AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: venetoclax (Venclyxto®) with azacitidine for the treatment of relapsed/refractory acute myeloid leukaemia in adults following at least one line of intensive chemotherapy before or following allogenic haematopoietic stem cell transplant (HSCT) as an alternative to intensive chemotherapy. (OW32).

Report prepared by the All Wales Therapeutics and Toxicology Centre October 2025

Key findings

Licence status
Venetoclax (Venclyxto®) with azacitidine is not licensed for the treatment of relapsed/refractory acute myeloid leukaemia in adults following at least one line of intensive chemotherapy before or following allogenic haematopoietic stem cell transplant (HSCT) as an alternative to intensive chemotherapy; its use for this indication is off-label.

Clinical evidence
The clinical evidence for venetoclax in combination with azacitidine comes from real-world, multicentre, and single-arm studies. Wood et al. (2022, 2025) and Pelland et al. (2024) reported that 40–46% of patients achieved complete remission or complete remission with incomplete count recovery rate, with higher responses in those treated for molecular relapse. Median overall survival ranged from 7 to 20 months. Up to a quarter of patients were subsequently bridged to allogeneic HSCT, with generally favourable post-transplant outcomes. These findings suggest that venetoclax-based lower-intensity regimens can provide meaningful disease control in heavily pretreated, high-risk patients. Studies are presented for the medicine most likely to be displaced which is Flag-Ida (fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor). However, there are considerable limitations with the comparison of the patients treated with FLAG-Ida and those treated with venetoclax and azacitidine due to heterogeneity between baseline characteristics of patients in the respective studies.

Safety
No new safety signals emerged with venetoclax in combination with azacitidine in R/R AML compared with its use in other indications.

Patient factors
Patients with R/R AML have few treatment options and generally poor outcomes. A stem cell transplant can potentially cure the disease, but it is only an option if patients reach remission and have a suitable donor. Intensive chemotherapy has limited efficacy and is associated with significant toxicity, particularly in older patients or those with poor overall health. Venetoclax with azacitidine provides a

lower-intensity option, administered in an outpatient setting.

Cost-effectiveness
An All Wales Therapeutics and Toxicology Centre (AWTTC) literature review did not identify any published studies reporting the cost-effectiveness of venetoclax with azacitidine for the indication under consideration.

An AWTTC cost consequence analysis (CCA) compares the costs and outcomes of venetoclax with azacitidine versus FLAG-Ida. The base case analysis finds venetoclax with azacitidine to be associated with cost savings [commercial in confidence text removed] a shorter median overall survival (8.9 months versus 10.2 months) and a lower response rate (52% versus 71%) when compared with FLAG-Ida. A range of sensitivity and scenario analyses assess the influence of parameters and characterise uncertainty.

The analysis includes a number of limitations. Notably, the clinical comparisons are based on separate studies of different patient populations. Caution should be applied when drawing conclusions from the economic analysis.

Budget impact
Use of venetoclax with azacitidine in place of FLAG-Ida has been estimated to result in cost savings of [commercial in confidence text removed] per year. Results are subject to the same limitations as outlined in the clinical and cost-effectiveness sections of the report. In practice the budget impact is expected to be largely neutral as patients in Wales are already accessing venetoclax with azacitidine via the Individual Patient Funding Request route.

Impact on health and social care services
Venetoclax with azacitidine is administered in an outpatient setting, potentially reducing healthcare resource use. In contrast, conventional salvage chemotherapy requires prolonged inpatient admission and is associated with higher needs for blood product support and intensive management of neutropenia-related infections.

Innovation and/or advantages
Clinical experts indicate the main benefit of this treatment is that it is safer, easier, can be given locally mostly as an outpatient, and requires less hospital time and fewer blood transfusions.

Background

Adults with relapsed or refractory acute myeloid leukaemia (R/R AML) following at least one line of intensive chemotherapy, with or without prior allogeneic haematopoietic stem cell transplant (HSCT), have poor prognosis and incurable disease[1]. The therapeutic goals are to control disease progression, achieve remission (where possible), control symptoms, preserve quality of life, and minimise treatment-related adverse effects[2].

Current treatment options are limited and often poorly tolerated, typically involving intensive salvage chemotherapy or palliative care[3]. There is a recognised need for better-tolerated therapies that improve quality of life and reduce hospitalisation. Venetoclax combined with azacitidine may offer a less toxic alternative, potentially

improving remission rates and survival, particularly in younger, fitter patients as a bridge to allogeneic HSCT.

Clinicians in Wales have identified a patient cohort likely to benefit from venetoclax with azacitidine which was considered suitable for assessment through the One Wales Medicines process.

Twelve applications for this indication have been submitted through the Individual Patient Funding Request (IPFR) process between January 2024 to March 2025, all of which were approved.

Target group

Patients with R/R AML who have relapsed following, or are refractory to, at least one line of intensive chemotherapy before or following HSCT.

Marketing authorisation date: Not applicable, off-label

Venetoclax (Venclyxto®) with azacitidine is not licensed for the indication under consideration.

Venetoclax was first licensed in the UK in 2016, it is licensed for the treatment of newly diagnosed AML in adults ineligible for intensive chemotherapy, in combination with a hypomethylating agent (e.g. azacitidine) or low-dose cytarabine[4]. It is also licensed in chronic lymphocytic leukaemia (CLL) [4].

Azacitidine is licensed in the UK for the treatment of adult patients not eligible for HSCT with intermediate-2/high-risk myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML), and AML (≥20% blasts by WHO classification)[5].

Dosing information

Venetoclax and azacitidine are administered in 28-day cycles[4]. For most R/R AML patients, clinical experts recommend a lower venetoclax dose of 100 mg orally daily when given with an azole antifungal (posaconazole or voriconazole). Venetoclax is metabolised by enzyme cytochrome P450 3A4 (CYP3A4), therefore co-administration with strong CYP3A4 inhibitors such as azole antifungals necessitates a dose reduction to mitigate toxicity. Venetoclax 400 mg oraly daily is only used in patients who cannot take azole antifungals or who achieve remission with normal blood counts and no longer require antifungal prophylaxis[4].

Venetoclax dosing begins with 100 mg orally on day 1, increasing to 200 mg on day 2, 400 mg on day 3, then reduced back down to 100 mg daily on day 4 and thereafter. Azole antifungals start on day 4. In cases of drug-induced cytopenia, treatment cycles may be shortened to 14–21 days. If neutrophil counts normalise, the azole antifungal is stopped and venetoclax increased to 400 mg daily. It should be noted that this dosing approach reflects local practice for treatment of R/R AML, rather than Summary of Product Characteristics (SmPC) recommendations, as confirmed by NHS Wales clinical experts. Patients should be adequately hydrated and receive anti-hyperuricaemic agents to reduce the risk of tumour lysis syndrome before the first dose and during titration[4].

Azacitidine is administered at 75 mg/m² via subcutaneous injection into the upper arm, thigh or abdomen on days 1–7, though in practice it is often given on days 1–5 and 8–9 to avoid weekend hospital visits.

Treatment typically continues until disease relapse. Patients who are medically fit and achieve remission may proceed to allogeneic HSCT, at which point venetoclax and azacitidine are stopped[6,7]. Clinical experts suggest treatment is discontinued on disease progression or if there is no response after 3 cycles.

Clinical background

AML is a clonal haematopoietic stem cell disorder characterised by the accumulation of myeloblasts in the bone marrow and blood[8]. Diagnosis is generally made when blasts exceed 10% or when other defining disease features are present. AML is a heterogeneous disease, and cytogenetic and molecular evaluation is important to inform prognosis and guide treatment[8]. It predominantly affects adults, with incidence increasing with age, and has a poor prognosis, especially in R/R cases after initial treatment[9]. AML predominantly affects older adults, with a median age at diagnosis in England of 72 years and survival strongly decreases with age[10]. Five-year survival rates ranges from 55% in patients under 40 to 1–16% in age groups over 60[11]. Relapsed disease and treatment-related complications are the leading causes of death[12], with median overall survival in R/R AML reported as 5.3 months and 5-year survival rate of 12.6%[13].

Treatment of R/R AML is challenging due to limited effective options and marked treatment-associated toxicity. Standard treatment approaches, including intensive salvage chemotherapy or palliative regimens, are often poorly tolerated in older patients or those with significant comorbidities.

Venetoclax is an oral, selective B-cell lymphoma 2 (BCL-2) inhibitor that restores apoptotic signalling, promoting apoptosis of malignant myeloid cells[4]. In combination with the hypomethylating agent azacitidine, venetoclax has shown improved remission rates and overall survival in AML patients ineligible for intensive chemotherapy[9,14].

Azacitidine is a DNA methyltransferase inhibitor that induces hypomethylation and direct cytotoxicity, promoting differentiation and apoptosis of malignant haematopoietic cells[5]. Combined with venetoclax, azacitidine enhances pro-apoptotic effects, leading to higher remission rates in newly diagnosed and selected R/R AML populations[8].

Incidence/prevalence

In 2021, Wales reported 85 new cases of AML, corresponding to an incidence of approximately 3 per 100,000 population[15]. Specific data on R/R AML in Wales are limited. International evidence provides context, a systematic review reported a median cumulative relapse incidence of 46.8% after induction chemotherapy and 29.4% following stem cell transplantation[16], suggesting that roughly half of all patients experience relapse.

Clinical experts in Wales estimate that approximately 9–10 R/R AML patients per year would be eligible for treatment with venetoclax in combination with azacitidine.

Current treatment options and relevant guidance

Management of R/R AML is challenging due to limited treatment options, treatment-associated toxicity, and poor prognosis. For patients lacking targetable mutations, particularly those unable to tolerate intensive chemotherapy, there is no single standard of care[17]. Instead, regimens such as venetoclax with azacitidine, low-dose cytarabine, or other low-intensity therapies are selected based on individual patient suitability.

Salvage chemotherapy for R/R AML typically involves regimens such as FLAG-Ida (fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor), MACE (mitoxantrone, cytarabine, and etoposide), or MEC (mitoxantrone, etoposide, and cytarabine), with FLAG-Ida often preferred by clinicians in Wales. For patients where the focus is on controlling the disease rather than curing it, palliative regimens may be used. These can include IV low dose cytarabine, oral hydroxycarbamide, or oral etoposide for cytoreduction, alongside supportive measures such as transfusions and antibiotics.

Targeted therapy options for R/R AML are limited. Gilteritinib is recommended by National Institute for Health and Care Excellence (NICE) Technology Appraisal (TA) 642 (2020) for adults with FLT3 mutations, present in approximately 25% of cases, while no licensed targeted agents exist for the remaining 75% without these mutations[3].

Venetoclax with azacitidine is licensed and recommended by NICE TA765 (2022) for patients with untreated AML where intensive chemotherapy is unsuitable[18]. Venetoclax with azacitidine is currently off-label for R/R AML and has not yet been appraised by NICE for this indication. The NICE appraisal ID6468, assessing venetoclax in combination with azacitidine for AML before and after HSCT, is currently under development, [commercial in confidence text removed] [19].

Other therapies in the NICE development pipeline, both currently awaiting appraisal, include:

- Liposomal cytarabine–daunorubicin for treating R/R AML in people aged 1 to 21 years (ID4017)[20]
- Iodine-131–apamistamab for relapsed or refractory AML prior to HSCT (ID6355)[21]

International guidance highlights broader use:

- The 2025 guidelines from the National Comprehensive Cancer Network (NCCN) in the United States recommend venetoclax combined with hypomethylating agents, such as azacitidine, for relapsed or refractory acute myeloid leukaemia, especially in patients who are unfit for intensive salvage therapy or as a bridge to HSCT[22].
- European LeukemiaNet (ELN) 2022 and the British Society for Haematology (BSH) support the combination in older or unfit patients, with dose modifications advised when co-administered with strong CYP3A4 inhibitors such as azole antifungals[8]. The guidelines recommend a risk-adapted approach, including HSCT for eligible patients and low-intensity regimens for those unsuitable for intensive therapy[8].

Summary of evidence on clinical effectiveness

The All Wales Therapeutics and Toxicology Centre (AWTTC) conducted a literature search during August 2025 to look for evidence about the use of venetoclax with azacitidine for the treatment of R/R AML in adults. Searches were performed using the Cochrane library, Central Register of Controlled Trials, EMBASE, MEDLINE and TRIP database with the search terms venetoclax, venclyxto, azacitidine, vidaza, onureg, acute myeloid leukaemia, AML, relapsed or refractory, and adults.

The primary outcomes were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), adverse events (AE), health related quality of life (HRQoL) and resource use. A literature search identified 225 records which were assessed for eligibility, with 197 excluded following removal of duplicates and screening of title and abstracts. Following eligibility screening, 8 publications were included in the report, 5 were retrospective cohort studies and 3 were real-world observational data reports (2 studies and 1 update). Any remaining records were excluded due to small patient numbers, incorrect cohort or unsuitable study design (see Appendix 1). An additional 6 studies were identified by the company, 5 of which were considered eligible for inclusion.

Of the included studies, the real-world, UK-based, observational study by Wood et al.[6,7] and the multicentre retrospective analysis by Pelland et al.[23] were deemed the most relevant sources of evidence pertinent to the indication in this report and were therefore included in the main analysis. The remaining supplementary studies are summarised in Appendix 2.

Clinical efficacy of venetoclax with azacitidine

Wood et al. (2022) reported UK-wide, real-world outcomes of venetoclax-based non-intensive combinations used as salvage therapy for adults with relapsed or refractory AML or high-risk myelodysplastic syndromes (MDS)[6]. The study included 126 patients, with a median age of 58 years (range 17–83 years); 46% were aged 60 years or older. The cohort included 117 patients with AML and 9 with high-risk MDS. At the time of venetoclax initiation, 30 patients (24%) had primary refractory disease, 45 patients (36%) had relapsed after prior chemotherapy but before undergoing allogeneic stem cell transplantation, and 51 patients (40%) had relapsed following transplantation.

Venetoclax was combined with a hypomethylating agent (HMA) in 75 patients (60%) either azacitidine or decitabine (allocation not specified), with low-dose cytarabine in 44 patients (35%), and was administered in combination with other low-intensity agents in 7 patients (5%). The best responses were typically seen within the first treatment cycle, with a median of one cycle required (range 1–6). Among patients treated for morphologic relapse: 46% (47/103) responded to venetoclax-based therapy. Complete response (CR) or complete response with incomplete count recovery (CRi) was achieved in 37%; 4% had partial remission (PR); and 40% remained refractory. In contrast, patients treated for molecular relapse showed markedly greater sensitivity: 84% (16/19) achieved molecular remission.

Across the entire study cohort, the CR or CRi was 44% (56/126). With a median follow-up of 16.6 months, the median overall survival (OS) for the entire group was 8.5 months (95% confidence interval [CI], 4.8 to 12.2 months). Patients treated for

molecular relapse lived longer than those treated for morphologic relapse, with a median survival of 18.4 months compared with 7.1 months, a difference that was statistically significant (p = 0.004).

A total of 34 patients (27%) underwent allogeneic HSCT following venetoclax salvage, including 21 first transplants (17%) and 13 second transplants (10%). At a median follow-up of 11.8 months, median survival from the time of transplantation was not reached, with similar outcomes regardless of whether patients were refractory or in relapse at the start of venetoclax treatment. Among the 51 patients who relapsed after a prior transplant, 41% achieved remission, 31% received donor lymphocyte infusion (DLI), and 25% proceeded to a second transplant[6].

Following the above 2022 study Wood et al. (2025) reported updated outcomes incorporating longer follow-up and an expanded cohort[7]. The study included 165 patients with a median age 58 years (range 17–88) 46% were aged 60 years or older. Venetoclax was given with a hypomethylating agent as salvage therapy to 107 patients (65%): 95 (55%) with azacitidine and 12 (7%) with decitabine. Most patients (86%) received venetoclax at ≤100 mg/day, typically with concomitant azole prophylaxis. Among 165 evaluable patients, the overall response rate to venetoclax-based therapy was 52%, with 41% of patients with morphologic disease achieving CR or CRi. Responses were typically observed within the first two cycles. Consolidation with cellular therapy occurred in 38% of patients, including allogeneic HSCT in 31%, while 9% received concurrent DLI. Median follow-up was 15.3 months (95% CI: 13.0 to 17.6 months), median OS for all patients was 8.9 months (95% CI: 5.9 to 11.9), and responders had significantly improved survival compared to non-responders (median OS 15.9 versus 3.8 months; hazard ratio [HR] 0.229, 95% CI, 0.142 to 0.369, p < 0.001).

Patients treated for molecular MRD persistence/relapse had higher overall response rate (ORR [74%]) and longer median OS (17.6 months) than those with morphologic/immunophenotypic disease (ORR 49%, median OS 8.2 months). Among responders, 56% (48/85) proceeded to consolidation with cellular therapy, including HSCT (38/85) or DLI (10/85). In patients treated for post-HSCT relapse, the overall response rate was 46%, with median overall survival of 18.4 months in responders versus 2.9 months in non-responders (p < 0.001; HR 0.191, 95% CI, 0.094 to 0.387). Most responders (79%) received consolidation with cellular therapy, including second HSCT (38%) or DLI alone (42%)[7].

Pelland et al. (2024) conducted a multicentre retrospective study analysing 81 adults with R/R AML receiving first salvage therapy in three hospitals in Canada[23]. The study compared venetoclax combined with azacitidine (n = 20) to salvage chemotherapy regimens, including intensive therapies such as mitoxantrone with etoposide, cytarabine with daunorubicin, FLAG-Ida, high-dose cytarabine, CPX-351, and targeted agents like gilteritinib and sorafenib (n = 61). Patients in the venetoclax and azacitidine group were older, with a median age of 61 versus 58 years, had worse performance status (p < 0.001), higher rates of secondary AML (65% versus 18%, p < 0.0001), and more adverse-risk disease at diagnosis (60% versus 25%, p = 0.01).

ORR, including CR and CRi, were similar (55% versus 57%, p = 0.85), with median relapse-free survival (RFS) of 6.9 months versus 11.1 months (p = 0.49) in the venetoclax with azacitidine group compared to the salvage chemotherapy regimen

group respectively. Median OS was 6.8 months versus 11.2 months (p = 0.053), and median RFS was 6.9 months versus 11.2 months (p = 0.49). Among patients treated with venetoclax and azacitidine, those with secondary leukaemia had significantly longer OS (7.1 versus 5.4 months, p = 0.02) and RFS (12.6 versus 5.0 months, p = 0.001) than those with primary leukaemia. Sub-group analysis of patients receiving other therapies indicated improved OS if; younger than 60 years (18.9 versus 5.9 months, p = 0.002); had primary disease (16.3 versus 5.4 months, p < 0.01); had adverse-risk disease (15.9 versus 6.8 months, p = 0.02); or underwent allogeneic HSCT after salvage therapy (18.9 versus 6.1 months, p < 0.01). In sub-group analysis of patients treated with venetoclax and azacitidine who had received a transplant prior to relapse ORR was higher (83.3% versus 41.2%, p = 0.07), though median OS and RFS were similar (p = 0.4 and p = 0.36, respectively)[23].

Comparator clinical efficacy data

To support comparison with venetoclax with azacitidine, clinical efficacy data for FLAG-Ida, the main comparator regimen, were also reviewed. Published studies were evaluated to describe treatment outcomes and provide a benchmark for comparison.

Doma et al. (2024) conducted a retrospective analysis of 130 adults with relapsed (n = 48), refractory (n = 56), or secondary AML (n = 26) treated with FLAG (n = 41) or FLAG-Ida (n = 89) in a single centre in Slovenia[24]. The median age was 60 years (range 19–79) with 47% aged over 60. The ORR was 70%, including CR in 53 patients (41%), CRi in 36 (28%), and PR in 2 (1.5%), while 34 patients (26%) had treatment failure and 5 (3.8%) died before response assessment. Median OS for the entire cohort was 9.4 months, with significantly longer OS in patients < 60 years compared to ≥ 60 years (14.0 versus. 6.9 months; p = 0.006. In the whole cohort, 61 patients (47%) proceeded to allogeneic HSCT, with a median age significantly younger than those who did not (median age 52 versus 63 years, p = 0.001). There were no significant differences in median OS in patients treated with FLAG compared to FLAG-Ida (7.5 versus 10.2 months; p = not significant). Transplanted patients achieved a median OS of 63 months compared with 4.2 months in non-transplanted patients (p < 0.001), and 57% remained alive at the time of analysis (31 December 2022). Multivariate analysis confirmed HSCT as the only factor significantly associated with survival (HR 0.24, 95% CI 0.14 to 0.43, p < 0.001)[24].

Delia et al. (2017) conducted a retrospective analysis of 108 adults with refractory or first-relapsed AML treated with FLAG-Ida as salvage therapy[25]. The median age was 49 years (range 17–72), with 61% (66/108) having primary refractory disease and 39% (42/108) first relapse. ORR, including CR, CRi, and CR in the absence of total platelet recovery (CRp) was 44%, with 36 patients achieving CR and 12 achieving CRi; 13 patients had PR, while 47 remained refractory. Among patients who responded to FLAG-Ida, 24 (50%) proceeded to allogeneic HSCT, contributing to a total of 50 patients who ultimately underwent transplantation. Median OS for the whole cohort was 15–16 months, with uncensored OS significantly improved in patients receiving HSCT (6 versus 19 months; p < 0.001) and in responders to FLAG-Ida (11 versus 37 months; p < 0.001); transplanted responders had a median OS of 60 months (p < 0.001). Post-transplant (responders and non-responders), 30% of patients relapsed and 12% died from treatment-related causes[25].

Westhus et al. (2019) conducted a retrospective real-world analysis of 132 patients with largely primary refractory or first-relapsed AML treated with FLAG-Ida[26]. The median age was 52 years (range 18–72), with 30% of patients (n = 39) over 60 years. Early relapse within 12 months had occurred in 45 out of 66 patients (68%). Overall, 58 patients (44%) achieved CR, 13 patients (10%) achieved CRi, and 12 patients (9%) achieved PR, resulting in a total of 84 responders (65%). Among responders, 77 patients proceeded to post-remission therapy with 72 patients (86%) receiving allogeneic HSCT, of patients who relapsed following transplantation, three patients (4%) receiving donor lymphocytes, and two patients (2%) receiving consolidation chemotherapy. With a median follow up of 63 months, median OS for the entire cohort was 15 months, with a 1-year OS of 53%. Among patients achieving CR or CRi, median OS was 65 months, and 1-year disease-free survival was 72%, with median disease-free survival not reached. Patients who underwent allogeneic HSCT had improved 1-year disease-free survival of 80%, compared with 33% in those who did not receive consolidation. Response rates were similar across age groups, with patients over 60 years achieving CR or CRi in 47% of cases (n = 18), compared with 59% in younger patients (n = 54), and survival among responders was comparable[26].

Safety

The adverse events associated with venetoclax in combination with azacitidine are outlined in the SmPC for each agent[4,5]. Both sources identify hematologic toxicities (neutropenia, thrombocytopenia, anaemia), febrile neutropenia, infections, and gastrointestinal disturbances (nausea, diarrhoea, constipation) as common adverse effects of venetoclax plus azacitidine therapy[5].

In studies of venetoclax in combination with azacitidine for R/R AML following at least one line of intensive chemotherapy or allogeneic HSCT as an alternative to intensive chemotherapy, the regimen was generally well-tolerated. Results collated from clinical trial data, including Wood et al. and Pelland et al. reflect patients treated according to approved dosing regimens, with approximately 100 patients across the studies[6,7,23]. No patients were reported to have permanent treatment interruptions solely due to adverse events. Grade 3/4 adverse event (AE) toxicities were frequent, occurring in up to 60–70% of patients, primarily including neutropenia, thrombocytopenia, anaemia, and febrile neutropenia. Infections, such as pneumonia and sepsis, were also commonly observed[6,23].

The SmPC for venetoclax highlights the risk of tumour lysis syndrome (TLS), a potentially life-threatening condition caused by the rapid breakdown of tumour cells, leading to metabolic disturbances such as hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia[4]. TLS can occur as early as 6 to 8 hours after the first dose of venetoclax and at each subsequent dose increase. To reduce this risk, a gradual dose escalation is recommended, along with prophylactic hydration and anti-hyperuricemic therapy before initiating treatment[4]. In clinical studies of venetoclax plus azacitidine, TLS was rare, which is consistent with the SmPC, and all cases were manageable with standard prophylactic measures[6,7,23].

Overall, the adverse events observed in these clinical studies align closely with those described in the SmPC, supporting the established safety profile of venetoclax plus azacitidine therapy, with most toxicities being manageable and not resulting in permanent treatment discontinuation.

Discussion

Outcomes in R/R AML are influenced by patient selection, prior therapy, and transplant eligibility, with treatment completion generally high and chronological age alone appearing less predictive of response in certain cohorts. Wood and Pelland demonstrated that venetoclax combined with azacitidine achieved overall response rates of 44% to 52% and CR/CRi rates of 37% to 41% in relapsed or refractory AML, translating to a median overall survival of 8 to 9 months in real-world series. [6,7,23]. HSCT increased OS, with one study reporting an OS of 18.9 months following HSCT post salvage therapy[23]. In contrast, intensive regimens such as FLAG-Ida, as reported by Westhus, Delia, and Doma, can achieve substantially longer survival (median OS reported ranging between 9.4 and16 months), particularly in transplanted patients, with some cohorts reporting an OS of up to 63 months[24-27]. These differences likely reflect patient selection, since FLAG-Ida cohorts were typically younger, earlier in their relapse course, and less exposed to prior transplant compared with venetoclax-based studies.

Ye and Pelland both reported that more than half of patients receiving venetoclax plus azacitidine were refractory[23,28], whereas Ganzel[29], Tenold[30], and Wood[6,7] observed refractory rates of 26% to 48% in venetoclax plus HMA cohorts. FLAG-Ida studies, such as those by Westhus and Doma, generally captured patients at first relapse or refractory only to induction, representing a less heavily pretreated population[24,26].

Prior therapy exposure also differed across regimens, Garciaz, Pelland, and Wood showed that patients receiving venetoclax with azacitidine had one to three prior lines of therapy and 18% to 30% prior transplant exposure[7,23,31], whereas Ganzel and Tenold reported that venetoclax plus HMA patients had one to six prior lines and 20% to 42% transplant exposure[29,30]. In contrast, FLAG-Ida cohorts studied by Westhus, Delia, and Doma mostly included first-relapse or induction-refractory patients, whist prior transplant exposure was lower than the venetoclax plus azacitidine studies, ranging from 0% to 8%[24,26,27].

Disease risk distributions were broadly similar, with most patients classified as intermediate or adverse, although some FLAG-Ida studies, such as those by Westhus and Delia, included higher proportions of intermediate-risk patients, potentially favouring outcomes[26,27]. Importantly, heavily pretreated patients, defined as those with two or more prior lines of therapy and/or prior allogeneic transplant, were more frequent in venetoclax plus HMA cohorts, which likely contributed to inferior outcomes compared with FLAG-Ida populations.

Disease risk, as defined by the European LeukemiaNet (ELN)[8], is used to stratify prognosis and broadly guide treatment decisions. Age, in turn, influences treatment primarily through its impact on functional status, which encompasses ECOG performance, frailty, and comorbidities. Patients over 60 years generally experience more frequent hospitalisations due to higher rates of cytopenias, infections, and reduced treatment tolerance, although a fit older patient with preserved functional status may tolerate intensive therapy similarly to younger adults[32]. Patients treated with venetoclax plus azacitidine in the studies by Garciaz, Ye, and Pelland were generally older, with median ages ranging from 50 to 73 years[23,28,31], whereas cohorts reported by Ganzel, Tenold, and Wood receiving venetoclax plus HMA tended to be slightly younger, with median ages in the mid-50s to 60s[7,29,30]. In

comparison, Westhus, Delia, and Doma reported median ages of 49 to 60 years in FLAG-Ida studies, and included fewer patients over 60 years and may partly explain differences in tolerability and transplant eligibility[24,26,27].

Outcomes with venetoclax-based regimens are significantly improved when used in molecular relapse (median OS 17.6–18.4 months) or when bridging to HSCT, underscoring the prognostic impact of disease burden and transplant eligibility[6,7]. Overall, venetoclax plus azacitidine balances efficacy and tolerability, serving as a valuable salvage strategy in older or heavily pretreated patients, while still permitting consolidation with HSCT in a meaningful proportion (27–38%) of responders[6,7,23].

Safety findings from these studies are consistent with the profile described in the SmPC for venetoclax and azacitidine[4,5]. Most AEs are manageable and do not typically result in permanent treatment discontinuation. Grade 3/4 hematologic toxicities, including neutropenia, thrombocytopenia, anaemia, and febrile neutropenia, were reported in 60–70% of patients. Infections such as pneumonia and sepsis occurred frequently, while TLS was rare (<5%) and manageable with standard prophylactic measures. Supportive interventions, including dose interruptions, growth factor administration, and transfusions, were commonly required. The consistency between trial findings and the SmPC reinforces that venetoclax and azacitidine is generally tolerable, although careful monitoring for cytopenias, TLS and infection is essential to ensure safe administration[4,5].

Overall, while venetoclax with azacitidine provides an alternative to intensive chemotherapy for patients with R/R AML, differences in trial design, small sample sizes, patient characteristics, and follow-up durations complicate direct comparisons with other salvage regimens. These limitations necessitate cautious interpretation of efficacy outcomes, and larger controlled studies are needed to better define long-term benefits, comparative effectiveness, and optimal patient selection.

COST-EFFECTIVENESS

Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any studies relevant to the cost-effectiveness of venetoclax (Venclyxto®) in combination with azacitidine for the treatment of R/R AML in adults following at least one line of intensive chemotherapy before or following allogenic HSCT.

Context

An AWTTC cost-consequence analysis (CCA) compares selected resource use and clinical outcomes associated with venetoclax (Venclyxto®) with azacitidine versus FLAG-Ida in the treatment of R/R AML. The analysis adopts a lifetime time horizon and an NHS Wales/Personal and Social Services perspective. As median overall survival is less than one year costs and outcomes are undiscounted.

The patient pathway for R/R AML consists of initial therapeutic interventions followed by potential HSCT, additional therapy cycles or palliative care. In the analysis, clinical outcomes, the number of treatment cycles, and the clinical pathway are informed by a UK observational study for venetoclax with azacitidine and a European observational

study for FLAG-Ida [7,24]. The model pathways are a simplification of those reported in the observational studies, defined by clinical experts to represent delivery within Wales.

Patients receiving venetoclax with azacitidine complete an initial two cycles followed by treatment according to their response status. Over half of patients (52%) respond to therapy, with 55% continuing treatment with three additional cycles. The remaining 45% of patients receive allogenic HSCT. Patients who do not respond (48%) receive palliative care, as informed by discussion with clinical experts in Wales. Patients receiving FLAG-Ida receive a single cycle, almost half receive HSCT (47%). The HSCT rate is derived from the whole cohort in the Doma et al. study which includes patients treated with both FLAG-Ida and FLAG without idarubicin (FLAG-only) regimens[24]. Based on clinical expert opinion in Wales, 50% of patients receiving HSCT are assumed to have an additional bridging cycle of FLAG-only to minimise toxicity, particularly cardiac toxicity. The remainder (53%) are assumed to progress to palliative care.

Cost of intervention: medicine acquisition and administration costs

The medicine acquisition costs and delivery schedule for venetoclax with azacitidine are displayed in Table 1. Hospital admission to receive this treatment is not routine, based on clinical expert opinion in Wales.

Table 1. Venetoclax with azacitidine: medicine acquisition costs, treatment schedule and medicine administration costs

	Dose	Cost/regimen	Reference
Venetoclax	100mg tablet	¶¶	WPAS
Azacitidine	100mg vial	¶¶	AWDC
Posaconazole	24 x 100mg tablets	¶¶	WPAS
Average patient surface area(m^2)		1.79	Sacco et al., 2010[33]
First cycle			
Venetoclax	100mg	day 1	SmPC[4]
	200mg	day 2	SmPC[4]
	400mg	day 3	SmPC[4]
	100mg	days 4-28	Clinical expert opinion[4]
Azacitidine 75mg/m^2	134.25mg	7 days (1-5 then 8-9)	SmPC[5]
Posaconazole	600mg	day 4	Clinical expert opinion and SmPC[34]
	300mg	Days 5-28	Clinical expert opinion and SmPC[34]
Second cycle +			
Venetoclax	100mg	days 1 - 28	Clinical expert opinion
Azacitidine 75mg/m^2	134.25mg	7 days (1-5 then 8-9)	SmPC[5]
Posaconazole	300mg	Days 1-28	Clinical expert opinion and SmPC[34]
Administration			
SB12Z Deliver simple parenteral chemotherapy at first attendance		£418	NHS reference costs[35]
SB15Z deliver subsequent elements of a chemotherapy cycle – day case		£426	NHS reference costs[35]

AWDC: All Wales Drug Contract; SmPC: Summary of Product Characteristics; WPAS: Wales Patient Access Scheme
¶¶ commercial in confidence data removed

Table 2 details medicine acquisition cost and administration cost of venetoclax with azacitidine, delineated by cycle number. It is assumed that vial wastage occurs, pack sharing is practiced and that patients fully adhere to treatment regimens. The differences in cycle costs are driven by the initial treatment titration of venetoclax.

Table 2. Venetoclax with azacitidine: total medicine acquisition and administration costs by cycle

	Dose/calculations	Cost
First cycle		
Venetoclax	3,200mg	¶¶
Azacitidine 75mg/m^{2*}	1,400mg	¶¶
Posaconazole	7,800 mg	¶¶
First cycle medicine cost	-	¶¶
7 days simple chemotherapy delivery	1x SB12Z + 6 x SB15Z	£2,974
First cycle total cost	¶¶	¶¶
Second cycle +		
Venetoclax	2,800mg	¶¶
Azacitidine 75mg/m^{2*}	1,400mg	¶¶
Posaconazole	8,400mg	¶¶
Second cycle + medicine cost	-	¶¶
7 days simple chemotherapy delivery	1x SB12Z + 6 x SB15Z	£2,974
Second cycle + total cost	¶¶	¶¶
*Assumes vial wastage ¶¶ commercial in confidence data removed		

Cost of comparators: medicine acquisition and administration costs

Clinicians in Wales identify FLAG-Ida as the most appropriate comparator for venetoclax with azacitidine in the targeted patient group. FLAG-Ida medicine acquisition costs, administration costs and inpatient costs are reported in Table 3. More detailed costs are reported in Appendix 3.a – 3.c.

Table 3. Total cost of medicines, administration and inpatient stays for one FLAG-Ida cycle

	Cost	Reference
Medicine acquisition cost	¶¶	Appendix 3.a – 3.b
Administration and inpatient cost	£8,937	Appendix 3.c
Total cost per cycle	¶¶	

Adverse events

A targeted literature review informed the adverse event rates for venetoclax with azacitidine and FLAG-Ida. Serious adverse events (grade 3 or higher) are included in the analysis if the associated incidence rate is ≥5% in either treatment arm. Adverse event rates for venetoclax with azacitidine are based on evidence from a phase 3 randomised controlled trial[9], for FLAG-Ida they are sourced from NICE TA642[3]. These sources were selected based on their data granularity and relative compatibility. Included adverse events are either treatment emergent or treatment related (within 30 days of treatment). The total costs of adverse events per patient are detailed in Table 4. Further details are reported in Appendix 3.d.

HSCT and palliative care costs

The weighed cost of HSCT over a 3-month horizon reported by Wales Joint Commissioning Committee is [commercial in confidence text removed], details are included in appendix 3.e. Palliative care costs are not included in the analysis due to variability of delivery and uncertainty of duration.

Total costs

Table 4 reports total costs for the treatment comparison.

Table 4. Total costs

	Venetoclax with azacitidine	FLAG-Ida
Cost per cycle	¶¶	¶¶
Average number of cycles	2.858	1.235
Total cost of cycles	¶¶	¶¶
Adverse event cost per patient	£967	£1,146
HSCT unit cost	¶¶	¶¶
HSCT percentage	23.4%	47.0%
HSCT cost	¶¶	¶¶
Total cost	¶¶	¶¶

*Second cycle FLAG without idarubicin
HSCT: haematopoietic stem cell transplant
¶¶ commercial in confidence data removed

Clinical outcomes

The clinical outcomes associated with the delivery of venetoclax with azacitidine and with FLAG-Ida are reported by Wood et al., 2025 and Doma et al., 2024[7,24]. The median overall survival of patients receiving venetoclax with azacitidine is 8.9 months (95% CI: 5.9 to 11.9) with an overall response rate of 52%. FLAG-Ida is associated with a median overall survival of 10.2 months and an overall response rate of 71%.

Results

The results of the base case are detailed in Table 5. When compared with FLAG-Ida, the incremental saving generated is [commercial in confidence text removed] per patient. The main cost difference can be attributed to fewer patients undergoing HSCT. Patients receiving venetoclax with azacitidine are also associated with an incremental overall survival loss of 1.3 months.

Table 5. Base case analysis

	Venetoclax with azacitidine	FLAG-Ida
Drug acquisition	¶¶	¶¶
Administration	£8,500	£11,037
Adverse events	£967	£1,146
HSCT	¶¶	¶¶
Total	¶¶	¶¶
Incremental cost	¶¶	
Overall survival (months)	8.9	10.2
Incremental overall survival (months)	-1.3	
Response rate	52%	71%*
Incremental overall response rate	-19%	

HSCT: haematopoietic stem cell transplant
*This response rate includes patients receiving FLAG-Ida and FLAG=only.
¶¶ commercial in confidence data removed

Sensitivity and scenario analysis

A range of sensitivity and scenario analyses, reported in table 6, were conducted to test the influence of parameters and to characterise uncertainty within the modelled costing approach. Due to data limitations, these analyses do not include any variability in clinical and health outcomes.

Table 6. Sensitivity and scenario analysis

Sensitivity and scenario analysis	Difference in cost/outcomes	Plausibility/insight
Equality of HSCT rates in the FLAG-ida arm reduced to the lower venetoclax with azacitidine level.	¶¶	This analysis provides insight into the impact of relative HSCT rates, highlighting the significant impact of this key cost driver, and allows a comparison of remaining costs. This analysis does not offer a plausible alternative to the base case.
Variability in the number of venetoclax with azacitidine cycles (±40%)†	¶¶	This analysis has potential to offer plausible alternatives to the base case given the variability in the number of cycles delivered to the venetoclax with azacitidine treatment group in the Wood et al study[6].
Increase/decreased number of inpatient days associated with FLAG-Ida cycle 10 – 30 days †	¶¶	The plausibility of this scenario is uncertain; this scenario demonstrates the impact to costs of inpatient stay duration.
Inpatient duration: Venetoclax with azacitidine Ranges from 0 – 20 days †	¶¶	This scenario explores the impact of the number of inpatient days per cycle of venetoclax with azacitidine.
HSCT: haematopoietic stem cell transplant. Sensitivity and scenario analysis are detailed in appendix 3.f – 3.i. † ranges selected are arbitrary. ¶¶ commercial in confidence data removed		

Threshold analysis

To characterise the scale of the differences in costs and overall survival a range of threshold analyses are undertaken applying cost-effectiveness thresholds of £20,000 and £30,000 per quality adjusted life year (QALY). In the base case, venetoclax with azacitidine is less costly but also less effective than FLAG-Ida. Therefore, the threshold analysis seeks to identify the number of QALYs it would be acceptable to forego given the projected cost saving. The threshold analyses suggest that it would be acceptable to forego [commercial in confidence text removed] QALYs at a threshold of £20,000 per QALY, and [commercial in confidence text removed] QALYs at a threshold of £30,000 per QALY, in the context of a 1.7 severity modifier (see Table 7 for severity modifier considerations).

Exploratory cost-utility analysis

Due to data and population limitations, it was considered inappropriate to undertake a cost-utility analysis as the AWTTC base case. However, an additional scenario analysis was conducted to offer further contextualisation of incremental cost and

clinical outcomes, applying cost-utility methodology. Expanding on the threshold analysis to include an estimate of health-related quality of life (HRQoL) an AWTTC targeted literature review sought disease specific HRQoL data for adult patients with relapsed/refractory AML. A UK based utility analysis was selected to inform the analysis based on recency and patient matching[36]. Accordingly, a utility value of 0.628 for adults with relapsed AML is used for both the venetoclax with azacitidine and the FLAG-Ida groups[36]. Due to data limitations, the simplified model structure assumes a constant utility value over time. Therefore, the model does not capture variation in utility according to response status. Adverse events reduce the HRQoL of patients, the range of treatment emergent adverse events described in the costing section each have corresponding negative utility estimates reported in NICE TA765[18]. The utility decrements due to adverse events are calculated as 0.018 for venetoclax with azacitidine and 0.014 for FLAG-Ida (see Appendix 3.d for further details).
The results of the exploratory analysis are detailed in Table 7. Incremental-cost-effectiveness ratios (ICERs) are reported with and without application of the severity modifier. These ICERs are for contextualisation purposes only. There is a high degree of uncertainty around these estimates, and they should be interpreted with caution.

When compared with FLAG-Ida, the point estimate for the ICER falls within the southwest quadrant of the cost-effectiveness plane (i.e. venetoclax with azacitidine is less costly and less effective than comparator FLAG-Ida), producing an ICER of [commercial in confidence text removed] saved per QALY forgone. When the severity modifier is applied the saving per QALY foregone is [commercial in confidence text removed]. In the southwest quadrant, an ICER > £20,000 saved per QALY forgone is generally desirable.

Table 7. Exploratory cost-utility analysis

	Venetoclax with azacitidine	FLAG-Ida
Relapsed AML utility value	0.628	0.628
Median OS (months)	8.9	10.2
Adverse events utility decrement	0.018	0.014
Total QALYs	0.448	0.520
Incremental QALYs	-0.072	
Incremental cost	¶¶	
ICER	¶¶	
ICER with severity multiplier (1.7)	¶¶	
AML: acute myeloid leukaemia; ICER: incremental cost-effectiveness ratio; OS: overall survival QALY: quality-adjusted life-year; ¶¶ commercial in confidence data removed		

Analysis limitations

- The clinical comparison is subject to uncertainty and potential bias due to the variability in trial characteristics and the potential for selection bias.

- It is uncertain whether the populations in the intervention and comparator arms are sufficiently comparable to support direct comparison. This uncertainty increases the risk of bias and reduces the potential for analysis validity. If the populations are not comparable, differences in outcomes and costs may reflect underlying population characteristics rather than true treatment effects.
- The prior HSCT rate of the population informing venetoclax with azacitidine clinical effectiveness was 32% compared to 8% for FLAG-Ida. The difference in pretreated status of the populations may influence clinical outcomes. Therefore comparisons of the populations may be inappropriate.
- The average age at diagnosis for the AML population in England is 72 years[10]. The cohorts used to inform the analysis had average ages of 58 and 60 for patients receiving venetoclax with azacitidine and FLAG-Ida respectively. Survival is reported as having a strongly negative correlation with age[10]. If the population in Wales is older than that of the clinical evidence cohorts, the analysis may overestimate overall survival.
- Age is also related to HSCT rate. Younger patients are associated with a higher rate of HSCT[24]. If the rate of HSCT in the Welsh population is lower than the modelled rate, the overall survival and associated costs may be lower than reported.
- Incremental cost is highly sensitive to changes in HSCT rates. HSCT rates and pre-treated HSCT rates vary between the study arms, this uncertainty reduces the comparability between the two populations and any subsequent conclusions.
- The use of median OS, due to data limitations, has associated limitations. A Kaplan-Meier survival curve or a parameterised long-term survival would be preferential. The use of median OS effectively ignores longer-term outcomes, treatment benefits and costs. The impact of this limitation is uncertain.
- Adverse events are reported as treatment emergent adverse events. Venetoclax with azacitidine is delivered over a longer period than FLAG-Ida. Therefore, adverse events may reflect a higher proportion of condition emergent events compared to treatment related events. Due to the frailty of the patient cohort, this approach may overestimate the adverse events related to venetoclax with azacitidine.
- The incremental cost of venetoclax with azacitidine is sensitive to the base case assumptions relating to inpatient stay. These inputs are informed by expert clinicians in the absence of observed data, which introduces uncertainty. Variation in inpatient stay could have a significant impact on the costs associated with venetoclax and azacitidine.
- Adverse event costs are calculated according to the additional treatment required, this may lead to double counting in the FLAG-Ida arm as the estimate of inpatient stay duration includes consideration of additional care. This may bias the analysis in favour of venetoclax with azacitidine.
- Clinical experts report that patients not responding to treatment would not proceed directly to HSCT. The evidence informing HSCT rates for the venetoclax with azacitidine include only patients who have responded to treatment. In contrast, the FLAG-Ida rates are not delineated by response

status. This lack of data granularity may bias in favour of venetoclax and azacitidine.
- The FLAG-Ida HSCT rate incorporates the complete study cohort, including both FLAG-Ida and FLAG only. It is unknown what impact this may have on associated costs and outcomes.
- The analysis adopts a limited costing approach which does not include palliative care or ongoing resource use, including additional monitoring, subsequent HSCT (beyond the initial HSCT included) or donor lymphocyte infusion. It is unknown what impact this has on the analysis aside from an increase in uncertainty.

AWMSG's policy for medicines for severe conditions

AWTTC believes that the use of venetoclax with azacitidine in the given patient population meets the QALY shortfall criteria set by the AWMSG policy on appraising medicines for severe conditions.

The AWMSG QALY shortfall criteria for appraising medicines for severe conditions, and a discussion of the extent to which the medicine may meet these criteria, are provided in Table 8.

Table 8. Severity modifier considerations for One Wales medicines assessment group (OWMAG)

AWMSG criteria for applying a severity modifier weight	New Medicine considerations
AWMSG can: • apply a QALY weight of 1 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall < 12 and/or a proportional QALY shortfall < 0.85.	The general population expected life-year and expected total QALY estimates are taken from the pooled 2017–2019 with the population health state profiles offered by the health survey 2014 combination with the valuation model of Hernandez et al., 2022[37-39]. The median age of 72 and the gender distribution (44% female) are taken from Liu et al., 2024. The general population is estimated to achieve 8.38 QALYs. An annual discount rate of 3.5% has been used to calculate QALY shortfall estimates.
• apply a QALY weight of 1.2 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall ranging between 12 and 18 and/or a proportional QALY shortfall ranging between 0.85 and 0.95. • apply a QALY weight of 1.7 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall >18 and/or a proportional QALY shortfall ≥ 0.95. If the absolute and proportional QALY shortfalls imply different levels of severity, QALY weighting selection is guided by the shortfall that shows greatest severity.	Expected life-year and expected total QALY estimates for patients being treated with the current standard of care is estimated according to the line of therapy. The quality-of-life estimate of 0.628 sourced from Pratz et al., 2022[36]. Patients treated with FLAG-Ida achieved 0.362 QALYs. AWTTC considers the QALY shortfall estimates to be informed by recent and robust data sources. AWTTC considers the most plausible absolute QALY loss to be around 8.02, with a proportional reduction of 95.7%, given this estimate the relative shortfall meets the AWMSG criteria for the 1.7 QALY modifier weight. This estimate is deemed plausible due to the very low median overall survival expected for this patient cohort.
QALY: quality-adjusted life-year	

If the One Wales Medicines Assessment Group (OWMAG) conclude that venetoclax with azacitidine should be considered under the AWMSG policy for appraising medicines for severe conditions, OWMAG usually need to consider:

- the effect of the severity QALY weight applied, and whether the weighted QALY benefits in this patient group result in a most plausible ICER that falls within the current cost-effectiveness threshold range.

In addition, OWMAG usually need to be satisfied that:

- The estimates of the expected life years and total QALYs for the general population and for patients being treated with the comparator medicines(s) are sourced from recent and robust data sources.
- The assumptions used in the economic modelling are plausible, objective and robust.

However, as previously noted, there is a considerable uncertainty around the ICER estimates in the exploratory cost-utility analysis, and they should therefore be interpreted with caution. In this assessment, consideration of the severity modifier enables an explicit evaluation of whether the condition qualifies as severe under AWMSGs criteria and provides additional context to inform the threshold analysis.

Budget impact

The Patient Access Scheme (PAS) price of venetoclax is [commercial in confidence text removed] per 100 mg tablet. The All Wales Drug Contract (AWDC) price for azacitidine is [commercial in confidence text removed] per subcutaneous (SC) 1 ml vial (100 mg) and for posaconazole is [commercial in confidence text removed] per 100 mg tablet. All costs exclude VAT. The dose of azacitidine is as per the SPC, 75 mg per m^2 of BSA by SC injection daily for the first 7 days of a 28-day cycle. In practice azacitidine is administered on days 1 to 5 and 8 to 9 to avoid weekend hospital attendance. The SC and oral formulations allow for patients to be typically treated at haematology day units on an outpatient basis. Venetoclax is an oral tablet taken daily, with an initial ramping of dose on days 1,2 and 3 of a cycle with 100 mg, 200 mg and 400 mg taken daily. From day 4 onwards and for subsequent cycles the venetoclax dose is reduced to 100 mg daily to coincide with the start of taking the posaconazole. Clinical experts consider that fewer than 10% of patients would have contra-indication to posaconazole and that the majority of patients will require antifungal prophylaxis for the duration of treatment. The daily dose of venetoclax therefore remains at 100 mg daily from day 4 until treatment discontinues. Monitoring costs have not been included in the budget impact, clinical experts report that no additional monitoring is required for patients treated with venetoclax with azacitidine. Table 9 shows the estimated medicine acquisition costs and drug administration costs for venetoclax with azacitidine for one patient per cycle.

Table 9. Estimated cost of venetoclax with azacitidine in Wales (per patient, per cycle)

	Cost 1st cycle	Cost 2nd cycle and beyond	Source
Azacitidine SC 100 mg vial 75 mg/m^2 BSA* per day for 7 days (1-5 then 8-9) per cycle	¶¶	¶¶	AWDC price
Venetoclax 100 mg tablets Cycle 1: 100 mg, 200 mg, 400 mg daily on days 1,2 and 3; 100 mg daily from day 4-28. Cycle 2 and beyond: 100 mg daily	¶¶	¶¶	PAS price
Posaconazole 100 mg tablets 600 mg (300mg twice a day) on day 4 of 1st cycle, then 300mg daily onwards	¶¶	¶¶	AWDC price
Drug administration costs (azacitidine)	£2,974	£2,974	HRG Cost Codes[35] SB12Z Deliver simple parenteral chemotherapy at first attendance – day case. SB15Z deliver subsequent elements of a chemotherapy cycle – day case.
Total cost per patient per cycle	¶¶	¶¶	
*Average BSA 1.79 m^2 AWDC: All Wales Drug Contract; BSA: body surface area; PAS: Patient Access Scheme; SC: sub-cutaneous. ¶¶ commercial in confidence data removed			

The comparator treatment is salvage chemotherapy; clinical experts consider the most appropriate regimen to be FLAG-Ida although others such as MEC (mitoxantrone, etoposide and cytarabine) or MACE (amsacrine, cytarabine and etoposide) may also be used depending upon patient characteristics. For the purposes of the budget impact calculations FLAG-Ida has been used as the comparator treatment. One 28-day cycle of FLAG-Ida comprises fludarabine and cytarabine on days 1 to 5, idarubicin on days 3-5 and granulocyte-colony stimulating factor (G-CSF) on days 1-7. Administration requires central venous access, and patients will be in-patients for the duration of the drug administration, clinical experts estimate that patients will require in-patient care for a total of 20 days, administration costs include an additional 13 days of in-patient care. The estimated cost for one cycle of FLAG-Ida for one patient, including medicine acquisition costs and drug administration costs is shown in Table 10. Clinical experts advise that idarubicin is usually omitted from an additional cycle, cost of a cycle of FLAG is included.

Monitoring costs are not included as clinical experts advise that monitoring will not differ between treatment regimens.

The cost of HSCT is [commercial in confidence text removed] as reported by Wales Joint Commissioning Committee and detailed in the cost effectiveness section and appendix 3.e.

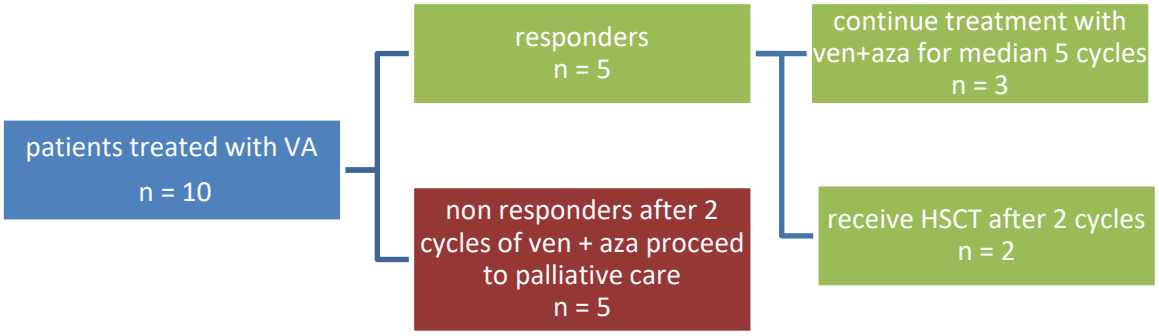
Table 10. Estimated cost for 1 cycle of FLAG+/-Ida per patient

	Cost	Source
Fludarabine 30 mg/m^2 BSA* on days 2 to 6 (5 doses)	¶¶	AWDC price
Cytarabine 2 g/m^2 BSA*on days 2 to 6 days (5 doses)	¶¶	AWDC price
Idarubicin 8 mg/m^2 BSA* on days 4,5 and 6 (3 doses)	¶¶	AWDC price
G-CSF 5 mcg/kg† per days 1- 7	¶¶	AWDC price
Drug administration costs§	£8,937.00	SB14Z Deliver complex parenteral chemotherapy at first attendance - elective inpatients; SB14Z Deliver complex parenteral chemotherapy at first attendance - day or night unit cost; SA25K Acute Myeloid Leukaemia with CC Score 4-5
Total cost per patient	¶¶	
Total cost cycle 2 (FLAG) per patient	¶¶	

*Average BSA 1.79 m^2
†Average body weight 79 kg
§Administration costs include 7 days of in-patient administration followed by 13 days of additional hospitalisation days
AWDC: All Wales Drug Contract; BSA: body surface area; G-CSF: granulocyte-colony stimulating factor
¶¶ commercial in confidence data removed

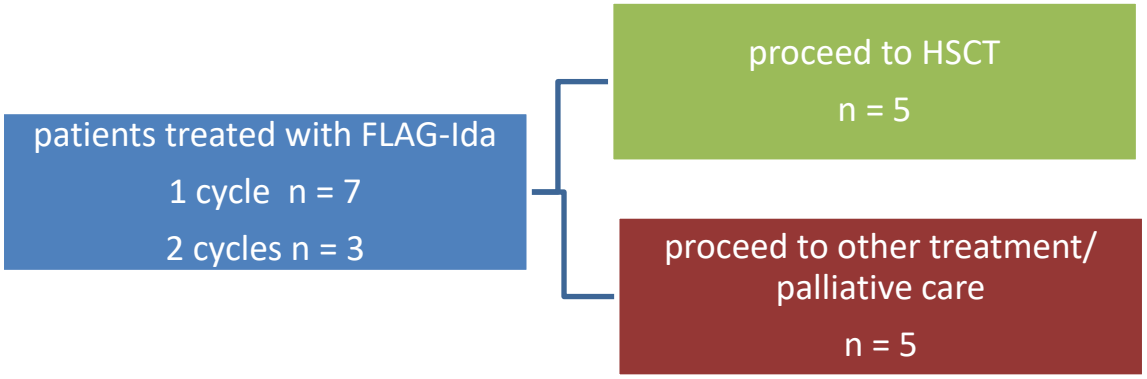
Treatment response and duration for venetoclax with azacitidine has been estimated from the results of the Wood et al (2025) study; 48% of patients are non-responders and discontinue treatment after a median of 2 cycles[7]. Of patients who respond to treatment; 45% receive HSCT after a median of 2 cycles (as per Wood et al, 2025). In those patients not receiving cellular therapy in Wood et al, 2025, treatment continued for a median of 5 cycles. It is assumed that the remaining 55% receive a median of 5 cycles before disease progression or discontinuation. Clinical experts estimate that 10 patients per year would be eligible for treatment. The flow diagram below (Figure 1) shows the distribution of treatment with venetoclax with azacitidine for these 10 patients based on results of the Wood et al study, patient numbers have been rounded.

Figure 1. Patient flow for treatment with venetoclax with azacitidine



Clinical experts estimate that patients would usually receive up to 2 cycles of salvage chemotherapy. The second cycle may be required if response is partial following the first cycle or if remission is achieved but there is a delay in HSCT, for example whilst a suitable donor is found. The study by Doma et al (2024) has been used to inform the duration and response to treatment with FLAG-Ida as this was the best matched for patient age and detail on number of cycles[24]. In the study 36 (28%) patients received a second cycle of FLAG+/-Ida and 61 (47%) patients proceeded to receive HSCT. The flow diagram below shows the distribution of treatment with FLAG-Ida based on the results of the Doma et al study, patient numbers have been rounded. Patients receiving a second cycle are assumed to receive FLAG only.

Figure 2. Patient flow for treatment with FLAG-Ida



In the absence of clinical trial data adverse event rates for venetoclax with azacitidine have been taken from the results of the VIALE-A trial which evaluated efficacy and safety in newly diagnosed AML patients ineligible for intensive chemotherapy[9]. Adverse event rates for FLAG-Ida have been taken from the comparator arm for the NICE TA765 which evaluated gilteritinib versus chemotherapy in patients with FLT3-mutated R/R AML[3]. Clinical experts have confirmed that the adverse events would not expected to be different in patients with FLT3 mutated AML. Costs of adverse events have been taken from NICE TA765 (venetoclax with azacitidine for untreated acute myeloid leukaemia). Mean adverse event treatment costs are estimated to be

£967 per patient for venetoclax with azacitidine and £1,146 for FLAG-Ida. For more detail refer to the cost-effectiveness section above and Appendix 3. d.

Table 11 provides the estimated budget impact for treatment of 10 patients with venetoclax with azacitidine in Wales including medicines acquisition costs, administration and adverse event costs.

Table 11. Estimated annual costs in Wales

	Number of patients	Cost
Number of people eligible for treatment	**10**	
Venetoclax with azacitidine		
Patients receiving 2 cycles of ven+aza	7	¶¶
Patients receiving 5 cycles of ven+aza	3	¶¶
Patients proceeding to allogenic HSCT	2	¶¶
Adverse events	10	£9,670
Total cost		¶¶
FLAG-Ida		
Patients receiving 1 cycle of FLAG-Ida	7	¶¶
Patients receiving 2 cycles of FLAG-Ida*	3	¶¶
Patients proceeding to allogenic HSCT	5	¶¶
Adverse events	10	£11,460
Total cost		¶¶
Annual net cost	¶¶	
*Second cycle FLAG without idarubicin ¶¶ commercial in confidence data removed		

Budget impact issues

- The budget impact estimates show that the expected impact to be cost saving at [commercial in confidence text removed] per year. However, there are several assumptions made to inform the budget impact. There were differences in baseline patient characteristics in the venetoclax with azacitidine patients (Wood et al) and in the FLAG-Ida patients (Doma et al)[7,24]. In particular, 30% of venetoclax with azacitidine patients and 8% of FLAG-Ida patients had received allogenic HSCT prior to relapse. Also, patients in the venetoclax with azacitidine study had received more prior treatments (47% received ≥ 2 prior treatments) than in the FLAG-Ida study (1.5% patients experienced 2nd or 3rd relapse)[7,24]. Although difficult to establish from the baseline patient characteristics reported we would expect patients considered suitable for treatment with FLAG-Ida to be fitter with fewer co-morbidities than those selected for treatment with venetoclax with azacitidine.
- The main driver of the budget impact is the cost of allogenic HSCT. The proportion of patients who proceeded to receive allogeneic HSCT was 47% in the FLAG-Ida group and 23% in the venetoclax with azacitidine group. The characteristics of patients under consideration for treatment with venetoclax with azacitidine are expected to align with those treated in the Wood et al

study, we would expect the allogenic HSCT rate to be similar. As mentioned above, 30% of patients treated with venetoclax with azacitidine had received prior allogenic HSCT compared to 8% in the FLAG-Ida study.

- If the rate of HSCT is assumed to be equal following treatment with venetoclax with azacitidine or with FLAG-Ida the budget impact would be [commercial in confidence text removed]. This is driven by the higher administration and in-patient costs associated with FLAG-Ida.
- There is considerable variation in the number of cycles of venetoclax with azacitidine that patients received in the study by Wood et al[7]. A median of 5 cycles for patients responding to treatment has been used for the purposes of the budget impact although the results reported a range of 1 to 13 cycles for patients who responded to treatment without proceeding to allogenic HSCT.
- The rate of adverse events have been taken from trial data as reporting in the retrospective studies is less consistent. For venetoclax with azacitidine data was taken from the VIALE-A study which was conducted in patients with newly diagnosed AML which were ineligible for intensive chemotherapy, it may be that the rates of adverse events differ in patients with R/R AML. Adverse events for FLAG-Ida were taken from the chemotherapy comparator treatment in NICE TA642, although FLAG-Ida was most used comparator only 40% of patients received it, adverse events were not reported separately for the different comparator treatments.
- A limitation of the budget impact is that estimates for costs of further treatments other than HSCT or for palliative care have not been included. In the Wood et al study, 10 patients (6%) received consolidation therapy with donor lymphocyte infusion (DLI), usually administered as hospital outpatient. There are no published costs for palliative care of AML patients, patients who do not respond to treatment and for whom treatment options are exhausted are expected to receive palliative care. Patients with relapsed or refractory AML are heterogeneous in terms of their clinical presentation and therefore palliative care needs vary greatly on relapse. Clinical experts advise that some patients will opt for full blood product support (red cells and platelets) involving hospital visits twice per week, others will opt for red cells only every one to two weeks, others may prefer less intervention and go on to an end-of-life care pathway. The HRG daycase unit cost for AML patients with a complication/comorbidity score of 4-5 (range 0-10) is £411 (HRG code SA25K)[35]. Low dose cytotoxic treatments such as hydroxycarbamide or etoposide (oral treatments) or low dose cytarabine (IV injection at home by district nurse) may be given for a few weeks following relapse to control blood blast count.
- Administration costs for venetoclax with azacitidine do not include hospitalisation for additional monitoring. Clinical experts advise that patients with more proliferative releases may require hospitalisation for elevated white blood cell counts to monitor for TLS. This would typically be for a few days rather than weeks at a cost of £411 per day (HRG Code SA25K)[35].
- The cost for FLAG-Ida assumes 7 days of treatment with G-CSF, this may be an underestimate as in some cases treatment may be required beyond one week.
- HSCT is the most costly procedure included in the budget impact. Treatment with venetoclax with azacitidine for patients with R/R AML is expected to provide a bridge to HSCT for a proportion of patients who are not suitable for treatment with salvage chemotherapy.

- There have been twelve IPFRs for this treatment over a period of 15 months, all of which were approved for funding. As the number of eligible patients is anticipated to be 10 per annum, the actual budget impact is anticipated to be low based on the cost of the venetoclax and azacitidine alone. If a patient responds to treatment and is eligible for HSCT this cost would be routinely funded by the health board as part of their treatment pathway.

Equality and health impact assessment

AWTTC have completed an Equality and Health Impact Assessment in parallel with each development stage of the project. This follows the five ways of working for public bodies, and work to achieving the wellbeing goals, outlined in the Well-Being of Future Generations (Wales) Act 2015.

It is not expected that venetoclax with azacitidine will have significant potential negative impact on people based on the protected characteristics of the Equality Act 2010.

Additional factors

Prescribing unlicensed medicines

Venetoclax with azacitidine is not licensed to treat this indication and is therefore ‘off label’. Providers should consult the relevant guidance on prescribing unlicensed medicines before any off-label medicines are prescribed.

References

1. Ramos NR, Mo CC, Karp JE et al. Current Approaches in the Treatment of Relapsed and Refractory Acute Myeloid Leukemia. *Journal of Clinical Medicine.* 2015;4(4):665–695.
2. Stubbins RJ, Francis A, Kuchenbauer F et al. Management of Acute Myeloid Leukemia: A Review for General Practitioners in Oncology. *Current Oncology.* 2022;29(9):6245–6259.
3. National Institute for Health and Care Excellence. Technology Appraisal 642. Gilteritinib for treating relapsed or refractory acute myeloid leukaemia. August 2020. Available at: https://www.nice.org.uk/guidance/ta642. Accessed August 2025.
4. AbbVie Ltd. Summary of Product Characteristics: Venclyxto 100 mg film-coated tablets. 26 Feb 2025. Available at: https://www.medicines.org.uk/emc/product/10476/smpc. Accessed August 2025.
5. Zentiva. Summary of Product Characteristics: Azacitidine 25 mg/mL powder for suspension for injection. Available at: https://www.medicines.org.uk/emc/product/12470/smpc#gref. Accessed August 2025.
6. Wood H, Bourlon C, Kulasekararaj A et al. Venetoclax-Based Non-Intensive Combinations Successfully Salvage Molecular Relapse of Acute Myeloid Leukemia and Are an Important Bridge to Cellular Therapy in Relapsed/Refractory Disease - Real-World Data from a UK-Wide Programme. *Blood.* 2022;140(Supplement 1):9016–9018.
7. Wood H, O'Nions J, Chan WY et al. Venetoclax-based non-intensive combinations for relapsed/refractory acute myeloid leukaemia-Real-world data from a UK-wide programme. *British Journal of Haematology.* 2025.
8. Döhner H, Wei AH, Appelbaum FR et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood.* 2022;140(12):1345–1377.
9. DiNardo CD, Jonas BA, Pullarkat V et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *The New England Journal of Medicine.* 2020;383(7):617–629.
10. Liu H, Stanworth SJ, McPhail S et al. Impact of patient demographics on treatment outcomes in AML: a population-based registry in England, 2013-2020. *Blood Advances.* 2024;8(17):4593–4605.
11. Haematological Malignancy Research Network. Statistics: Acute myeloid leukaemia. Available at: https://hmrn.org/statistics/survival. Accessed August 2025.

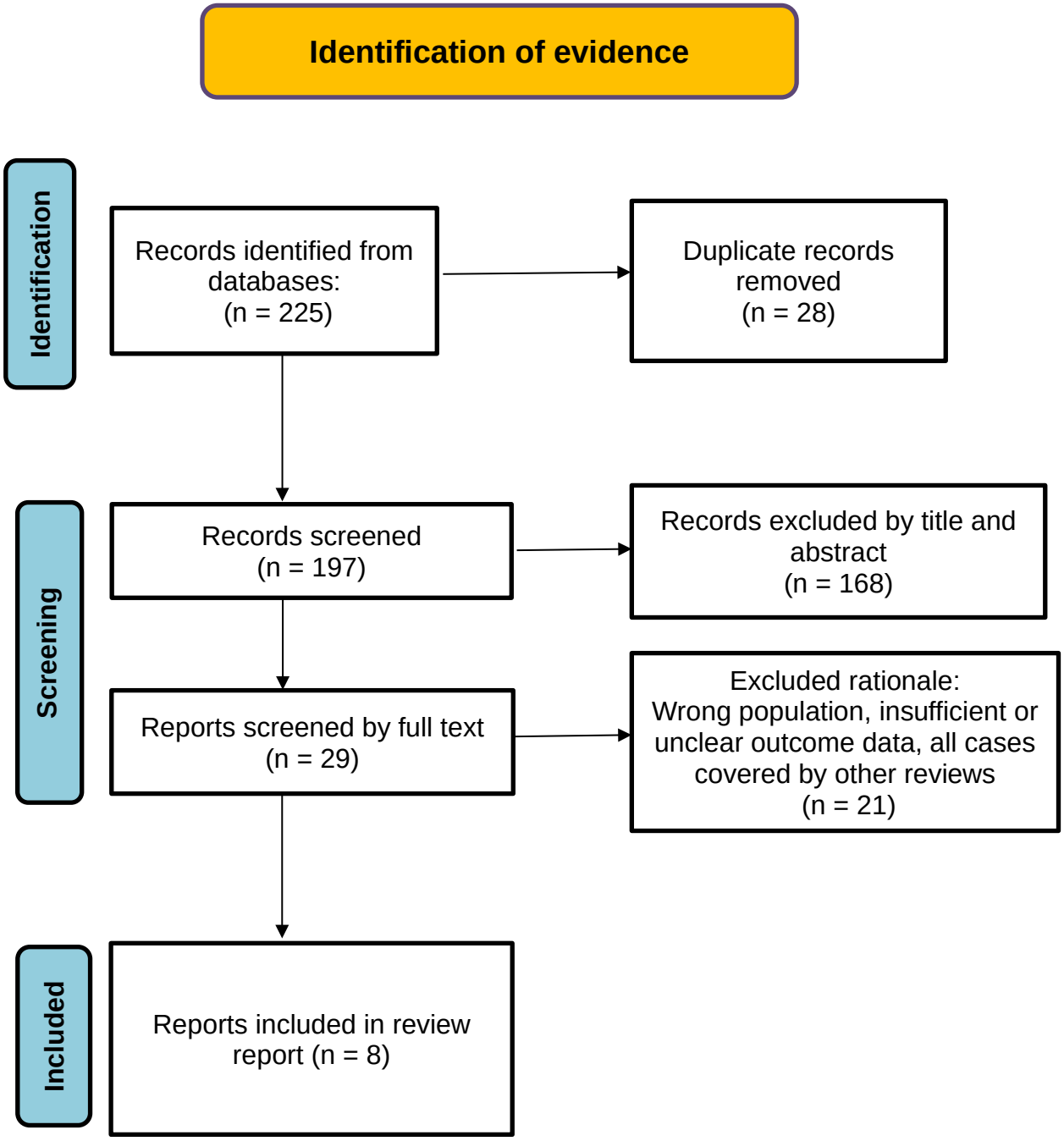
12. Patel A, Agha M, Raptis A et al. Outcomes of Patients With Acute Myeloid Leukemia Who Relapse After 5 Years of Complete Remission. *Oncology Research.* 2021;28(7):811–814.
13. Brandwein JM, Saini L, Geddes MN et al. Outcomes of patients with relapsed or refractory acute myeloid leukemia: a population-based real-world study. *American Journal of Blood Research.* 2020;10(4):124–133.
14. Wei AH, Loo S, and Daver N. How I treat patients with AML using azacitidine and venetoclax. *Blood.* 2025;145(12):1237–1250.
15. Public Health Wales. Cancer reporting tool wales, Acute myeloid leukaemia (C920). 2025. Available at: https://publichealthwales.shinyapps.io/Cancer_Reporting_Tool_PHW/. Accessed August 2025.
16. Oliva EN, Ronnebaum SM, Zaidi O et al. A systematic literature review of disease burden and clinical efficacy for patients with relapsed or refractory acute myeloid leukemia. *American Journal of Blood Research.* 2021;11(4):325–360.
17. Stone A, Zukerman T, Flaishon L et al. Efficacy outcomes in the treatment of older or medically unfit patients with acute myeloid leukaemia: A systematic review and meta-analysis. *Leukemia Research.* 2019;82:36–42.
18. National Institute for Health and Care Excellence. Technology Appraisal 765. Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable. February 2022. Available at: https://www.nice.org.uk/guidance/ta765. Accessed August 2025.
19. National Institute for Health and Care Excellence. Technology Appraisal ID6468. Venetoclax with azacitidine for treating acute myeloid leukaemia before and after an allogeneic stem cell transplant. TBC. Available at: https://www.nice.org.uk/guidance/awaiting-development/gid-ta11581. Accessed August 2025.
20. National Institute for Health and Care Excellence. Technology Appraisal ID4017. Liposomal cytarabine–daunorubicin for treating relapsed or refractory acute myeloid leukaemia in people aged 1 to 21 years. TBC. Available at: https://www.nice.org.uk/guidance/awaiting-development/gid-ta10916. Accessed August 2025.
21. National Institute for Health and Care Excellence. Technology Appraisal ID6355. Iodine (131I)–apamistamab for treating relapsed or refractory acute myeloid leukaemia before an allogeneic haematopoietic stem cell transplant. TBC. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta11425. Accessed August 2025.

22. National Comprehensive Cancer Network (NCCN). NCCN Guidelines: Acute Myeloid Leukemia. Version 2.2025. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1411. Accessed August 2025.
23. Pelland A-A, Deschenes-Simard X, Savard X et al. Outcomes of adults with refractory or relapsed acute myeloid leukemia treated with azacitidine and venetoclax compared to other therapies: a multicenter retrospective study. *Leukemia & lymphoma.* 2024;65(13):1974–1982.
24. Doma S, Sever M, Jakoš G et al. FLAG/FLAG-Ida Regimen in Secondary and Relapsed/Refractory Acute Myeloid Leukemia-Even in the Era of New Treatment Modalities Still a Significant Player. *Journal of Clinical Medicine.* 2024;13(7).
25. Delia M, Pastore D, Carluccio P et al. FLAG-Ida Regimen as Bridge Therapy to Allotransplantation in Refractory/Relapsed Acute Myeloid Leukemia Patients. *Clinical Lymphoma, Myeloma & Leukemia.* 2017;17(11):767–773.
26. Westhus J, Noppeney R, Dührsen U et al. FLAG salvage therapy combined with idarubicin in relapsed/refractory acute myeloid leukemia. *Leukemia & lymphoma.* 2019;60(4):1014–1022.
27. Delia M, Gagliardi VP, Carluccio P et al. Long term follow-up of refractory/relapsed acute myeloid leukemia patients treated with the FLAG-Ida regimen as bridge therapy to allotransplantation: 10-year results from a single centre experience. *Leukemia Research.* 2023;129:107069.
28. Ye Y, Liu X, Dai H et al. Venetoclax plus azacitidine with or without homoharringtonine followed by allogeneic haematopoietic cell transplantation in patients with relapsed/refractory acute myeloid leukaemia: A multicentre cohort study. *British Journal of Haematology.* 2025;207(1):151–161.
29. Ganzel C, Ram R, Gural A et al. Venetoclax Is Safe and Efficacious in Relapsed/ Refractory AML. *Leukemia & lymphoma.* 2019;134(Supplement 1):5091.
30. Tenold ME, Moskoff BN, Benjamin DJ et al. Outcomes of Adults With Relapsed/Refractory Acute Myeloid Leukemia Treated With Venetoclax Plus Hypomethylating Agents at a Comprehensive Cancer Center. *Frontiers in Oncology.* 2021;11:649209.
31. Garciaz S, Dumas PY, Bertoli S et al. Outcomes of acute myeloid leukemia patients who responded to venetoclax and azacitidine and stopped treatment. *American Journal of Hematology.* 2024;99(10):1870–1876.
32. Abedin S, Uy GL, and Michaelis LC. The fit older adult with acute myeloid leukemia: clinical challenges to providing evidence-based frontline treatment. *Blood.* 2025;145(24):2840–2846.

33. Sacco JJ, Botten J, Macbeth F et al. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLoS One.* 2010;5(1):e8933.
34. Thornton & Ross Ltd. Summary of Product Characteristics: Posaconazole 100 mg Gastro-resistant tablets. Jul 2025. Available at: https://www.medicines.org.uk/emc/product/12017/smpc#gref. Accessed September 2025.
35. NHS England. National Cost Collection Data Publication: National Schedule 2023/24. Available at: https://app.powerbi.com/view?r=eyJrIjoiNjI5YjA1OWMtOGNmOC00NGQzLWIxZDYtZDAyMDQ5YWVkZjU0IiwidCI6IjM3YzM1NGIyLTg1YjAtNDdmNS1iMjIyLTA3YjQ4ZDc3NGVlMyJ9. Accessed August 2025.
36. Pratz K, Lachaine J, and Suh H. POSB357 Health State Utilities for Patients with Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy. *Value in Health.* 2022;25(1):S230.
37. Office for National Statistics. National life tables – life expectancy in the UK: 2017 to 2019. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2017to2019. Accessed September 2025.
38. NatCen Social Research UCL, Department of Epidemiology and Public Health. (2023). Health Survey for England, 2014. [data collection]. Available at: http://doi.org/10.5255/UKDA-SN-7919-4. Accessed September 2025.
39. Hernández M A, S Pudney, A Wailoo. Estimating EQ-5D by Age and Sex for the UK. NICE DSU report. 2022. Available at: https://sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d. Accessed September 2025.
40. Garciaz S, Hospital MA, Alary AS et al. Azacitidine Plus Venetoclax for the Treatment of Relapsed and Newly Diagnosed Acute Myeloid Leukemia Patients. *Cancers (Basel).* 2022;14(8).
41. Graveno M, Carulli A, and Freyer C. Venetoclax in combination with hypomethylating agents or low dose cytarabine for relapsed and refractory acute myeloid leukemia. *Leukemia & lymphoma.* 2022;63:1645–1650.
42. Weng G, Zhang Y, and Yu G. Genetic characteristics predict response tovenetoclax plus hypomethylating agents in relapsedor refractory acute myeloid leukemia. *Journal of Internal Medicine.* 2022;293(3):271–406.
43. Piccini M, Pilerci S, and Merlini M. Venetoclax-Based Regimens for Relapsed/Refractory Acute Myeloid Leukemia in a Real-Life Setting: A Retrospective Single-Center Experience. *Journal of Clinical Medicine.* 2021;10(8):1684.

44. Stahl M, Menghrajani K, and Derkach A. Clinical and molecular predictors of response and survival following venetoclax therapy in relapsed/refractory AML. *Blood Advances.* 2021;5(5):1552–1564.
45. Todisco E, Papayannidis C, and Fracchiolla N. AVALON: The Italian cohort study on real-life efficacy of hypomethylating agents plus venetoclax in newly diagnosed or relapsed/refractory patients with acute myeloid leukemia. *Cancer.* 2022;129:992–1004.
46. NHS England. 2023-25 NHS Payment Scheme (amended). Available at: https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/. Accessed August 2025.
47. NHS England. Health Survey for England, 2021 part 1. *Part 4: Trends. Height and weight.* 2022. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2021/part-4-trends. Accessed September 2025.
48. UK & ROI Transplant Activity Table by Disease. *British Society of Blood and Marrow Transplantation and Cellular Therapy.* 2022. Available at: https://bsbmtct.org/activity/2022/. Accessed October 2025.

Appendix 1. PRISMA flow diagram – clinical evidence



Appendix 2. Supplementary Clinical Studies

Author / Year	Study Design & Patient Characteristics	Treatment Details	Efficacy Results	Limitations
Ye et al. 2025[28]	Multicentre retrospective cohort study (n =350) R/R AML with 154 patients (median age 50 years, 57.1% male) treated with venetoclax plus azacitidine (VA) as salvage therapy.	The VA regimen consisted of venetoclax (100 mg on day 1, 200 mg on day 2, and 400 mg on days 3–28) and azacitidine 75 mg/m² on days 1–7. Venetoclax doses were reduced by at least 50% in patients receiving moderate or strong CYP3A4 inhibitors, and FLT3 inhibitors were administered to patients with FLT3 mutations.	In the VA group (n = 154), the CRc rate was 39.6% after one cycle and 46.1% after two cycles of salvage therapy. The 3-year overall survival (OS) and event-free survival (EFS) from the start of VA therapy were 36.6% and 13.5%, respectively. Among the 44/154 (28.6%) patients who proceeded to allo-HSCT, 70.5% were in CRc and 64.5% were MRD-negative at transplantation. The 3-year post-transplant OS and EFS were 59.1% and 38.6%, respectively, with a 3-year cumulative incidence of relapse of 43.2% and transplant-related mortality of 18.2%.	Retrospective, non-randomised design, heterogeneous patient characteristics and prior therapies, limited follow-up in some subgroups, and the possibility of underreported adverse events, which may affect the interpretation of VA's efficacy and safety.
Garciaz et al. 2024[31]	Retrospective multicentre study of 84 adult AML patients (62 newly diagnosed, 22 R/R). Median age of R/R patients	The study did not specify the dosing or schedule; R/R AML patients received at	In 22 R/R AML patients, a median of 4 venetoclax plus azacitidine cycles (range 1–17) led to responses in all	Small, retrospective cohort; heterogeneous treatment approaches (variable number of venetoclax plus azacitidine

	was 73. Median prior treatment lines were 1 (range 1–3).	least one cycle of venetoclax plus azacitidine and achieved a response (CR, CRi, or MLFS) before discontinuing therapy.	patients: 54.5% achieved CR, 27.3% CRi, and 18.2% MLFS. Among the 10 evaluable patients, all achieved MRD negativity. With a median follow-up of 26 months, median OS was 19 months and median TFS 10 months; 5 patients were retreated at relapse, and 2 achieved a second CR/CRi lasting 4–6 months.	cycles and discontinuation of venetoclax alone versus venetoclax plus azacitidine); limited follow-up on post-HSCT outcomes; MRD assessments not standardized; and absence of a control group.
Garciaz et al. 2022[40]	Single centre retrospective study included 39 R/R AML patients treated with azacitidine plus venetoclax. Median age was 69 years. Most had adverse cytogenetics and prior therapies and were deemed to be ineligible for intensive chemotherapy (rationale not provided).	Standard-dose azacitidine (75 mg/m² daily for 7 days) combined with venetoclax, ramped over 3 days to 400 mg daily. For patients on strong CYP3A inhibitors, venetoclax was reduced to 100 mg. The first cycle lasted 14–28 days depending on age/comorbidities, with subsequent cycles adjusted for toxicity and marrow response.	In the R/R cohort (n = 39), the ORR was 37%, with a median OS of 5.9 months and EFS of 2.3 months. Early mortality within the first 56 days occurred in six patients. Among responders, median LFS was 10.3 months, and responses were generally durable. Four patients underwent HSCT, with three relapsing between 3–8 months post-transplant.	Small single-centre cohort; heterogeneous prior treatments and mutations, and short follow-up, which restrict the ability to generalise results or fully assess long-term response durability.
Graveno et al 2022[41]	Single centre retrospective study included 77 patients with R/R AML 60 of whom received VA. Median age for all patients	The combination of venetoclax and any treatment adjustments were made at treating	For the whole cohort after a median follow up of 9.9 months, 28% of patients were alive with median OS of 13.1	Single centre cohort; short follow-up.

	was 64 (IQR 54-69). The majority (72%) were ELN adverse risk.	physician discretion. Dosing schedule was not specified.	months. The ORR was 68% and composite CR rate 53%. Median time to response was 1 month and median PFS 12 months. 17 patients were bridged to HSCT and 6 to DLI. For the VA cohort (n = 60) median OS was 14.4 months.	
Weng et al 2022[42]	A multicentre retrospective study included 150 R/R AML patients, 135 of whom received VA. The median age of all patients was 53.5 years (range 40-62). 24% of patients had previously received HSCT.	Standard-dose azacitidine (75 mg/m² daily for 7 days) combined with venetoclax, ramped over 3 days to 400 mg daily over a 28-day cycle, adjusted as clinically required.	Results are reported for the whole cohort. With median follow up of 11.2 months (95% CI 7.2-14.8 months) 1- and 2- year OS was 46.9% (95%CI, 37.8%–58.1%) and 38.9% (95% CI, 28.7%–52.9%) respectively. Median OS was 10.0 months (range 7.4-NR). ORR was 56.2% and CR was achieved for 22% of all patients,	Results are not reported separately for the VA regimen limiting generalisability. Short follow up time.
Piccini et al 2021[43]	Single centre retrospective study included 47 R/R AML patients, 29 treated with VA. The remaining 18 received venetoclax in combination with decitabine or low dose cytarabine. Median age of all study patients was 56 years (range 33-74). 23% of patients had relapsed following previous HSCT.	Standard-dose azacitidine (75 mg/m² daily for 7 days) combined with venetoclax, ramped over 3 days to 400 mg daily over a 28-day cycle. Venetoclax was reduced to 21 days in the first cycle and 21 or 14 days in subsequent cycles due to evidence	Results are reported for the whole cohort, the median number of venetoclax based cycles was 2 (range 1-24). Composite complete response rate was 55% (26/47) and 13 of 26 responders obtained CRi/CRp status. DFS for all patients with CR (n = 26) was 10.6 months. EFS for the whole cohort (n = 47) was 4.5	Small, single centre retrospective study. Results not reported for VA regimen separately limiting generalisability.

		of treatment-related myelosuppression.	months. 13 patients went on to receive HSCT. Overall survival was 10.7 months. Median follow up was 10.7 months (range 0.8-30).	
Stahl et al. 2021[44]	Single centre retrospective study included 35 R/R AML patients treated with azacitidine plus venetoclax. Median age was 65 years. Median prior treatment lines was 1 (range 0-4), most (57%) had adverse ELN risk, 17% had previously received HSCT.	Standard-dose azacitidine (75 mg/m² daily for 7 days) combined with venetoclax, ramped over 3 days to 400 mg daily. Venetoclax dose was reduced to 100 mg daily if azole antifungal prophylaxis was required.	Results are reported separately for the VA cohort. The median number of cycles of VA was 2 (range 1-15). 26% of patients achieved CR and 11% achieved Cri. The ORR was 49% with a median OS of 25 months (5.8-NR). OS censored for HSCT was 8.1 months (range 5.7-NR). The relapse rate after response to venetoclax therapy was 41% with a median duration of response of 10.2 months.	Single centre, retrospective design.
Todisco et al. 2022[45]	A multicentre observational cohort study with 190 patients included in the final analysis. 67.4% of patients received VA and 32.6% received venetoclax with decitabine. Patients with newly diagnosed AML were included in the study as well as R/R, results are reported separately. The study included 68 refractory and 79 relapsed patient (total 147). Median age of R/R	Venetoclax dose ranged from 100 to 400 mg daily, dependent upon use of azole antifungals. Azacitidine dose not specified.	Median follow up was 20.9 months (95% CI, 17–25.9). Median duration of treatment was 2.8 months (IQR 1.5-6.9 months) for refractory patients and 2.8 months (IQR 1.2-6.3) for relapsed patients. In relapsed and in refractory patients CRc was reported in 38.2% and 34.2%; ORR was 51.5% and 41.8%; and median DOR was 6.8 months (range 4.4-12.6) and 8.3	Results are not reported separately for patients treated with VA.

	patients was 64 years. Of the R/R patients: 69% were considered fit; 29% unfit for intensive chemotherapy and 2% frail. 37% of R/R had previously received HSCT.		months (range 4.7-11.9) respectively. Median EFS was 6.2 and 4.4 months; OS was 9.1 and 6.3 months in relapsed and in refractory patients respectively. VA was a bridge to HSCT in 38 (26%) of R/R patients.	
Tenold et al. 2021[30]	Retrospective single-centre analysis of 25 patients with R/R AML: 14 received venetoclax plus azacitidine, and 11 received venetoclax plus decitabine. The median age was 57 years (range 25–86), and all patients had received at least one prior therapy (median 2, range 1–6).	azacitidine 75 mg/m^2 intravenously or subcutaneously daily on days 1–7 and venetoclax orally on days 1–28 of cycle 1. Venetoclax doses were ramped up with adjustments for CYP3A4 inhibitors under inpatient monitoring to ensure safety.	Results are reported for the entire cohort; the authors did not provide a separate breakdown of response or survival outcomes by treatment arm. The ORR was 52%, with a CR + CRi of 32%. Median OS for the cohort was 5.5 months (95% CI: 2.9–21.6), with one-year estimated survival of 38%. Among patients achieving CR, median OS was 21.6 months (95% CI: 15.2–not reached). Median duration of response was 14.7 months, with a median relapse-free survival of 17.0 months (95% CI: 3.0–not reached). Of the 13 responders, five patients eventually relapsed and died.	Small, single-centre, retrospective design, heterogeneous patient population, incomplete genomic profiling, and lack of a control group. Efficacy was reported only for the full cohort, preventing comparisons between azacitidine and decitabine subgroups, which limits generalizability and precludes conclusions about relative efficacy.
Ganzel et al. 2020[29]	Retrospective multicentre analysis included 40 patients with R/R AML from 11 Israeli medical centres. The median	The median daily dose was venetoclax 400 mg (range 100–800 mg), and patients	The study does not provide a separate CR/CRi rate or survival specifically for the venetoclax in combination	Small heterogeneous cohort; retrospective design; Venetoclax dosing was inconsistent, with a median daily dose of 400 mg

	age was 67 years (range 21–82). Patients received venetoclax mostly in combination with HMA (n = 25) or low-dose cytarabine (n = 9), while a few received monotherapy or other combinations. Patients had received a median of 2 prior lines of treatment (range 1–4), not including prior allogeneic hematopoietic cell transplantation, and 42.5% had previously undergone allogeneic HSCT.	received a median of 2.75 cycles (range 0.5–14). Dosing adjustments for concomitant CYP3A4 inhibitor treatment were individualised by the treating physicians, as no standardised guidelines were applied.	with HMA so all outcome measures reported entire cohort, not just HMA-treated patients. Among the 29 patients who survived more than 2 months, 52% achieved CR or Cri. Neutrophil recovery was observed in 76% of these patients and strongly correlated with improved OS (median 18 vs. 3 months, $p < 0.001$). The median OS was 5.5 months for all patients and 6.5 months for those surviving beyond 2 months.	(range 100–800 mg), and 17.5% of patients receiving lower doses. Dose adjustments for CYP3A4 inhibitors were not standardised.
CR: Complete remission; CRc: Composite complete remission; Cri: Complete remission with incomplete haematologic recovery; DFS: Disease-free survival; EFS: Event-free survival; HMA: Hypomethylating agent; HSCT / allo-HSCT: Haematopoietic stem cell transplant / allogeneic HSCT; LFS: Leukaemia-free survival; LDAC: Low-dose cytarabine: MLFS: Morphologic leukaemia-free state; MRD: Measurable residual disease; OS: Overall survival; R/R-AML: Relapsed or refractory acute myeloid leukaemia: TFS: Treatment-free survival; VA: Venetoclax with azacitidine				

Appendix 3.a FLAG-Ida unit costs.

	Details	Figure	Reference
Fludarabine	50mg in 2ml vial	¶¶	All Wales Drug Contract price
Cytarabine	2g in ml vial	¶¶	All Wales Drug Contract price
Idarubicin	5mg in 5ml vial	¶¶	All Wales Drug Contract price
G-CSF	0.5ml syr 480 mcg/ml x 5	¶¶	All Wales Drug Contract price
SB14Z Deliver complex parenteral chemotherapy at first attendance - elective inpatients		£3,024	NHS reference cost[35]
SB14Z Deliver complex parenteral chemotherapy at first attendance - day or night unit cost		£493	NHS reference cost[35]
SA25K: Acute Myeloid Leukaemia with CC Score 4-5		£379	2024/25 NHS Payment Scheme[46]
¶¶ commercial in confidence data removed			

Appendix 3.b FLAG-Ida regimen doses and costs.

	Daily dose	Dose per day	Units required per day	Days per cycle	Cost per cycle
Fludarabine*	30mg/m^2	53.7	1	5	¶¶
Cytarabine*	2g/m^2	3.58	2	5	¶¶
Idarubicin*	8mg/m^2	14.32	3	3	¶¶
G-CSF†	5mcg/kg	395	0.4 (2 syr)	7	¶¶
Per cycle medicine cost					¶¶
*dose per day calculated using 1.79 m^2[33] † dose per day calculated using the average UK adult weight of 79kg[47]. ¶¶ commercial in confidence data removed					

The administration of FLAG-Ida Is calculated with a hospitalisation duration of 20 days, this is informed by clinical experts. The initial SB14Z elective inpatient has a trim point of 5 days, therefore, an additional active therapy cost of 2 days is applied at the SB14Z day or night cost to total the 7 days of treatment. A further 13 days are applied at a cost of SA25Z AML to total the average duration of 20 days. The total cost of administration and hospitalisation for a FLAG-Ida cycle is £8,937. The total cost for a cycle of FLAG-Ida is £10,449.

Appendix 3.c FLAG-Ida administration and hospitalisation costs.

	Cost	Reference
SB14Z Deliver complex parenteral chemotherapy at first attendance - elective inpatients	£3,024	NHS reference cost[35]
SB14Z Deliver complex parenteral chemotherapy at first attendance - day or night unit cost	£493	NHS reference cost[35]
SA25K: Acute Myeloid Leukaemia with CC Score 4-5	£379	2024/25 NHS Payment Scheme[46]
Total administration and hospitalisation cost	£8,937	(3024 + (2*493) + (13* 379))
¶¶ commercial in confidence data removed		

Appendix 3.d. Adverse event rates, costs and disutilitites

	Cost	QALY decrement	Ven Aza	FLAG-Ida	HRG or TA765 reported cost	Reference
Anaemia	£420	0.008	26.0%	30.3%	SA08H	NICE TA 765[18]
Febrile Neutropenia	£420	0.008	42.0%	36.7%	SA08H	NICE TA 765[18]
Hypokalaemia	£365	0.010	11.0%	11.0%	303.57	NICE TA 765[18]
Leukopenia	£1,234	0.008	21.0%	missing	1026.11	NICE TA 765[18]
Neutropenia	£420	0.008	42.0%	13.8%	SA08H	NICE TA 765[18]
Neutrophil Count Decreased	£1,234	0.008	missing	11.0%	1026.11	NICE TA 765[18]
Platelet Count Decreased	£1,234	0.008	missing	24.8%	1026.11	NICE TA 765[18]
Pneumonia	£216	0.018	20.0%	4.6%	179.96	NICE TA 765[18]
Thrombocytopenia	£361	0.008	45.0%	16.5%	SA12K	NICE TA 765[18]
White Blood Cell Count Decreased	£1,234	0.008	missing	17.4%	1026.11	NICE TA 765[18]
Hypoglycemia	£490	0.013	missing	8.3%	KB04K	NICE TA 642[3]
Total cost			**£967**	**£1,146**		

Appendix 3.e. Hematopoietic Stem Cell Transplantation costs

	Cost/figure	Reference / calculation
Matched unrelated donor HSCT	¶¶	WJCC
Sibling donor HSCT	¶¶	WJCC
Activity: Matched unrelated donor HSCT	1099	BSBMT[48]
Activity: Sibling donor HSCT	520	BSBMT[48]
Weighted average cost of HSCT	¶¶	
WJCC: Wales Joint Commissioning Committee BSBMT: British Society of Blood and Marrow Transplantation and Cellular Therapy ¶¶ commercial in confidence data removed		

Appendix 3.f. Equality in HSCT rates.

	Cost
Venetoclax with azacitidine	¶¶
FLAG-Ida	¶¶
Incremental cost	¶¶
¶¶ commercial in confidence data removed	

Appendix 3.g. One way sensitivity analysis: varying number of venetoclax with azacitidine treatment cycles

	40% fewer cycles	20% fewer cycles	10% fewer cycles	baseline	10% more cycles	20% more cycles	40% more cycles
Venetoclax with azacitidine	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶
Incremental cost	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ commercial in confidence data removed							

Appendix 3.h. One way sensitivity analysis: varying number of FLAG-Ida hospitalisation days

	10 days	15 days	18 days	baseline (20 days)	22 days	25 days	30 days
FLAG-Ida	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶
Incremental cost	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ commercial in confidence data removed							

Appendix 3.i. One way sensitivity analysis: varying number of venetoclax with azacitidine hospitalisation days

	baseline (0 days)	5days hospitalisation	10 days hospitalisation	15 days hospitalisation	20 days hospitalisation
Venetoclax with azacitidine	¶¶	¶¶	¶¶	¶¶	¶¶
Net cost	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ commercial in confidence data removed					