Current UK Approaches to the treatment of APL

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UK Protocols post AML17

- Summary of long term follow up from AML17
- AML19 prior to NICE ATO Approval
- NICE ATO Approval for standard risk APL
- Special measures for high risk APL during COVID pandemic
- Future proposals regarding oral ATO

AML17 (2009-2013)
Arsenic Trioxide Schedule

Induction: ATO 0.3mg/kg days 1-5 in week 1
(8 weeks) then: 0.25mg/kg X 2/ week for 7 weeks

Consolidation: ATO 0.3mg/kg d 1-5 in week 1.
(4 cycles) 0.25mg/kg x 2 per week for 3 weeks

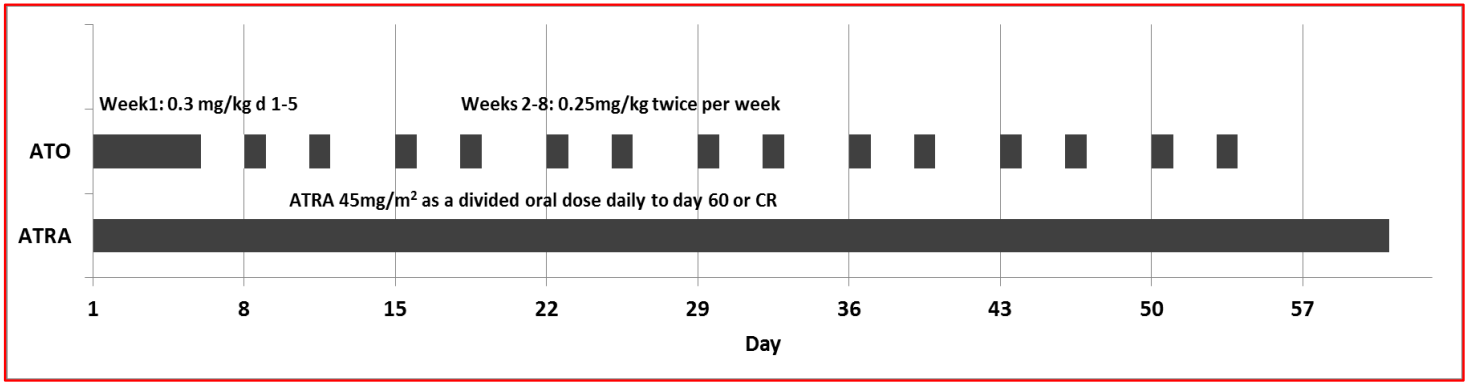
Total of 63 days of ATO

High risk patients received Mylotarg within the first 4 days of induction (6mg/m^2)

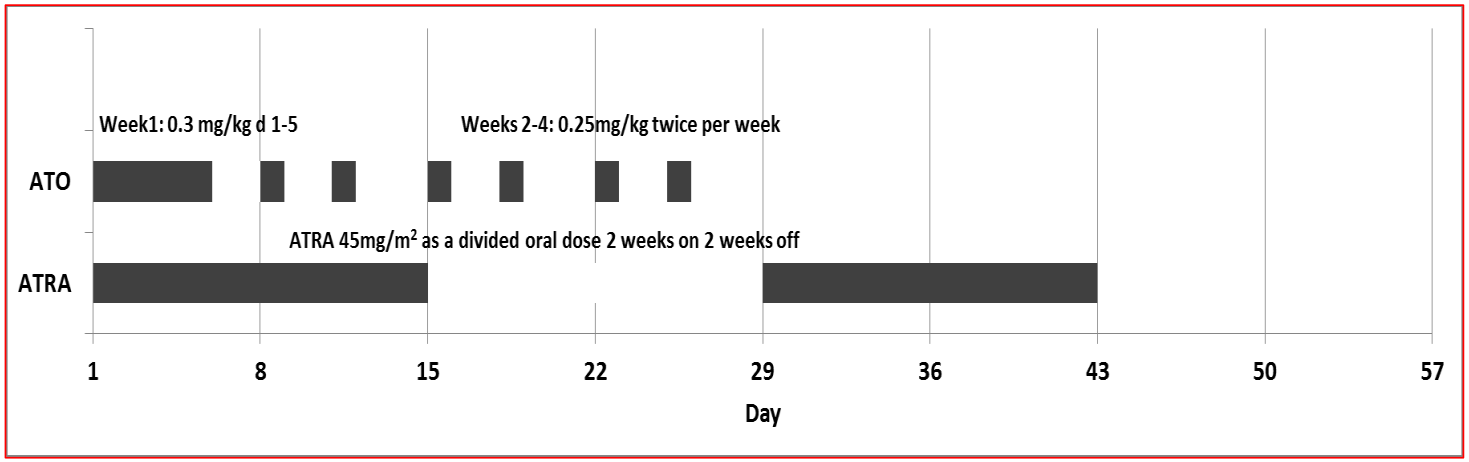
Provision was made for relapse post AIDA to receive the same schedule of ATO

AML17: ATRA + ATO Schedule

Induction

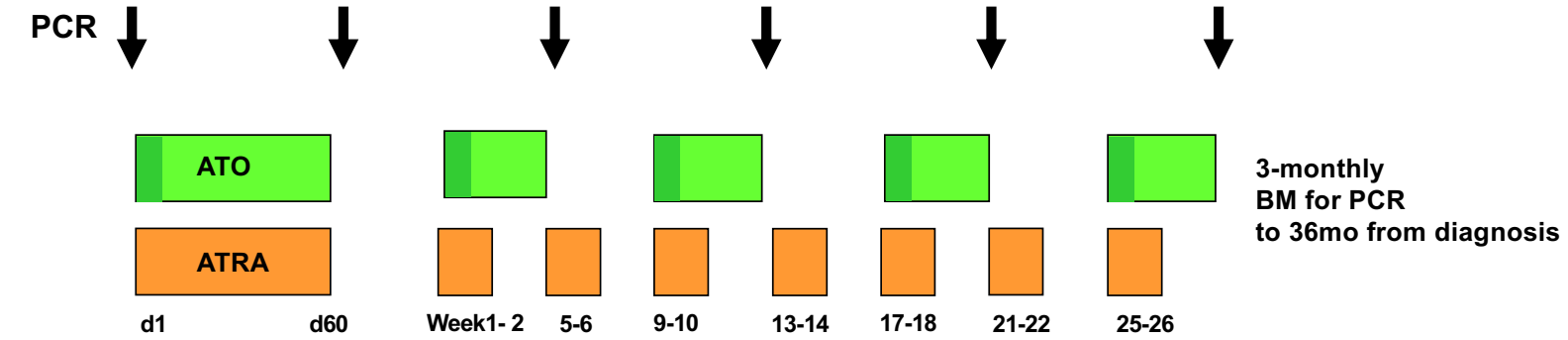


Consolidation

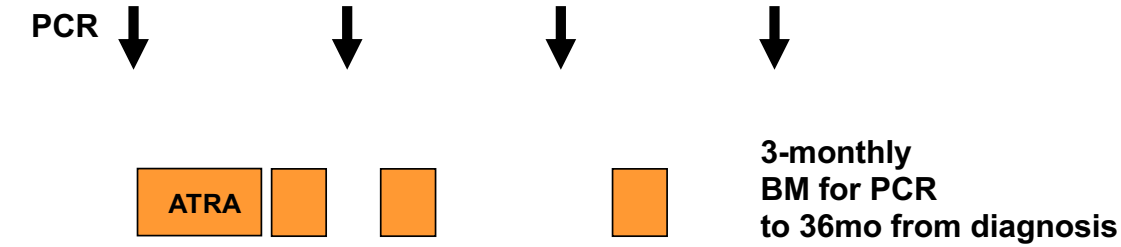


Strict Centralised MRD monitoring to guide treatment in NCRI AML17 trial

ATO-ATRA



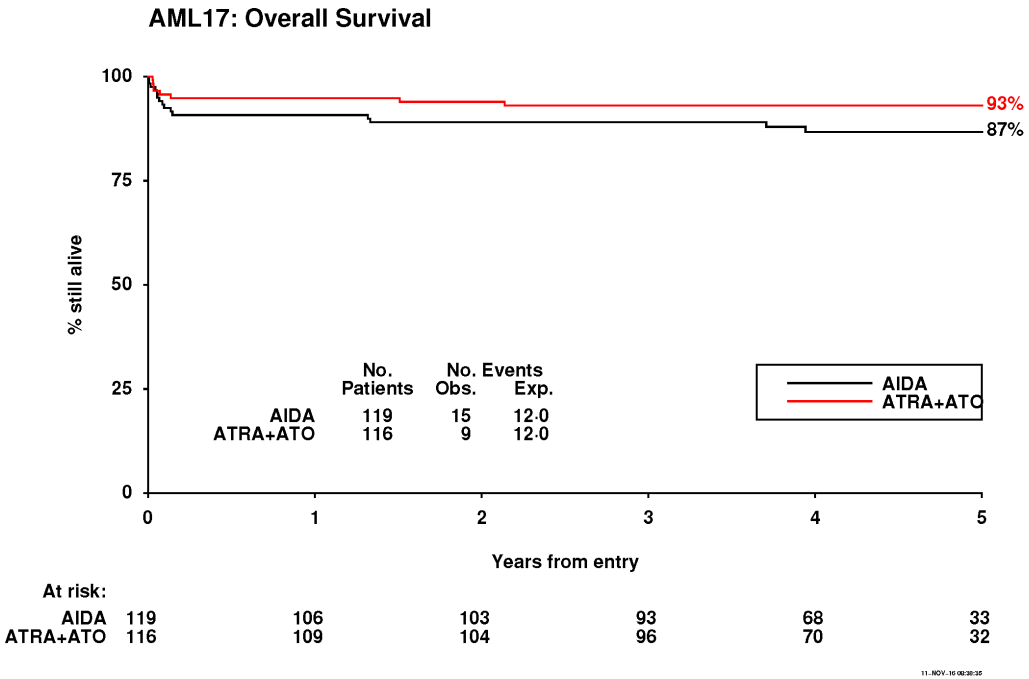
AIDA



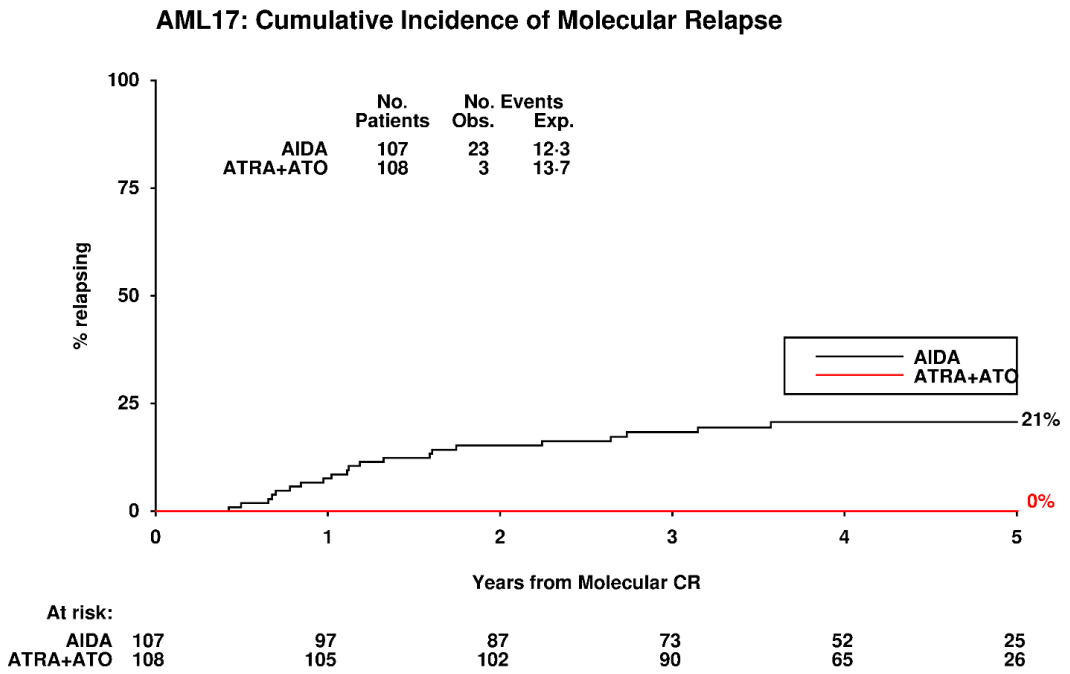
AML 17 APL Randomisation: Outcomes

Outcome	AIDA	ATRA+ATO	HR/OR & CI	p-value
CR	91%	96%	0.46 (0.17-1.27)	0.13
Molecular negativity	90%	93%	0.67 (0.27-1.66)	0.4
30-day mortality	6%	4%	0.72 (0.23-2.31)	0.6
Resistant disease	3%	0%	0.14 (0.02-0.97)	0.05
60-day mortality	9%	5%	0.55 (0.21-1.43)	0.2
5-year survival	87%	93%	0.61 (0.27-1.35)	0.2
5-year EFS	79%	93%	0.38 (0.19-0.77)	0.007
5-year Frank RFS	87%	97%	0.33 (0.13-0.85)	0.02
5-year Molecular RFS*	77%	98%	0.19 (0.09-0.41)	<.0001
5-year CIDCR	2%	2%	1.72 (0.18-16.6)	0.6
5-year CIHR	10%	1%	0.16 (0.05-0.48)	0.001
5-year CIMR*	21%	0%	0.12 (0.05-0.30)	<.0001
5-year CITAML	1%	0%	0.15 (0.003-7.48)	0.3

Overall Survival



Cumulative Incidence of Molecular Relapse



AML17 Scheduling of ATO patients relapsing post AIDA

- In AML17 a total of 189 patients were treated with AIDA
- 30 patients relapsed following AIDA therapy (including 5 with CNS disease)
- 1 patient died in relapse before any salvage could be initiated
- 29 patients were treated with the same attenuated ATO+ATRA schedule
- 18 were treated at molecular relapse, reflecting the value of centralized MRD monitoring
- **All 29 treated patients achieved molecular CR post ATO+ATRA**

Russell et al. Blood 132,13 (2018):

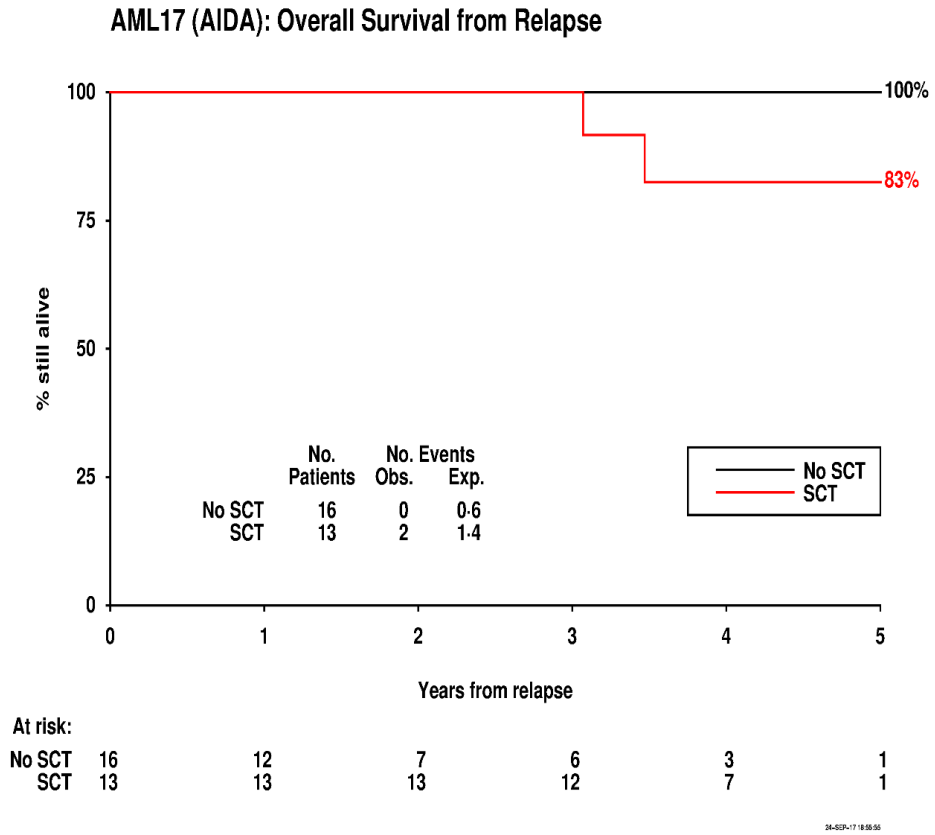
Survival after ATO/ATRA salvage in AML17

- Of the 29 patients 13 were transplanted in molecular remission (10 autograft, 3 allograft) including 4 of the 5 patients with CNS disease
- 16 patients were treated with a full course (induction plus 4 consolidation) of ATO/ATRA alone without chemotherapy
- 3/16 patients had a second molecular relapse after ATO + ATRA salvage (1 later transplanted and 2 not transplanted)
- All patients treated with ATO/ATRA alone remain alive

Russell et al. Blood 132,13 (2018):

AML17. Survival after relapse (n=29)

18/29 treated at molecular relapse All 29 patients became MRD-

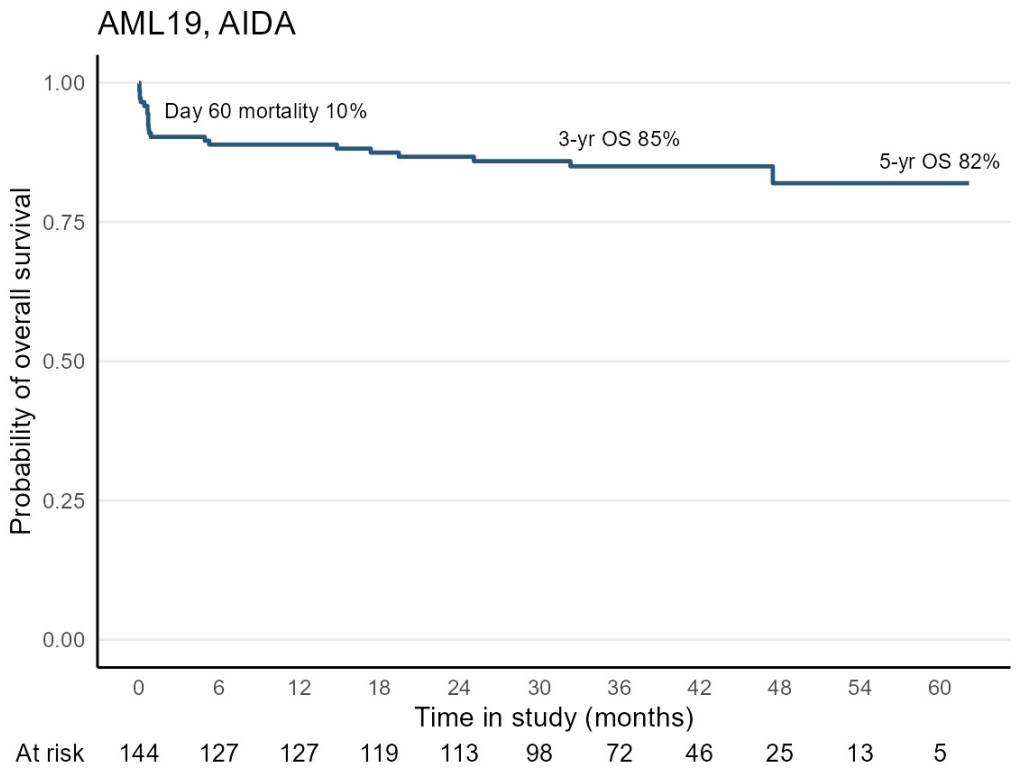


Russell et al. Blood 132,13 (2018):

Post AML17 APL in UK

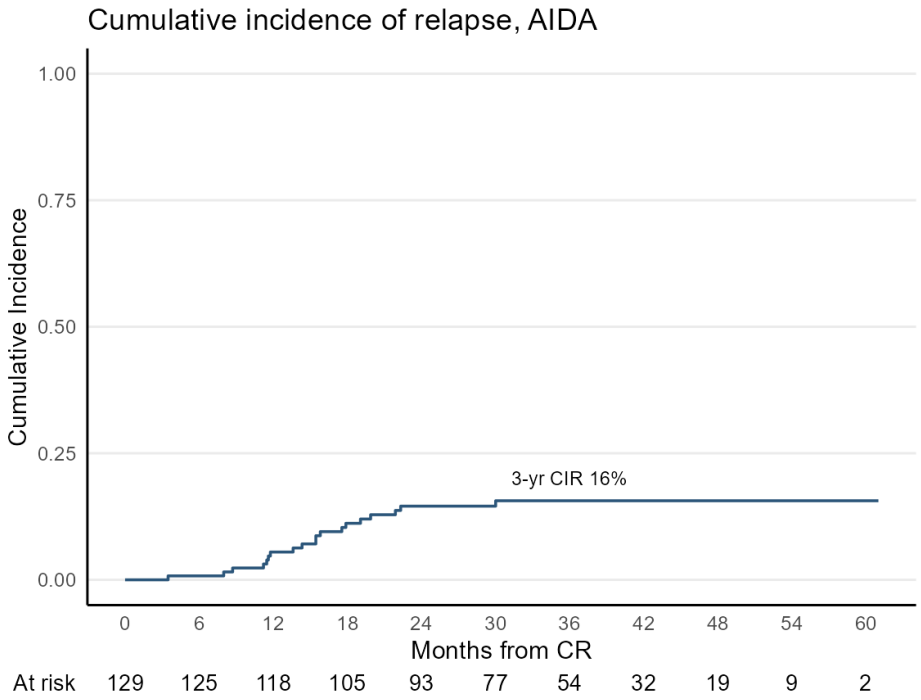
- Following closure of the AML17 trial ATO was not available for front line treatment until NICE approval in June 2018
- In the interim APL patients could be registered on the AML19 trial and receive AIDA as first line therapy
- 146 patients were registered
- 44 (25%) had a WCC >10 which was comparable to 24% with high risk disease in AML17
- ATO only available only for relapse

AML19 AIDA pre ATO approval



Russell and Othman 2024 unpublished

AML19. AIDA. Relapse



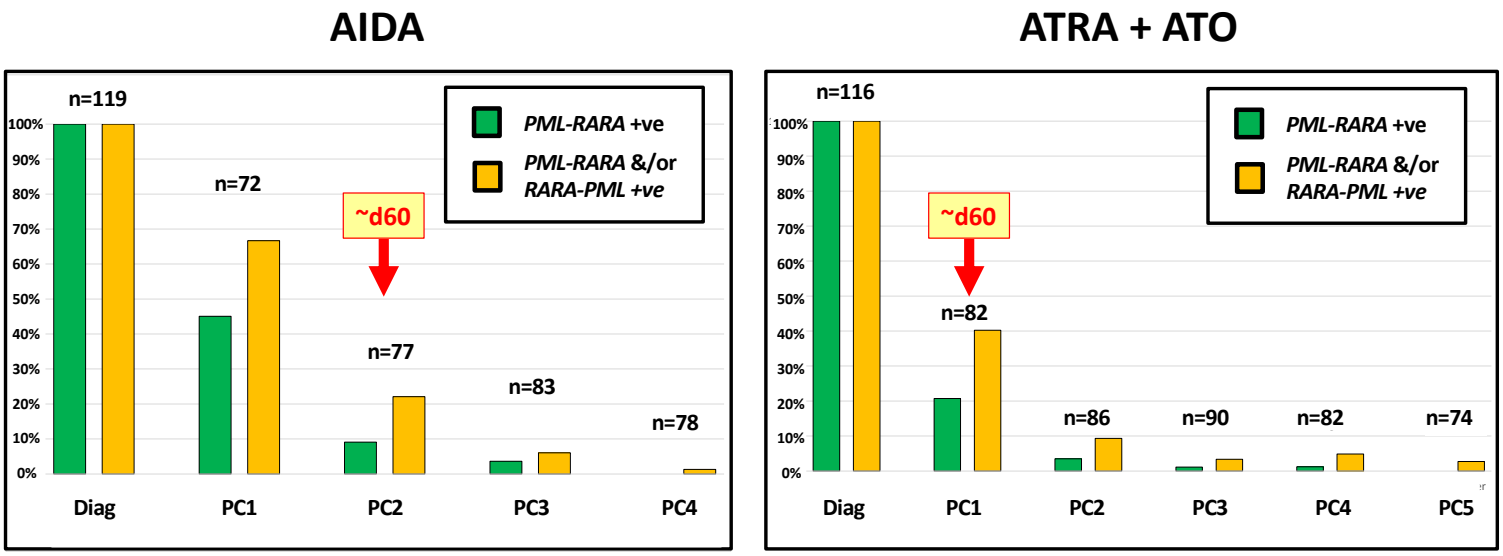
NICE ATO approval

- ATO approved by NICE and reimbursed for low and intermediate risk APL as first line therapy (June 2018.)
- All patients in the UK in these groups are now treated with ATO/ATRA
- Although both AML17 schedule and GIMEMA-AMLSG-SAL schedule were approved for funding the AML17 schedule is universally used.
- NICE also approved ATO for relapsed or refractory APL following first line treatment with chemotherapy.
- Refractory APL was not defined so has been variably interpreted to include persisting MRD positivity during or following AIDA

NCRI AML17: Kinetics of molecular response to AIDA and ATRA/ATO protocols

Median time to molecular remission: AIDA 83 days, ATO+ATRA 111days (p=0.06)

60-day PCR negativity: AIDA 73%, ATO+ATRA 56% (p=0.03).



High Risk APL in the UK

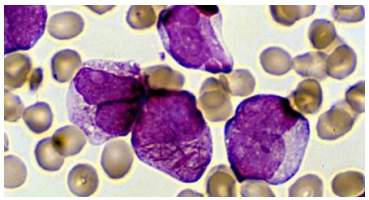
- Currently ATO not routinely approved or reimbursed although some local approval has been given for high risk patients in special situations (t-APL, older patients) on an ad-hoc basis
- High risk APL usually treated with AIDA.
- Recent (May 2020) NICE guidance for COVID precautions permitted ATO consolidation after initial 1st course of AIDA induction.
- Possibility that ATO will be approved for high risk APL including paediatric APL

Proposed APL Study

OVATION 👏

A randomised comparison of **O**ral and intra**V**enous **A**rsenic **T**r**IO**xide consolidation therapy i**N** acute promyelocytic leukaemia

Steve Knapper / Richard Dillon

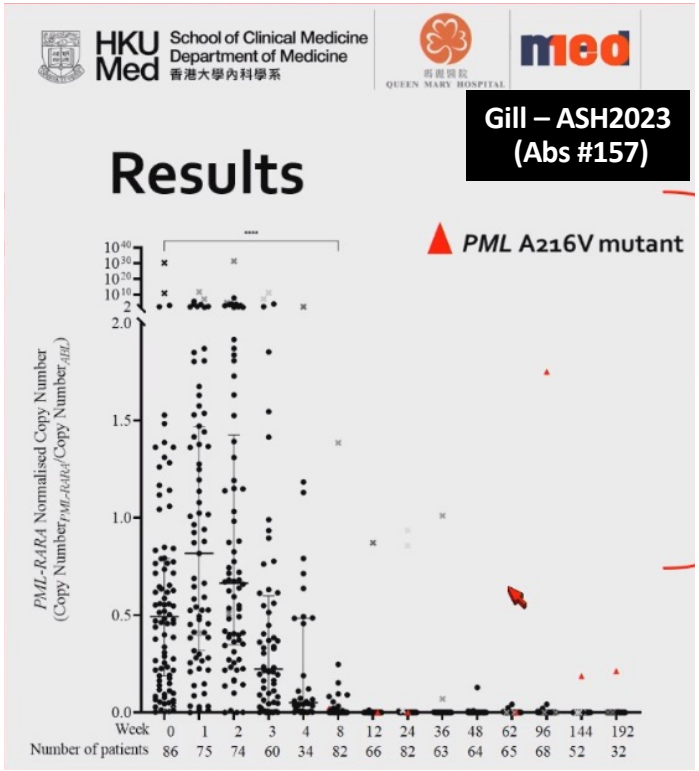


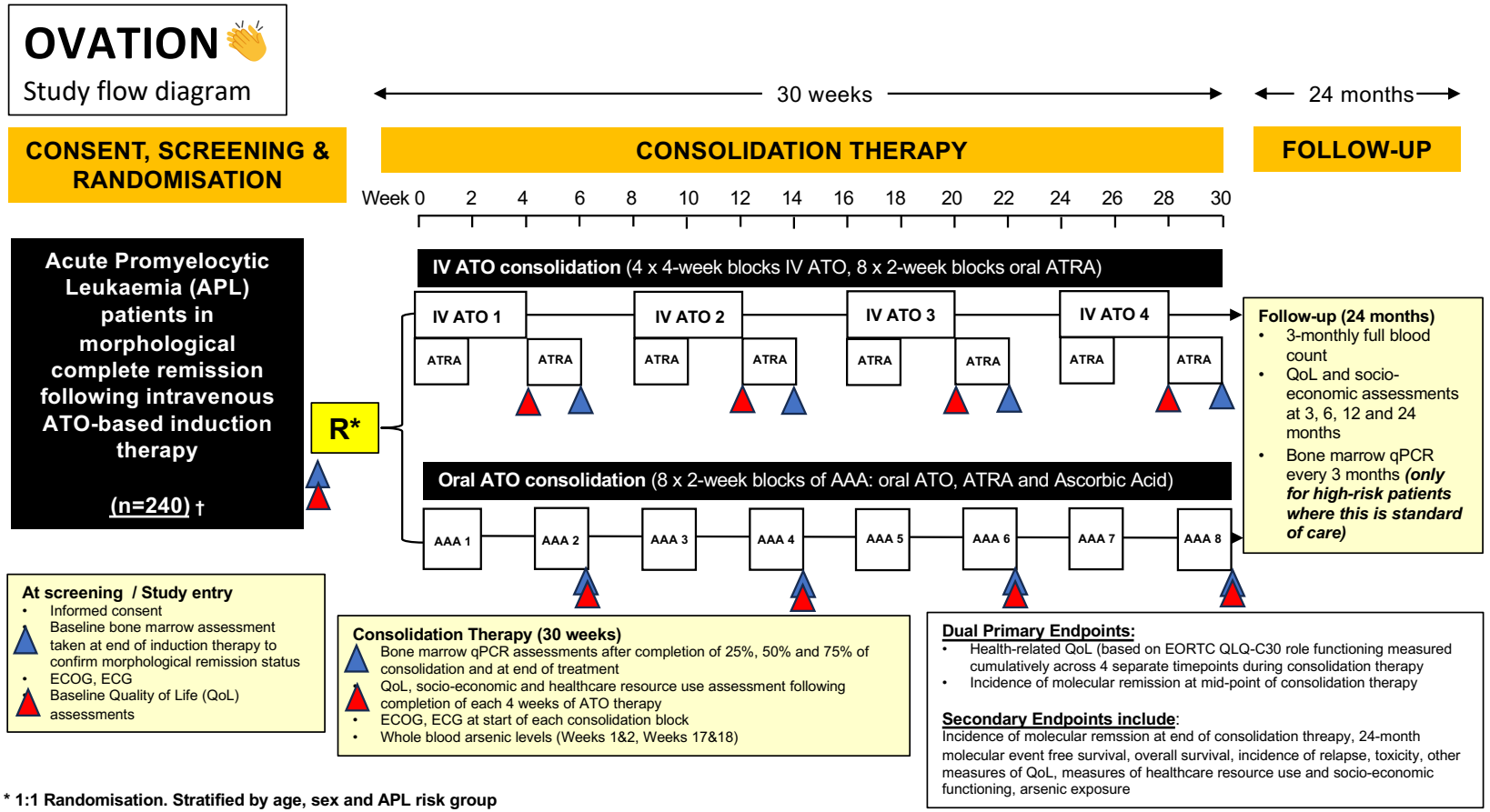
Oral Arsenic Trioxide

- Patented by Hong Kong University
- Systemic bioavailability similar to IV ATO

<u>Evaluation to date in</u>:

- APL at 1st relapse (n=73): 100% molecular CR2
- As maintenance following 1st line Chemo+ATRA (n=129)
- As front-line induction in combination with daunorubicin/ATRA (n=62)
- Front-line schedule with no or minimal chemotherapy (n=114; 5 paeds, 90 standard risk/24 high risk)
  - all achieved CR
  - 100% MRD negative at end of consolidation
  - 97% 3-year OS and RFS

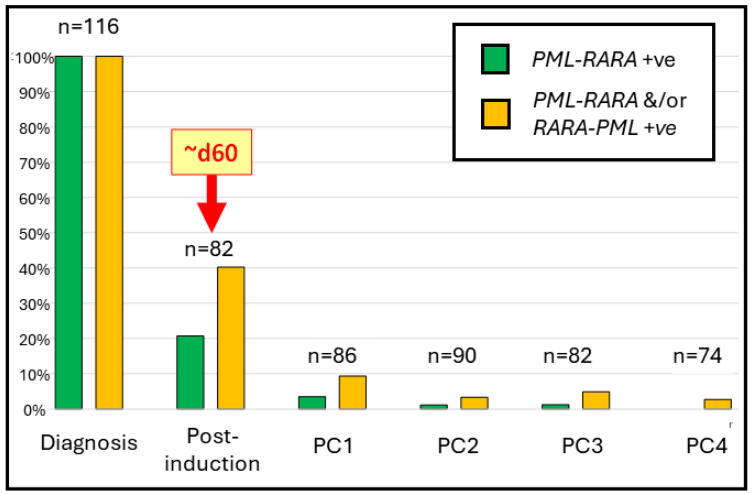




*** 1:1 Randomisation. Stratified by age, sex and APL risk group**

† Allows for 10% dropout rate (n=216 required for primary endpoint analysis) + 9-12 additional paediatric APL patients

Fig 3: Kinetics of molecular response for APL patients receiving IV ATO with ATRA in the previous NCRI AML17 Trial



Bone marrow assessments were taken at baseline and following each cycle of IV ATO therapy

Histogram illustrates % of assessed patients with residual *PML/RARA or RARA/PML* positivity at each timepoint

- 'Diagnosis' = point of APL diagnosis (AML17 trial entry)
- 'Post-induction' = end of ATO/ATRA induction (this will equate to the point of entry to the OVATION study)
- 'PC1' = end of 1st consolidation IV ATO block
- 'PC2' = end of 2nd consolidation IV ATO block (this will be the point of primary endpoint analysis of non-inferiority of molecular response with PO ATO in OVATION)
- 'PC3' = end of 3rd consolidation IV ATO block
- 'PC4' = end of 4th consolidation IV ATO block (end of therapy)

In AML17:

- 60-day PCR negativity: 56%
- Post-consolidation cycle 2 PCR negativity: 97%

from Burnett AK et al, Lancet Oncology. 2015; 16(13): 1295-1305