in terms of transfusion independence, these estimated differences were not statistically significant.
- Both GLAS+LDAC and VEN+LDAC are more effective than treatment with LDAC alone, and treatment decisions should be made taking into account patient preference, administration burden and drug safety profiles.

Acknowledgments

Parts of this study were previously published in an abstract and presented in an oral session at the American Society of Hematology Conference held during December 2020.

Financial & competing interests disclosure

The study was sponsored by Pfizer, Inc. JC Cappelleri, T Bell, G Chan and A Brown are employees and stockholders of Pfizer, Inc. G Tremblay and P Daniele are employees of Purple Squirrel Economics who were paid consultants to Pfizer in connection with the conduct of the study and development of this manuscript. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing assistance was provided by Purple Squirrel Economics. The authors are fully responsible for all content and editorial decisions in this manuscript.

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