Therapy-free remission: Good practice, bad practice

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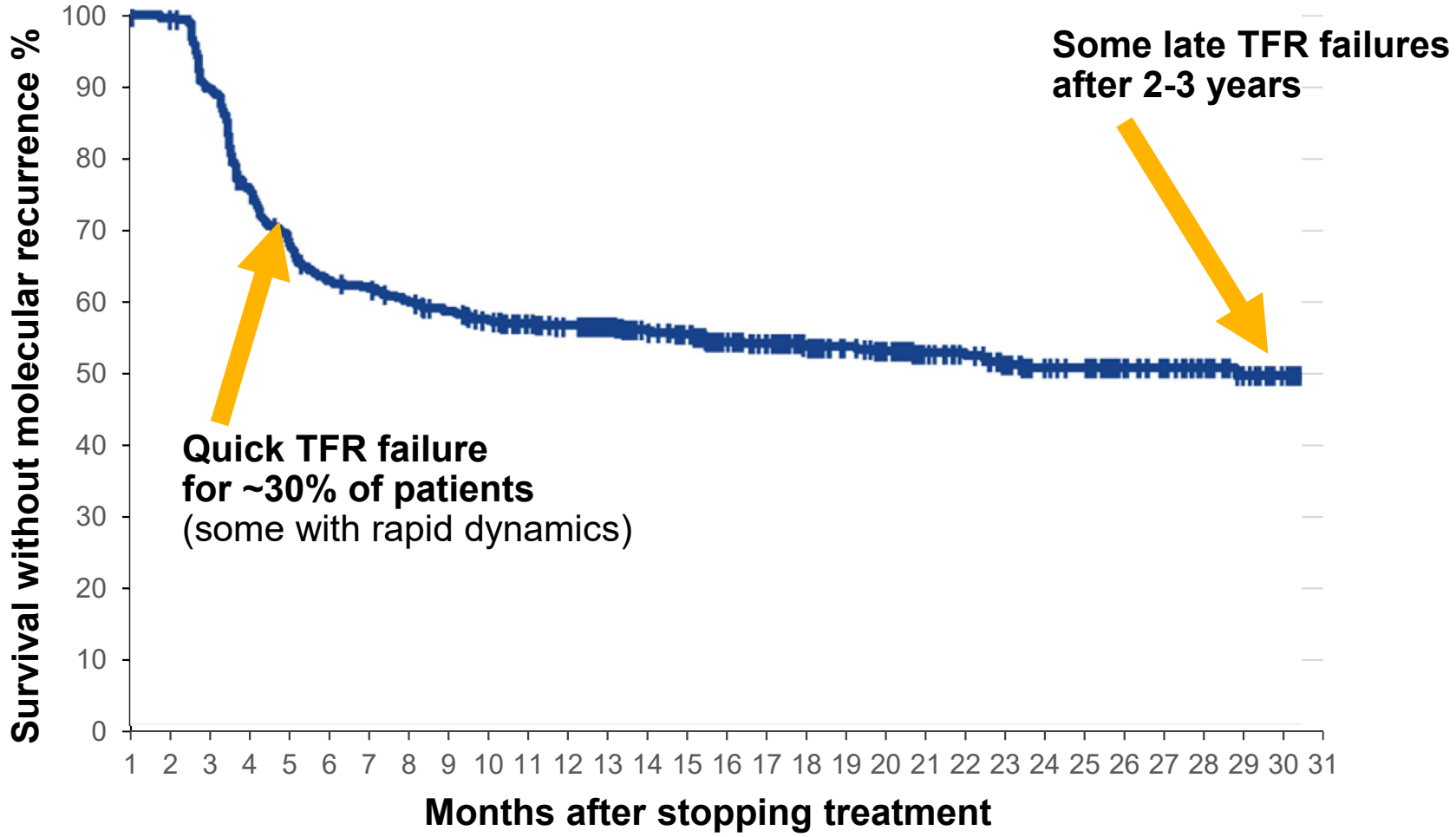
Patients in deep remission and on TKI seem to have have a near-normal life expectancy

Therapy-free remission in CML is an adorable goal and a great opportunity

- With all we know, about 30-40% of CML patients are likely to be successful in stopping treatment
  - with no prior history of progression or resistance
  - after many years of TKI treatment
  - after some years of deep remission (MR4 or MR4.5)
- Multiple studies have consistently demonstrated the safety and feasibility of stopping treatment: No risk to life
- All patients who failed TFR got back into the „safe harbour“ (below MMR). Almost all returned to deep molecular response

…in clinical studies!

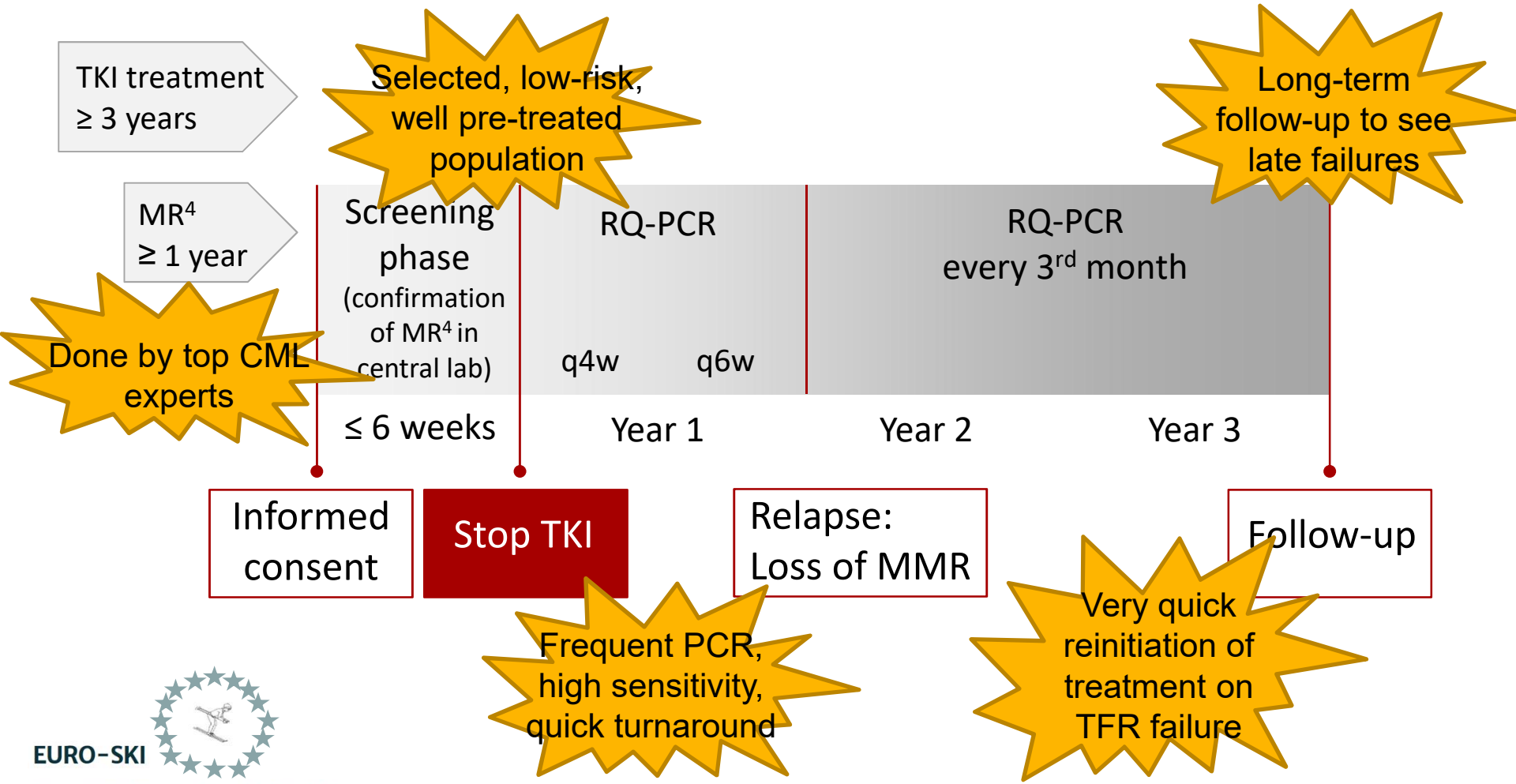
We can already see in current studies: Life-long monitoring seems to be required



EURO-SKI, European Stop TKI.
Richter et al, Haematologica 2016 [abstract S145]

ELN European LeukemiaNet

Let‘s talk about more about „safe harbour“: Stringent criteria of current STOP trials



EURO-SKI
European Stop Tyrosine Kinase Inhibitor Study

Recommendations on stopping treatment: Patient characteristics

	NCCN Guidelines 2017	ESMO Guideline 2017
CML phase	**Chronic phase,** no prior accelerated or blast phase	**Chronic phase,** optimal response to 1st line therapy
Prior TKI therapy	≥ 3 years	≥ 5 years
Response level before stopping	MR4 ≥ 2 years	MR 4.5 reached, MR4 ≥ 2 years
Restart criteria	Loss of MMR	Loss of MMR
BCR-ABL transcript	Quantifiable BCR-ABL transcript	Quantifiable BCR-ABL transcript (typical B2a2 or b3a2)

Source: CML Advocates Network ASH Report 2017

Recommendations on stopping treatment: Institutional requirements

	NCCN Guidelines 2017	ESMO Guideline 2017
Clinical center	CML speciality center	Institution that has structured follow-up to enable rapid intervention when BCR-ABL rises
Lab requirements	Reliable PCR with 4.5 log sensitivity (IS) and provides results in 2 weeks	High quality PCR on IS that provides results within 4 weeks and can perform PCR every 4-6 weeks
Monitoring schedule after stopping	Months: 1-6: monthly 7-24: every 2 months afterwards 3-monthly if in MMR	(Not defined)
Monitoring schedule after TFR failure	Months 0-6: monthly, then every 3 months infinitely. Mutation testing if MMR is not regained after 6 months	Loss of MMR

Source: CML Advocates Network ASH Report 2017

So what‘s happening on TFR out in the field?

Wish and reality in clinical practice: My personal ASCO 2017 shock poster…

Tyrosine Kinase Inhibitor (TKI) Therapy Discontinuation in Patients with CML in Chronic Phase: A US Clinical Practice Perspective

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Background and Objectives

- With the advent of tyrosine kinase inhibitors (TKIs), chronic myeloid leukemia (CML), which was a fatal condition a little less than two decades ago, is now managed as a chronic condition[1]
- Patients responding to TKI therapy had the possibility of lifelong therapy even when achieving deep remission as TKI therapy was recommended to be used until disease progression
- TKI therapy requires daily medication and frequent monitoring, which may impact quality of life, in addition to being relatively costly. Thus, the lifelong therapy option may not be feasible (or preferred) for all patients
- A number of clinical trials have assessed the impact of TKI therapy discontinuation on the risk of relapse/recurrence providing evidence to suggest that TKI therapy should only be discontinued under a specific framework to be considered as a safe option[2-5]
- Based on findings from these clinical studies, new practice guidelines were initially published in November 2016 (NCCN guidelines, CML, V1.2017) and in January 2017 (V2.2017), including recommendations on TKI therapy discontinuation for patients with CML in chronic phase (CML-CP):
  - TKI therapy discontinuation is recommended for patients who achieved MR4.0, ≤0.01% international scale (IS) for ≥2 years and TKI therapy duration of ≥3 years, prompt resumption of TKI is recommended upon loss of MMR (MR3, ≥0.1% IS).
- This study aimed to assess the TKI therapy discontinuation practice in the US before the publication of these new guidelines

Methods

- Hematologists/oncologists, who had experience with CML patients, from various practice settings (e.g., community and academic practice) and geographic locations in the US, were recruited from an existing panel of physicians
- The physicians were eligible to participate in the study if they fulfilled all of the following criteria:
  - Completed medical subspecialty training in hematology/oncology
  - Reported hematology, medical oncology, or any oncology subspecialties (e.g., surgical oncology, radiation oncology, pediatric hematology/oncology) as the primary medical subspecialty
  - Were responsible for treatment decisions and follow-up for at least one adult patient with Philadelphia chromosome positive (Ph+) CML-CP who received a TKI therapy since January 2013 (date from which molecular monitoring response on the IS became a more standard procedure/commonly available)
- The survey collected information on the following:
  - Physician and practice setting characteristics
  - CML monitoring practice
  - TKI therapy discontinuation practice: physician's perspective on adequate response patients should achieve before considering TKI therapy discontinuation (i.e., minimum response to TKI, response duration, and TKI therapy duration)
  - Relapse after TKI therapy discontinuation: physician's perspective on the minimum level of change in response to be considered a relapse and actions taken after a relapse
- The physician survey was web-based; physicians received an invitation by email and made the decision to participate in the study or not
- There was no requirement for IRB review nor exemption as no patient-level data and no personal identification numbers were collected

Results

Physician and Practice Setting Characteristics

- A total of 300 US-based hematologists/oncologists completed the survey between October 12 and November 9, 2016
- The majority of the participating physicians reported medical oncology (66%) followed by hematology (61%) as their primary medical subspecialty
- Community-based practice (59%) and academic-based practice (39%) were the most-commonly reported primary practice settings
- About one half of the participating physicians (52%) were from a large practice (i.e., 10 or more physicians) and had been practicing more than 10 years (47%) since completing medical subspecialty training
- In terms of their primary practice location, 34% of participating physicians were from the south, 30% from the northeast, 21% from the west, and 15% from the midwest US Census regions; in addition, 49% were from urban, 40% from suburban, and 11% from rural areas

CML Monitoring Practice

- Among these 300 physicians, approximately 90% reported testing for molecular response using peripheral blood RT-PCR during the first three years of TKI therapy with most of them doing so every three months (year 1: 73%, year 2: 56%, and year 3: 39%)
- Among the physicians testing for molecular response to TKI therapy using peripheral blood RT-PCR, 97% received tests reported on the IS within a typical turn-around time of one to two weeks (87%)
- The main reasons reported for testing for molecular response were to assess response to TKI therapy as recommended per treatment guidelines (87%), and when loss of response was suspected (64%) or a progression to AP/BC was suspected (53%) and a confirmation was needed
- The majority of physicians reported that they would always test for molecular response to TKI therapy (54%); however, the most common reasons reported for not testing for molecular response were that testing for cytogenetic response to TKI therapy would be sufficient (18%) and when the cost was too high for the patient (18%)

TKI Therapy Discontinuation Practice

- One third of the participating physicians reported having attempted TKI therapy discontinuation (102 of 300), of whom 66 did so outside of a clinical trial (**Table 1**)
- Physicians who reported TKI therapy discontinuation were more likely to practice in academic centers. They were also more experienced clinicians (i.e., more than 10 years in practice), and followed a larger number of CML patients than those who did not (**Table 1**)

TKI Therapy Discontinuation Practice in the Subgroup of Physicians Who Did So Outside of a Clinical Trial Setting

- Over the 300 participating physicians, 66 physicians reported at least one patient who had TKI therapy discontinued after achieving an adequate response, and who also reported that TKI therapy discontinuation was attempted outside a clinical trial for all of their patients. This subgroup of 66 physicians was analyzed to assess the TKI discontinuation practice outside of a clinical trial setting
- Among these 66 physicians, the majority reported they would consider TKI therapy discontinuation for medical reasons (76% adverse events, 47% pregnancy planning), but fewer would consider TKI therapy discontinuation for economic reasons (35%), while 12% reported they would consider it for all of their patients who achieve an adequate response (**Figure 1A**)
- There was no consensus on
  - the minimum response to achieve to consider TKI therapy discontinuation (56% would consider a decrease in BCR-ABL of at least 4.5 log, 21% 3 log, 11% 2 log, and 20% 1 log, **Figure 1B**)
  - the minimum response duration to consider TKI therapy discontinuation (29% would consider a response maintained for at least 3 years, 24% 2 years, and 20% 1 year, **Figure 1C**), and
  - the minimum TKI therapy duration to consider TKI therapy discontinuation (44% would consider TKI therapy duration of at least 3 years, 20% 2 years, 20% 1 year, **Figure 1D**)
- In addition, there was no consensus on the frequency of CML monitoring post-discontinuation with less than 10% of physicians considering monthly molecular monitoring and 58% of physicians considering molecular monitoring every 3 months in the first year after TKI therapy discontinuation
- Severe adverse event (79%) and pregnancy (73%) were the most common exceptions for which physicians would consider TKI therapy discontinuation if patients had not achieved the adequate response

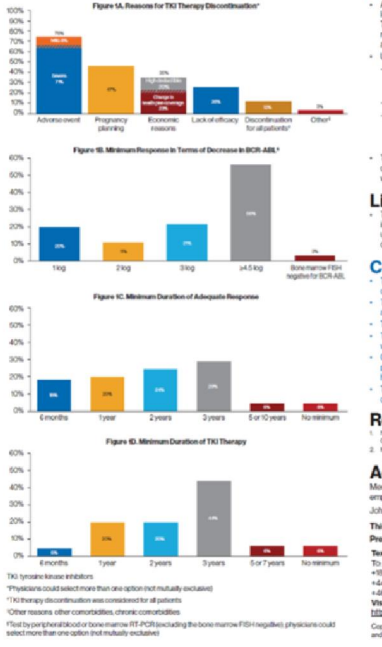
Table 1. Description of Physician and Practice Setting Characteristics

	Physicians who have attempted TKI therapy discontinuation for ≥1 patient	Physicians who have not attempted TKI therapy discontinuation for any patients
	N = 102	N = 198
Primary medical subspecialty,* N (%)		
Medical oncology	87 (85.3%)	171 (86.4%)
Hematology	65 (63.7%)	117 (59.1%)
Primary practice setting, N (%)		
Community-based practice	55 (53.9%)	123 (62.1%)
Academic-based practice	**46 (45.1%)**	72 (36.4%)
Military practice	1 (1.0%)	3 (1.5%)
Primary practice size, N (%)		
Large (≥10 physicians)	**58 (56.9%)**	98 (49.5%)
Small/intermediate (2-9 physicians)	40 (39.2%)	94 (47.5%)
Individual	4 (3.9%)	6 (3.0%)
Primary practice setting environment, N (%)		
Rural	8 (7.8%)	**25 (12.6%)**
Suburban	46 (45.1%)	75 (37.9%)
Urban	48 (47.1%)	98 (49.5%)
US Census region of primary practice, N (%)		
Northeast	28 (27.5%)	63 (31.8%)
Midwest	**20 (19.6%)**	26 (13.1%)
South	35 (34.3%)	66 (33.3%)
West	19 (18.6%)	43 (21.7%)
Years of practice since completing medical subspecialty training, N (%)		
< 5 years	14 (13.7%)	48 (24.2%)
5-10 years	24 (23.5%)	73 (36.9%)
>10 years	**64 (62.7%)**	77 (38.9%)
Experience with patients diagnosed with Ph+ CML-CP since TKI therapy has been available (2001)		
N	**8,245**	7,841
Mean (SD)	**80.8 (106.4)**	38.6 (49.1)

Ph+ CML-CP: Philadelphia positive chronic myeloid leukemia in chronic phase. SD: standard deviation. TKI: tyrosine kinase inhibitors. US: United States

* Physicians could select more than one option (not mutually exclusive)

Figure 1. Physician's Perspective on Adequate Response Patients with CML-CP should Achieve before Considering TKI Therapy Discontinuation (N=66)



TKI: tyrosine kinase inhibitors

*Physicians could select more than one option (not mutually exclusive)

†TKI therapy discontinuation was considered for all patients

‡Other reasons: other comorbidities, chronic comorbidities

§Test by peripheral blood or bone marrow RT-PCR (excluding the bone marrow FISH negative). physicians could select more than one option (not mutually exclusive)

Relapse after TKI Therapy Discontinuation in the Subgroup of Physicians Who Did So Outside of a Clinical Trial Setting

- Among these 66 physicians, there was no consensus on the definition of relapse (i.e., minimum level of change in molecular response). For a hypothetical case of a patient who discontinued TKI therapy following achievement of MR4.5 (BCR-ABL1/ABL1=0.0032%), 21% would define relapse based on an increase in BCR-ABL1/ABL1 to ≥1%, 47% an increase to ≥1%, and 27% an increase to ≥10%
- Upon relapse:
  - 76% of physicians reported they would request a second test to confirm when a relapse was suspected/observed, 68% would do so within a month and 20% would do so within a week
  - 73% would order an ABL1-mutation test
  - 64% would re-initiate the patient on the same TKI (same dose: 50%, lower dose: 9%, higher dose: 12%), 44% would initiate the patient on a different TKI, 8% would initiate the patient on omacetaxine, and 8% would refer the patient for hematopoietic stem cell transplantation (HSCT)
- The 66 physicians reported that a proportion of 30% of their patients for whom the TKI therapy was discontinued relapsed; 26% of the physicians reported that these relapses occurred, on average, within six months after and 58% approximately one year after TKI therapy discontinuation

Limitations

- This study may be subject to potential biases, including a potential reporting bias (e.g., bias in favor of specific practice per guideline recommendations), selection bias, recall bias (e.g., unknown, not sure response options), and non-random incomplete data (e.g., specifically omitting a particular answer option across questions)

Conclusions

- TKI therapy discontinuation in patients with CML-CP responding to TKI was attempted outside of clinical trials without clear guidelines
- There was no consensus on the minimum response achieved, the minimum response duration, and the minimum TKI therapy duration, before TKI discontinuation
- There was no consensus on the frequency of CML monitoring post-discontinuation
- There was no consensus on the appropriate time to re-initiate treatment and choice of therapy when molecular relapse is detected
- Conditions under which TKI therapy was discontinued differed from new recommended practice guidelines,[1] which may have resulted in discontinuation where deep response may have not been achieved and disease not adequately monitored
- The recommended practice guidelines need to be communicated to physicians as TKI therapy discontinuation is likely to be conducted in a broader population

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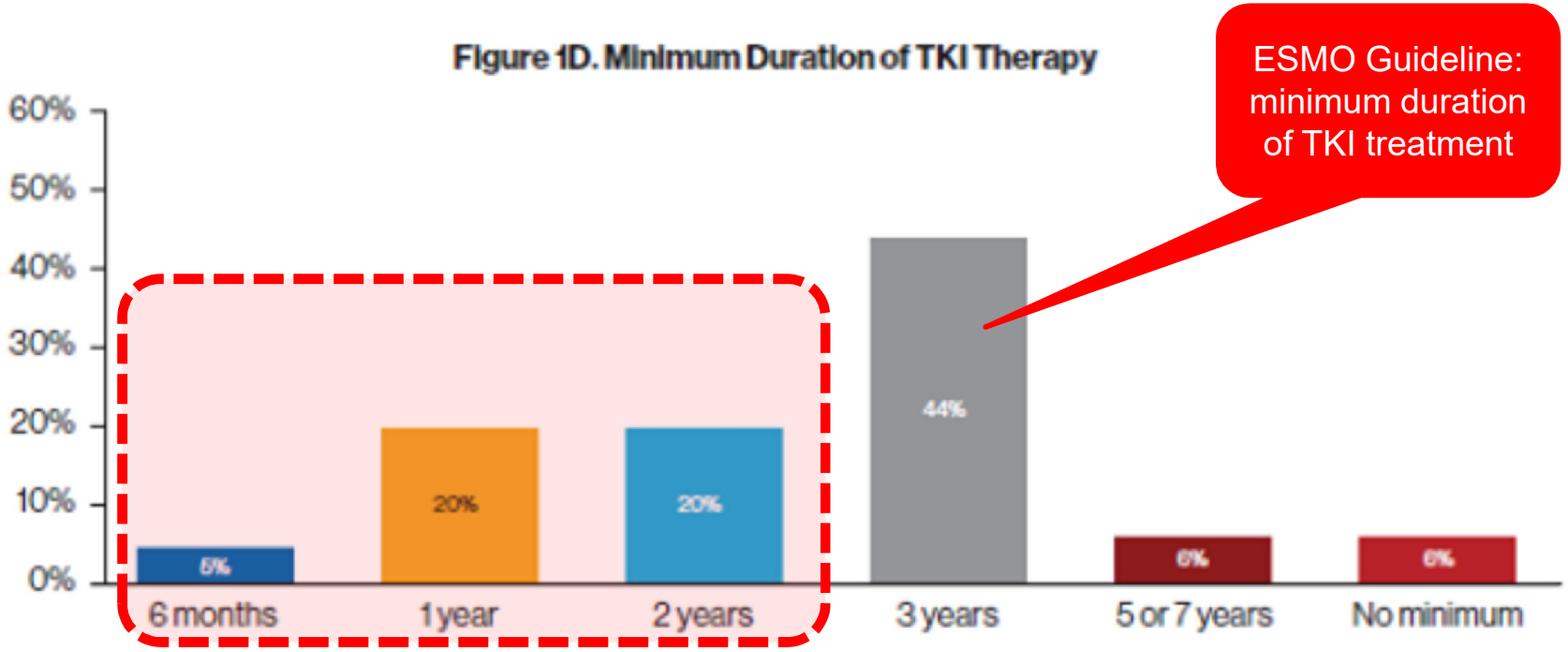
Survey of 300 US-based hematologists/ oncologists in Oct-Nov 2016

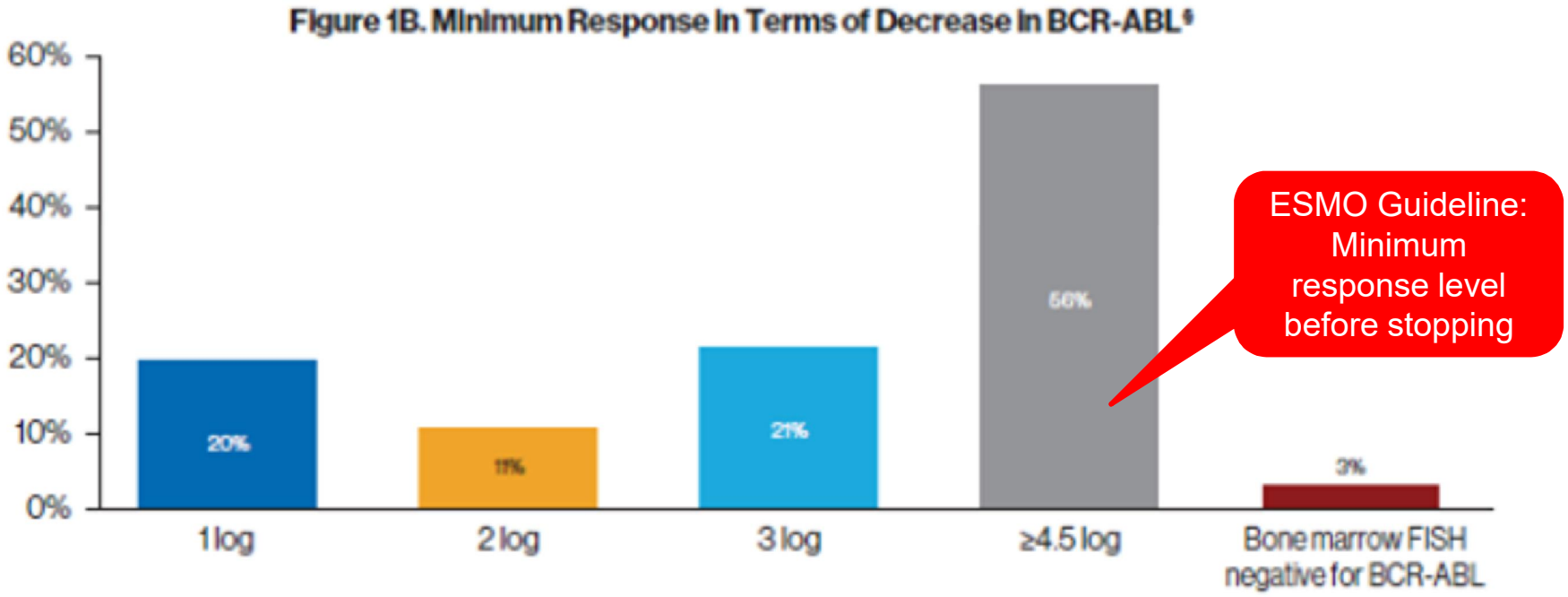
- 300 US-based hema/oncologists surveyed in Oct/Nov 2016, half of them from larger practices with >10 years as hematology specialists
- 66 of them had discontinued patients in (some) remission outside of clinical trials without clear guidelines

Conditions under which TKI therapy was discontinued **differed from new recommended practice guidelines** (or the requirements of prior STOP trials), resulting in **discontinuation without deep response and with inadeqate monitoring**

A considerable number of physicians stopped patients very early



20% of hemato/oncologists thought 1 log reduction would be sufficient to stop



Post-discontinuation, less than 10% of physicans considered monthly molecular monitoring (ESMO: monthly in months 1-6, every 3 months thereafter)

No consensus on the definition of relapse: only 26% would restart at loss of MMR

For the hypotheical case of a patient who discontinued TKI therapy in MR4.5,

- 21% would define TFR failure on BCR/ABL >0.1% (MMR)
- 47% on BCR-ABL increase to ≥1% (MR2)
- 27% on BCR-ABL increase to ≥ 10%

ESMO Guideline: criterium for restarting treatment

TFR, done right, does not mean leaving the safe harbour – but any CML patient lost to bad practice would be one too many!