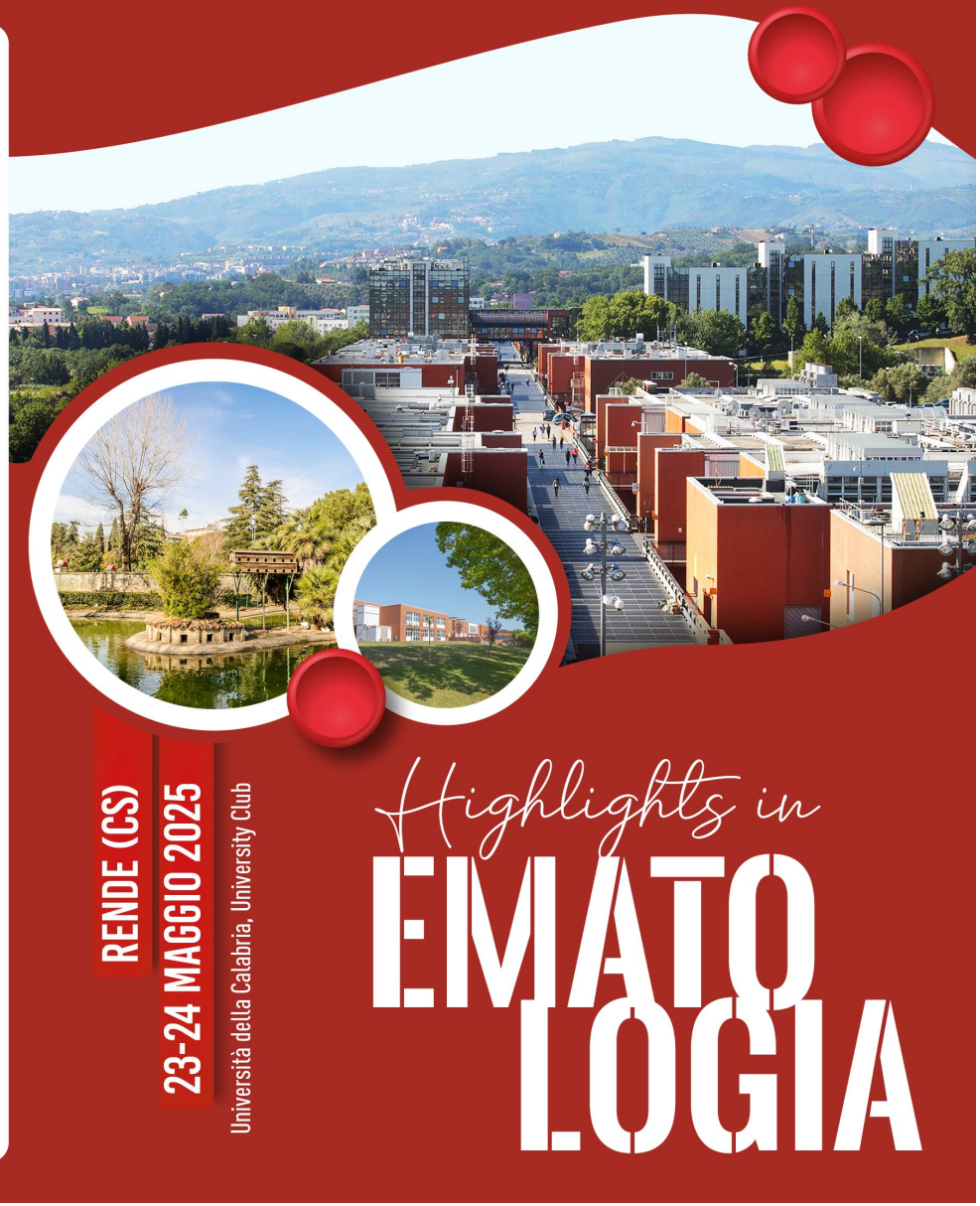
HIGHLIGHTS NELLA LEUCEMIA MIELOIDE CRONICA

Sara Galimberti – Ematologia Pisa



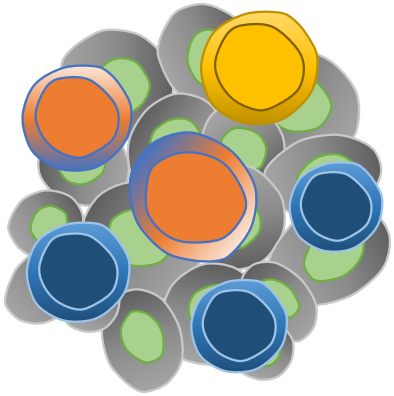
HIGHLIGHTS on CML: WHY in 2025?

- 20% of patients must stop TKI…for intolerance or resistance
- Only 30% of patients reaches and maintains TFR

HIGHLIGHTS: WHAT ARE THEY?

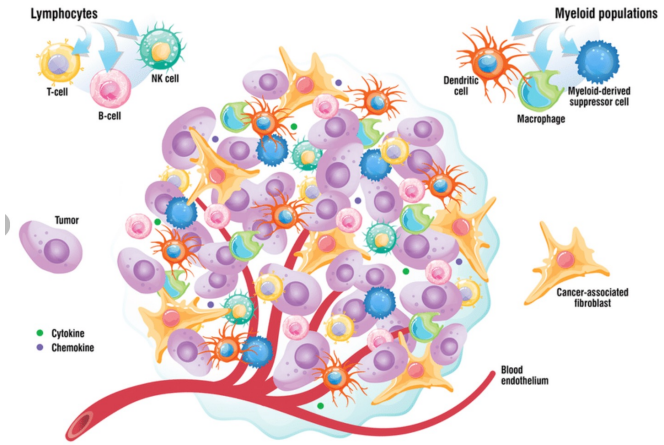
1. New drugs (asciminib)
2. From OS to QoL: the management of adverse events
3. The resistance: a phenomenon still unknown
4. CML is not only BCR::ABL1

DIFFERENT ACTORS



TUMOR

+



TME

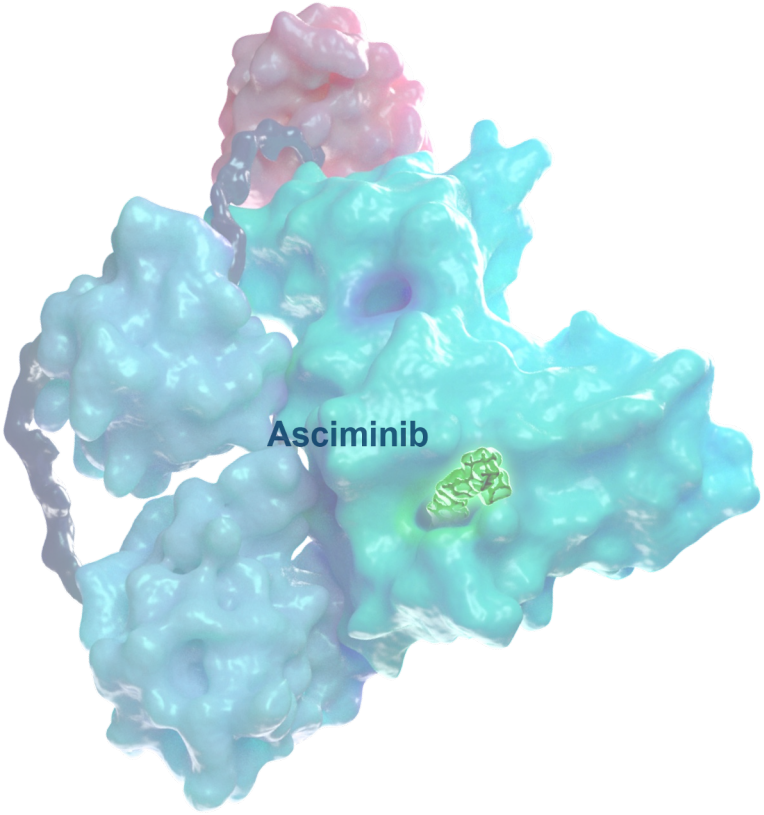
+

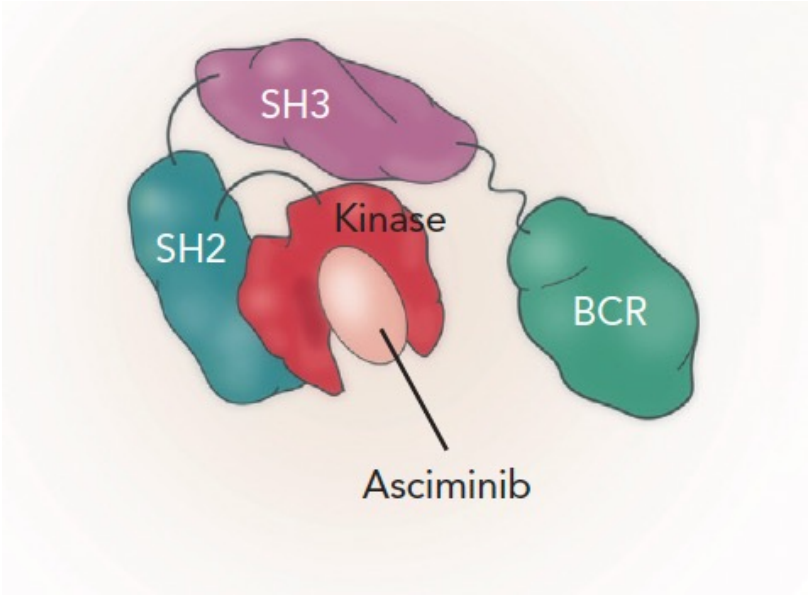
PATIENT

HIGHLIGHTS: WHAT ARE THEY?

1. New drugs (asciminib)
2. Lower toxicities, better results
3. The resistance: a phenomenon still unknown
4. CML is not only BCR::ABL1

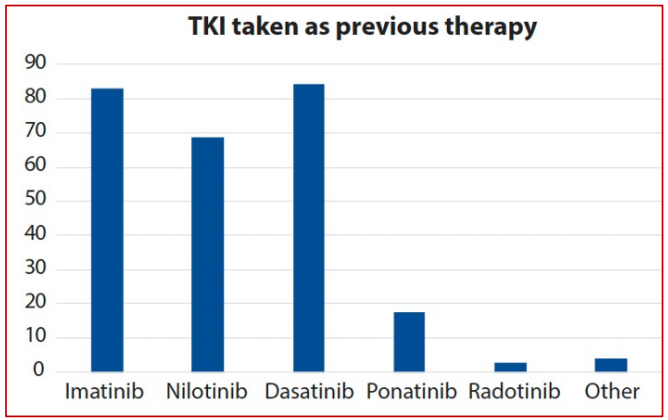
ASCIMINIB: a new concept of drug



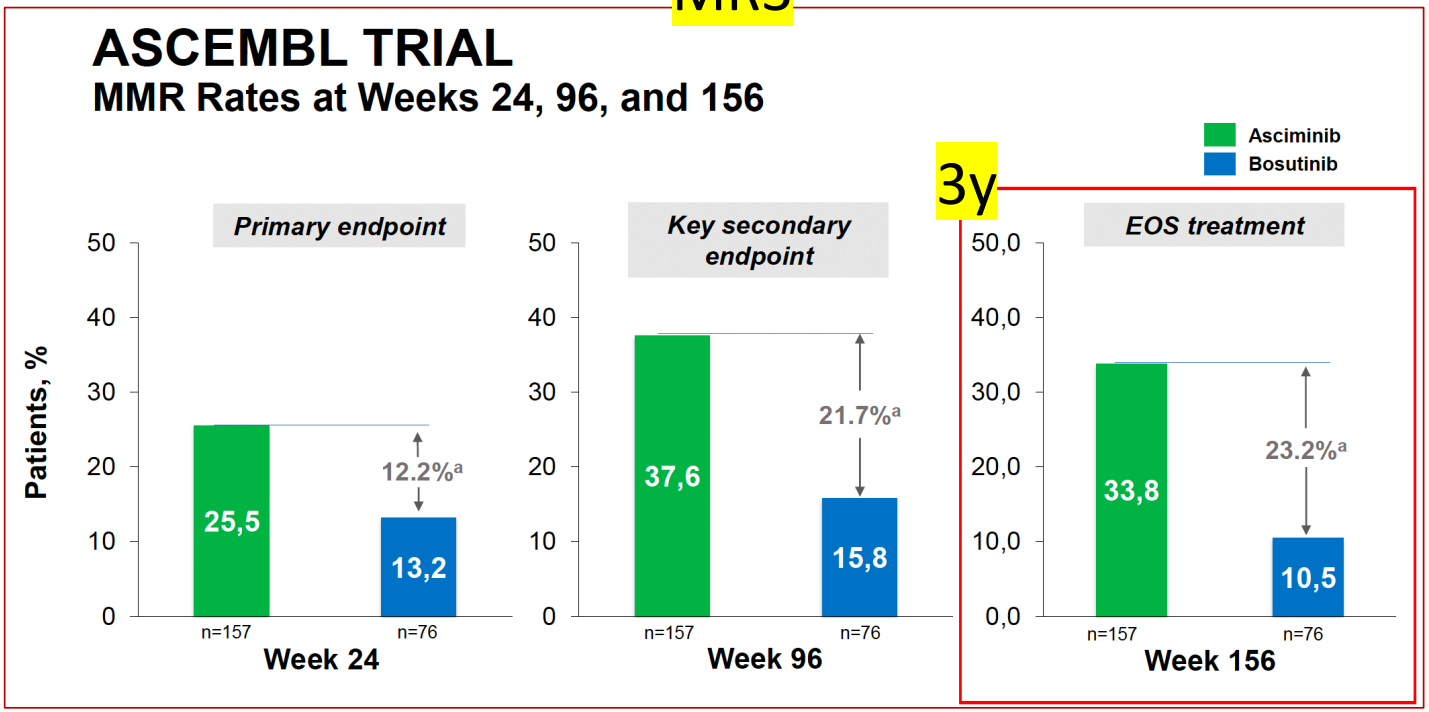


ASCEMBL TRIAL

233 pts



MR3

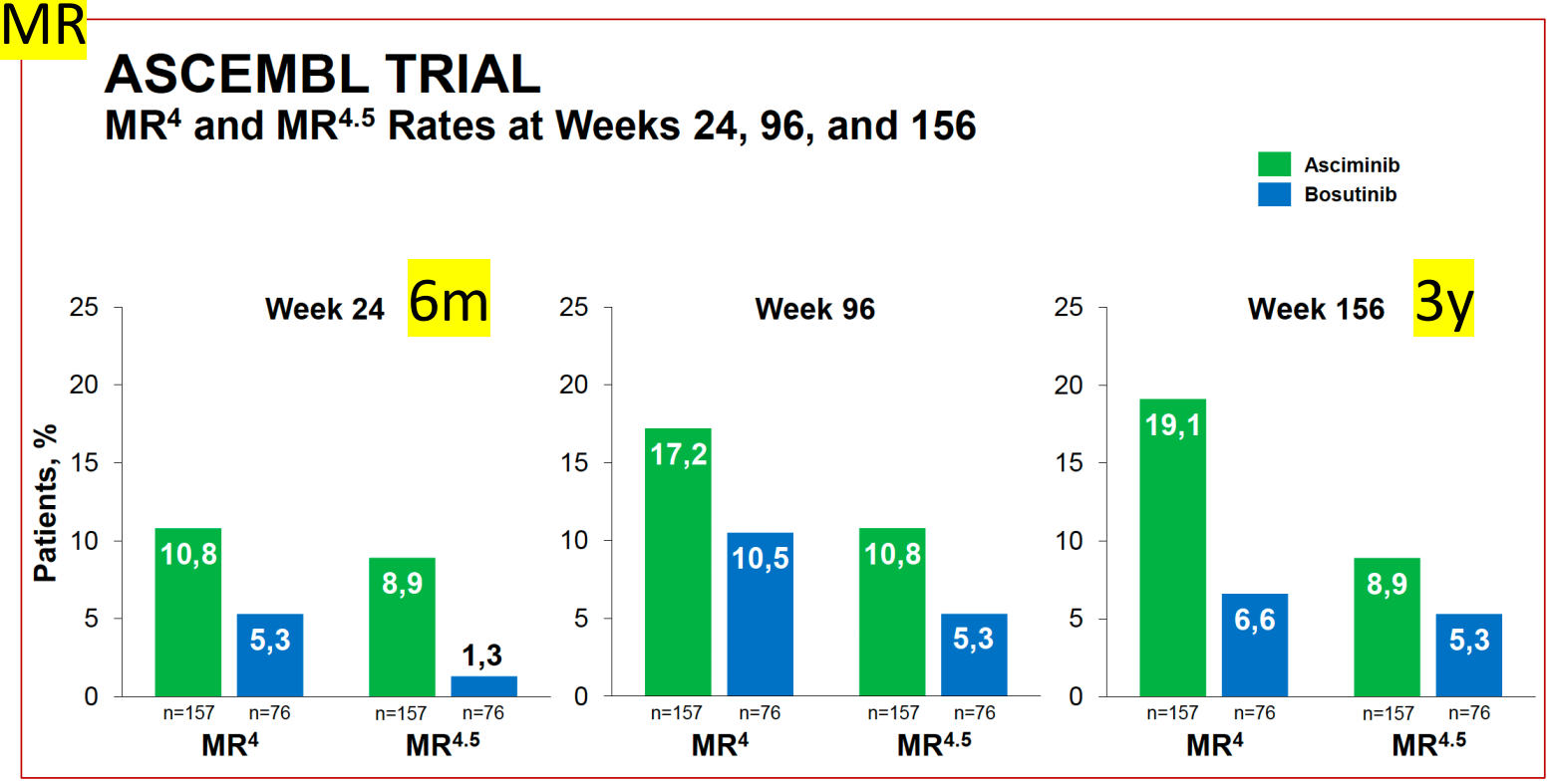


1y CCyR = 51%

- Mauro MJ, ASH 2023 poster 4536

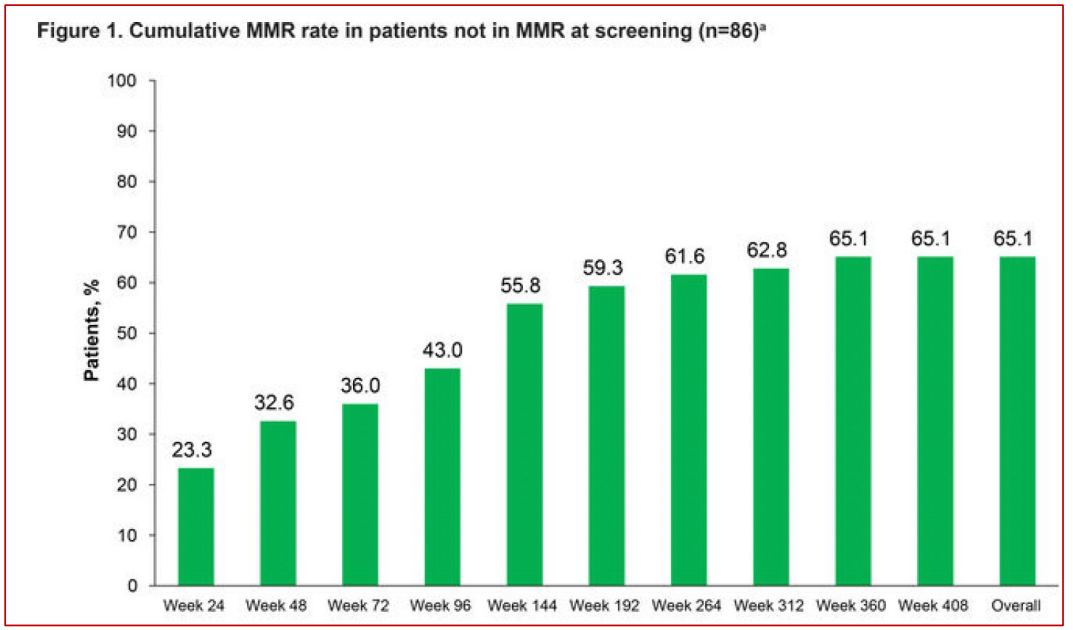
ASCEMBL TRIAL

DMR



ASCIMINIB: phase-1 trial – long-term follow-up

- 115 pts, 71% IV line
- Stop 13% for AEs, 7% for resistance
- Median time to MR3 = 16m
- MR3 @6m = 23%
- MR3 @12m = 33%
- MR3 @3y = 56%
- MR3 @5y = 52%
- MR4 @5y = 24%



ASCIMINIB in PISA real-life

16 pts, 40-80 y
III line = 3
IV line = 4
V line = 1
I line = 8

Kidney cancer =1
breast cancer =1
Lung cancer = 1
hypertension = 4
arthritis =1
Thyroid =2

I LINE

IMATINIB = 6
NILOTINIB = 2
5 stop x tox
1 stop x res
1 stop x both

II LINE

BOSUTINIB = 4
NILOTINIB = 1
DASATINIB = 1
PONATINIB = 2
5 stop x tox
3 stop x both

ASCIMINIB in PISA real-life (advanced cases)

BASAL	BASAL BCR::ABL1
>10% = 1	>10% = 0
1-10% = 2	1-10% = 3
0.1-1% = 3	0.1-1% = 2
DMR = 2	DMR = 3

3/8 loss >1 log

ASCIMINIB in JAPANESE real-life

New sequencing?

Table 2 Response to asciminib

	Resistant ($n=7$)			Intolerant ($n=13$)			Total ($n=20$)
	Non prior ponatinib ($n=4$)	Prior onatinib ($n=3$)	Total ($n=7$)	Non prior ponatinib ($n=4$)	Prior ponatinib ($n=9$)	Total ($n=13$)	
MR2	3/4 (75%)	1/3 (33%)	4/7 (57%)	4/4 (100%)	8/9 (89%)	12/13 (92%)	16/20 (80%)
MMR	3/4 (74%)	1/3 (33%)	4/7 (57%)	3/4 (75%)	5/9 (56%)	8/13 (62%)	12/20 (60%)
MR4	3/4 (75%)	0/3 (0%)	3/7 (43%)	0/4 (0%)	0/9 (0%)	0/13 (0%)	3/20 (15%)
Patients without response at baseline							
MR2	1/2 (50%)	0/3 (0%)	1/3 (33%)	3/3 (100%)	2/3 (67%)	5/6 (83%)	6/9 (67%)
MMR	1/2 (50%)	0/3 (0%)	1/3 (33%)	2/3 (67%)	1/3 (33%)	3/6 (50%)	4/9 (44%)
MR4	1/2 (50%)	0/3 (0%)	1/3 (33%)	0/3 (0%)	0/3 (0%)	0/6 (0%)	1/9 (11%)

ASCIMINIB or PONATINIB?

After propensity score matching, no significant differences

CCyR	70% vs 78%
MR3	53% vs 66%
MR4	42% vs 43%

ASCIMINIB: CV safety…our opinion…

Efficacious & safe

- imatinib
- asciminib
- bosutinib
- dasatinib
- nilotinib
- ponatinib

HIGHLIGHTS: WHAT ARE THEY?

1. New drugs (asciminib)
2. From OS to QoL: the adverse events
3. The resistance: a phenomenon still unknown
4. CML is not only BCR::ABL1

ASCEMBL TRIAL

...In the ASCEMBL trial, after a median follow-up of 4 years, no new arterial occlusive events occurred with asciminib since the week 96 analysis.

After approximately 8 years of exposure, arterial occlusive events were reported in 4 new patients since the previous analysis ***(overall incidence, 12.2%)*** *...*

ASCIMINIB & CV TOXICITIES (from FDA registry)

System Organ Class (SOC)	Asciminib cases reporting SOC	ROR (95% two-sided CI)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
Blood and lymphatic system disorders	125	3.45 (2.88–4.14)[a]	3.29 (203.42)[a]	1.72 (1.43)[a]	3.29 (2.74)[a]
Renal and urinary disorders	80	2.36 (1.88–2.95)[a]	2.30 (59.87)[a]	1.20 (0.96)[a]	2.30 (1.84)
Cardiac disorders	90	2.32 (1.88–2.87)[a]	2.26 (64.30)[a]	1.17 (0.95)[a]	2.26 (1.83)
Investigations	212	2.16 (1.88–2.50)[a]	2.03 (117.88)[a]	1.02 (0.89)[a]	2.03 (1.76)
Metabolism and nutrition disorders	55				
Musculoskeletal and connective tissue disorders	10				
Gastrointestinal disorders	156	1.26 (1.07–1.48)[a]	1.24 (7.55)	0.31 (0.26)[a]	1.24 (1.05)
Vascular disorders	53	1.19 (0.90–1.56)	1.18 (1.50)	0.24 (0.18)[a]	1.18 (0.90)
Hepatobiliary disorders	21	1.14 (0.74–1.75)	1.14 (0.36)	0.19 (0.12)[a]	1.14 (0.74)
General disorders and administration site conditions	360	1.08 (0.96–1.21)	1.06 (1.69)	0.09 (0.08)[a]	1.06 (0.95)
Endocrine disorders	7	1.08 (0.51–2.27)	1.08 (0.04)	0.11 (0.05)[a]	1.08 (0.51)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	84	1.02 (0.82–1.27)	1.02 (0.04)	0.03 (0.02)[a]	1.02 (0.82)

9%

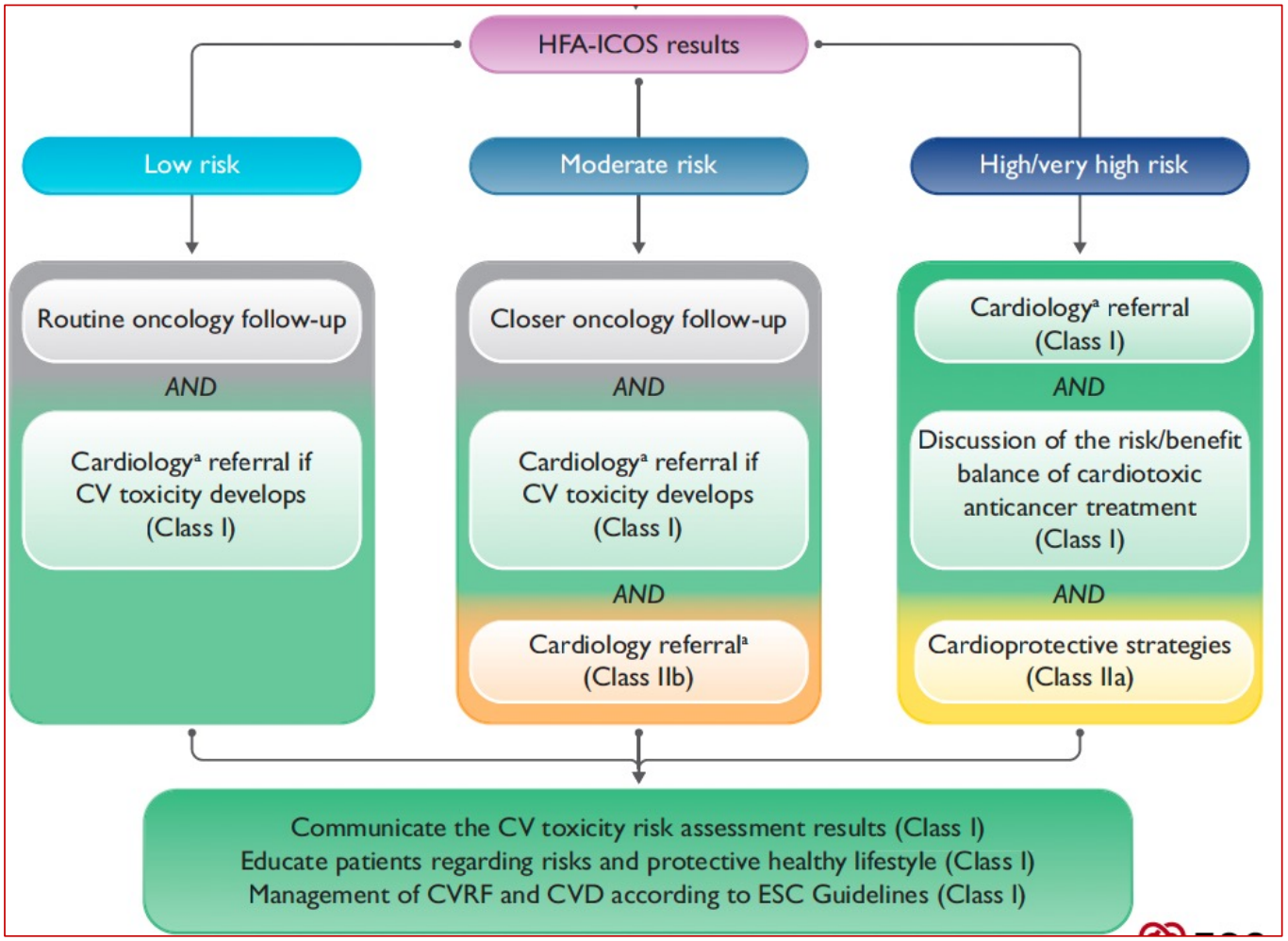
5%

0,02% of all CV events 2021-2023

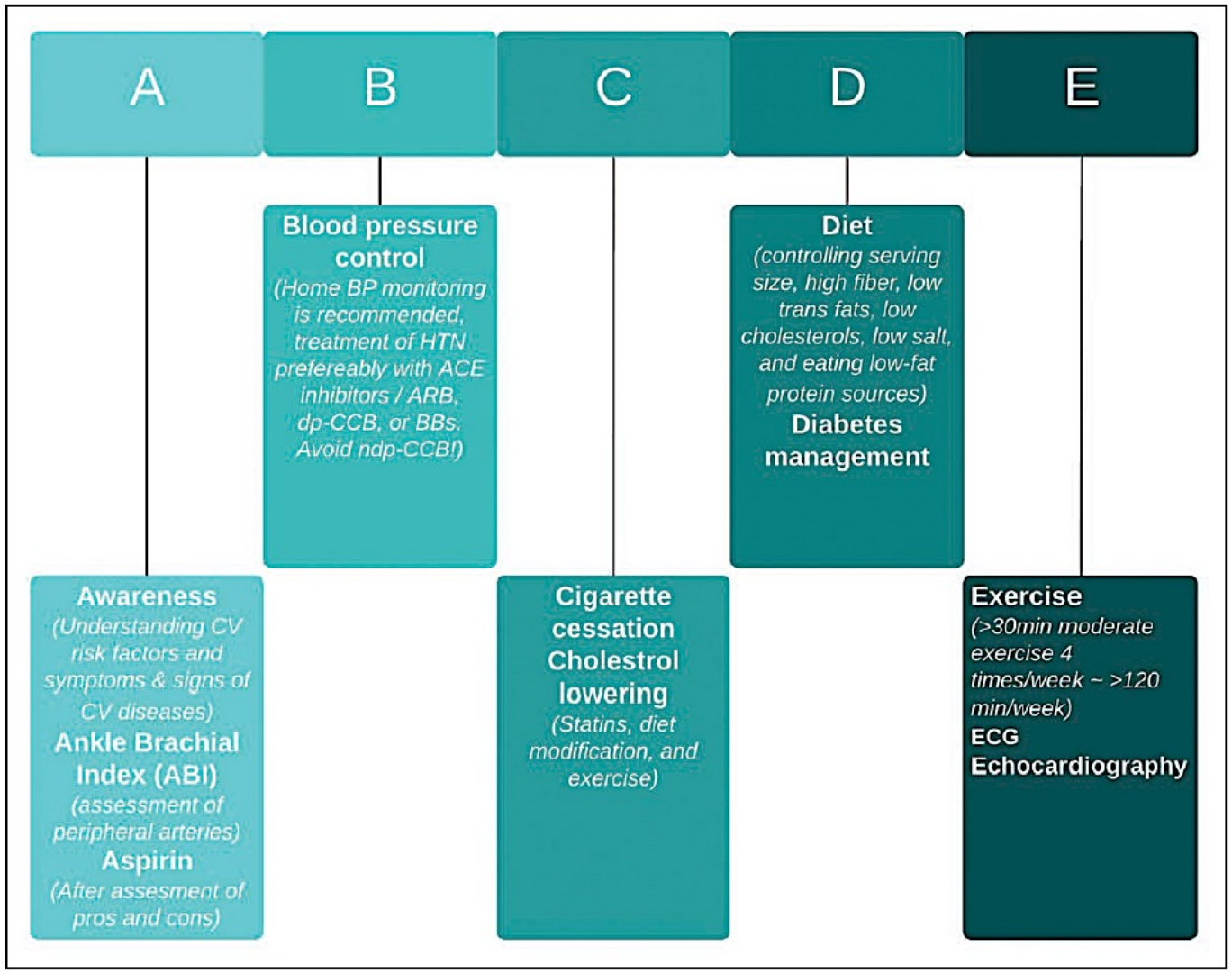
Liu Z, Oncology 2024

CV TOXICITIES

HFA-ICOS SCORE



THE RIGHT ADVICES



DOSE: DASATINIB 50 mg vs 100 mg

50 vs 100 mg

MMR @3y = 92% vs 84%

MR4 = 74% vs 66%

MR4.5 = 77% vs 62%

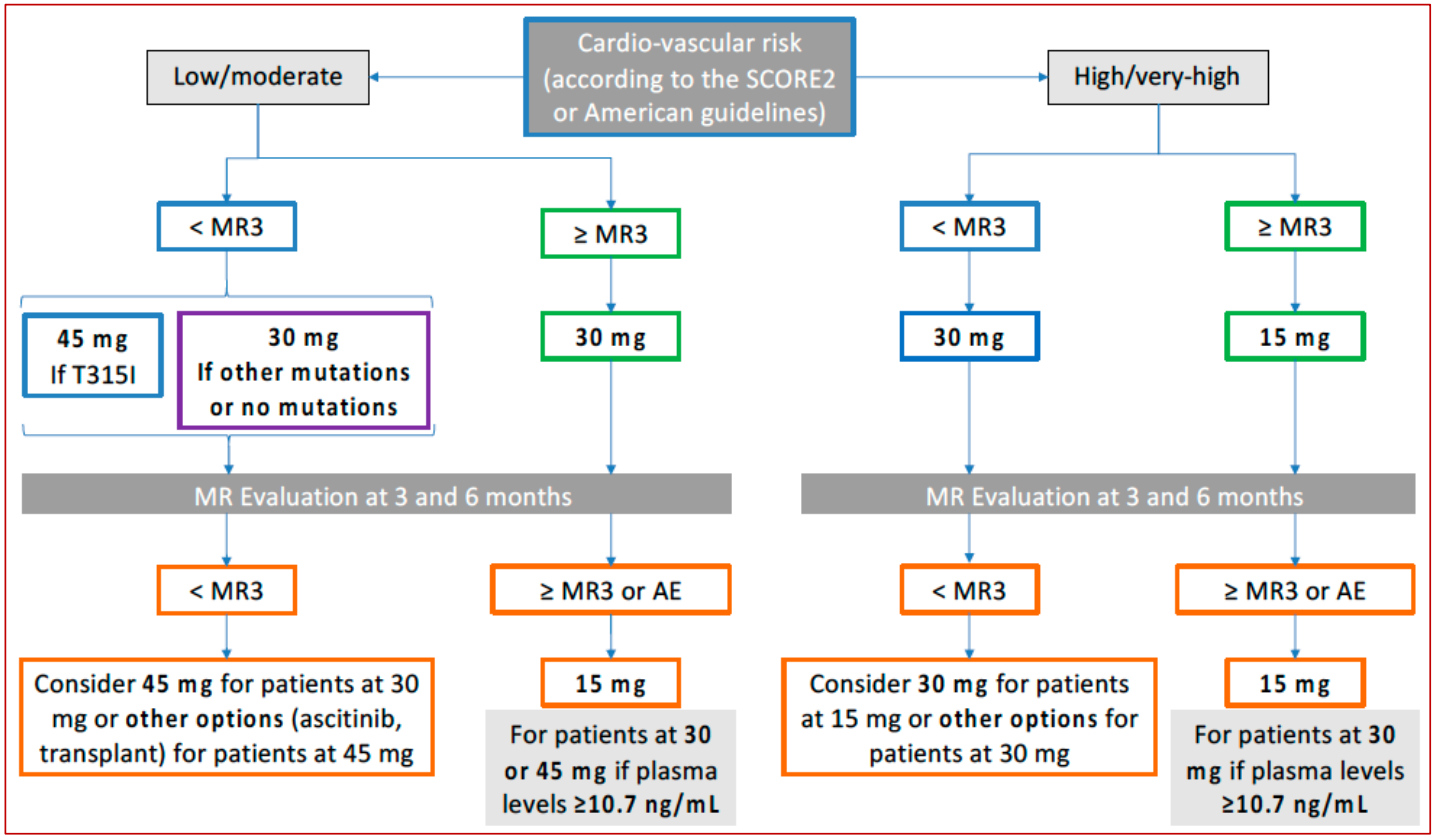
FFS @4y = 89% vs 77%

EFS @4y = 95% vs 92%

OS @4y = 97% vs 96%

Pleural effusions: 5% vs 21%

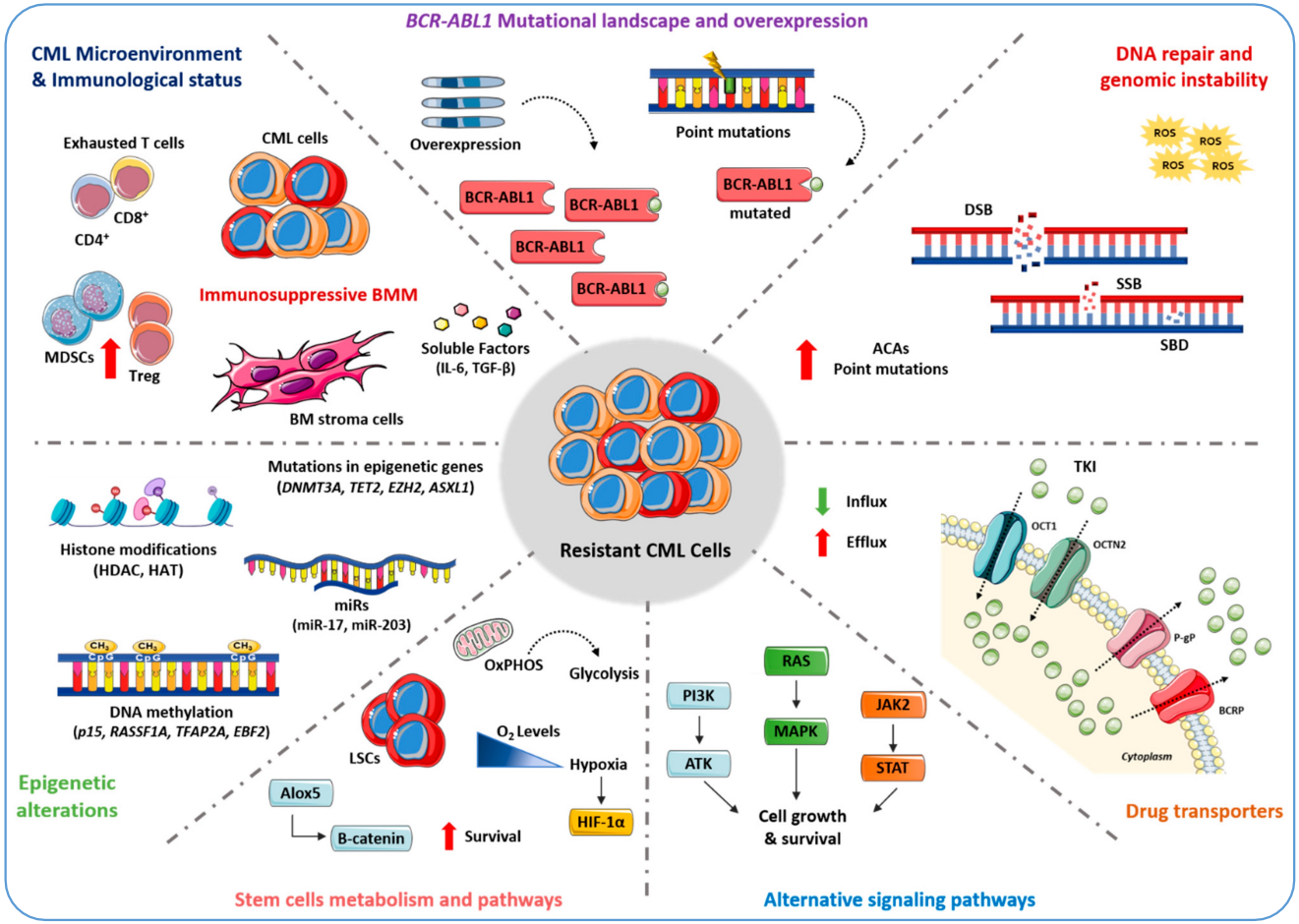
DOSE: PONATINIB (with plasma levels)



HIGHLIGHTS: WHAT ARE THEY?

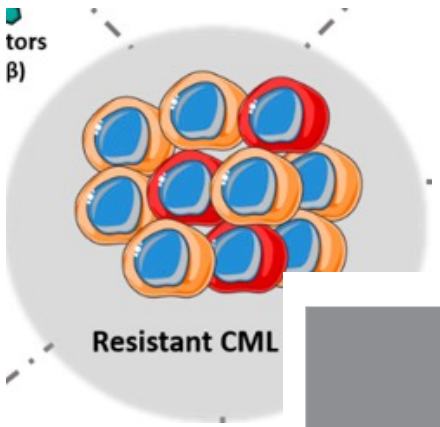
1. New drugs (asciminib, olverembatinib)
2. Lower toxicities, better results
3. The resistance: a phenomenon still unknown
4. CML is not only BCR::ABL1

A COMPLEX SCENARIO



Alves R, Cancers 2021

THE LEUKEMIC STEM CELL



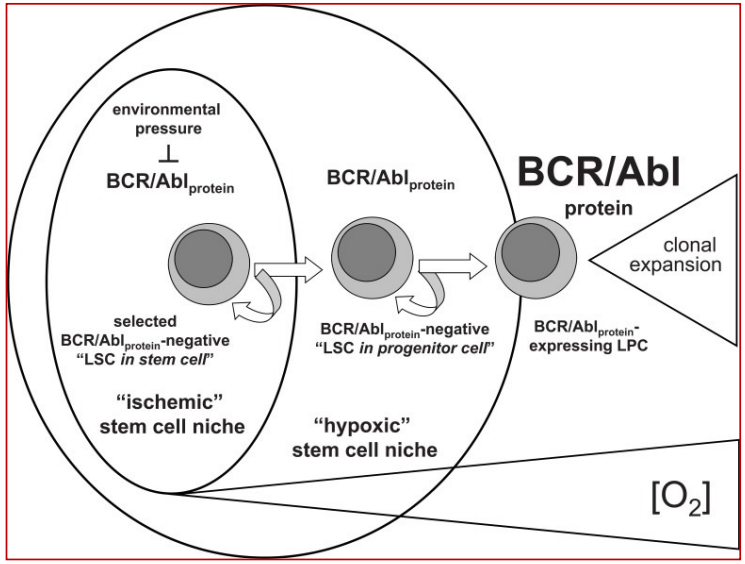
CD34+, CD38-, CD26+, CD35-

	CD26+LSCs detectable	CD26+LSCs undetectable	CD26+LSCs detectable	CD26+LSCs undetectable
	BCR::ABL1 detectable	BCR::ABL1 undetectable	BCR::ABL1 undetectable	BCR::ABL1 detectable
Patients (n = 109)	25/109 (22.9%)	21/109 (19.3%)	36/109 (33.0%)	27/109 (24.7%)
TFR LOSS (n = 38)	11/38 (29.0%)	8/38 (21.0%)	12/38 (31.6%)	7/38 (18.4%)
TFR SUSTAINED (n = 71)	14/71 (19.7%)	13/71 (18.3%)	24/71 (33.8%)	20/71 (28.2%)

Raspadori D, Cytometry B Clin Cytometry 2019
Pacelli P, Frontiers in Pharmacology 2023

THE DIET

- In hypoxic conditions, CD26+ LSC increase (4.5 x) and carry stem cell features



Hypoxic/ischemic niche induces **NO expression of BCR-ABL protein**

FURTHER PATHWAYS

Athena study

JAK-STAT

B-CATENIN/WNT

	1	2	3	4	5	6	7	8	9	10
A2M	1,8		18,5	5,2	1,2		26,8	6,5		-1,6
AKT1	1,6	2,2	2,7	1,9	2,0	1,6	4,7	1,9	2,9	1,5
B2M	4,7	4,3	5,8	3,4	2,2	2,5	9,6	4,2	3,4	2,5
BCL2L1	1,8	4,6	1,6	2,9	1,7	1,6	3,5	0,9	1,4	1,5
CCND1	-1,2	4,2	1,5	3,5	-3,3	-1,2	2,9	0,9	-2,3	-1,6
CDKN1A	7,4	9,7	2,1	3,9	1,7	1,9	31,7	2,2	7,1	-4,7
CEBPB	4,6	4,8	6,9		2,0	3,2	4,7	5,7	4,1	3,1
CEBPD	1,9	5,0	6,1	1,9	2,8	-1,4	6,0	3,9	3,1	5,2
CRK	1,1	3,9	2,5	1,5	2,9	1,8	5,4	1,9	2,8	1,7
CRP			87,3	-6,3						
CSF1R	5,0	11,5	7,6	4,2	3,6	2,6	17,3	4,7	7,4	1,3
CXCL9	36,3	8,4	4,7	1,3	1,2	16,4	27,4	20,3	14,0	-2,1
EPOR	-2,6	1,0	2,7	1,0	1,7	8,1	2,8	-1,3	1,9	-2,8
F2	-2,3	1,3	4,4	2,1	2,7	4,3	4,9	4,0	1,6	2,1
F2R	11,2	22,2	5,1	12,9	2,1	-1,4	24,7	4,2	3,1	5,8
FAS	4,9	6,9	4,9	3,2	1,8	3,8	8,1	4,2	2,9	2,7
FCER2	6,7	9,2	3,3	2,6	1,5	1,9	34,2	26,4	2,8	1,1
FCGR1A	4,2	4,4	2,2	3,1	3,8	22,6	8,0	3,6	13,4	1,1
GATA3	19,4	22,5	5,5	15,9	3,8	3,2	49,7	43,5	4,3	11,3
GRB2	1,0	2,0	1,3	1,1	2,4	77,6	6,1	1,4	3,0	1,0
HMGA1	-2,5	1,7	-1,2	1,2	1,1	-1,6	2,1	-2,3	1,8	-1,5
IFNAR1	2,8	4,0	5,0	2,4	2,7	3,7	8,1	4,4	4,0	1,7
IFNG	35,0	50,4	6,6	25,6	4,3	2,3	20,6	81,1	1,6	13,8
IFNGR1	2,1	9,0	6,4	1,8	1,4	1,1	9,2	4,1	2,1	2,3
IL10RA	5,7	16,9	3,3	4,8	2,7	1,8	20,5	5,9	3,7	1,9
IL20	4,6		5,0	-7,9	1,3	4,0	9,3			8,9
IL2RA	3,7	14,5	1,2	2,5	-1,5	1,9	10,9	5,7	-1,3	2,8
IL2RG	4,7	3,2	1,9	3,5	1,9	1,6	6,5	3,3	4,3	2,1
IL4	1,1	1,1	-2,5	-1,7	-8,2	-1,3	-1,5	-3,3	-2,9	-2,6
IL4R	-1,2	2,0	2,8	-1,3	1,3	2,2	3,2	2,1	-1,2	1,1
IL6ST	8,6	13,6	5,1	6,2	1,4	2,9	24,7	9,9	3,1	4,9
INSR	-4,0	1,3	-1,5	-2,5	-1,7	-2,0	1,7	-1,9	1,0	1,0
IRF1	4,7	2,1	2,0	3,3	2,4	5,2	7,6	2,8	3,5	1,2
IRF9	3,2	7,0	2,1	1,9	3,1	2,5	7,2	2,5	3,5	2,0
ISG15	9,3	2,7	3,2	4,6	3,7	4,6	6,6	4,3	5,3	1,3
JAK2	1,3	1,8	2,1	1,2	1,0	1,4	2,6	1,7	1,4	-1,5
JAK3	7,5	6,3	3,8	5,0	5,0	4,2	21,9	10,2	6,5	1,8
JUN	1,7	2,0	2,8	2,0	1,4	2,4	1,1	0,9	-3,0	-2,6

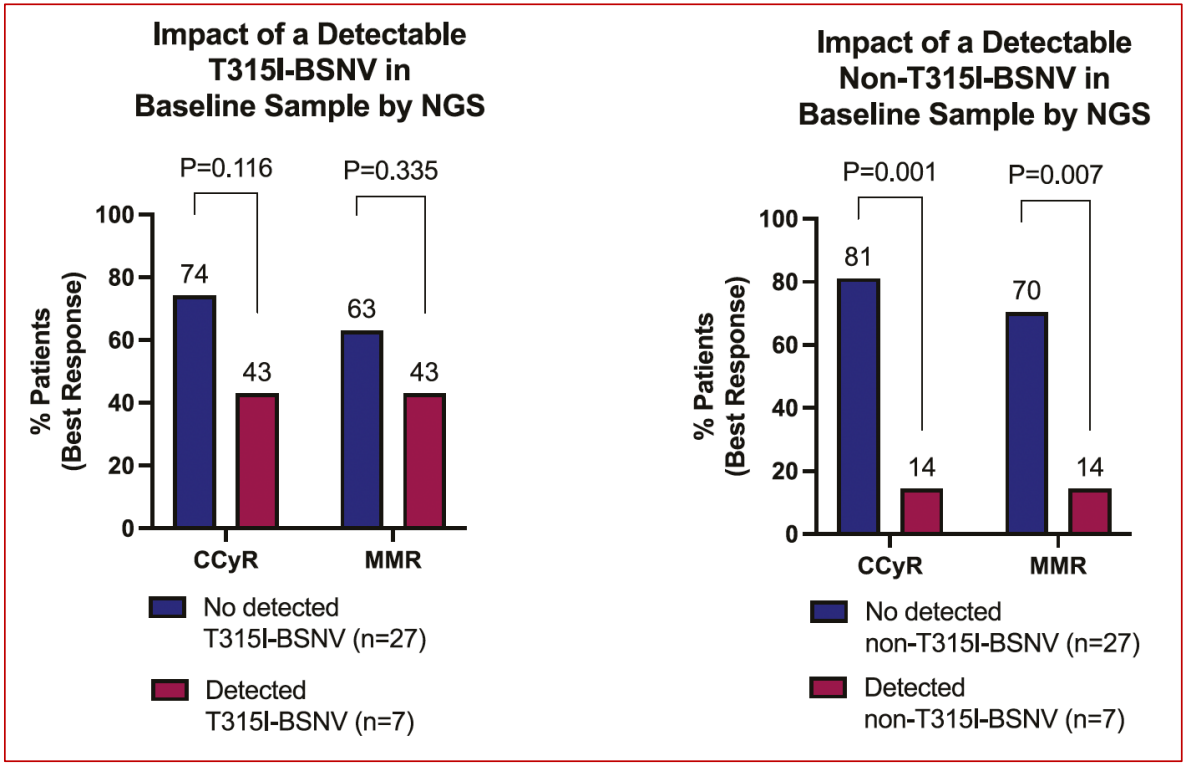
MUTATIONS: OUR TRAFFIC LIGHT

Mutated region	BaF3 (*BCR::ABL*) Mutant Cells	Anti-proliferation Assay (IC50, nM)					
		Imatinib	Nilotinib	Dasatinib	Asciminib	Ponatinib	HQP1351
Wild-type	-	565 ± 656	31 ± 4	10 ± 3	31 ± 4	11	6 ± 3
SH2-contract region	M351T	1298 ± 542	37 ± 4	8 ± 4	47 ± 34	13 ± 1	9 ± 1
Substrate-binding region	F359V	>10000	1710 ± 635	598 ± 624	6066 ± 355	466 ± 73	50 ± 16
P-loop	E255K	8222 ± 484	648 ± 395	14 ± 1	10	49 ± 4	22 ± 13
	Y253H	8936±1774	497 ± 122	11 ± 2	28 ± 13	37 ± 4	7 ± 1
	E255V	7565±3268	587 ± 151	29 ± 15	24 ± 4	56 ± 1	27 ± 11
	M244V	2963 ± 83	236 ± 152	40 ± 1	5223 ± 4899	75 ± 42	41 ± 8
Gate keeper	T3151	>10000	3425 ± 650	2525 ± 322	148 ± 14	33 ± 11	24 ± 10
Hinge region	F317L	526 ± 56	89 ± 8	11 ± 1	6 ± 3	7 ± 1	8 ± 3
	F311I	3547 ± 223	226 ± 122	13 ± 0	107 ± 1	30 ± 8	23 ± 13
SH3-contact region	V299L	1987 ± 1237	103 ± 6	118 ± 2	562 ± 552	10 ± 4	8 ± 4
T3 151 + Other Compound Mutation	T315I/E255V	>10000	646 7± 4431	3571 ± 1385	93 ± 86	244 ± 125	26 ± 11
	T315I/F359V	>10000	4586 ± 1397	3392 ± 211	6631 ± 1201	101 ± 22	20 ± 10
	T315I/G250E	>10000	8511 ± 5599	5001 ± 2939	7451 ± 3057	130 ± 16	33 ± 2
	T315I/E255K	>10000	>10000	470 6± 803	8944 ± 748	339 ± 12	40 ± 5
	T315I/E453K	8466 ± 1628	>10000	4724 ± 155	2931 ± 74	130 ± 5	61 ± 27
	T315I/M351T	7603 ± 1498	>10000	7683 ± 3645	>10000	127 ± 5	67 ± 44
	T315I/F311I	7144 ± 2459	>10000	4789 ± 1739	7061 ± 1423	438 ± 88	78 ± 46
	T315I/H396R	8953 ± 5314	>10000	9286 ± 3386	>10000	211 ± 134	79 ± 54
	T315I/Y253H	>10000	>10000	7080 ± 3233	6981 ± 2481	889 ± 100	114 ± 1
	T315I/F317L	>10000	>10000	>10000	860 ± 96	688 ± 412	117 ± 23
	T315M	>10000	>10000	>10000	996 ± 405	1987 ± 1414	217 ± 131
Other Compound Mutation	G250E/V299L	6486 ± 2622	641 ± 368	570 ± 599	2601 ± 2903	12 ± 3	14 ± 2
	F317L/F359V	7195 ± 1729	926 ± 24	50 ± 12	5214 ± 810	24 ± 12	25 ± 13
	Y253H/E255V	>10000	7026 ± 2183	231 ± 92	5014 ± 2920	772 ± 220	122
	T253H/F359V	>10000	>10000	110 ± 1	>10000	432 ± 23	311 ± 35

	Sensitive. $IC_{50} \leq 100nM$
	Intermediate sensitive IC_{50}=100 -1000 nM
	Insensitive IC_{50}>1000 nM

MUTATIONS & ASCIMINIB (UK real-life)

49 pts



DOSE>?

MUTATIONS & ASCIMINIB

25% acquires mutations

ASCEMBL: *BCR::ABL1* mutations[a] at study discontinuation

Patients discontinuing asciminib due to lack of efficacy or disease progression

n (%)	Asciminib 40 mg twice daily (n=39)
No mutations detected at end of treatment	22 (56.4)
Missing assessments at end of treatment	1 (2.6)
Mutations detected at end of treatment	16 (41.0)
Newly emerging mutations at end of treatment	**10 (25.6)**
ATP-binding site	• M244V (n=3)[b] • E355G (n=1)[c] • F359V (n=1) • T315I (n=1)
Myristoyl pocket	• A337T (n=3) • P465S (n=1)
Mutations at baseline and end of treatment	**6 (15.4)**
ATP-binding site	• F317L (n=2) • F359C/V (n=3) • Y253H (n=1)

Rea D, EHA 2022 poster 4005

MUTATIONS: THE "NEXT in CML" STUDY

Table 2. Breakdown of the frequency of mutations as assessed by SS vs NGS by level of nonresponse and line of therapy

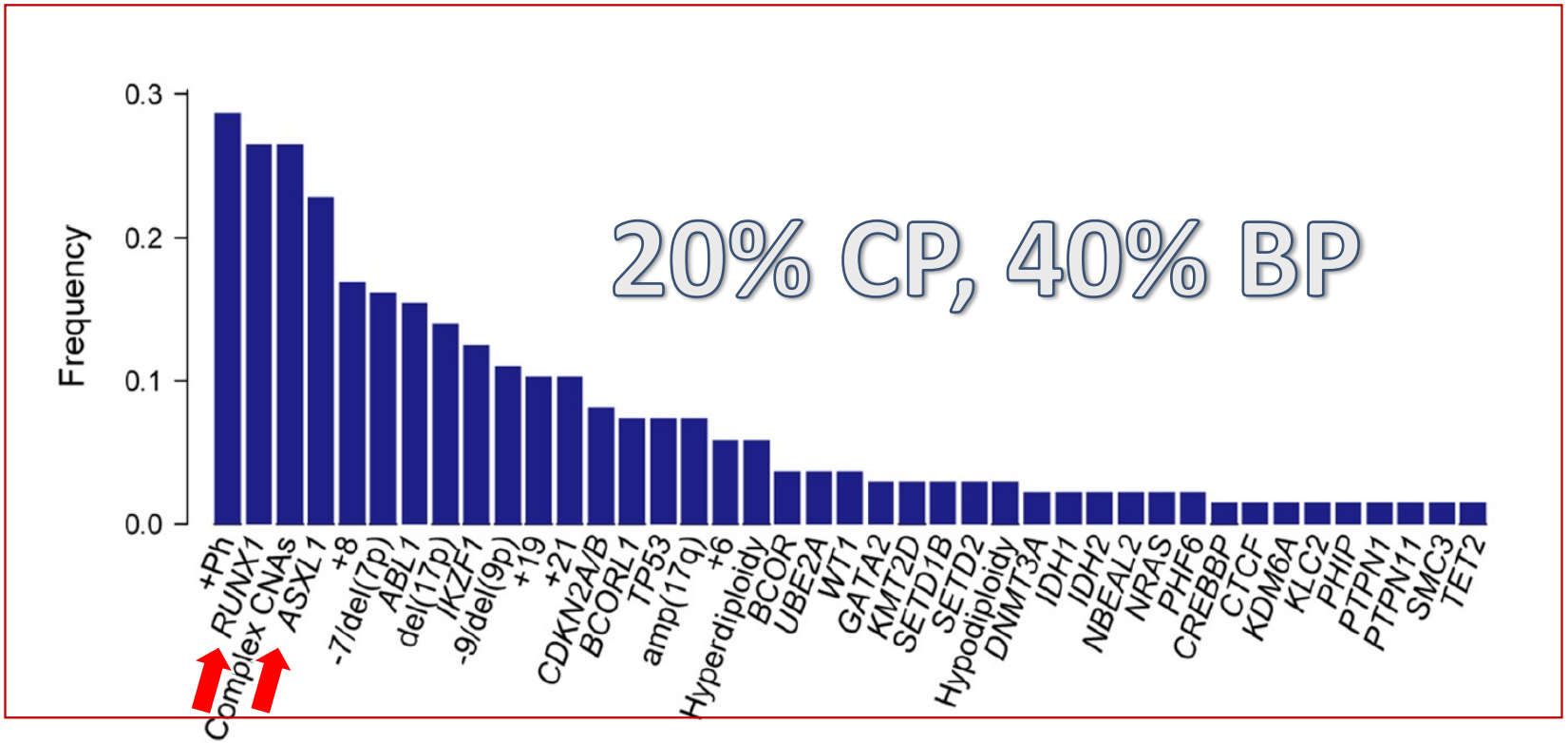
	Patients positive for mutations by SS	Patients positive for mutations by NGS
First-line failure	13/57 (23)	27/57 (47)
First-line warning	7/68 (10)	23/68 (34)
Second-line failure	15/39 (38)	20/39 (51)
Second-line warning	6/37 (18)	17/37 (49)
Third-line failure	14/21 (67)	17/21 (80)
Third-line warning	1/7	3/7
Fourth-/fifth-line failure	4/7	4/7
Total	60/236 (25)	111/236 (47)

HIGHLIGHTS: WHAT ARE THEY?

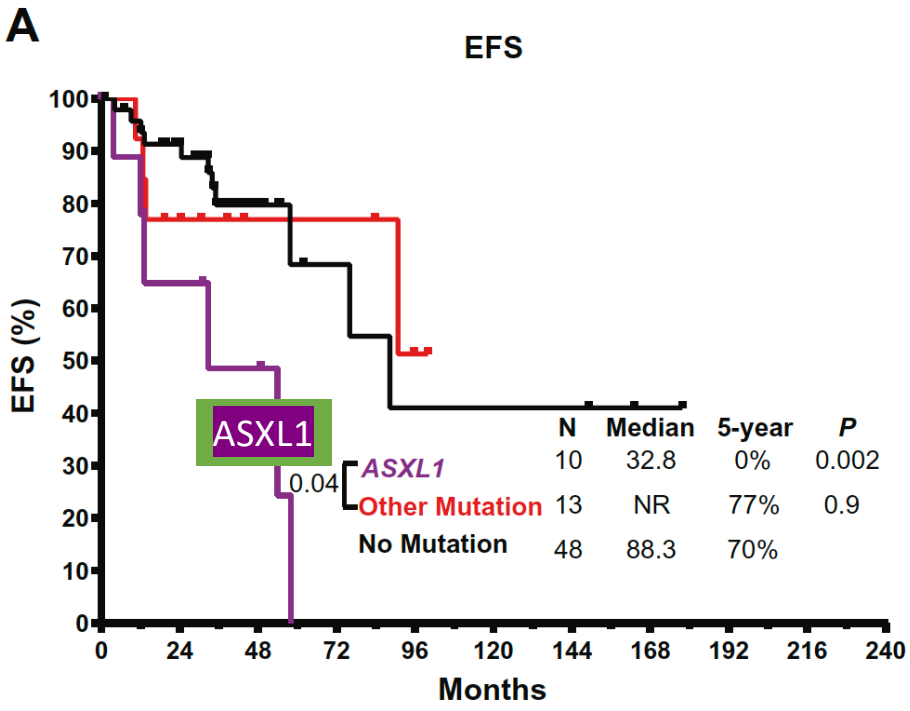
1. New drugs (asciminib, olverembatinib)
2. Lower toxicities, better results
3. The resistance: a phenomenon still unknown
4. CML is not only BCR::ABL1

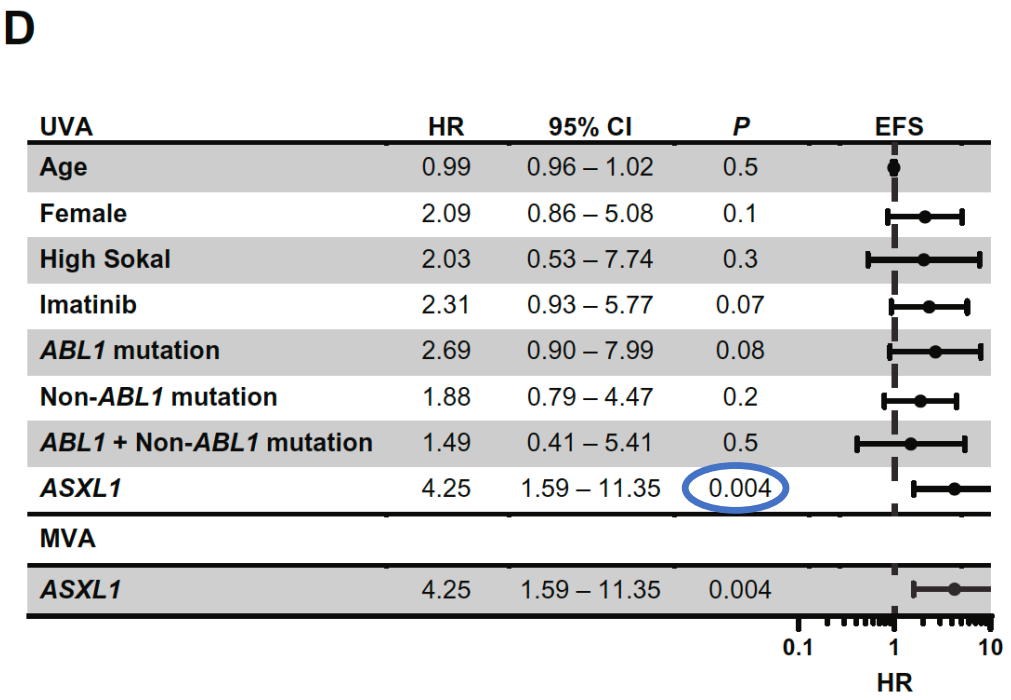
ADJUNCTIVE MUTATIONS

136 pts



ASXL1 mutations: IMATINIB





ASXL1 mutations: ASCIMINIB

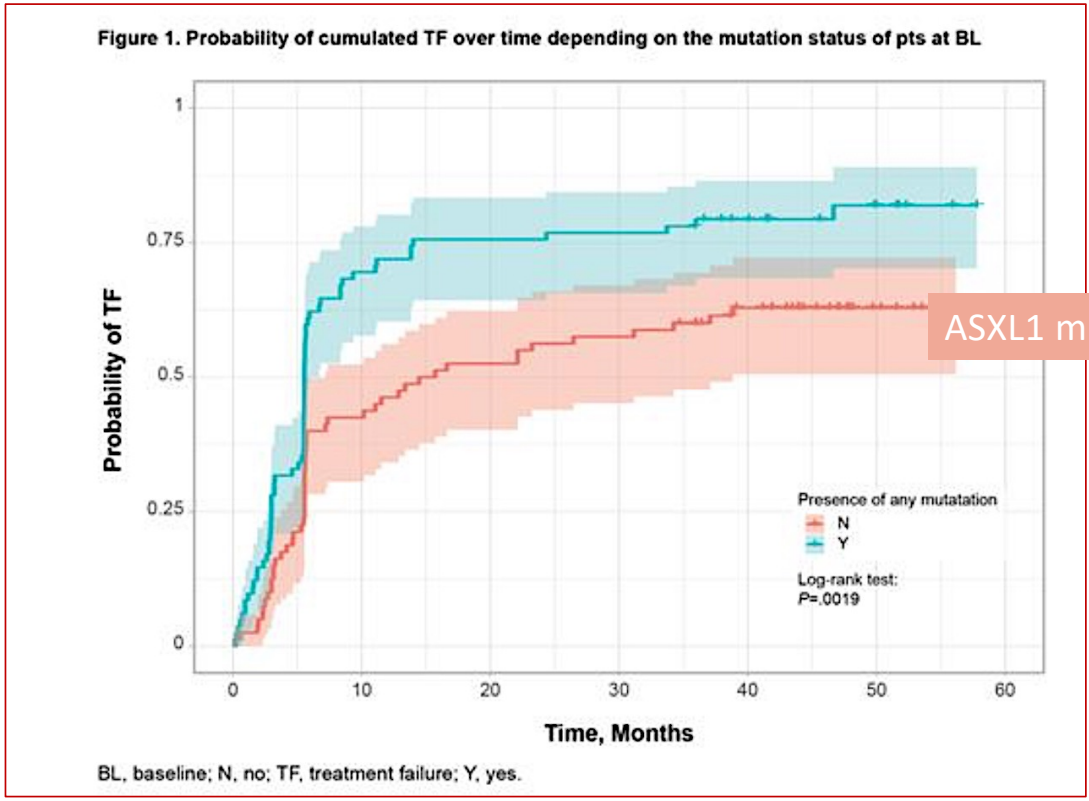
ASCEMBL trial

31% presented ASXL1 mutations,

with a median VAF of 20%;

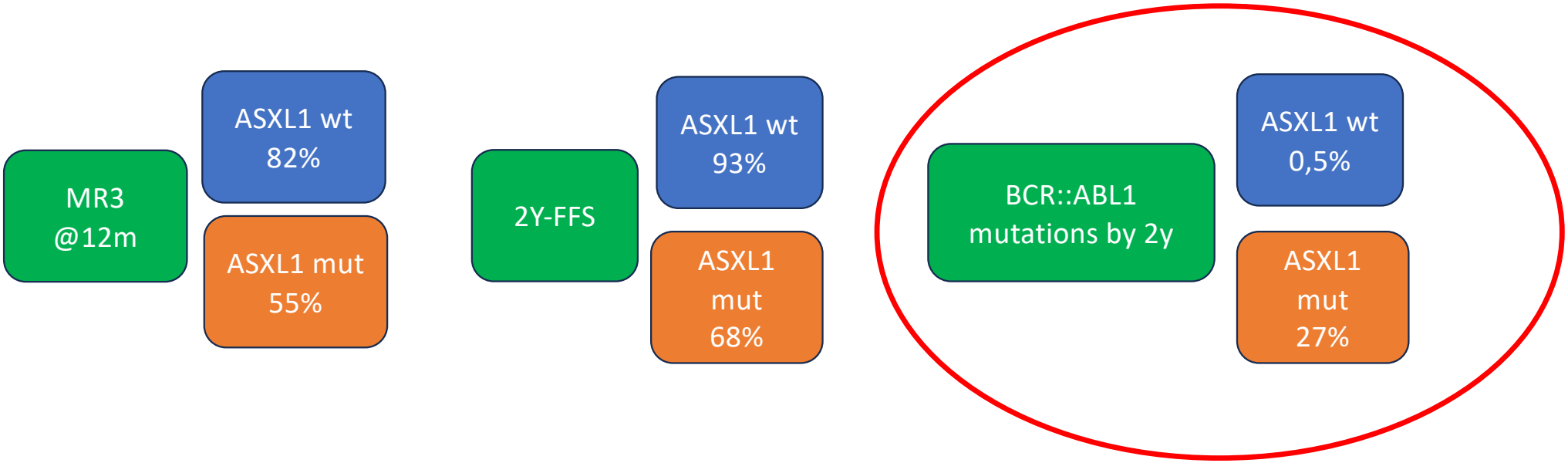
7% showed both ASXL1 and

BCR::ABL1 mutatons.



ASXL1 & ASCIMINIB

8% ASXL1 mutated @diagnosis; 27%@2y

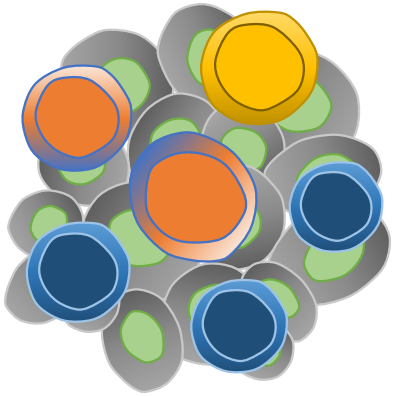


MYELOID NGS

Recommendations:

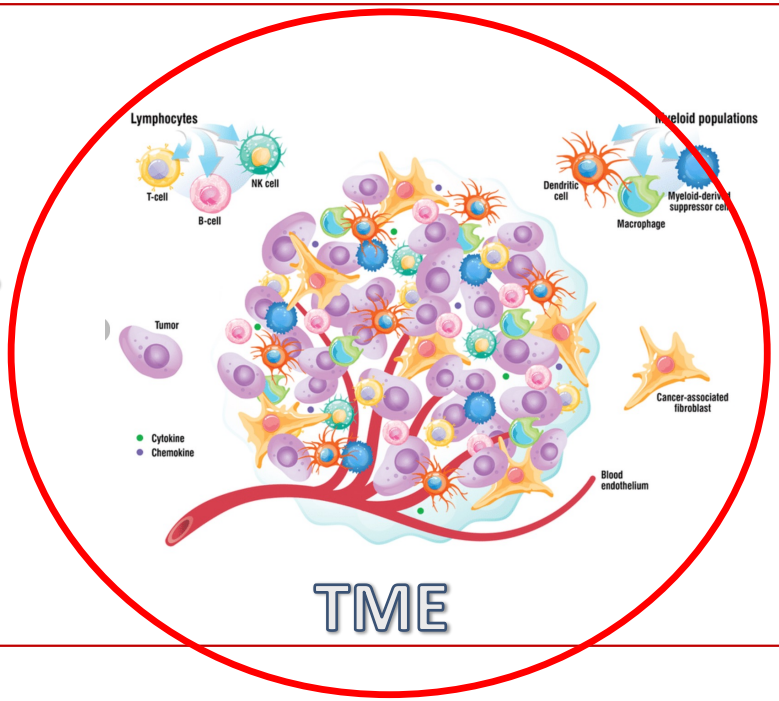
- Gene panel analysis pretreatment, including *ASXL1* mutation screening, is not currently recommended for routine clinical management but should be performed in investigational studies.
- NGS panel analysis for patients who present in, or progress to, BP is recommended to identify potential targets for treatment in addition to *BCR::ABL1*.

RESISTANCE & DIFFERENT ACTORS



TUMOR

+



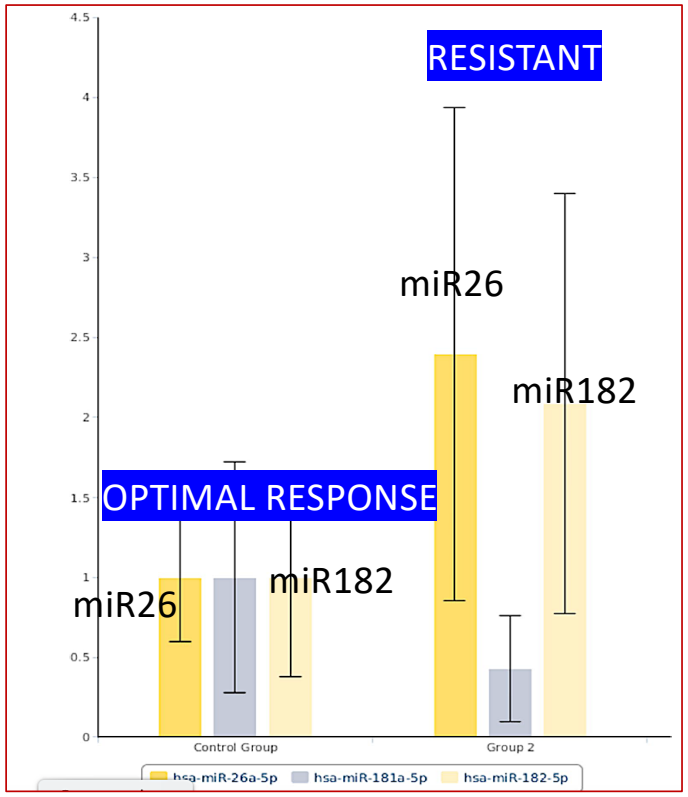
TME

+

PATIENT

THE MICROENVIRONMENT: miRNAs

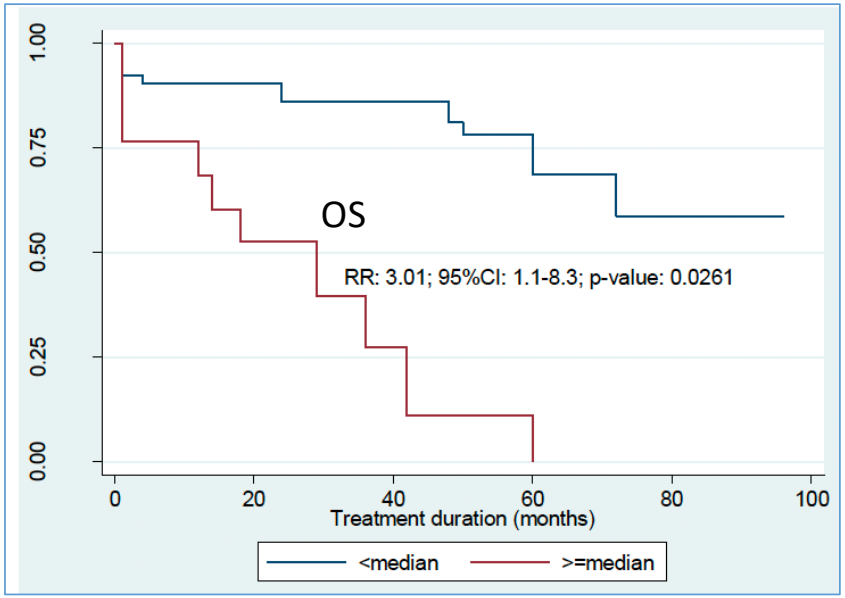
- hsa-miR-182-5p and hsa-miR-26a-5p were significant up-regulated only in the non responsive group (2x)



SNPs & CYTOKINES

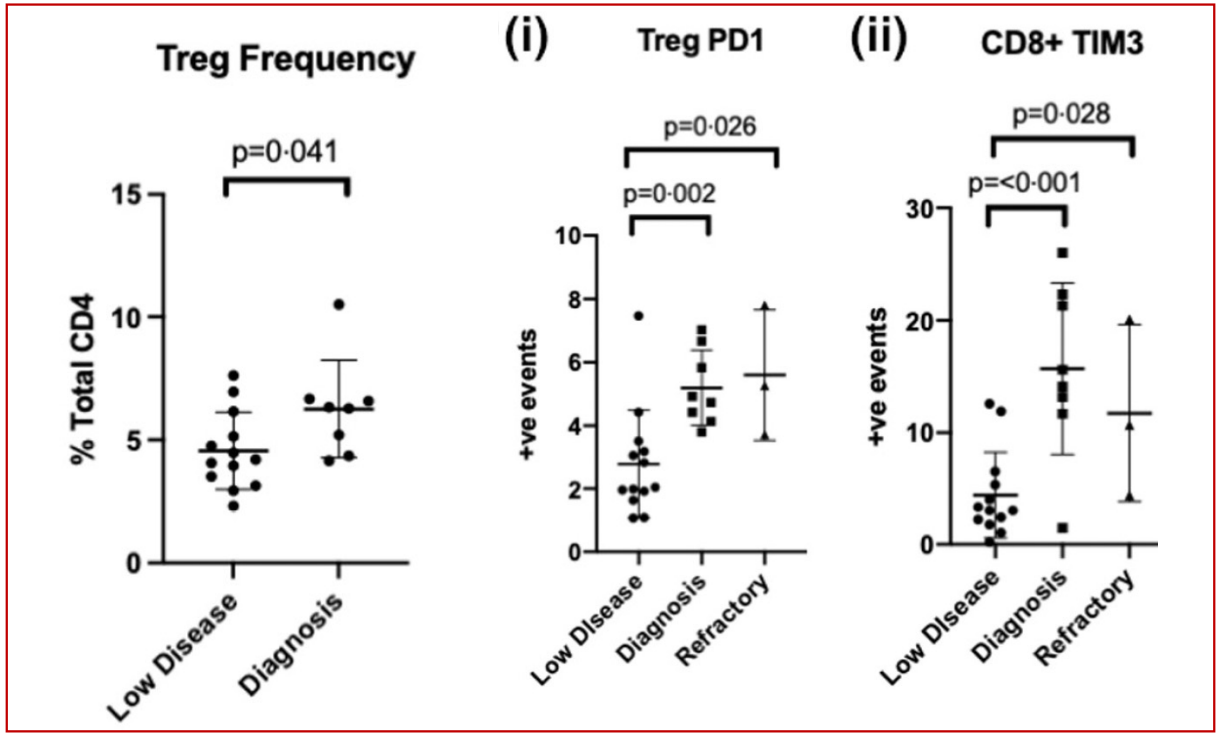
TNFa + TGFB1 + IL6

IFNg + IL10



T CELLS

In resistant pts:
Tregs higher,
T phenotype exhausted

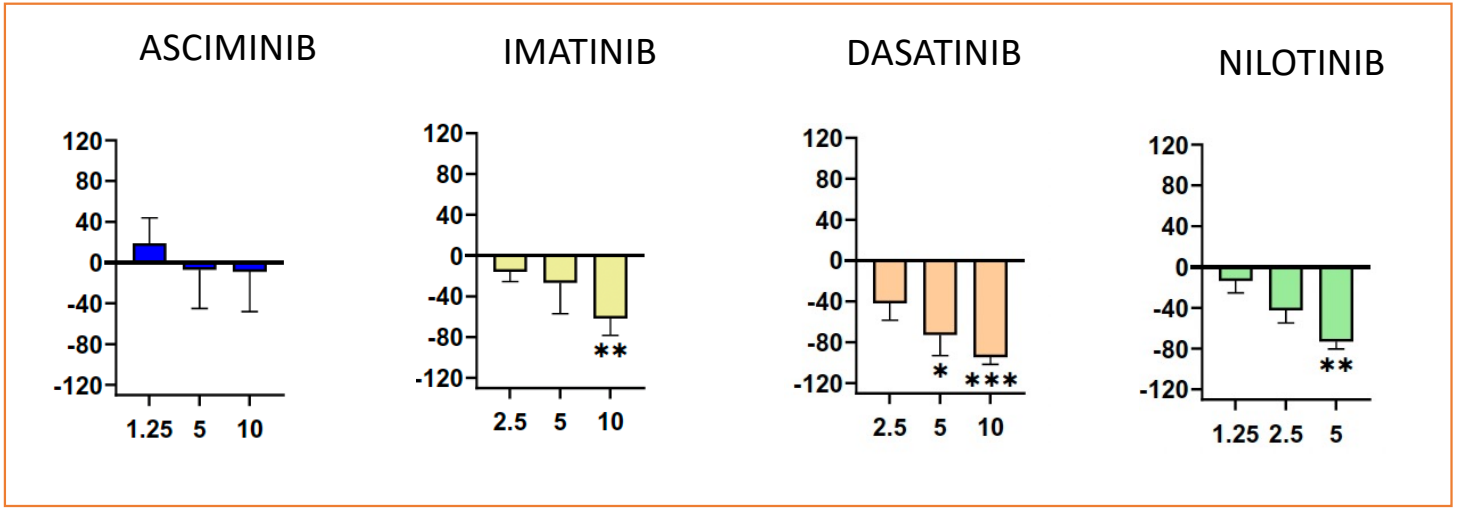


THE IMMUNITY

GENE ID	function	output on inflammation	ref
CCL5	activates NK	pro immun	122
CCR4	high in asthma	pro	123
CCR5	activates NK	pro immun	124
CD28	inactivated by PD1	pro immun	125
CD74	increases MCHII expression	pro immun	126
CX3CR1	high in antifungal resp	pro immun	127
CXCL16	high in anti-viral resp	pro-immun	91
CXCR3	high in T effector	pro immun	128
FYN	high in inflamm/sustains NK	pro / pro imm	129
HAVCR2	high in anti-viral resp	pro-immun	92
IFNG	antiviral	pro immun	93
JAK3	shift from M1 to M2 resp	anti	88
NFATC2	increases T memory	pro immun	130
PDE4A	low in sepsis	anti	131
SERPINB9	activates CD8	pro immun	132
SOCS3	low in arthritis	anti	89
STAT5A	high in colon inflamm	pro	133
TLR3	anti-viral/anti-inflamm	anti / pro imm	90

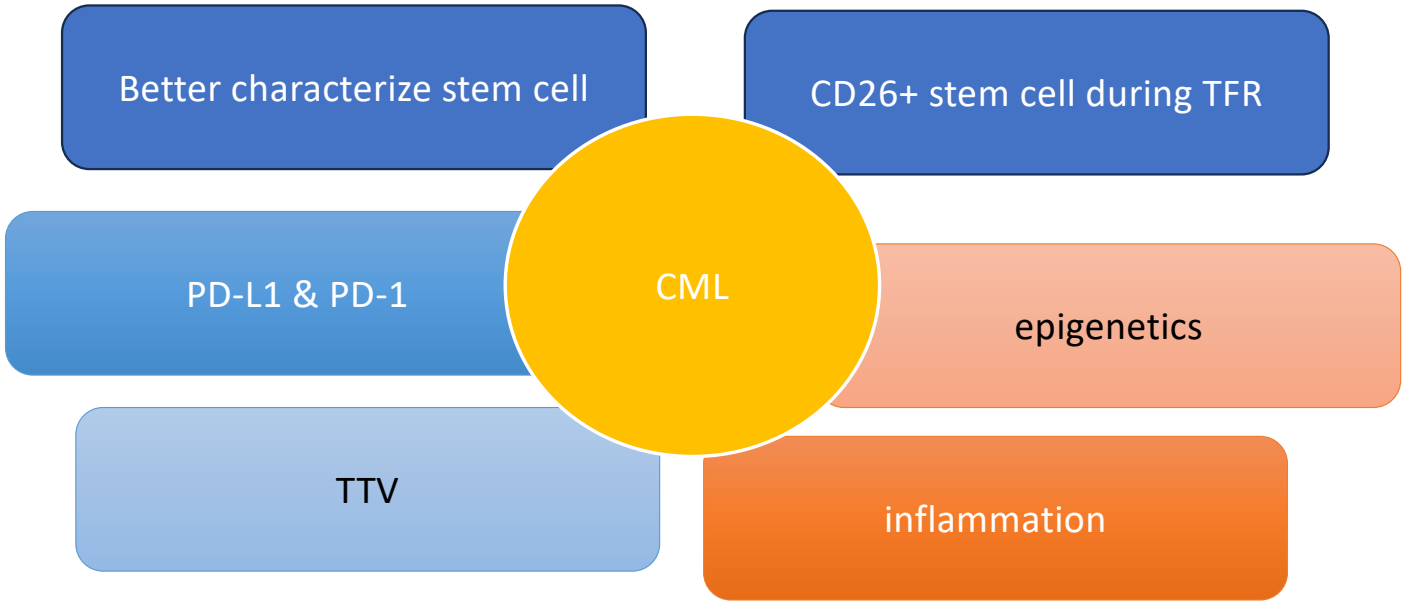
ASCIMINIB & IMMUNITY

- Asciminib makes T lymphocytes more “fit”



The puzzle is –almost- done

THE «STEM CML CURE» PROJECT



54 pts
21 pts in TFR

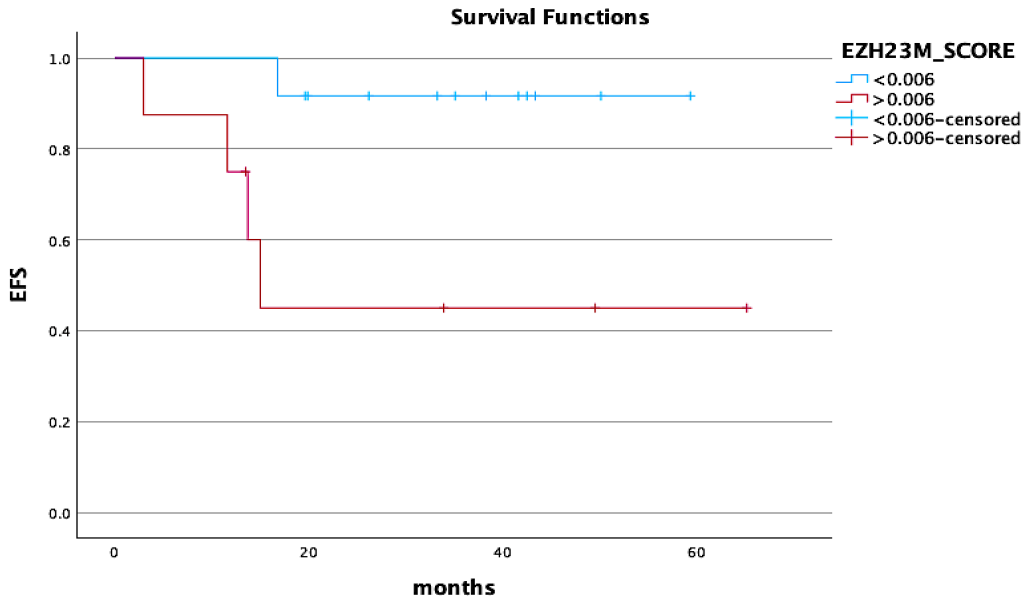
THE «STEM CML CURE» PROJECT

EZH2 @3m & EFS

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	6.020	1	.014

Test of equality of survival distributions for the different levels of EZH23M_SCORE.



THE «STEM CML CURE» PROJECT

INFLAMMATION (SIRI score)

PD-L1

53% pos (12%-82%)

No correlation with BCR::ABL1

Trend for PDL1: the probability of optimal response is twice for pts with lower PD-L1 expression

TTV does not replicate

TAKE HOME MESSAGES

- CML is still alive…that requires many efforts to better understand the biology that is not only BCR::ABL1
- CML is a perfect link between lab & clinics
- The OS is wonderful…thus we can choice the best therapeutic strategy…for a better QoL
- The networks are fundamental

THANKS!!!

sara.galimberti@unipi.it