Lead team presentation - clinical

Arsenic trioxide (ATO) for treating acute promyelocytic leukaemia [ID446] – STA

1st appraisal committee meeting

Committee C

Lead team:

Clinical: Andrew Renehan and Judith Wardle

Cost: Mike Chambers

ERG: Kleijnen Systematic Reviews

NICE technical team: Kirsty Pitt and Alex Filby

21 March 2018

Key issues – clinical effectiveness

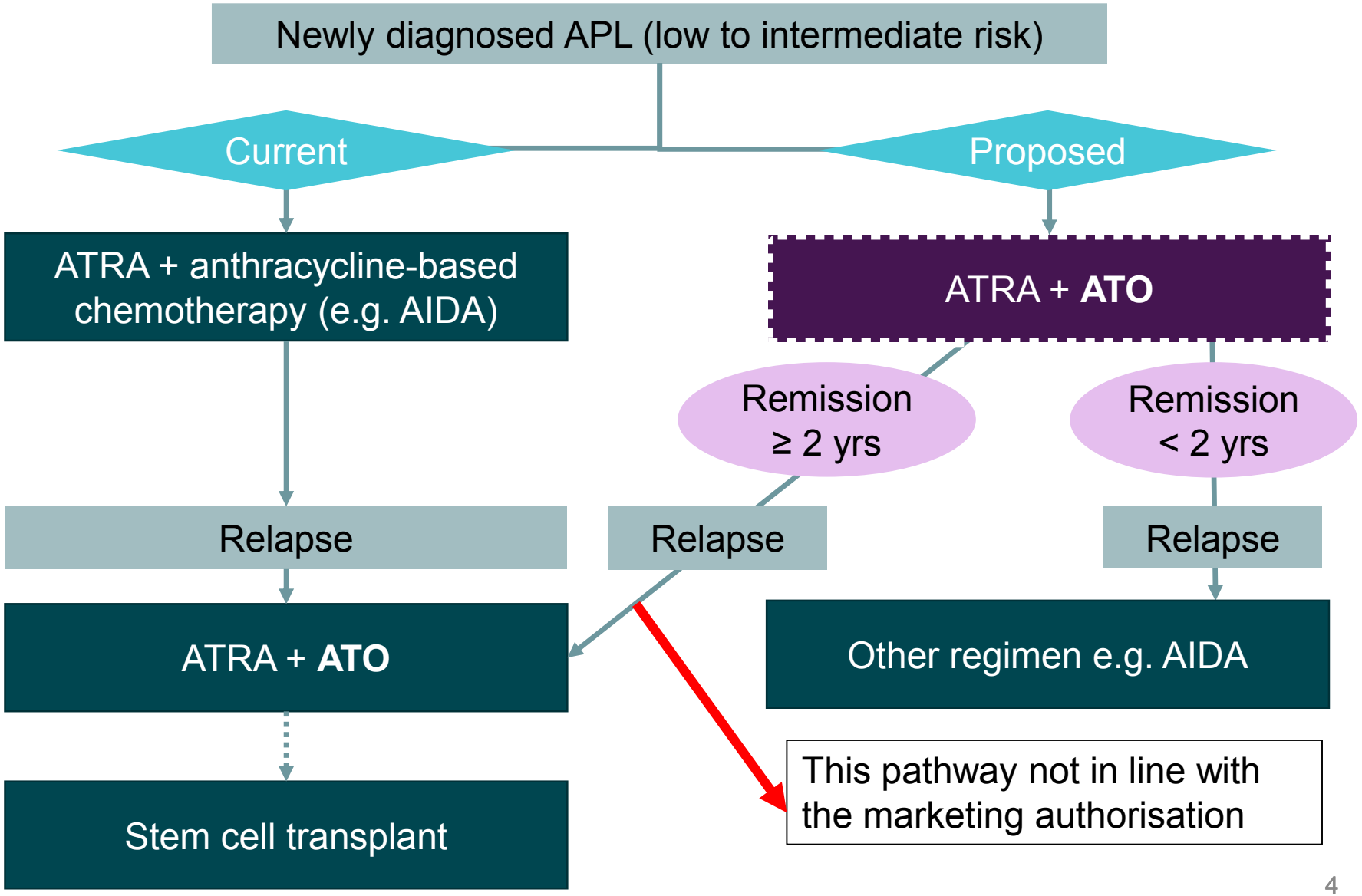
- Are the results of the APL0406 trial generalisable to UK practice?
- Is arsenic trioxide with ATRA clinically effective in newly diagnosed APL?
- Are the comparators appropriate
  - for newly diagnosed APL?
  - for relapsed or refractory APL?
- Is arsenic trioxide clinically effective in relapsed or refractory APL?
  - Can the results be generalised to use of arsenic trioxide without ATRA in relapsed or refractory APL?
  - Should data from studies other than randomised controlled trials be explored?
- Is arsenic trioxide innovative?
- Are there any equality issues?

Disease background

- Acute promyelocytic leukaemia (APL) is a subtype of acute myeloid leukaemia, associated with a genetic abnormality
- Median age at diagnosis is about 47
- APL can progress rapidly and have a poor survival prognosis
- Assessment of relapse risk, primarily based on white blood cell count, is important in choosing the most appropriate treatment options
- Incidence in Europe is estimated to be 0.11-0.14 per 100,000 people

UK treatment pathway

No previous NICE guidance for acute promyelocytic leukaemia



Impact on patients and carers

- Because acute promyelocytic leukaemia progresses rapidly and patients have to start treatment quickly, it has a large emotional effect on patients and families
- Most common symptoms: fatigue, weakness, breathlessness, pain, sleep disturbance
- Impact on mobility and activities of daily living
  - Consequent impact on education or employment, and thus has financial impact

Patient/carer views on arsenic trioxide

- Current treatments have high toxicity – over half of patients hospitalised. Long-term effects of chemotherapy can include risk of secondary cancers and loss of fertility in younger patients
- Need treatments that reduce high level of early deaths and reduce chance of relapse
- Arsenic trioxide has good progression-free survival in first-line treatment, and high complete response rate in second line
  - Also offers alternative for people who cannot tolerate currently offered chemotherapy
- Initial treatment requires high rate of hospital attendance, but patients can continue to work
- Side effects are tolerable

Comments from professional groups

- ATO would remove the requirement to treat standard risk APL patients with chemotherapy and protracted molecular monitoring
- First line therapy with ATO is associated with a very low risk of relapse in APL, unlike current chemotherapy
  - Therefore if arsenic trioxide is used as a first-line treatment, the use of second-line treatment would decrease
- ATO has been routinely commissioned for relapsed/refractory disease for 10 years

Comments from NHS England

- ATO is commissioned routinely for relapsed/refractory disease and rarely used as a single agent
  - However use in this setting in combination with ATRA is off-label use not within the marketing authorisation (MA)
- Re-treating with ATO+ATRA is also off-label as MA states second line use should follow chemotherapy
- The marketing authorisation is limited to adults. If ATO were recommended in adults, NHS England would ensure funding within baseline commissioning extended to relevant people under the age of 18 years.

Arsenic trioxide (Trisenox, Teva)

UK marketing authorisation	Indicated for induction of remission, and consolidation in adult patients with: • Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (white blood cell count, ≤ 10 x 103 /µl) in combination with all-trans-retinoic acid (ATRA) • Relapsed/refractory acute promyelocytic leukaemia (previous treatment should have included a retinoid and chemotherapy) characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/ Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.
Mechanism of action	Believed to have multiple mechanisms of action including inducing cell death by damaging or degrading the PML/RARα fusion protein in acute promyelocytic leukaemia
Administration and dosage	Administered intravenously at 0.15 mg/kg/day (duration of treatment varies for newly diagnosed/relapsed or refractory disease, and for induction and consolidation therapy)
List price	£2,920 for 10 ampoules of 10mg/10ml concentrate for solution for infusion (BNF)

Decision problem [1]

	Final scope issued by NICE	Company submission	Rationale for difference
Population	Adults with: • untreated low-to-intermediate risk acute promyelocytic leukaemia • relapsed/refractory acute promyelocytic leukaemia (APL)	…characterised by the presence of the t(15;17) translocation and/or the presence of the promyelocytic leukaemia/retinoic-acid-receptor-alpha (PML/RAR-alpha) gene.	N/A
Intervention	Arsenic trioxide (ATO) (with or without ATRA)	ATO + ATRA	ATO alone rarely used in the relapsed/ refractory setting.

Decision problem [2]

	Final scope issued by NICE	Company submission	Rationale for difference
Comparators	• AIDA regimen • Haematopoietic stem cell transplantation (HSCT) (relapsed or refractory APL) • best supportive care (relapsed or refractory APL)	Single model evaluating ATO+ATRA vs AIDA as first-line treatment, with second-line treatments included	After relapse, choice of therapy depends on prior treatments - difficult to separate first- and second-line ATO. Use of ATRA+ATO usually precedes HSCT. Best supportive care used where disease is refractory to ATO in second-line.
Outcomes	Overall survival (OS) Progression-free survival (PFS) Response rates (bone marrow remission) Adverse effects of treatment Health-related quality of life	Additionally: • Event-free survival • Complete remission rates • Cumulative incidence of relapse • Disease-free survival or relapse-free survival	PFS not measured in trials – event-free survival presented instead

Clinical trials

Trials included in company's submission:

Newly diagnosed APL

- APL0406
- AML17

Relapsed/refractory APL

- Raffoux et al.
  - Compared ATRA+ATO with ATO
  - Used for supporting information

ERG comments on trials included:

- No trials that compared ATO with haematopoietic stem cell transplant or best supportive care, as specified in scope (relapsed/refractory setting)
- No trials of ATO alone in relapsed/refractory setting – company states ATO rarely used alone in UK
- Non-randomised clinical trials could have been included for relapsed/refractory APL as well as untreated APL as no directly relevant RCT evidence presented
  - Company states use of ATO in relapsed/refractory APL is so well-established it is difficult to provide novel information

Summary of included trials
Newly diagnosed APL

	APL0406 (n=266, final cohort)	AML17 (n=235)
Design	Phase 3, randomised, open-label, non-inferiority trial	Phase 3, randomised, open-label trial
Population	• No UK patients • Low and intermediate risk disease only	• Based in UK, Denmark and New Zealand • Included people with high risk disease
Intervention	• Compared ATRA+ATO with ATRA+idarubicin (AIDA) • Dosing of ATO in line with marketing authorisation	• Compared ATRA with AIDA • Dosing of ATO different to marketing authorisation • 93% in high risk group, and 7 people in other risk groups received gemtuzumab ozogamicin
Primary outcome	Event-free survival at 2 years after diagnosis	Quality of life

Baseline characteristics

Newly diagnosed APL

Study population	APL0406 final cohort		AML17	
Treatment arm	ATRA +ATO (n=129)	AIDA (n=137)	ATRA +ATO (n=116)	AIDA (n=119)
Median age (years)	46.6	46.6	47	47
Male gender; n (%)	60.0 (46.5)	70.0 (51.1)	60 (52)	60 (50)
White blood cell count, $\times 10^9$/L; median	1.4	1.5	3.0	2.2
Low risk, n (%)	57 (45.2)	55 (41.3)	86 (74)	92 (77)
Intermediate risk, n (%)	69 (54.7)	78 (58.6)	Not reported	Not reported
High risk, n (%)	N/A	N/A	30 (26)	27 (23)

ERG on APL0406: groups are similar and appear to reflect UK patients, based on comparing with patients in AML17

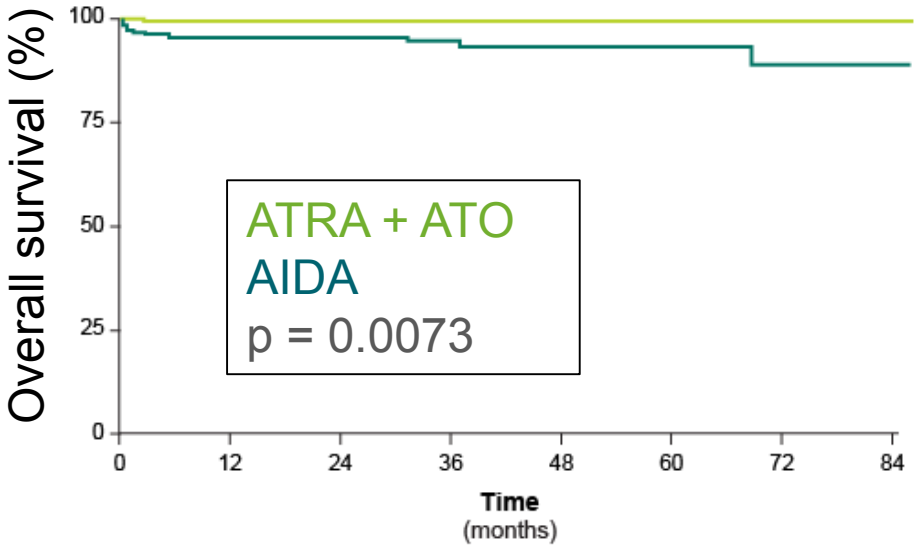
APL0406 results
Summary

Endpoint	Final cohort		
	ATRA+ATO (n = 129)	AIDA (n = 137)	P value
Event-free survival at 50 months, % (95% CI)	97.3 (94.3 to 100)	80.0 (72.9 to 88.0)	< 0.001
Overall survival at 50 months, % (95% CI)	99.2 (97.7 to 100)	92.6 (87.9 to 97.5)	0.007
Disease-free survival at 50 months, % (95% CI)	97.3 (94.3 to 100)	82.6 (75.6 to 90.3)	< 0.001
Haematological CR rate after induction; n (%)	127 (100)	132 (97.0)	0.120
Molecular CR rate after third consolidation cycle; n (%)	115 (100)	117 (98.3)	Not reported
Cumulative incidence of relapse at 50 months, % (95% CI)	1.9 (0.0–4.5)	13.9 (7.1–20.6)	0.0013

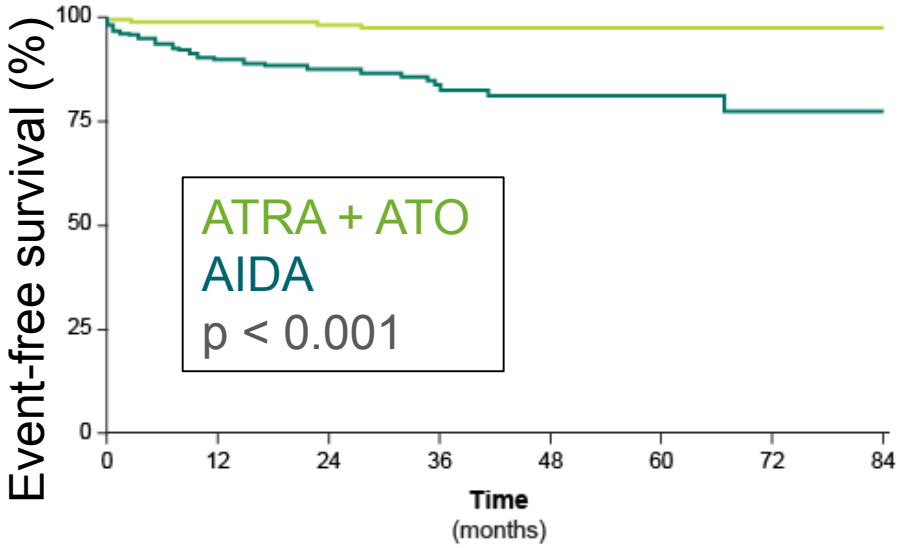
Survival results

APL0406

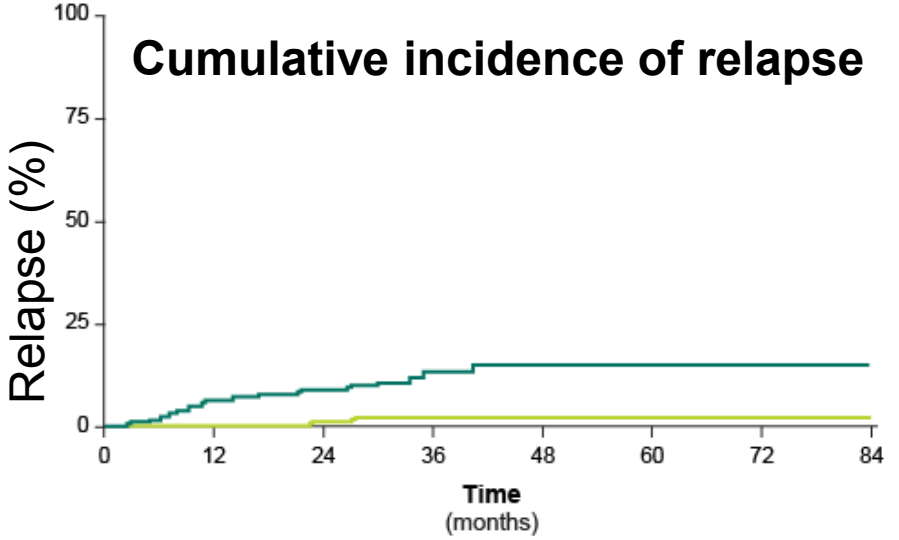
Overall survival



Event-free survival



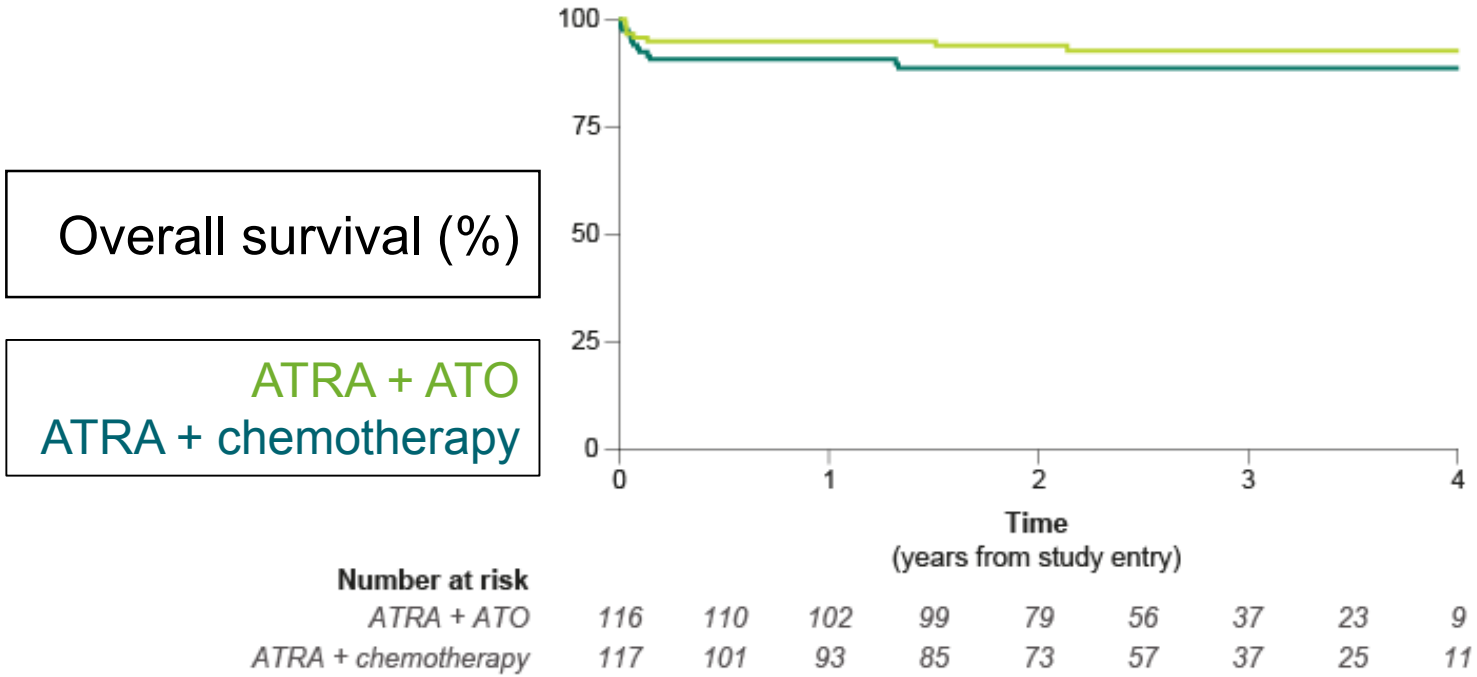
Cumulative incidence of relapse



AML17 results

Endpoint and time frame	ATRA+ATO (n = 77)	AIDA (n = 79)	Hazard ratio	P value
Event-free survival at 4 years, % (95% CI)	91% (84–95)	70% (56–80)	0.35 (0.18–0.68)	0.002
Overall survival at 4 years, % (95% CI)	93% (86–96)	89% (81–93)	0.60 (0.26–1.42)	0.250

ATO = arsenic trioxide; ATRA = All-trans retinoic acid; AIDA = ATRA + idarubicin; CI=confidence intervals



Health-related quality of life

APL0406

- Only available for initial patient cohort
  - Long-term analysis in final patient cohort not yet reported
- No baseline assessment performed
- Significant difference between treatment groups (measured on EORTC QLQ-C30 scale) only detected for fatigue (p=0.022)
  - ATRA+ATO associated with lower fatigue severity after induction but not after third consolidation course

AML17

- Measured on EORTC QLQ-C30 scale
- No statistically significant difference detected in the primary outcome of global functioning, but study may have been underpowered
- Small but statistically significant benefits of ATRA+ATO over AIDA seen for cognitive functioning and role functioning

Adverse events [1] APL0406 final cohort

Event	Time frame	ATRA + ATO	AIDA	p value
Induction-specific adverse events, n (%)				
Patients with moderate to severe differentiation syndrome	During induction	21 (17)	17 (13)	0.38
Leukocytosis	During induction	56 (43)	NR	NR
Haematological adverse events, n (%)				
Patients with grade 3–4 neutropenia lasting >15 days	During induction	61 (35)	109 (64)	< 0.001*
	1st consolidation cycle	8 (16)	40 (67)	< 0.001*
	2nd consolidation cycle	7 (7)	90 (92)	< 0.001*
	3rd consolidation cycle	5 (15)	28 (85)	< 0.001*
Patients with grade 3–4 thrombocytopenia lasting >15 days	During induction	74 (38)	120 (62)	< 0.001*
	1st consolidation cycle	6 (26)	17 (74)	< 0.001*
	2nd consolidation cycle	6 (7)	77	< 0.001*
	3rd consolidation cycle	8 (23)	16 (76)	< 0.001*
Fever of unknown origin and infection episodes, n (%)	During induction	30 (23)	75 (55)	< 0.001*
	1st consolidation cycle	10 (8)	8 (6)	0.540
	2nd consolidation cycle	4 (3)	46 (38)	< 0.001*
	3rd consolidation cycle	2 (1.6)	2 (1.7)	1.000

Adverse events [2] APL0406 final cohort

Event	Time frame	ATRA + ATO	AIDA	p value
Non-haematological adverse events, n (%)				
Patients with QTc prolongation	During induction	11 (8.5)	1 (0.7)	0.002*
	1st consolidation cycle	3 (2)	0	0.110
	2nd consolidation cycle	3 (2)	0	0.110
	3rd consolidation cycle	2 (1.5)	0	0.230
Patients with grade 3–4 hepatic toxicity	During induction	51 (40)	4 (3)	< 0.001*
	1st consolidation cycle	5 (4)	1 (0.7)	0.110
	2nd consolidation cycle	1 (0.8)	0	0.490
	3rd consolidation cycle	0	0	NA
Patients with grade 3–4 gastrointestinal toxicity	During induction	3 (2)	25 (18.2)	< 0.001*
	1st consolidation cycle	0	1 (0.8)	1.000
	2nd consolidation cycle	0	6 (4.9)	0.03*
	3rd consolidation cycle	0	0	1.000
Patients with grade 3–4 cardiac function abnormalities	During induction	0	5 (3.7)	0.060
	1st consolidation cycle	0	0	NA
	2nd consolidation cycle	0	0	NA
	3rd consolidation cycle	0	0	NA

Adverse events [3] APL0406 final cohort

Event	Time frame	ATRA + ATO	AIDA	p value
Neurotoxicity (all grades), n (%)	During induction	1 (0.7)	0	0.480
	1st consolidation cycle	5 (4.2)	0	0.020*
	2nd consolidation cycle	6 (5)	0	0.010*
	3rd consolidation cycle	7 (5.9)	0	0.006*
Hypercholesterolemia, n (%)	During induction	14 (10)	12 (8.7)	0.550
	1st consolidation cycle	19 (16)	12 (9.6)	0.130
	2nd consolidation cycle	19 (16)	12 (9.7)	0.140
	3rd consolidation cycle	16 (14)	11 (9.0)	0.270
Hypertriglyceridemia, n (%)	During induction	29 (22)	29 (22)	0.760
	1st consolidation cycle	22 (18.4)	19 (15.2)	0.490
	2nd consolidation cycle	17 (14.4)	10 (8)	0.120
	3rd consolidation cycle	16 (14)	13 (11)	0.500

Company notes that adverse events in the trials were mostly managed with temporary treatment discontinuation and supportive care, with few permanent discontinuations reported.

*Statistically significant at 5% level

ERG comments on APL0406 trial

- Open-label: bias could be introduced
- No UK patients, but patients appear to reflect those seen in UK clinical practice
- Intention-to-treat analysis only included patients who received at least one dose of assigned therapy after randomisation
- Knowledge of long term toxicity of ATRA+ATO is very limited - long term safety study recommended by EMA

Raffoux et al. trial (n=20)
Relapsed or refractory APL

Methods

- Patients randomised to receive ATO alone or ATRA+ATO
- 1 patient in ATO alone group received maintenance treatment with ATO

Results

- Primary objective was to achieve a 2 week reduction in time needed to obtain haematological complete remission
  - 16 patients evaluated
- Median time needed to reach haematological complete remission was 42 days in both treatment groups (p=0.58)
- Results for cumulative percentage of complete remission, overall survival and disease-free survival were similar in the 2 treatment groups

Innovation and equality considerations

Innovation

- Company comments
  - Offers a chemotherapy-free treatment option for people newly diagnosed with low- to intermediate-risk APL
    - reduces toxicity
    - option for people not suitable for chemotherapy
- Royal College of Pathologists/British Society for Haematology
  - Reduces risk of relapse
  - Reduces need for bone marrow transplant

Equality considerations

- Are there any equalities issues?
  - Company highlighted that older people who can not have chemotherapy would be eligible for treatment with ATO
  - Company highlighted that ATO+ATRA may decrease blood transfusions compared to AIDA, which may be more acceptable to people who are Jehovah's Witnesses and cannot have blood transfusions

Key issues – clinical effectiveness

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Lead team presentation - cost

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ERG: Kleijnen Systematic Reviews

NICE technical team: Kirsty Pitt and Alex Filby

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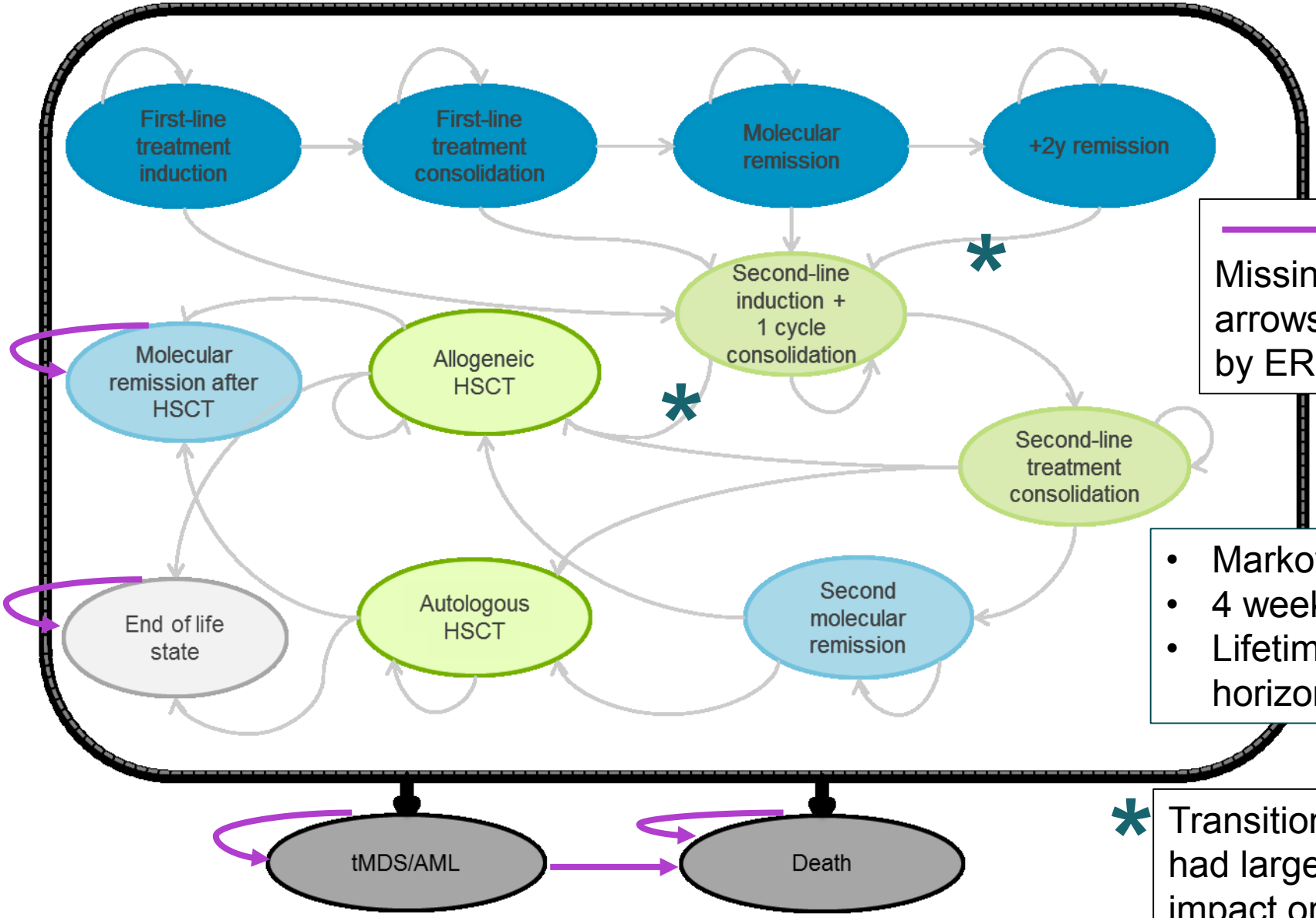
Company's economic model

Includes untreated and treated APL

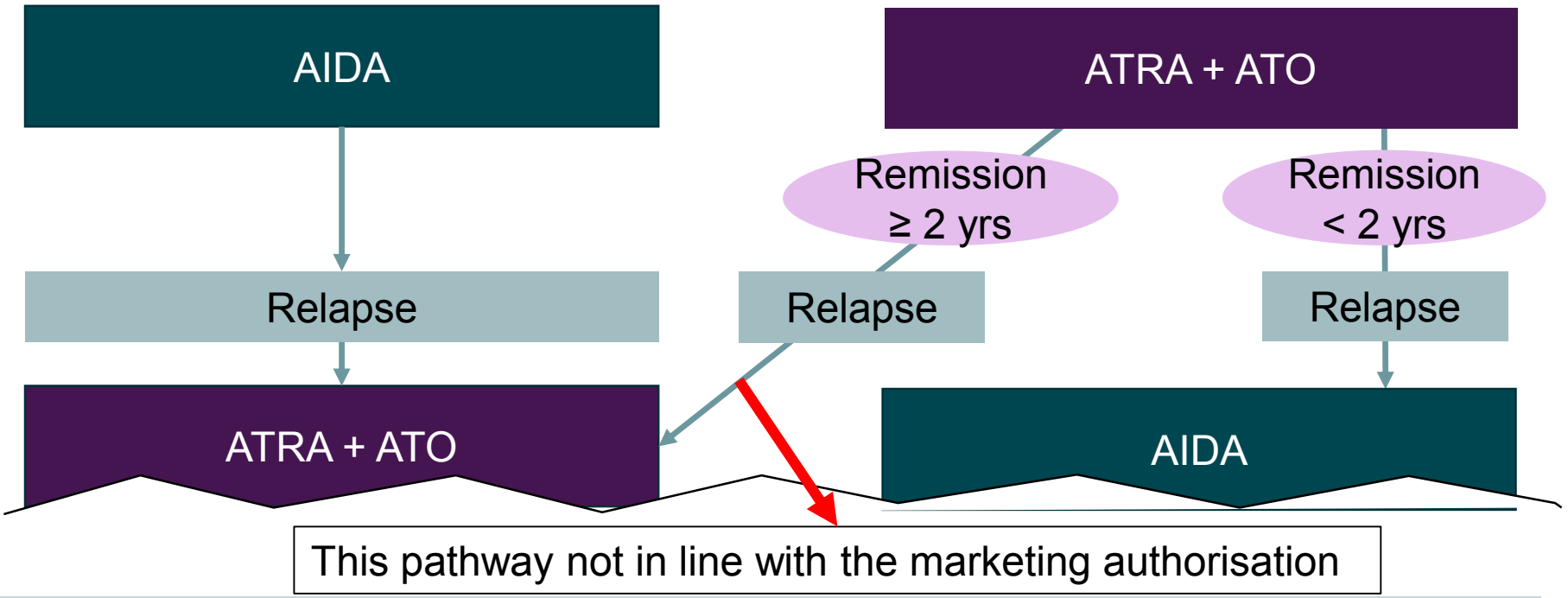


Missing arrows added by ERG

- Markov model
- 4 week cycle
- Lifetime horizon

* Transitions that had largest impact on ICER

Company's economic model structure



ERG comments on model structure

- Some inconsistencies and omissions in the cost-effectiveness literature search could have led to relevant evidence being missed
- Company's de novo model is more complex than models identified in literature, but ERG considers structure appropriate
- >40% of patients in the ATRA+ATO first line and AIDA second line group still alive after 40 years (company's model time horizon)
  - ERG use 56 years in base case but unclear of the face validity of the relatively long life expectancy calculated by the model (close to general population life expectancy)

Company's economic model inputs

Treatment effectiveness and extrapolation

- Efficacy in newly diagnosed APL estimated through remission rates and rate of relapse in APL0406 trial
- Rate of relapse was higher for the first 2 years of remission (molecular remission state) and lower in '+2y remission' state, where rate was constant until death
- Efficacy data for relapsed/refractory APL derived from studies by Raffoux *et al.*, Tallman *et al.,* Russell *et al.,* and Platzbecker *et al.* clinical expert opinions and an existing US cost-effectiveness model
- Safety data from APL0406 and Raffoux *et al.* trials
- Except for cardiac events, adverse events did not lead to a change of treatment, but impacted on costs and quality of life

ERG comments on treatment effectiveness and adverse events

- Model assumes treatment benefits are maintained for entire time horizon
- Transition probabilities and evidence sources not clearly described
- Transitions from second line health states: evidence weak and method of obtaining probabilities not transparently reported
- Should have used conditional probabilities for relapse after first line treatment
- Unclear why specific adverse events chosen and unclear justification for sources, e.g. why reversible arrhythmia not considered

Company's economic model inputs
Utility values

- Utility values obtained from literature for other diseases (e.g. chronic lymphocytic leukaemia and acute myeloid leukaemia) because data from EQ-5D not available for APL
  - Adjusted for age (average age of modelled population is 45 years)
  - Adjusted for the utility representing perfect health
  - Disutilities for adverse events included in induction and consolidation

ERG comments on utility values

- Company's method of selecting utility values unclear
- Unclear why values from chronic lymphocytic leukaemia chosen
- Adjustments made by company unjustified
  - Need for age-adjustment is unclear as the impact of disease would outweigh the impact of age
  - No evidence to support method of adjusting for utility representing perfect health – over time, utility values are higher than in general population
  - Adjustments not applied to all health states and rationale for this is unclear

Utility values in the model

State	Mean utility value	Reference
First-line induction treatment	0.739	Woods et al., 2012 Szende et al., 2014
First-line consolidation treatment	0.739	Woods et al., 2012 Szende et al., 2014
First molecular remission	0.773	Beusterien et al., 2010 Szende et al., 2014
First long-term molecular remission (>2 years)	0.849	Szende et al., 2014
Second-line induction + 1 cycle consolidation	0.673	Woods et al., 2012 Beusterien et al., 2010
Second-line treatment consolidation	0.702	Beusterien et al., 2010
Second molecular remission	0.849	Szende et al., 2014
Allogeneic HSCT	0.687	Breitscheidel L., 2008
Autologous HSCT	0.687	Breitscheidel L., 2008
Allogeneic HSCT molecular remission	0.849	Szende et al., 2014
End of life state	0.4	Morton et al., 2009
tMDS/AML	0.4	Cooperberg et al., 2013
Hospitalisation	-0.01	Assumption

Company's economic model inputs

Treatment costs

Phase	ATRA+ATO			AIDA		
	ATRA	ATO	**Total ATRA +ATO**	ATRA	Chemo (IDA+MTZ)	**Total AIDA**
First line: Induction	£464	£16,079	£16,542	£507	£2,097	£2,604
First line: Consolidation	£1,521	£40,196	£41,718	£652	£1,723	£2,375
First line: Total	£1,985	£56,275	**£58,260**	£1,159	£3,820	**£4,979**
Second line: Induction	£362	£12,561	£12,924	£507	£2,097	£2,604
Second line: Consolidation	£1,521	£12,561	£14,083	£652	£1,723	£2,375
Second line: Total	£1,884	£25,123	**£27,006**	£1,159	£3,820	**£4,979**

Company's economic model inputs

Medical costs

Items	Value	Reference
Cost per follow-up appointment	£52.50	Personal Social Services Research Unit (PSSRU)
Cost per polymerase chain reaction monitoring test	£280.00	Expert opinion: Guy's Hospital tariff (NHS Foundation Trust)
Cost per allogeneic HSCT	£27,907.53	National Schedule of Reference Costs
Cost per autologous HSCT	£7,122.97	National Schedule of Reference Costs
Allogeneic HSCT remission costs (annual)	£21,585.75	Leunis et al., 2013
Autologous HSCT remission costs (annual)	£5,776.01	Leunis et al., 2013
End of life costs per month	£4,670.68	Marie Curie Cancer Care

Company's economic model inputs

Resource use [1]

	Items	Cost	ATRA+ATO	AIDA	References for resource use
Induction	Bed days per patient	£396.47	First line: 32 Second line: 25	35	AATO: First line: Lo-Coco et al., 2013 Second line: Douer et al., 2005 AIDA: Lo-Coco et al., 2013
	Supportive care transfusions	0	15	22	Burnett et al., 2015
	Annual PCR tests	£280.00	5	4	Expert opinion
Consolidation	Bed days per patient	£396.47	0	4	ATRA+ATO: Expert opinion AIDA: assumption based on treatment schedule
	Ambulatory days per patient	£162.00	First line: 10 Second line: 12.5	0	ATRA+ATO: Expert opinion AIDA: Inpatient treatment assumed
	Number of days of antibiotics	£1.65	1	2	Burnett et al., 201513
	Annual PCR tests	£280.00	5	4	Expert opinion

Company's economic model inputs

Resource use [2]

	Items	Cost	ATRA +ATO	AIDA	Reference for resource use
Molecular remission (first, second, allo- and auto-HSCT)	Duration of follow-up	£210	3	3	First remission: Platzbecker et al., 2015 Others: Expert opinion
	Annual appointments	£52.50	4	4	First remission: Platzbecker et al. Others: Expert opinion
	Annual PCR tests	£280	4 (0 at first remission)	4	First remission: ATRA+ATO: Expert opinion AIDA: Platzbecker et al. Others: Expert opinion
Allo HSCT	Hospitalisation duration	£27,907.53	4 weeks	4	Expert opinion
Auto HSCT	Hospitalisation duration	£7,122.97	3 weeks	3	Expert opinion

ERG comments on costs and resource use

- Lack of justification of sources for cost and resource data
- Monitoring of haematological response costs not included – costs would be higher in ATRA+ATO group because more frequent relapses in second line for AIDA group so less monitoring needed

Total costs – company's base case

ATRA+ATO for untreated APL

Cost category	ATRA+ATO	AIDA	ATRA+ATO vs. AIDA
Total treatments	£60,336	£21,604	£38,731
Administration	£25,402	£31,660	-£6,259
Supportive care and antibiotics	£3,575	£6,487	-£2,912
Follow-up and monitoring	£2,991	£10,389	-£7,398
Adverse events	£4,142	£12,378	-£8,236
Myelodysplastic syndrome	£0	£226	-£226
HSCT	£7,645	£48,326	-£40,681
Palliative care	£906	£5,196	-£4,290
Total	**£104,996**	**£136,267**	**-£31,270**

- Costs generated by the model for the average patient over a lifetime horizon
- Largest cost offsets are for HSCT, adverse events and monitoring

Company's base case results
ATRA+ATO for untreated APL

Discounted deterministic base case

	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	NMB (£)
AIDA	136,267	13.72	-	-	-	-
ATRA+ATO	104,996	16.34	-31,270	2.62	Dominant	109,871

Inc., incremental; NMB, net monetary benefit (calculated by NICE technical team based on a £30,000/QALY threshold)

- Undiscounted life years:
  - AIDA = 26.84
  - ATRA+ATO = 33.22
  - Life years gained = 6.38

End of life criteria:
The company did not make a case for end of life criteria to apply.
NB. Median overall survival not reached in the APL0406 trial after 84 months.

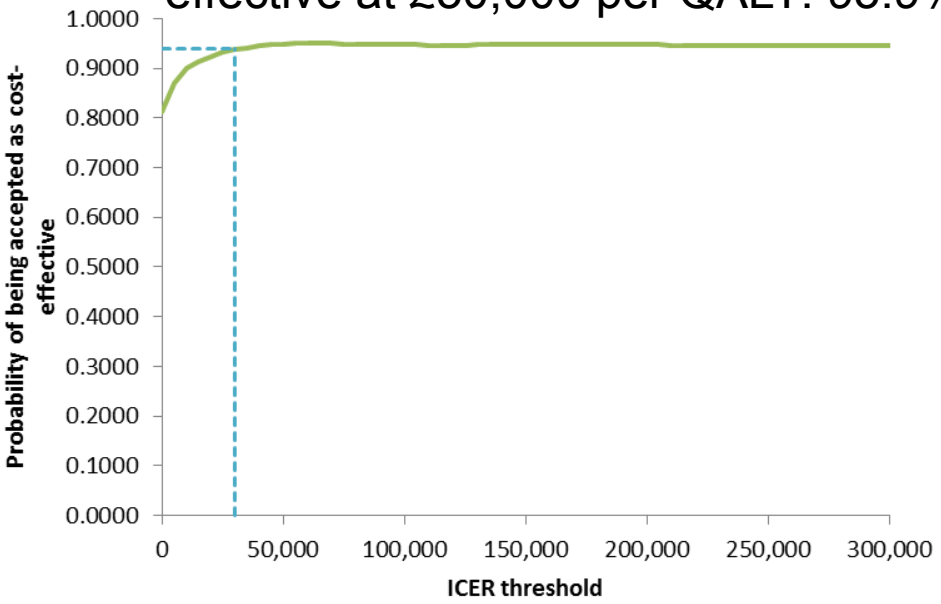
Company's probabilistic sensitivity analysis results

ATRA+ATO for untreated APL

ATRA+ATO vs AIDA	Incremental costs	Incremental QALYs	ICER (£/QALY)
Mean	-£31,088	2.55	Dominant

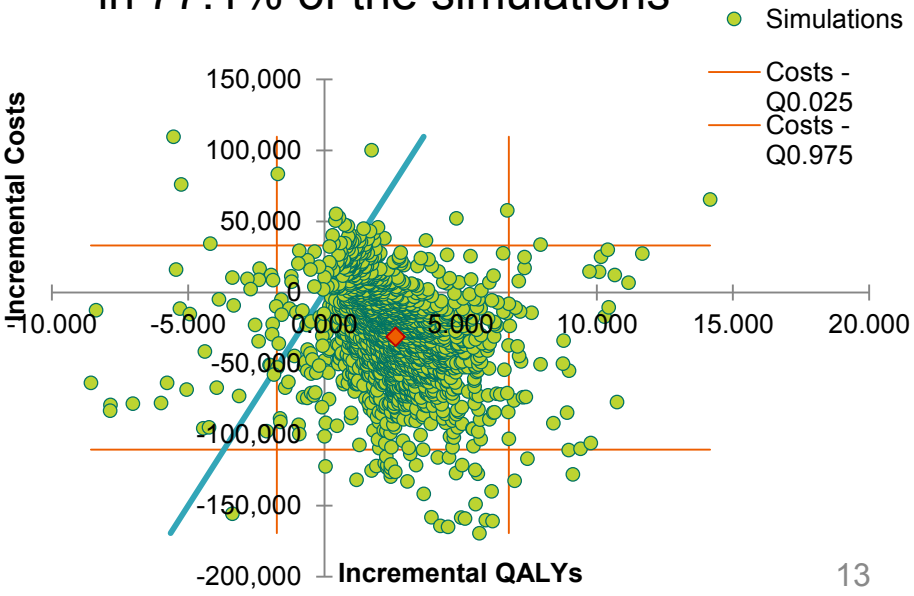
Cost-effectiveness acceptability curve for ATRA+ATO vs AIDA

- Probability of ATRA+ATO being cost-effective at £30,000 per QALY: 93.9%



Incremental cost-effectiveness plane for ATRA+ATO vs AIDA

- ATRA+ATO dominated AIDA in 77.1% of the simulations



Company's deterministic sensitivity analysis

ATRA+ATO for untreated APL

- ICER only computable in 4 cases (in all other cases, ATRA+ATO dominant over AIDA):

Parameters	Base case value	Lower case		Higher case	
		ICER (£/ QALY)	NMB (£)	ICER (£/ QALY)	NMB (£)
Company base case	-	*Dominant*	*109,870*	-	
Time horizon (5 to 30 years)	40 years	148,179	-17,628	Dominant	87,308
Relapse rate after remission (for 48 months) – AIDA (0.082-0.209)	0.139	25,658	4,299	Dominant	179,946
CHR rate, first line - ATRA+ATO (0.4922–1.0000)	0.9845	11,927	13,919	Dominant	109,727
CMR rate, first line - ATRA+ATO (0.5–1.0)	1.0	1,472	31,375	Dominant	109,870

Inc, incremental; CHR, complete haematological remission; CMR, complete molecular remission; NMB, net monetary benefit calculated by NICE technical team based on a £30,000 threshold

Company's scenario analyses (untreated APL)

Scenario	Description
a. AIDA used in second line following both first-line treatments	To investigate impact of subsequent treatments on cost-effectiveness
b. Utility values from Tallman *et al.*	Values used in an existing model
c. AML17 protocol used	Schedule, dosage, efficacy and safety inputs
d. 'Worst-case' scenario	Includes unfavourable inputs for ATRA+ATO
e. Probability of undergoing HSCT reflecting clinical practice	Lower proportion of patients undergo autologous HSCT and allogeneic HSCT is reserved for patients not in molecular remission after second line induction
f. Including disease-related mortality	For induction and consolidation phases
g. Including maintenance treatment	2 years of maintenance in AIDA group
h. 26 cycles in consolidation state	Cycle length is 4 weeks so 1 year is 13 cycles
i. Time horizon of 56 years	40 years used in base case
j. Not assuming probability of relapse was the same at 48 months as 50	In base case, probability of relapse at 48 months in first molecular remission assumed to be equal to that at 50 months
k. Assuming no relapse after 24 months in first line remission	In base case, relapse transition probability constant from 2 years after remission

Company's scenario analyses results

ATRA+ATO vs AIDA for untreated APL

Scenario	Inc. costs (£)	Inc. QALY	ICER (£/QALY)	NMB (£)
Company's base case	-£31,270	2.62	Dominant	109,870
a. AIDA used in second line following both first-line treatments	-£21,593	2.72	Dominant	103,193
b. Utility values from Tallman *et al.*	-£31,270	2.93	Dominant	119,170
c. AML17 schedule, dosage, efficacy and safety	-£66,384	3.39	Dominant	168,084
d. 'Worst-case' scenario	-£9,986	1.58	Dominant	57,386
e. Probability of undergoing HSCT reflecting clinical practice	-£28,664	2.43	Dominant	101,564
f. Including disease-related mortality	-£21,099	3.80	Dominant	135,099
g. Including maintenance treatment	-£33,012	2.62	Dominant	111,612
h. 26 cycles in consolidation state	-£31,813	2.63	Dominant	110,713
i. Time horizon of 56 years	-£32,922	2.83	Dominant	117,822
j. Not assuming probability of relapse was the same at 48 months as 50	-£28,555	2.53	Dominant	104,455
k. No relapse after 24 months in first line remission	£10,671	1.40	£7,610	31,329

ERG base case – main changes

- Time horizon
  - Used 56 years instead of 40 years in company's base case
- Alternative utility values
  - Removed utility adjustments and used same value (0.70) for first and second induction and consolidation
  - Utility values capped so as not to exceed general population
- Alternative remission probabilities
  - Based remission probability for all patients on APL0406 trial data and used molecular remission rate to inform probability of transitioning to remission for patients who could be evaluated with PCR testing

ERG base-case results - Untreated APL

Including summary of exploratory analyses

Deterministic results	ATRA+ATO vs. AIDA			
	Inc. costs	Inc. QALYs	ICER incremental (£/QALY)	Net monetary benefit (£)
Company base case	**-£31,270**	**2.62**	**Dominant**	**£109,870**
1. Company base case – errors corrected	-£25,914	2.43	Dominant	£98,814
2. Time horizon 56 years	-£27,540	2.63	Dominant	£106,440
3. Alternative utility values	-£25,914	2.41	Dominant	£98,214
4. Utility values capped	-£25,914	2.26	Dominant	£93,714
5. Alternative remission probabilities	-£21,853	2.27	Dominant	£89,953
ERG base case (1-5 combined)	**-£23,502**	**2.25**	**Dominant**	**£91,002**
Net monetary benefit calculated by NICE technical team based on a £30,000 threshold				

ERG scenario analyses

Untreated APL

Issue	ERG comment
6. Disease-related mortality	No disease-related mortality modelling during on treatment and remission phases. ERG considers that mortality risk likely to be higher than in the general population (consistent with evidence from AML17 trial).
7. Stem cell transplant (HSCT)	In the model, patients can have autologous or allogeneic HSCT. Clinical expert stated that allogeneic HSCT is generally not recommended in APL in the UK.
8. Transition from second line molecular remission to HSCT	Adjusted using the median time to relapse following second line remission. Unadjusted probabilities seem high but unsure of justification for adjustment.
9. Reversible arrhythmia	Expert opinion suggested 2% of patients on ATRA+ATO experience reversible arrhythmia and switch treatment – not modelled.
10. Extrapolation of treatment effectiveness	Company's model assumes treatment benefits are maintained for entire time horizon, e.g. relapse transition probability in first line is constant from 2 years after remission.

ERG scenario analyses – results

ATRA+ATO vs AIDA for untreated APL

Scenario	Inc. costs	Inc. QALYs	ICER (£/QALY)	NMB (£)
ERG base case	**-£23,502**	**2.254**	**Dominant**	**91,122**
6. Adding disease-related mortality in induction phases (first and second line)	-£17,066	2.682	Dominant	97,526
7. Replacing transitions to allogeneic HSCT for transitions to autologous HSCT	-£9,865	1.624	Dominant	58,585
8a. Transitions to HSCT states from second line remission removed	-£24,848	2.281	Dominant	93,278
8b. Transitions to HSCT states from second line remission 'uncorrected'	-£22,723	2.242	Dominant	89,983
9. Incorporating 2% cardiac events for ATRA+ATO in induction phase	-£23,606	2.285	Dominant	92,156
10. Assuming equal relapse probability for all treatments 2 years after first-line remission	£20,407	1.034	£19,734	10,613
All of the above scenarios (except 8b)	**£27,067**	**1.252**	**£21,622**	**10,493**

NMB, net monetary benefit calculated by NICE technical team based on a £30,000 threshold

Additional scenarios (untreated APL)

Calculated by NICE technical team, verified by ERG

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Equal relapse probability for all treatments 2 years after first-line remission (ERG scenario 10) AND zero costs post-HSCT					
AIDA	£67,318	15.10			
ATRA+ATO	£99,418	16.13	£32,100	1.03	£31,042
ERG scenarios 6-8a, 9-10 AND zero costs post-HSCT					
AIDA	£61,120	14.41			
ATRA+ATO	£95,597	15.66	£34,476	1.25	£27,541
Equal relapse probability for all treatments 2 years after first-line remission (ERG scenario 10) AND costs post-HSCT = £5,000/year					
AIDA	£76,605	15.1			
ATRA+ATO	£103,045	16.1	£26,441	1.03	£25,569
ERG scenarios 6-8a, 9-10 AND costs post-HSCT = £5,000/year					
AIDA	£71,217	14.4			
ATRA+ATO	£99,652	15.7	£28,435	1.25	£22,715

Relapsed or refractory APL

Company's results

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
AIDA	188,877	8.84	-	-	-
ATRA+ATO	198,959	9.44	£10,082	0.60	£16,733

- Provided following request for clarification
- Implemented by changing health states representing first line therapy to second line, and neutralising states representing second line (no transitions to these states were possible)
- Company state that if ATO is used for untreated APL, the number of relapses will decrease so a very small population will have relapsed/refractory APL
- No efficacy data found for ATO alone in relapsed or refractory disease so not modelled
  - Clinical experts stated ATO is rarely used alone in relapsed or refractory disease
- Clinical experts stated that best supportive care is not a relevant comparator – analysis not carried out

ERG analysis of relapsed/refractory APL

- ERG unsure how company's analysis performed
  - No detail about sources of transition probabilities
- ERG's analysis implemented by removing first line health states
  - Based on ERG base-case model
- ERG state that this analysis should be considered exploratory given the concerns with the evidence informing the second line health states

Relapsed /refractory APL	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)
AIDA	£191,158	8.620	-	-	-
ATRA+ATO	£209,365	9.204	£18,207	0.584	£31,184

ATO in combination with ATRA is not in line with the marketing authorisation for ATO in the relapsed/refractory setting.

Key issues – cost effectiveness

- Is the company's model appropriate for decision making?
  - Are the results generalisable to use of ATO within its marketing authorisation?
- Are the model inputs used plausible?
  - Are the costs of remission after stem cell transplant plausible?
  - Is the extrapolation of relapse rate for the whole time horizon appropriate?
- Should allogeneic stem cell transplant be modelled?
- Is arsenic trioxide (ATO) with ATRA cost-effective in newly diagnosed APL?
- Should best supportive care and stem cell transplant be included as comparators for relapsed or refractory APL?
- Can the evidence for ATO with ATRA in relapsed or refractory APL be generalised to use of ATO alone?
- Is ATO cost-effective in relapsed or refractory APL?
- Does ATO meet the end of life criteria?