Gilteritinib for Treatment of Pediatric Patients with FLT3/ITD AML

Pediatric Subcommittee of the

Oncologic Drugs Advisory Committee

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Gilteritinib for Treatment of Pediatric Patients with FLT3/ITD AML

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Astellas Pharma

Gilteritinib Introduction

- Unmet medical need for pediatric treatment options in rare and deadly form of AML – FLT3/ITD mutated disease
- Gilteritinib demonstrated significant, durable anti-leukemic activity and well-tolerated in adults with $FLT3^{MUT}$ AML
- Proposed global pediatric development plan intended to provide sufficient data for label to inform prescribers

Proposed Pediatric Study Population

- Proposed population based on
  - Gilteritinib mechanism of action as FLT3-inhibitor
  - Greatest potential for benefit
- Proposed indication
  - Treatment of pediatric patients with FLT3/ITD mutation positive AML, in newly diagnosed patients or in patients who are refractory to or have relapsed after initial induction chemotherapy

Agenda

- Disease description and unmet need in target population
- Gilteritinib’s mechanism of action
- Adult development program
- Proposed pediatric development program

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AML: Rare, Rapidly Progressing, Life-Threatening Cancer of Blood and Bone Marrow

- Aberrant differentiation and proliferation of malignant progenitor cells
- Often accompanied by severe neutropenia and/or thrombocytopenia
- Rapidly fatal
- Despite initial remission, relapse is common

Tallman, 2005

Outcomes Poor After Relapse in Adult Patients with FLT3/ITD Mutated AML

- 21% achieve composite complete remission (CRc) after salvage therapy
- 1st relapse: mOS 4.3 months
- 2nd relapse: mOS <8 weeks

CRc = CR + CRp + CRi. Levis et al, 2011; Rowe et al, 2010; Giles et al, 2005

Outcomes Especially Poor for Children With Rare FLT3/ITD Mutated AML

- Pediatric patients: 10-20% have FLT3/ITD mutated AML
- Overall survival
  - All children with AML: 65% alive at 5 years
  - FLT3/ITD mutated AML: 20-30% alive at 5 years
- No approved targeted therapy for FLT3/ITD pediatric population
  - Guidelines recommend clinical trial
- New treatment options needed

Zwaan, 2003; Meshinchi, 2006; Govedarovic, 2011; Wagner, 2011; Schneider, 2012; Masetti, 2014; NCCN, 2015

Agenda

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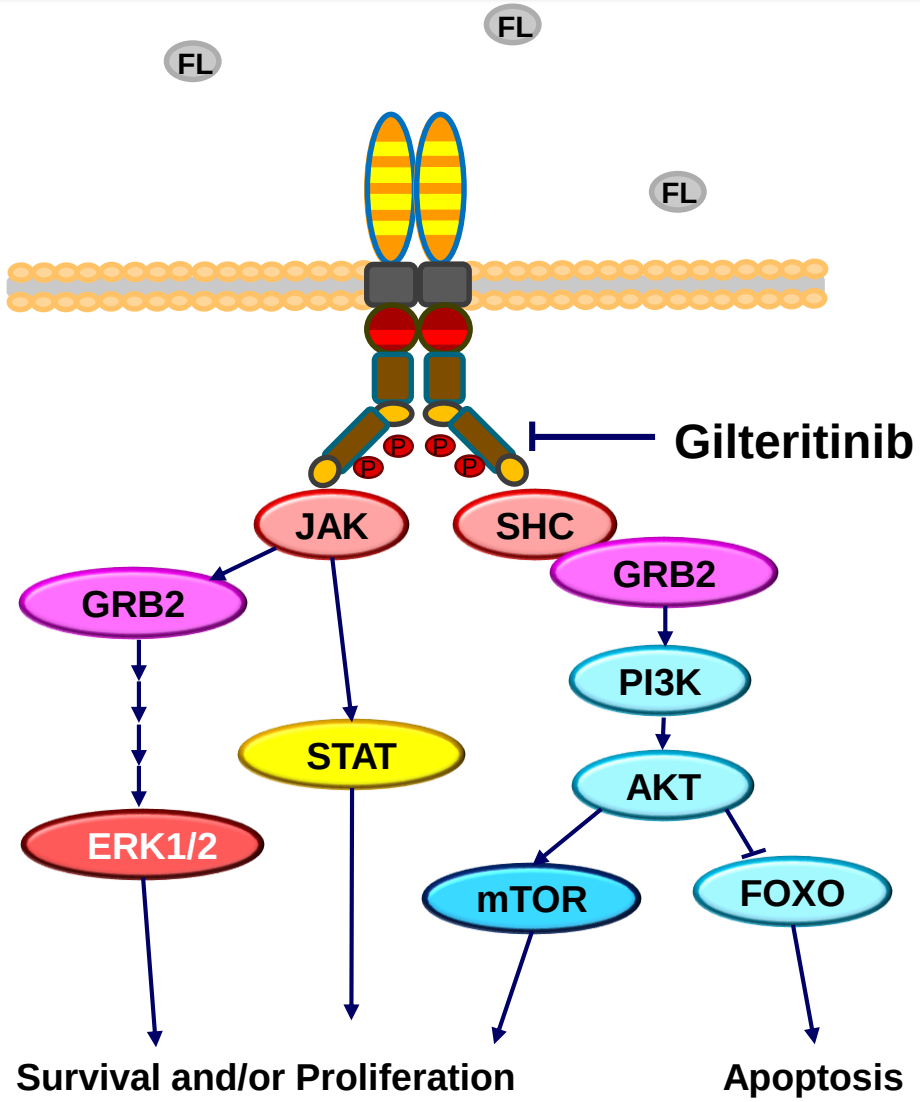
Gilteritinib is Novel Oral Tyrosine Kinase Inhibitor Highly Potent for FLT3



Kinase	IC_{50} nM	IC_{50} 95% CI
FLT3	0.29	0.26, 0.32
LTK	0.35	0.29, 0.43
AXL	0.73	0.51, 1.0
EML4-ALK	1.2	0.68, 2.0
c-KIT	230	190, 280

Agenda

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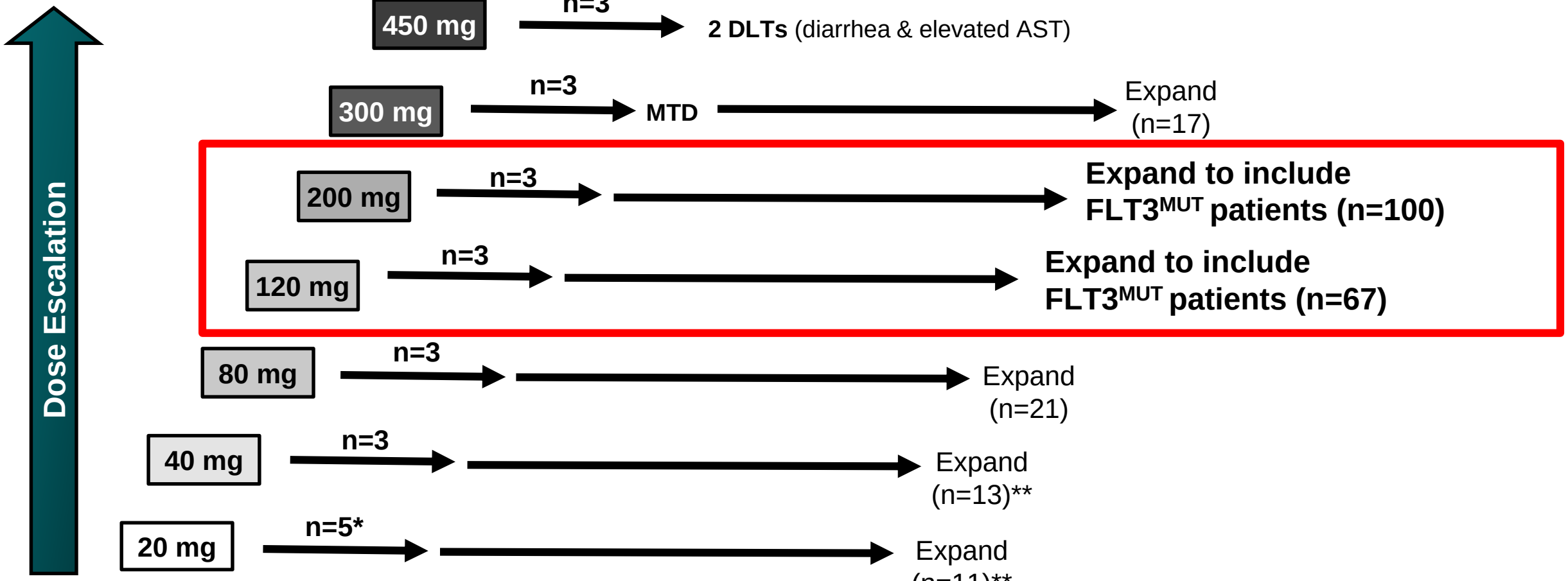
Gilteritinib Exposure (As of April 2017)

- Clinical trials
  - 16 completed or ongoing Phase 1 - 3 studies
  - 179 healthy volunteers and 574 patients received at least 1 dose of gilteritinib
    - Study 0101: 252 patients received gilteritinib

Study 0101: Monotherapy Dose-Escalation Study in Adults with Relapsed / Refractory AML



* Three evaluable subjects ** Enrollment stopped early for low response rate. DLT: dose limiting toxicity. MTD: maximum tolerated dose.

Study 0101: Demographics

	Safety Population N=252	
	n	%
Median age, years (range)	62 (21–90)	
Male	129	51%
$FLT3^{MUT}$ positive	191	76%
FLT3-ITD only	162	64%
FLT3-ITD and FLT3-TKD (D835)	16	6%
FLT3-TKD (D835) only	13	5%
Prior AML lines of therapy		
1	75	30%
≥ 2	177	70%
Prior stem cell transplant		
0	179	71%
≥ 1	73	29%
Prior TKI therapy	63	25%

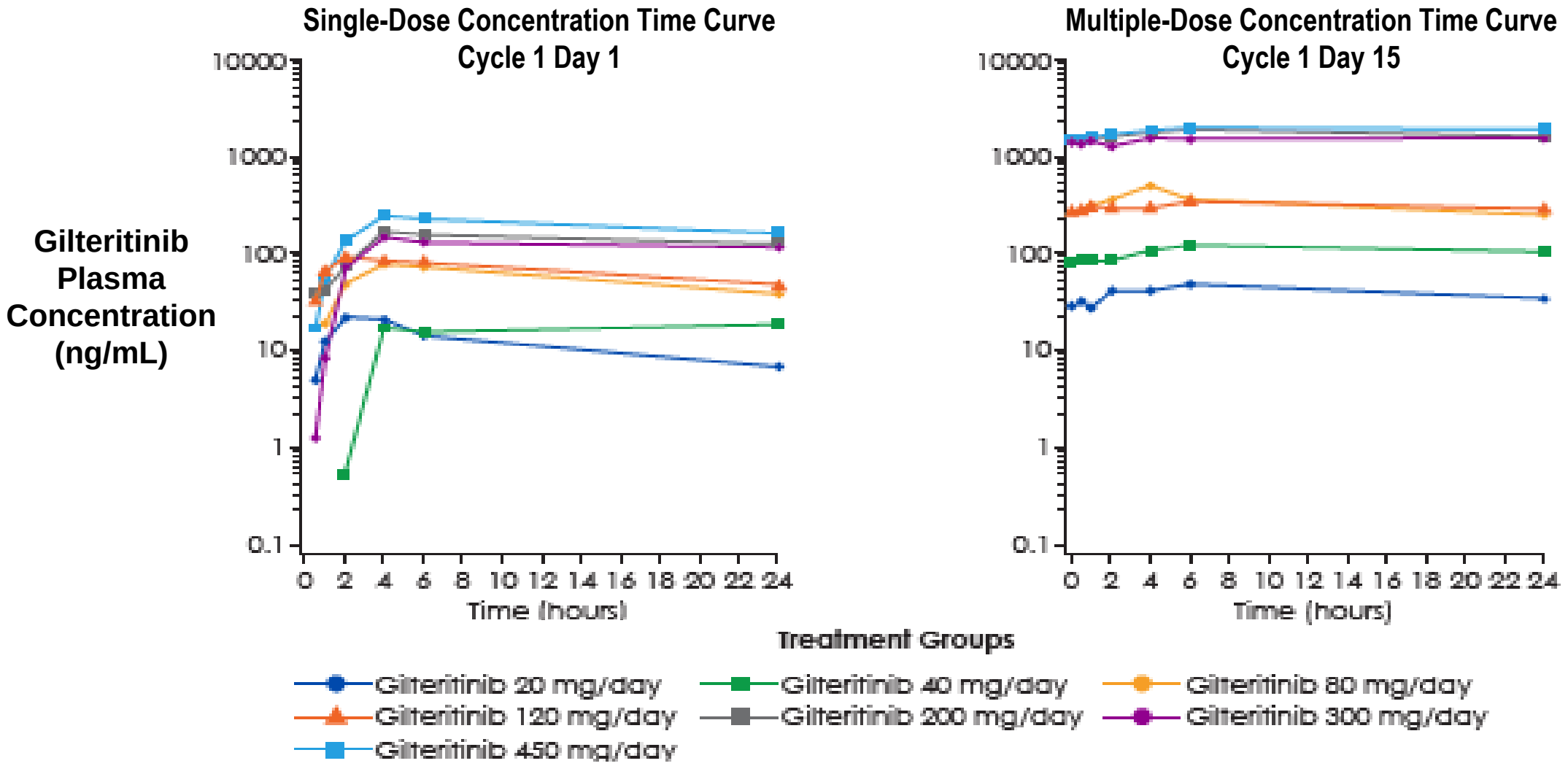
Data on file

Study 0101: Patient Disposition

	All Enrolled Patients N=265*	
	n	%
Patients continuing treatment	31	12%
Treatment discontinuations	234	88%
Progressive disease	75	28%
Lack of response	44	17%
Adverse events	34	13%
Death	29	11%
Other	25	9%
Subject withdrawal	17	6%
Never received drug	8	3%
Lost to follow-up	2	1%
Underwent transplantation	37	14%
Resumed treatment after transplant	13	5%

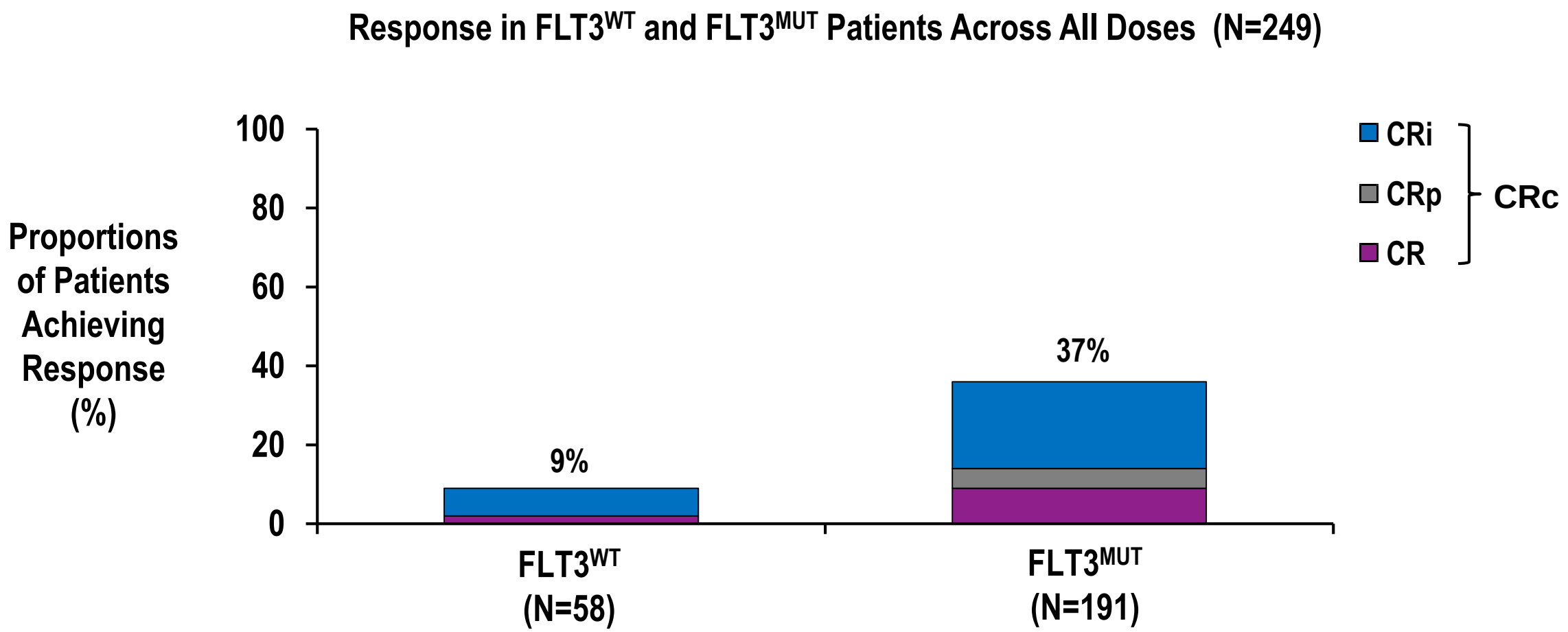
*8 patients did not receive drug, 5 re-enrolled. Data on file.

Study 0101: Gilteritinib Exhibited Linear and Dose-Proportional Pharmacokinetics



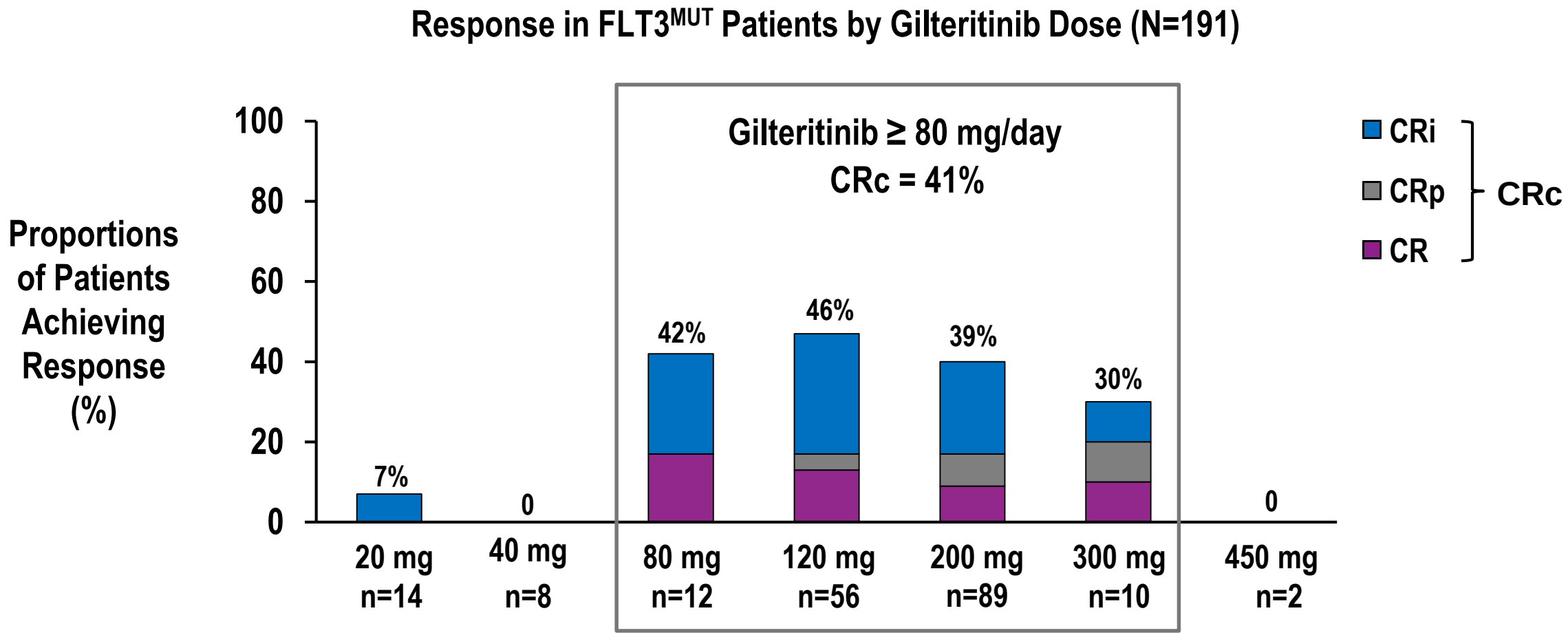
Data on file

Study 0101: Anti-Leukemic Activity Seen in Adults with $FLT3^{MUT}$ AML



Data on file

Study 0101: Robust Anti-Leukemic Activity Seen in Adults with FLT3^{MUT} AML in ≥ 80 mg/day Dose



Data on file

Study 0101: Overall Survival in Relapsed / Refractory $FLT3^{MUT}$ AML Patients

	Gilteritinib ≥ 80 mg
Median OS, months (range)	7.1 (0.4 – 17.1)
26-week OS	57%
1-year OS	22%

Data on file

Study 0101: Analysis of Molecular Response to Gilteritinib

- 80 patient subset of FLT3/ITD population
  - Treated with 120 or 200 mg of gilteritinib
  - Analyzed for molecular response
- Molecular response defined as
  - FLT3-ITD to total FLT3 ratio of $\leq 10^{-2}$

Study 0101: Deep Molecular Response with Gilteritinib Associated with Longer OS

Response Outcomes in FLT3-ITD^{MUT} Patients	N=80
Molecular response (ITD signal ratio ≤ 10^{-2}), n (%)	20 (25%)
MRD negative status (ITD signal ratio ≤ 10^{-4}), n (%)	13 (16%)

Achieved Molecular Response ITD signal ratio ≤ 10^{-2}	Median OS (weeks)	95% CI
Yes	59.6	35.1 – NA
No	28.4	20.3 – 33.4

Data on file

Study 0101: Gilteritinib Well-Tolerated in Adult AML Patients

TEAEs Occurring in ≥ 20% of Patients	All Grades N=252		Grade ≥ 3 N=252	
	n	%	n	%
Febrile neutropenia	98	39%	98	39%
Diarrhea	92	37%	13	5%
Anemia	86	34%	62	25%
Fatigue	83	33%	15	6%
Peripheral edema	67	27%	3	1%
Pyrexia	65	26%	13	5%
Elevated AST	66	26%	15	6%
Constipation	57	23%	0	0
Dyspnea	59	23%	12	5%
Cough	54	21%	0	0
Nausea	54	21%	5	2%

Data on file

Study 0101: Most Common Drug-Related AEs - Diarrhea, Fatigue, Elevated AST

TEAEs Occurring in ≥ 7% of Patients	All Grades N=252		Grade ≥ 3 N=252	
	n	%	n	%
Diarrhea	41	16.3%	5	2.0%
Fatigue	37	14.7%	8	3.2%
AST increased	33	13.1%	6	2.4%
ALT increased	24	9.5%	6	2.4%
Anemia	23	9.1%	21	8.3%
Peripheral edema	23	9.1%	1	0.4%
CK increased	22	8.7%	11	4.4%
Constipation	21	8.3%	0	0
Nausea	21	8.3%	2	0.8%
Platelet decreased	20	7.9%	17	6.7%
Dysgeusia	18	7.1%	0	0

Data on file

Study 0101: Most Common AEs Leading to Discontinuation

AEs Leading to Discontinuation >1.5% Preferred Term	Gilteritinib N=252	
	n	%
Total	76	30.2%
Acute myeloid leukemia (disease progression)	15	6.0%
Sepsis	7	2.8%
Respiratory failure	4	1.6%

Data on file

Study 0101: Most Common AE Leading to Death was Disease Progression

AEs Leading to Death (at least 1.5% of patients) Preferred Term	Gilteritinib N=252	
	n	%
Total	95	37.7
Acute myeloid leukemia (disease progression)	41	16.3
Multiple organ failure	7	2.8
Sepsis	7	2.8
Respiratory failure	7	2.8
Pneumonia	4	1.6
Septic shock	4	1.6

- Seven deaths assessed as possibly related to gilteritinib

Data on file

Key Safety Issues Observed in Adult Patients with AML Treated with Gilteritinib

- Posterior Reversible Encephalopathy Syndrome (PRES)
- QTc prolongation
- Musculoskeletal effects
- Liver enzyme abnormalities

Posterior Reversible Encephalopathy Syndrome (PRES)

- Study 0101: 2 patients (120 mg and 200 mg)
  - Seizure, altered mental status
  - Following study drug discontinuation
    - Mental status changes returned to baseline
    - No further seizures
- Compassionate use program: 1 patient (120 mg)
  - Attributed to intrathecal cytarabine
  - Gilteritinib restarted without recurrence of symptoms

Cardiac: QTc Prolongation

QTc Prolongation Events	Gilteritinib N=251
Predicted mean change from baseline QTcF	<10 msec
Predicted upper bound of 95% CI	<10 msec
Maximum post baseline QTc interval of >480 msec (n, %)	25 (10.0%)
Concurrently taking ≥ 1 QTc prolonging medication (n/N, %)	23/25 (92.0%)
Maximum post baseline QTc interval of >500 msec (n, %)	11 (4.4%)
Increase in maximum QTc >60 msec (n, %)	22 (8.8%)

- Study protocols include
  - Exclusion criteria: QTcF >450 msec, history of long QT syndrome, hypokalemia or hypomagnesemia
  - Time-matched PK & electrocardiogram assessments at multiple timepoints

Data on file

Musculoskeletal Effects: Creatine Kinase (CK) Elevations Mostly Grade 1 - 2, Asymptomatic

- Study 0101: clinical musculoskeletal events
  - Drug-related Grade 3 AEs: 2.4%
  - 5 (2.0%) drug-related SAEs
    - 1 patient with rhabdomyolysis (300 mg dose)
      - Resolved after pravastatin & gilteritinib discontinuation
- Clinical study protocols include
  - CK assessments

Data on file

Liver Enzyme Abnormalities: Low Incidence of Grade ≥ 3 Drug-Related AST Elevations

- Grade ≥ 3 drug-related AEs (6.0%)
- No confirmed Hy's Law case
  - No indication of drug-induced liver injury
- Clinical study protocols include
  - Standard hepatobiliary monitoring

Data on file

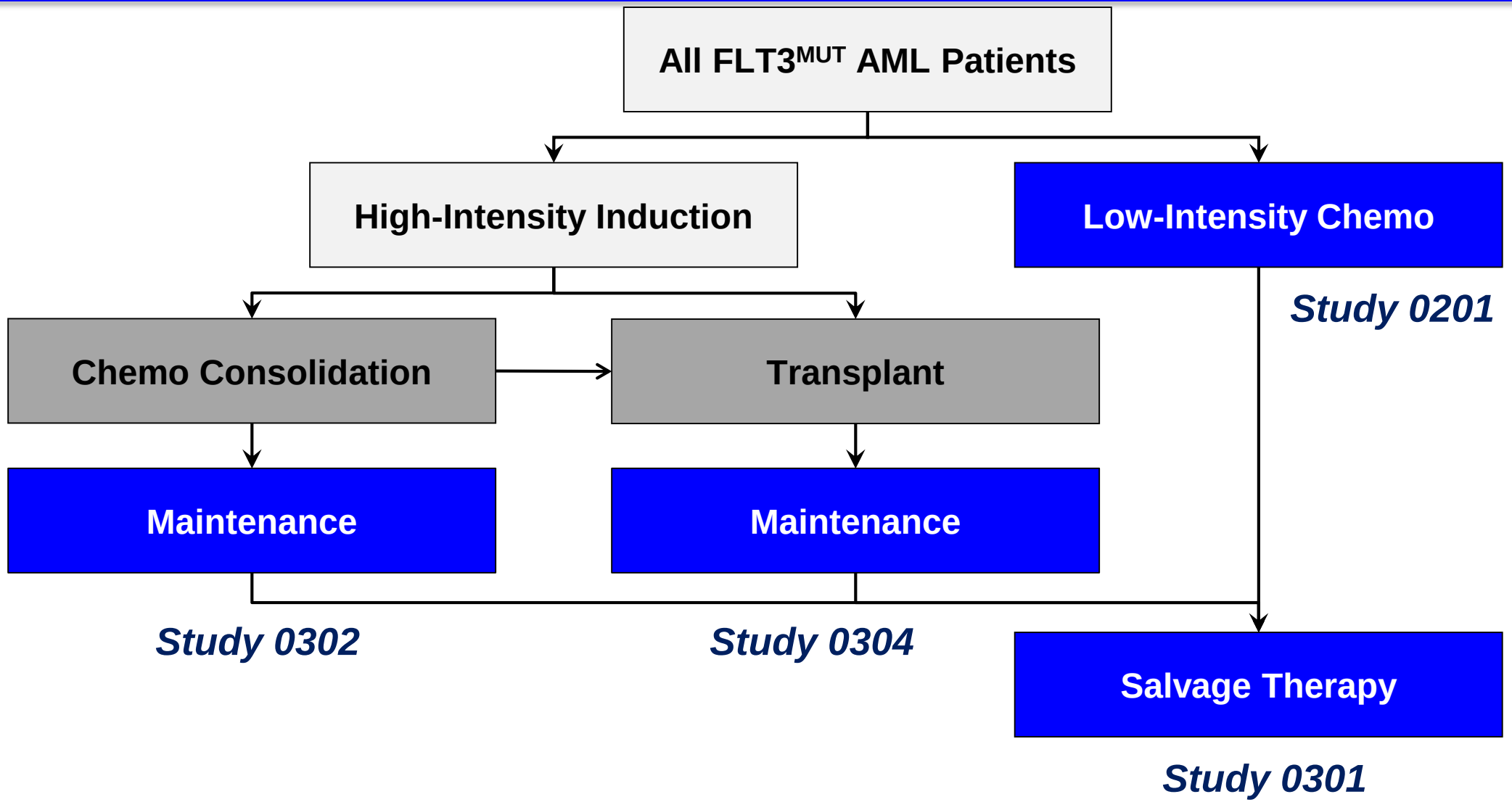
Study 0101: Adult Phase 3 Dose Selected Based on Efficacy, Safety & PK/PD Analyses – 120 mg

- Response plateau with ≥ 80 mg initial dose
- Full target inhibition in most patients at 120 mg

Dose (mg)	CRc in FLT3/ITD^{MUT} AML	
	n/N	%
80 mg	5/12	41.7%
120 mg	26/56	46.4%
200 mg	35/89	39.3%
300 mg	3/10	30.0%

Data on file

Ongoing Gilteritinib Adult Development Program in FLT3 Mutated AML



Summary of Gilteritinib in Adults with Relapsed / Refractory AML

- Robust anti-leukemic activity demonstrated in FLT3/ITD^{MUT} AML
- Oral treatment well-tolerated in adults
- Adult data foundation for pediatric study

Agenda

- Unmet Need in target patient population
- Gilteritinib’s mechanism of action
- Adult development program
- Proposed pediatric development program

Pediatric Development Plan to Provide Sufficient Data for Label in Orphan Population (FLT3/ITD^{MUT})

- 2 clinical studies: gilteritinib in combination with chemotherapy
- Conducting nonclinical juvenile toxicology study
- Pediatric formulation under development

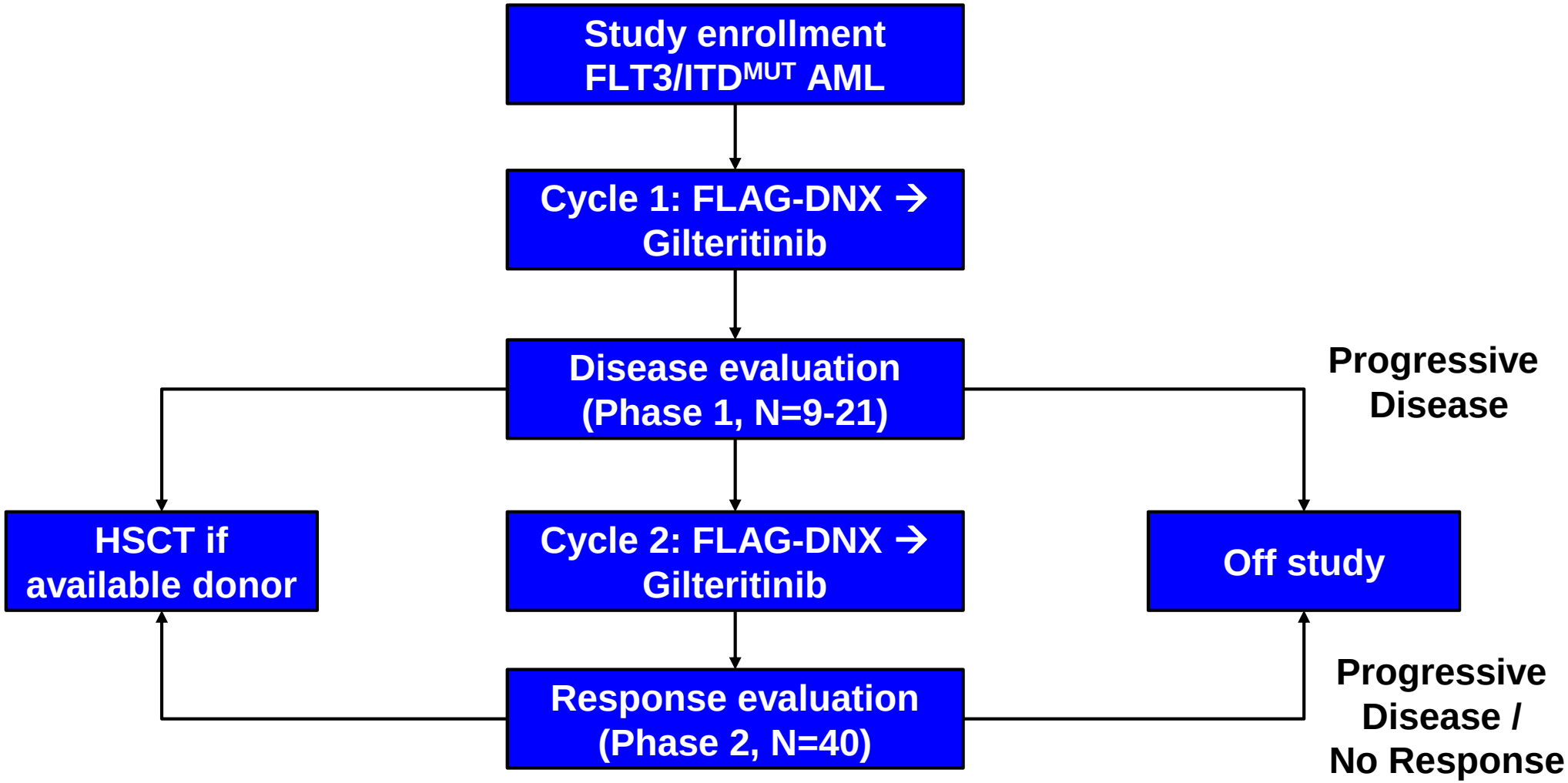
Proposing Use of Historical Control

- Rationale based on feedback from pediatric experts
  - Poor outcomes with standard therapy
  - Emerging adult data
  - Small patient numbers
    - ~100 newly diagnosed patients with FLT3/ITD^{MUT} AML each year in US

Study 0603: Open-label, Single Arm Phase 1/2 Study

- Relapsed / Refractory FLT3/ITD^{MUT} AML
- Anticipate enrolling
  - Phase 1 = 9-21 patients
  - Phase 2 = 40 patients
- 6 months - 21 years of age
- <2 years enrollment pending acceptable juvenile toxicology

Study 0603: Design



Study 0603: Phase 1 Dose and Recommended Phase 2 Dose Criteria

- Starting dose 40 mg/m^2
  - One dose level lower than adult starting dose
  - De-escalate to 20 mg/m^2, escalate to 60 or 90 mg/m^2 based on toxicity
- Recommended Phase 2 dose based on
  - Acceptable safety profile
  - Biologic activity measured by PIA assay

Study 0603: Phase 2 to Evaluate Composite Complete Remission (CRc) Rate

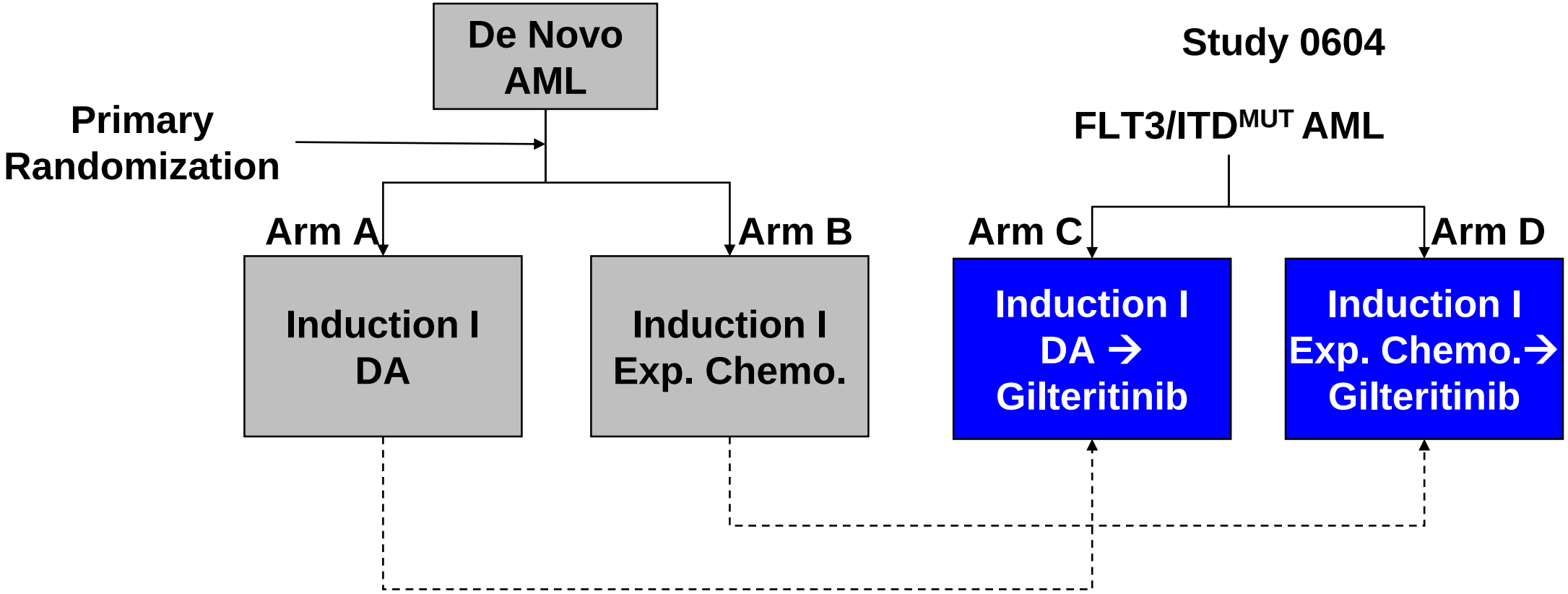
- Two-stage open label design
- N = 40 enrolled
- Primary endpoint
  - CRc rate after two cycles vs. 35% historical CR rate[1]
- Type 1 error = 5%
- 80% power to detect 21% increase CRc (56% vs 35%)

1. COG AAML 06P1, I-BFM AML 2001-01, Costa dataset

Study 0604: Open-label, Parallel Group Phase 2 Study

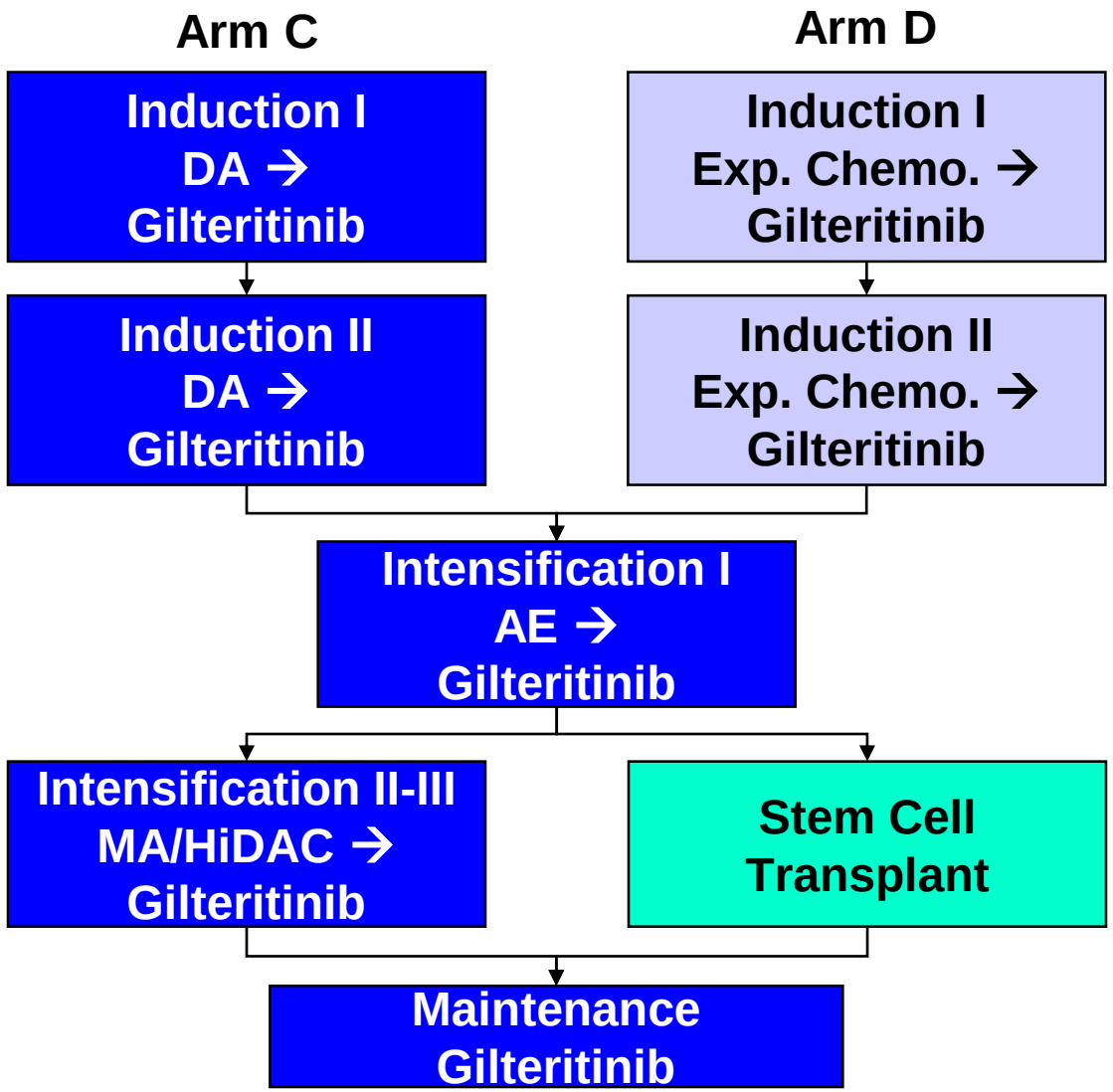
- Newly diagnosed FLT3/ITD^{MUT} AML
- Anticipate enrolling ~56 patients per arm
  - 6 months - 21 years of age
  - <2 years enrollment pending acceptable juvenile toxicology
- Starting dose – Study 0603 recommended Phase 2 dose

Study 0604: Within Pediatric Oncology Cooperative Group Phase 3 Study



DA: daunorubicin + cytarabine
Exp. Chemo.: Experimental Chemotherapy

Study 0604: Trial Design for Patients with FLT3/ITD^{MUT} AML

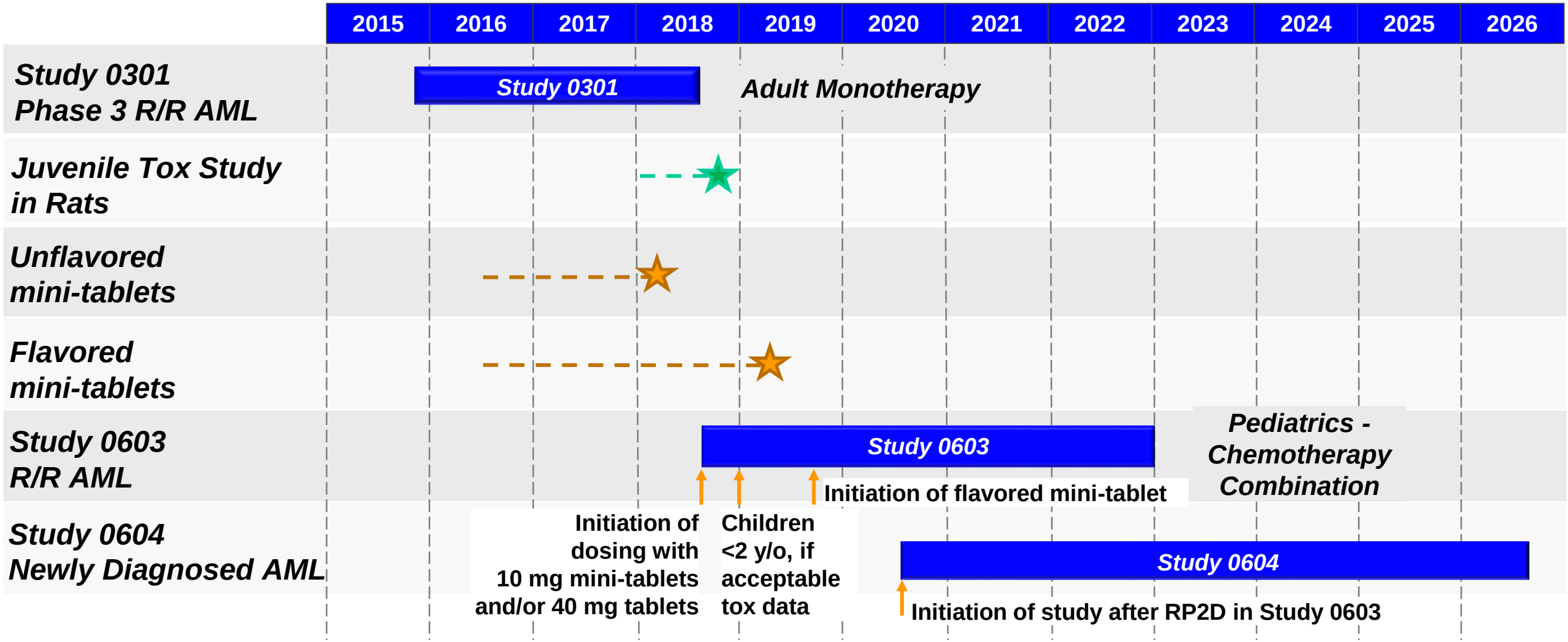


DA: daunorubicin + cytarabine
AE: cytarabine + etoposide
MA: mitoxantrone
HiDAC: high dose cytarabine
Exp. Chemo.: Experimental Chemotherapy

Study 0604: Primary and Key Secondary Endpoints

- Primary endpoint
  - 2-year event free survival
- Key secondary endpoints
  - Complete remission
  - Overall survival

Gilteritinib Proposed Pediatric Development Plan



Gilteritinib Summary

- Encouraging single-agent anti-leukemic activity in FLT3/ITD^{MUT} AML in adults
- Acceptable and well-characterized safety profile
- Pediatric plan designed to inform pediatric labeling
  - Safety – cardiovascular effects for combination daunorubicin → gilteritinib
  - Efficacy – CRc, EFS, OS, MRD
  - Pharmacokinetics

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BACKUP SLIDE

Table 14: Study 2215-CL-0101: Drug-related Adverse Events Leading to Death

Dose Level (mg)	MedDRA (V16.0) Preferred Term	Day of Death	Last Dose Day	Relationship to Study Drug	Sponsor Comment
20	**Haemorrhage intracranial**	11	11	Possible	The Sponsor assessed the event of intracranial hemorrhage as possibly related to the study drug, based on the available information and in alignment with the investigator; however, the underlying AML was considered a confounder. Concurrent conditions included decreased platelets which may have predisposed the patient to bleeding.
80	**Septic Shock** Renal failure acute Hyponatraemia	14	12	Possible Not related Not related	The Sponsor assessed the event of septic shock as possibly related to study drug considering a plausible temporal relation and known drug profile, however, reduced immunity due to underlying malignancy may have provided a more plausible alternative etiology for the event. The Sponsor assessed the event of acute kidney injury as not related to study drug as current conditions of hypertension, mild chronic kidney disease, disease under study, and anti-hypertensive medications provided more plausible explanations. The Sponsor assessed the event of hyponatremia as not related to study drug as it was probably due to poor oral intake by the patient, additionally multiple concomitant medications may have played a contributory role.
80	**Hemoptysis**	61	57	Possible	The Sponsor assessed the event of hemoptysis as possibly related to study drug per the implied time line. A confounder was underlying AML. Autopsy summary showed that lung involvement of AML and/or concurrent fungal pneumonia likely contributed to the erosion of a pulmonary vessel leading to massive hemoptysis in the setting of chronic pancytopenia and coagulopathy.
120	**Ventricular fibrillation***	12	10	Possible	The Sponsor assessed the event of ventricular fibrillation as possibly related to study drug. Considering the plausible temporal relationship, a causal role of the study drug in the reported event could not be excluded. However, electrolyte abnormalities preceding the reported event, supraventricular tachycardia prior to initiation of study drug, history of smoking, cardiac disorders, concomitant use of levofloxacin, baclofen, amphotericin-B, meropenem, and caspofungin with the potential risk of cardiac adverse reactions were confounders for the reported event.
120	**Respiratory failure** Subdural haematoma Sepsis	15	8	Probable Not related Not related	The Sponsor assessed the event of respiratory failure as probably related to study drug based on the temporal association present and a potential risk of differentiation syndrome and capillary leak with the study drug treatment. The Sponsor assessed, in agreement with reporting Investigator, the event of subdural hematoma as not related to study drug. Of note, the underlying AML and bleeding associated with it may have provided an alternative explanation for the event. The Sponsor assessed the event of sepsis as not related to study drug. The underlying AML with concurrent pleural and pericardial effusions was considered a strong confounding factor.
120	**Neutropenia** Diarrhoea	94	72	Possible Not related	The Sponsor assessed the event of neutropenia as possibly related to study drug based on the plausible temporal relationship present. However, the underlying AML was deemed a strong confounding factor for the fatal event. The patient died due to severe neutropenia with anemia and thrombocytopenia. The Sponsor assessed the event of diarrhea as not related to study drug; the event was attributed to an unspecified concurrent illness.
300	**Pulmonary embolism**	8	8	Possible	The Sponsor assessed the event of pulmonary embolism as possibly related to study drug based on temporal relationship; confounded by underlying disease. Patient was on do-not-resuscitate orders. An autopsy was performed and the cause of death was pulmonary embolism.

Bolded MedDRA Preferred Term indicates the AE that resulted in death

* Same patient described in the table below in Table 15