AML – EHA® 2021

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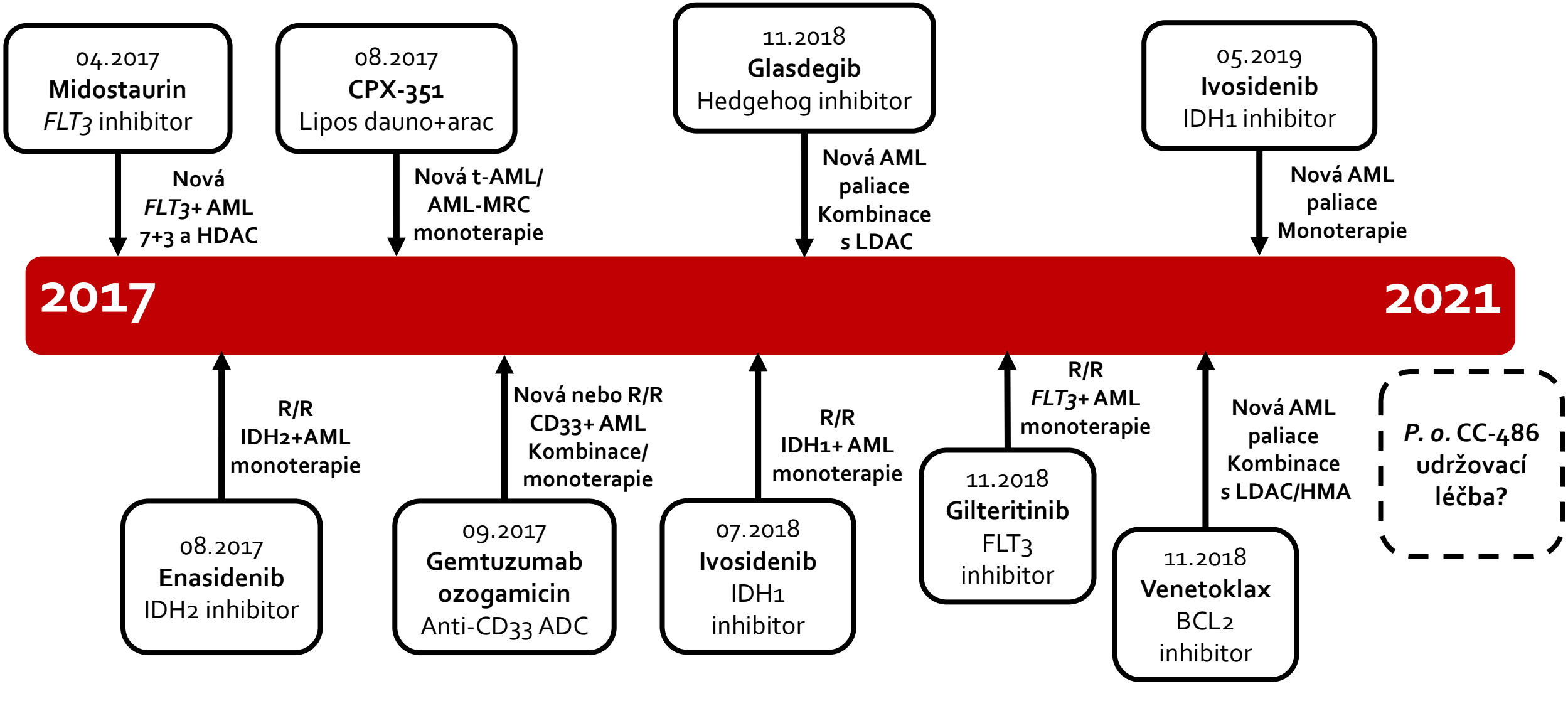
FAKULTNÍ NEMOCNICE BRNO

MUNI MED


04.2017
Midostaurin
FLT3 inhibitor
Nová
FLT3+ AML
7+3 a HDAC
08.2017
CPX-351
Lipos dauno+arac
Nová t-AML/
AML-MRC
monoterapie
11.2018
Glasdegib
Hedgehog inhibitor
Nová AML
paliace
Kombinace
s LDAC
05.2019
Ivosidenib
IDH1 inhibitor
Nová AML
paliace
Monoterapie
2017
2021
R/R
IDH2+AML
monoterapie
08.2017
Enasidenib
IDH2 inhibitor
Nová nebo R/R
CD33+ AML
Kombinace/
monoterapie
09.2017
Gemtuzumab
ozogamicin
Anti-CD33 ADC
R/R
IDH1+ AML
monoterapie
07.2018
Ivosidenib
IDH1
inhibitor
R/R
FLT3+ AML
monoterapie
11.2018
Gilteritinib
FLT3
inhibitor
Nová AML
paliace
Kombinace
s LDAC/HMA
11.2018
Venetoklax
BCL2
inhibitor
P. o. CC-486
udržovací
léčba?

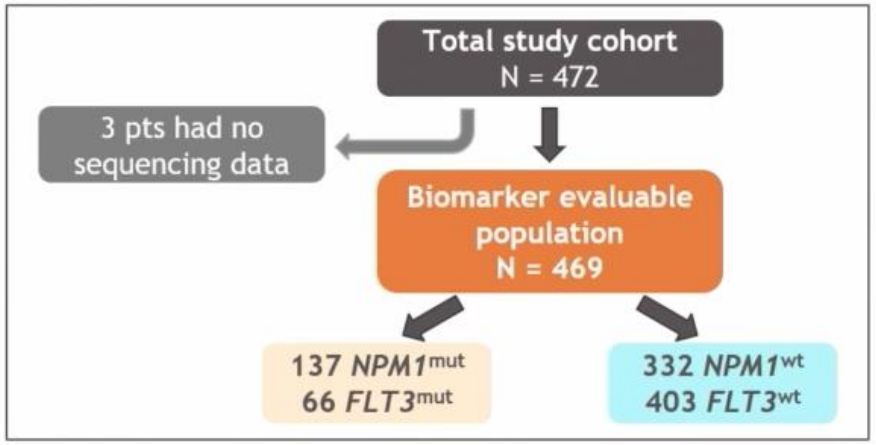
Udržovací léčba u AML	**1. CC-486 efekt udržovací léčby v závislosti na typu AML**
	2. Udržovací léčba po aloSCT – metaanalýza
Venetoklax v léčbě AML	**3. Venetoklax + decitabin – efekt v závislosti na cytogenetice**
	4. Venetoklax u *RUNX1* mutované AML
	5. Venetoklax + gilteritinib u *FLT3* + R/R AML
Nová (re-) klasifikace a stratifikace u AML	**6. Robustní molekulárně-cytogenetická analýza**
Antimykotika v éře nových léků u AML	**7. Doporučení odborníků EHA®**

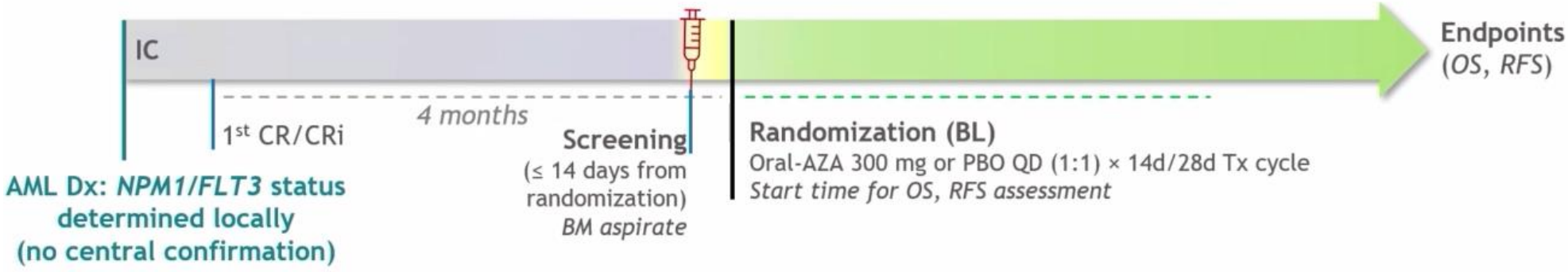
Udržovací léčba u AML v 1. CR

Udržovací azacytidin ~ typ AML

SURVIVAL OUTCOMES FROM THE QUAZAR AML-001 TRIAL WITH ORAL AZACITIDINE FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA IN REMISSION BY DISEASE SUBTYPE, CYTOGENETIC RISK, AND NPM1 MUTATION STATUS AT DIAGNOSIS

- Pts were age ≥55 years, with *de novo* or secondary AML, ECOG PS score ≤ 3, intermediate- or poor-risk cytogenetics, and not candidates for HSCT
  - Cytogenetic risk classification was based on the 2012 NCCN AML guidelines[a]
- Pts had attained first CR/CRi after induction ± consolidation ≤ 4 months before randomization





Udržovací azacytidin ~ typ AML

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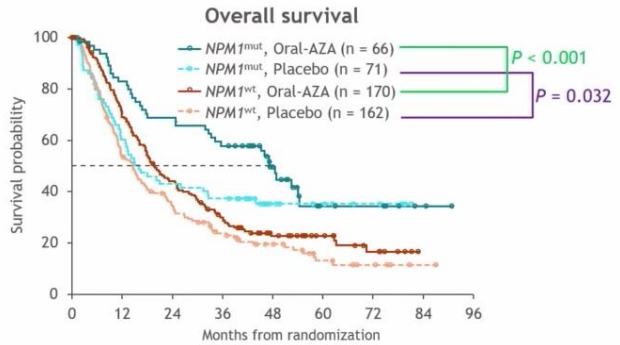
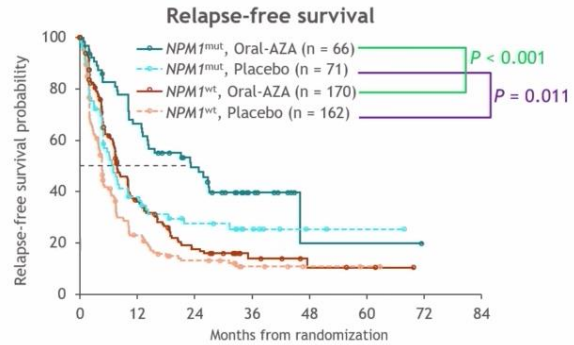
- *NPM1*^{mut} at AML Dx was both prognostic of better OS and RFS, and predictive of OS/RFS benefits with Oral-AZA maintenance vs PBO for pts in remission
- Median OS was prolonged with Oral-AZA vs. PBO in pts with *FLT3*-ITD/TKD mutations at Dx, but the difference was not statistically significant in this small pt population ($P = 0.114$)
- RFS was significantly improved with Oral-AZA vs. PBO in pts with *FLT3*-ITD/TKD mutations at Dx, despite small sample sizes



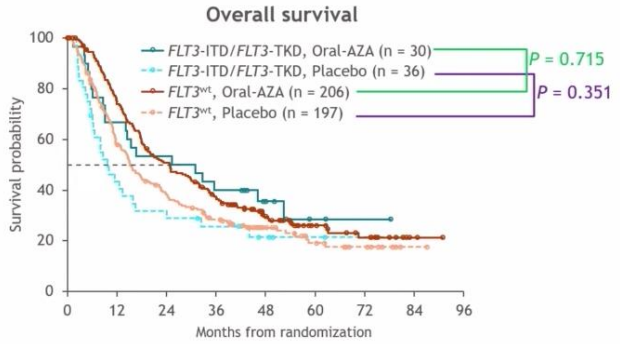
Median OS, months

NPM1^{mut}, Oral-AZA	47.2	*NPM1*^{wt}, Oral-AZA	19.6
NPM1^{mut}, Placebo	15.9	*NPM1*^{wt}, Placebo	14.6



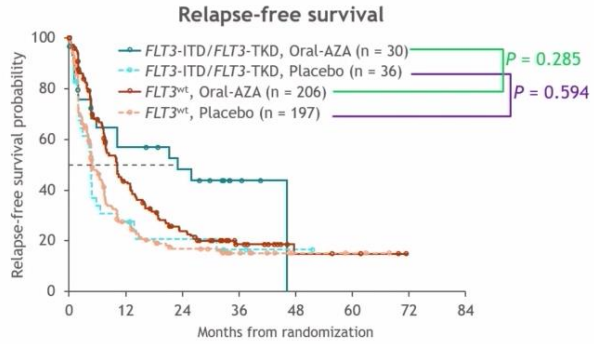
Median RFS, months

NPM1^{mut}, Oral-AZA	23.2	*NPM1*^{wt}, Oral-AZA	7.8
NPM1^{mut}, Placebo	6.9	*NPM1*^{wt}, Placebo	4.6



Median OS, months

FLT3-ITD/TKD, Oral-AZA	28.2	*FLT3*^{wt}, Oral-AZA	24.7
FLT3-ITD/TKD, Placebo	9.7	*FLT3*^{wt}, Placebo	15.2



Median RFS, months

FLT3-ITD/TKD, Oral-AZA	23.1	*FLT3*^{wt}, Oral-AZA	10.2
FLT3-ITD/TKD, Placebo	4.6	*FLT3*^{wt}, Placebo	4.9

Udržovací azacytidin ~ typ AML

SURVIVAL OUTCOMES FROM THE QUAZAR AML-001 TRIAL WITH ORAL AZACITIDINE FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA IN REMISSION BY DISEASE SUBTYPE, CYTOGENETIC RISK, AND NPM1 MUTATION STATUS AT DIAGNOSIS

OS multivariate analysis (*NPM1*^{mut}, *FLT3*-ITD/TKD^{mut}, Tx Arm)

- OS multivariate analysis confirmed the independent prognostic impact of *NPM1*^{mut} (favorable vs. *NPM1*^{wt} [HR 0.54; $P < 0.001$]) and *FLT3*-ITD/TKD^{mut} (unfavorable vs. *FLT3*^{wt} [HR 1.54; $P < 0.012$]) when controlling for each mutation and for randomized Tx arm (Oral-AZA vs. PBO)
- Oral-AZA also significantly improved OS independent of *NPM1* and *FLT3* mutation status (HR 0.72; $P = 0.003$)

Multivariate OS analysis
Includes NPM1, FLT3, and Tx arm as covariates

	HR	SE (coeff.)	z	p
NPM1^{mut} (n = 137) vs. *NPM1*^{wt} (n = 332)	0.5351	0.1403	-4.458	8.26E-06
FLT3^{mut} (n = 66) vs. *FLT3*^{wt} (n = 403)	1.5447	0.1723	2.523	0.01163
Oral-AZA (n = 236) vs. PBO (n = 233)	**0.7236**	**0.1089**	**-2.971**	**0.00297**

Udržovací léčba po aloSCT – metaanalýza

MAINTENANCE THERAPY AFTER ALLOGENEIC HEMATOPOIETIC TRANSPLANT FOR ACUTE MYELOID LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

OBJECTIVE

- The aim of the present study was to evaluate the efficacy and safety of maintenance therapy for AML patients after allogeneic HSCT.

METHODS

- We searched PubMed until February 2021; CENTRAL, published in The Cochrane Library, until March 2021, and the following conference proceedings: ASH, ASCO, EHA EBMT and TCT.
- We included all randomized controlled trials (RCTs) that compared maintenance therapy with observation or placebo in patients with AML after allogeneic HSCT.
- Primary outcome was overall survival (OS). Secondary outcomes included relapse free survival (RFS), relapse rate and safety (including adverse events and GVHD).

Udržovací léčba po aloSCT – metaanalýza

MAINTENANCE THERAPY AFTER ALLOGENEIC HEMATOPOIETIC TRANSPLANT FOR ACUTE MYELOID LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Study	AML type eligibility criteria	Start of maintenance post transplant (days)	Primary endpoint	Length of follow up (months)	Treatment regimen	Number of patients included	Age (Median, range)	Sex (male, percentage)
Burchert 2020	Flt3-ITD mutated AML	60-100	RFS	42	sorafenib	43	54 (24-75)	42%
					placebo	40	54 (19-76)	58%
Maziarz 2020	Flt3-ITD mutated AML	28-60	RFS	24	midostaurin	30	48 (20-61)	53%
					SOC	30	56 (20-68)	60%
Xuan 2020	Flt3-ITD mutated AML	30-60	relapse rate	21	sorafenib	100	35 (26-42)	50%
					SOC	102	35 (26-43)	51%
Gao 2020	High risk AML	60-100	relapse rate	28	decitabine + GCSF	102	30(3-62)	56%
					SOC	102	28(2-52)	60%
Oran 2020	High risk AML/MDS	42-100	RFS	52	azacitidine	93	57 (19-72)	59%
					SOC	94	58 (20-75)	61%

Udržovací léčba po aloSCT – metaanalýza

MAINTENANCE THERAPY AFTER ALLOGENEIC HEMATOPOIETIC TRANSPLANT FOR ACUTE MYELOID LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

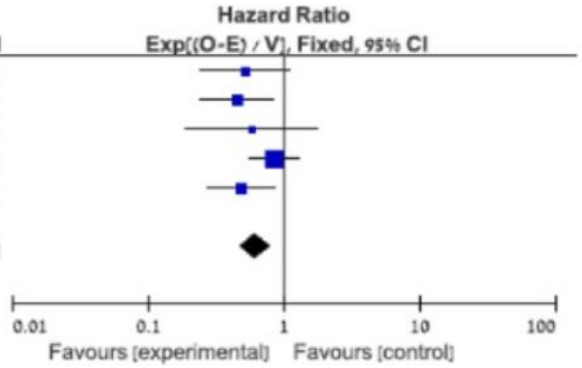
Primary outcome

- Maintenance therapy after allogeneic HSCT was associated with an improved OS, HR=0.61 (95% CI 0.47-0.80).

	maintenance therapy		Control/placebo					Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI
Burchert 2020	0	0	0	0	-4.3	6.5	12.2%	0.52 [0.24, 1.11]
Gao 2020	0	0	0	0	-7.97	9.98	18.7%	0.45 [0.24, 0.84]
Maziarz 2020	0	0	0	0	-1.66	3.05	5.7%	0.58 [0.19, 1.78]
Oran 2020	0	0	0	0	-3.92	22.48	42.1%	0.84 [0.56, 1.27]
Xuan 2020	0	0	0	0	-8.4	11.45	21.4%	0.48 [0.27, 0.86]
Total (95% CI)		**0**		**0**			**100.0%**	**0.61 [0.47, 0.80]**
Total events	0		0					

Heterogeneity: $Chi^2 = 4.07$, $df = 4$ ($P = 0.40$); $I^2 = 2\%$

Test for overall effect: $Z = 3.59$ ($P = 0.0003$)



- Subgroup analyses by type of maintenance therapy also showed advantage in OS with either TKI or HMA maintenance [HR=0.50 (95% CI 0.33-0.77) and HR=0.69 (95% CI 0.49-0.98), respectively].

Udržovací léčba po aloSCT – metaanalýza

MAINTENANCE THERAPY AFTER ALLOGENEIC HEMATOPOIETIC TRANSPLANT FOR ACUTE MYELOID LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Secondary outcomes

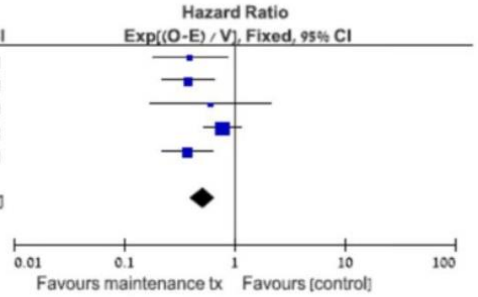
Maintenance therapy was associated with:

- Improved RFS, HR=0.51 (95% CI 0.40 - 0.66).
- Decreased relapse rate, RR=0.41 (95% CI 0.20-0.88).

	Maintenance therapy		Control/Placebo					Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI
Burchert 2020	0	0	0	0	-6	6.38	10.8%	0.39 [0.18, 0.85]
Gao 2020	0	0	0	0	-12.32	12.73	21.5%	0.38 [0.22, 0.66]
Maziarz 2020	0	0	0	0	-1.22	2.4	4.1%	0.60 [0.17, 2.13]
Oran 2020	0	0	0	0	-6.21	23.75	40.2%	0.77 [0.51, 1.15]
Xuan 2020	0	0	0	0	-13.8	13.88	23.5%	0.37 [0.22, 0.63]
Total (95% CI)		0		0			100.0%	0.51 [0.40, 0.66]
Total events	0		0					

Heterogeneity: Chi² = 7.08, df = 4 (P = 0.13); I² = 44%

Test for overall effect: Z = 5.14 (P < 0.00001)



There was no difference between the maintenance and control arms in:

- Risk of any grade 3 or 4 adverse events, RR=1.0 (95% CI 0.83-1.20).
- All infections, RR=0.98 (95% CI 0.83-1.16, I2=0%).
- Grade 3 or 4 infections, RR=0.96 (95% CI 0.68-1.36).
- Grade 3 or 4 thrombocytopenia or in grade 3 or 4 neutropenia.
- Grade 2-4 acute GVHD, mild-moderate chronic GVHD or severe chronic GVHD.

Venetoklax v léčbě AML

Venetoklax + decitabin ~ cytogenetika

PROGNOSTIC IMPACT OF CONVENTIONAL CYTOGENETICS IN ACUTE MYELOID LEUKEMIA (AML) TREATED WITH DECITABINE AND VENETOCLAX (DEC10-VEN)

Multivariable logistic model for CR/CRi

Effect	Odds ratio	95% Wald Confidence Limits		P-value
-5, -5q,-7,-17	0.17	0.05	0.65	0.009
Complex	0.26	0.09	0.72	0.009
Non-diploid intermediate	1.06	0.39	2.87	0.914
Non-complex adverse	0.33	0.07	1.56	0.161

- On multivariable analysis : Compared to diploid CG, pts with complex (OR 0.26; 95% CI 0.09,0.72; P =0.009) and those harboring Chr 5,7,17 abnormalities were significantly less likely to achieve CR/CRi (OR 0.17; 95% CI 0.05,0.65; P=.009)

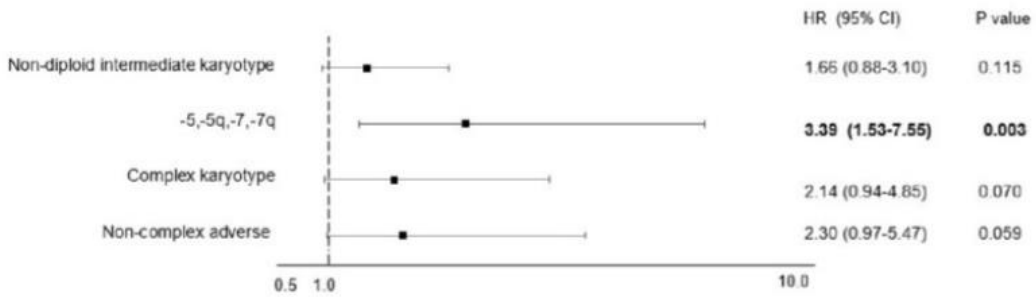
- In the multivariable logistic model for CR, compared to diploid, non-complex adverse karyotype was significantly less likely to achieve CR (OR 0.07,95% CI 0.01,0.76;P=0.028)

Venetoklax + decitabin ~ cytogenetika

PROGNOSTIC IMPACT OF CONVENTIONAL CYTOGENETICS IN ACUTE MYELOID LEUKEMIA (AML) TREATED WITH DECITABINE AND VENETOCLAX (DEC10-VEN)

- In the entire cohort, achievement of CCyR was an independent predictor of improved OS compared to those who did not achieve CCyR (mOS 16.2 vs. 8.0 mo, HR 0.4, 95% CI 0.2, 0.9, p=.01). OS benefit with CCyR was more pronounced in the previously treated cohort (mOS NR vs 8.8 mo, HR 0.3; 95% CI 0.06,1.56;P=.15)

Figure 3 : Multivariable Cox analysis for overall survival (OS)



- On multivariable Cox analysis for OS (Figure 3) : Compared to diploid CG, pts with abnormalities of chr 5,7,17 have a significant chance of death. (HR 3.39; 95%CI 1.53,7.55; p=0.003)

Conclusion

- Adverse risk and complex cytogenetics is associated with poor outcomes
- Attainment of CCyR is associated with improved outcomes in older and intensive chemotherapy ineligible pts with AML treated with DEC10-VEN

Venetoklax u *RUNX1*+ AML

RUNX1 **MUTATIONS IN NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA DO NOT ADVERSELY IMPACT CLINICAL OUTCOMES IN THE MODERN ERA**

RUNX1 Mutations in AML: Patients (N=907)

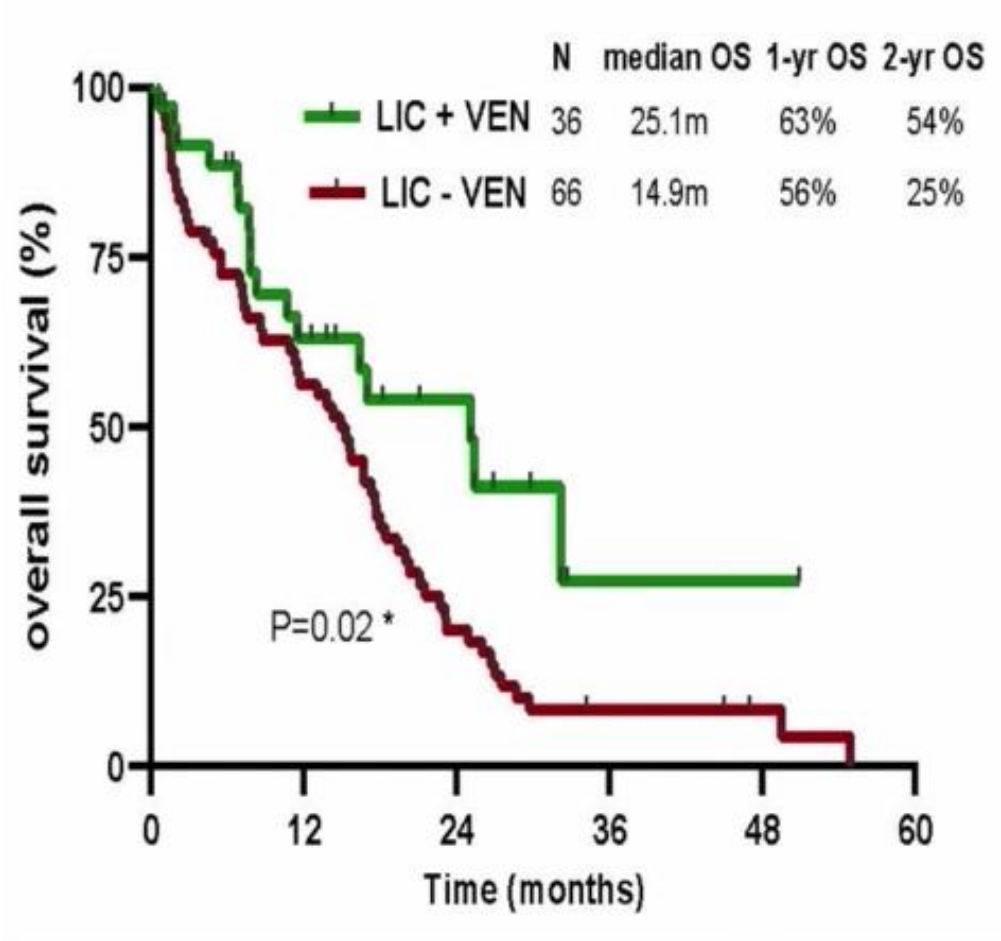
Characteristic n (%) / median [range]	m*RUNX1* (N=137; 15%)	wt*RUNX1* (N=770; 85%)	P value
Age (years)	71 [31-92]	66 [17-90]	<0.001
Age ≥60 years	102 (74)	497 (65)	0.04
t-AML	6 (4)	54 (7)	0.19
s-AML	28 (20)	100 (13)	0.03

- Among pts with mRUNX1 AML treated with LIC, response rates were significantly higher in those who received Ven (72% vs. 44%, P=0.007)

Venugopal, Session: AML classification, S132

Venetoklax u *RUNX1* + AML

RUNX1 MUTATIONS IN NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA DO NOT ADVERSELY IMPACT CLINICAL OUTCOMES IN THE MODERN ERA



- **Pts with mRUNX1 AML who received LIC with Ven had superior OS compared to those who received LIC without Ven (median OS 25.1 m vs. 14.9 m; P=0.02).**

Venetoklax + gilteritinib u *FLT3*+ R/R AML

EFFICACY AND SAFETY OF VENETOCLAX IN COMBINATION WITH GILTERITINIB FOR RELAPSED/REFRACTORY *FLT3*-MUTATED ACUTE MYELOID LEUKEMIA: UPDATED ANALYSES OF A PHASE 1B STUDY

Key Eligibility Criteria

- R/R AML
- WT or *FLT3*$^{mut+}$ (dose escalation) and *FLT3*$^{mut+}$ (dose expansion)
- ≥1 prior line of therapy[a]
- WBC count ≤ 25 x 10^9 /L at start of study drug
- ECOG PS 0–2

Dose escalation phase
WT and *FLT3*$^{mut+}$

- Ven 400 mg + Gilt 80 mg (n = 7)
- Ven 400 mg + Gilt 120 mg (n = 8)

DLT monitoring[b]

Dose expansion
FLT3^{mut+} only

- Ven 400 mg + Gilt 120 mg (RP2D) (n = 46)[c]

DLT monitoring[b]

Follow-up

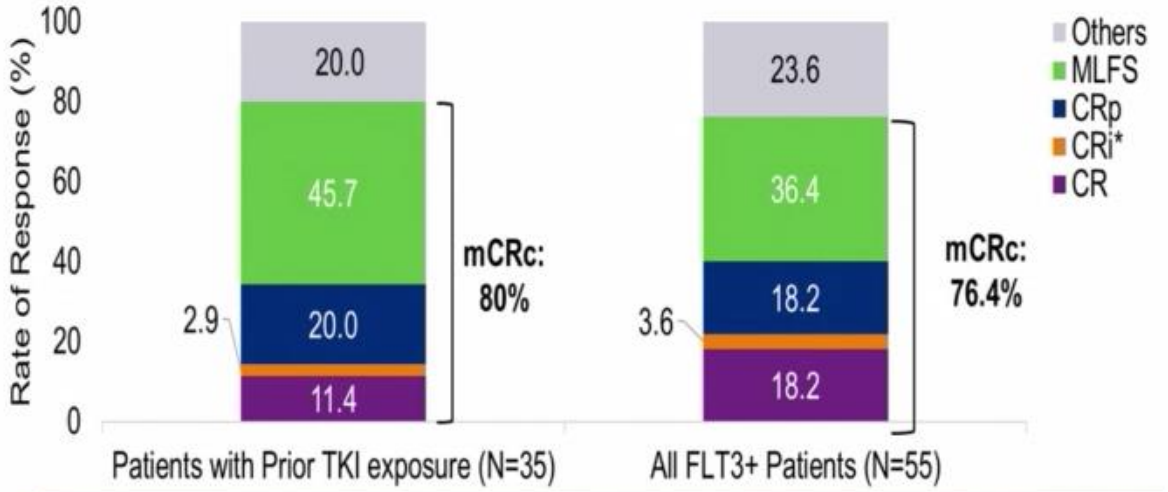
- Post-treatment follow-up monthly for up to 1 year, following last dose of study drug

Primary Endpoints	Secondary Endpoints	Exploratory Endpoints
• mCRc[d]	• CR + CRh • DoR of mCRc	• OS in *FLT3*$^{mut+}$ subgroups • Allelic burden of FLT3 mutations

Venetoklax + gilteritinib u *FLT3*+ R/R AML

EFFICACY AND SAFETY OF VENETOCLAX IN COMBINATION WITH GILTERITINIB FOR RELAPSED/REFRACTORY *FLT3*-MUTATED ACUTE MYELOID LEUKEMIA: UPDATED ANALYSES OF A PHASE 1B STUDY

- **AEs** were common with acceptable 30-day mortality rate of 0%, and 60-day mortality rate of 10.9%
- **Overall Survival** with prior TKI use was 9.6 mo; with no prior TKI use was 10.6 mo; OS in those who attained CRc was 20.9 mo; OS was NR for HSCT
- **Molecular response** of under 10^{-2} achieved in 60.6% of evaluable patients



	FLT3+ Patients with Prior TKI (N=35)	All FLT3+ Patients (N=55[a])
mCRc, n (%)	28 (80.0)	42 (76.4)
CR+CRp+CRi*	12 (34.3)	22 (40.0)
MLFS	16 (45.7)	20 (36.4)
Time to mCRc (months), median (range)	0.9 (0.7, 4.2)	0.9 (0.7, 4.6)

Altman, Oral Presentations, Session: Developments in AML therapy, S135

Venetoklax + gilteritinib u *FLT3*+ R/R AML

EFFICACY AND SAFETY OF VENETOCLAX IN COMBINATION WITH GILTERITINIB FOR RELAPSED/REFRACTORY *FLT3*-MUTATED ACUTE MYELOID LEUKEMIA: UPDATED ANALYSES OF A PHASE 1B STUDY

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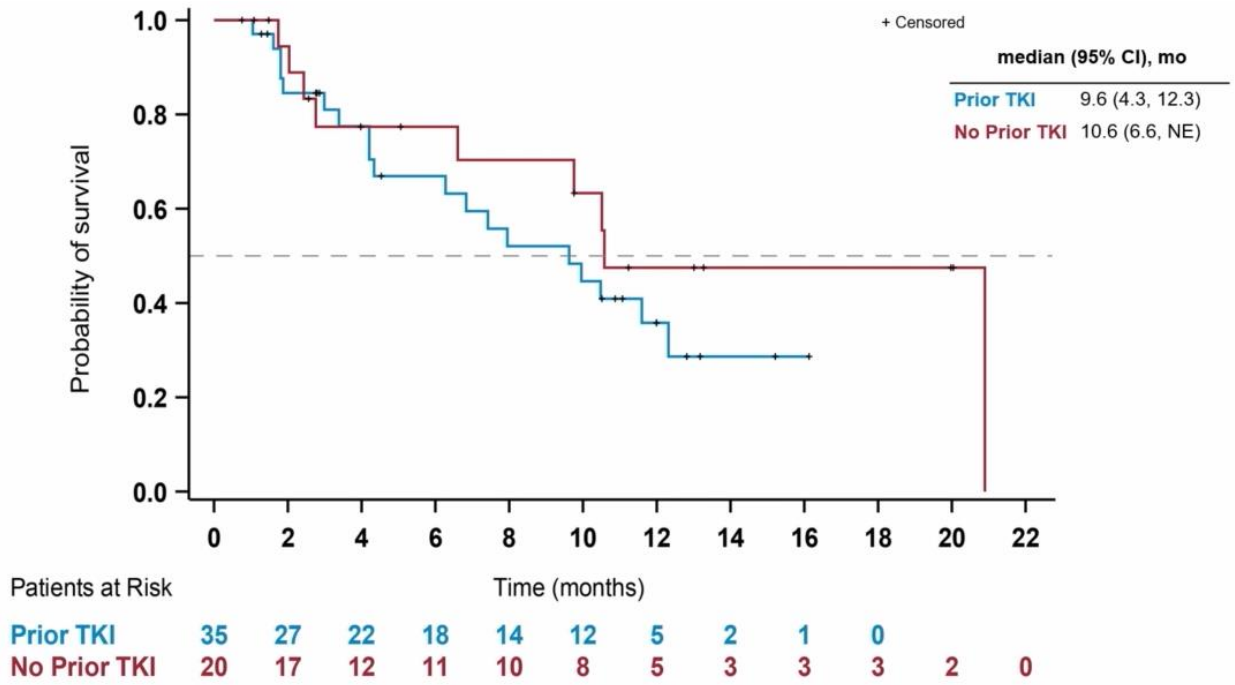
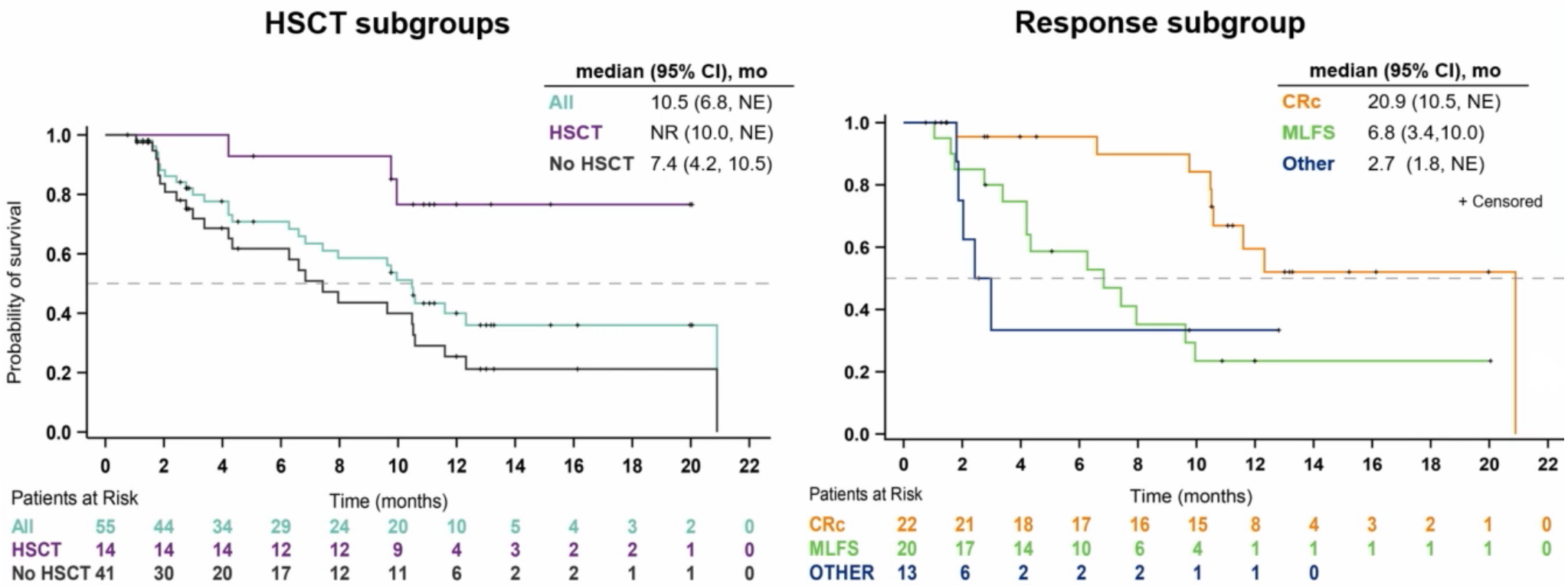


Venetoklax + gilteritinib u *FLT3*+ R/R AML

EFFICACY AND SAFETY OF VENETOCLAX IN COMBINATION WITH GILTERITINIB FOR RELAPSED/REFRACTORY *FLT3*-MUTATED ACUTE MYELOID LEUKEMIA: UPDATED ANALYSES OF A PHASE 1B STUDY



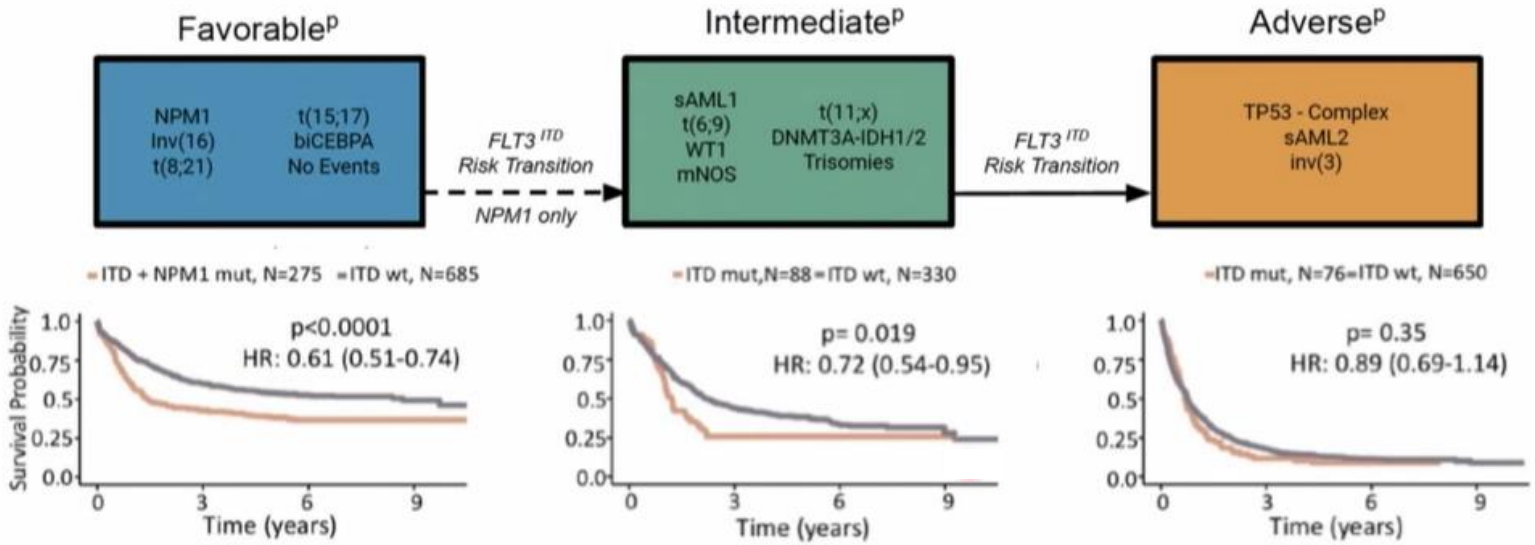
Median (range) duration of follow-up: 12 months (0.8–20.9)

Nová AML (re-) klasifikace

Algoritmus stratifikace AML

A UNIFIED CLASSIFICATION AND RISK STRATIFICATION ALGORITHM TO SUPPORT CLINICAL DECISIONS IN ACUTE MYELOID LEUKEMIA

- **Model predictors of outcome**
- **Class membership + FLT3^{ITD} capture prognostic information attributed to genetic features**



Three tier schema informed by class membership + FLT3^{ITD} status.

Algoritmus stratifikace AML

A UNIFIED CLASSIFICATION AND RISK STRATIFICATION ALGORITHM TO SUPPORT CLINICAL DECISIONS IN ACUTE MYELOID LEUKEMIA

- Derivation of a complete molecular ontogeny in AML. 16 molecular subgroups.
- Strong associations between class membership and clinical endpoints (CR, Relapse, OS).
- sAML captures 25% of AML patients, associated with high risk disease. Independent of MRD status at CR1, with suggestive benefit from transplant.
- Class membership and $FLT3^{ITD}$ informs extension of ELN^{2017} into a 3-tier risk score.
- Re-stratification of 1 in 4 AML patients, significant improvement in prognostic accuracy.
- With publication, open access web-based clinical decision support tool for classification and risk stratification.

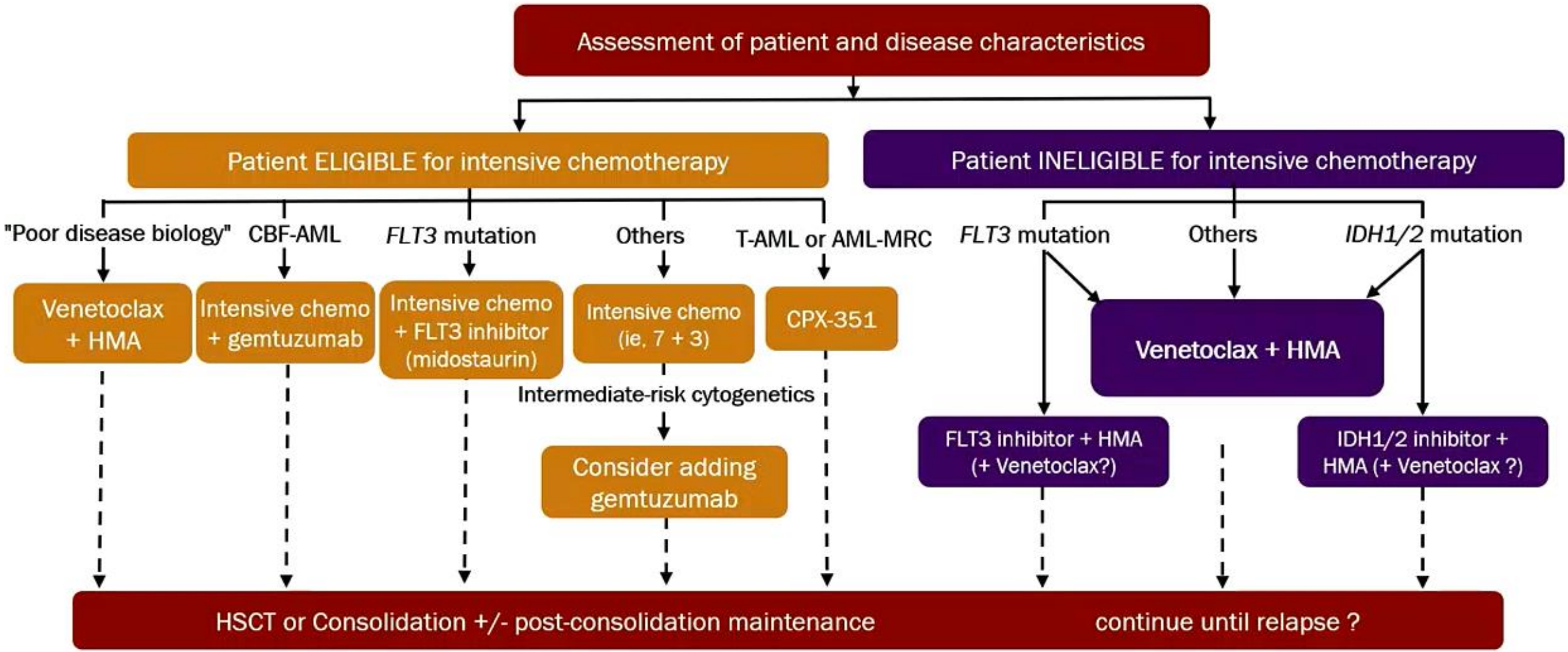
Antimykotika v éře nových léků u AML

ATM profylaxe v éře nových léků u AML

EHA GUIDELINE: ANTIFUNGAL PROPHYLAXIS IN ACUTE MYELOID LEUKEMIA TREATED WITH NOVEL AGENTS

Agent	Recommendation for/ against AF prophylaxis	Comment
HMA	Weak against…	No prospective studies regarding prophylaxis, risk of IFI from 2-14% in retrospective studies; consider AF prophylaxis in high-risk setting (local incidence; heavily pre-treated patient; prolonged neutropenia)
Ven+HMA	Conditional for…	Need to be harmonized with recommendation for HMA. VEN ramp up until 70mg if concomitant with posaconazole
Gem-Ozo	Monoth.: Weak against.. Combin.: strong for…	No evidence for potentail toxicity due to DDI
Glasdegib	Weak against (especially triazoles)	strong impact of potential toxicity, specifically QTc prolongation; consider dose reduction to 50% if strong CYP3A4 inhibitors are used
Ivosidenib	Monoth.: Weak against.. Combin.: strong for…	If azole co-admin.: Monitor AE, specifically QTc prolongation

Agent	Recommendation for/ against AF prophylaxis	Comment
Midostaurin	Monoth.: strong against.. Combin.: strong for…	More evidence needed for dose reduction; or TDM
Sorafenib	Monoth.: against.. Combin.: strong for…	addition of SORA to intensive chemotherapy in elderly pat: significantly more deaths due to infection; co-admin. With azoles: QTc prolongation, elevated SORA levels
Lestaurtinib	Conditional for…	Dose reduction of lestaurtinib from 80 to 40/60mg if strong CYP3A4 inhibitor is administered for antifungal prophylaxis
Crenolanib	Weak against…	against strong CYP3A4 inhibitors; more data needed
Gilteritinib	Monoth: conditional for..	if azole co-admin.: reduce dose or monitor closely for AE; more data needed
Idanasutlin	Weak for…	Avoid strong CYP3A4 inhbitors; if co-admin: strong for dose adaptation (not specified)
Dasatinib	Strong for…	


Assessment of patient and disease characteristics
Patient ELIGIBLE for intensive chemotherapy
Patient INELIGIBLE for intensive chemotherapy
"Poor disease biology"
CBF-AML
FLT3 mutation
Others
T-AML or AML-MRC
FLT3 mutation
Others
IDH1/2 mutation
Venetoclax + HMA
Intensive chemo + gemtuzumab
Intensive chemo + FLT3 inhibitor (midostaurin)
Intensive chemo (ie, 7 + 3)
CPX-351
Venetoclax + HMA
Intermediate-risk cytogenetics
FLT3 inhibitor + HMA (+ Venetoclax?)
IDH1/2 inhibitor + HMA (+ Venetoclax ?)
Consider adding gemtuzumab
HSCT or Consolidation +/- post-consolidation maintenance
continue until relapse ?