AC220 (Quizartinib) Can Be Safely Combined With Conventional Chemotherapy In Older Patients With Newly Diagnosed Acute Myeloid Leukaemia: Experience From The AML18 Pilot Trial

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LEUKAEMIA & LYMPHOMA RESEARCH

Beating Blood Cancers

ECMC

AC220 (Quizartinib)

- A novel second generation Class lll tyrosine kinase inhibitor
- Potent FLT3 inhibitory activity in mutated and un-mutated AML perhaps mediated through an active metabolite AC886
- High response rate as monotherapy in relapsed FLT3 mutated (46%) or un-mutated (32%) AML

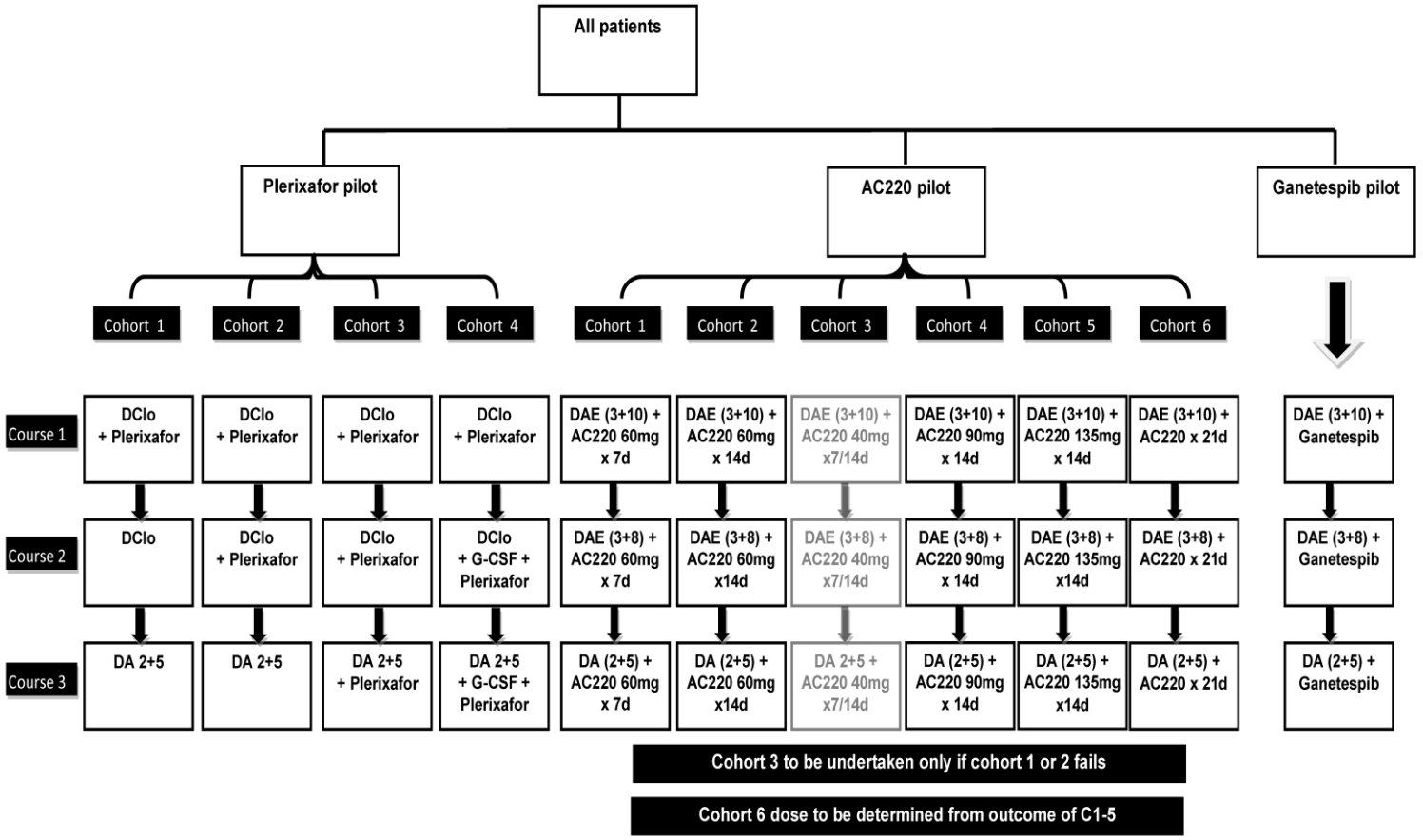
  * Cortes et al, Blood (ASH Abstract) 2012 120: Abstract 48

- KIT inhibitory activity at higher dose levels

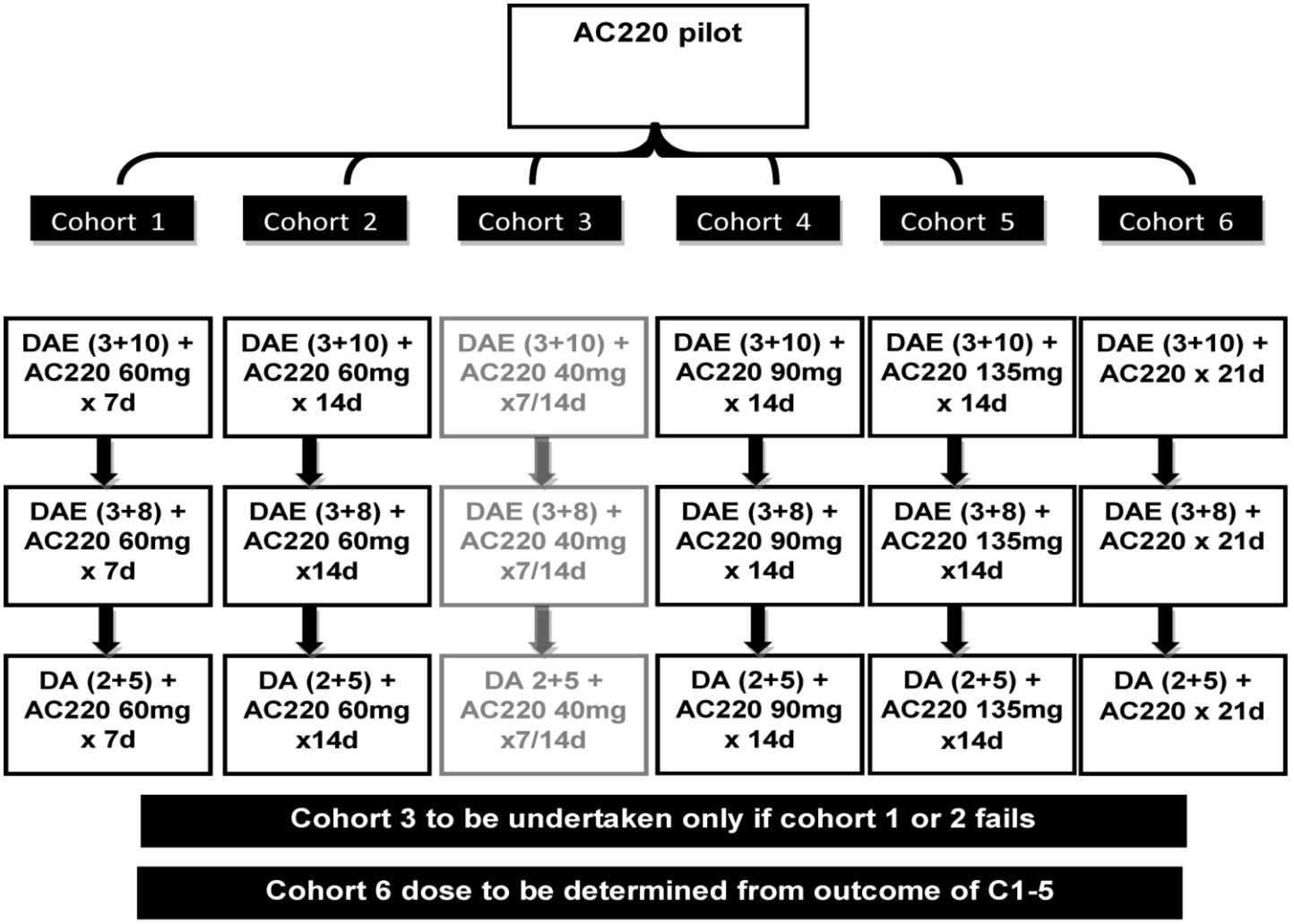
AC220 (Quizartinib): BUT

- Asymptomatic QTc prolongation at higher doses.
- The clinical responses seen are mostly CRi raising concerns about myelosuppression.

AML18 Pilot Design

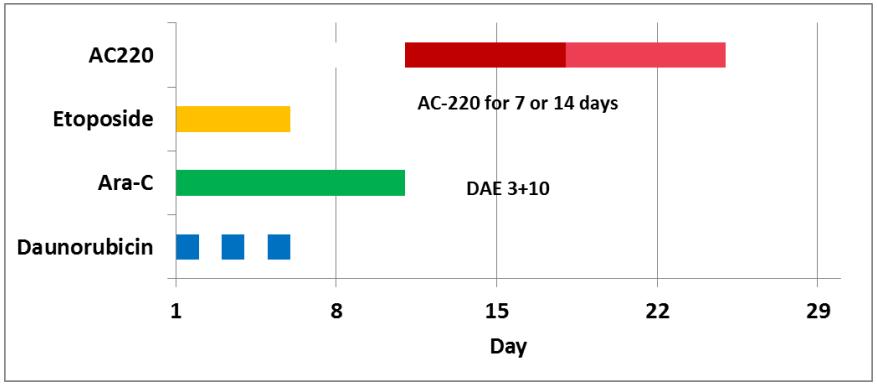


AML18 Pilot Trial: AC220

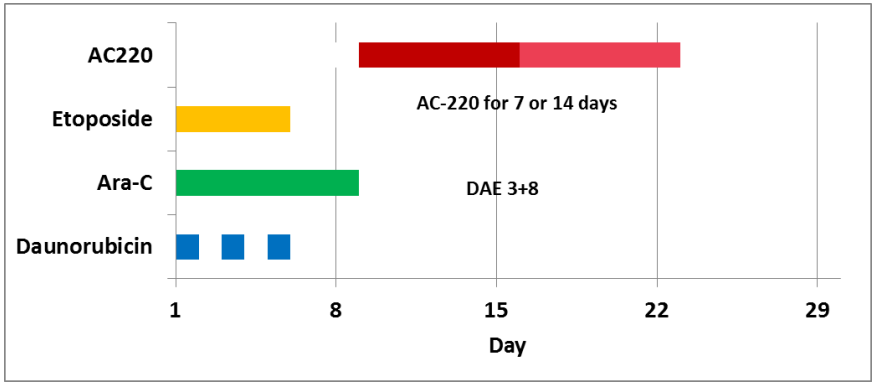


AML18 Pilot Schedule

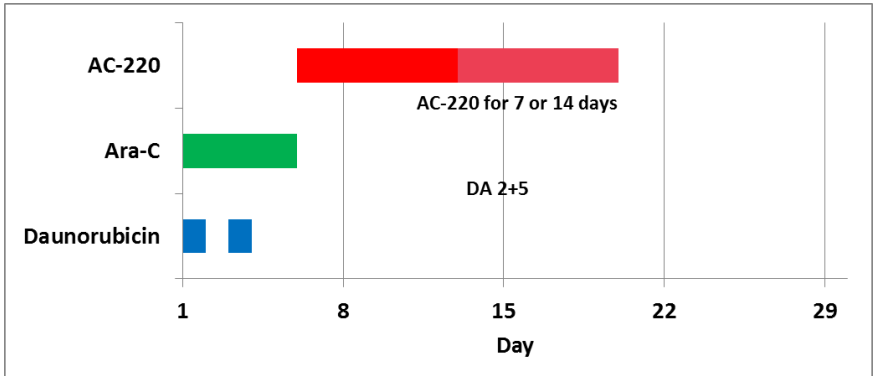
Course 1



Course 2



Course 3



Pilot rules

- Based on a 3 + 3 design
- If 1 DLT is seen, expand cohort to 6, and require no more than 2/6 DLTs for progression to next cohort
- Each cohort was assessed separately for men and women, because of differential QTc susceptibility in females.
- Allow for patients to drop out and be non-evaluable, cohorts over-recruited
- Patients who did not receive any AC220 are deemed not evaluable for toxicity or outcome

Definition of a DLT

- death within 30 days
- grade 4 non-haem toxicity (excl. fatigue, nausea, diarrhoea, alopecia, myalgia, arthralgia) or grade 3 failing to resolve in 7 days
- failure to recover counts in 42 days from ***end*** of course

Inclusion/ Exclusion

Inclusion:

- Untreated WHO defined AML or RAEB-2/ >60 years
- Creatinine/ bilirubin < 1.5xULN
- AST, ALT <2.5xULN

Inclusion/ Exclusion

Exclusion:

- Uncontrolled angina or MI within 12 months
- NYHA class 3 or 4 CHF unless LVEF >45%
- Congenital long QT synd. /significant ventricular arrhythmia or heart rate <50/m.
- $2^{nd}/3^{rd}$ heart block unless pacemaker
- QTcF >450ms pre-entry

Recruitment

- A total of 55 patients were recruited between 1 September 2011 and 29 April 2013
- 48 evaluable patients = exposed to AC220
- There were 11 recruiting centres
- Median age is 69 years (range 62-75)
- Follow-up is complete to end July 2013

Males: Cohort 1 60mg for 7 days

Number recruited	Number evaluable	Demographics	DLTs (details)
4	4	Median age 67 (62-74)	0
		Secondary n=1	
		Intermediate cytogenetics n=4	
		WHO >2 n=0	

Summary conclusion: proceed to cohort 2 ✓

Males: Cohort 2 60mg for 14 days

Number recruited	Number evaluable	Demographics	DLTs (details)
8	7	Median age 69 (64-76)	4
		Secondary n=2	Grade 3 QTC (n=3)
		Intermediate cytogenetics n=5	Grade 3 loss of
			appetite
		Unknown cytogenetics n=3	
		WHO >2 n=0	

Summary conclusion: proceed to cohort 3

Males: Cohort 3 40mg for 7 days

Number recruited	Number evaluable	Demographics	DLTs (details)
11	9	Median age 69 (66-76)	0
		Secondary n=1	
		Intermediate cytogenetics n=7	
		Adverse cytogenetics n=1	
		Unknown cytogenetics n=3	
		WHO >2 n=0	

Summary conclusion: proceed to cohort 3 for 14 days

Males: Cohort 3 40mg for 14 days

Number recruited	Number evaluable	Demographics	DLTs (details)
5	5	Median age 65 (64-75)	1
		Secondary n=0	Failure to recover
		Intermediate cytogenetics n=4	neutrophils
		Unknown cytogenetics n=1	
		WHO >2 n=0	

Summary conclusion: schedule acceptable ✓

Females: Cohort 1 60mg for 7 days

Number recruited	Number evaluable	Demographics	DLTs (details)
9	8	Median age 69 (64-87)	3
		Secondary n=1	Grade 4 MI
		Intermediate cytogenetics n=6	Grade 4
			Hypokalaemia
		Unknown cytogenetics n=3	Grade 4 oral
		WHO >2 n=1	

Summary conclusion: proceed to Cohort 3

Females: Cohort 3 40mg for 7 days

Number recruited	Number evaluable	Demographics	DLTs (details)
9	9	Median age 69 (62-79)	2
		Secondary n=0	Grade 4
		Intermediate cytogenetics n=4	pulmonary
			Grade 3 lung
		Unknown cytogenetics n=1	infection
		WHO >2 n=0	

Summary conclusion: proceed to Cohort 3 for 14 days ✓

Females: Cohort 3 40mg for 14 days

Number recruited	Number evaluable	Demographics	DLTs (details)
9	8	Median age 69 (63-75)	0
		Secondary n=1	
		Intermediate cytogenetics n=5	
		Unknown cytogenetics n=4	
		WHO >2 n=0	

Summary conclusion: schedule acceptable ✓

Dose limiting toxicities

Cohort	No of DLTs/ No of patients	Details of DLTs
Males 60mg x 7d	0/3	No DLT
Females 60mg x 7d	3/8	2008: Grade 4 cardiac (MI) 2010: Grade 4 hypokalemia 2019: Grade 4 oral
Males 60mg x 14d	4/7	2012: Grade 3 QTc 2013: Grade 3 loss of appetite 2014: QTc 2021: QTc, leading to withdrawal
Males 40mg x 7d	0/9	No DLT
Females 40mg x 7d	2/7	2022: Grade 4 pulmonary 2027: Grade 3 lung infection
Males 40mg x 14d	1/5	2044: Failure to recover neutrophils
Females 40mg x14d	0/8	No DLT

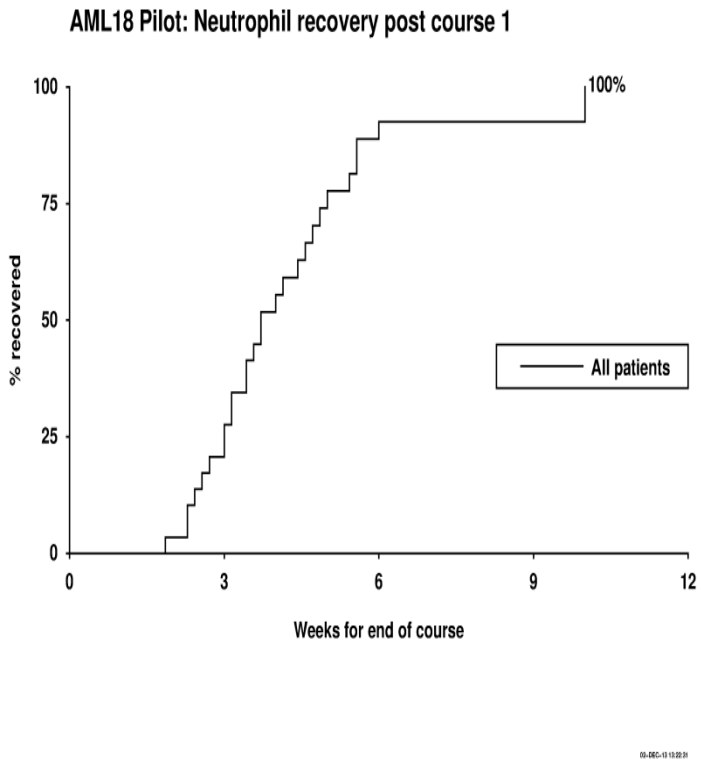
The QTc Issue

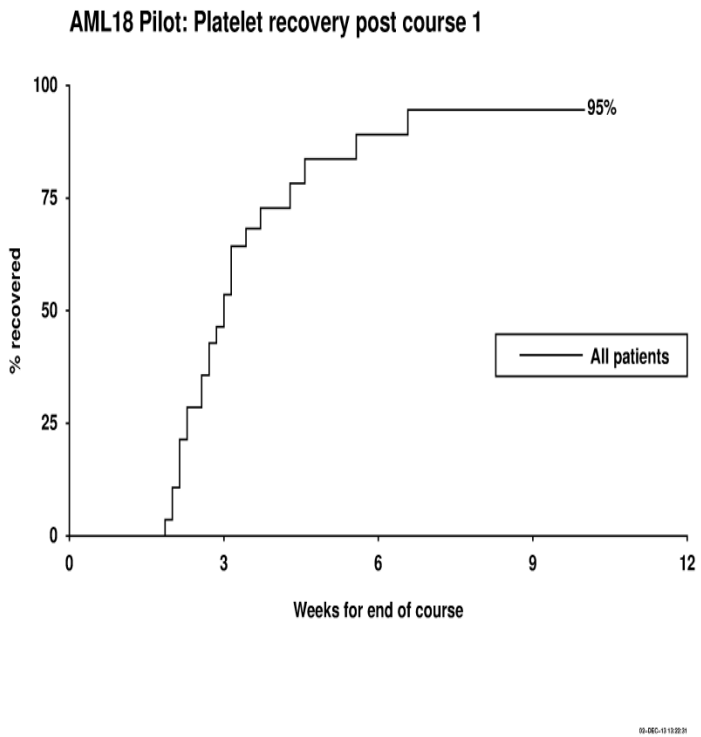
3 of 48 evaluable patients

All in males on 60mg dose level for 14 days:

- Day 7 515/519 ms. +4hrs 500ms. Continued on reduced dose
- Day 9 312 to 462ms. atrial flutter Died of infection
- Day 14 resolved in 24 hrs. Died refractory disease

Count Recovery Issue (CR patients)





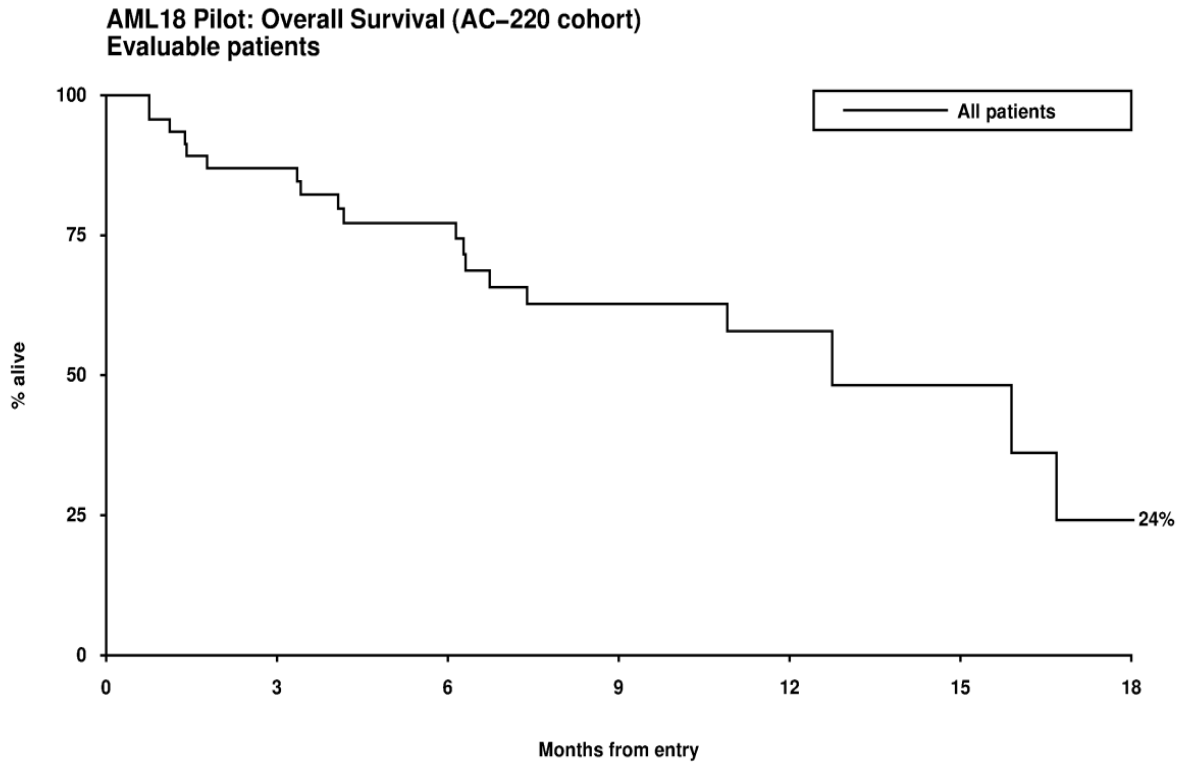
Median recovery: 26 days (neutrophils)

21 days (platelets)

Efficacy Related to FLT-3 Mutation Status

- 31/48(65%) with survival and a marrow assessment for CR
- FLT-3 mutation status is known on 51 patients
  - FLT3-ITD
    - 8/51 patients (16%) had a FLT3-ITD mutation
    - 4/4 assessable patients achieved a CR
  - FLT3 TKD
    - 4/51 patients had TKD mutation (8%)
    - 3/3 assessable patients achieved a CR

Survival outcomes



Median survival 484 days (16 months)
30/48 evaluable patients still alive at last Follow-Up

CONCLUSIONS

- Combining AC220 with standard chemotherapy is feasible in older patients at a dose of 40mg for 14 days.
- Prolongation of QTc (6%) was the most frequent DLT but was asymptomatic and of modest extent.
- The CR rate was at least comparable to expected.
- Neutrophil/platelet regeneration not impaired.
- Schedule will now be incorporated into the NCRI AML18 trial with a maintenance component to assess efficacy

Acknowledgements

- Leukaemia and Lymphoma Research for funding the AML18 Pilot
- Cancer Research UK for funding of Experimental Cancer Centre
- Ambit Biosciences for provision of AC220
- Physicians and research staff of the 11 institutions and patients who participated