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POLICLINICO DI
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New Drugs in Hematology

New drugs

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Disclosures of MASSIMILIANO BONIFACIO

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						X	
Ascentage Pharma						X	
Bristol Myers Squibb						X	
Incyte						X	
Novartis						X	
Pfizer						X	

Do we really need new drugs in CML?

YES: failure of treatment options in later lines is a common situation

	Nilotinib[1] 400 mg bid	Dasatinib[2] 100 mg	Bosutinib[3] 500 mg	Ponatinib[4] 45 mg	Asciminib[5] (range of doses)
Follow-up	4 years	7 years	5 years	5 years	8 years
Total discontinuation	70%	78%	60%	63%	39%
Lack of efficacy	30%	21%	23%	17%	17%
Adverse events	21%	24%	24%	21%	13%

[1] Giles et al. *Leukemia* 2013;27:107-112. [2] Shah et al. *Am J Hematol* 2016;91:869-874. [3] Gambacorti-Passerini et al. *Haematologica* 2018;103:1298-1307. [4] Cortes et al. *Blood* 2018;132:393-404. [5] Hochhaus et al. *ASH annual meeting* 2023;abs#450

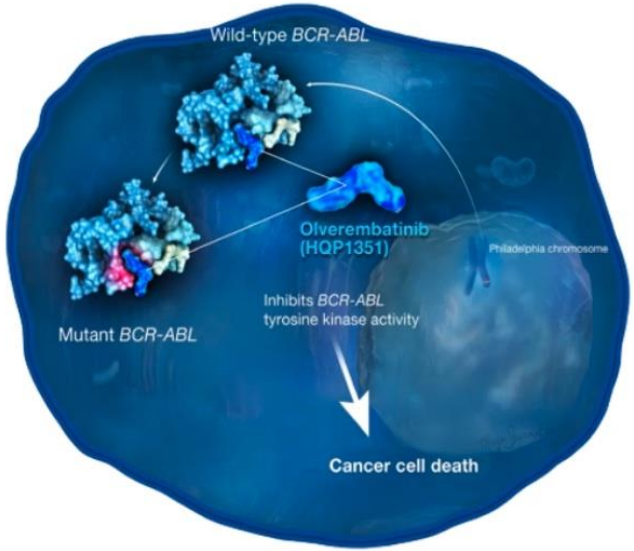
Do we really need new drugs in CML?

YES: adverse events may impair quality of life in the long term

Toxicity (any grade)	Dasatinib[164] (100 mg once daily)	Nilotinib[165] (400 mg twice daily)	Bosutinib[167] (500 mg once daily)	Ponatinib[169] (45 mg once daily)	Asciminib (40 mg twice daily)[172]
Rash	33%	31%	28%	47%	7%
Headache	—	18%	27%	43%	16%
Fatigue	37%	21%	24%	30%	10%
Myalgias/Arthralgias	38%	11%	18%	24%/33%	9%
Pleural effusion	28%	—	17%	—	—
Hypertension	—	—	8%	37%	12%
Hemorrhage	26%	—	—	—	—
Diarrhea	42%	12%	83%	20%	12%
Constipation	—	13%	13%	41%	—
Nausea	27%	25%	48%	29%	12%
Vomiting		13%	38%	19%	7%
Increased blood creatinine	—	—	13%	—	—
Increased lipase	—	—	—	27%	
Increased ALT/AST	—	—	15%	—	4%

Shah et al. *NCCN guidelines* version 2.2024

Olverembatinib (HQP1351)



- 3rd generation TKI, with *in vitro* activity against BCR::ABL1^{WT} and BCR::ABL1^{T315I} mutant kinases
- Significant antiproliferative activity in enginereed cells with BCR::ABL1 compound mutations
- It is administered every other day (48 hours)
- 2021: approved and commercialized in China for adult patients with TKI-resistant CP- and AP-CML harboring T315I mutation

Olverembatinib: summary of efficacy from phase 1/2 trials

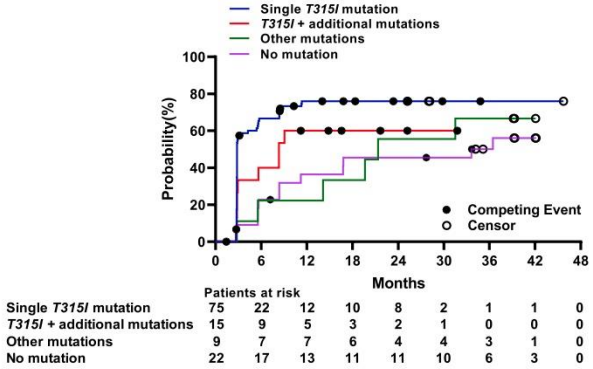
CP: 127 patients, median follow-up 37 months

- Mutational status: - T315I single mutation, n=77 (60.6%)
  - T315I compound mutations, n=16 (12.6%)
  - other mutations, n=11 (8.7%)
  - no mutations, n=23 (18.1%)
- Previous TKIs: 1 (n=21, 16.5%), 2 (n=71, 55.9%), ≥3 (n=35, 27.6%)
- All 84 patients without CHR at baseline achieved it (100%)
- Of 121 patients without MCyR at baseline: - 79% achieved at least MCyR
  - 69% achieved at least CCyR
- Of 126 patients without MMR at baseline: - 55% achieved at least MMR
  - 44% achieved at least MR$^{4.0}$
- PFS 92% (5 events)

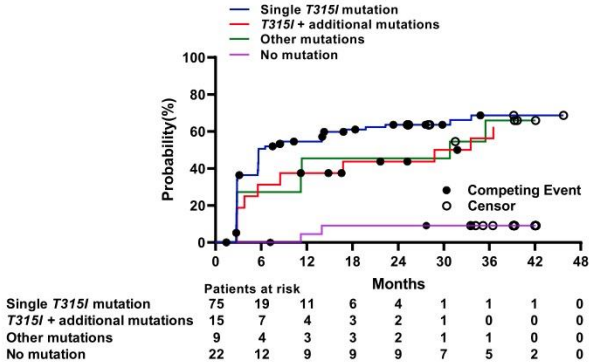
AP: 38 patients, median follow-up 27 months

- 27/37 (73%) without CHR achieved CHR; 18/38 (47%) without MCyR achieved CCyR

CCyR



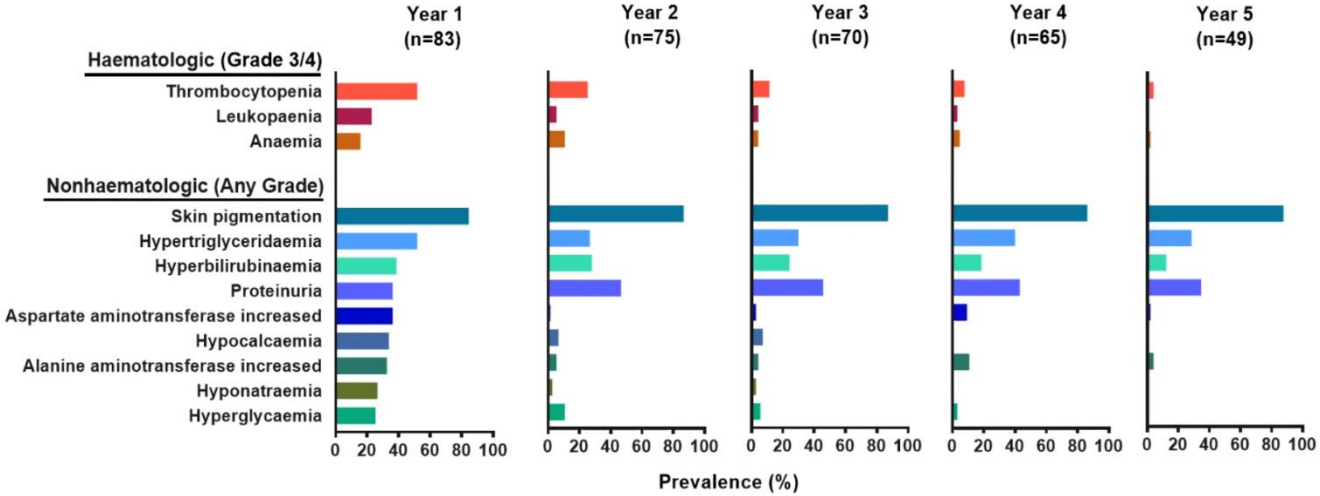
MMR



Jiang et al. *J Hematol Oncol* 2022;15:113

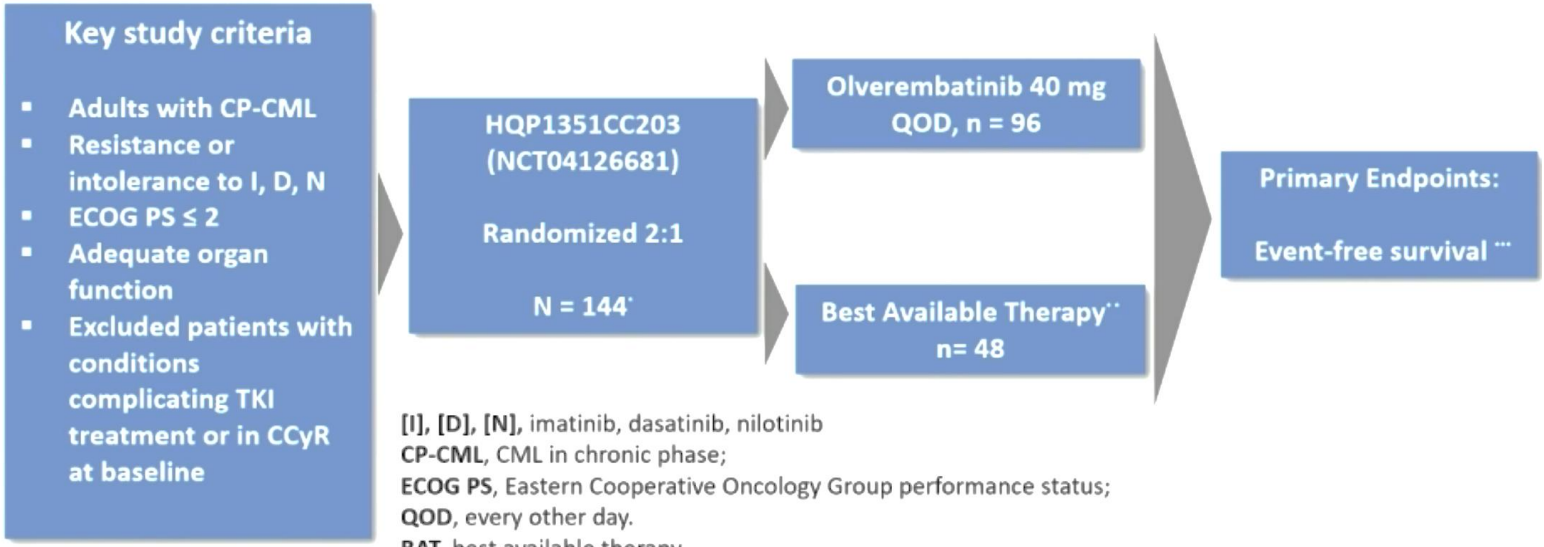
Olverembatinib: clinical safety data

- Most serious adverse events were hematologic
- Most common adverse events were skin pigmentation an lab abnormalities
- Recurrent adverse events declined over time
- Low incidence of Arterial Occlusive Events (AOEs), hepatotoxicity and pancreatitis



Jiang et al. *J Hematol Oncol* 2022;15:113

Registrational randomized study of Olverembatinib vs Best Available Therapy: design



[I], [D], [N], imatinib, dasatinib, nilotinib
CP-CML, CML in chronic phase;
ECOG PS, Eastern Cooperative Oncology Group performance status;
QOD, every other day.
BAT, best available therapy
*2 patients in BAT group had been randomized successfully but not dosed .
** **BAT includes interferon, hydroxyurea, and homoharringtonine or TKIs I, D, and N and combinations**

*** EVENT definition: no CHR within 3 months, loss of achieved CHR, MCyR or CCyR, disease progression, death, unacceptable toxicity

Actual BAT treatments included: NIL (n=22), DAS (n=16), IMA (n=2), NIL + HU (n=2), DAS + IFN (n=2), NIL + IFN (n=1), IFN + HU + omacetaxine (n=1)

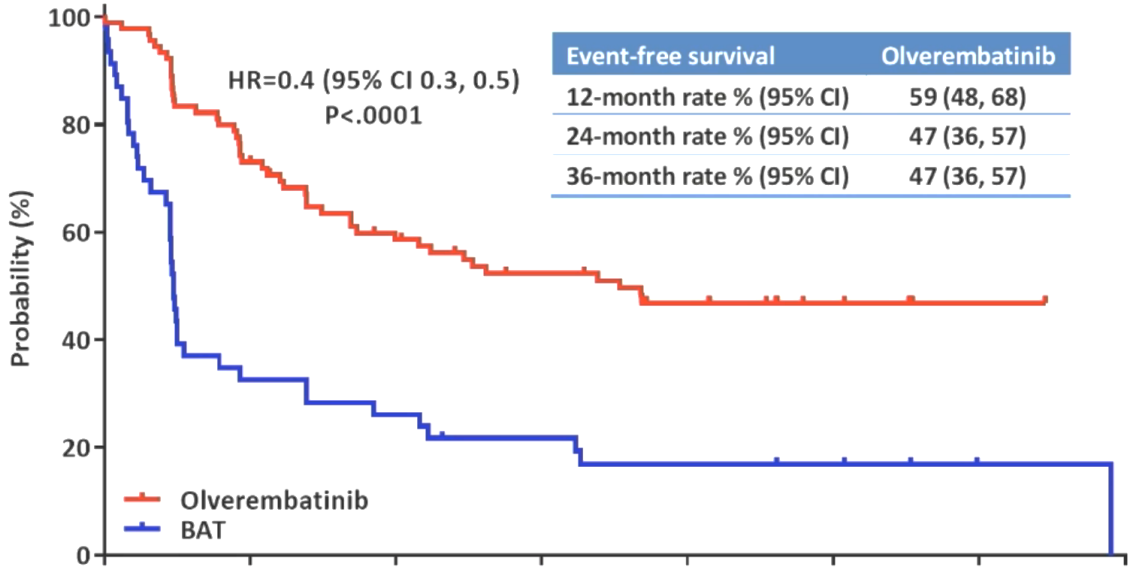
Jiang et al. *ASH annual meeting* 2023;abs#869.

Randomized study of Olverembatinib vs BAT: patient disposition

	Olverembatinib (n=96)	Best Available Therapy (n=48)
Treatment duration, months	**21** (0.6-44.2)	**3** (0.2-40.5)
Study follow-up, months	**31** (1.3-46)	**30** (0-45.8)
Continuing on treatment, n (%)	40 (41.7)	6 (12.5)
Discontinued, n(%)	56 (58.3)	42 (87.5)
Reason for D/C		
Adverse events	**27 (28.0)**	**15 (31.3)**
Treatment failure	**13 (13.5)**	**22 (45.8)**
Consent withdraw	9 (9.4)	1 (2.1)
Poor compliance	3 (3.1)	1 (2.1)
Death	1 (1.0)	1 (2.1)
Lost to follow-up	0	1 (2.1)
Other	3 (3.1)	1 (2.1)
Switched to olverembatinib	**NA**	**35 (72.9)**

Jiang et al. *ASH annual meeting* 2023;abs#869.

Randomized study of Olverembatinib vs BAT: Event-Free Survival



Event-free survival	Olverembatinib
12-month rate % (95% CI)	59 (48, 68)
24-month rate % (95% CI)	47 (36, 57)
36-month rate % (95% CI)	47 (36, 57)

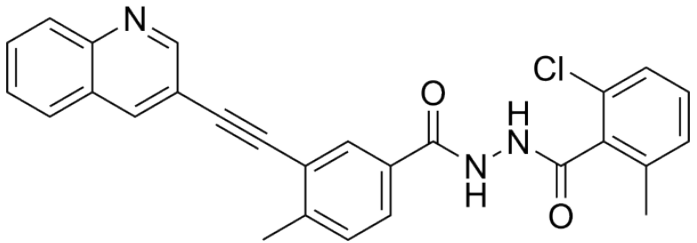
Patients at risk

Olverembatinib	96	63	48	40	32	17	6	0
BAT	48	15	12	9	7	5	1	0

Jiang et al. *ASH annual meeting* 2023;abs#869.

Vodobatinib (K0706)

- 3rd generation TKI effective against *wild-type* and mutated BCR::ABL1 (except T315I) with limited off-target activity
- Phase 1 trial enrolled patients progressing or intolerant to ≥3 prior TKIs (<3 TKIs if available TKIs not clinically feasible, advisable or approved; patients with T315I mutation were not eligible)
- Phase 1 dose range: 12 to 240 mg daily; the dose selected for phase 2 expansion was 174 mg daily.
- Currently, the drug is also under investigation for Parkinson's Disease.



Vodobatinib: summary of efficacy and safety

41 patients in dose escalation (including 9 AP/BP-CML) and 11 CP-CML patients in dose expansion (N=52)

- Response to previous TKI: refractory (n=31, 59.6%), intolerant (n=21, 40.4%)
- Mutational status: single mutation (n=17, 32.7%), double mutation (n=3, 5.8%)

- Of 35 CP-CML patients without PCyR at baseline: - 60% achieved at least PCyR
  - 48% achieved at least CCyR
- Of 41 CP-CML patients without MMR at baseline: - 36% achieved at least MMR
- Median duration of treatment was 23 months in the dose escalation and 16 months in the dose expansion.

- Most common any grade TEAEs included thrombocytopenia (33%), cough (19%), anemia (17%) and diarrhoea (17%).
- Ten patients (19%) reported cardiovascular TEAEs, only 1 (arterial hypertension) related to the drug.

Cortes et al. *ASH annual meeting* 2021;abs#309.

Vodobatinib: efficacy according previous lines of treatment

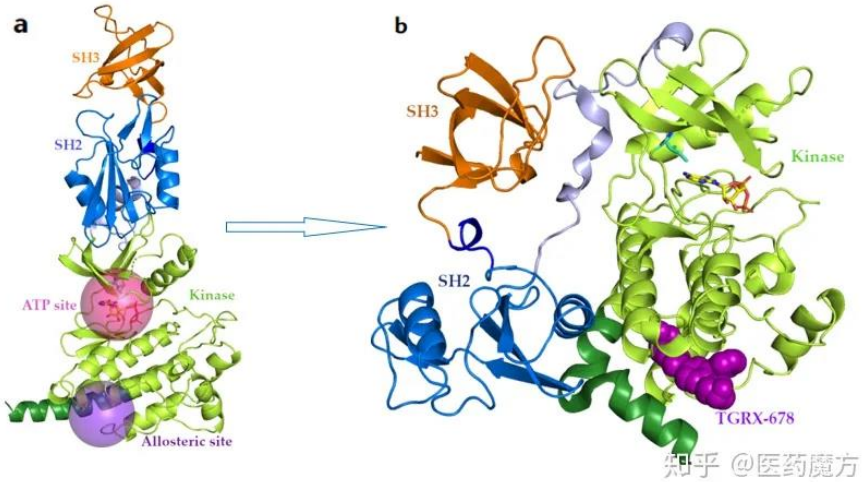
28 patients received ≥3 lines of TKI (3T group)
15 patients received ≥3 lines of TKI including ponatinib with or without asciminib (PON group)
3 patients received ≥3 lines of TKI including ponatinib AND asciminib (ASC group)

	3T group	PON group	ASC group
Complete Hematologic Response	100%	100%	100%
Major Cytogenetic Response	60.7%	66.7%	33.3%
Complete Cytogenetic Response	50%	46.7%	33.3%
Major Molecular Response	53.6%	53.3%	0
Deep Molecular Response ($MR^{4.0}$)	32.1%	26.7%	0

Cortes et al. *ASH annual meeting* 2022.

TGRX-678

- Novel, potent and selective BCR::ABL1 tyrosine kinase inhibitor targeting the ABL myristoyl pocket (STAMP)
- Phase 1 trial enrolling CP- and AP-CML patients resistant and/or intolerant to IMA, NIL or DAS
- Doses ranging from 10 to 240 mg daily



TGRX-678: patient characteristics

	Patients (N=150)
Age, median (range)	46 (19-74)
Male, n (%)	87 (58)
ECOG, n (%) 0 1	 79 (53) 71 (47)
Disease phase CP AP	 102 (68) 48 (32)
Median interval from CML diagnosis to TGRX-678, months	90
Cytogenetic status at baseline No CyR Less than PCyR PCyR	 98 (65) 35 (23) 17 (11)

	Patients (N=150)
Mutations at baseline Single T315I mutation T315I + additional mutation Other mutation No mutation	 38 (25) 9 (6) 28 (19) 75 (50)
Previous lines of TKI therapy 1L 2L ≥3L	 5 (3) 32 (21) 113 (75)
Prior TKI used Non 3G TKI only Ponatinib and/or HQP-1351 Asciminib	 83 (55) 54 (36) 13 (9)

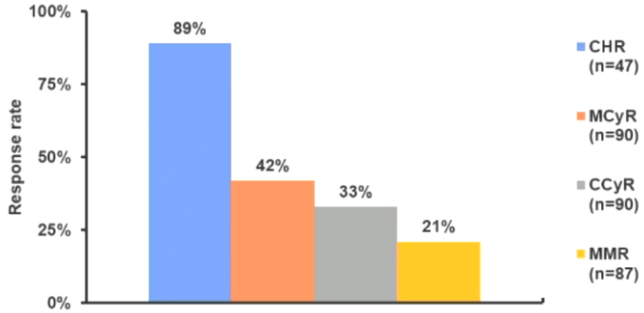
Jiang et al. *ASH annual meeting* 2023;abs#867.

TGRX-678: patient disposition

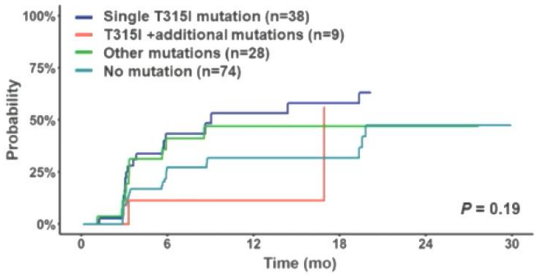
	Total (N=150)	CP-CML (N=102)	AP-CML (N=48)
Treatment duration, months	7 (0.1-30)	not reported	not reported
Study follow-up	8 months	8 months	9 months
Continuing on treatment, n (%)	**122 (81)**	93 (91)	29 (60)
Discontinued, n(%)	**28 (19)**	9 (9)	19 (40)
Reason for D/C			
Adverse events	**3 (2)**	1 (1)	2(4)
Treatment failure	**8 (5)**	0	8 (17)
Consent withdraw	**10 (7)**	6 (6)	4 (8)
Death	**1 (1)**	0	1 (2)
Other	**6 (4)**	2 (2)	4 (8)

Jiang et al. *ASH annual meeting* 2023;abs#867.

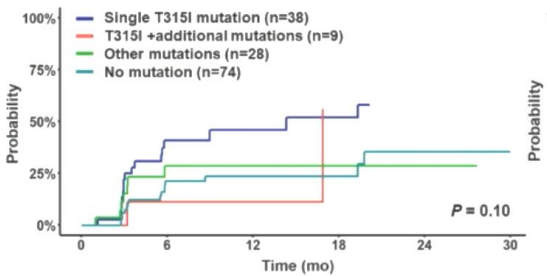
TGRX-678: response in CP patients



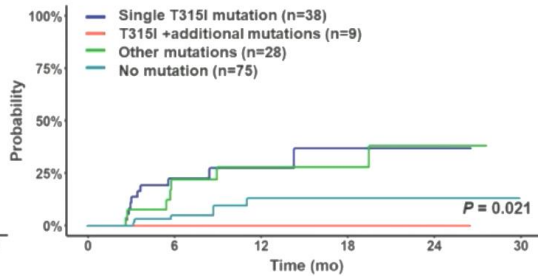
MCyR



CCyR

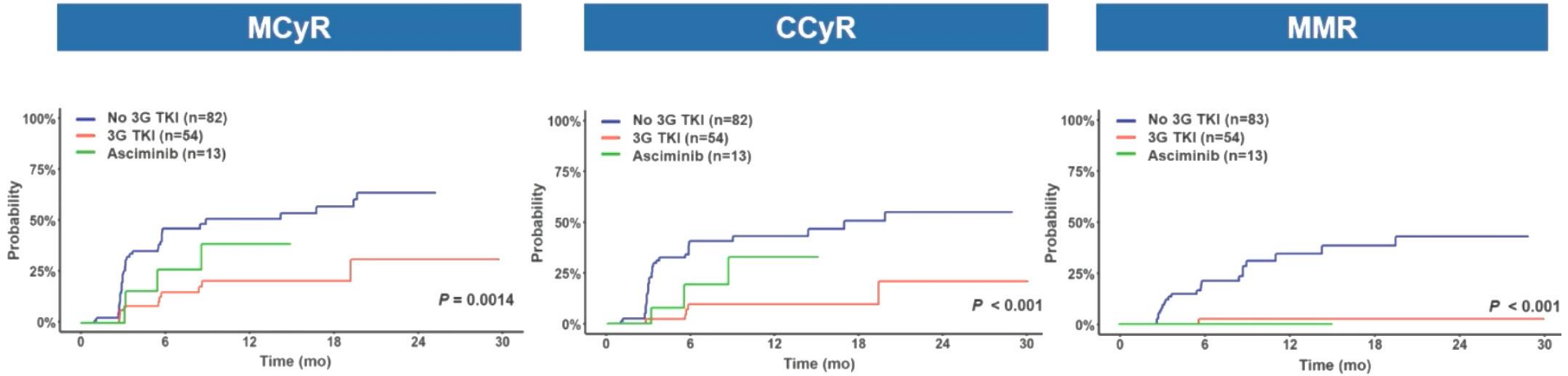


MMR



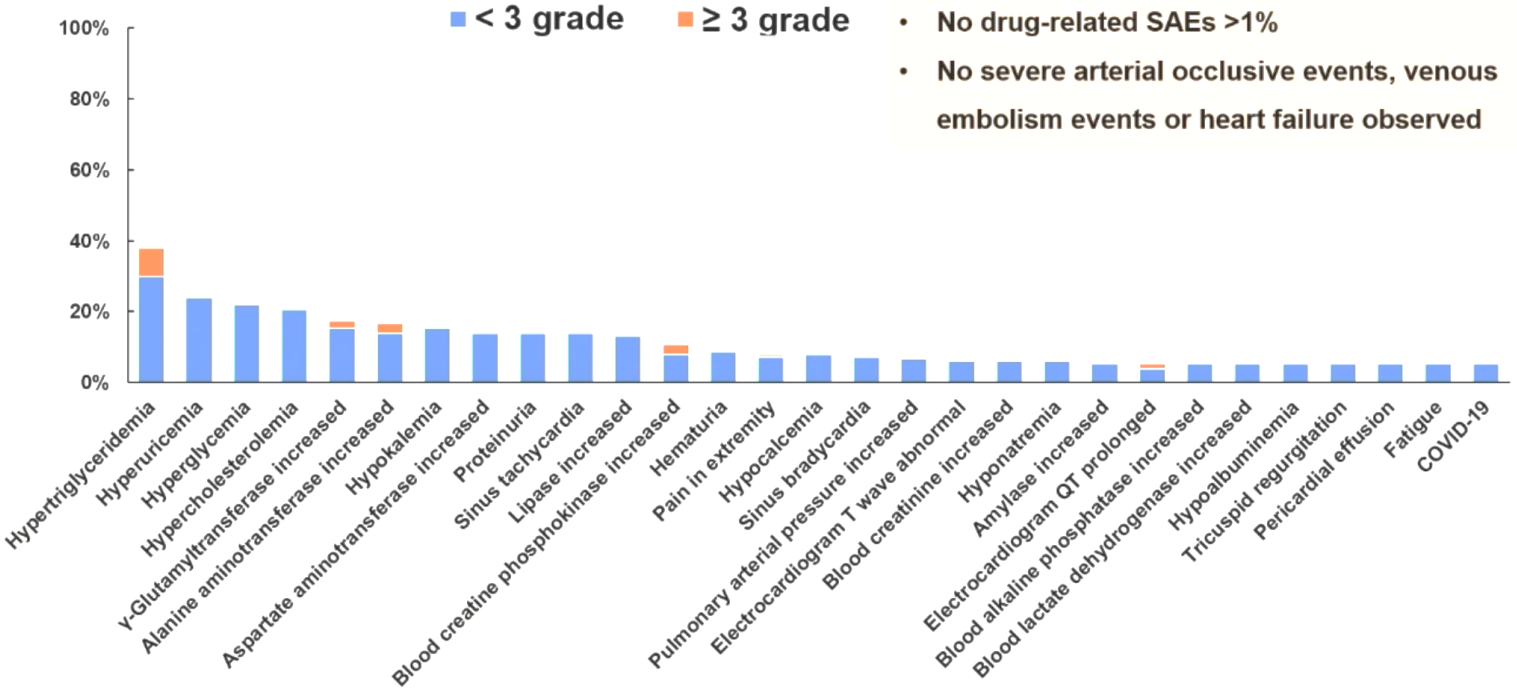
Jiang et al. *ASH annual meeting* 2023;abs#867.

TGRX-678: response according to previous lines of treatment



Jiang et al. *ASH annual meeting* 2023;abs#867.

TGRX-678: non-hematologic adverse events



Jiang et al. *ASH annual meeting* 2023;abs#867.

Conclusions

- **Olverembatinib** (HQP1351) is effective in patients resistant or intolerant to other TKIs, and has a peculiar efficacy in patients with BCR::ABL1^{T315I}, including those with compound mutations.
- *A global (US) randomized phase IIb study of PK, safety and efficacy of 3 different dosages of olverembatinib (30 mg QOD, 40 mg QOD, 50 mg QOD) in subjects with refractory CML and Ph+ ALL is ongoing.*
- *A global pivotal registration phase III study of ovelerembatinib combined with chemotherapy vs imatinib combined with chemotherapy in patients with newly diagnosed Ph+ ALL has recently started.*

- **Vodobatinib** (K0607) has a favorable safety profile and is effective also in patients exposed to many previous lines of TKI treatment, inclunding ponatinib, but it is not active against BCR::ABL1^{T315I}.
- *The phase 2 doxe expansion cohort of the study is ongoing.*

- **TGRX-678** is an investigational BCR::ABL1 allosteric which demonstatred preliminary efficacy in CP and AP-CML heavily pretreated, including patients with BCR::ABL1^{T315I}.
- *The phase 1 study is ongoing and two doses (80 mg and 240 mg/d) were selected for further exploration.*