National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG127 Arsenic trioxide in combination with all-trans retinoic acid (ATRA [tretinoin]) | Advice Document v1.0 | July 2026

Arsenic trioxide in combination with all-trans retinoic acid (ATRA [tretinoin]) for the treatment of high-risk acute promyelocytic leukaemia [A]

NCMAG Decision | This off-label use is **supported**

This advice applies only in the context of the confidential pricing agreements in NHSScotland, upon which the decision was based, or confidential pricing agreements or list prices that are equivalent or lower.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith SMC remit. For more detail on NCMAG remit please see our website.

Decision rationale

After consideration of the available evidence regarding the clinical benefits and harms, the Council were **satisfied** with the clinical effectiveness case for arsenic trioxide plus tretinoin in the proposed population. After consideration of relevant information under the Decision-making framework for value judgements the Council made a decision to **support** this use.

Governance Arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	NHSScotland haematologists
Medicine Name	Arsenic trioxide plus all-trans retinoic acid (ATRA [tretinoin])
Cancer type	Acute promyelocytic leukaemia
Proposed off-label[B] use	Arsenic trioxide in combination with all-trans retinoic acid for the induction of remission, and consolidation in adult patients with newly diagnosed high-risk acute promyelocytic leukaemia.

Medicine Details	Form Arsenic trioxide concentrate solution for infusion, intravenous (IV). All-trans retinoic acid (ATRA [tretinoin]) oral capsules. Dose **Induction phase:** Arsenic trioxide plus all-trans retinoic acid (ATRA [tretinoin]) given for a maximum of 60 days (8.5 weeks). **Consolidation phase:** Arsenic trioxide plus all-trans-retinoic acid (ATRA [tretinoin]) given for a total of 28 weeks. See Appendices 1 and 2 for further dose information. **Note**: Dosing of arsenic trioxide in this population with high-risk disease is different from the licenced dosing for low-to-intermediate-risk disease.
Advice eligibility criteria	**Inclusion criteria** All patients over 16 years with newly diagnosed high-risk APML as confirmed by: • A white cell count ≥10,000/microlitre (or 10 x 10^9/L) **AND** • Presence of the promyelocytic leukaemia / retinoic acid receptor alpha (PML/RARA) gene fusion **AND** • Performance status 0 to 4 **Exclusion criteria** Patients that meet any of the following criteria are excluded from treatment with arsenic trioxide: • Patients with isolated myeloid sarcoma (myeloblastoma, chloroma, including

	leukaemia cutis) but without evidence of APML by bone marrow or peripheral blood morphology • Patients with a pre-existing diagnosis of a prolonged QT syndrome (even if QTc is normal at the time of APML diagnosis), a history or presence of significant ventricular or atrial tachyarrhythmia, right bundle branch block plus left anterior hemiblock, bifascicular block • Patients on active dialysis for renal dysfunction • Patients who are pregnant or plan to become pregnant while on treatment • Hypersensitivity to arsenic trioxide or all-trans-retinoic acid (ATRA[tretinoin])

[B] Arsenic trioxide has a marketing authorisation for the following indications[1]

- For induction of remission, and consolidation in adult patients with:
    - Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APML) (white blood cell count ≤ 10 x 10^3/µl) in combination with all-trans-retinoic acid (ATRA[tretinoin])
    - Relapsed/refractory acute promyelocytic leukaemia (APML) (previous treatment should have included a retinoid and chemotherapy) characterised by the presence of the (15;17) translocation and/or the presence of the promyelocytic leukaemia/retinoic-acid-receptor-alpha (PML/RARA) gene.

1. Current Management Context

Acute promyelocytic leukaemia symptoms, incidence and prognosis

Acute promyelocytic leukaemia (APML) is a form of white blood cell cancer (leukaemia), which is extremely aggressive and associated with a severe disturbance in blood clotting leading to both excessive bleeding and abnormal clot formation. APML is a clinically and biologically distinct subtype of acute myeloid leukaemia (AML) and is driven by translocation of the chromosome t(15;17) leading to the rearrangement of the retinoic acid receptor alfa with the PML gene (PML-RARA)[2]. This PML-RARA fusion affects promyelocytes, preventing them from maturing, leading to the accumulation of immature abnormal neutrophils in the bone marrow inhibiting normal cell production and results in reduced blood cells circulating the body.

Early mortality in APML remains a major concern, with a mortality rate of 30% within 30 days of diagnosis due to bleeding complications[3]. Early recognition of APML is therefore critical, as timely diagnosis and treatment may prevent the development of some of the complications. APML often presents with symptoms related to pancytopenia including unexplained bleeding or bruising, fatigue or breathlessness and recurring infections[4]. APML is categorised into low-, intermediate- and high-risk of relapse, based on white blood cell and platelet counts at diagnosis[5].

In Scotland, 163 patients were diagnosed with AML in 2023[6]. Acute myeloid leukaemia occurs at any age however a higher incidence was reported for patients aged 75 to 80 years[6]. Approximately 5 to 10%[7] of patients with AML will develop APML[8]. Assuming similar proportions within a Scottish population this would equate to approximately 16 to 24 patients per year. This proposal focuses on a subgroup of APML patients with high-risk disease, which is estimated to equate to 25% of APML cases. This corresponds to an incidence of fewer than 5 per 10,000 people per year in NHSScotland and meets orphan-equivalent criteria.

Current treatment pathway in NHSScotland

APML is considered a haematological emergency and rapid initiation of treatment is essential upon diagnosis. First line treatment for low-to-intermediate risk APML is arsenic trioxide plus tretinoin (SMC 2181)[9, 10]. First line treatment of high-risk APML is idarubicin and tretinoin (also known as AIDA). Treatment with AIDA is a multiphase regimen involving an induction phase followed by three consolidation phases which each include 4 or 5 days of IV chemotherapy with idarubicin, cytarabine or mitoxantrone. Alongside treatments for APML, patients routinely receive hydroxycarbamide and steroids such as prednisolone or dexamethasone prophylactically to reduce the risks associated with differentiation syndrome and as a cytoreductive agent for rapid control of white cell counts[11]. The combination of idarubicin and tretinoin can involve a prolonged hospital inpatient stay, the need for an indwelling line and is associated with long term complications including impaired fertility, risk of anthracycline mediated cardiac damage and longer-term potential increased risk of secondary malignancy.

Arsenic trioxide and tretinoin is currently utilised in the relapsed and/or refractory setting after AIDA treatment for patients with high-risk APML.

International context for proposed treatment

The British Society of Haematology (BSH), the European society of medical oncology (ESMO), the European Leukaemia Network and the haematology society of Australia and New Zealand (HSANZ) recommend or include as an option, the use of arsenic trioxide plus tretinoin in patients with high-risk APML [10,11,12].

Pharmacology of arsenic trioxide

Arsenic trioxide causes DNA fragmentation and degradation of the fusion protein pro-myelocytic leukaemia/retinoic acid receptor-alpha (PML/RARA). This causes cell death of leukaemic cells[1].

Pharmacology of all-trans-retinoic-acid (ATRA[tretinoin])

Tretinoin is thought to bind a nuclear retinoic acid receptor (RAR) and induce proteolytic degradation of the PML/RARA protein, which is linked to APML. This action may restore the wild-type RARA function and normal maturation of blood cells[13].

2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were acute promyelocytic leukemia, high risk, all-trans-retinoic acid/ATRA/tretinoin and arsenic trioxide. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer when required. The included key studies were critically appraised using version 2 of the Cochrane risk-of-bias tool[14].

3. Clinical Evidence Review Summary

Clinical efficacy evidence

Three studies were identified as providing relevant evidence for this proposal. Among these, AML17 is considered the most directly relevant, while APOLLO and HARMONY are considered supportive studies. AML17 was a randomised, controlled, multicentre, open-label phase III study that evaluated the efficacy and safety of arsenic trioxide plus tretinoin compared with chemotherapy (idarubicin) plus tretinoin in adults with newly diagnosed low- and high-risk APML. At the time AML17 was conducted, standard-of-care was chemotherapy plus tretinoin which was associated with high cure rates in patients with APML[15]. This trial therefore aimed to determine whether a chemotherapy-free consolidation regimen (arsenic trioxide plus tretinoin) may improve quality of life (QoL) without compromising survival outcomes in patients with APML[16]. The study included patients 16 years or older, with a confirmed diagnosis of APML, verified by presence of the *PML-RARA* transcript who had received no prior treatment for APML. Patients were

randomised 1:1 to receive arsenic trioxide plus tretinoin (arsenic trioxide: 0.3 mg/kg IV on days 1 to 5 of each course, and at 0.25 mg/kg twice weekly in weeks 2 to 8 of course 1 and weeks 2 to 4 of courses 2 to 5; tretinoin: daily divided oral dose of 45 mg/m² body surface area (BSA) until remission, or until day 60, and then in a 2 weeks on–2 weeks off schedule;) or idarubicin plus tretinoin (idarubicin: 12 mg/m² BSA IV on days 2, 4, 6, and 8 of course 1, and then at 5 mg/m² BSA on days 1 to 4 of course 2; mitoxantrone at 10 mg/m² BSA on days 1 to 4 of course 3, and idarubicin at 12 mg/m² BSA on day 1 course 4; tretinoin: as described previously). Patients with high-risk APML (white blood cell count of ≥10 × 10^9 cells/L at diagnosis) in the arsenic trioxide arm could receive gemtuzumab ozogamicin (6 mg/m²) as a single infusion within 4 days of course 1 (see Appendices 1 to 3 for further details).

All analyses were conducted in the intent-to-treat (ITT) population. The primary outcome was QoL, assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the Hospital Anxiety and Depression Scales (HADS). Secondary outcomes included overall survival (OS), relapse-free survival (RFS), event-free survival (EFS) and complete remission. At data cut-off of 1 January 2014, median follow-up was 30.5 months (interquartile range [IQR] 22.3 to 41.2). Baseline characteristics were generally comparable between arsenic trioxide and idarubicin groups for key factors: median age (47 years in both), proportion categorised as high-risk based on median white blood cell count (26% versus 23%) and WHO performance status 0 (71% versus 67%). Among high-risk patients in the arsenic trioxide arm, 93% (28/30) received gemtuzumab ozogamicin as intended; the remaining two patients received an anthracycline due to lack of available gemtuzumab ozogamicin at the site pharmacy. The study closed enrolment early with 235 of the intended 300 patients recruited.

Selected key efficacy results are summarised in Table 1. Results for the primary outcome, QoL, are discussed in the patient-reported outcomes section below. Results of the ITT analysis for the secondary efficacy outcomes suggest comparable efficacy for the arsenic trioxide and idarubicin arms in terms of complete remission, 30-day and 60-day mortality and overall survival (OS), with a trend toward more favourable outcomes with the arsenic trioxide regimen. In the overall population, 4-year EFS was higher in the arsenic trioxide (91%) versus idarubicin (70%) arm, while 4-year OS rates were similar between groups (93% versus 89%). Among patients with high-risk APML treated with the arsenic trioxide or idarubicin regimens, 4-year OS and 4-year EFS rates (Table 1) were generally consistent in direction and magnitude with the overall population[16].

Table 1 | Selected key efficacy results from AML17[A,16]

	Arsenic trioxide plus tretinoin (n=116)	Idarubicin plus tretinoin (n=119)
Complete remission, n (%)	109 (94)	106 (89)
30-day mortality, % (95% CI)	4 (2 to 10)	6 (3 to 12)
60-day mortality, % (95% CI)	5 (2 to 11)	9 (5 to 16)
	Patients with high-risk APML	
	Arsenic trioxide plus tretinoin (n=30)	**Idarubicin plus tretinoin (n=26)[C]**
EFS[B]		
4-year EFS rate, % (95% CI)	87 (68 to 95)	64 (42 to 79)
HR (95% CI)	0.34 (0.11 to 1.08)	
OS		
Events, n	4	4
4-year OS rate, % (95% CI)	87 (68 to 95)	84 (63 to 94)
HR (95% CI)	HR 0.82 (0.20 to 3.31)	

[A] Data cut-off: 1 January 2014. Although the publication did not explicitly define the ITT population, the standard definition is: all participants who were randomised were included in the statistical analysis and analysed according to the group they were originally assigned, regardless of what treatment (if any) they received[17].

[B] Defined as time from randomisation to death, treatment-related MDS or AML, or morphological relapse for patients entering remission; patients who do not achieve a complete remission are defined as experiencing an event on day 1.

[C] One patient in the idarubicin plus tretinoin group had no follow-up data for survival or relapse.

AML = acute myeloid leukaemia; APML = acute promyelocytic leukaemia; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; ITT = intent-to-treat; MDS = myelodysplastic syndrome; OS = overall survival.

Long-term follow-up data from AML17 were published in 2018 (data cut-off: 1 July 2017; median follow-up of 67.4 months). Results for efficacy outcomes were broadly consistent with the early data cut for AML17. A reduction in frank relapse (1% versus 10% at 5 years; HR 0.18; 95% CI: 0.05 to 0.6) resulted in a higher 5-year RFS rate (outcome not defined by authors) in patients with high-risk APML who received arsenic trioxide versus idarubicin regimens (100% versus 83%; HR: 0.12 [95% CI: 0.02 to 0.84]). Updated EFS data were not reported in the long-term follow-up publication[18].

Supportive evidence

Two studies were identified as being supportive of this proposal: APOLLO, a randomised, open-label, phase III trial conducted as a European intergroup study[19] and the European HARMONY APML project that leveraged data from four European national registries (HOVON, AMLSG,

Swedish AML Registry, and SAL) and two international, multicentre clinical trials (GIMEMA-APL0406 and AML17, described above)[2].

APOLLO study

The APOLLO study evaluated the efficacy and safety of arsenic trioxide plus tretinoin (different dosing to the proposed regimen) compared with anthracycline-based chemotherapy plus tretinoin in patients with newly diagnosed high-risk APML. The study included adults with newly diagnosed high-risk APML (WBC at diagnosis >10 x 10^9/L) who were randomised 1:1 to receive either arsenic trioxide (plus two doses of idarubicin during induction) plus tretinoin or chemotherapy (idarubicin and cytarabine or mitoxantrone) plus tretinoin. Patients were stratified by country and age (≤40 years versus >40 years). The primary outcome was 2-year EFS and key secondary endpoints included rate of haematologic complete response after induction, rate of early death after induction, 2-year OS, toxicity, minimal residual disease status and QoL.

In the arsenic trioxide and idarubicin groups, the median ages of patients with high-risk APML were 46.5 years and 44 years, (both range 18 to 65 years) respectively. Median treatment duration (induction to end of consolidation phase) was 35 weeks (IQR, 34 to 36) in patients receiving the arsenic trioxide regimen and 21 weeks (IQR, 19 to 23) in patients receiving the idarubicin regimen. Patients in the idarubicin arm who achieved complete remission or complete remission with incomplete recovery and were in molecular remission were eligible to begin maintenance therapy (50 mg/m^2 oral 6-mercaptopurine on days 1 to 91, 15 mg/m^2 methotrexate administered intramuscularly or orally once per week until day 91 and 45 mg/m^2 tretinoin administered orally in two single doses on days 92 to 106 of cycles 1 to 6 only) for seven 106-day cycles. Of these, 77% (50/65) proceeded to maintenance therapy and 28% (14/50) did not complete maintenance therapy. Median follow-up in APOLLO was 37 months (range, 1.7 to 88.6)[19]. Investigators had aimed to recruit 280 patients; however, the study was discontinued prematurely due to slow accrual related to the COVID-19 pandemic and only 135 were recruited. Key efficacy results are summarised in Table 2.

Table 2| Key efficacy results from APOLLO[A,19]

	Arsenic trioxide plus tretinoin (n=68)	Chemotherapy plus tretinoin (n=65)
Early death rate[B] before complete remission, %	7.4	9.2
2-year OS rate, %	93	87
HR (95% CI)	0.60 (0.20 to 1.80)	
2-year EFS rate[C], %	88	71
HR (95% CI)	0.40 (0.17 to 0.92)	
2-year cumulative incidence of relapse, %	1.8	17

[A] Last patient last visit: Jan 2025.

[B] Defined as death within 30 days after randomisation.

[C] Defined as time to one of the following events: failure to achieve haematologic complete response or complete response with incomplete recovery within 60 days after induction therapy, failure to achieve molecular remission after the last consolidation course (molecular resistance), haematologic relapse, molecular relapse, death, or development of secondary myelodysplasia or leukaemia (whichever occurred first).
CI = confidence interval; EFS = event-free survival; HR = hazard ratio; OS = overall survival.

HARMONY APML project

The European HARMONY APML project captured clinical trial and registry data to evaluate treatment outcomes in patients with APML (n=1,438) including patients receiving arsenic trioxide plus tretinoin (n=562) and idarubicin plus tretinoin (n=747). This was a pooled analysis of individual patient data that were harmonised and transformed using the Observational Medical Outcomes Partnership Common Data Model. Median age was 50 years (16 to 94) and 37% and 63% of included patients were treated in a trial and clinical practice setting, respectively. High-risk APML accounted for 21.1% (n=300) of the overall population and the median follow-up was 5.5 years (IQR, 3.2 to 7.5)[2].

Among patients with high-risk APML treated with arsenic trioxide (n=49) or idarubicin (n=193) regimens, efficacy outcomes were broadly comparable for 7-year OS (85% versus 74%) and 7-year cumulative incidence of relapse (27% versus 16%), respectively. Seven-year EFS (defined as time from diagnosis to death by any cause, failure to achieve complete remission, relapse (molecular or haematological), or the last known follow-up visit for censored patients) was lower in the idarubicin versus arsenic trioxide group (66% versus 85%; HR [95% CI]: 2.5 [1.14 to 5.47]). The 7-year efficacy findings for patients with high-risk APML are unpublished data and kindly provided by Professor Voso and colleagues (University of Rome Tor Vergata, Rome, Italy).

Safety evidence

In the AML17 study, fewer serious adverse events were reported in the arsenic trioxide group than in the idarubicin group (64 versus 82 respectively). During treatment course one, Grade ≥3 adverse events reported in the arsenic trioxide and idarubicin groups included alopecia (5% versus 23%), diarrhoea (1% versus 6%), oral (1% versus 19%), cardiac (2% versus 6%) and raised alanine transaminase (25% versus 10%). During treatment course 2, far fewer Grade ≥3 adverse events were reported, with alopecia the most frequently reported: 3% and 28% in the arsenic trioxide and idarubicin groups, respectively. Among patients receiving gemtuzumab ozogamicin, no excess liver toxicity or myelosuppression was reported. Beyond course 2, cardiac toxicity was more frequent in the arsenic trioxide versus idarubicin arm (Grade ≥3: 3% versus 0%)[16]. Incidence of neutropenia was not reported in the AML17 study.

Dose modifications were required in both groups, with more tretinoin adjustments in the arsenic trioxide versus idarubicin arms during course 1 (30 versus 13 patients). During course 2, 18 patients in the arsenic trioxide arm experienced treatment modifications or delays (including six patients who switched to idarubicin based on clinician's decision). By day 60, 17 deaths were reported across both groups but these were not assessed for relatedness to study drug[16].

Supportive care needs (blood, platelets and hospital stay) were significantly lower in the arsenic trioxide versus idarubicin group during the first two treatment courses for all measures except for antibiotic use in course two. The arsenic trioxide regimen was associated with 7.4 fewer days in hospital, 4.5 fewer units of blood, 4.3 fewer units of platelets and 10.7 fewer days of IV antibiotics compared with the idarubicin regimen[16].

Patient-reported outcomes

The AML17 trial collected patient-reported outcomes in the overall population using the EORTC QLQ-C30 and HADS instruments, with a total of 671 completed QoL forms received. Completion rates for the arsenic trioxide versus idarubicin groups were as follows: 80 versus 76 at baseline; 73 versus 64 at 3 months; 69 versus 70 at 6 months; 72 versus 64 at 12 months; and 54 versus 49 at 24 months. The AML17 study did not meet its primary endpoint as QoL was not significantly different between treatment arms among patients with APML[16].

Quality Appraisal

The quality of the AML17 study was assessed using version two of the Cochrane risk-of-bias tool for randomised trials[14]. Overall, the study was judged to have a high risk of bias, primarily because the trial was unblinded and so both clinicians and patients were aware of treatment allocation. The primary outcome was QoL, a measure that is inherently subjective and therefore particularly vulnerable to bias without blinding. Missing QoL data were noted but this was not adequately addressed in the publication, raising the possibility of biased estimates. Furthermore, the statistical analysis plan and/or study protocol did not appear to be available for this trial and so details on prespecified QoL analyses were uncertain.

Clinical effectiveness considerations

Clinical evidence from various studies suggests arsenic trioxide plus tretinoin regimens have at least similar efficacy to idarubicin plus tretinoin regimens in APML including in patients with high-risk disease.

The key randomised controlled study, AML17, suggests that there was comparable 4-year EFS for arsenic trioxide and idarubicin regimens in patients with high-risk APML. The supportive study, APOLLO, also showed comparable results for the primary outcome of 2-year EFS, with the trend favouring the arsenic trioxide regimen. The HARMONY study showed improved 7-year EFS for patients with high-risk APML suggesting the arsenic trioxide regimen has at least similar efficacy to the idarubicin regimen. These EFS results are consistent with later follow up results for 5-year RFS (AML17) and cumulative incidence of relapse (HARMONY). Across studies, despite different OS endpoints: 5-year OS (AML17), 2-year OS (APOLLO) and 7-year OS (HARMONY), OS is comparable between the arsenic trioxide and idarubicin regimens.

The AML17 and APOLLO studies showed similar early deaths within the first 30 days of diagnosis for patients treated with the arsenic trioxide and idarubicin regimens.

The adverse event profile with the arsenic trioxide regimen is different to the idarubicin regimen

The AML17 study showed a different toxicity profile with the arsenic trioxide regimen, including reductions in the need for blood products, number of hospital inpatient days and a reduced number of days on antibiotics during induction.

In the APOLLO study, Grade ≥3 neutropenia (4.4% versus 55%) and treatment-related serious adverse events (10% versus 37%) were reported for the arsenic trioxide and idarubicin regimens, respectively. The chemotherapy consolidation arm of APOLLO differed from current standard of care by including cytarabine doses, but this did not seem to affect the adverse event profile. The arsenic trioxide regimen was associated with increased cardiac toxicity and QTc alteration.

Despite differences in the reported adverse event profiles, seeming to favour treatment with the arsenic trioxide regimen over the idarubicin regimen, AML17 did not meet its primary outcome or show a statistically significant difference in quality-of-life measures. Incomplete enrolment resulted in reduced power to detect a difference in quality-of-life measures. In addition, not all recruited patients contributed quality of life data, making interpretation of this result uncertain.

The open-label design of the key studies increases the uncertainty of results for subjective outcomes due to an increased risk of bias

The AML17 study was an open-label study where the primary end point was QoL which is a subjective outcome that is at increased risk of bias with patient and investigator awareness of allocated treatment. The HARMONY study pooled randomized, controlled studies, including AML17, and non-randomised real-world studies with clinician-determined treatments, which increases the risk of bias in patient selection and study results should be interpreted with caution.

There are differences in the proposed arsenic trioxide regimen and the regimens used in the studies

The proposed dosing of arsenic trioxide aligns with the dose used in AML17, however the proposed regimen includes up to three doses of idarubicin for rapid control of white cell counts during induction rather than gemtuzumab ozogamicin used in AML17. In the APOLLO study, the use of idarubicin for rapid control within an arsenic trioxide regimen was shown to be similarly effective as induction phase treatment, providing reassurance that using idarubicin instead of gemtuzumab ozogamicin as part of induction treatment is unlikely to reduce clinical effectiveness. Clinical experts consider these optional induction treatments may have similar cytoreductive effects. Patients in the APOLLO study received a lower dose of arsenic trioxide than the proposed regimen in both the induction and consolidation phases of treatment, with a dosing schedule similar to the on-label arsenic trioxide dosing in patients with low- and intermediate risk APML. For the idarubicin regimen, idarubicin induction was similar to current standard of care treatment, but cytarabine was included in the consolidation phase of treatment, and the regimen also included maintenance treatment which is no longer standard of care in NHSScotland. These differences may affect the generalisability of longer-term results from APOLLO.

The study populations are likely to represent the NHSScotland population

The AML17 study was conducted in the UK; this provides some reassurance that the study population may represent patients that will be treated in NHSScotland. High-risk patients are rare, therefore multicentre, multinational studies are required to ensure recruitment of a sufficient number of participants. The AML17 study allowed the inclusion of patients with a performance status of 0 to 4, aligned with this proposal, however, the majority of patients in the study were categorised as performance status 0 to 1. Patients in AML17 ranged from 16 to 77 years of age, suggesting a similar population to those in Scotland who could be treated with this regimen.

4. Patient group summary

We received a statement from Leukaemia Care (UK) which is a registered charity. Leukaemia Care reported 9.48% of their annual funding came from the pharmaceutical industry in 2025. No representative from Leukaemia Care attended the NCMAG council meeting.

Their statement was informed by findings from the Living with Leukaemia survey, which highlighted the rapid progression of APML, with most patients starting treatment within a week of diagnosis. This urgency leaves little time to process the diagnosis and contributes to a high emotional burden; 43% of patients report depression or anxiety following diagnosis, and families also experience significant strain. Common symptoms reported by patients include bruising, bleeding, fatigue, breathlessness, headaches, fever or night sweats, bone or joint pain, and sleep disturbance. These symptoms can impair daily functioning, mobility, and the ability to work or study, with associated financial impacts.

Standard treatment with tretinoin plus anthracycline-based chemotherapy is effective but can be poorly tolerated, particularly in less fit patients. In one survey, 56% of patients reported hospitalisation due to treatment-related side effects. Patients receiving the arsenic trioxide regimen reported side effects such as cardiovascular events, gastrointestinal symptoms, rash or itching and neuropathy, indicating a different adverse event profile and treatment burden compared with anthracycline-based chemotherapy. Overall, arsenic trioxide plus tretinoin provides an important alternative to anthracyclines for newly diagnosed patients with high-risk APML.

5. Benefit-risk balance

Arsenic trioxide plus tretinoin for the treatment of adults with high-risk APML is an off-label use. Clinical evidence from randomised and non-randomised studies suggest arsenic trioxide plus tretinoin regimens have at least similar efficacy to idarubicin plus tretinoin regimens in APML, including in patients with high-risk disease. The randomised, controlled, phase 3 AML17 study, suggested comparable 30-day and 60-day mortality, 4-year EFS and 4-year OS for arsenic trioxide plus tretinoin when compared to current standard of care, idarubicin plus tretinoin. Arsenic trioxide plus tretinoin was associated with a different adverse event profile and resulted in reduced inpatient hospital days and need for supportive care such as blood products and

antibiotic treatment days. Supportive studies reported efficacy and safety results for arsenic trioxide plus tretinoin in the high-risk APML setting that were consistent with AML17. There were no unexpected safety signals compared to the on-label use of arsenic trioxide and tretinoin in low-risk APML.

6. Council Review |Clinical benefit-risk balance evaluation

After consideration of all the available evidence regarding the clinical benefits and risks, the Council were **satisfied** that the case had been made for the clinical effectiveness of arsenic trioxide plus tretinoin.

7. Economic Evidence Review Summary

Economic Overview

The literature search for economic evidence returned no cost-effectiveness publications which evaluated arsenic trioxide plus tretinoin for the treatment of APML in the proposed high-risk population.

Type of economic evaluation

In the absence of a cost-effectiveness analysis, a de-novo cost-comparison analysis has been performed to support this assessment.

Population, Intervention, Comparator, Outcome

- The population used in the study were patients aged 16 years and above with newly-diagnosed high-risk APML.
- The intervention was arsenic trioxide plus tretinoin and the comparator was idarubicin plus tretinoin. Full details of these regimens are presented in Appendices 1 and 3, respectively. These formed the basis for costs on medicine acquisition and administration.
- As a cost-comparison analysis has been performed, quality-adjusted life-years (QALYs) were not included in the analysis.

Costs

Costs included were medicine acquisition, administration and adverse event costs for time on treatment for both arms. In the intervention arm for arsenic trioxide plus tretinoin, optional idarubicin was also included in the economic analysis. Confidential NHSScotland National Framework prices for off-patent medicines were used (accessed May 2026). The lowest prices were used for each medicine according to doses calculated using standardised dose banding tables for NHSScotland.

Based on clinical data from the AML17 patients in the arsenic trioxide plus tretinoin arm spent on average 33.8 days in hospital during Courses 1 and 2, and patients in the idarubicin plus tretinoin arm spent 41.2 days in hospital during Courses 1 and 2. During this time, in addition to patients

receiving treatment according to their assigned regimen, they received blood and platelet transfusions and antibiotics to treat adverse events. Therefore, an inpatient cost per bed day for oncology treatment was sourced from Public Health Scotland 23/24[20] and included in the economic analysis during Courses 1 and 2. This was assumed to cover the cost of administration, monitoring and treatment for Grade ≥3 adverse events.

During courses 3 and 4, the administration cost for delivery of IV medicines was based on delivery of subsequent elements of chemotherapy cycles (NHS National Reference costs 2024-25).

Costs were not discounted as the treatment duration did not exceed one year.

Results

All figures in the cost-comparison analysis exclude value added tax (VAT).

Based on medicine acquisition cost alone, arsenic trioxide plus tretinoin costs more per patient compared with idarubicin plus tretinoin (NHSScotland confidential prices, accessed May 2026). Overall, including medicine administration and adverse event costs, treatment with arsenic trioxide plus tretinoin is estimated to increase per patient costs compared to idarubicin plus tretinoin. The cost-comparison results are presented in Table 3.

Table 3 | Summary of cost-comparison results (confidential price, excluding VAT)

Cost category	Medicine acquisition (£)	Medicine administration including adverse event[B] (£)	Total costs per patient (£)
Arsenic trioxide plus tretinoin[A]	CIC	70,087	CIC
Idarubicin plus tretinoin[A]	CIC	74,122	CIC
Cost difference	CIC (cost increasing)	-4,035 (cost decreasing)	CIC (cost increasing)

CIC = commercial in confidence; VAT = value added tax.

[A] The dosing schedule for arsenic trioxide plus tretinoin is described in Appendix 1 and 2 and idarubicin plus tretinoin in Appendix 3.

[B] Administration, adverse event and monitoring costs are assumed to be covered in the hospital bed day cost during Courses 1 and 2 of the intervention and comparator regimens. Administration costs during Courses 3 and 4 were based on the required doses for IV treatments.

Generalisability of the cost-comparison

The dosing schedule of arsenic trioxide plus tretinoin reflects the proposed dosing in NHSScotland. NHSScotland National Framework prices for medicines were considered in confidence to increase the generalisability of the net costs.

Limitations of the cost-comparison

Adverse events could not be accurately costed

The study highlighted that patients experienced oral and cardiac-related adverse events and also required blood and platelet transfusions and antibiotics. As these adverse events were recorded during courses 1 and 2, when patients were already in hospital for treatment, it was not feasible to identify specific adverse event-related costs without double-counting existing inpatient costs, therefore, these have not been presented. Additionally, as limited information was available on the type of treatment given for oral and cardiac adverse events and type of antibiotics, there was a high degree of uncertainty and therefore, these could not be accurately measured in the costing.

Hospital bed day cost may lead to an overestimate

The use of the hospital bed day cost from Public Health Scotland data may lead to a slight overestimate in total costing. This value includes 'pharmacy' costs which may relate to chemotherapy treatment and could therefore double count some treatment costs.

Subsequent treatment costs were not considered in the cost comparison

This cost comparison analysis only considered costs in the proposed setting and did not consider subsequent treatments. Patients with an initial response may relapse at later timepoints. The choice of treatment on relapse depends on multiple clinical factors. Relapse rates were broadly comparable between the proposed treatment and current standard of care. Subsequent costs related to relapse are uncertain and have not been accounted for.

Summary

The cost-comparison indicated that the arsenic trioxide plus tretinoin treatment regimen is a more costly intervention compared to idarubicin plus tretinoin for adult patients with newly-diagnosed high-risk AMPL. However, in the absence of a lifetime cost-effectiveness analysis, it is difficult to quantify treatment benefits in relation to costs and the actual cost-effectiveness remains unknown.

8. Council review | Cost-effectiveness evaluation

After considering the available evidence, the Council accepted that in the absence of a cost-effectiveness analysis, the cost-effectiveness remained unknown. In this situation Council was able to consider additional relevant information including service impact and estimated net medicines budget impact under the Decision-making Framework for Value Judgements.

9. Service Impact

Arsenic trioxide plus tretinoin is an alternative treatment proposed to replace an idarubicin plus tretinoin regimen. Evidence suggests the first two cycles of this proposed treatment is likely to shorten the duration of hospital inpatient stay by 7.4 days, reduce the need for resources such as blood transfusion by 4.5 units and platelet transfusions by 4.3 units. Trial data suggested 10.7 days fewer of antibiotic treatment for the arsenic trioxide groups, and a lower risk of neutropenia with a resulting lower potential risk of sepsis. Taken together, these benefits may lessen the impact on the NHS service and be capacity sparing.

10. Budget Impact

The total estimated number of patients nationally expected to routinely access arsenic trioxide plus tretinoin for the proposed use on an annual basis is three. This estimate is based on clinical opinion.

Results

A budget impact was calculated using only medicine acquisition costs with VAT applied. This used the same dosing for arsenic trioxide plus tretinoin as in the cost-comparison analysis.

The results for the estimated total annual patient uptake were presented as the base case in Table 4, which assumes that three patients will be eligible to receive arsenic trioxide plus tretinoin annually and this will displace idarubicin plus tretinoin use for these patients. The uptake is assumed to remain constant in subsequent years. A scenario where six patients receive arsenic trioxide plus tretinoin was also explored in Table 4. This estimate was based on Public Health Scotland data for patients diagnosed with AML, adjusted to account for potential subgroup of patients with high-risk APML.

Budget impact costs were calculated over the full time on treatment for the regimens. Discontinuation and mortality rates were not included.

Table 4 | Budget impact base case and scenario analysis results (confidential prices, including VAT)

#	Scenario	Base case	Arsenic trioxide plus tretinoin acquisition cost per patient (£)	Idarubicin plus tretinoin acquisition cost per patient (£)	Annual patient uptake	Budget impact – Net medicine costs
	-	Base case	CIC	CIC	3	CIC (budget increase)

1	Six patients[A]	Three patients	CIC	CIC	6	CIC (budget increase)

CIC = commercial in confidence; VAT = value added tax.

[A] Considering uncertainty around the true population expected to access treatment, an estimate of six patients has been presented as a scenario.

Limitations

A limitation of the analysis is the uncertainty around the true budget impact, as the patient number expected to receive arsenic trioxide plus tretinoin is not known. Scenario 1 was therefore considered in Table 4 to explore an upper limit of patients who would be eligible to receive arsenic trioxide plus tretinoin.

Summary

The Council considered the net medicines budget impact using confidential NHSScotland medicine pricing agreements in decision-making. NCMAG is unable to publish the budget impact using confidential pricing due to commercial-in-confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with PAS contract pricing. Based on the NHSScotland PAS price of medicines (accessed May 2026, including VAT), the use of arsenic plus tretinoin is estimated to increase the net medicines budget for this patient group when compared to NHSScotland standard of care.

11. Council Review | Overall Proposal Evaluation

After consideration of all relevant information under the Decision-making Framework for Value Judgements the Council made a decision to support this use.

12. Acknowledgements

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- The patient group partners, Leukaemia Care (UK) for their valuable insights.
- Professor Maria Teresa Voso and colleagues from the University of Rome Tor Vergata, Rome, Italy, for providing additional data on patients with high-risk APML from the HARMONY APML project.

13. Appendix

Appendix 1 – Dosing schedule for arsenic trioxide in combination with tretinoin[21]

1. Induction therapy - 60 days

Course 1

Week 1	Tretinoin 45mg/m^2 BSA/day orally in two equal divided doses Starting on day 1 and continued for a maximum of 60 days
	Arsenic trioxide 0.30 mg/kg IV daily for 5 days (days 1 to 5)
	OPTIONAL (only during induction phase) Idarubicin 12mg/m^2 BSA IV on days 1, 3 and 5
Week 2 to 8	Arsenic trioxide 0.25mg/kg IV twice a week

- Prednisolone or dexamethasone can be given as prophylaxis for differentiation as per local guidelines.
- Hydroxycarbamide can be given to control the WBC count during the induction phase.

2. Consolidation therapy – 28 weeks (Commenced on count recovery from induction)

Course 2 (Week 1 to 8)

Week 1	Arsenic trioxide 0.30mg/kg IV daily for 5 days (days 1 to 5)
	Tretinoin 45mg/m^2 BSA/day orally in two equal divided doses for 14 days (weeks 1 and 2)
Week 2 to 4	Arsenic trioxide 0.25mg/kg IV twice a week.
Week 5	Tretinoin 45mg/m^2 BSA/day orally in two equal divided doses for 14 days (weeks 5 and 6)

Course 3 (Week 9-16)

Week 9	Arsenic trioxide 0.30mg/kg IV daily for 5 days (days 1 to 5)
	Tretinoin 45mg/m^2 BSA/day orally in two equal divided doses for 14 days (weeks 9 and 10)
Week 10 to 12	Arsenic trioxide 0.25mg/kg IV twice a week

Week 13	Tretinoin 45mg/m^2 BSA/day orally in two equal divided doses for 14 days (weeks 13 and 14)

Course 4 (Week 17-24)

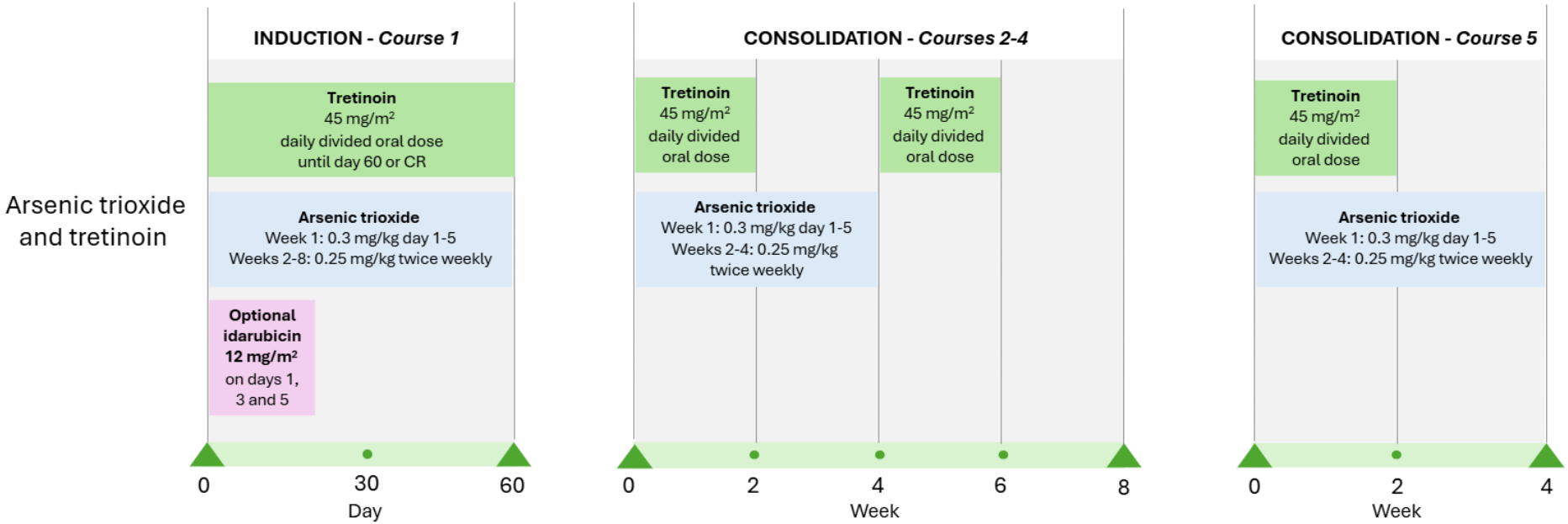
Week 17	Arsenic trioxide 0.30mg/kg IV daily for 5 days (days 1 to 5)
	Tretinoin 45mg/m^2/day orally in two equal divided doses for 14 days (weeks 17 and 18)
Week 18 to 20	Arsenic trioxide 0.25mg/kg IV twice a week.
Week 21	Tretinoin 45mg/m^2/day orally in two equal divided doses for 14 days (weeks 21 and 22)

Course 5 (Week 25 to 28)

Week 25	Arsenic trioxide 0.30mg/kg IV daily for 5 days (days 1 to 5)
	Tretinoin 45mg/m^2 BSA/day orally in two equal divided doses for 14 days (weeks 25 and 26)
Week 26 to 28	Arsenic trioxide 0.25mg/kg IV twice a week

BSA = body surface area; WBC = white blood cell.

Appendix 2 – Summary diagram of dosing schedule for arsenic trioxide in combination with tretinoin



CR = complete response.

Appendix 3 – Dosing schedule used for standard of care idarubicin in combination with tretinoin for economic evidence review[21]

1. Induction therapy

Course 1

Week 1	Tretinoin 45mg/m^2 BSA/day orally in two equal divided doses Starting on day 1 and continued until CR or for a maximum of 60 days
	Idarubicin 12mg/m^2 BSA IV on days 2, 4, 6 and 8

2. Consolidation therapy – (Each subsequent course commenced on count recovery)

Course 2

	Tretinoin 45mg/m^2 BSA/day orally in two equal divided doses for 15 days
	Idarubicin 5mg/m^2 BSA IV on days 1 to 4

Course 3

	Tretinoin 45mg/m^2 BSA/day orally in two equal divided doses for 15 days
	Mitoxantrone 10mg/m^2 BSA IV on days 1-5

Course 4

	Tretinoin 45mg/m^2 BSA/day orally in two equal divided doses for 15 days
	Idarubicin 12mg/m^2 BSA IV on day 1

BSA = body surface area; WBC = white blood cell.

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This advice represents the view of the NCMAG Council and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by