NICE National Institute for Health and Care Excellence

PART 1 – for public observers

Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia [ID1225]

– 1st appraisal committee meeting

Lead team presentation - clinical

Lead team: David Chandler, John Hampson, Natalie Hallas

ERG: CRD and CHE, University of York

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31st July 2018

Key issues – clinical effectiveness

- Is standard chemotherapy (3+7 daunorubicin and cytarabine) the appropriate comparator (versus 3+10 days in the UK)?
- What is the treatment decision based upon in clinical practice?
- Are the results from the trial in people aged 60-75 generalisable to adults of all ages?
- Are the results from the trial in a US/Canadian population generalisable to the UK?
- Is liposomal cytarabine and daunorubicin clinically effective?
- Is the follow-up period of the trial long enough to measure long-term post-stem cell transplant overall survival outcomes?

[redacted]

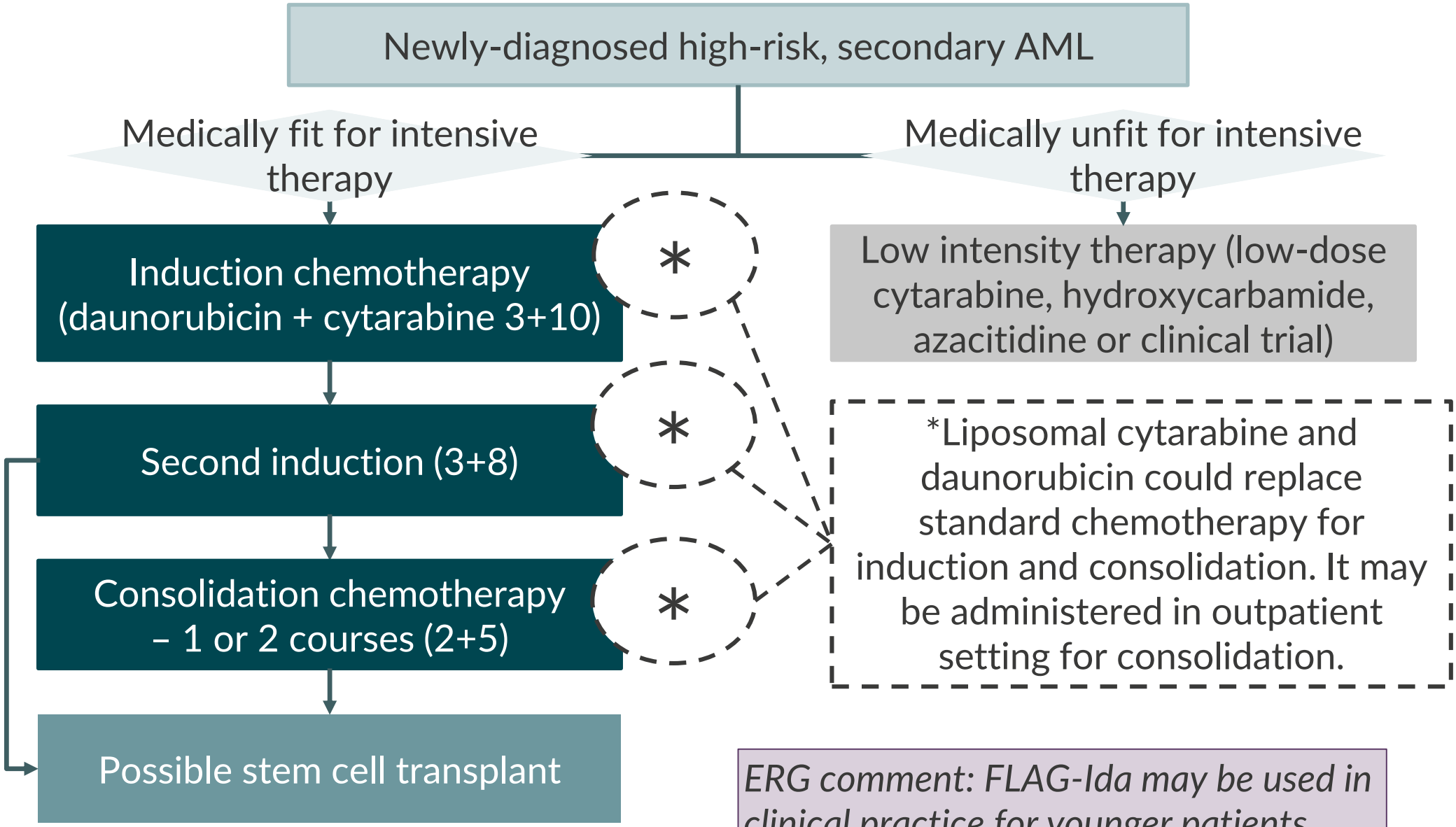
Disease background

2,662 new cases of AML in England in 2015

~25% are t-AML or AML-MRC

- Acute myeloid leukaemia (AML) causes reduced numbers of red blood cells, white blood cells and platelets, leading to an increased risk of bleeding, infection and mortality
- Secondary types of AML
  - Therapy-related AML (t-AML) and
  - AML with myelodysplasia-related changes (AML-MRC)
- These are high risk: poor survival outcomes due to reduced remission and increased relapse rates

UK treatment pathway



ERG comment: FLAG-Ida may be used in clinical practice for younger patients

[redacted]

Patient and professional groups comments*

- People with high risk AML have poor survival (end of life setting)
- Most common symptoms include:
  - Fatigue, feeling weak or breathless, loss of memory and concentration, bleeding and bruising, itching, nausea or vomiting
- Has huge emotional and financial impact, also affecting carers and family
- Bridge to transplant would be welcomed by patients as stem cell transplant is the only curative treatment
- Appears to have a more tolerable toxicity profile, including reduced hair loss
  - Although, higher rates of infection and hypertension reported
- Easier to use than standard chemotherapy
- There has been limited progress in the treatment of AML since the 1990s and there is an urgent need for access to improve treatment options.

* Leukaemia Care, National Cancer Research Institute (NCRI) AML Working Party, The Association of Cancer Physicians, The Royal College of Physicians, The Royal College of Pathologists and The British Society for Haematology

[redacted]

NHS England comments

- No biologically plausible reason why benefit in people aged 60-75 years old would not translate to adults of other ages
- Overall survival data seem immature and therefore long term benefit is uncertain
- Survival model appears optimistic in terms of the chance of long term survival, considering the immaturity of survival data available from the trial
- Lack of quality of life data collection in trial: utility data used instead has not captured the toxicity of treatment, leading to seemingly high utility values for treated patients
- Mortality rates are higher after stem cell transplant than in the general population
- Body surface area used in the model is lower than in the trial – a range of body surface areas should be used

[redacted]

Liposomal cytarabine and daunorubicin

(CPX-351, Vyxeos, Jazz Pharmaceuticals)

EAMS	Received Promising Innovative Medicine designation from the MHRA in Oct 17
CHMP positive opinion (June 2018)	Treatment of adults with newly diagnosed, therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
Mechanism of action	Liposomal cytarabine and daunorubicin is a liposomal delivery system which uses nanoparticle technology. The liposomes are taken up inside the leukaemic cells where they release a fixed molar ratio of 1:5 of daunorubicin: cytarabine.
Administration and dosage	Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2, administered intravenously over 90 minutes on days 1, 3, and 5 for the first course of induction therapy and on days 1 and 3 for subsequent courses of induction therapy, if needed. The recommended dosing schedule for consolidation is daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 administered intravenously over 90 minutes on days 1 and 3.
List price	[redacted] per vial. The company estimates that [redacted] There is a simple discount patient access scheme.

Decision problem [1]

	Final scope issued by NICE	Decision problem in the company's submission	Rationale if different
Population	People with newly diagnosed, high-risk (secondary) AML who are considered to be eligible for intensive therapy	High-risk (secondary) AML is defined by: • Therapy-related AML (t-AML) • AML with myelodysplasia related changes (AML-MRC)	In line with comments from British Society for Haematology (BSH) and diagnostic subgroups in WHO classification
Intervention	Liposomal daunorubicin and cytarabine	No change	N/A
Outcomes	Overall survival Event free survival Disease free survival Remission Health related quality of life Adverse effects of treatments	No change	N/A

Decision problem [2]

	Final scope issued by NICE	Decision problem in the company's submission	Rationale if different
Comparator	• Standard intensive induction and consolidation therapy • Azacitidine (for people who are not eligible for haematopoietic stem cell transplantation and have AML with 20-30% blasts and multilineage dysplasia) (TA218) • Midostaurin* (for people with FLT3-mutation-positive AML) (subject to ongoing NICE appraisal) • Gemtuzumab ozogamicin (subject to ongoing NICE appraisal) *TA523 – published June 2018	Standard intensive induction and consolidation therapy (induction and consolidation with daunorubicin and cytarabine)	• Azacitidine not recommended for people eligible for HSCT; typically used as palliative therapy for people who are older and unfit • Midostaurin* and gemtuzumab ozogamicin are added on to standard intensive chemotherapy, and not currently used in the NHS.

ERG comments on decision problem

Population

- Defining population difficult in practice, particularly *de novo* AML (25% of trial participants) – genetic test results available in 7-10 days: clinicians may begin the first cycle of treatment before receiving results
- Trial in company's submission included people aged 60-75
  - People older than 75 unlikely to be eligible for intensive treatment
  - 20-25% of people with high-risk AML are under 60

Comparators

- Appropriate not to consider azacitidine, midostaurin or gemtuzumab ozogamicin
- 3+10 regimen of daunorubicin+cytarabine is standard treatment in NHS, but reasonable to consider equivalent to 3+7 regimen presented in company submission
- FLAG-Ida may be used as an alternative chemotherapy for younger patients in practice

Key issues for committee

- What is the appropriate comparator?
- What is the treatment decision based upon in clinical practice?

[redacted]

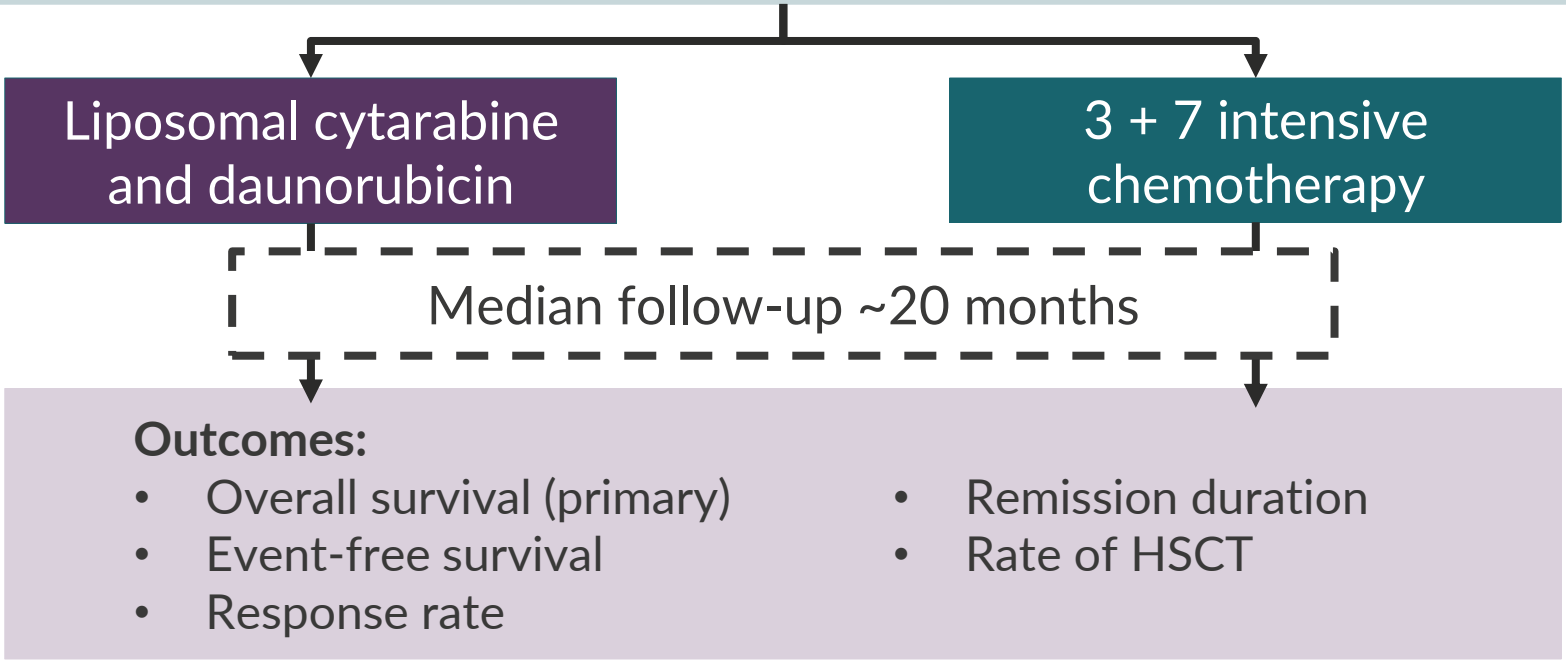
Study 301: (US and Canada, N=309)

Multicentre, open label, randomised, parallel arm, standard therapy, controlled phase 3

Comparator is daunorubicin plus cytarabine, 3+7 (days) (US treatment schedule – UK clinical advisory board supports equivalence with UK 3+10 schedule)

People **aged 60-75** with **high-risk AML** defined as:

- therapy-related AML (t-AML)
- AML with myelodysplastic syndrome (MDS-AML)
- de novo AML with MDS associated karyotypic changes
- chronic myelomonocytic leukaemia (CMMoL-AML)



Outcomes:

- Overall survival (primary)
- Event-free survival
- Response rate
- Remission duration
- Rate of HSCT

Key issue for committee

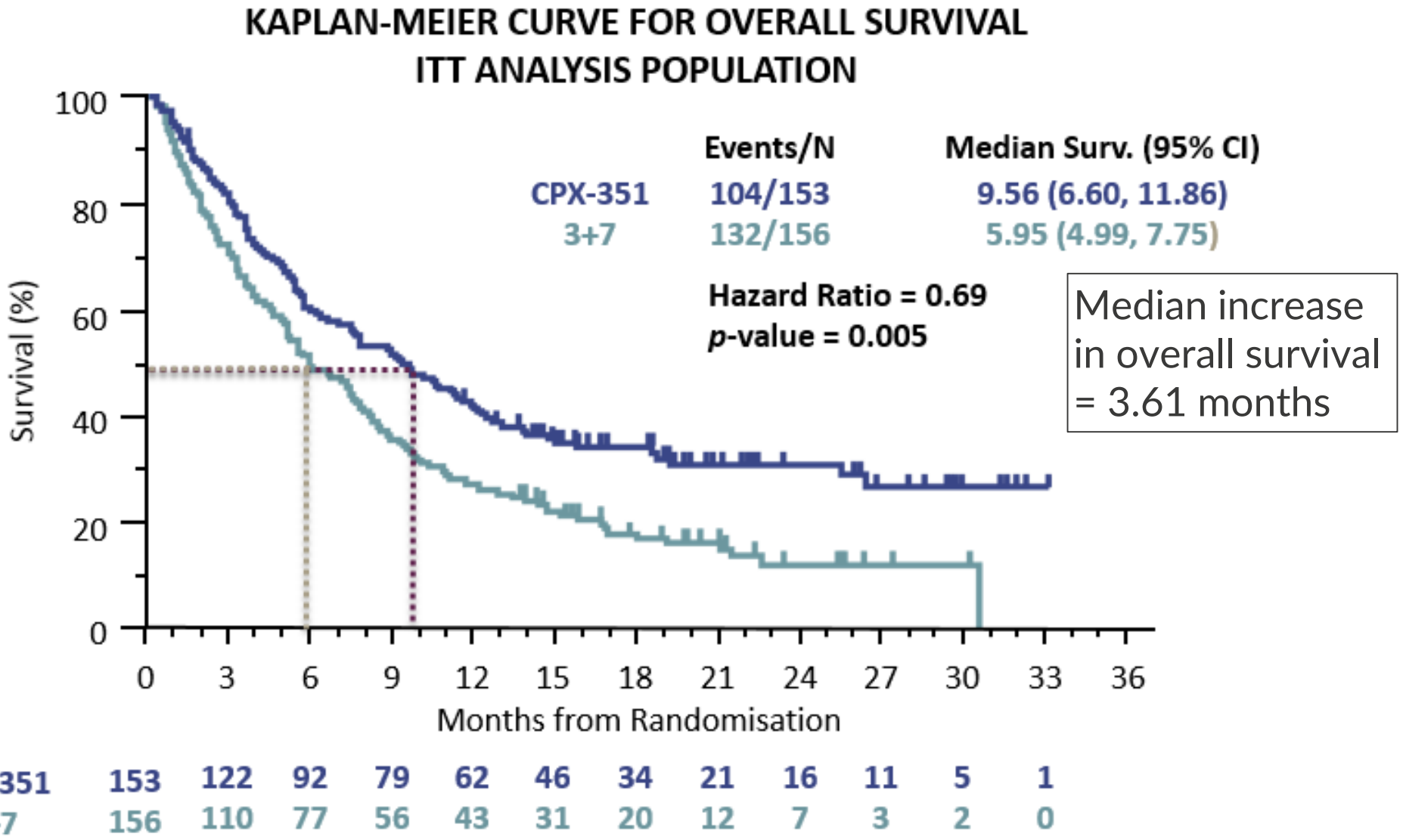
- Are the results from the trial (adults aged 60-75, US/Canadian population) generalisable to the eligible population in NHS clinical practice?

Study 301 baseline characteristics

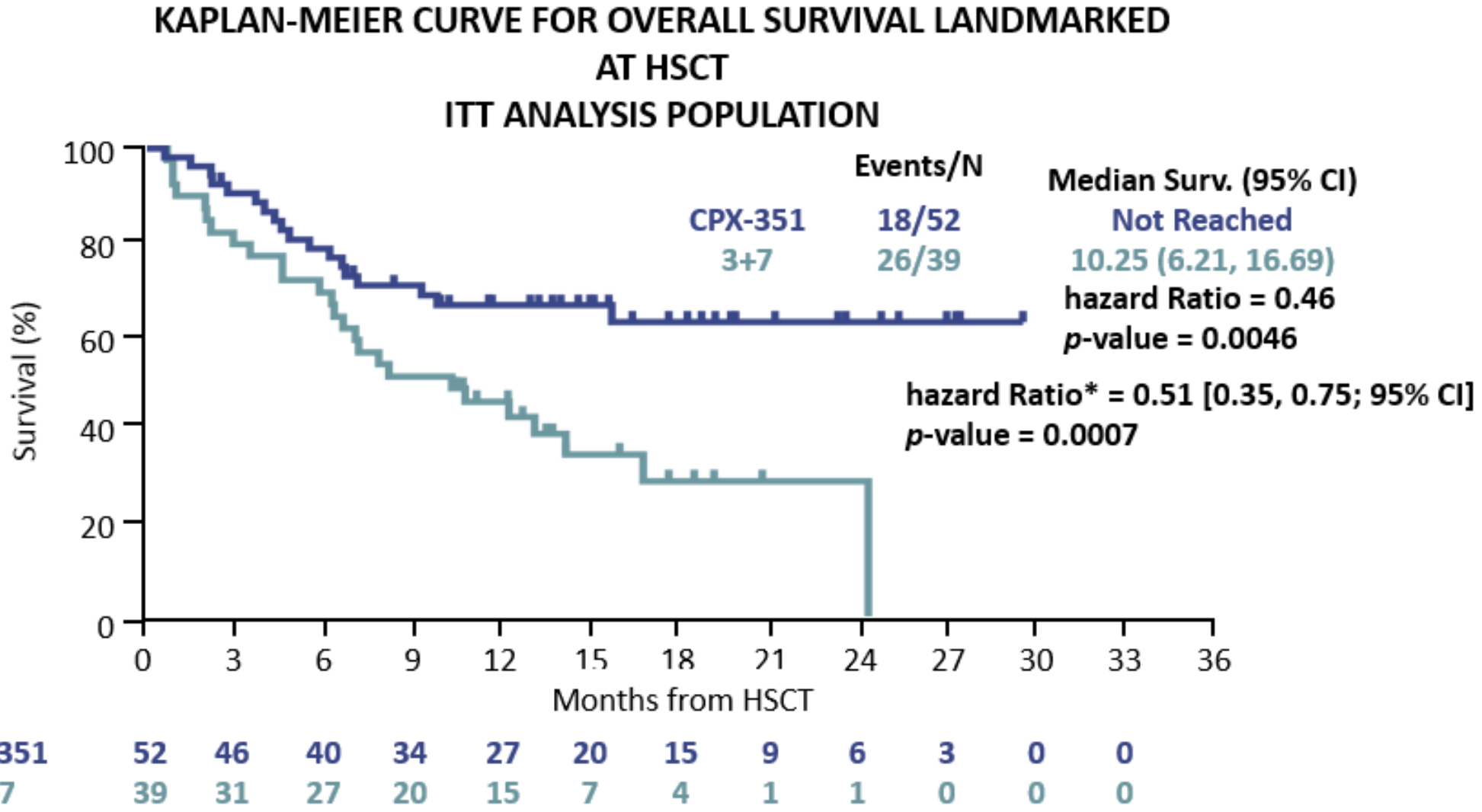
Intention-to-treat (ITT) population (US and Canada)

Characteristic	L. cyt+dauno (n=153)	3+7 (n=156)
Mean age (SD), years	[redacted]	[redacted]
Age, n (%)		
60-69 years	96 (62.7)	102 (65.4)
70-75 years	57 (37.3)	54 (34.6)
Male sex, n (%)	94 (61.4)	96 (61.5)
Race, n (%)		
White	128 (83.6)	139 (89.1)
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
American Indian or Alaska native	[redacted]	[redacted]
Other	[redacted]	[redacted]
Median weight (range), kg	82.0 (49.0, 134.0)	82.7 (46.0, 136.0)
Median height (range), cm	170.2 (149.0, 198.0)	170.2 (149.0, 189.0)
Median BSA (range), m^2	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)
ECOG performance group, n (%)		
PS = 0	37 (24.2)	45 (28.8)
PS = 1	101 (66.0)	89 (57.1)
PS = 2	15 (9.8)	22 (14.1)
PS ≥ 3	0	0

Study 301 results: Overall survival



Study 301 results:
Overall survival from time of HSCT



* HR with transplant as a time-dependent covariate

Study 301 results

Response rate

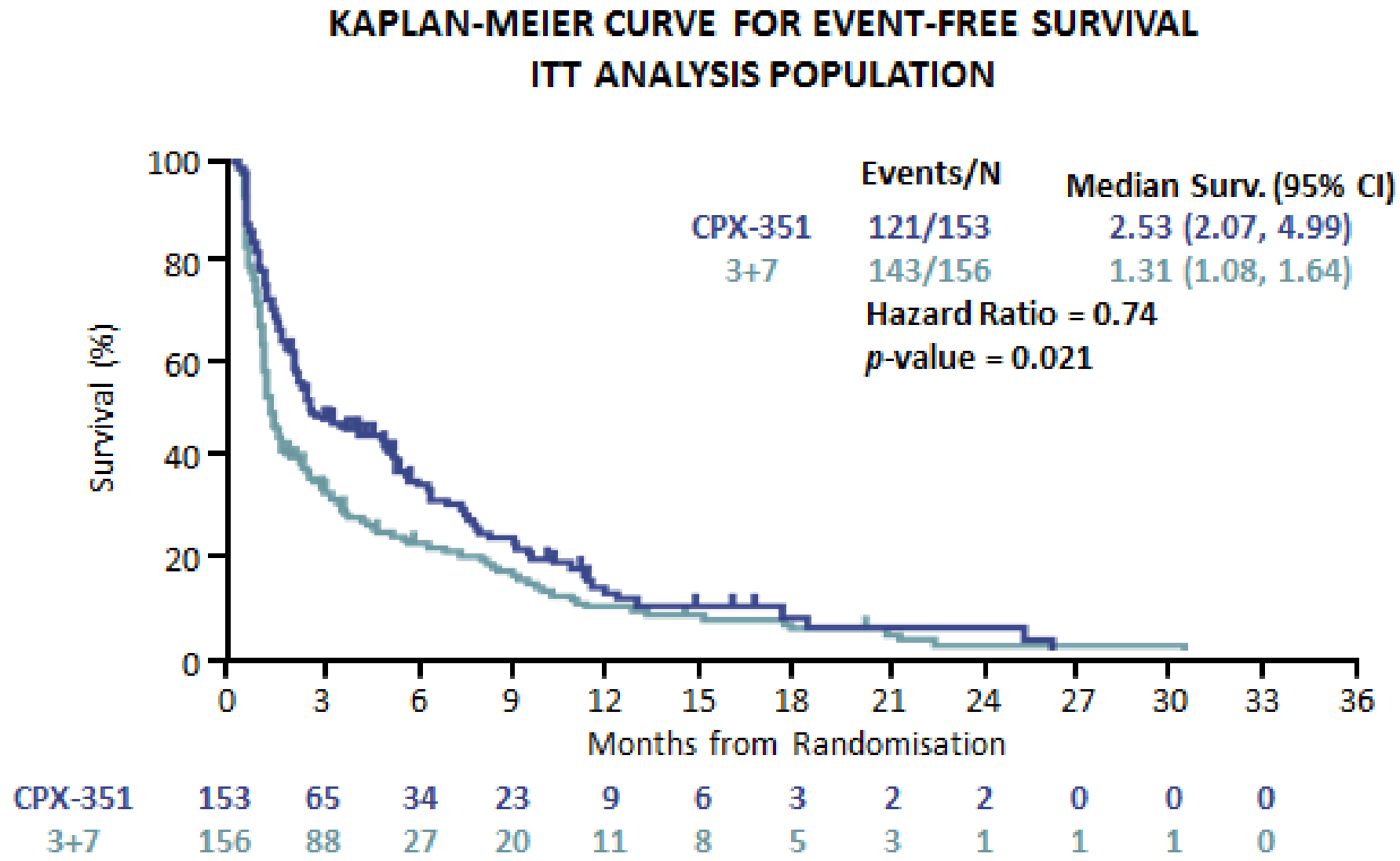
- CR: Complete remission
- CRi: Complete remission with incomplete platelet or neutrophil recovery

Endpoint, n (%)	Liposomal cytarabine and daunorubicin (n=153)	3+7 (n=156)	Odds ratio (95% confidence intervals)
CR+CRi	73 (47.7)	52 (33.3)	1.77 (1.11, 2.81), p=0.016
CR	57 (37.3)	40 (25.6)	1.69 (1.03, 2.78), p=0.040
CRi	16 (10.5)	12 (7.7)	Not reported
No response	80 (52.3)	104 (66.7)	Not reported

Rate of stem cell transplant

	Liposomal cytarabine and daunorubicin (n=153)	3+7 (n=156)	Odds ratio (95% confidence intervals)
Patients having HSCT	52 (34.0%)	39 (25.0%)	1.54 (0.92, 2.56)

Study 301 results: Event-free survival



Study 301 results: Adverse events

Adverse event	Liposomal cytarabine and daunorubicin (n=153)	3+7 (n=151)
	Grade ≥3 (n (%))	Grade ≥3 (n (%))
Febrile neutropenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Bacteraemia	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]

Company stated that adverse reporting to date indicates that there have been [redacted] known deaths in the liposomal cytarabine and daunorubicin group and [redacted] deaths in the 3+7 group since the December 2015 data cut.

[redacted]

ERG comments on Study 301 trial

Trial design and patient characteristics

- Phase 3 multi-centre, appropriately randomised and stratified by age and AML subtype
- Generalisability of results to adults under 60 unknown
- Lack of blinding may lead to risk of bias in subjective outcomes e.g. decision to transplant
- Limited information on selection and characteristics of patients who did not receive HSCT
- Health-related quality of life not collected

Results

- Analysis was based on December 2015 data cut with substantial censoring – trial follow-up stated as 5 years post-randomisation, first patient randomised December 2012
  - median follow-up 20.5 months in liposomal cytarabine and daunorubicin group, 21.2 months in 3+7 group - insufficient for measuring longer term post-HSCT overall survival
- Subgroup analysis by type of AML did not provide evidence that liposomal cytarabine and daunorubicin had beneficial impact on overall survival in patients with MDS with prior HMA (about a third of patients in the trial) (although should be treated with caution due to small numbers)
- Safety profiles of the 2 treatments are comparable
- Uncertainty about long term impact on overall survival, including after stem cell transplant, because of lack of long term follow-up data
- Unclear whether data on relapse after HSCT were systematically collected

Key issues for committee

- Is liposomal cytarabine and daunorubicin clinically effective?
- Is the follow-up period of the trial long enough to measure long-term post-stem cell transplant overall survival outcomes (and link into cost-effectiveness model)?

Key issues – clinical effectiveness

- Is standard chemotherapy (3+7 daunorubicin and cytarabine) the appropriate comparator (versus 3+10 days in the UK)?
- What is the treatment decision based upon in clinical practice?
- Are the results from the trial in people aged 60-75 generalisable to adults of all ages?
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[redacted]