

STATE OF 2023 in LMI:
HOW WILL CML DIAGNOSTICS AND THERAPY
EVOLVE IN LMI?
DO ALL TKI BECOMING GENERIC CHANGE
ACCESS IN ANY WAY?

DR. AMMA ANIMA BENNEH-AKWASI KUMA

Consultant, Department of Haematology, Korle-Bu Teaching Hospital, Accra, Ghana

Lecturer, College of Health Sciences, University of Ghana, Accra, Ghana

INTRODUCTION

- Currently the management of CML in LMI countries is faced with some challenges.
- These include the **availability and access to diagnostic and monitoring tools, costs of laboratory tests and access to all the different kinds tyrosine kinase inhibitors.**
- **Lack of awareness of CML** in the general populace also poses a problem.

- **Diagnosis of CML** in most centers in LMI countries **is based on morphology**; peripheral film comment and bone marrow aspirate
- Performing and reporting of these tests **require the expertise of haematologists** who are also few in number
- **Haematological remission** is most often the only type of response that can readily be accessed

- Access to PCR testing is also a challenge and even where it is available the cost can be a problem. This leads to inadequate monitoring.
- Thanks to the Cepheid, the **GeneXpert system** has simplified PCR testing making it much more accessible and affordable
- Through the efforts of **Cepheid, iCMLf** and the **Max Foundation** certain centres in LMI countries now have access to GeneXpert machines and PCR testing has been made very simple.
- Our centre has been a beneficiary and this has revolutionized our CML care

- **Imatinib is the commonest TKI** in most LMI countries and this has been made possible because of GIPAP and MAS(MAX access solutions)
- **Availability of second and third generation TKIs is not as common** and when there is a need to switch therapy choices are limited.
- **Lack of awareness** leads to advanced disease at diagnosis with prognostic implications.

HOW WILL DIAGNOSTIC TOOLS AND THERAPY IN CML EVOLVE /IMPROVE?

- Diagnostic tools will improve as the need to beef up the diagnostic capabilities in LMI is now an accepted fact.
- PCR testing will become much more accessible and affordable making it possible to quickly confirm the diagnosis and initiate treatment.
- Also various point of care diagnostic tools will evolve with the LMI population in mind so that testing will not require sophisticated infrastructure and equipment.

- There are research centres in LMI using techniques such as sequencing and FISH(**cytogenetics**).
- Personnel at these centres can be roped in to use their techniques to help in the diagnosis and monitoring of patients.

- They can further **train people** who will use the expertise acquired in clinical laboratories thus further enhancing diagnostic capabilities
- **Access to therapy** will also improve as various stakeholders continue to engage policy makers and private sector to find ways of making all TKI readily accessible .

WILL GENERIC CML TREATMENTS IMPACT ACCESS

- Generic CML treatments will impact access in terms of availability of especially the second and third generation tyrosine kinase inhibitors.
- However will it come at a cost?
- There will be different brands of generics and issues such as **efficacy and side effects may differ with different brands** posing therapeutic challenges.

- More work will need to be done in order to streamline the production of the generics, assess its efficacy and determine the side effects profile to ensure compliance.
- Pharmacovigilance will also be needed to ascertain the safety profile of the generics.

WHAT WILL BE THE SINGLE MOST IMPORTANT IMPROVEMENT EXPECTED TO BE SEEN IN CML CARE IN LMI

- The single most important improvement expected to be seen in CML care in LMI is in the area of **diagnosis and monitoring**.
- More people will have access to **affordable PCR testing** leading to a dramatic impact on CML care in LMI.

CONCLUSION

- The future of CML care in LMI countries looks bright.
- Challenges have already been identified.
- With unity of purpose all stakeholders can ensure optimum care for people living with CML IN LMI countries.



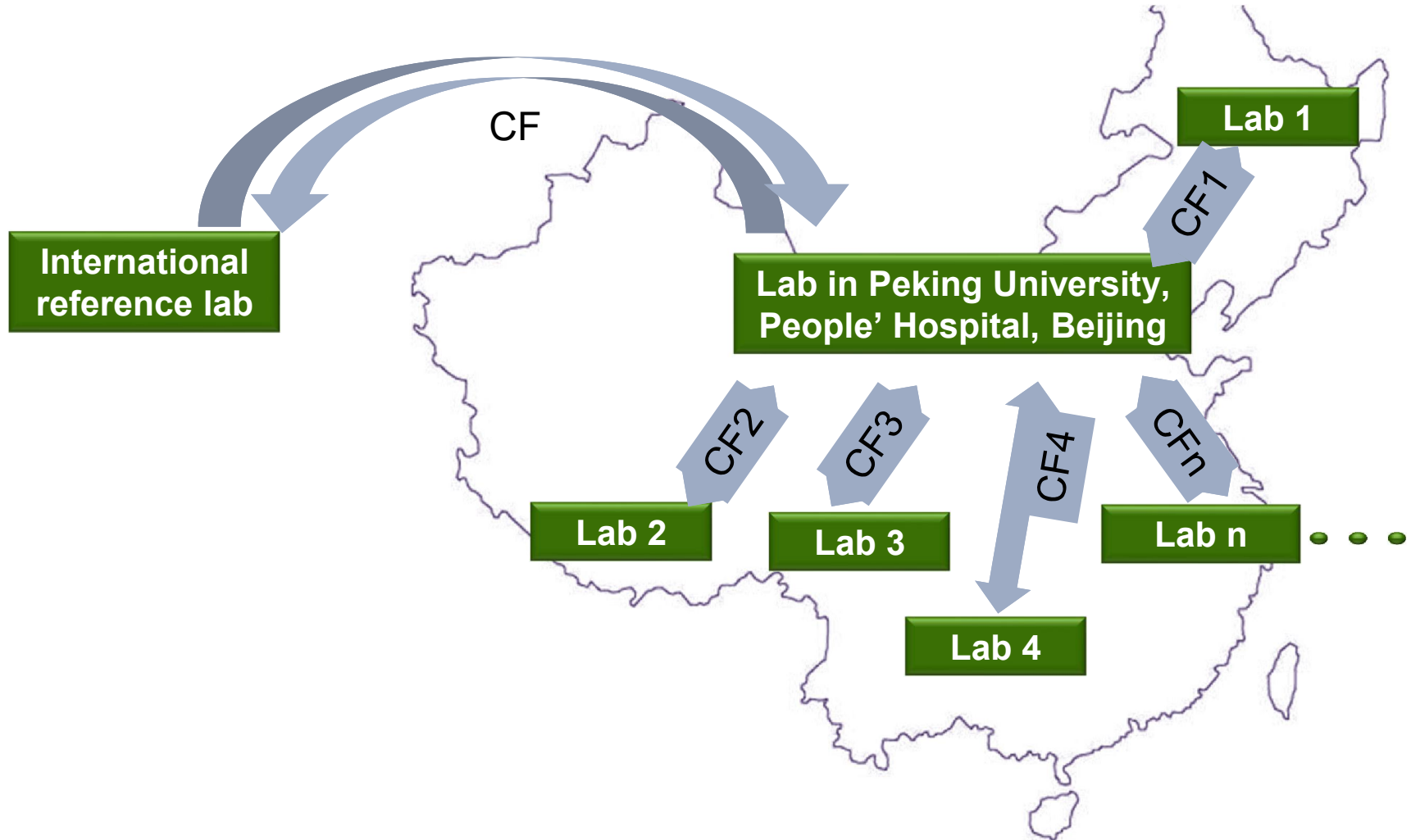
**State of 2023 in LMI Countries:
How will CML diagnostics and Therapy Evolve?
Do all TKI Becoming Generic Change Access in Any Way?**

Qian JIANG, M.D.

Peking University People's Hospital, Beijing, China

How will Diagnostic and Monitoring Tools Improve?

More than 50 international standardized labs in China



The GeneXpert Cartridge

Automated Sample Preparation and Multiplexed qRT-PCR



Key features:

- ✓ **Rapid results**, typically within several hours
- ✓ **Portability**, can be run anywhere
- ✓ **Ease-of use**, does not require a high complexity lab
- ✓ **Reduced the cost** from \$600 a test to \$50 a test
- ✓ **Accuracy, reproducibility, and standardization**

Spots to Seattle *Med 45 days; range 8-49 days*

Blood
50 ul x 4



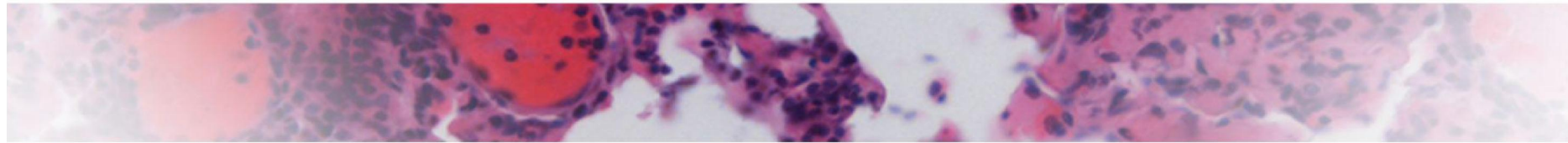
versus >\$500!!!!



How will TKI-Therapy Improve?



American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Safety and Efficacy of HQP1351, a 3rd Generation Oral BCR-ABL Inhibitor in Patients with Tyrosine Kinase Inhibitor-Resistant Chronic Myeloid Leukemia: Preliminary Results of Phase I Study

Qian Jiang, M.D.¹, Xiaojun Huang, M.D., Ph.D.¹, Zi Chen, M.D., Ph.D.², Lichuang Men², Wei Liu, M.D., Ph.D.², Xuemei Sun, M.D.², Jiao Ji, M.D., Ph.D.², Hengbang Wang, M.D., Ph.D.², Ting Zhao, M.D.¹, Yue Hou¹, Po Hu², Lei Zou², Hua Yan², Yingjie Huang, M.D.^{2,3}, Dajun Yang, M.D., Ph.D.^{2,3} and Yifan Zhai, M.D., Ph.D.^{2,3}

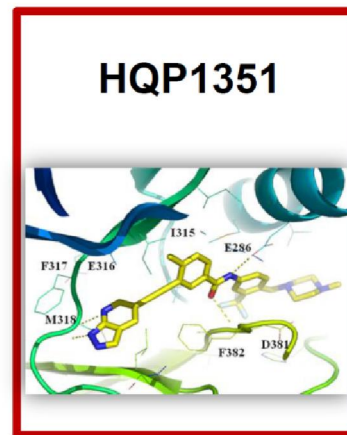
¹Peking University People's Hospital, Peking University Institute of Hematology, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing, China. ²HealthQuest Pharma Inc. Room F314, GIBI, No.3 Lanyue Road, Guangzhou, China. ³Ascentage Pharma Group Inc. 9400 Key West Avenue, Suite 280, Rockville, MD 20850.

New Drugs for TKI-resistant Patients

- Imatinib and 2nd generation TKIs have significantly improved the outcomes in patients with CML
- Unfortunately, none of these TKIs successfully inhibit clones with **T315I** mutation, which is a key challenge
- In order to overcome TKI-resistance, 3rd generation TKIs were developed

HQP1351(GZD824) is an orally active, novel and potent small molecule inhibitor against

- A broad spectrum of BCR-ABL mutations, including **T315I**, E255K/V, G250E, H396P, M351T, Q252H and Y253F/H mutations
- BCR-ABL^{WT}
- Other kinases, including KIT, BRAF, DDR1, PDGFR, FGFR, FLT3, RET, SRC, TIE1 and TIE2

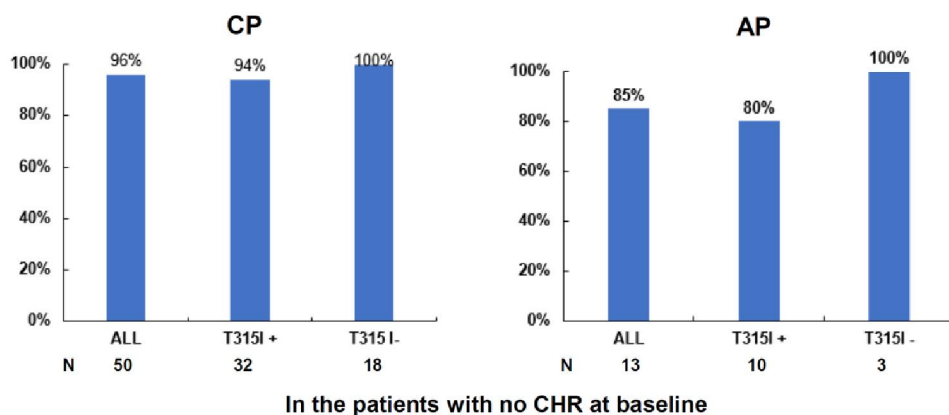


Adverse Events

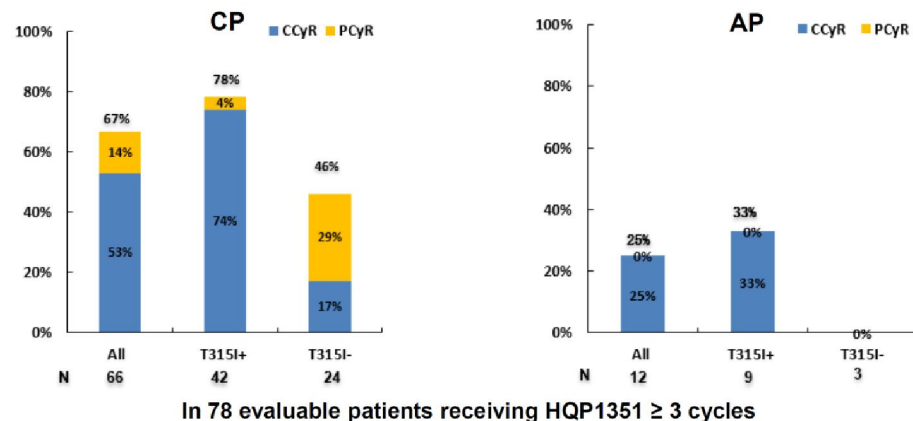
AEs (>10% of patients)	Any grade n (%)	Grade 3/4 n (%)	SAE n (%)
Thrombocytopenia	46 (46)	45 (45)	5 (5)
Leukopenia	17 (17)	15 (15)	0 (0)
Neutropenia	2 (2)	0 (0)	0 (0)
Anemia	10 (10)	9 (9)	2 (2)
Hypertriglyceridemia	51 (51)	4 (4)	0 (0)
Skin pigmentation	35 (35)	0 (0)	0 (0)
ALT elevation	29 (29)	2 (2)	0 (0)
AST elevation	31 (31)	2 (2)	0 (0)
Hypocalcemia	31 (31)	0 (0)	0 (0)
Hypebilirubinemia	28 (28)	1 (1)	0 (0)
CK elevation	19 (19)	1 (1)	0 (0)
Proteinuria	11 (11)	1 (1)	0 (0)

Responses

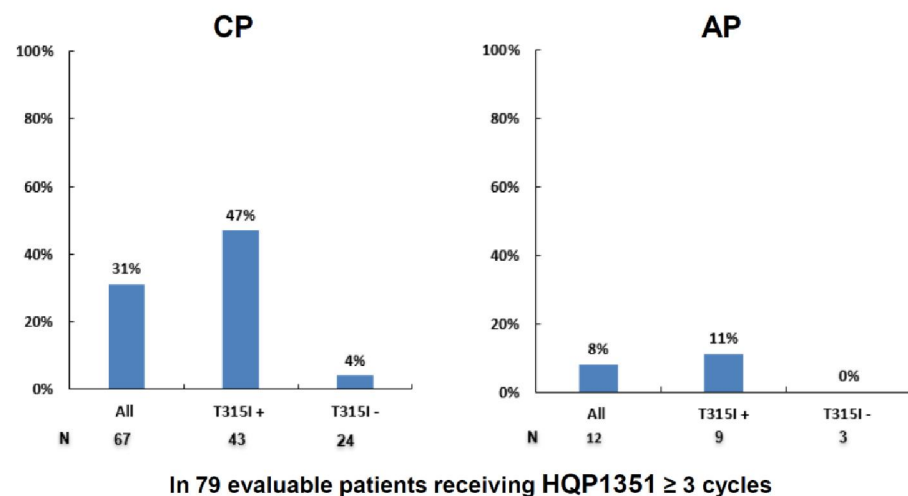
Complete Hematologic Response



Cytogenetic Response



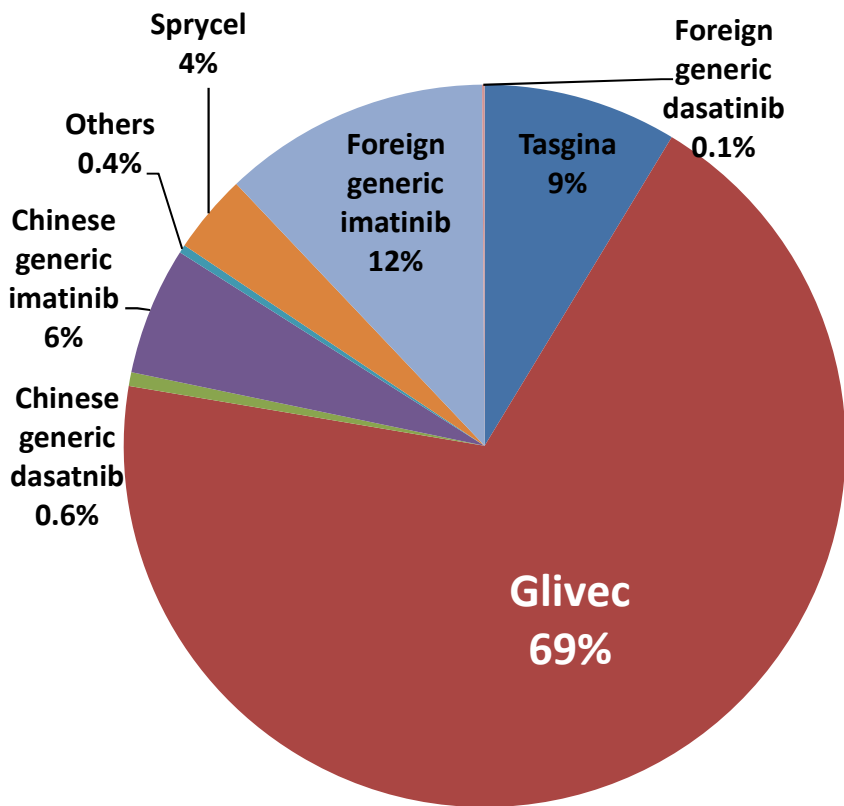
Major Molecular Response



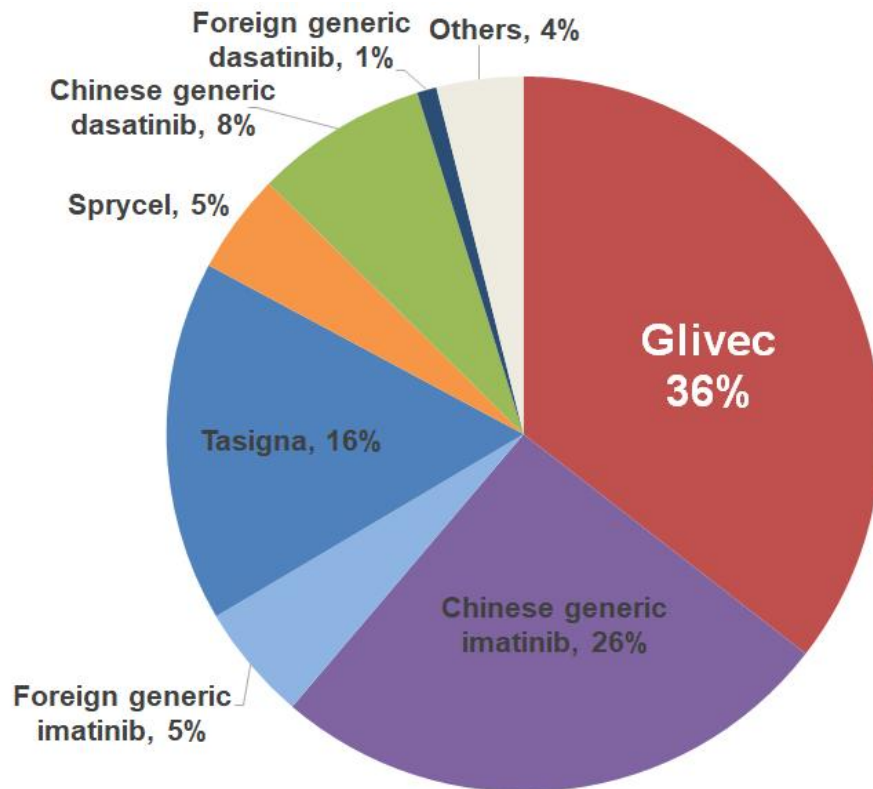
Preliminary Conclusions

- HQP1351, a novel 3rd-generation TKI, was well tolerated and highly active in the Chinese patients with CML in the CP and AP resistant to TKIs, including those with **T315I mutation**
- With a median follow-up of 7 (3-11) months, **96% CP** patients and **85% AP** patients achieved **CHR**; **67% CP** patients and **25% AP** patients, **MCyR**; those with **T315I** had **better response**
- HQP1351 displayed linear PK following multiple QOD dosing, the AUC and C_{max} were dose proportional ranging from 1mg to 60mg
- The reduction of p-CRKL, a surrogate marker, was dose-and time-dependent

Will Generics Impact Access?



- N=949, in 2014
- Generics: 19%



- N=3179, in 2019
- Generics: 40%

Comparison of the Efficacy of Chinese Generic Imatinib with Branded Imatinib as Front-line Therapy in Patients with Chronic Myeloid Leukemia in the Chronic Phase : Experience from Single Center

- Age \geq 18 years old
- Consecutive newly diagnosed CML-CP patients in our hospital between October 2013 and August 2018
- Chinese generic imatinib or Glivec 400mg/d as frontline therapy
- Monitoring according to ELN recommendations 2013
- Follow-up till March 2019

Patients Characteristics

Variables	Generic imatinib N=237	Glivec N=208	<i>P</i> value
Age (median, range)	41 (18-75)	41 (18-83)	0.817
Male (n, %)	155 (65.4%)	118 (56.7%)	0.061
Sokal risk groups (n, %)			0.111
Low risk	99 (41.8%)	111 (53.4%)	
Intermediate risk	81 (34.2%)	57 (27.4%)	
High risk	41 (17.3%)	28 (13.5%)	
Unknown	16 (6.8%)	12 (5.8%)	
WBC <100×10 ⁹ /L (n, %)	97 (41.5%)	99 (47.8%)	0.179
Hb >120g/L (n, %)	101 (43.2%)	98 (47.6%)	0.354

Patients Characteristics

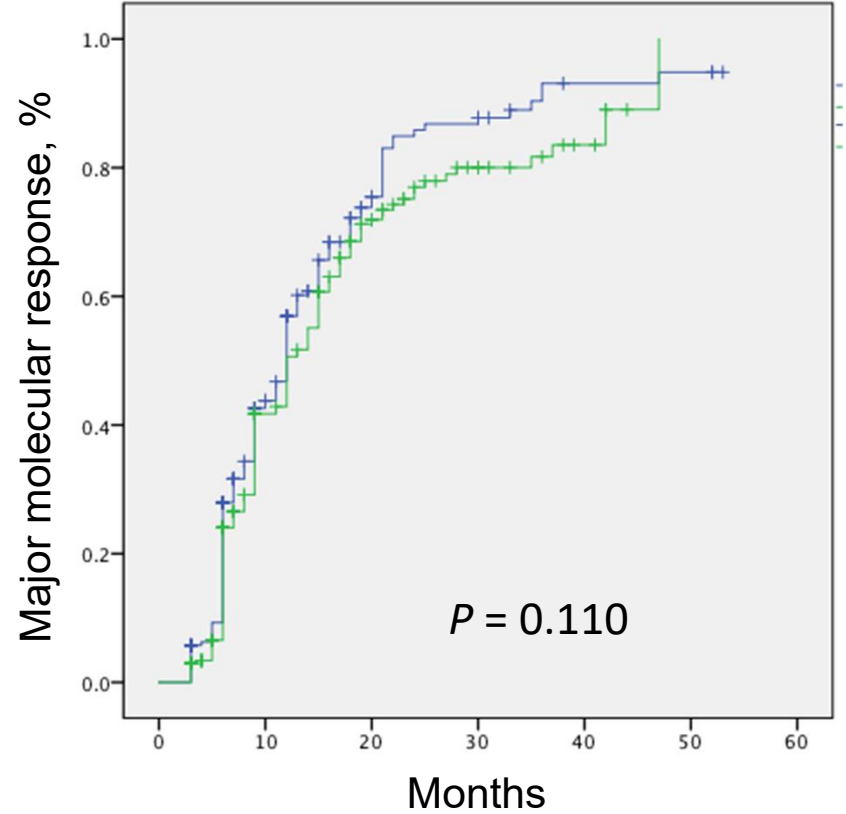
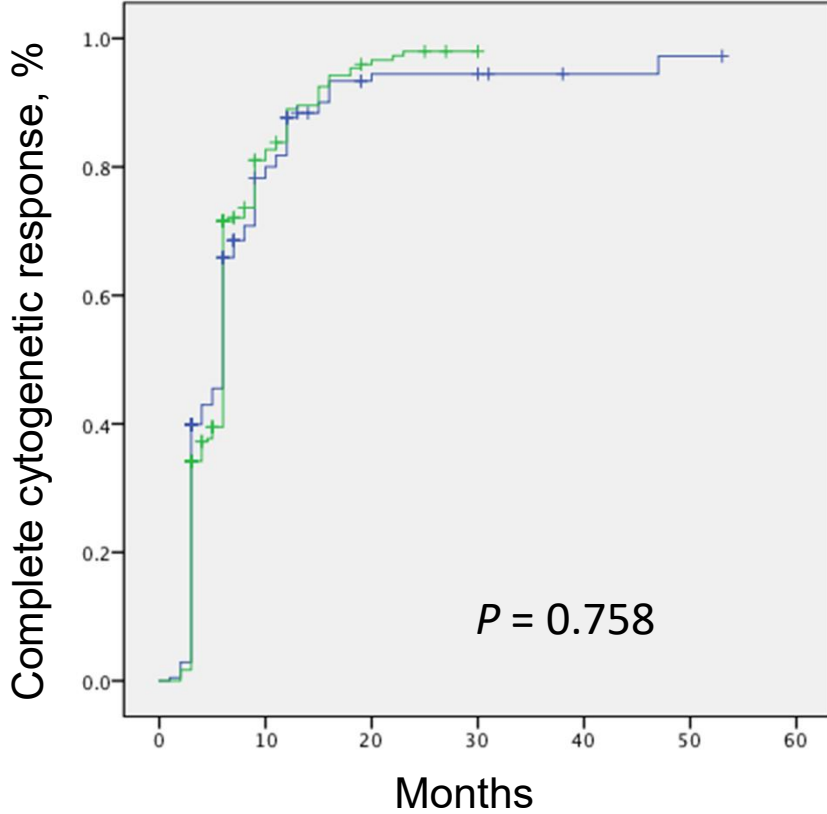
Variables	Generic imatinib N=237	Glivec N=208	<i>P</i> value
Education level (n, %)			<0.001
Compulsory (≤ 9 years)	83 (35.0%)	34 (16.3%)	
Moderate (10-12years)	61 (25.7%)	46 (22.1%)	
High (≥ 13 years)	93 (39.2%)	128 (61.5%)	
Marriage status (n, %)			0.008
Unmarried	41 (17.3%)	39 (18.8%)	
Married	180 (75.9%)	167 (80.3%)	
Ddivorced or widowed	16 (6.8%)	2 (1.0%)	
Urban household registration (n, %)	141 (59.5%)	158 (76.0%)	<0.001

Drug Switch

	Generic imatinib N=237		Glivec N=208	
	Switch to 2G TKI	Switch to Glivec	Switch to 2G TKI	Switch to generics
N (%)	30 (12.7%)	7 (3.0%)	27 (13.0%)	7 (3.4%)

Median follow up: 29 (3-65) mo

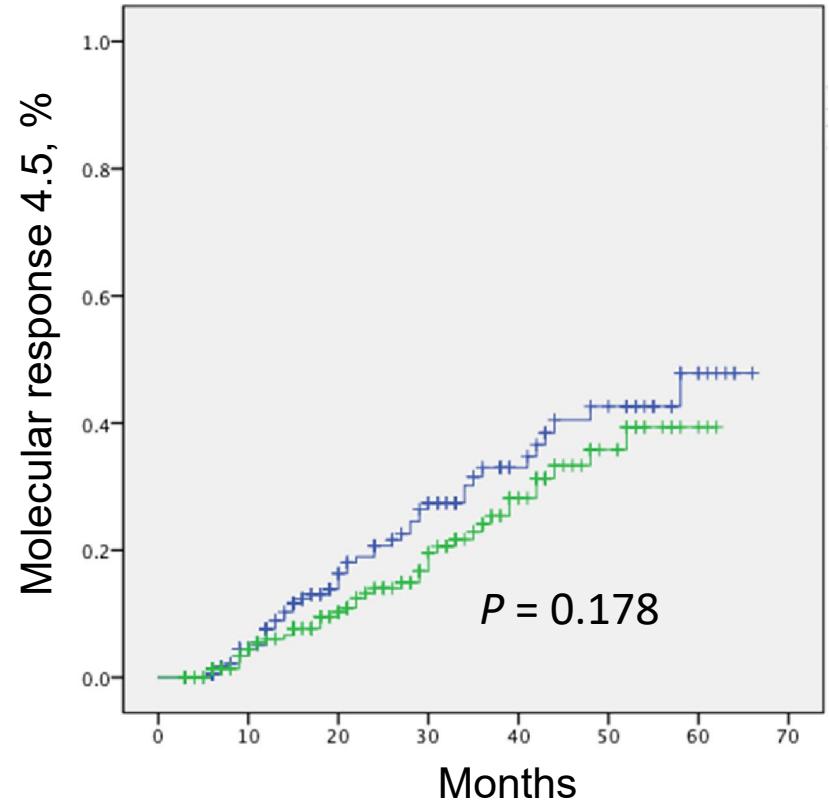
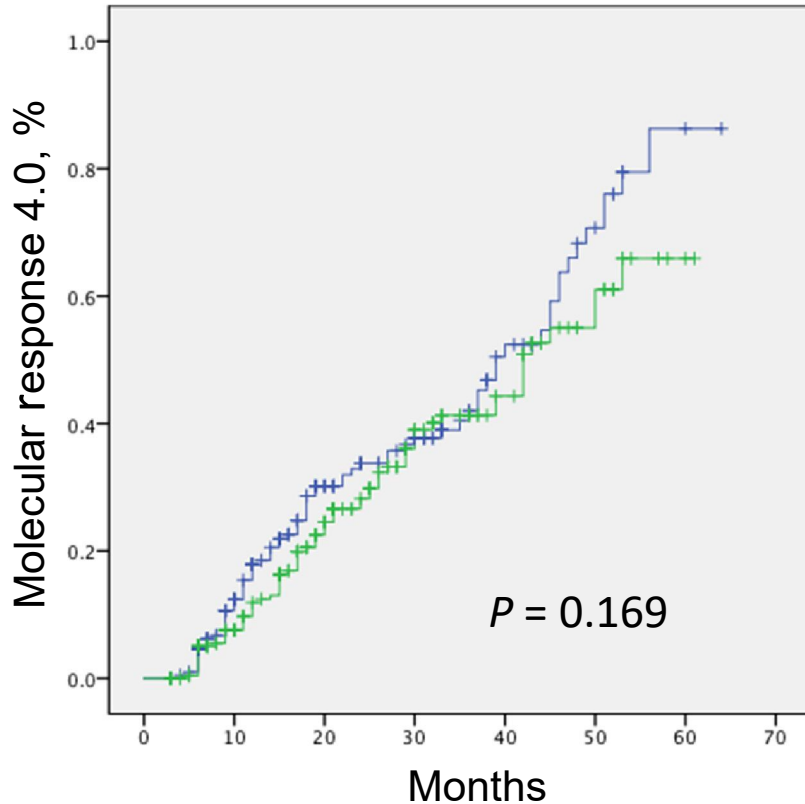
Cytogenetic and Molecular Responses



- Generic
- Glivec

- Complete cytogenetic response rates by 3 years: 98.0% vs. 94.5%
- Major molecular response rates by 3 years: 81.7% vs. 93.1%

Deep Molecular Responses



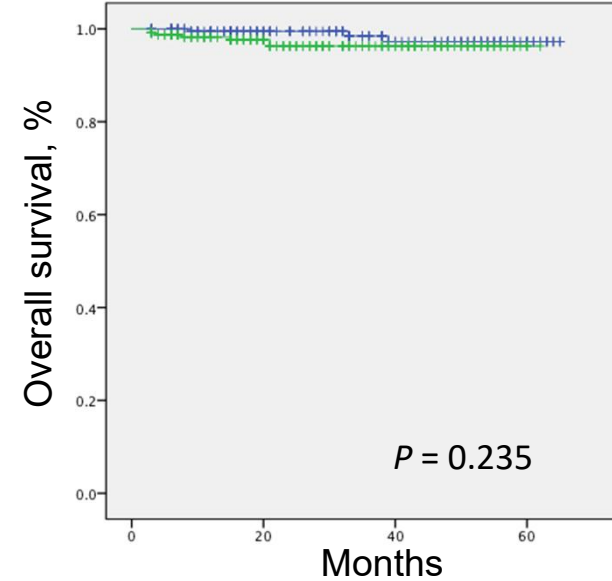
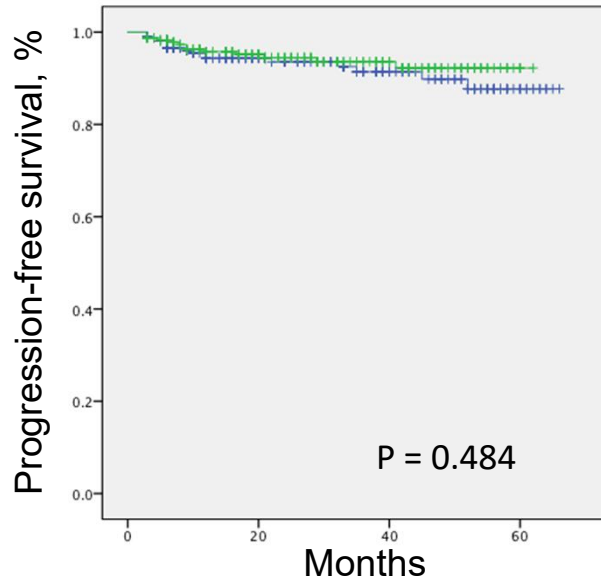
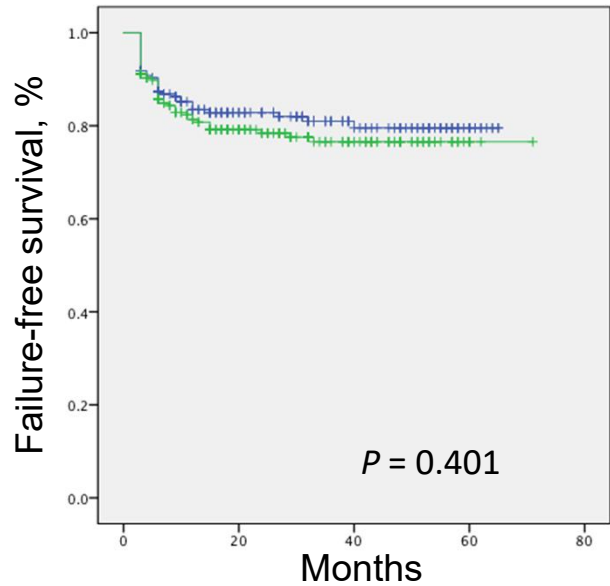
— Generic

• Molecular Response 4.0 rates by 3 years: 41.3% vs. 42.0%

— Glivec

• Molecular Response 4.5 rates by 3 years: 24.1% vs. 33.0%

Survivals

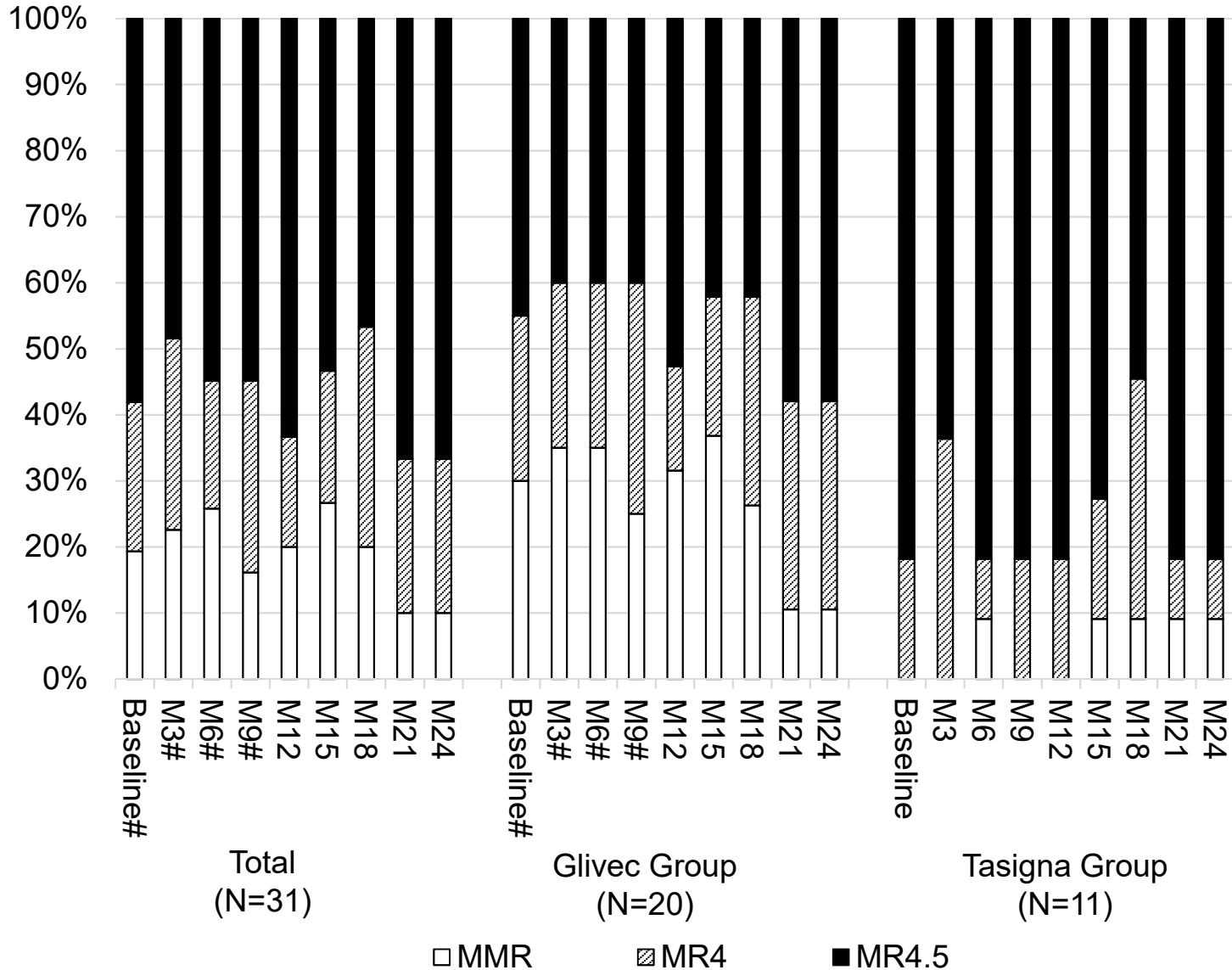


— Generic

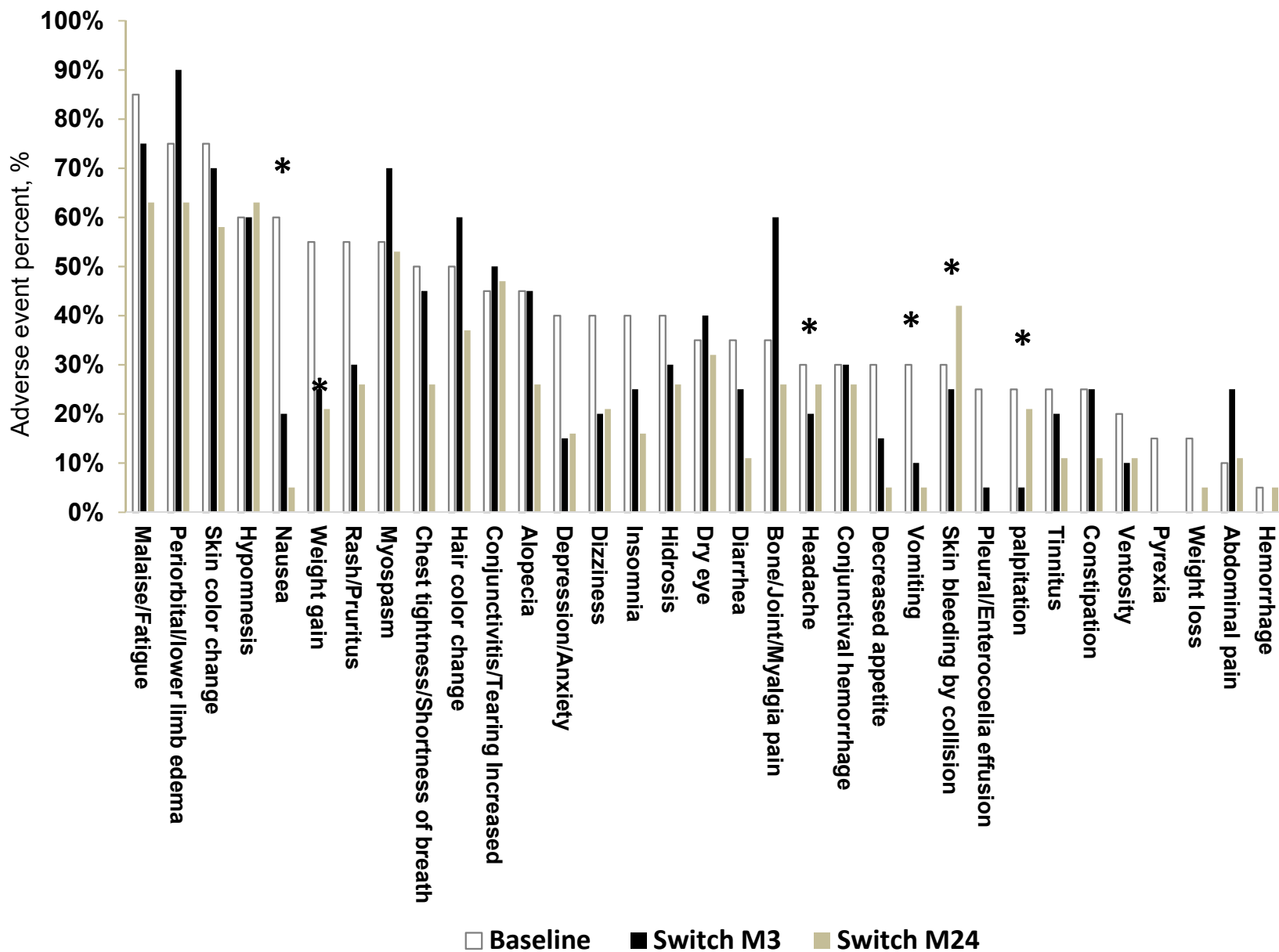
— Glivec

- Failure-free survival at 3 years: 76.6% vs. 81.0%
- Progression-free survival at 3 years: 92.7% vs. 96.3%
- Overall survival at 3 years: 96.3% vs. 98.5%

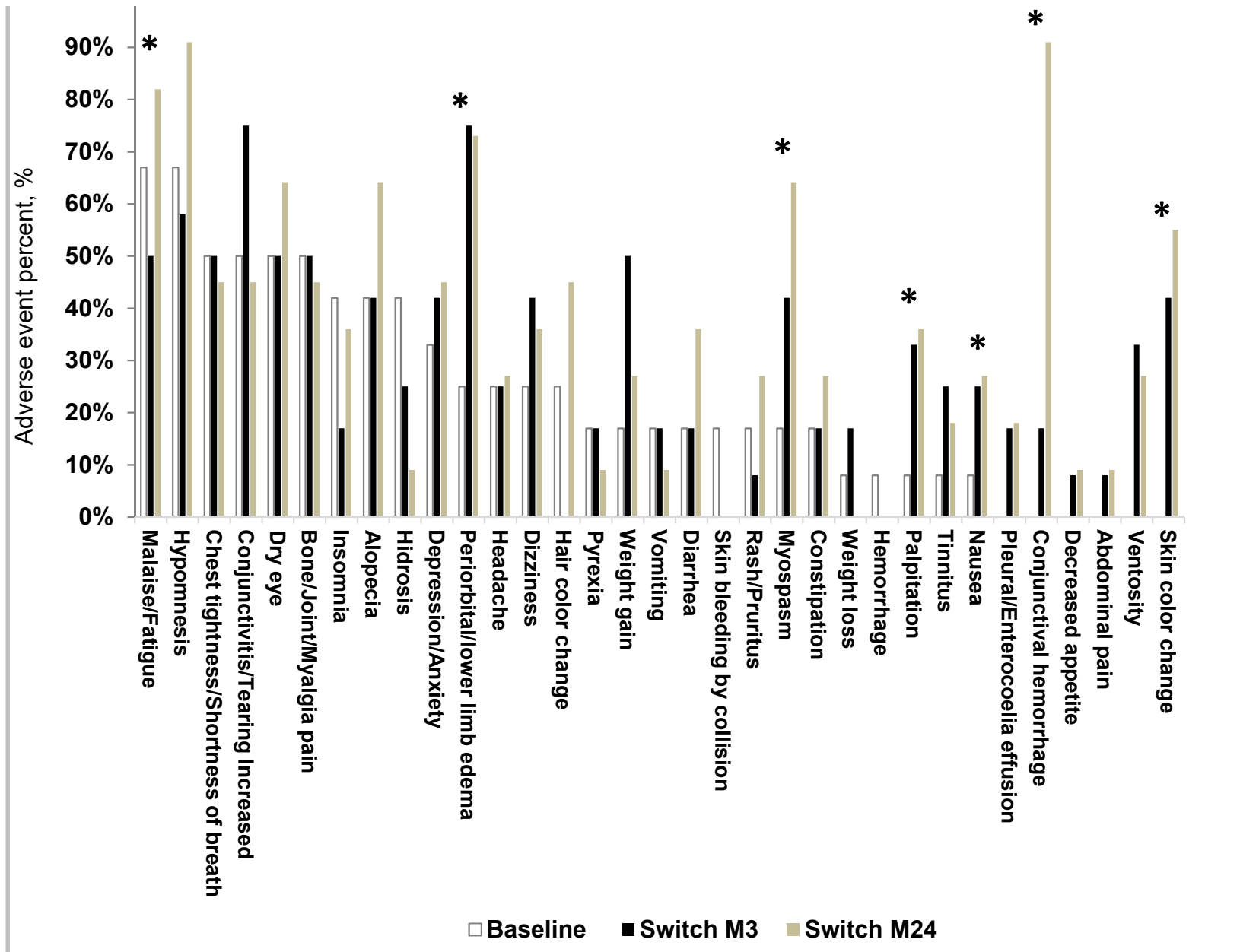
Responses after Switch to Generic Imatinib



Changes of Adverse Events in the Glivec Group



Changes of Adverse Events in the Tasigna Group



Conclusions

State of 2023 in low-middle income countries:

Q: How will CML diagnostics and therapy evolve?

A: Yes!

Q: Do all TKI becoming generic change access in any way?

A: Not all, but more and more!

Acknowledgments



Thanks for your attention!



jiangqian@medmail.com.cn