19th Post-ASH Meeting

Acute Leukemia

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AML

The decision-making process in AML

- Clinical evaluation
- Genetic informations
- MRD data

- Do I treat my patient with an intensive (= possibly curative) versus a non intensive (= probably never curative) approach ?
- Do I have therapeutic targets to improve the current treatment ?
- Is there an indication for SCT, maintenance therapy, …

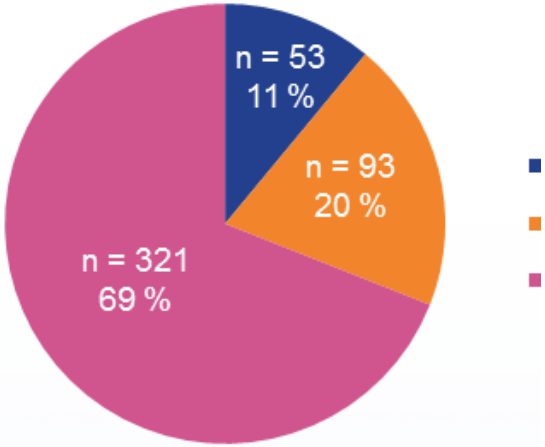
The headhache of prognostication

RISK STATUS	CYTOGENETICS	MOLECULAR ABNORMALITIES
Favorable-risk[5]	Core binding factor: inv(16)[2,3] or t(16;16)[2] or t(8;21)[2] t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined	
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[4]	Normal cytogenetics: with FLT3-ITD mutation[6] TP53 mutation **« AML with mutated RUNX1 »**

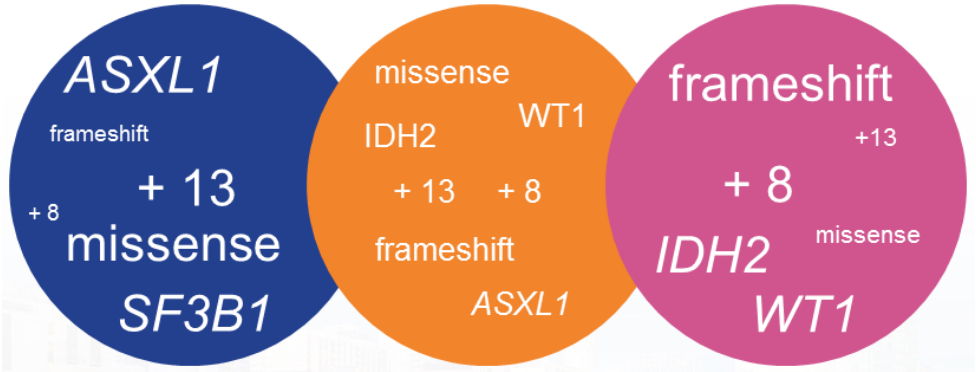
« AML with mutated RUNX1 » ?

Critical transcription factor involved in HSC differentiation

10-15% AML, associated with therapy-related disease, older age, increased cytopenias, shorter survival and chemoresistance



RUNX1 mut AML
n = 467



OS: 5 months

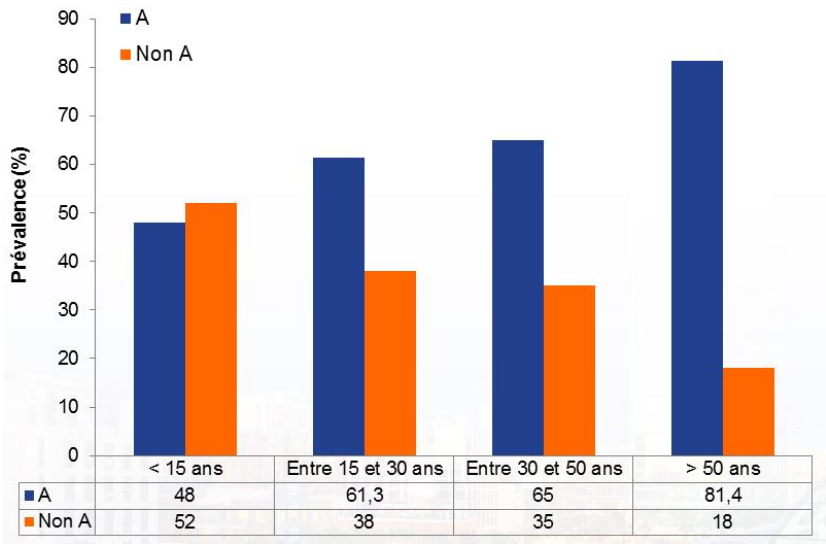
OS: 14 months

OS: 22 months
(p=0,002; p=0,048)

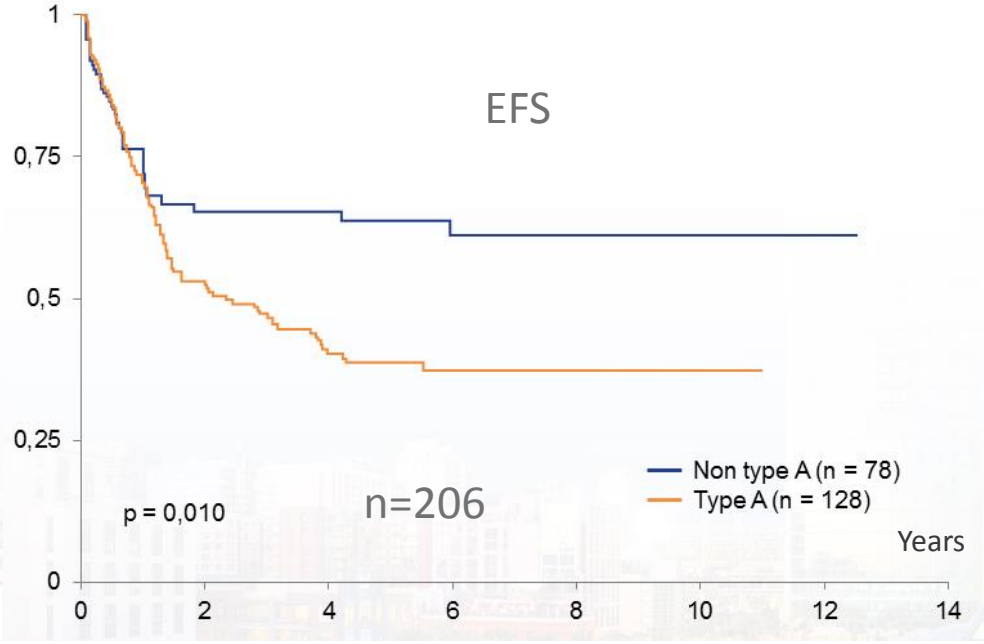
A. Stengel et al. Abstract 284, ASH 2016

NPM1 insertion type do matter

Frameshift mutations are the result of 4 base pair (bp) insertions in exon 12
There are several genomic subsets of insertions, type A variant (insertion of TCTG) being the most common



	< 15 ans	Entre 15 et 30 ans	Entre 30 et 50 ans	> 50 ans
A	48	61,3	65	81,4
Non A	52	38	35	18

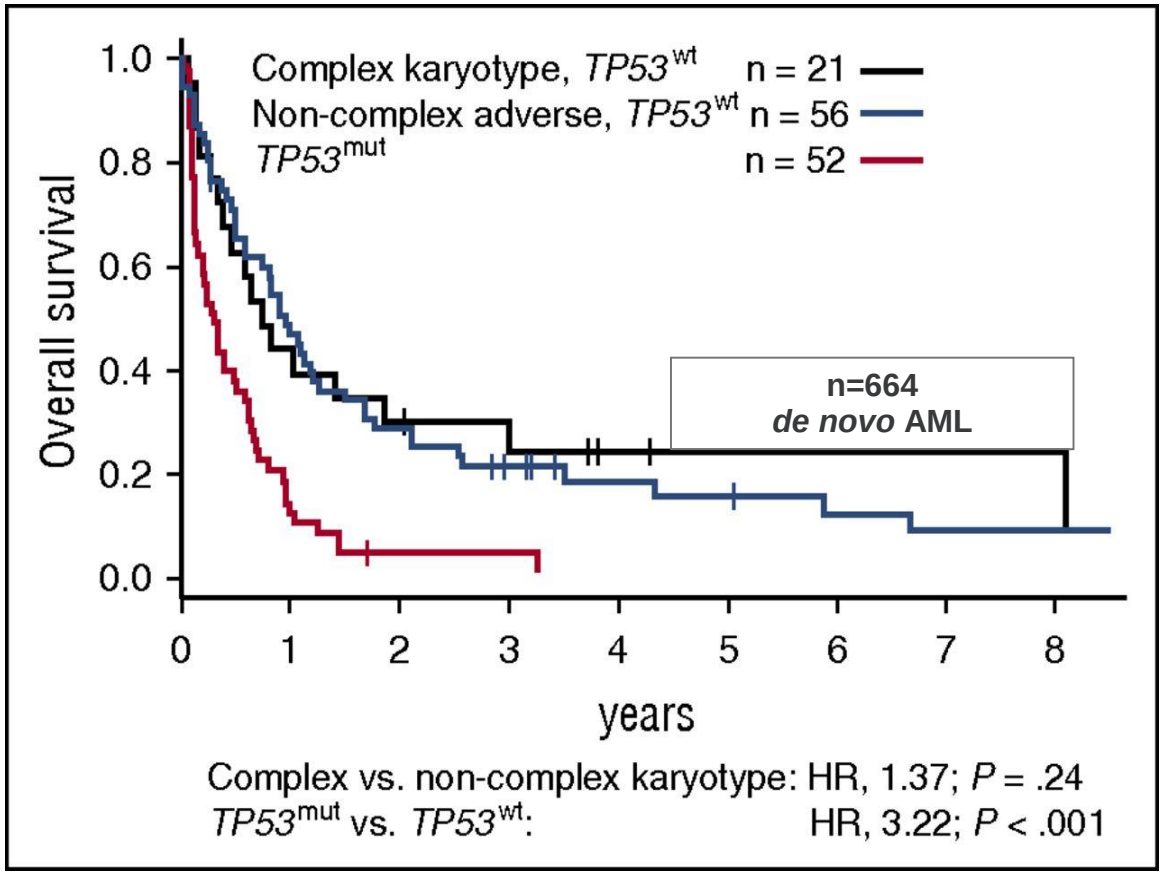


5 yr EFS of 39% vs. 64%, p=0.01
5 yr RFS of 41% vs. 70%, p=0.002
… regardless of age or FLT3/ITD status

D. Selim et al. Abstract 285, ASH 2016

TP53 mutations and prediction of response

Key TS involved in genomic stability, cell cycle regulation, metabolism and DNA repair
Associated with advanced age, complex karyotype, chemo-resistance, and dismal survival



Dohner H et al, NEJM 2015
Metzeler KH et al, Blood 2016

TP53 mutations and prediction of response

Prognostic value of TP53 mutation in the AZA-AML-001 study comparing azacytidine (AZA) vs conventional care regimen (CCR) in older patients with AML (Dombret et al, Blood 2015)
The biomarker cohort comprised 156 of all 488 pts (32%; AZA n=83, CCR n=73)

Table. Median OS associated with mutated genes: AZA vs CCR

Mutated Gene	Median OS AZA (mos)	Median OS CCR (mos)	*P* value
TP53	7.2 (3.9, 18.6)	2.4 (1.5, 7.1)	0.069
NRAS	11.8 (7.7, NR)	4.3 (2.3, NR)	0.047
FLT3 (-ITD or -TKD)	5.4 (4.5, NR)	6.4 (3.8, NR)	0.17
TET2	9.6 (4.5, 13.5)	11.1 (2.8, NR)	0.082
IDH1	11.1 (1.3, NR)	14.6 (3.7, NR)	0.773
IDH2	12.6 (4.4, NR)	12.5 (5.6, NR)	0.914
DNMT3A	12.6 (7.0, 20.8)	10.3 (3.8, NR)	0.963
Any DNA methylation gene (*IDH1*, *IDH2*, *DNMT3A*, *TET2*)	11.1 (5.8, 15.4)	12.5 (4.3,17.6)	0.497

Similar observations have been reported for decitabine in TP53 mutated and unfavorable karyotype AML

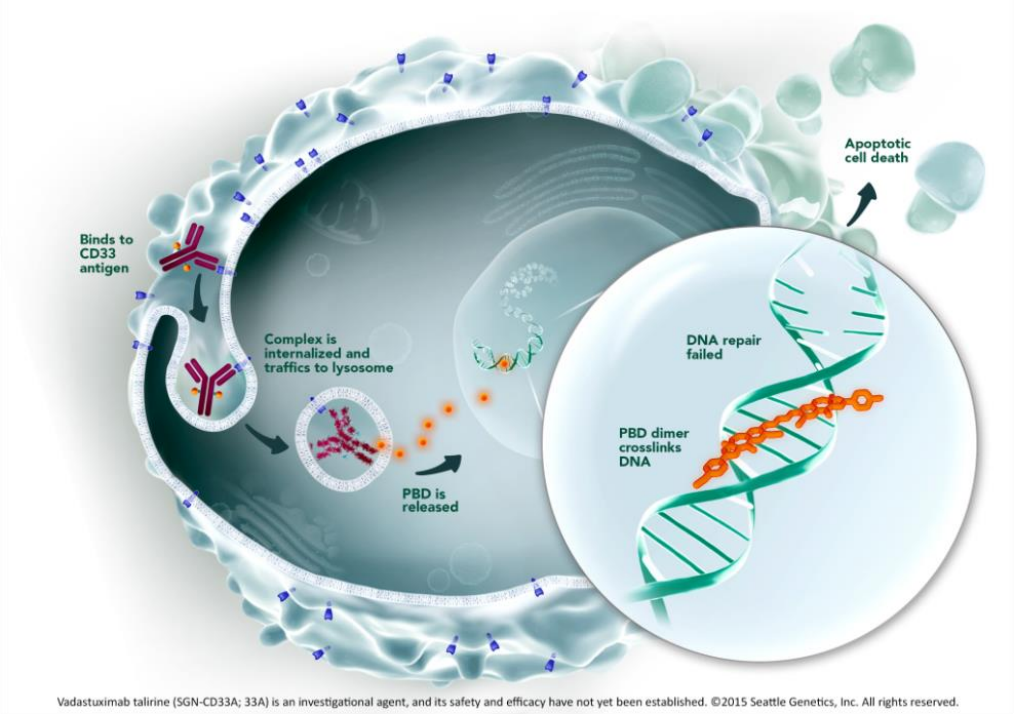
Welch JS et al. NEJM 2016

L. Tang et al. Abstract 2859, ASH 2016

The long parade of HMA combined therapies

HMA + vadastuximab talirine (33A)

New CD33-directed antibody-drug conjugate that links to 2 molecules of a pyrrolobenzodiazepine (PBD) dimer, a new agent that crosslinks DNA



Vadastuximab talirine + HMA

- Open-label, phase I combination cohort study

Previously untreated CD33+ AML pts aged ≥ 60 yrs ineligible for intensive induction/consolidation therapy (n=53)

→

Azacitadine 75 mg/m^2 SQ/IV x 7 days
or Decitabine 20 mg/m^2 IV x 5 days
+
Vadastuximab talirine
10 µg/kg IV on last HMA day
4 x 4-wk cycles

→

If clinical benefit, continue until recurrence

Follow-up every 3 months

AT. Fathi et al. Abstract 591, ASH 2016

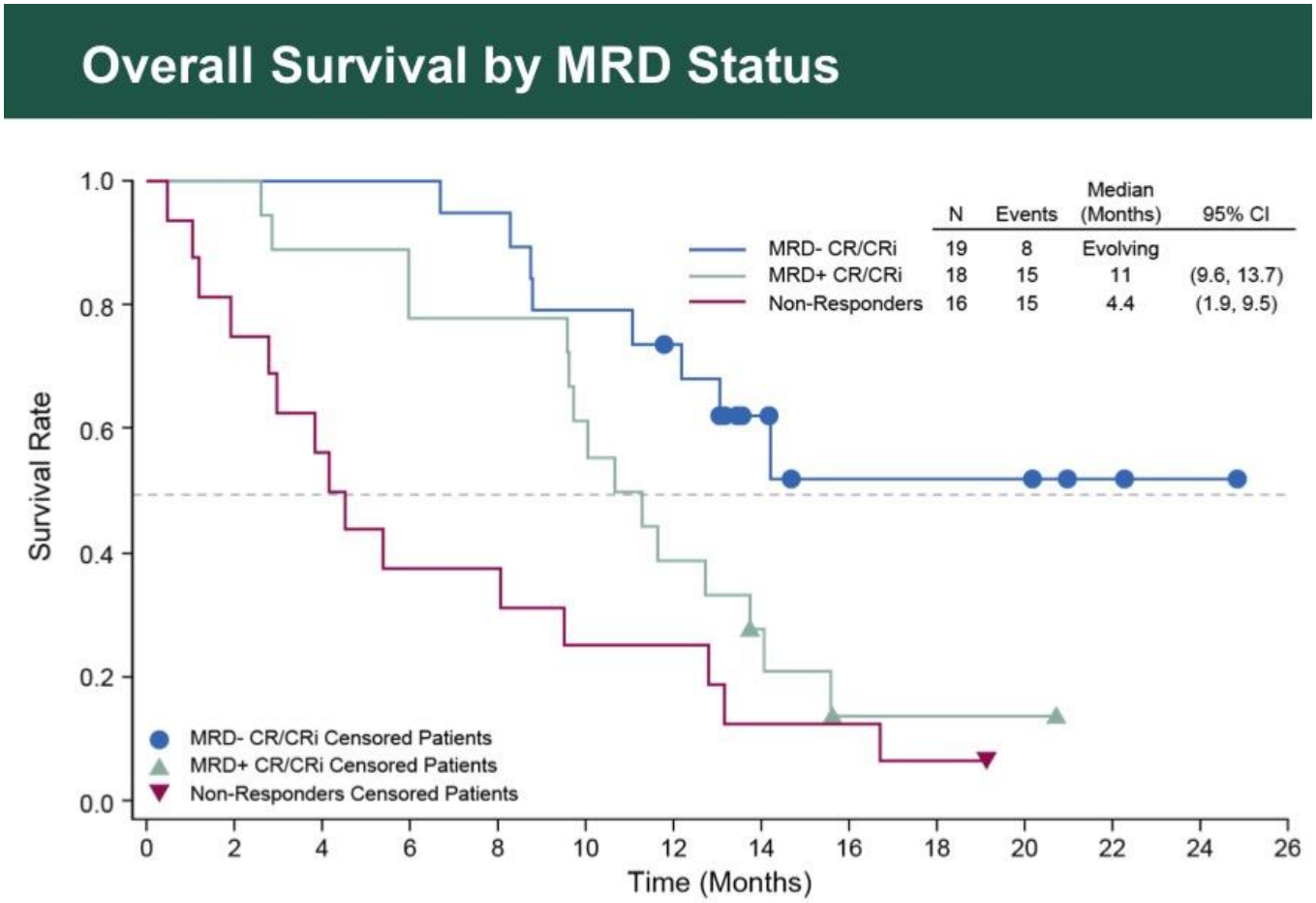
Vadastuximab talirine + HMA

Outcome, %	Evaluable Pts (n = 49)	Secondary AML Pts‡ (n = 22)	Pts with *FLT3/ITD*+ AML (n = 5)	Pts Aged ≥ 75 Yrs (n = 26)
Remission rate (CR + CRi)	73	77	100	65
CR	47	50	80	38
CRi (p)*	20	18	20	19
CRi (n)†	6	9	0	8
mLFS	2	5	0	4
ORR (CR+CRi+mLFS)	76	82	100	69

- 50% of pts with response achieved MRD negativity by FCT
- Thrombocytopenia was the main toxicity. No VOD signals

AT. Fathi et al. Abstract 591, ASH 2016

Vadastuximab talirine + HMA



AT. Fathi et al. Abstract 591, ASH 2016

Pracinostat + AZA

Potent oral HDAC inhibitor expected to induce a reexpression of silenced genes in a synergistic fashion

- Phase 2 study

Untreated *de novo* or secondary AML pts ≥ 65 yrs not eligible for induction (n=50)

→ Azacitadine 75 mg/m^2 SC or IV x 7 days
+
Pracinostat
60 mg orally 3 days/week on alternate days for 3 weeks

→ If clinical benefit, continue until recurrence

G. Garcia Manero. Abstract 100, ASH 2016

Pracinostat + AZA

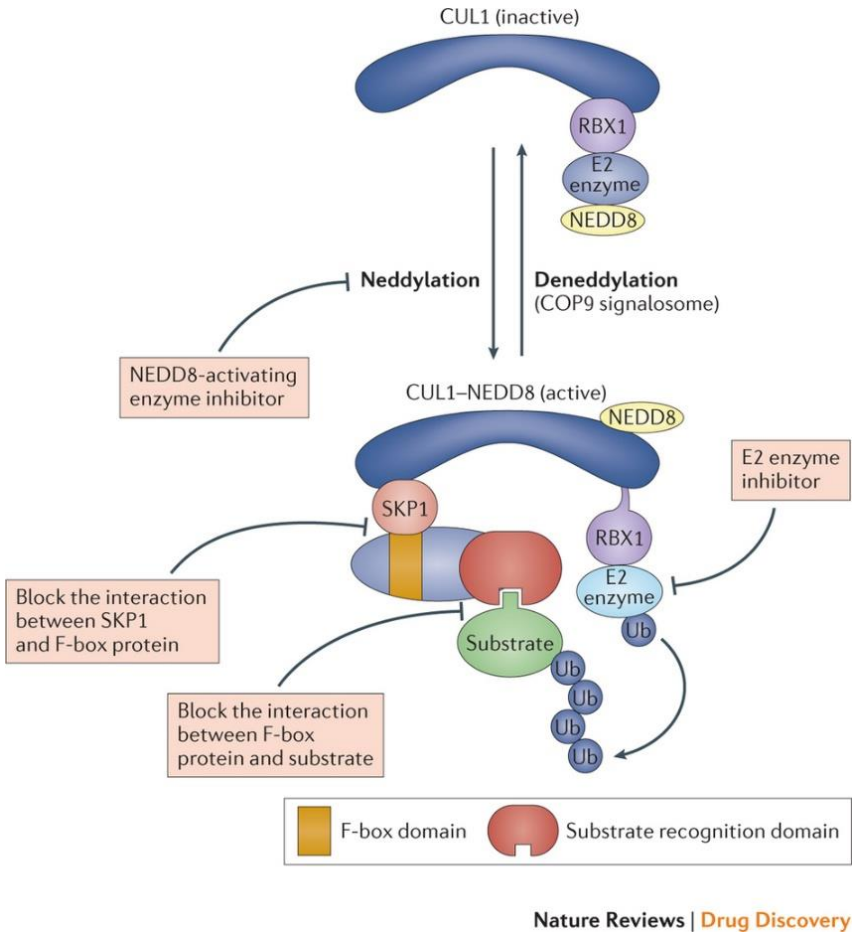
	CR Rate	cCR Rate	Survival (months) (Median, 95% CI)
Overall population (N = 50)	42%	52%	19.4 (10.0-NR)
Cytogenetics			
Intermediate (N = 27)	48.1%	59.3%	NR (10.7, NR)
High risk (N = 21)	38.1%	47.6%	13.5 (2.4, NR)
Age			
≥75 (N = 26)	42.3%	57.7%	13.5 (9.0, 21.5)
66-74 (N = 24)	41.7%	45.8%	26.5 (8.0, 26.5)
Type AML			
De novo (N = 33)	42.4%	51.5%	13.02 (5.7, 26.5)
Secondary (N = 17)	41.2%	52.9%	NR (>16.4, NR)
ECOG Performance Status			
0-1 (N = 42)	40.5%	50.0%	19.08 (10.0, 19.1)
2 (N = 8)	50.0%	62.5%	13.0 (8.0, 26.5)

CI = Confidence Interval, NR = Not Reached

- cCR (CR/CRi/morphologic leukemia free state) was achieved in 52% (42%/4%/6%)
- Median duration of cCR was 13.2 months, CI [10.9-21.5]
- Median OS of 19.1 months CI [10.0-not reached, median follow-up of 21 months)

Pevonedistat + AZA

First-in-class NEDD8-activating enzyme inhibitor disrupting proteasome-mediated protein degradation



Pevonedistat + AZA

- Phase I

Older AML pts unlikely to benefit from standard induction therapy (n=61) → Azacitadine 75 mg/m^2 SQ/IV x 7 days or Decitabine 20 mg/m^2 IV x 5 days + pevonedistat 20 or 30 mg/m IV on days 1, 3 and 5 → If clinical benefit, continue until recurrence

- CR/CRi was obtain in 44% of response-evaluable pts (n=52).
- Median OS was 7.0 months for the MTD cohort
- There was limited additional toxicity

RT. Swordset al. Abstract 98, ASH 2016

Pevonedistat + AZA

Figure 2: Kaplan-Meier curve of overall survival for MTD cohort (n=61) by baseline aspirate blast counts subgroup (<30% vs ≥30% marrow blasts)

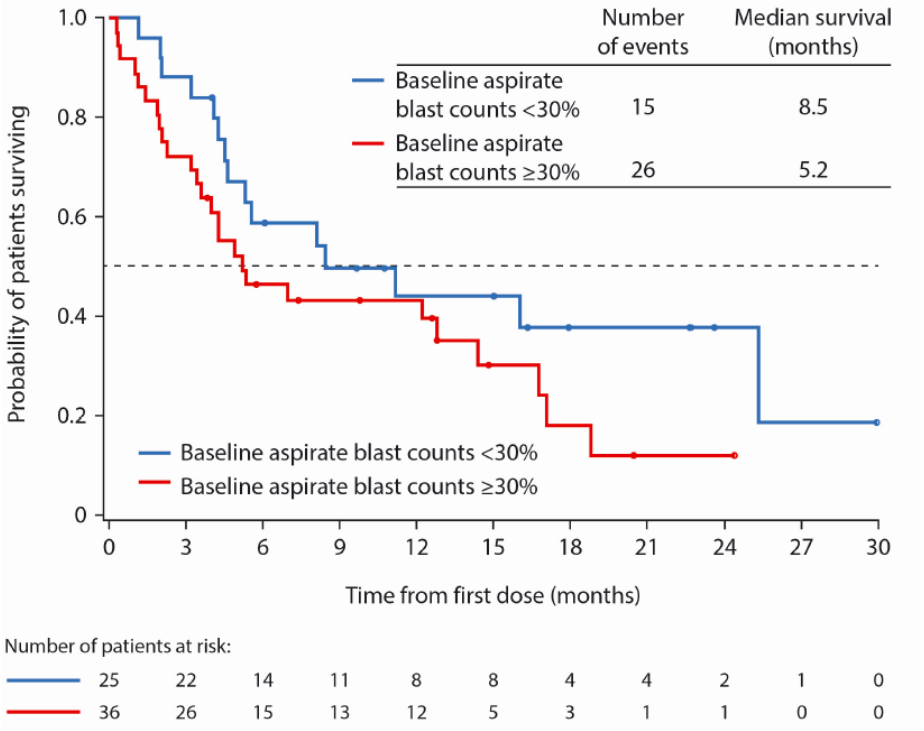
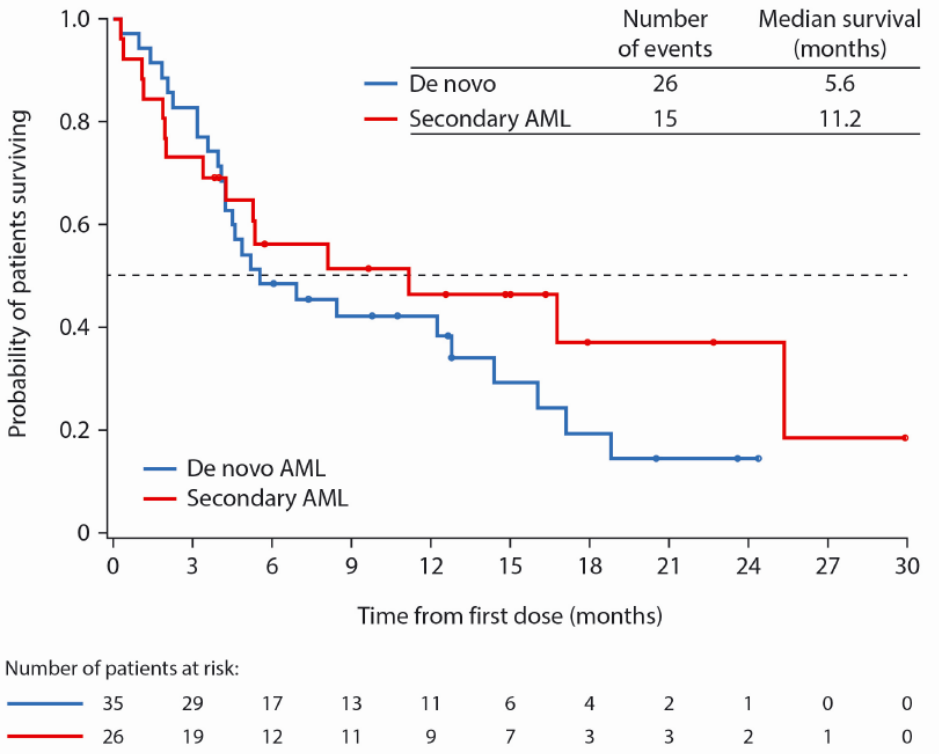


Figure 3: Kaplan-Meier curve of overall survival for MTD cohort (n=61) by disease characteristic subgroup (de novo vs secondary AML)



RT. Swordset al. Abstract 98, ASH 2016

Nivolumumab + AZA

Monoclonal antibody targeting programmed cell death protein 1 (PD-1)

AZA upregulates PD-1 and PD-L1 in AML → resistance to therapy

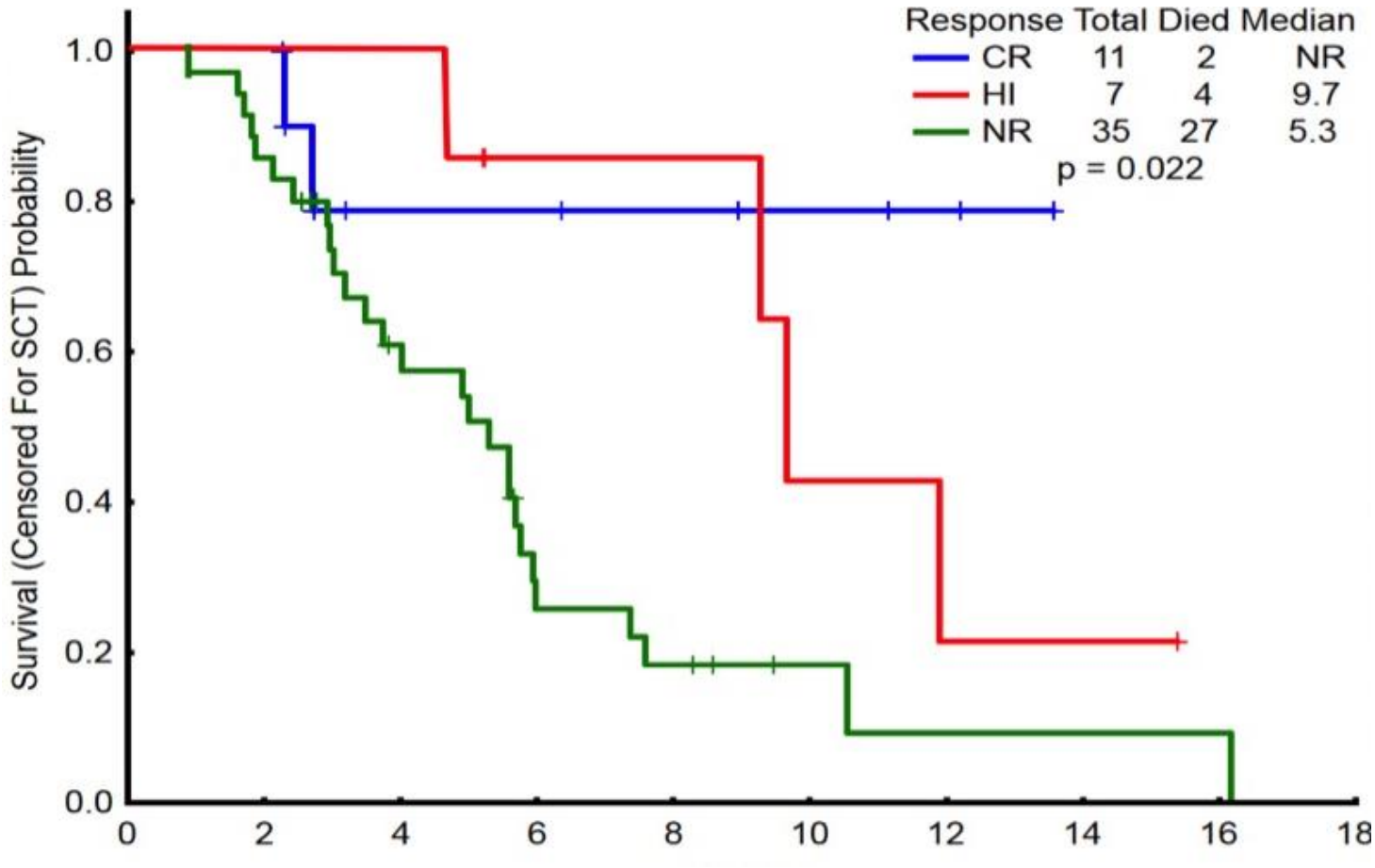
- Phase IB/II study conducted at the MDACC

In 51 R/R AML pts (n=51) → Azacitadine 75 mg/m^2 SQ/IV x 7 days + Nivolumumab 3mg/kg on day 1 and 14 → Responses were evaluated at the end of 3 courses of therapy so that **only 35/51 pts were evaluable**

- Durable CR/CRi or HI in 18% and 15% respectively
- Median OS was 9.3 months (range, 1.8–14.3)
- Compares favorably to historical survival with AZA-based salvage protocols

N. Daver et al. Abstract 763, ASH 2016

Nivolumumab + AZA



N. Daver et al. Abstract 763, ASH 2016

Quizartinib + HMA

Activating mutations of FLT3 occur in 30% of AML cases

Quizartinib is a potent, selective FLT3-ITD inhibitor, *in vitro* synergy with AZA/LDAC

- Phase I/II

R/R (phase I) and untreated (phase II) FLT3 mutated AML/MDS/CMML pts (n=52)

→

AZA (n=38)
LDAC (n=14)
+
Quizartinib 60 mg daily (phase II)

→

If clinical benefit, continue until recurrence

Follow-up every 3 mos

- ORR of 67% (CR=8, CRp=7, CRi=18, PR=2); 23% for LDAC arm and 77% for AZA arm
- Median OS: 14.8 months (7.5 months for the LDAC arm and not reached for the AZA arm)
- Clinically significant QTcF prolongation was infrequent

Similar results with sorafenib + AZA (M. Ohanian et al. Abstract 1611. ASH 2016)

W. Abdelall et al. Abstract 1642, ASH 2016

CD123, the perfect myeloid target?

Immunotherapy works best when the disease load is reduced and is therefore particularly indicated to eliminate MRD

Leukemic stem cell (LSC) participates to MRD persistence and reappearance. The ideal target for immunotherapy has to be expressed on LSC surface

CD123 (IL-3 receptor α chain) has emerged as a very promising target for immunotherapeutic strategies in AML

- aberrant expression frequently observed in a subset of leukemic disorders
- increased CD123 expression is associated with a poor prognosis

N. Arai et al. Abstract 2887, ASH 2016

Blastic plasmacytoïd dendritic cell neoplasm

BPDCN is a rare myeloid entity

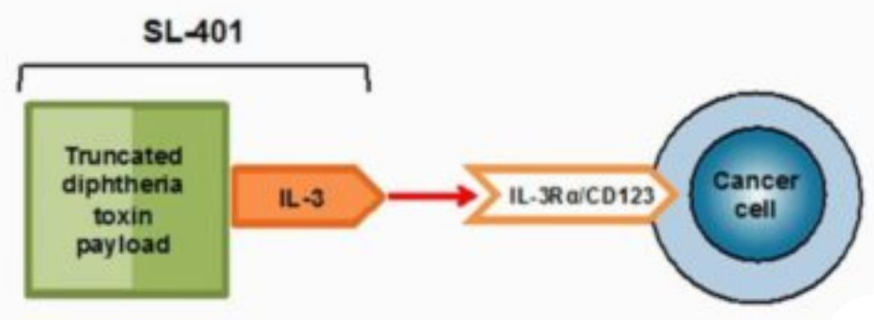
Caracterised by a particular CD4, CD56, CD123, TCL-1 expression profil, frequent skin involvement, sometimes as primary site

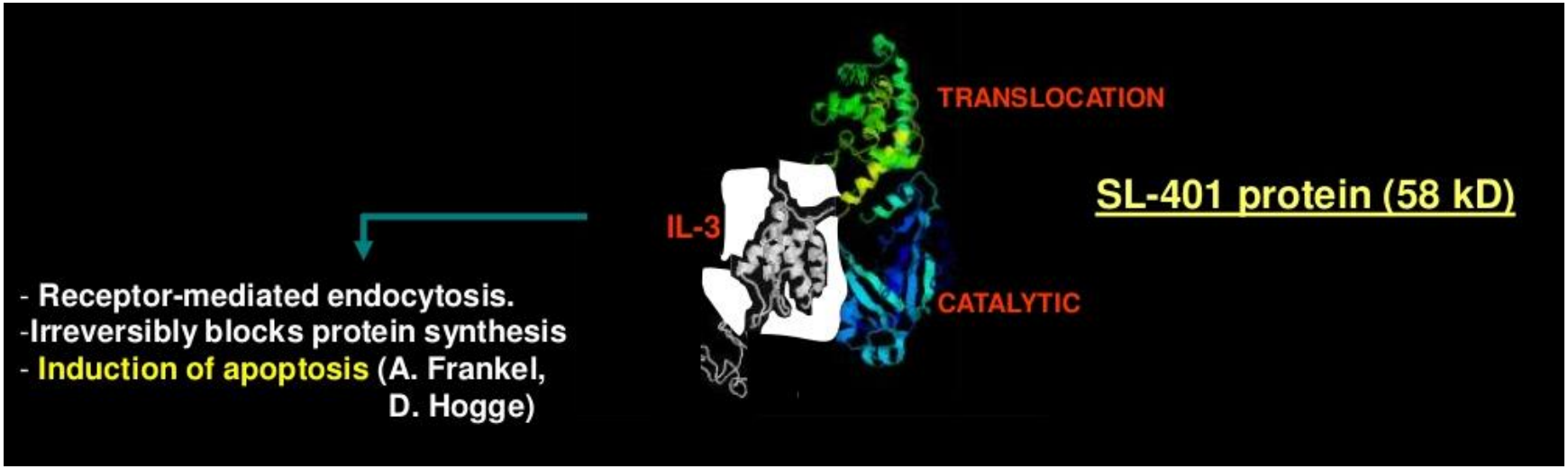
No standard of care. ALL type treatment usually proposed

OS is poor, arround 8-14 months.

CD123 is overexpressed in nearly 100% of pts with BPDCN

New strategies targeting CD123: SL-401





New strategies targeting CD123: SL-401

In pts with BPDCN

- Phase 2 trial ongoing expension stage of SL-401

Daily IV infusion dose of 12 µg/kg

CR/CRc: 81% (13/16) when used in 1ste line and 31% (4/13) in R/R setting

7/32 pts underwent allo or auto

In pts with AML in CR1 or CR2 with high risk of relapse

- Multicenter, single-arm phase 2 trial

Lead-in stage 1 completed without DLT or MTD, and stage 2 (expansion) still open

Safety profile similar to that observed in other SL-401 clinical studies

Potential to reduce this chemo-resistant cell population and to offer improved long-term outcomes

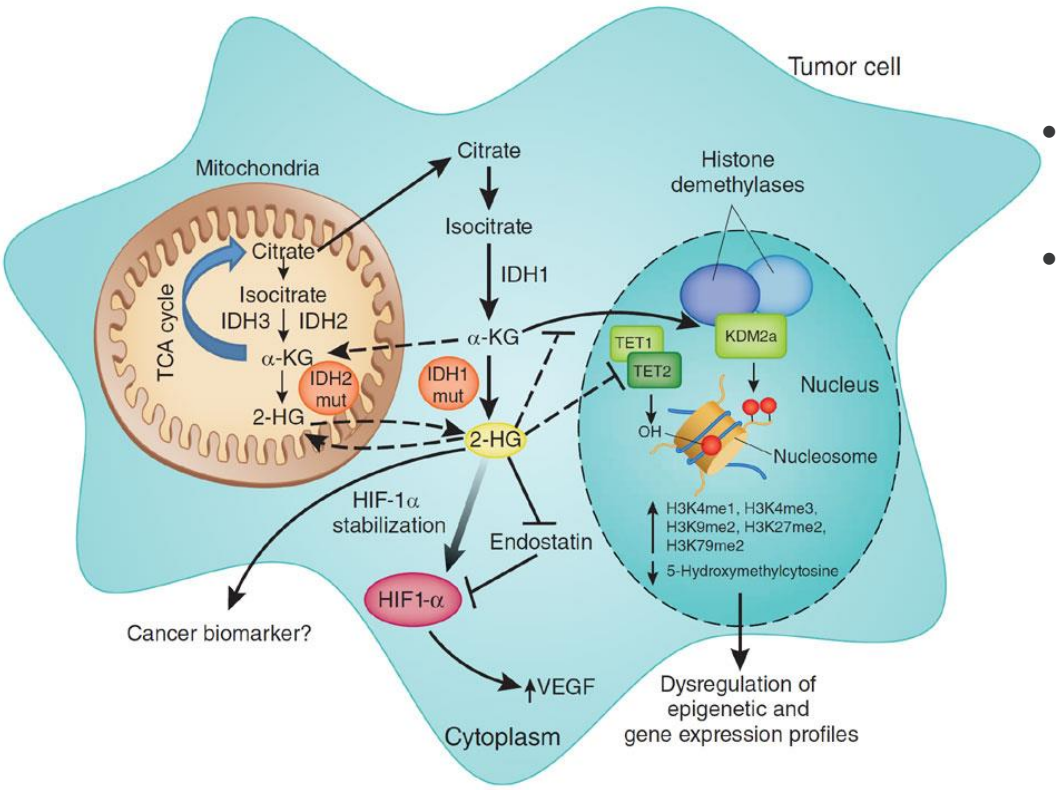
N. Pemmaraju et al. Abstract 342, ASH 2016
AA. Lane et al. Abstract 215, ASH 2016

Preclinical studies targeting CD123

- IMGN632
  - another CD123-directed antibody-drug conjugate
  - conjugation with indolinobenzodiazepine dimers for DNA alkylation
- JNJ-63709178
  - anti-CD3/CD123 bispecific humanized IgG4
  - recruits CD3+ T cells to CD123+ tumor cells and induces their killing
- Allogeneic TCRα/β deficient CAR T-cell targeting CD123
  - prolongs OS of AML and BPDCN patient-derived xenografts

Y. Kovtun et al. Abstract 768, ASH 2016
F. Gaudet et al. Abstract 2824, ASH 2016
R. Mani et al. Abstract 580, ASH 2016
T. Cai et al. Abstract 4039, ASH 2016

IDH1/2 inhibitors

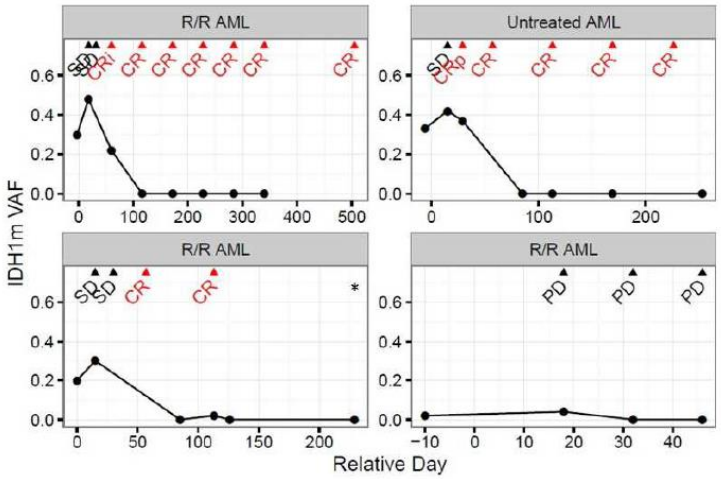


- IDH mutations in ~ 20% of AML, in founding clone
  - *6-10% IDH1-R132*
  - *9-15% IDH2-R140 or IDH2-R172*
- Associate with *NPM1* and *FLT3* mutations, CN-AML
- Accumulation of 2HG competitively inhibits αKG
  - Hypermethylated phenotype via silencing of TET family
  - Block in differentiation via inhibition of histone demethylases
  - Altered hypoxic response
  - BCL2 dependence

AG-120

AG-120, a first-in-class, oral, potent, reversible, selective inhibitor of the IDH1 mutant enzyme is under evaluation in multiple ongoing single agent and combination clinical trials

- Courtney D. DiNardo presented the first demonstration that treatment with single agent AG-120 can result in mutated IDH1 clearance as determined by NGS

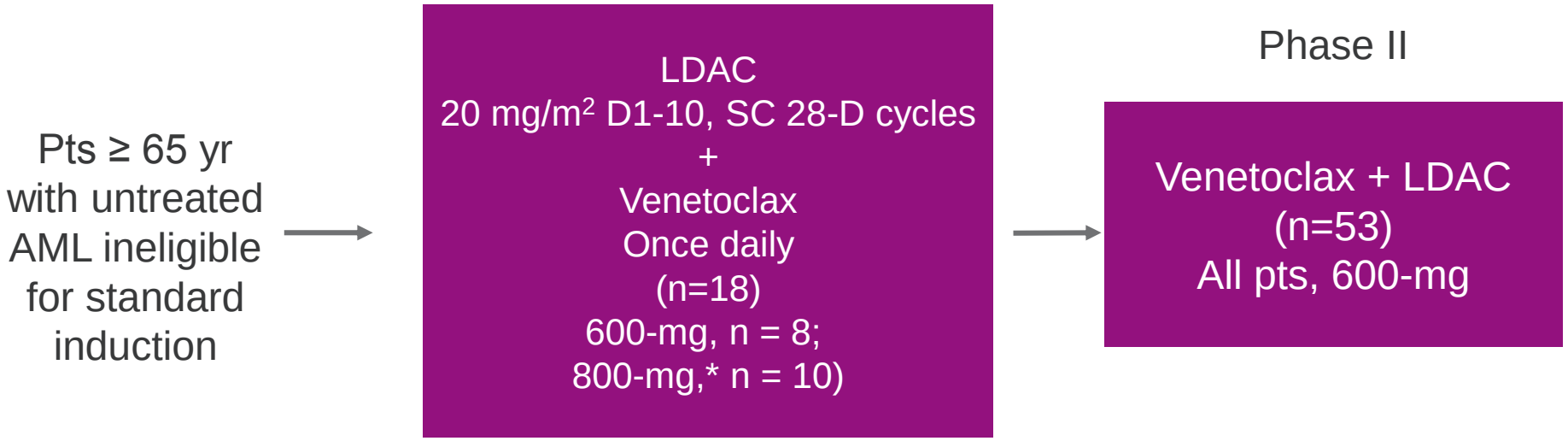


- Studies with the IDH2 inhibitor, enasidenib (AG221) and the pan IDH1/IDH2 inhibitor AG881 are also ongoing

CD. DiNardo et al. Abstract 1070, ASH 2016

Venetoclax for AML?

- Phase I (3+3 design)



*2 pts had dose-limiting toxicity at the 800-mg dose level.

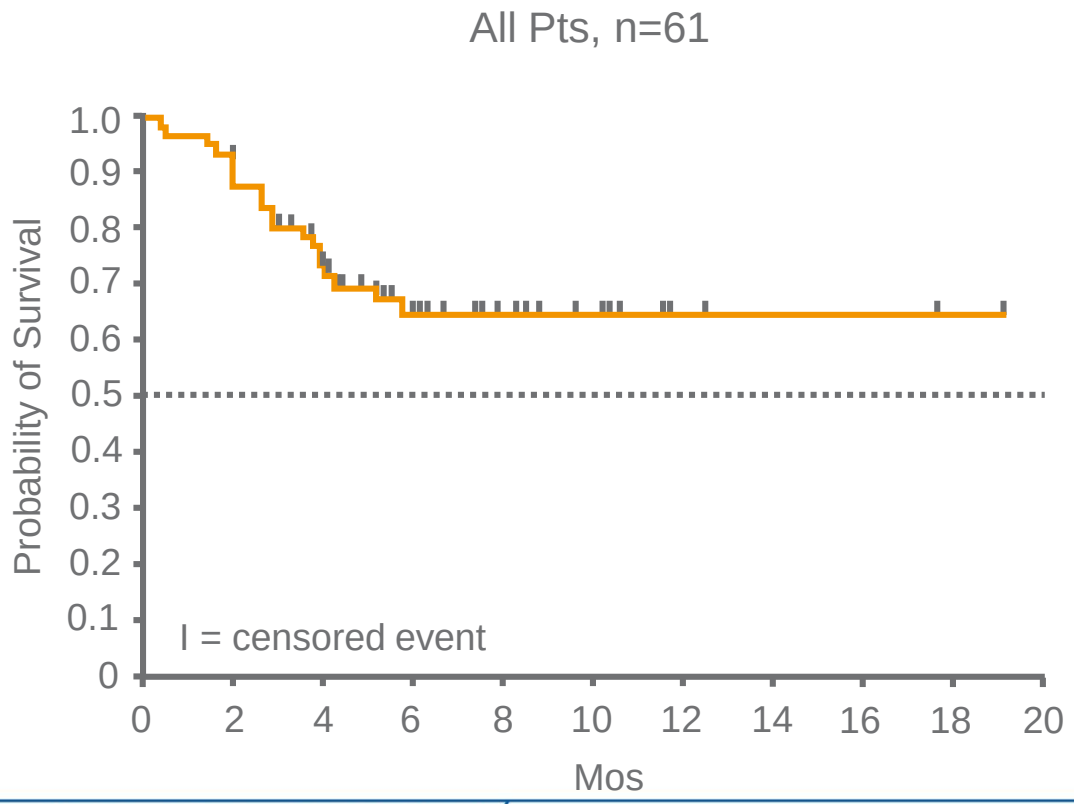
Venetoclax for AML?

Overall Response, %	Venetoclax 600 mg (n=61)
CR	21
CRi	33
CR + CRi*	54
PR	7
ORR (CR + CRi + PR)	61
Resistant/progressive disease	38

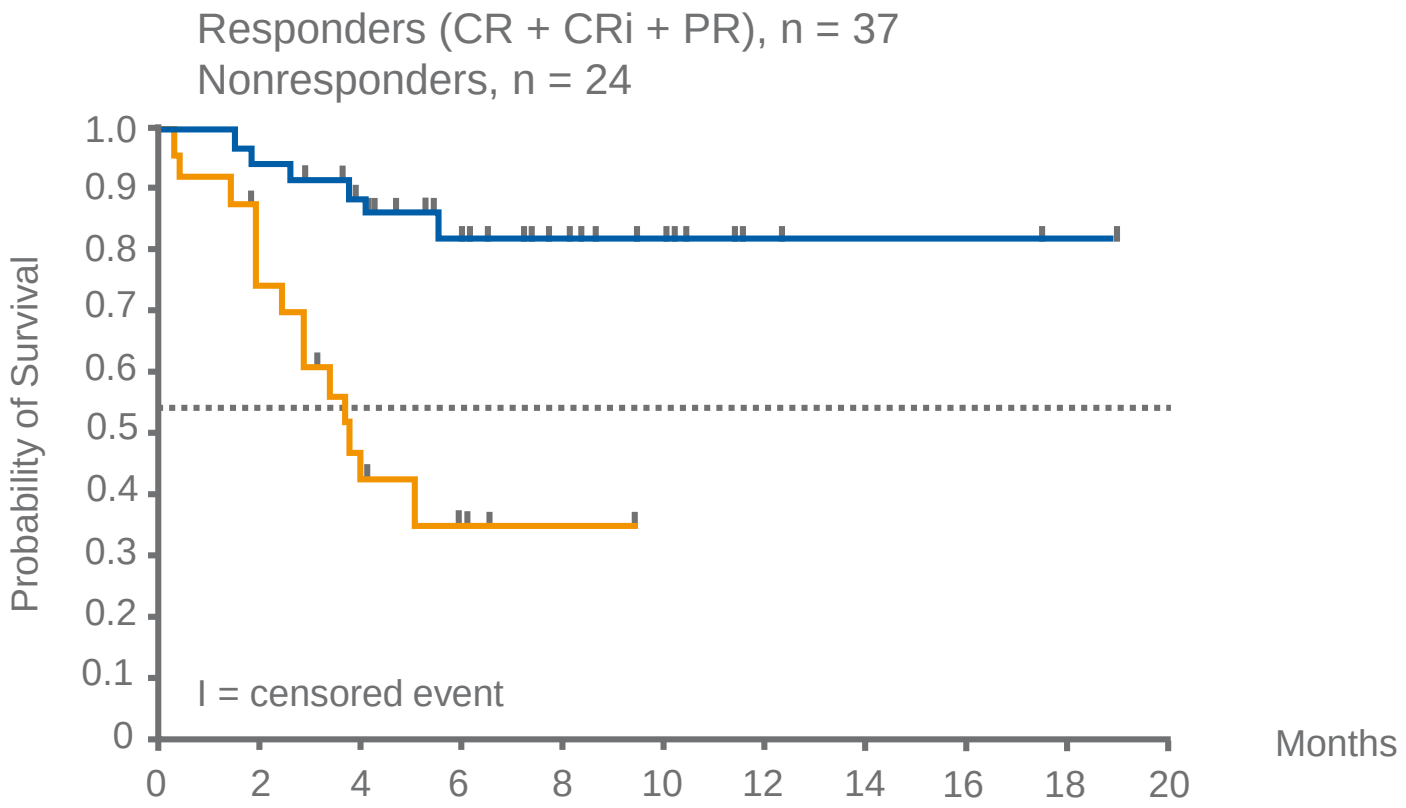
*70% of CR + CRi achieved during cycle 1 or cycle 2.

- Most frequent TRAEs (any grade) included nausea (72%), hypokalemia (46%), diarrhea (44%), fatigue (43%), decreased appetite (41%)
- Most frequent grade 3/4 TRAEs included febrile neutropenia (34%), hypokalemia (15%), hypophosphatemia (13%), hypertension (10%)

Venetoclax for AML?



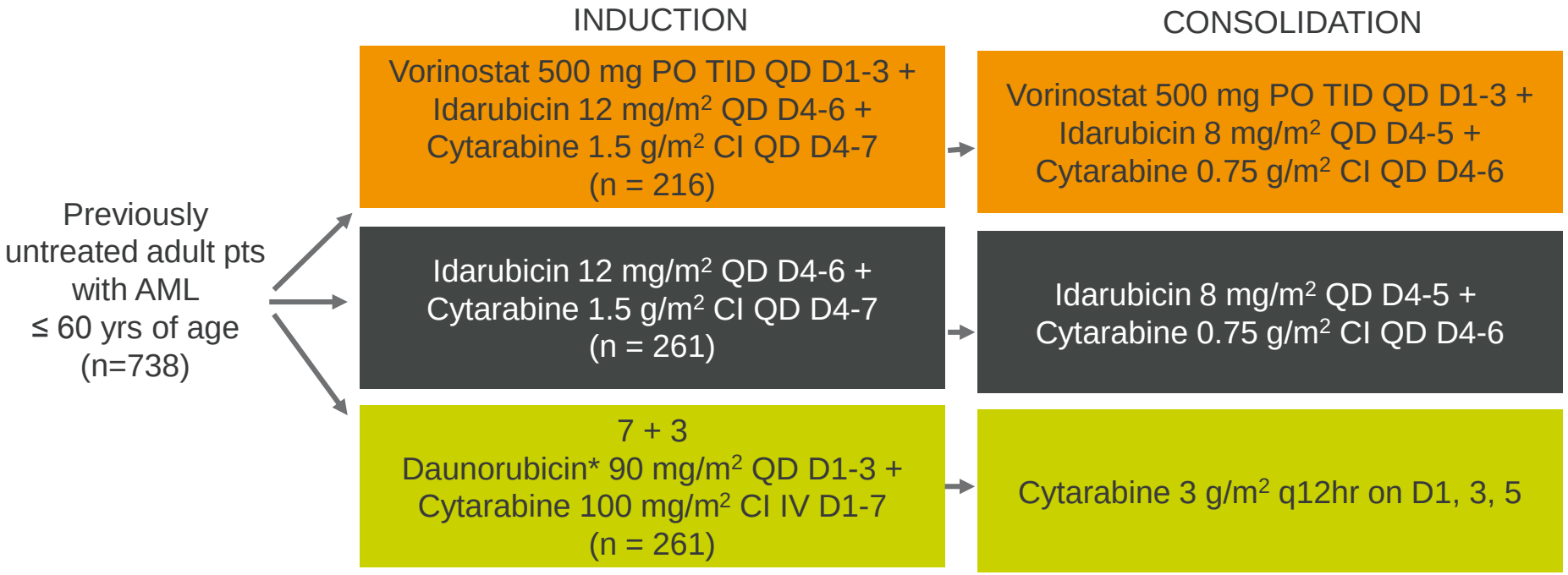
Venetoclax for AML?



Induction therapy : less is more ?

High response rate of idarubicin (ida) and high-dose ara-C (IA) in combination with the HDAC inhibitor vorinostat (IA+V) compared to IA or 7+3 (Garcia-Manero et al. JCO 2011)

- Randomized phase III superiority trial of the added value of vorinostat at induction



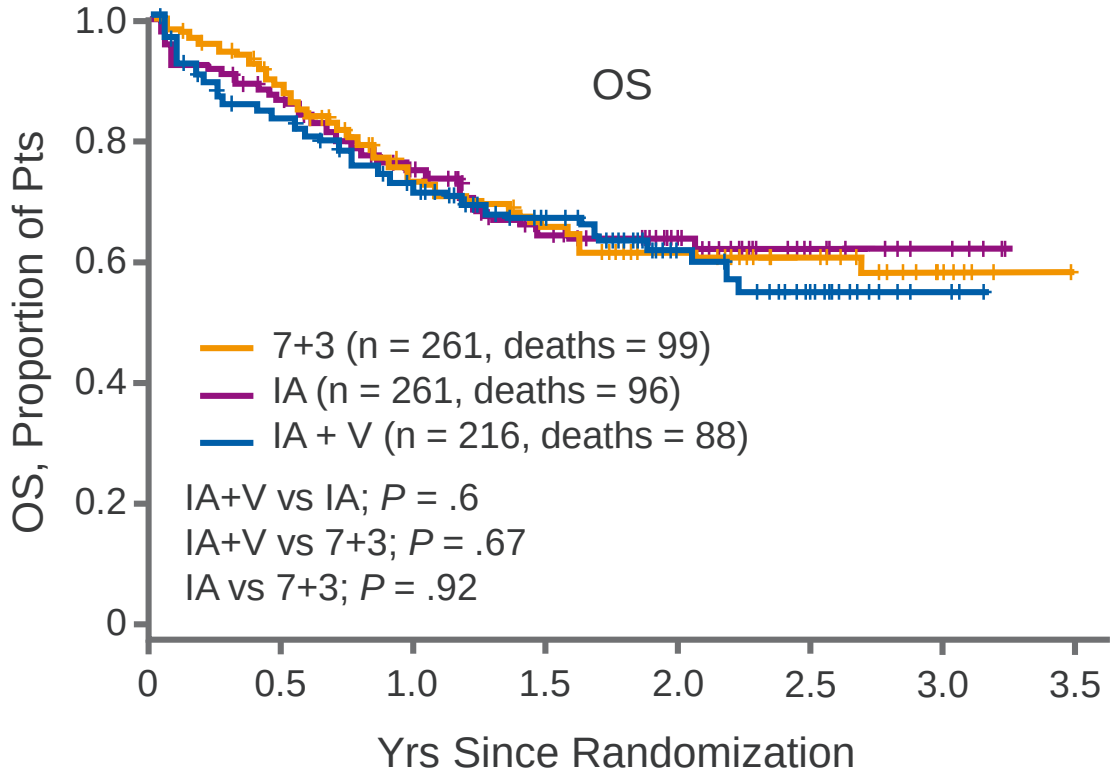
G. Garcia-Manero et al. Abstract 901, ASH 2016

No added value of vorinostat at induction

Outcome, %	Vorinostat + Ida + Ara-C (n = 216)	Ida + Ara-C (n = 261)	7 + 3 (n = 261)	All Pts (N = 738)	*P* Value
CR	60	64	63	62	.58
CRi	17	16	13	15	--
Failure	23	21	25	23	--
Mortality					
▪ 30 day	4	6	3	4	.013
▪ 60 day	9	9	5	7	.097

G. Garcia-Manero et al. Abstract 901, ASH 2016

No added value of vorinostat at induction



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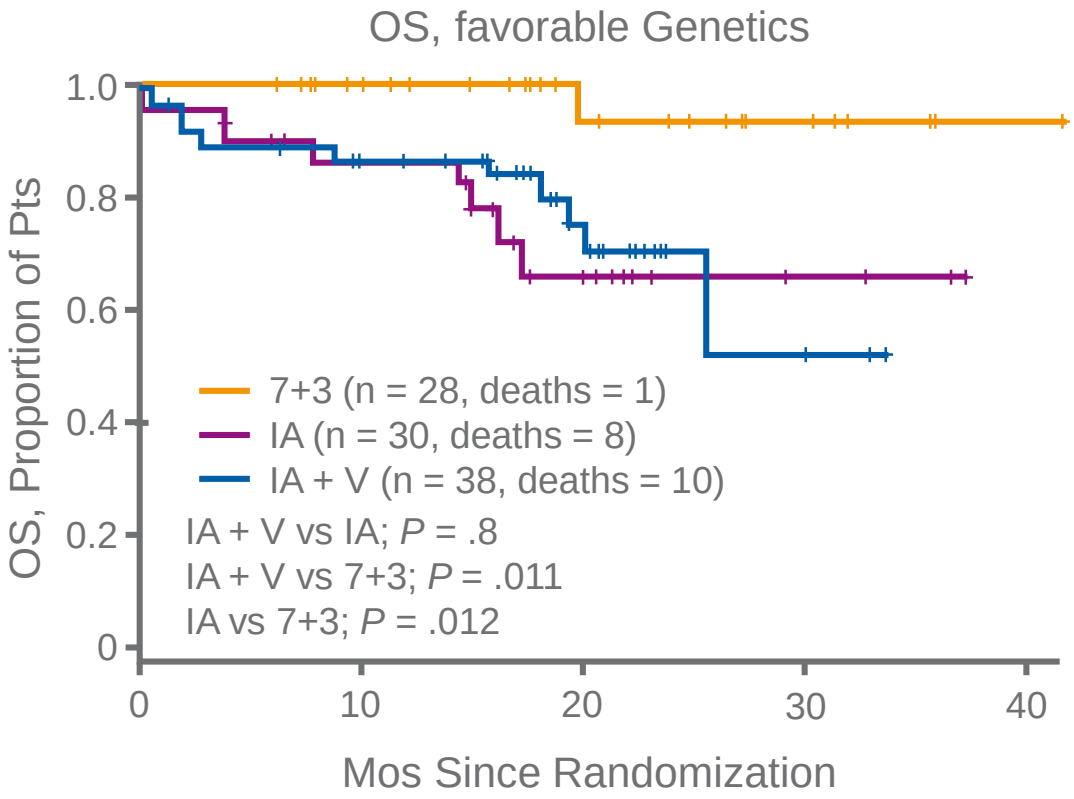
No added value of vorinostat at induction

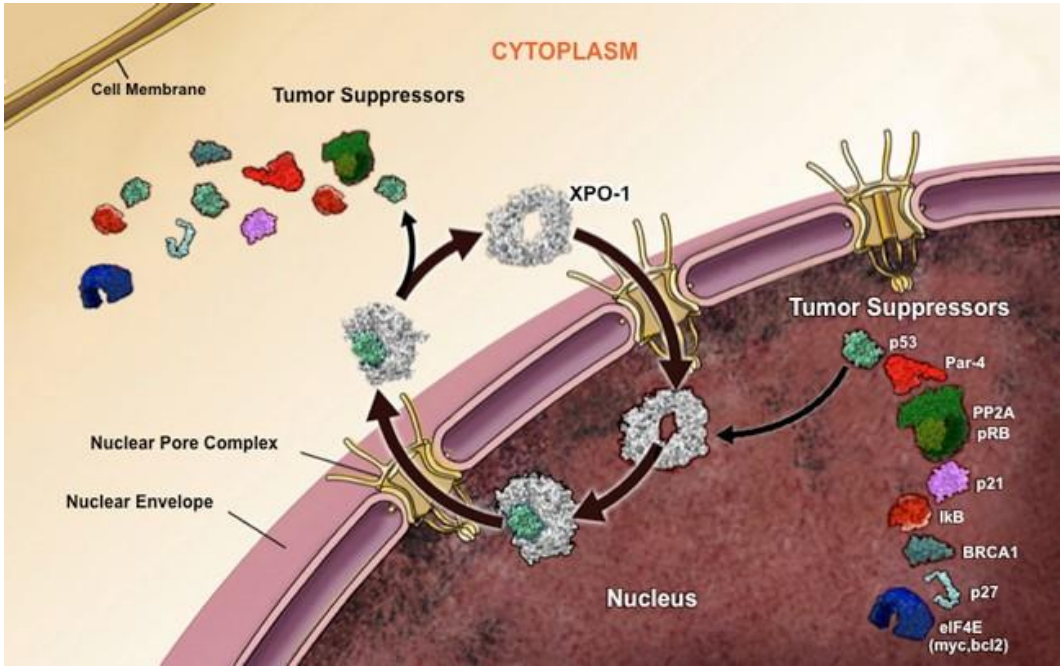


G. Garcia-Manero et al. Abstract 901, ASH 2016

Selinexor combined with 7+3

By inhibiting the primary export protein, XPO1, selinexor maintains tumor suppressor proteins to the nucleus leading to their activation and an anti-leukemic effect as a single agent

It inhibits DNA damage repair, rationalizing its use in combination with DNA damaging agents



Selinexor combined with 7+3

- Phase I of Selinexor in combination with daunorubicin and cytarabine in newly diagnosed poor-risk AML patients

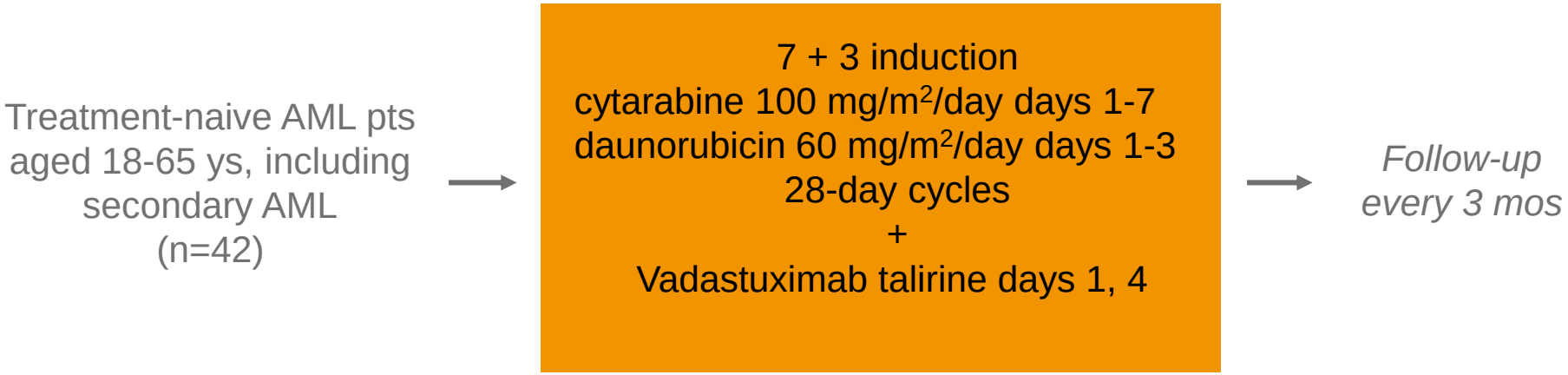
- Phase II of Ara-C and Idarubicin in combination with Selinexor (KPT-330) in R/R AML

➢ Both indicate that the combination can be safely administered. The encouraging activity presents as an interesting bridge to transplant

KL. Sweet et al. Abstract 4040, ASH 2016
W. Fiedler et al. Abstract 34, ASH 2016

Vadastuximab talirine combined with 7+3

- Phase Ib dose escalation/expansion study



dose escalation/expansion from 10 + 10 µg/kg to 20 + 10 µg/kg per SMC

HP. Erba et al. Abstract 211, ASH 2016

7+3 combined with vadastuximab talirine

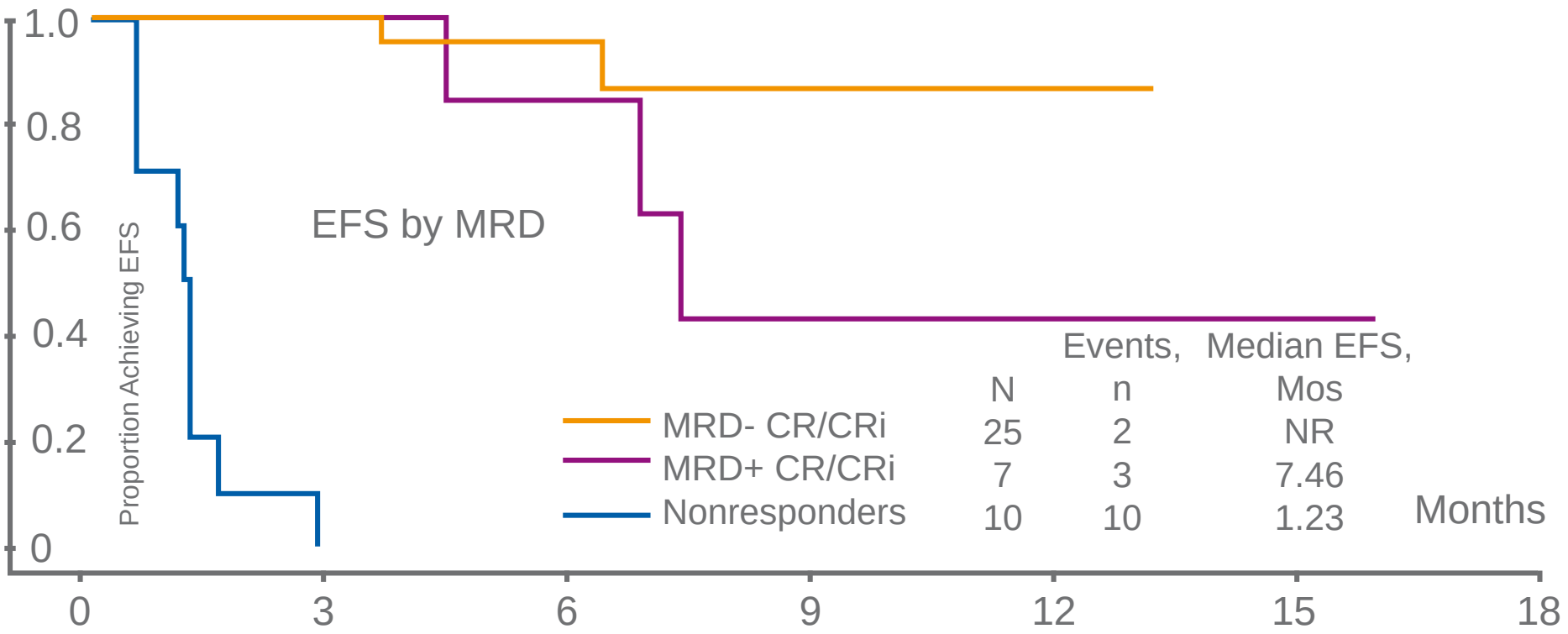
Response, %	CR	CRi*	CRc (CR + CRi)
Evaluable pts (n=42)	60	17	76
Cytogenetic risk by MRC			
▪ Favorable (n = 5)	100	0	100
▪ Intermediate (n = 21)	67	19	86
▪ Adverse (n = 15)	40	20	60

*All pts with CRi had CR with ANC ≥ 1000/uL, incomplete platelet recovery.

- 78% (25/32) of pts in CRc were MRD negative
- Similar AE rate to 7 + 3 alone
- 2% 30-day mortality rate
- 50% (21/42) of pts received allo-SCT

HP. Erba et al. Abstract 211, ASH 2016

7+3 combined with vadastuximab talirine



HP. Erba et al. Abstract 211, ASH 2016

7+3 combined with vadastuximab talirine

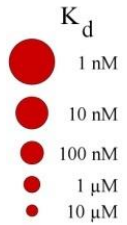
Characteristics	Vadastuximab talirine + 7 + 3 SWOG Eligible* (n=30)	7 + 3 ± GO SWOG 0106† (n=595)
Median age, yrs	45	48
Adverse cytogenetic risk, %	27	23
CRc rate (CR + CRi), %	80	75
CRc with 1 cycle, %	77	60
MRD-negative CRc, %	73	~ 54‡

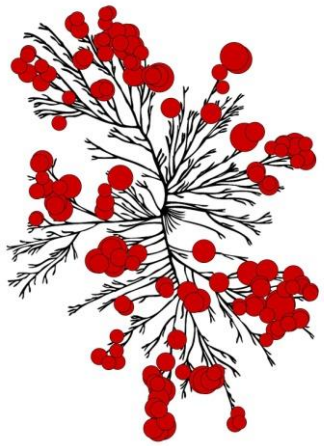
*SWOG eligibility: 60 yrs of age or younger, de novo only. †Aggregate data from Othus M, et al. Leukemia. 2016;30:2080-2083.
‡Calculated MRD-negative rate

HP. Erba et al. Abstract 211, ASH 2016

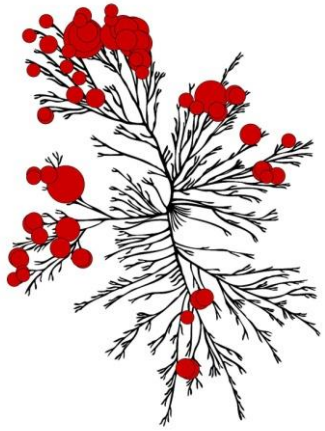
7+3 combined with crenolanib

Type I oral FLT3 TKI that inhibits both FLT3-ITD and FLT3-TKD mutations

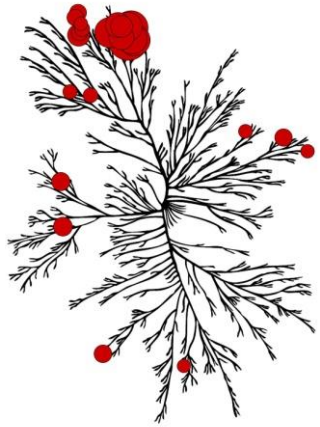




Midostaurin (PKC-412)



Sorafenib



Quizartinib (AC220)

Crenolanib

Zarrinkar PP et al, Blood 2009
Galanis A et al, Cancer Res 2012

7+3 combined with crenolanib

- Patients with newly diagnosed FLT3 mutant AML

Table 1. Overall Complete Response Rate in Newly Diagnosed FLT3 mutant AML

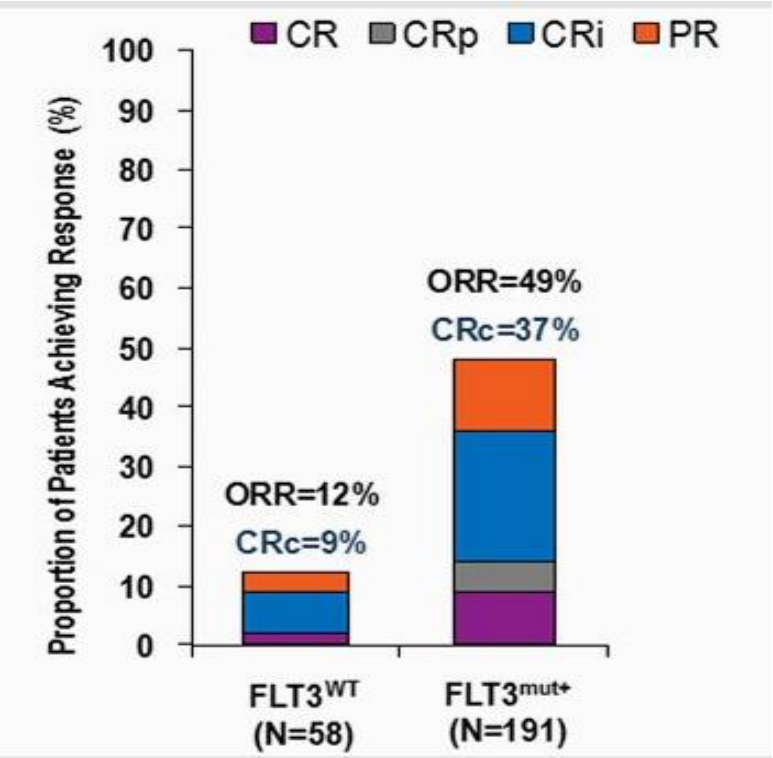
Induction Chemotherapy Regimen	# Evaluable Patients	CR after 1 Cycle of Induction	CR after Additional Cycle of Chemotherapy*	Overall Complete Response
Cytarabine + Daunorubicin (n=18)	18	16	1	17/18 (94%)
Cytarabine + Idarubicin (n=8)	7	6	1	7/7 (100%)
TOTAL (n= 26 pts)	25	22	2	24/25(96%)

**1 pt re-induced with cytarabine/idarubicin and 1 pt received HiDAC*

Gilteritinib (ASP2215): the winner ?

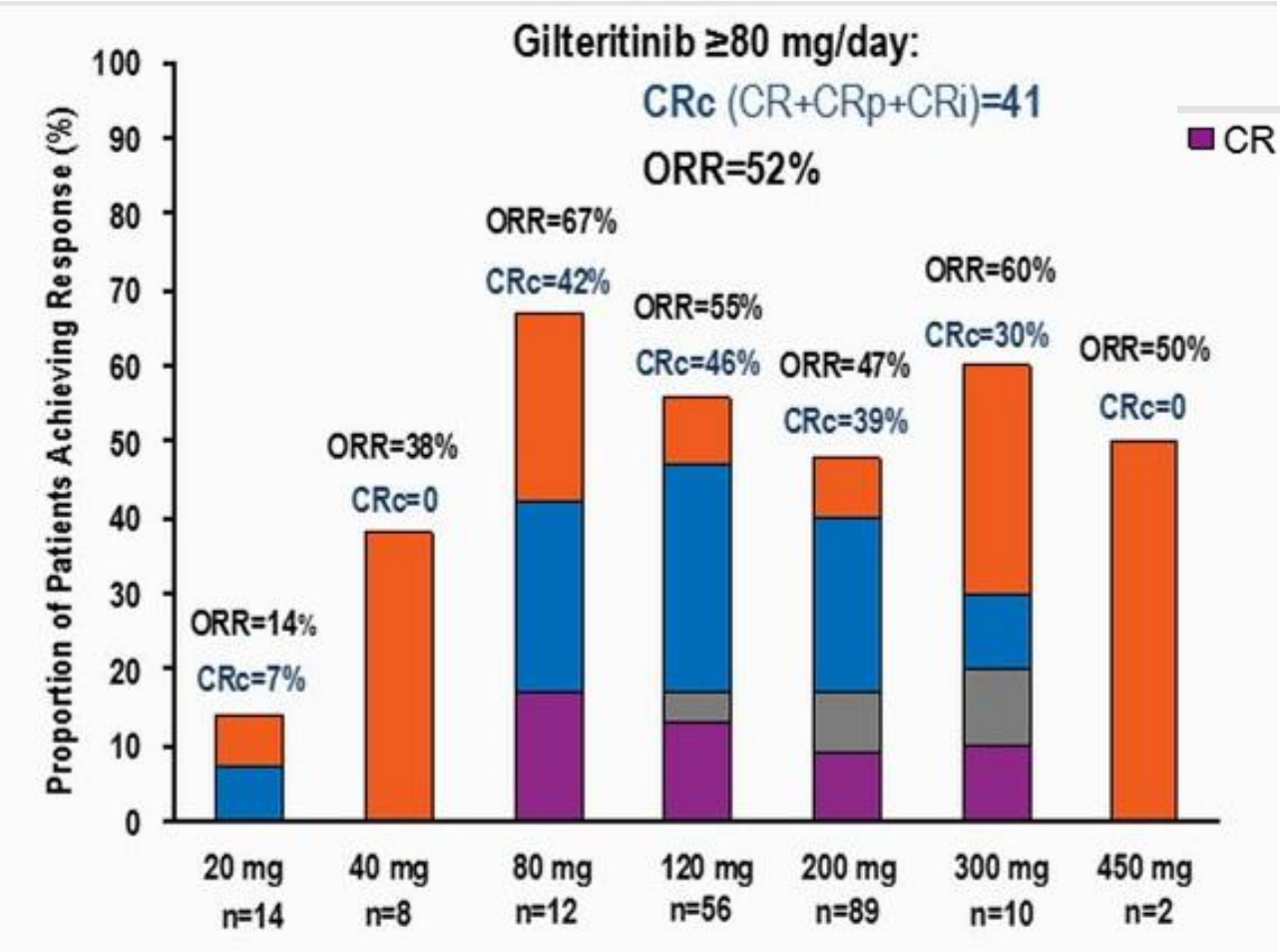
Novel, highly potent and selective oral FLT3 inhibitor with preclinical activity against FLT3-ITD activating and FLT3-D835 resistance mutations

- First-in-human phase 1/2 study (CHRYSALIS) of once-daily oral gilteritinib given to pts with R/R AML irrespective of FLT3 mutation status



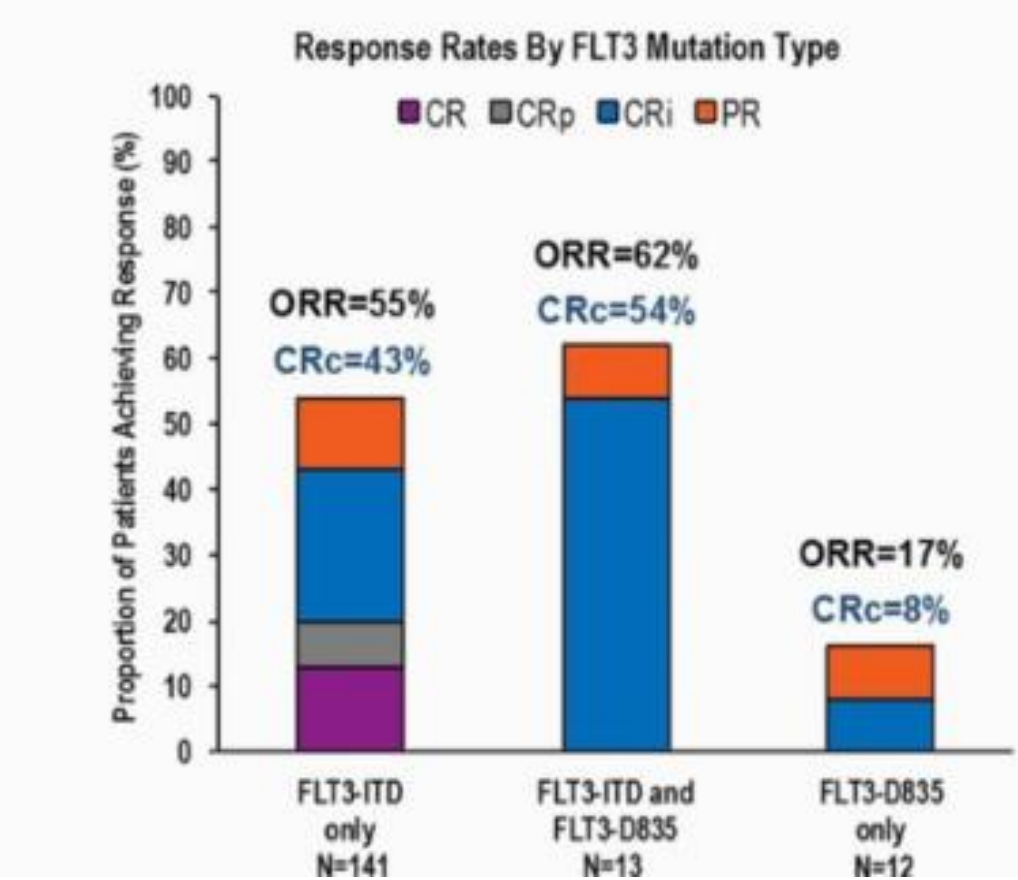
Response in FLT3 mut and FLT3 WT patients (n=249)

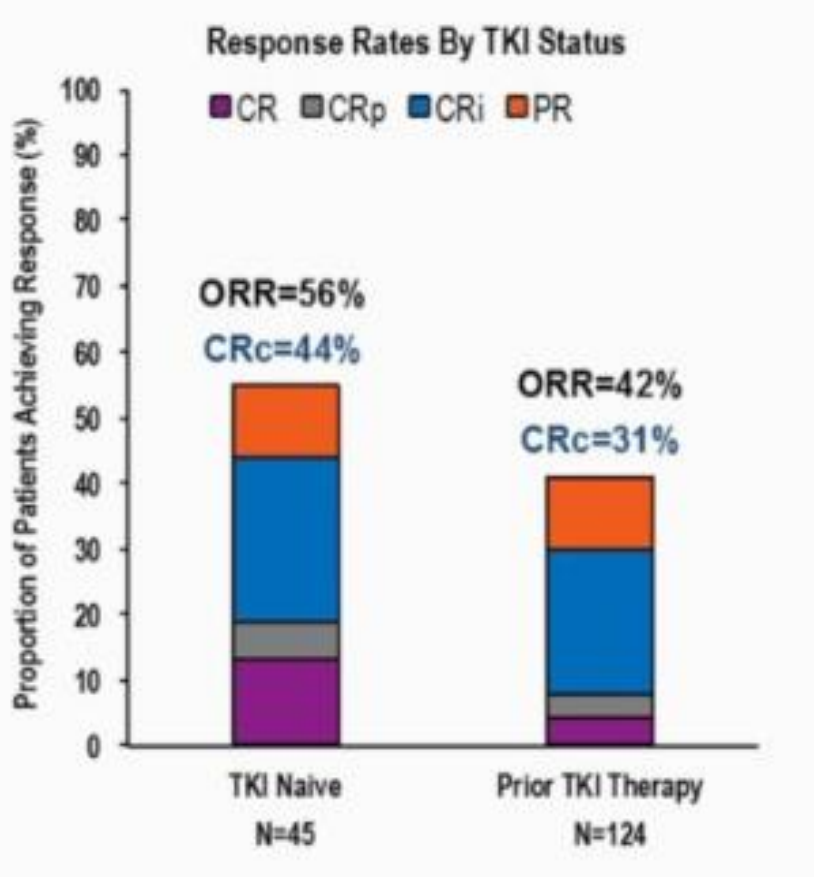
Gilteritinib (ASP2215): the winner ?



Response in FLT3mut patients by Giltertinib dose (n=191)

Gilteritinib (ASP2215): the winner ?






ALL

The good place for ponatinib in Ph+ ALL?

T315I mutations commonly associated with relapse to TKI
Potent BCR-ABL inhibitor effective against *T315I* mutant ALL

- Single-center, open-label phase II trial *8 x 21-day cycles*

Pts ≥ 18 yrs with untreated (n=50) or previously treated (n=8*) Ph+ ALL

*2 non responders, 6 in CR

Hyper-CVAD: cycle 1-3-5-7
- cyclophosphamide (300 mg/m^2 x 6; D1-3)
- vincristine (2 mg, D1, 11),
- doxorubicin (50 mg/m^2, D4),
- dexamethasone (40 mg, D1-4, D11-14)

MTX-Ara-C: cycle 2-4-6-8
- methotrexate (12 mg),
- cytarabine (3 mg/m^2, D2-3)

Ponatinib:
- cycle 1: 45 mg for d1-14
- cycle 2-8: 45 mg daily

Due to vascular toxicity at 45 mg, protocol amended to allow 30 mg daily beyond induction, then 15 mg daily in pts achieving CMR

!!!!!!! Rituximab given for first 4 courses, if CD20+!!!!!!!!!

Pts with CR received maintenance therapy of daily ponatinib + monthly vincristine and prednisone or hyper-CVAD for 2 yrs

Sasaki K, et al. ASH 2016. Abstract 757

The good place for ponatinib?

Response, n/N (%)	Pts
CR*	52/52 (100)
CCyR†	48/48 (100)
CyR after induction	
▪ Complete	44/48 (92)
▪ Minor	2/48 (4)
▪ Not done	2/48 (4)
CyR after second cycle	
▪ Complete	48/48 (100)
MMR	56/58 (97)
MMR after induction	31/48 (65)
CMR	46/58 (79)

*6 pts in CR at enrollment

- No early deaths on study
- Median time to
  - MMR: 3 wks (2-14)
  - CMR: 10 wks (2-96)
- Median follow-up: 39 mos (range: 2-59)
  - 10 pts received alloSCT
  - 21 pts (47%) remain on ponatinib
  - 11 pts (24%) switched to other TKI

Sasaki K, et al. ASH 2016. Abstract 757

The good place for ponatinib?

Outcome, %	Pts (N = 58)
3-yr CRD	78
3-yr OS	75
Landmark analysis at 4 mos by ASCT	
3-yr CRD*	
▪ ASCT	88
▪ No ASCT	75
3-yr OS†	
▪ ASCT	79
▪ No ASCT	86

*P = .36

†P = .81

Sasaki K, et al. ASH 2016. Abstract 757

The good place for ponatinib?

Grade 3/4 Nonhematologic AE, %	Pts (N = 58)
Infections during induction	52
ALT/AST increase	31
Bilirubin increase	17
Pancreatitis	17
Skin rash	16
Amylase/lipase	16
Hypertension	14
Hemorrhage	10
Mucositis	9
Abdominal pain	7
Thrombotic events	7
Myocardial infarction*	5

12%

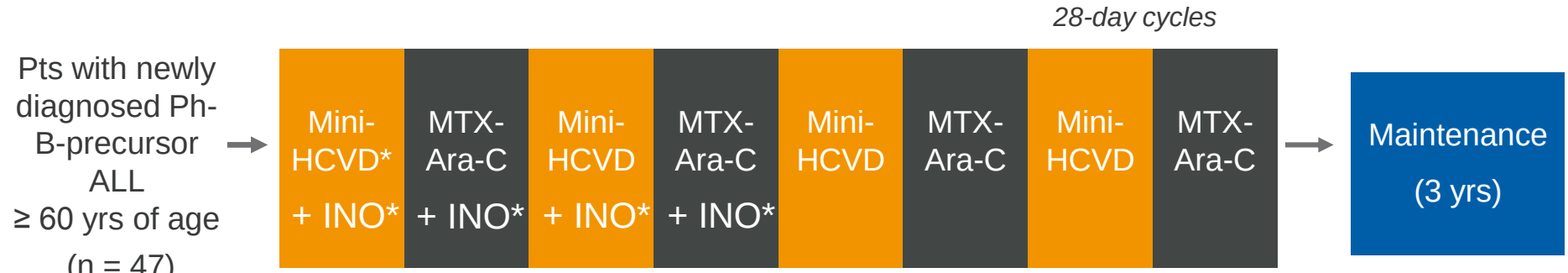
Sasaki K, et al. ASH 2016. Abstract 757

*Since protocol amendment, 1 pt with grade 2 angina possibly related to treatment

Frontline InO + Mini-HCVD in older ALL pts

Inotuzumab Ozogamicin (InO), an anti-CD22 antibody-calicheamicin conjugate
Superior clinical activity versus standard of care (SOC; intensive chemotherapy) R/R B-ALL in the phase 3 INO-VATE trial (Kantarjian. *N Engl J Med*. June 12, 2016)

- Single-center, open-label phase I/II trial



"Mini-HyperCVD": cyclophosphamide (150 mg/m^2 x 6), dexamethasone (20 mg)
MTX-Ara-C: methotrexate (250 mg/m^2), cytarabine (0.5 g/m^2 x 4)
InO given on day 3 of cycles 1-4
Rituximab given on days 2, 8 of cycles 1-4 if CD20+

INO dose, mg/m^2	First 6 Pts†	7-34	35 and Beyond‡
Cycle 1	1.3	1.8	1.3
Cycles 2-4	0.8	1.3	1.0

Koji Sasaki et al. Abstract 1606 ASH 2016

Frontline InO + Mini-HCVD in older ALL pts

Response, %	INO + Mini-HCVD (N = 43)
ORR	98
▪ CR	84
▪ CRp	12
▪ CRi	2
Cytogenetic CR*	100
MRD negativity	
▪ D21†	76
▪ Overall‡	96

No early deaths on study

Median follow-up: 24 mos (range: 1-55)

- 3-yr OS: 54%
- 3-yr CRD: 72%

Koji Sasaki et al. Abstract 1606 ASH 2016

Frontline InO + Mini-HCVD in older ALL pts

Grade 3/4 AEs in ≥ 10% of Pts, %	INO + Mini-HCVD (N = 47)
Prolonged thrombocytopenia	79
Infection (consolidation)	74
Infection (induction)	53
Hyperglycemia	53
Hypokalemia	34
ALT/AST elevation	19
Bilirubin elevation	17
Hemorrhage	15

- Thrombocytopenia > 6 wks in 37 pts (79%), 8 in induction, 36 in subsequent courses
- 4 pts experienced VOD after 2-4 cycles of INO
  - All received 1.8 mg/m^2 dose in cycle 1

Koji Sasaki et al. Abstract 1606 ASH 2016

Frontline InO + Mini-HCVD in older ALL pts

- Combination of inotuzumab ozogamicin with reduced-intensity mini-HCVD highly effective as frontline treatment in older pts with ALL
  - ORR: 98%
  - Low early mortality rate
- 54% 3-yr OS compares favorably with 31% 3-yr OS reported with HCVAD ± rituximab
- Manageable safety profile with inotuzumab ozogamicin plus mini-HCVD
  - VOD events in 4 pts led to inotuzumab ozogamicin dose reduction
- Investigators suggest inotuzumab ozogamicin + mini-HCVD may become a new frontline standard of care for older pts with ALL

Koji Sasaki et al. Abstract 1606 ASH 2016

Conclusion

- The effective translation of research-based innovations into the treatment of our AML patients will require collaborative efforts of accademics and companies to organise big trials that provide personalized treatment decisions, based on genomic informations

- It'll imply the characterisation of all known mutations in AML at the time of diagnosis and their monitoring during therapy

- NGS open new perspectives for clono specific evaluation of MRD

P. Hirsch et al. Abstract 1208, ASH 2016

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