Clinical priorities advisory group
4 December 2024

Agenda Item No	2.2
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	2320

Title
Arsenic trioxide in combination with all-trans retinoic acid for the treatment of high-risk acute promyelocytic leukaemia (age 12 months and over)

Actions Requested	1. Support the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Arsenic trioxide in combination with all-trans retinoic acid (ATRA) is recommended to be available as a routine commissioning treatment option for high-risk acute promyelocytic leukaemia (APML) within the criteria set out in this document. Acute Promyelocytic Leukaemia (APML) is a form of white blood cell cancer (leukaemia) and is the most aggressive type of leukaemia with a severe bleeding tendency and potentially fatal course. Arsenic trioxide is a chemotherapy drug that causes cell death (apoptosis) of leukemic cells. Arsenic trioxide in combination with ATRA is not licensed for use in high-risk APML. The policy is restricted to those aged 12 months and older in line with the findings from the evidence review. Delegation status – service delegated

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy proposition.

The committee is asked to receive the following assurance:

1.	The Deputy Director of Clinical Effectiveness confirms the policy proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Deputy Director of Cancer confirms the policy proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary and Public Health Report
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In high-risk acute promyelocytic leukaemia what is the clinical effectiveness and safety of arsenic trioxide and all trans retinoic acid compared with current standard care?

Outcome	**Evidence statement**
Clinical Effectiveness	
Critical outcomes	
Overall survival **Certainty of evidence:** Very low	This outcome is important to patients as patients with HR APML have a higher mortality rate due to risk of fatal haemorrhage. Improved overall survival is an important marker of effective treatment, although it does not provide information about a patient's health and wellbeing during that time. In total, one subgroup of the intervention arm of an RCT, one subgroup of the intervention arm of a non-randomised non-inferiority trial and one retrospective case series provided evidence relating to overall survival at either two years or 38 months follow-up. The RCT intervention arm included people with either non-HR or HR newly diagnosed APML, with a median age of 41 years (range 15 to 69). Only those with HR APML are included here. The intervention arm of the non-randomised non-inferiority trial included people with either standard-risk or HR newly diagnosed APML; only those with HR APML are included here (median age 12.6 years, range 1.1 to 20.8). The

Outcome	Evidence statement
	retrospective case series included 10 people with HR APL who had survived induction treatment. Only nine of these received ATO and are included here. 2-year overall survival rate • One subgroup of the intervention arm of an RCT (Wang et al 2022) showed that, following induction and consolidation with ATO+ATRA, the 2-year overall survival rate was 85% (18/21 patients[1]). One subgroup of the intervention arm of a non-randomised non-inferiority trial (Kutny et al 2022) showed that, following induction treatment with ATO+ATRA+idarubicin and consolidation with ATO+ATRA, the 2-year overall survival rate was 100% (90% CI 93.0% to 100%; 56/56 patients). (VERY LOW) Overall survival at median 38 months • One retrospective case series (Shah et al 2020) showed that 100% (9/9) of patients with HR APML who survived induction with ATO+ATRA+idarubicin and received ATO+ATRA during consolidation were still alive at a median of 38 months follow-up (range 14 to 63 months). (VERY LOW) **Two studies provided very low certainty non-comparative evidence that between 85% and 100% of people with HR newly diagnosed APML treated with ATO+ATRA (+idarubicin in one study) during induction and ATO+ATRA during consolidation were still alive at two years follow-up. There was very low certainty evidence from one small case series that 100% of patients with HR APML who survived induction with ATO+ATRA+idarubicin and received ATO+ATRA during consolidation were still alive at a median of 38 months follow-up.**
Event-free survival **Certainty of evidence:** Very low	This outcome is important to patients because it represents the time during which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. In total, one subgroup of the intervention arm of an RCT and one subgroup of the intervention arm of a non-randomised non-inferiority trial provided evidence relating to overall survival at two years. The RCT arm included people with either non-HR or HR newly diagnosed APML, with a median age of 41 years (range 15 to 69). Only those with HR APML are included here. The intervention arm of the non-randomised non-inferiority trial included people with either standard-risk or HR newly diagnosed

[1] In addition to two deaths in the Wang et al 2022 study, one person did not receive any post-remission therapy and disease monitoring.

Outcome	Evidence statement
	APML; only those with HR APML are included here (median age 12.6 years, range 1.1 to 20.8). 2-year event-free survival rate[2] • One subgroup of the intervention arm of an RCT (Wang et al 2022) showed that, following induction and consolidation with ATO+ATRA, the 2-year event-free survival rate was 85% (18/21 patients). One subgroup of the intervention arm of a non-randomised non-inferiority trial (Kutny et al 2022) showed that, following induction treatment with ATO+ATRA+idarubicin and consolidation with ATO+ATRA, the 2-year event-free survival rate was 96.4%, (90% CI 88.2% to 98.8%; 54/56 patients). (VERY LOW) **Two studies provided very low certainty non-comparative evidence that between 85% and 96.4% of people with HR newly diagnosed APML treated with ATO+ATRA (+idarubicin in one study) during induction and ATO+ATRA during consolidation were still alive at two years follow-up without having experienced an event such as failure to achieve haematologic/molecular remission, relapse or death.**
Disease-free survival or remission **Certainty of evidence:** Very low	This outcome is important to patients as it means that the signs and symptoms of cancer have reduced, either partially or completely and they are free of all detectable disease. In total, one subgroup of the intervention arm of an RCT, one subgroup of the intervention arm of one non-randomised non-inferiority trial and one retrospective case series provided evidence relating to disease-free survival or remission at either two years or 38 months follow-up. The RCT arm included people with either non-HR or HR newly diagnosed APML, with a median age of 41 years (range 15 to 69). Only those with HR APML are included here. The intervention arm of the non-randomised non-inferiority trial included people with either standard-risk or HR newly diagnosed APML; only those with HR APML are included here (median age 12.6 years, range 1.1 to 20.8). The retrospective case series included 10 people with HR APL who had survived induction treatment. Only nine of these received ATO and are included here. Cumulative incidence of APML relapse at two years • One subgroup of the intervention arm of one non-randomised non-inferiority trial (Kutny et al 2022)

[2] Kutny et al 2022 describe event-free survival as: “time from study entry until failure to achieve haematologic complete remission or haematologic complete remission with incomplete haematologic recovery by day 70 of induction therapy; time from study entry until failure to achieve molecular remission after consolidation cycle 2, including consolidation therapy, if needed, for those with molecular residual disease; or time from study entry until relapse or death”. Wang et al 2022 define event-free survival as: “time from diagnosis to first event, including death during induction therapy, failure to achieve remission, death during remission, relapse at any site, or the development of second malignant neoplasm”.

Outcome	Evidence statement
	showed that, following induction treatment with ATO+ATRA+idarubicin and consolidation with ATO+ATRA, 2/56 (3.9%)[3] patients had APML relapse[4] at up to two years. (VERY LOW) 2-year disease-free survival rate • One subgroup of the intervention arm of an RCT (Wang et al 2022) showed that, following induction and consolidation with ATO+ATRA, the 2-year disease-free survival rate[5] was 85% (18/21 patients). (VERY LOW) Patients still in remission at median 38 months • One retrospective case series (Shah et al 2020) showed that 100% (9/9) patients with HR APML who survived induction treatment with ATO+ATRA+idarubicin and were treated with ATO+ATRA during consolidation were still in remission at a median of 38 months follow-up (range 14 to 63 months). (VERY LOW) **Three studies provided very low certainty non-comparative evidence about the disease-free survival rate. Following induction and consolidation with ATO+ATRA, 85% of patients with HR newly diagnosed APML had survived without relapse at two years. For HR newly diagnosed APML patients treated with ATO+ATRA+idarubicin during induction and ATO+ATRA during consolidation, 3.9% had relapsed within two years. There was very low certainty evidence from one small case series that no patients with HR APML who survived induction with ATO+ATRA+idarubicin and were treated with ATO+ATRA during consolidation had relapsed at a median of 38 months follow-up.**
Important outcomes	
Quality of life **Certainty of evidence:** Not applicable	Quality of life (QOL) is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. **No evidence was identified for this outcome.**

[3] As reported by Kutny et al 2022: denominator unclear.

[4] Kutny et al 2022 describe APML relapse as: "time from the end of induction therapy (for patients in haematologic complete remission or haematologic complete remission with incomplete haematologic recovery) to relapse or death, in which deaths without relapse were considered competing events. Disease relapse was defined as the reappearance of promyeloblasts or abnormal promyelocytes (>5%) or 2 consecutive positive results for the presence of PML-RARα on qPCR tests of the bone marrow".

[5] Wang et al 2022 define disease-free survival as: "time from haematological complete remission (HCR) to either haematological or molecular relapse or death from APL".

Outcome	Evidence statement
Hospitalisation **Certainty of evidence:** Very low	This outcome is important to patients as it may represent either disease progression or treatment toxicity. It may have a bearing on the patient's quality of life and inform their treatment decision making. In total, one subgroup of the intervention arm of an RCT provided non-comparative evidence relating to hospitalisation. The RCT arm included people with either non-HR or HR newly diagnosed APML, with a median age of 41 years (range 15 to 69). Only those with HR APML are included here. During induction phase (until HCR[6]) • One subgroup of the intervention arm of an RCT (Wang et al 2022, n=21) showed that the median hospital stay during induction with ATO+ATRA was 29 days (range 16 to 39). (VERY LOW) **One study provided very low certainty non-comparative evidence that the median hospital stay during induction with ATO+ATRA for people HR with newly diagnosed APML was 29 days, with a range of 16 to 39 days.**
Activities of daily living **Certainty of evidence:** Not applicable	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Very low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. In total, one subgroup of the intervention arm of an RCT and one subgroup of the intervention arm of a non-randomised non-inferiority trial provided non-comparative evidence relating to safety during the induction phase, and one non-randomised non-inferiority trial provided non-comparative evidence about safety at a median follow-up of 22.8 months (range 0 to 47.7 months). The RCT arm included people with either non-HR or HR newly diagnosed APML, with a median age of 41 years (range 15 to 69). Only those with HR APML are included here. The induction phase in the RCT lasted until HCR, which was not described for

[6] Time to HCR was not specified for HR patients. For the whole intervention arm (n=62), median time to HCR was 32.5 days (14-54 days).

Outcome	Evidence statement
	the HR patients specifically[7]. The intervention arm of the non-randomised non-inferiority trial included people with either standard-risk or HR newly diagnosed APML; only those with HR APML are included here (median age 12.6 years, range 1.1 to 20.8). For these patients, induction treatment was from 28 days until a maximum of 70 days. During induction phase[8] • One subgroup of the intervention arm of an RCT (Wang et al 2022) showed that two of 21 patients died during induction treatment with ATO+ATRA. One subgroup of the intervention arm of one non-randomised non-inferiority trial (Kutny et al 2022) showed that none of the 56 patients died during induction treatment with ATO+ATRA+idarubicin. (VERY LOW) • One subgroup of the intervention arm of one non-randomised non-inferiority trial showed that 17 of 56 (30.4%) patients treated with ATO+ATRA+idarubicin induction therapy had symptoms of differentiation syndrome (Kutny et al 2022). Of these 17/56 patients with symptoms, 64.7% had respiratory distress, 41.2% hypoxia, 58.8% fever, 11.8% erythematous rash, 23.5% pulmonary infiltrates, 17.6% weight gain, 11.8% peripheral oedema, and 11.8% had hypotension. None had pericardial effusion, acute renal failure or congestive heart failure. (VERY LOW) • One subgroup of the intervention arm of one non-randomised non-inferiority trial (Kutny et al 2022) reported the proportion of patients with ECG QT corrected interval prolonged (by grade). Grade 1 prolonged ECG QT corrected interval was reported for 32.1% of 56 patients, Grade 2 prolonged ECG QT corrected interval for 19.6% and Grade 3 for 7.1%. (VERY LOW) • One subgroup of the intervention arm of one non-randomised non-inferiority trial (Kutny et al 2022) presented adverse events reported at a frequency of 10% or greater for any treatment cycle (either during induction or during one of the consolidation cycles). During the induction phase.17.9% of 56 patients had no adverse events, 7.1% had ALT increase, 7.1% had AST increase, 58.9% had a prolonged ECG QT corrected interval, 10.7% had decreased fibrogen and 12.5% had hyperglycaemia. (VERY LOW) • One subgroup of the intervention arm of an RCT (Wang et al 2022) reported that the median duration of IV

[7] Time to HCR was not specified for HR patients. For the whole intervention arm (n=62), median time to HCR was 32.5 days (14-54 days).
[8] Overall trial median follow-up was 22.8 months (range 0-47.7 months).

Outcome	Evidence statement
	antibiotics during induction was 17 days (range 5 to 31 days). (VERY LOW) During consolidation phase[9] • One subgroup of the intervention arm of one non-randomised non-inferiority trial (Kutny et al 2022) reported the proportion of patients with ECG QT corrected interval prolonged (by grade). During consolidation cycles one to four: o Grade 1 prolonged ECG QT corrected interval was reported for 47.3% of 56 patients during consolidation cycle 1, 32.7% in cycle 2, 31.5% in cycle 3 and 26.4% during consolidation cycle 4. o Grade 2 prolonged ECG QT corrected interval was reported for 5.5% of patients during consolidation cycle 1, 7.3% in cycle 2, 3.7% in cycle 3, and 3.8% during consolidation cycle 4. o Grade 3 prolonged ECG QT corrected interval was reported for 1.8% of patients during consolidation cycle 1, not reported in cycle 2, 1.9% in cycle 3, and 1.9% during consolidation cycle 4. (VERY LOW) • One subgroup of the intervention arm of one non-randomised non-inferiority trial (Kutny et al 2022) presented adverse events reported at a frequency of 10% or greater during each of the four consolidation phases. o No adverse events were reported by 40% of 55 patients during consolidation cycle 1, 54.5% of 55 patients in cycle 2, 53.7% of 54 patients in cycle 3 and 62.3% of 53 patients during consolidation cycle 4. o An AST increase was reported by 1.8% of patients during consolidation cycle 1 only. o Prolonged ECG QT corrected interval was reported by 54.5% during consolidation cycle 1, 40.0% in cycle 2, 37.0% in cycle 3 and 32.1% during cycle 4. (VERY LOW) **Two studies provided very low certainty non-comparative evidence about adverse events during the induction phase. Median duration of IV antibiotics during induction with ATO+ATRA was the only adverse event reported separately for the subgroup of patients with HR newly diagnosed APML in one arm of one RCT. Symptoms of differentiation syndrome were experienced during the induction phase (with ATO+ATRA+idarubicin) by 30% of patients in a**

[9] Overall trial median follow-up was 22.8 months (range 0-47.7 months).

Outcome	Evidence statement
	subgroup of the intervention arm of one non-randomised non-inferiority trial. Whilst 18% of patients in that study had no adverse events during induction, 59% of patients had a prolonged ECG QT corrected interval during induction. The study also provided very low certainty non-comparative evidence about adverse events during the consolidation phase. Between 40% and 62% of patients experienced no adverse events across the four consolidation cycles. The proportion of patients with a prolonged ECG QT corrected interval ranged from 32% to 55% across the consolidation cycles. **None of the studies reported on longer-term adverse effects.**
Abbreviations ALT: alanine amino-transferase; APLM: acute promyelocytic leukaemia; AST: aspartate amino-transferase; ATO: arsenic trioxide; ATRA: all trans retinoic acid; ECG: electrocardiogram; HCR: haematological complete remission; HR: high risk; RCT: randomised controlled trial	

In high-risk acute promyelocytic leukaemia what is the cost effectiveness of arsenic trioxide and all trans retinoic acid compared with current standard care?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for cost effectiveness.

From the evidence selected, are there any subgroups of patients that may benefit from arsenic trioxide and all trans retinoic acid more than the wider population of interest?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from treatment with arsenic trioxide in combination with all trans retinoic acid.

From the evidence selected, what are the criteria used by the research studies to define high-risk acute promyelocytic leukaemia?

Outcome	Evidence statement
Definition of high-risk acute promyelocytic leukaemia	Kutny et al 2022 defined high-risk APML as a WBC count of 10000/µL or higher. Shah et al 2020 assigned patients to risk groups based on laboratory assessment prior to receiving ATRA, but no specific definition of high-risk APML was provided. Diagnosis was confirmed by fluorescence in situ hybridization (FISH) analysis for the promyelocytic leukaemia/retinoic acid receptor alpha (PML/RARA) gene fusion.

	Wang et al 2022 based risk stratification on WBC count, categorising high-risk APML as a WBC of at least 10×10^9/L.

Abbreviations

APML: acute promyelocytic leukaemia; WBC: white blood cell

From the evidence selected, what are the treatment regimens used to treat high-risk acute promyelocytic leukaemia?

Outcome	Evidence statement
Treatment regimens	Kutny et al 2022 treated patients with ATRA at the first suspicion of APML. Induction therapy included twice daily oral ATRA (12.5mg/m^2 per dose), and daily intravenous ATO (0.15mg/kg) for 28 to 70 days. Patients with high-risk APML also received 4 doses of idarubicin, 12.0mg/m^2 per dose (patients with body surface area <0.6m^2 received 0.4mg/kg per dose) on days 1, 3, 5, and 7 as well as empirical therapy for differentiation syndrome with twice daily dexamethasone, 2.5mg/m^2, on days 1 to 14. All patients received 4 cycles (3 cycles of 8 weeks' duration and 1 cycle of 4 weeks' duration) of ATO/ATRA consolidation therapy and no maintenance therapy. Shah et al 2020 incorporated idarubicin (age adjusted) with ATRA (45mg/m^2/day) + ATO (0.15mg/kg/day) for induction. Consolidation was as per APL0406 regimen.[10] Wang et al 2022 treated high-risk patients with ATRA (40mg/d (BSA < 1.5m^2) or 60 mg/d (BSA ≥ 1.5m^2) (20 to 45mg/m^2/d) in divided doses) and ATO (0.15mg/kg/d) for induction (until HCR), consolidation (until MCR), and maintenance. Both ATO and ATRA were administered for 2 weeks every 4 weeks in the consolidation and maintenance therapy. Synchronous administration of mannitol and ATO was used to prevent central nervous system leukaemia in high-risk patients during consolidation and maintenance phase. Hydroxyurea was given to control the WBC count during the induction phase, at a mean dose of 36.03g (range 19.5 to 59g).

Abbreviations

APML: acute promyelocytic leukaemia; ATO: arsenic trioxide; ATRA: all trans retinoic acid; HCR: haematological complete remission; MCR: molecular complete remission

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** Patients have moderate problems in walking about

[10] The reference provided by Shah et al 2020 for the APL0406 regimen describes this as ATRA 45mg/m^2/day for 15 days, starting on weeks 0, 4, 8, 12, 16, 20 and 24 of the consolidation phase, with ATO 0.15mg/kg/day 5 days per week starting on weeks 0, 8, 16 and 24.

- **ability to provide self-care:** Patients have moderate problems in washing or dressing
- **undertaking usual activities:** Patients have moderate problems in doing their usual activities
- **experience of pain/discomfort:** Patients have moderate/severe pain or discomfort
- **experience of anxiety/depression:** Patients are moderately/severely anxious or depressed

Further details of impact upon patients:

Acute promyelocytic leukaemia can affect people of all ages. It presents initially as extreme fatigue and aching, which can then proceed to development of bruises and difficulty breathing. Many patients are often diagnosed late in the disease, due to the non-specific symptoms which can lead to high levels of distress and anxiety. They may have trouble moving and performing activities of daily living, due to shortness of breath, pain and fatigue. Those diagnosed with high-risk disease often present very unwell, with many having catastrophic bleeds, including a major haemorrhage or stroke. Patients having chemotherapy may require a prolonged stay in hospital or suffer with symptoms which may require them to take long periods off school or out of work. There is an additional anxiety for young people undergoing chemotherapy who have to think about the potential impact and impairment of future fertility.

Further details of impact upon carers:

The impact on carers and family can be significant. It can be extremely difficult to see a relative so unwell or go through difficult treatments such as chemotherapy. Carers may be required to take large amounts of time off work, especially carers of small children who are often very in hospital for long periods. This can also be very hard on siblings, who may struggle with the absence of a parent and sibling.

Considerations from review by Rare Disease Advisory Group

Not applicable.

Pharmaceutical considerations

The Clinical Commissioning Policy proposition recommends arsenic trioxide, in combination with all-trans retinoic acid, for the treatment of high-risk acute promyelocytic leukaemia for people aged 12 months and over. This recommendation is outside of arsenic trioxide's Summary of Product Characteristics.

Arsenic trioxide is included on the NHS Payment Scheme Annex A, so is considered a high-cost drug.

Considerations from review by National Programme of Care
The policy proposition received the full support of the Cancer PoC on the 10 October 2024