LEUKEMIA2020-2021

ASSOCIAZIONE ITALIANA CONTRO LE LEUCEMIE-LINFOMI E MIELOMA ONLUS

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Practice Changing Treatments

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GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

SIE - Società Italiana di Ematologia

Disclosures

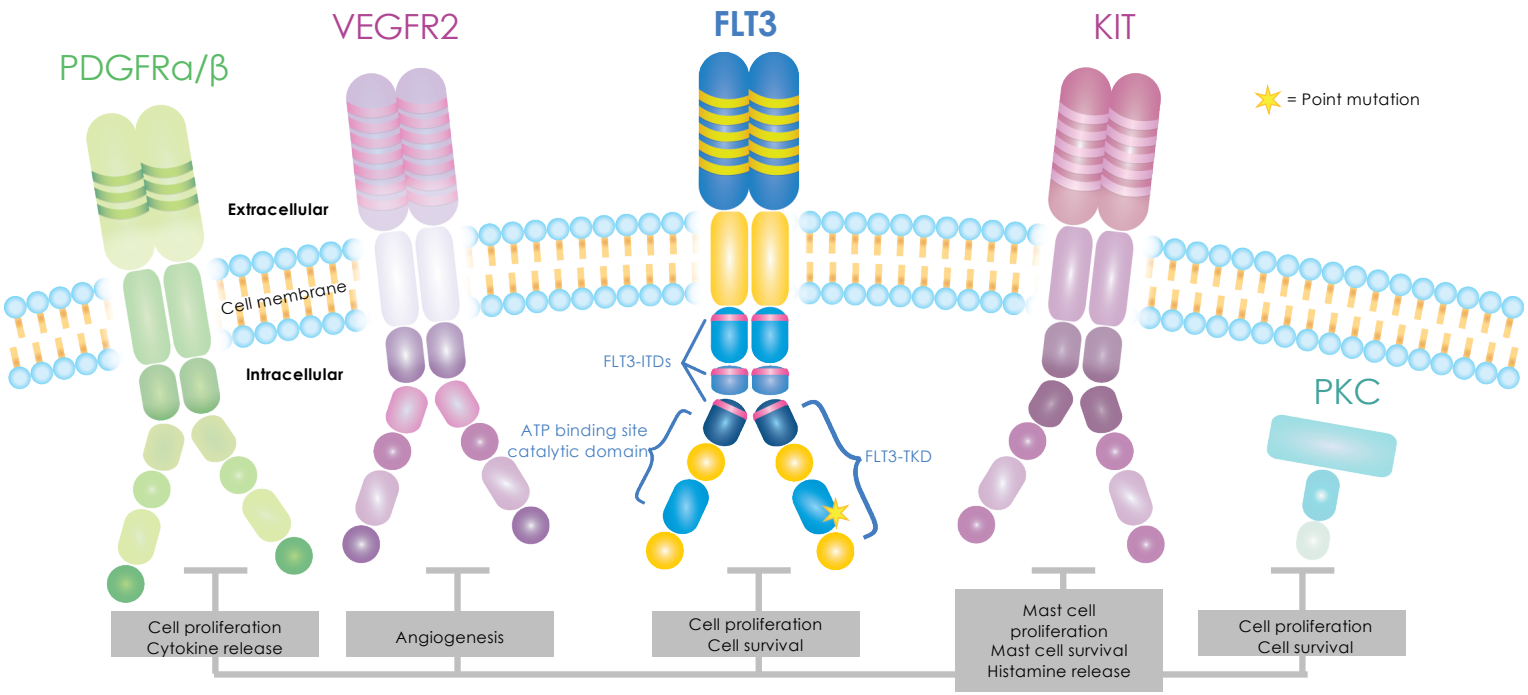
- Pfizer. Research Support, Advisory Board
- Astellas. Speakers Bureau
- Abbvie. Speakers Bureau
- Jazz. Research Support

Practice Changing Treatments

Agents with recent approvals and reimbursement

- **Midostaurin** - standard of care for newly diagnosed *FLT3* mutated AML but not approved as post BMT maintenance in UK
- **Gilteritinib -** for relapsed *FLT3*mut AML. Issues concerning effective deployment
- **Gemtuzumab** Should we use in intermediate risk cytogenetics as well as CBFs? Dosing issues
- **CPX-351**- variable usage in UK. Issues concerning applicability of pivotal randomised trial to younger patients with secondary AML
- ***Venetoclax****- recent approval for emergency use instead of IC during COVID*

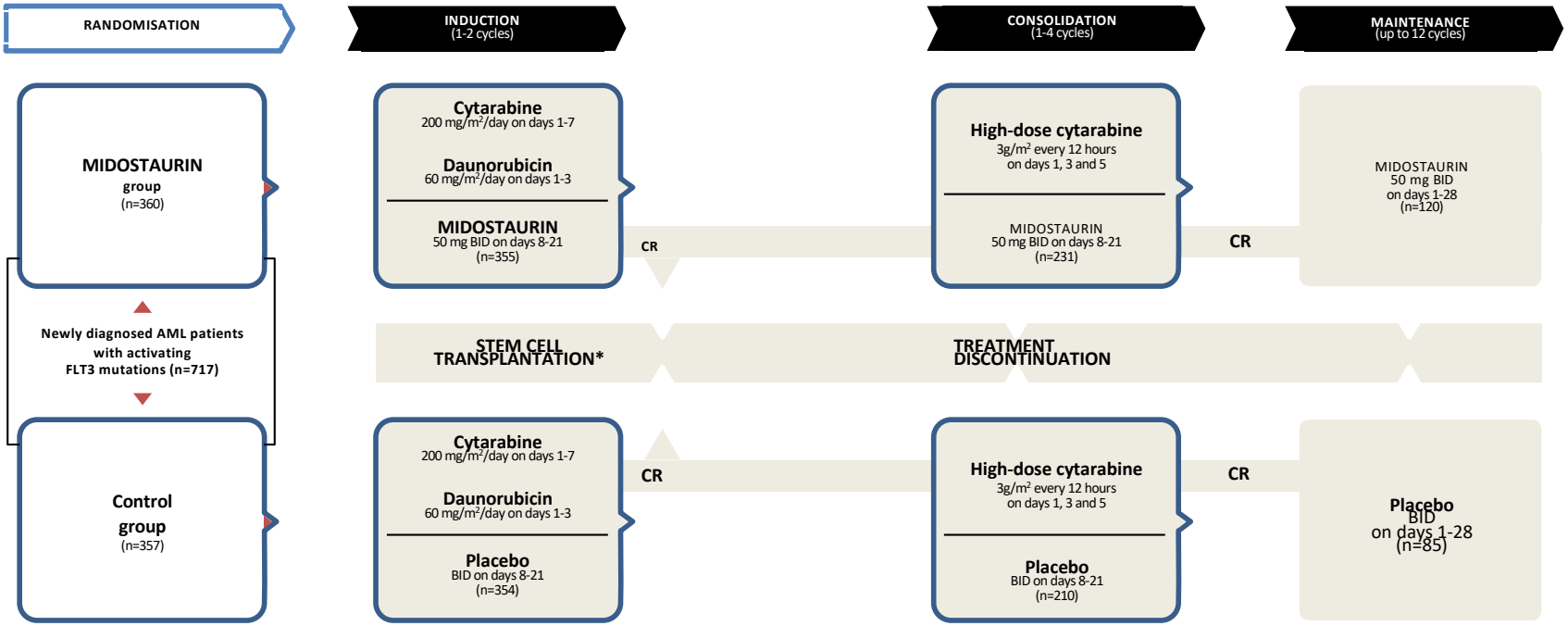
Midostaurin- a multikinase inhibitor



ATP, adenosine triphosphate; FLT3, FMS-like tyrosine kinase-3;
ITD, internal tandem duplication; PKC, protein kinase C; TKD, tyrosine kinase domain.

1. Rydapt Summary of Product Characteristics. Novartis. 2020

RATIFY Trial Design



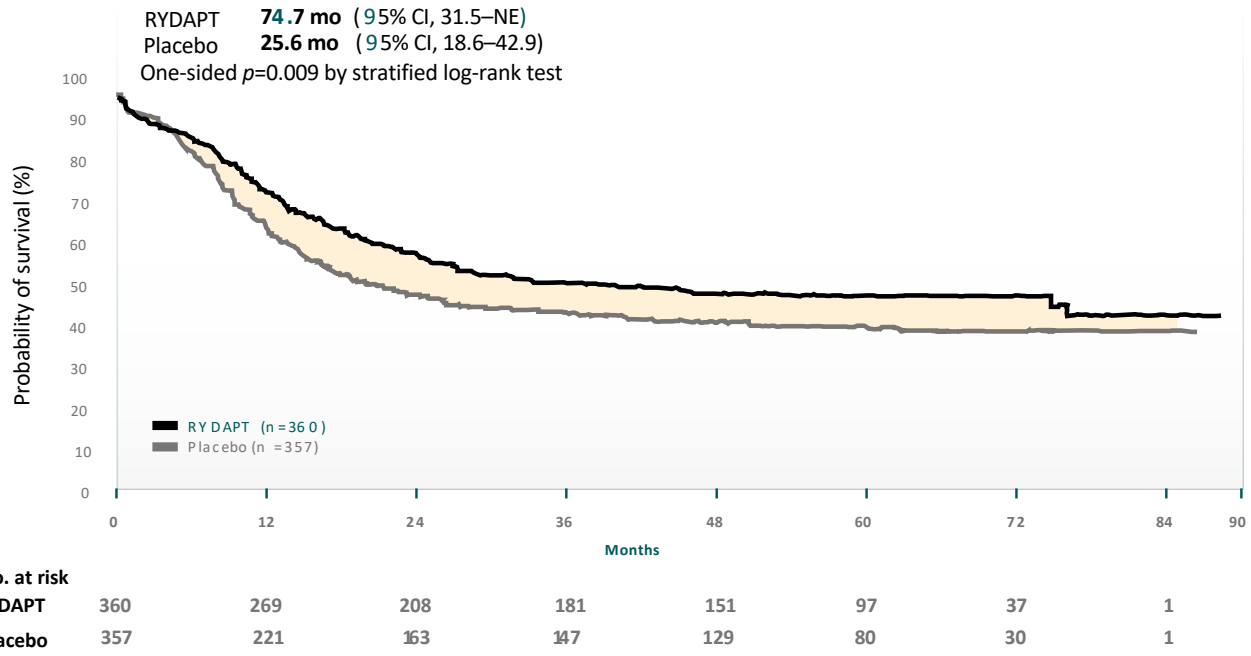
Age <60 yr with FLT3 ITD or TKD

60% of all patients underwent SCT during the study*

Stone et al. *NEJM*. 2017; 377:454-64

* Patients eligible for SCT discontinued study therapy before commencing conditioning treatment.[13]
AML, acute myeloid leukaemia; BID, twice daily; CR, complete response; SCT, stem cell transplant.

RATIFY Overall Survival

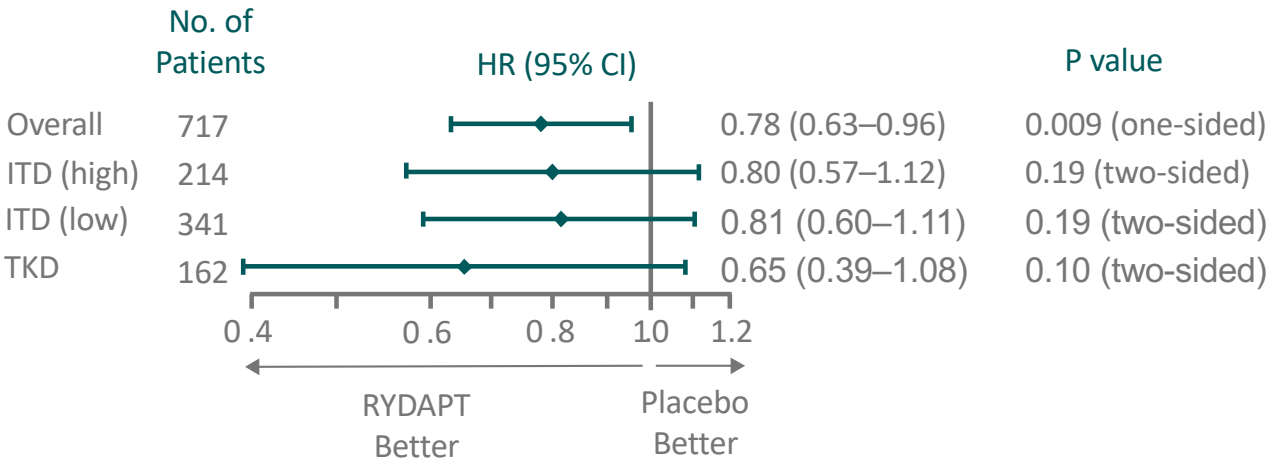


- HR for death, 0.78; (p=0.009)*[13]
- 4-year OS rate was 51.4% in the RYDAPT group and 44.3% in the placebo group[13]

* Median follow-up 59 months; data not censored for SCT.[13]
CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimated; OS, overall survival; SCT, stem cell transplant.
Adapted from Stone RM, Mandrekar S, Sanford BL, *et al.* Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454–464.

RATIFY Subgroup Analysis

Midostaurin + standard intensive chemotherapy provide a survival benefit in all FLT3 mutation subgroups* vs. placebo + standard intensive chemotherapy, but the differences were not statistically significant[13]



* Patients with FLT3 mutations can be classified in three groups: patients with point mutations in the TKD; patients with duplication ITD mutations with a high ratio (>0.7) of mutant to wild-type alleles (ITDhigh), patients with ITD mutations with a low ratio (0.05 to 0.7) of mutant to wild-type alleles (ITDlow).

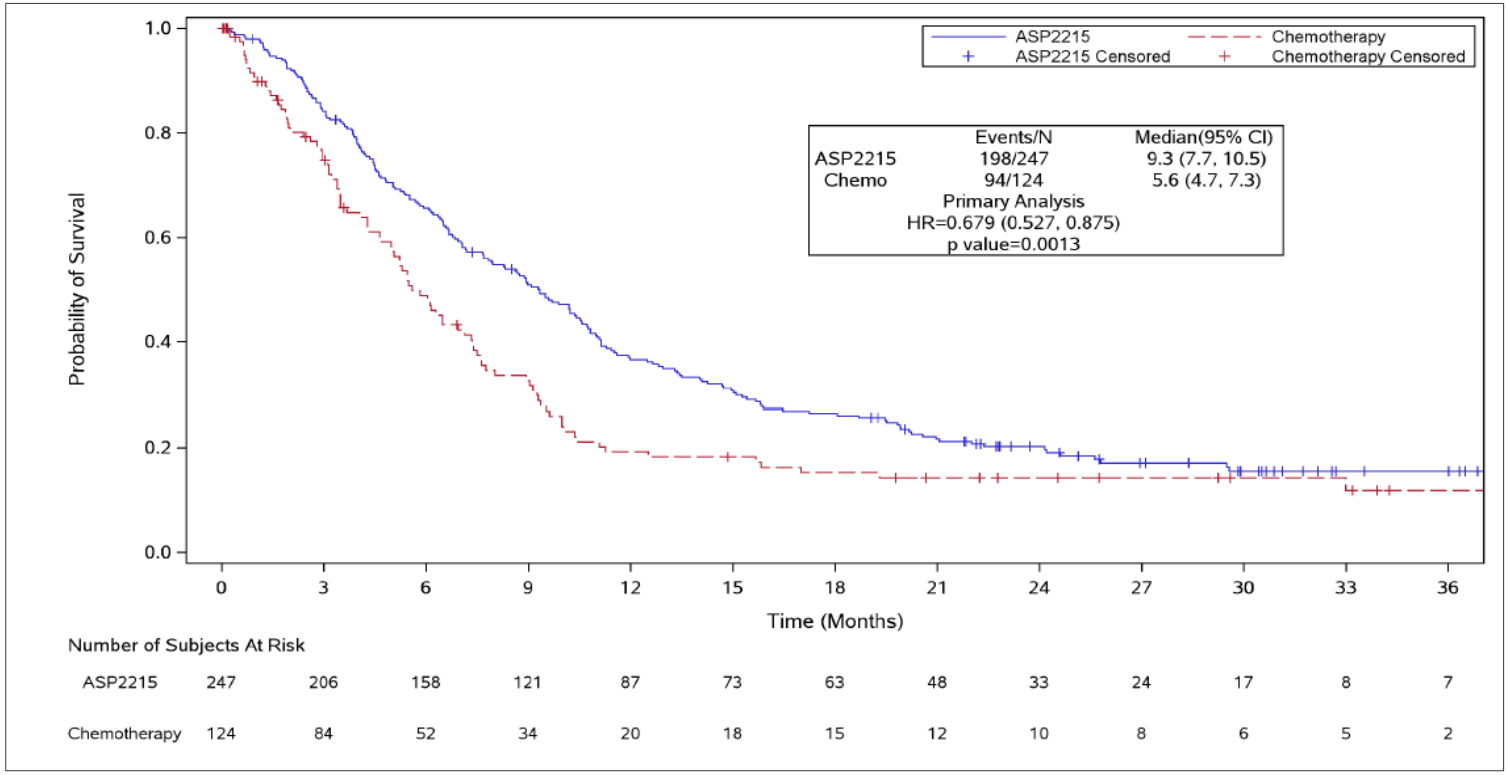
CI, confidence interval; HR, hazard ratio; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

Adapted from Stone RM, Mandrekar S, Sanford BL, *et al*. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-464.

Relapsed *FLT3*mut AML Gilteritinib

- Despite the therapeutic advance of Midostaurin many patients will be refractory or suffer a relapse. The prognosis of patients with relapsed *FLT*- ITD+*ve* AML is poor
- Gilteritinib has shown superior results to intensive salvage regimens. CR / CRi was achieved in 34% vs 15.3% in the standard arm in the ADMIRAL trial
- The Food and Drug Administration (FDA) and European Medicines Agency (EMA) have both approved Gilteritinib for relapsed or refractory *FLT3* mutated AML patients

Gilteritinib is recommended, within its marketing authorisation, for treating relapsed or refractory FLT3-mutation-positive AML in adults



Statistically significant improvement in overall survival
Gilteritinib: 9.3 months; salvage chemotherapy: 5.6 months;
hazard ratio (HR): 0.64 (95% CI 0.49 to 0.83, p<0.001)

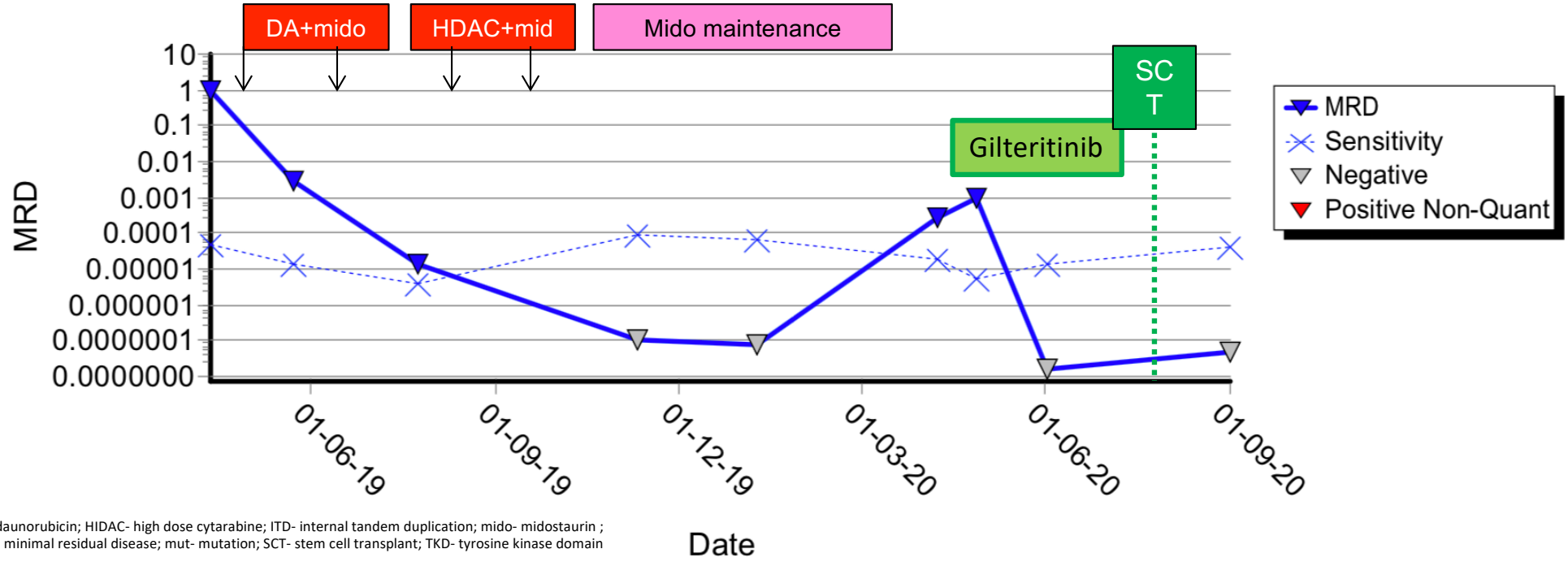
25.5% vs **15.3%** of people went on to HSCT in the Gilteritinib and chemotherapy arm, respectively

Gilteritinib Issues

- Only 5.7% of patients in the ADMIRAL Trial had received prior Midostaurin exposure raising the issue of how transferrable are the RATIFY results to the current paradigm?
- Recently a retrospective analysis (Numan et at al ASH, 2020) investigated the response in relapsed *FLT3* mutated patients previously treated with 7+3+midostaurin (n=46). Gilteritinib produced composite CR rates of 58% and OS of 7.8 months.
- However less than half (46%) of patients relapsing off the Midostaurin arm of RATIFY had retained a *FLT3* mutation (Schmalbrock et al, Blood 2021) so repeat testing at relapse is essential
- In the UK many patients are treated at molecular relapse and confirming the presence of an *FLT3* mutation is challenging as assays lack sensitivity although response rate appears high

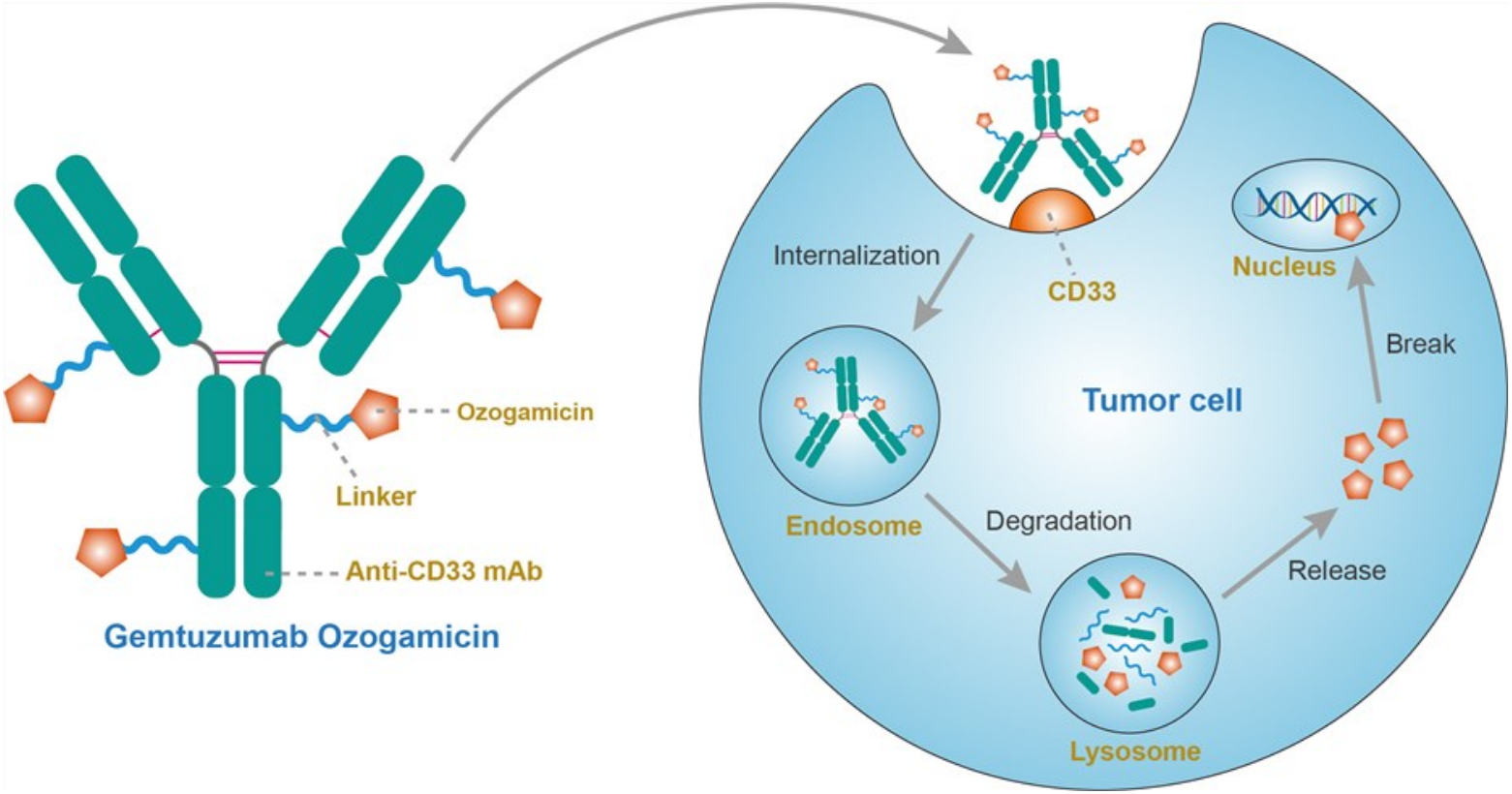
Patient case. Molecular relapse of *FLT3* ITD+ AML treated with Giteritinib

Normal karyotype
NPM1 mutation
FLT3 ITD 0.46
NRAS G12D

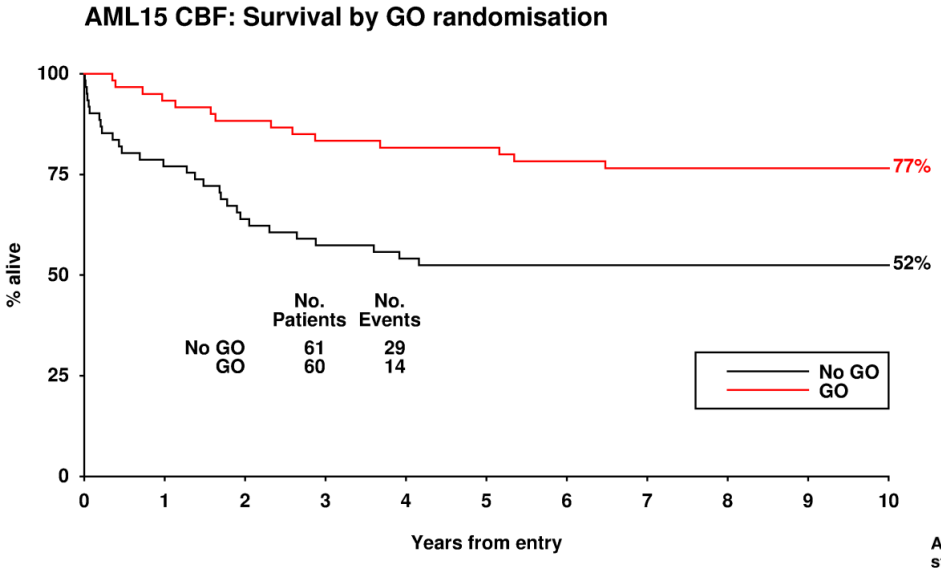


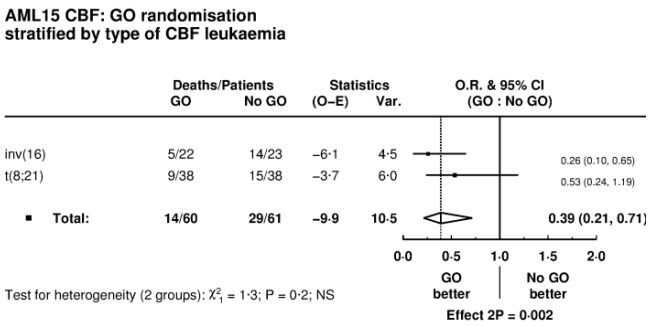
DA- daunorubicin; HIDAC- high dose cytarabine; ITD- internal tandem duplication; mido- midostaurin ; MRD- minimal residual disease; mut- mutation; SCT- stem cell transplant; TKD- tyrosine kinase domain

Gemtuzumab Ozogamicin



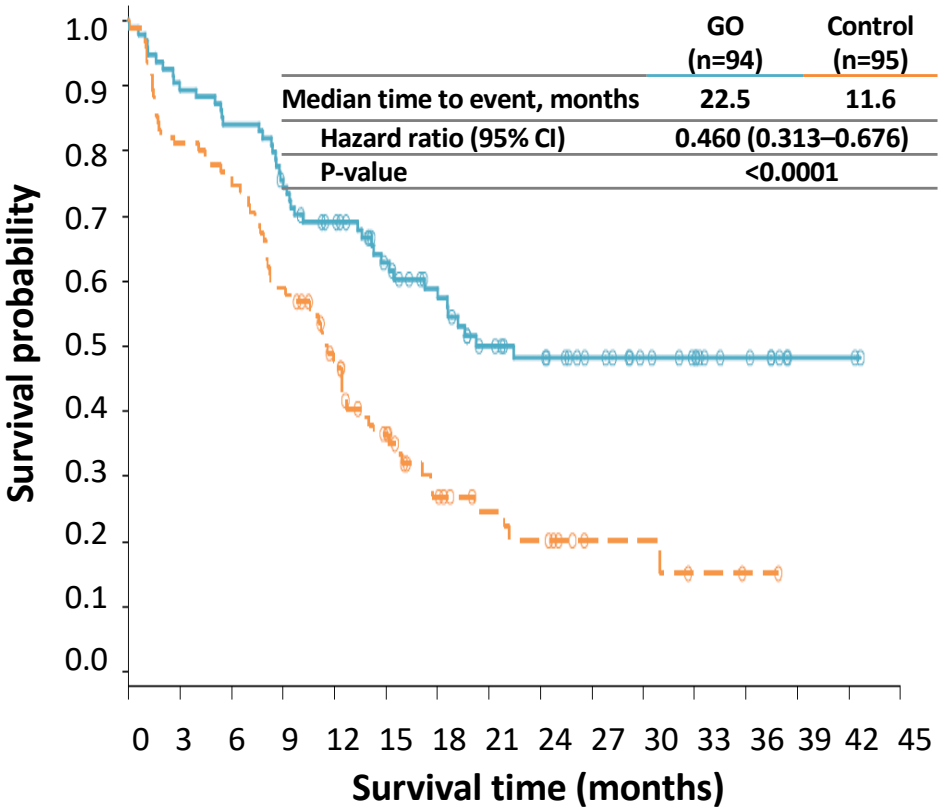
NCRI AML15 Trial (age 16-59): results of Gemtuzumab randomisation in CBF-AML





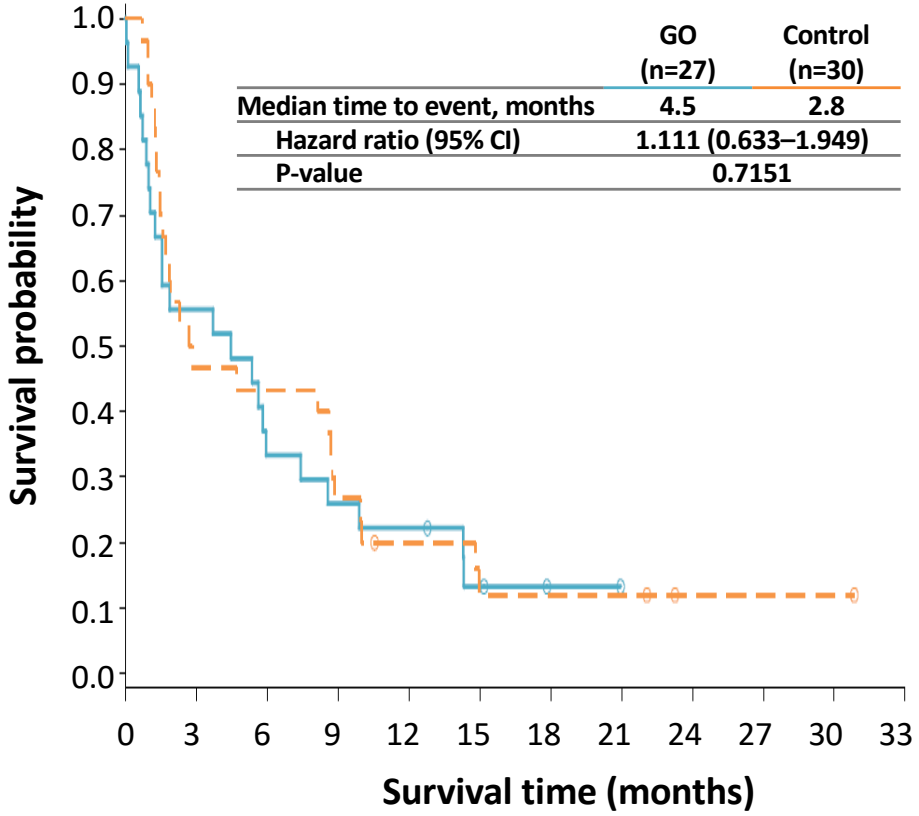
ALFA 0701 Trial. The advantage in EFS with GO was seen in intermediate cytogenetic risk

Favourable/intermediate



No. at risk																
GO	94	84	79	70	61	49	41	31	27	21	16	13	8	2	2	0
Control	95	77	73	56	41	27	16	11	9	4	4	2	1	0		

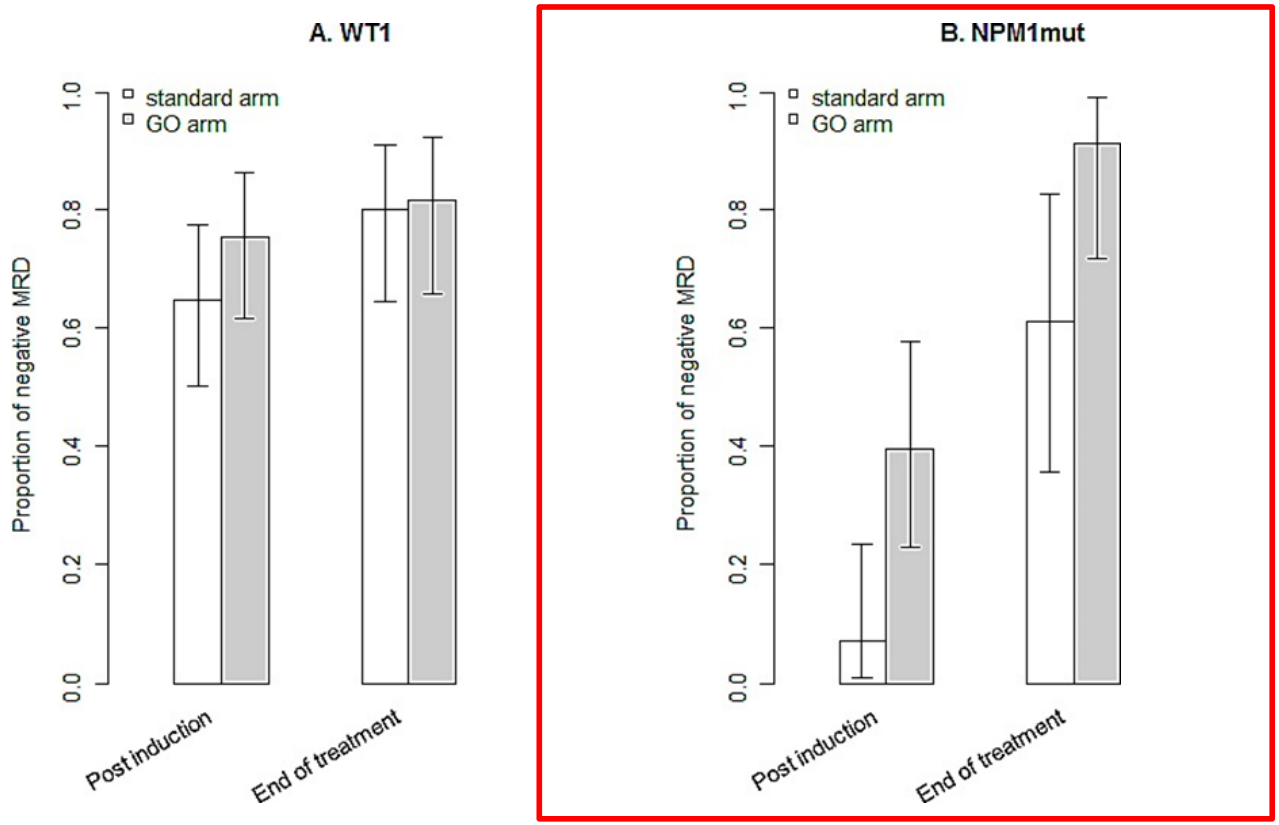
Adverse



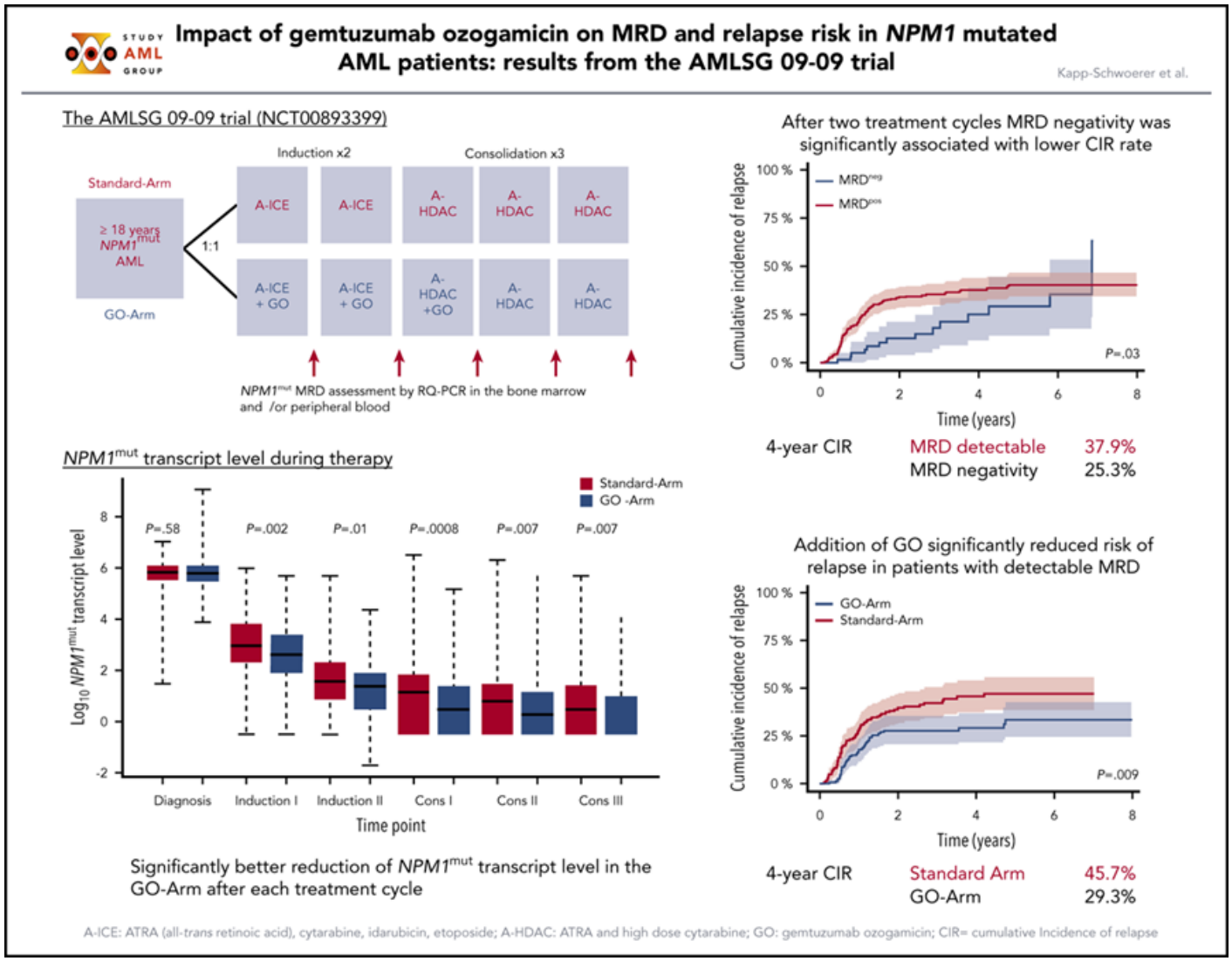
27	15	9	7	6	3	1	0					
30	14	13	8	5	3	3	3	1	1	1	0	

Pfizer CSR. Data on file, 2016

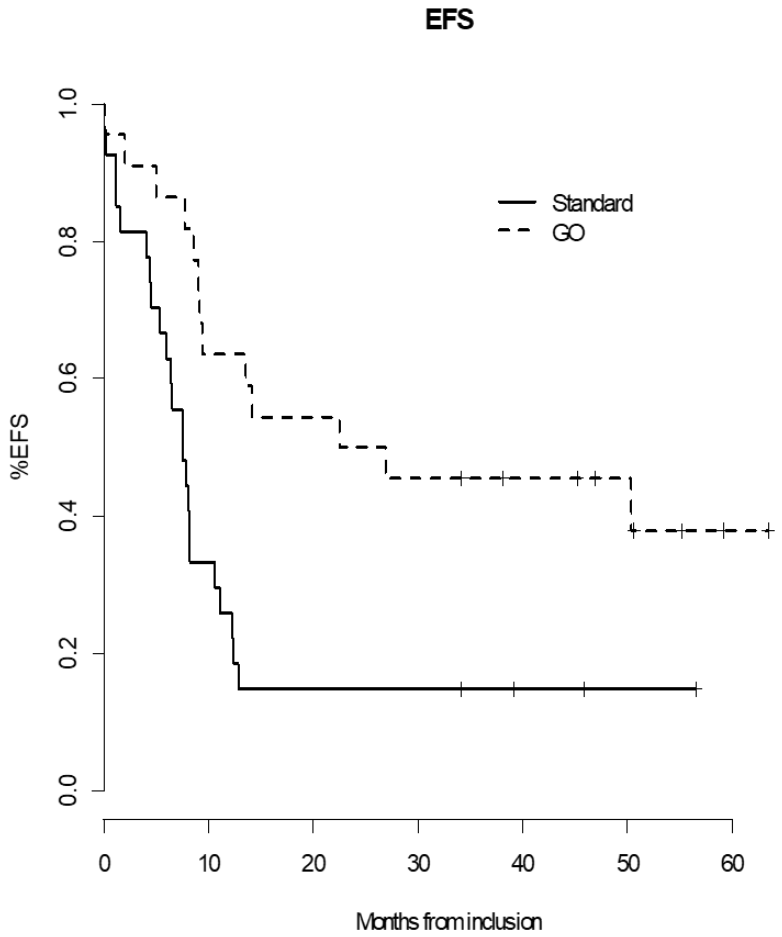
*NPM1*mut receiving GO in the randomised ALFA0701 trial were more likely to achieve MRD negativity



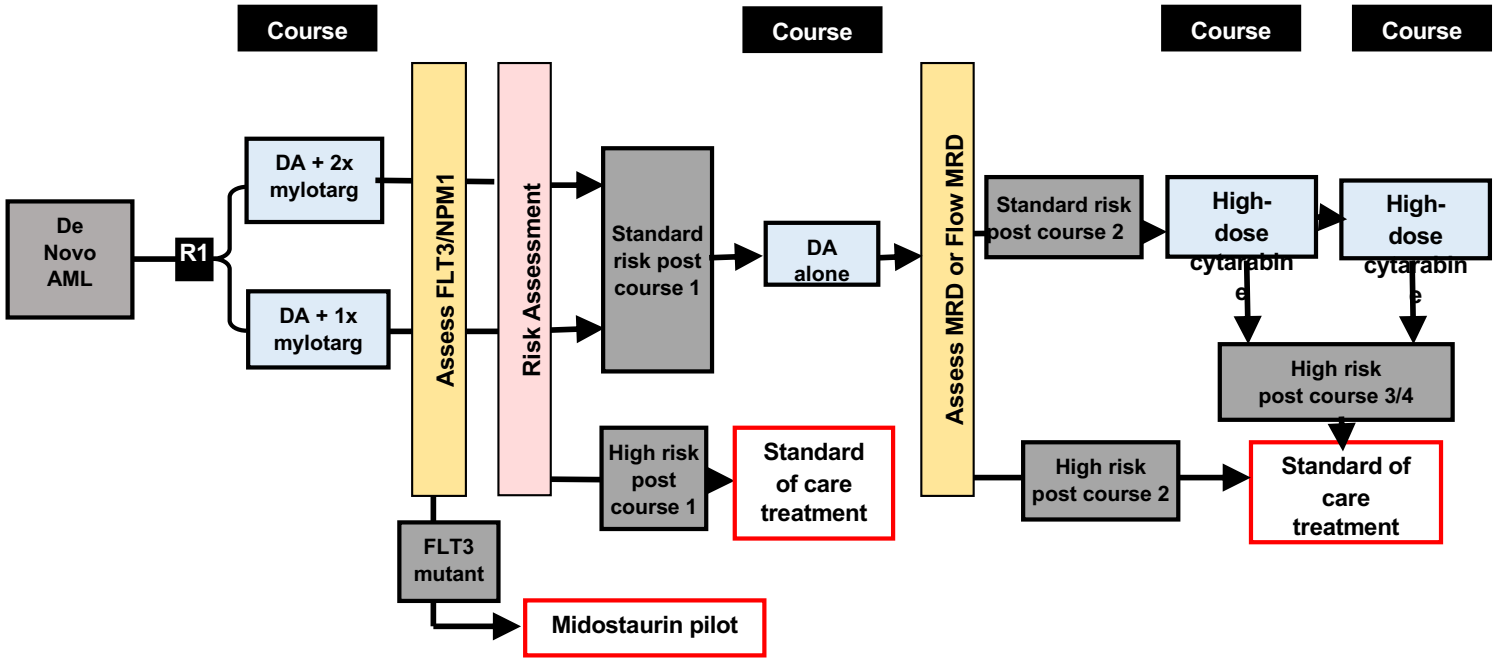
Gemtuzumab targets *NPM1*mut (AMLSG 09-09)



Evidence of benefit for Gemtuzumab in *FLT3*mut AML in ALFA0701 Trial



AML19 Mido-targ Design



AML 19

CANCER RESEARCH UK

NCRI National Cancer Research Institute

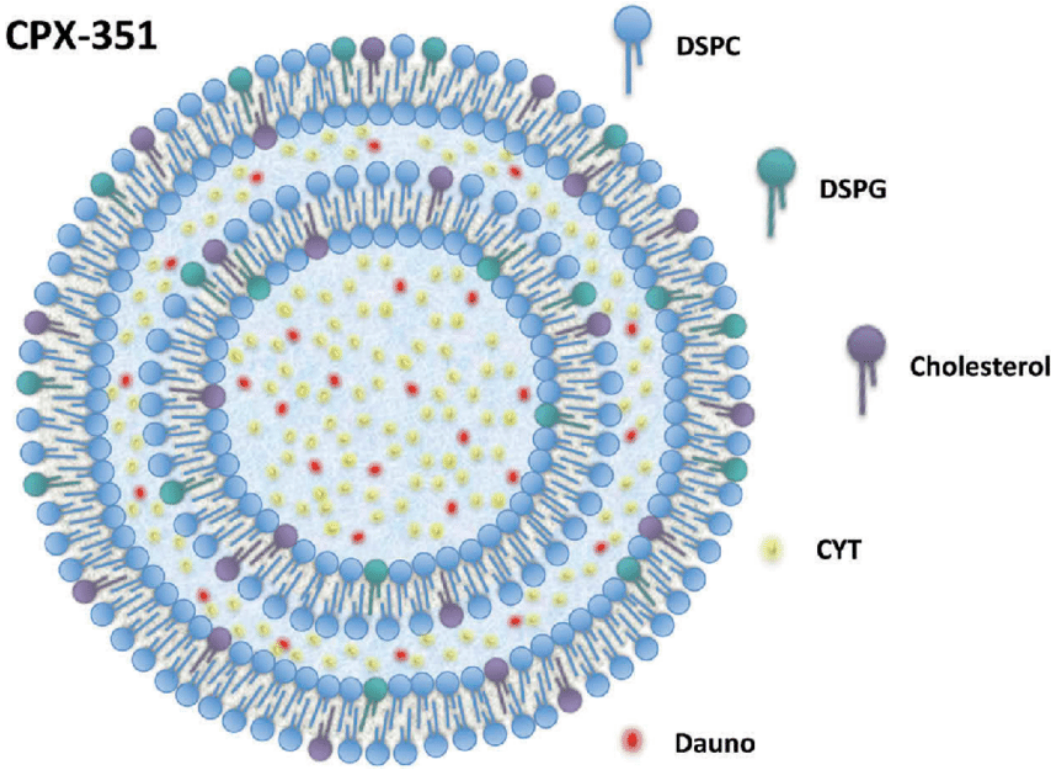
CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

AML 19

NCRI National Cancer Research Institute

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

CPX-351 - lipid particle formulation of daunorubucin + cytarabine



Brunetti et al. *Expert Review of Hematology.* 2017: 1747

Study 301: Phase III Randomised, Open-label, Multicentre Study

- Older patients: aged 60-75 years
- CPX-351 n=153 vs 7+3 n=156

AML with history of CMML or MDS . Therapy-Related AML

De novo AML with MDS karyotype

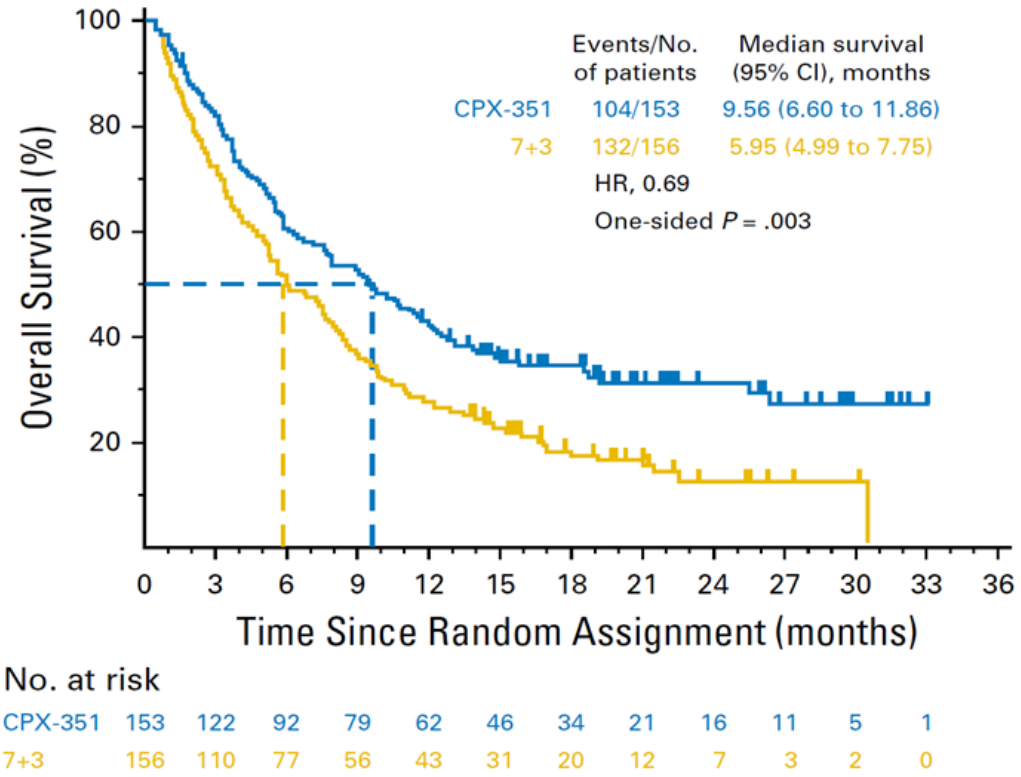
Previously untreated

Able to tolerate intensive therapy (ECOG PS 0-2)

Inclusion criteria did not include AML with mult-lineage dysplasia with no history of MDS or AML secondary to MPN

Study 301 Primary Endpoint - Overall Survival

- **31% reduction in the risk of death for patients treated with CPX-351 vs 7+3 (HR 0.69; 95% CI 0.52 to 0.90)[1]**

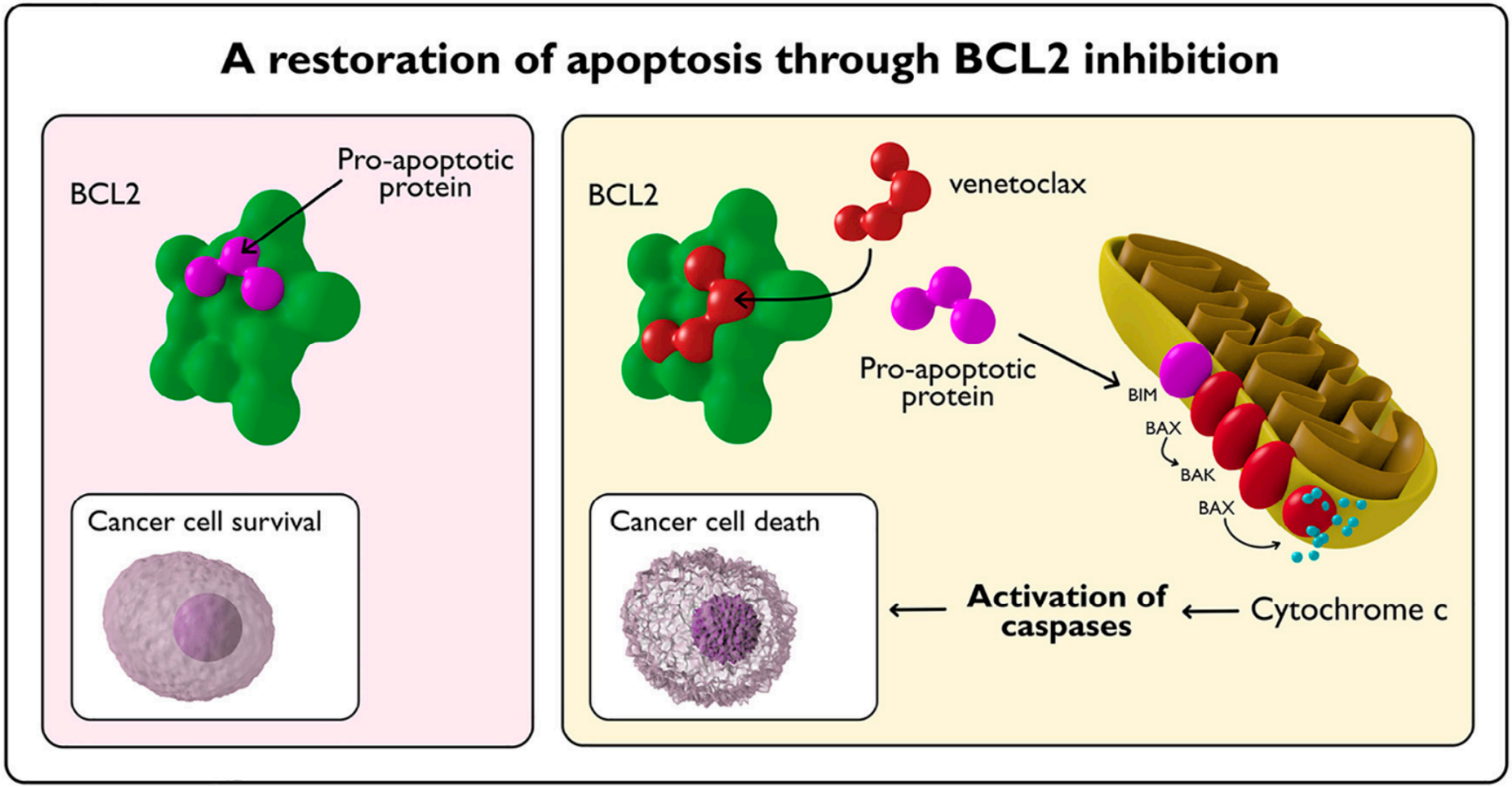


Adapted from Lancet et al. 2018

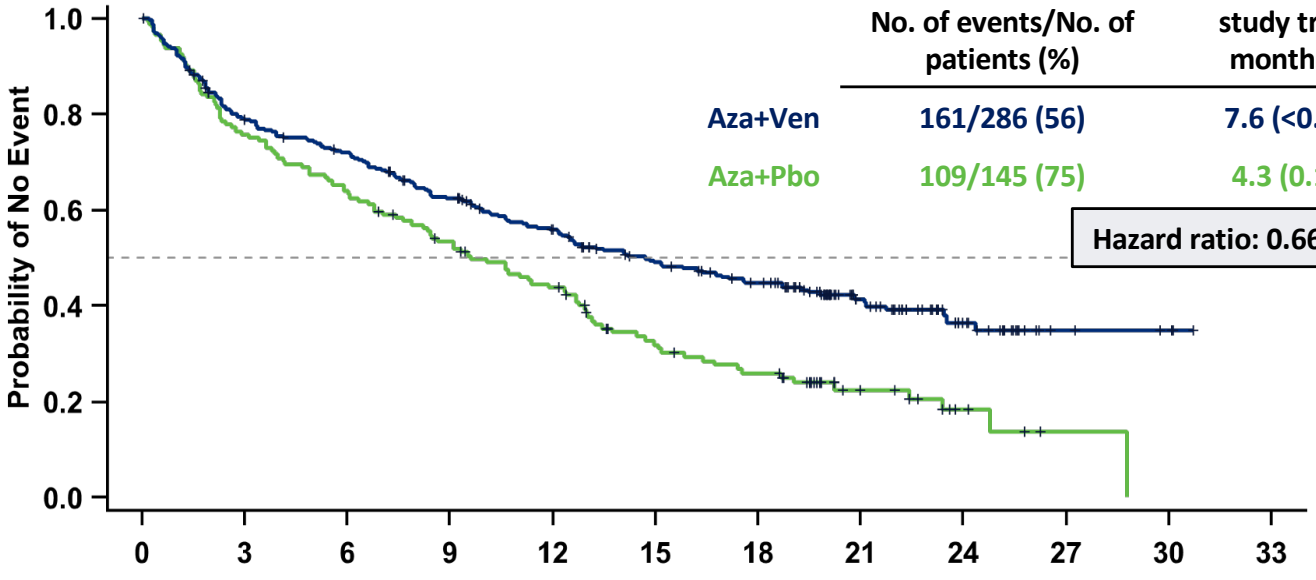
CPX-351 Unknowns

- The trial was limited to 60-75 yrs. Can these results be extrapolated to younger patients? In the NCRI AML15 trial we observed that FLAG-Ida was superior to DA in secondary AML.
- The trial did not include patients with AML-MRC diagnosed on morphological criteria only. Can the positive results be extrapolated to these patients? (This indication is not approved in the UK)
- The number of patients with a secondary AML genomic signature is greater than those with a history of secondary AML. Can the positive results be extrapolated to these patients with no prior history of MDS

Venetoclax


A restoration of apoptosis through BCL2 inhibition
BCL2
Pro-apoptotic protein
Cancer cell survival
BCL2
venetoclax
Pro-apoptotic protein
BIM
BAX
BAK
BAX
Cancer cell death
Activation of caspases
Cytochrome c

Overall Survival. Viale A Trial. Ven/Aza vs Azacytidine



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001

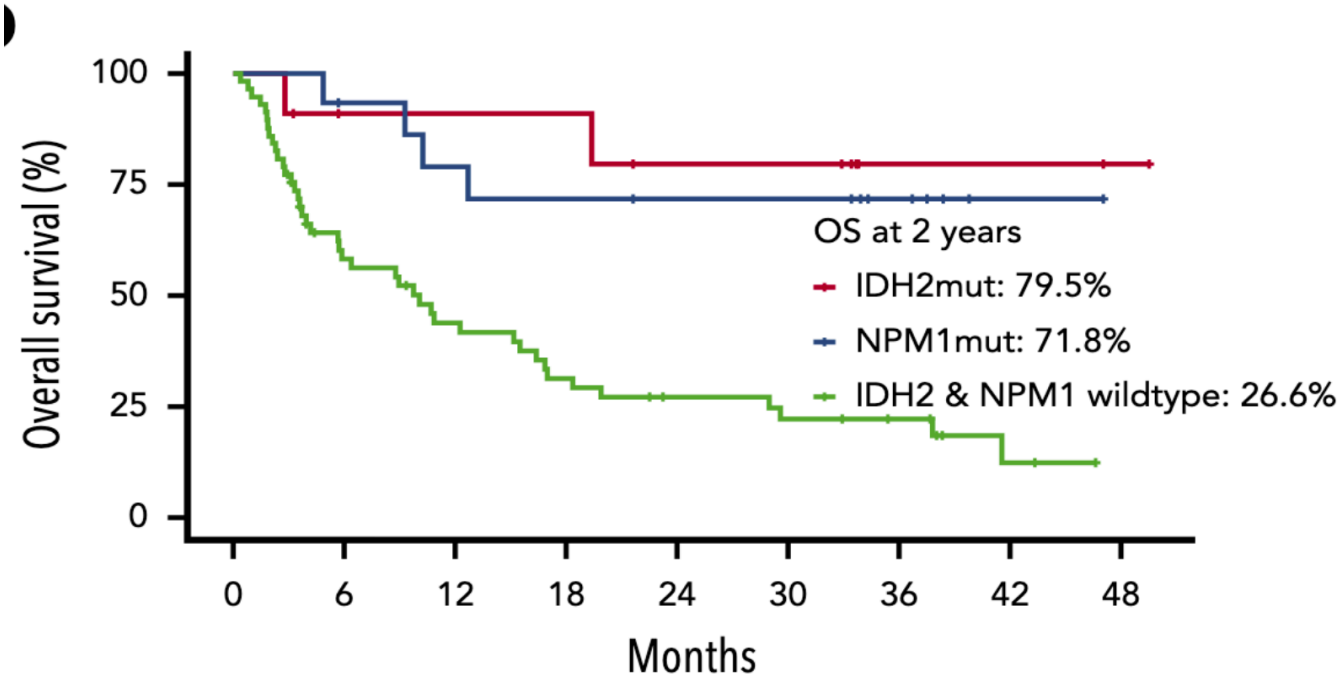
Patients at Risk

Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

Courtesy C.Dinardo

Response to venetoclax is genotype dependent



DiNardo et al, Blood 2020

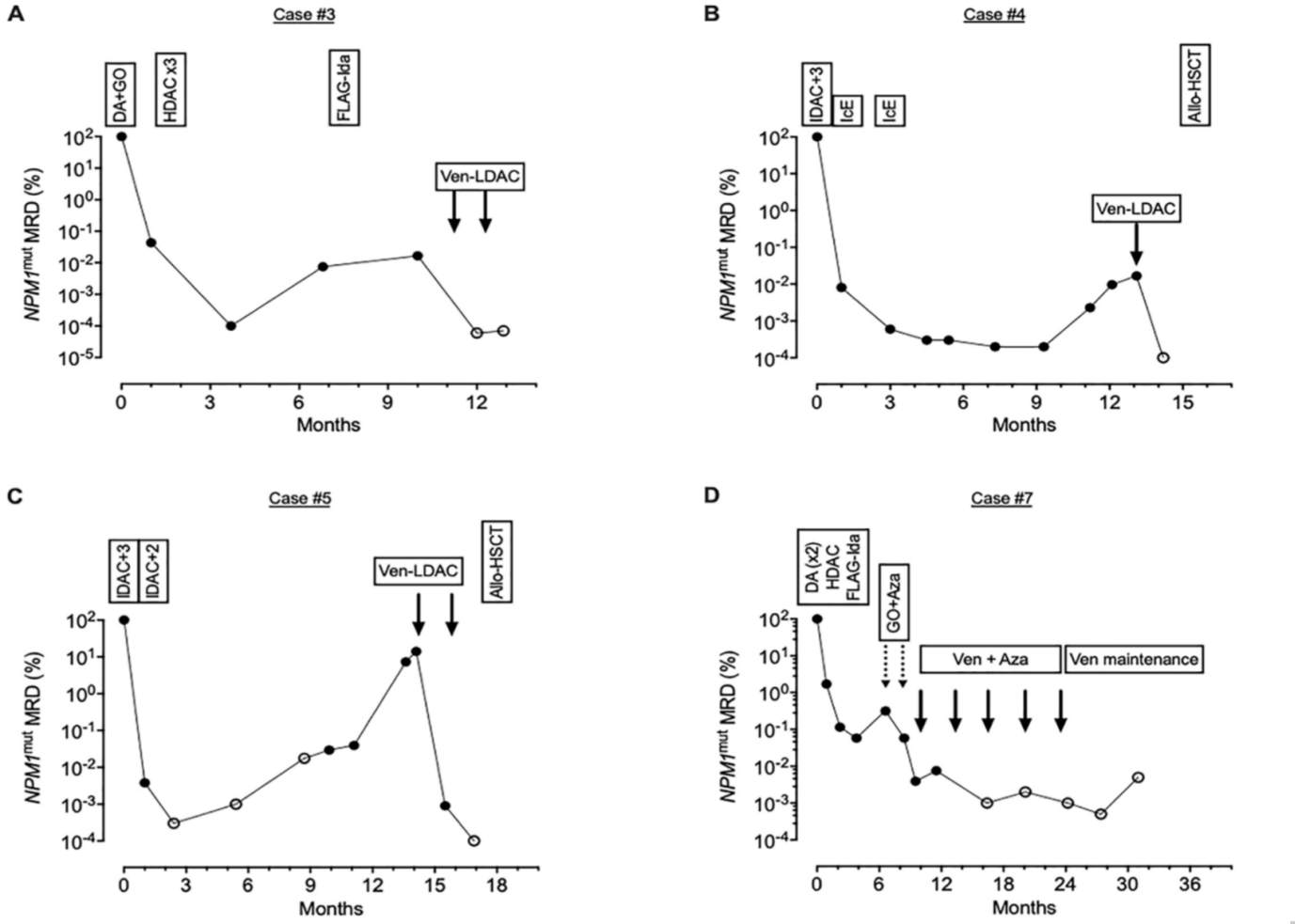
UK COVID criteria for use of Venetoclax as an alternative to intensive chemotherapy

- Any non-CBF patient aged >60y
- Patients with an *NPM1* or *IDH1/2* mutation aged >50y or with comorbidities
- Molecular relapse or persistence of *NPM1* +ve AML

Cureleukaemia. *AML Working Party COVID-19 Recommendations.* http://www.cureleukaemia.co.uk/page/news/523/aml-working-party-covid-19-recommendations. [Accessed October 2020]

Rapid erasure of *NPM1* MRD with venetoclax–cytarabine / azacidine

Figure 1. Quantitative MRD profile of *NPM1*mut by RT-qPCR. Positive detection is shown as solid-filled black circles, whereas negative detection is shown as open circles, indicating the assay sensitivity relative to amplification of the *ABL* gene.



Summary
Are they Practice Changing?

- **Midostaurin** – Yes. Standard of care for newly diagnosed *FLT3*mut AML >18years. Uncertainty about role in maintenance
- **Gilteritinib –** an advance for relapsed *FLT3*mut AML. But still inadequate therapy for many patients
- **Gemtuzumab** Yes for CBF-AML. Better definition of other molecular groups that might benefit is needed
- **CPX-351**- Yes within the confines of the inclusion criteria of the pivotal 301 trial
- ***Venetoclax***- *Yes. Improves outcome for patients not fit for intensive therapy (and perhaps some older patients fit for intensive therapy)*

A Randomized, Double-blind, Placebo-controlled Study of Venetoclax with Azacitidine vs

Eligibility

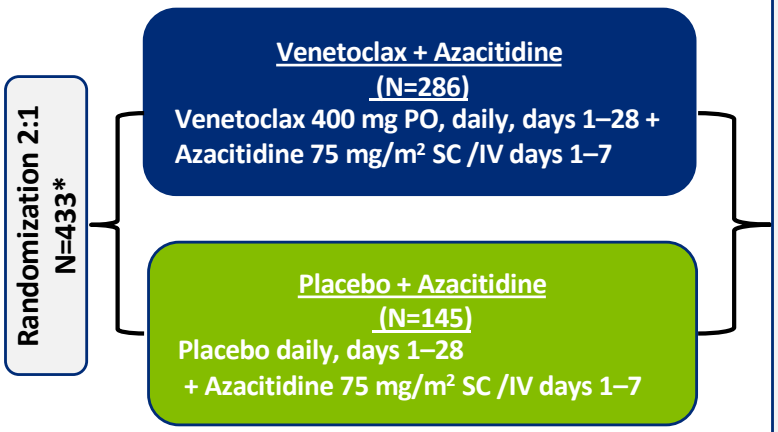
Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ❖ ≥75 years of age
  - ❖ 18 to 74 years of age with at least one of the co-morbidities:
    - – CHF requiring treatment or Ejection Fraction ≤50%
    - – Chronic stable angina
    - – DLCO ≤ 65% or FEV1 ≤ 65%
    - – ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment



Endpoints

Primary

- Overall survival

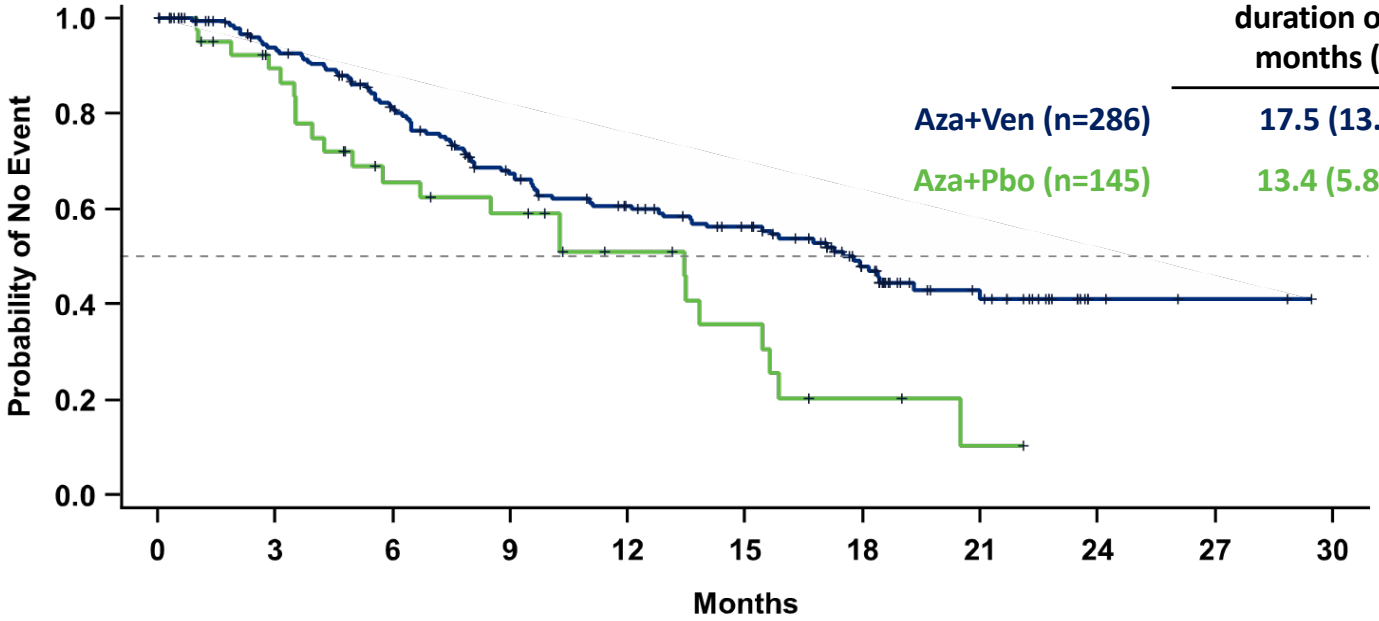
Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up **Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg
Cycle 2 → Day 1-28: 400 mg

Duration of Response After Achieving CR/CRi



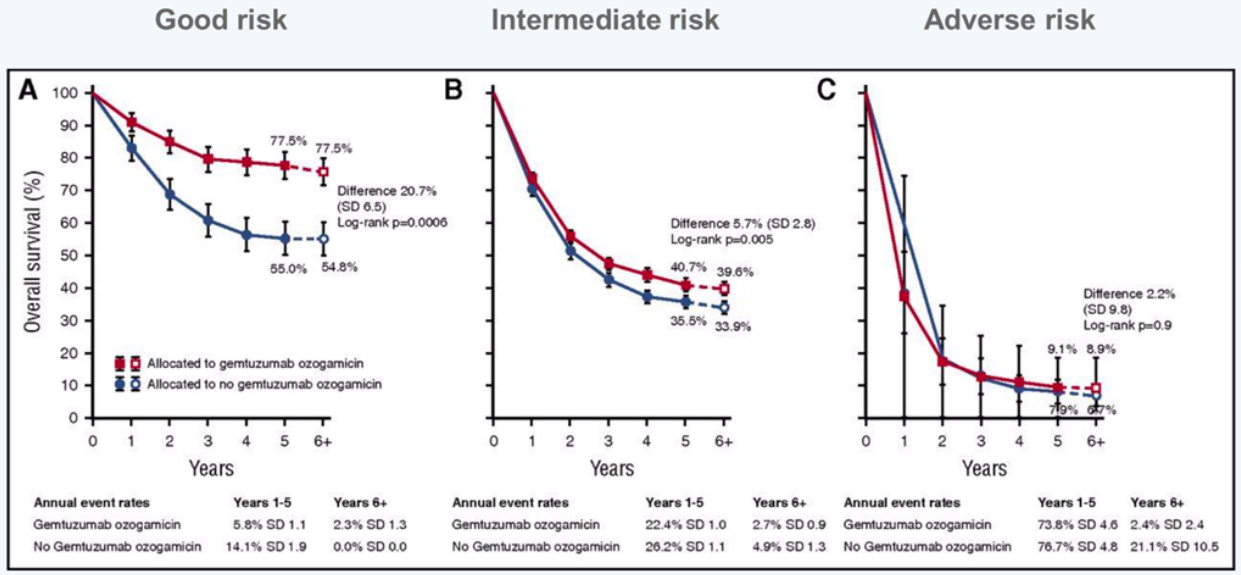
	Median duration of CR/CRi, months (95% CI)	Median duration of CR, months (95% CI)
Aza+Ven (n=286)	17.5 (13.6 – NE)	17.5 (15.3 – NE)
Aza+Pbo (n=145)	13.4 (5.8 – 15.5)	13.3 (8.5 – 17.6)

Patients at Risk

Aza+Ven	190	161	133	101	85	72	44	23	4	2	0
Aza+Pbo	41	31	20	17	11	7	3	1	0	0	0

Aza: Azacitidine; CR: Complete remission; CRi: CR with incomplete count recovery ; NE: Not estimable; Pbo: Placebo; Ven: Venetoclax

GO Meta-analysis by cytogenetic risk Group



Patients included:	
AML15	1099
AML16	1115
SWOG	595
GOELAMS	238
ALFA	278
TOTAL	**3325**

Intermediate Risk Cytogenetics had a 6% improvement in survival at 5 years.

CD33 levels are high in NPM1+ve and FLT3-ITD