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First line decision-making: Update on treatment guidelines

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Conflict of interest disclosure

- Honoraria: BMS, Incyte, Novartis and Pfizer
- Membership on scientific advisory boards: BMS, Novartis
- Clinical trial steering committee member: BMS, Novartis

First line TKI treatment in chronic phase CML: options: NCCN CML V2.2017

- **NCCN 2017**
  1. Determine CML risk score
  2. Preferred TKI according to risk score:
     1. Low-risk: imatinib 400mg QD, dasatinib 100mg QD or nilotinib 300mg BID.
     2. Intermediate or high: dasatinib 100mg QD or nilotinib 300mg BID.
  3. Also take into account comorbidities and drug toxicities.

First line TKI treatment in chronic phase CML: options: ELN 2013

- **ELN 2013**
  1. Any of the 3 TKI approved in this indication: imatinib 400mg QD, dasatinib 100mg QD or nilotinib 300mg BID.
  2. Take into account patient characteristics (comorbidities), drug safety and tolerability.

Baccarani M. et al. Blood 2013; 122: 872-884.

First line TKI treatment in chronic phase CML: options: ESMO 2017

- **ESMO 2017**
  1. Any of the 3 TKI approved in this indication: imatinib 400-800mg QD, dasatinib 100mg QD or nilotinib 300mg BID.
  2. TKI selection based on treatment goals, age and comorbidities
  3. Discuss treatment goals with the patient.
  4. Also take into account adverse event profile of each TKI

	Treatment goals	CML risk score	Age	Comorbid patients	Cost Reimbursement
Item	**Treatment-free remission in younger patients (especially females)**	**Non-low**	**Elderly patients**	**Present**	**If major issue**
Best choice	**2nd generation TKI**	**2nd generation TKI**	**Imatinib**	**Lung disorder: Avoid dasatinib Diabetes or cardiovascular disease: caution with nilotinib**	**Generic imatinib**
Reason	**Deep molecular responses more frequently achieved**	**Lower risk of progression**	**Tolerance profile**	**Safety profile of each TKI**	**Cost-effectiveness**

Hochhaus A et al. Annals of Oncology 2017; 28 (Supplement 4): iv41-iv51.

Response milestones and treatment options: NCCN CML V2.2017

BCR-ABL1 (IS)	3 months	6 months	12 months	>12 months
>10%				
1-≤10%				
0.1-<1%				
<0.1%				

Monitor response and side effects
Continue same TKI

Evaluate compliance and drug interactions, mutation analysis
Continue same TKI or switch to alternate or dose escalation of imatinib to a max of 800mg QD

Evaluate compliance and drug interactions, mutation analysis
Switch to alternate TKI or evaluate for HSCT

Response milestones and treatment options: ELN 2013 and ESMO 2017

Milestone	Failure	Warning	Optimal
3 months	No CHR Ph >95%	Ph 36-95% BCR-ABL >10%	Ph ≤35% BCR-ABL <10%
6 months	Ph >35% BCR-ABL >10%	Ph 1-65% BCR-ABL 1-10%	Ph 0% BCR-ABL <1%
12 months	Ph>0% BCR-ABL >1%	BCR-ABL 0.1-1%	BCR-ABL <0.1%
> 18 months (ESMO)		BCR-ABL 0.1-1% (ESMO)	BCR-ABL <0.01%* (ESMO)
Any time	Relapse, loss of MMR		

* For patients with the aim of treatment-free remission

Continue same TKI

Monitor carefully, continue same treatment or consider to change treatment

Change treatment

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Assessment of response

- **Complete hematologic response (CHR)**
  - Leucocytes < 10000/mm3, basophiles < 5%, platelets <450000/mm3
  - No immature granulocytes
  - No palpable spleen
- **Cytogenetic response (at least 20 bone marrow metaphases)**
  - Complete (CCyR): no Ph+
  - Partial (PCyR): 1-35% Ph+
  - Minor: 36-65 Ph+
  - Minimal: 66-95 Ph+
  - None: >95% Ph+
- **Molecular response (blood RT-qPCR)**
  - Major molecular response (MMR): BCR-ABL ≤0.1% IS
  - Deep molecular response (DMR)
    - MR4: BCR-ABL ≤0.01% IS or undetectable with at least 10000 copies of ABL control gene
    - MR4.5: BCR-ABL ≤0.032% IS or undetectable with at least 32000 copies of ABL control gene

Monitoring the response to treatment: NCCN CML V2.2017

Tool	Frequency
Bone marrow cytogenetics	- Failure to reach response milestones - Any sign of loss of response
Blood RT-qPCR	Every 3 months after treatment initiation. After BCR-ABL 0.1-1% IS has been achieved, every 3 months for 2 years, and every 3 to 6 months thereafter
BCR-ABL kinase domain mutation analysis	- Failure to reach response milestones - Any sign of loss of response - 1-log increase of BCR-ABL and MMR loss - Progression to accelerated phase or blast crisis

Monitoring the response to treatment: ELN2013 and ESMO 2017

Tool	Frequency
Blood cell counts and differentials	Every 2 weeks until CHR in the absence of significant cytopenia, then every 3 months
Bone marrow karyotype	At 3 and 6 months, then every 6 months until CCyR has been achieved
Blood RT-qPCR	Every 3 months
Mutation analysis	In case of failure

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Other treatment options in the 1st line setting

- Clinical trials whenever available.
- Generic dasatinib earlier than expected?
- Bosutinib 400mg QD:
  - USA (FDA): marketing authorization in 2018
  - EU (EMA): positive opinion by CHMP (committee for medicinal products for human use) in 2018