NO allo in 1st line Ph+ ALL

Michel van Gelder

MUMC+

Belangenverklaring

In overeenstemming met de regels van de Inspectie van de Gezondheidszorg (IGZ)

Naam: Michel van Gelder

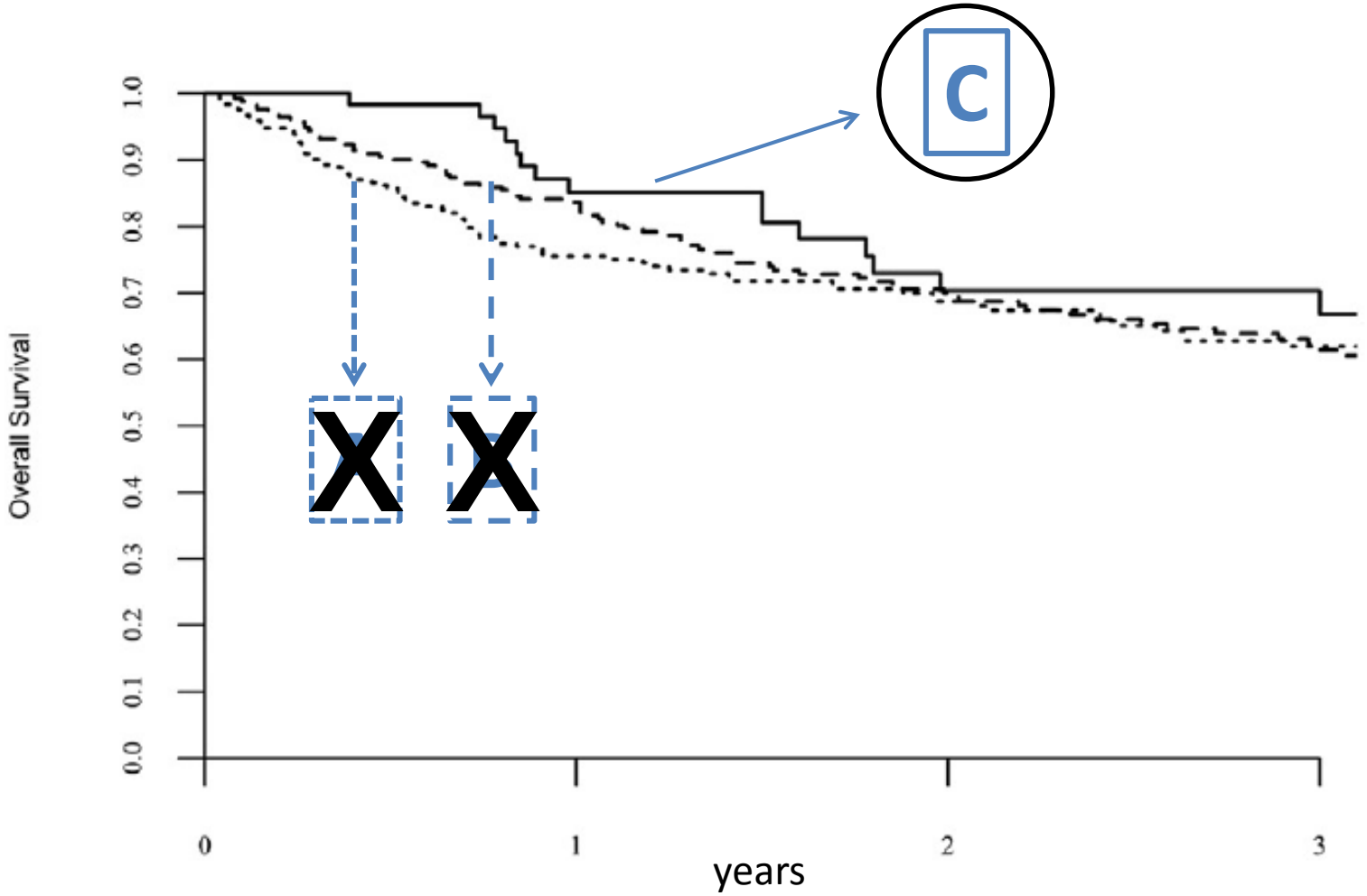
Organisatie: Maastricht Universitair Medisch Centrum

☑ Ik heb geen 'potentiële' belangenverstrengeling

☐ Ik heb de volgende mogelijke belangenverstrengelingen:

Type van verstrengeling / financieel belang	**Naam van commercieel bedrijf**
Ontvangst van subsidie(s)/research ondersteuning:	
Ontvangst van honoraria of adviseursfee:	
Lid van een commercieel gesponsord ‘speakersbureau’:	
Financiële belangen in een bedrijf (aandelen of opties):	
Andere ondersteuning (gelieve te specificeren):	
Wetenschappelijke adviesraad:	

OS



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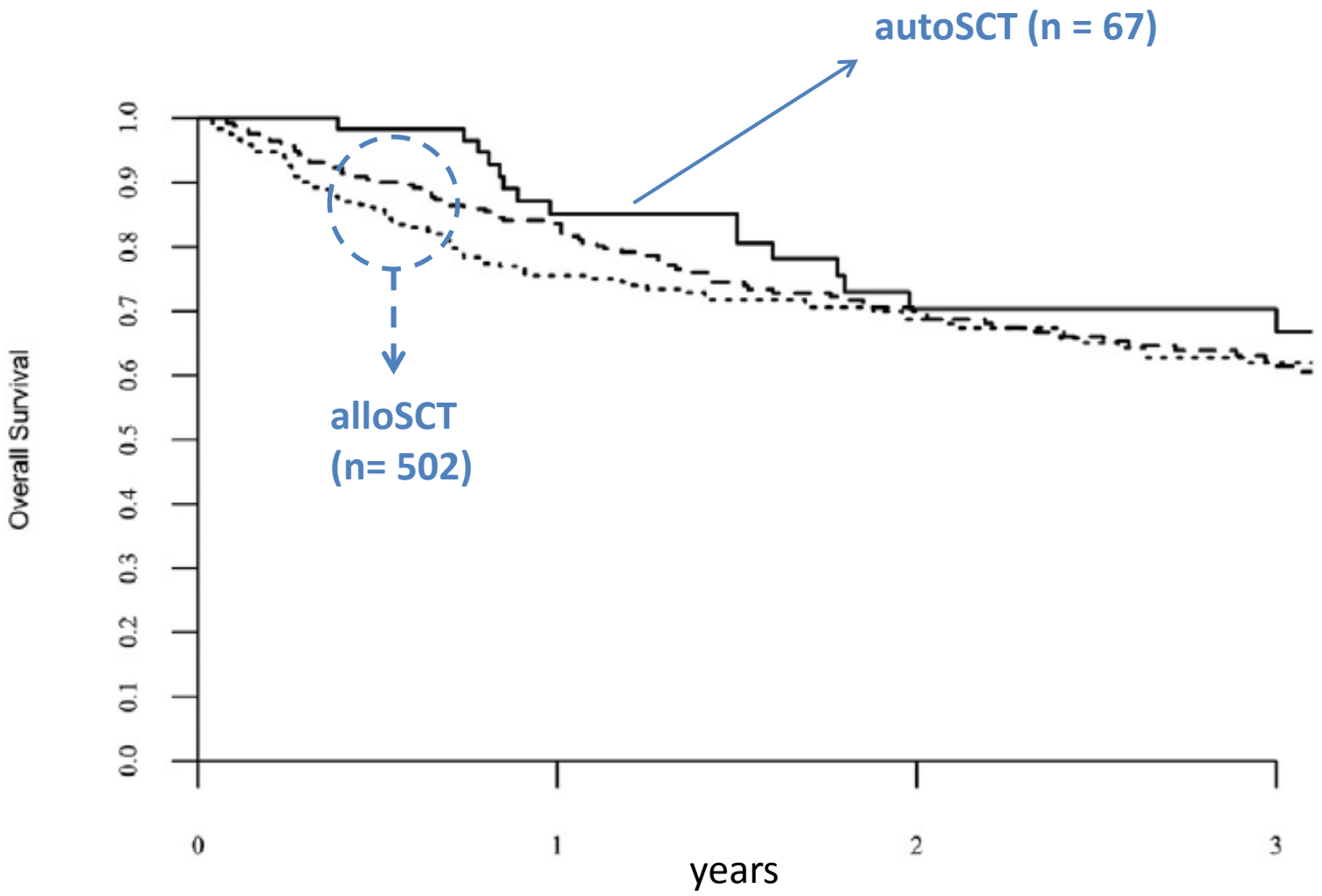
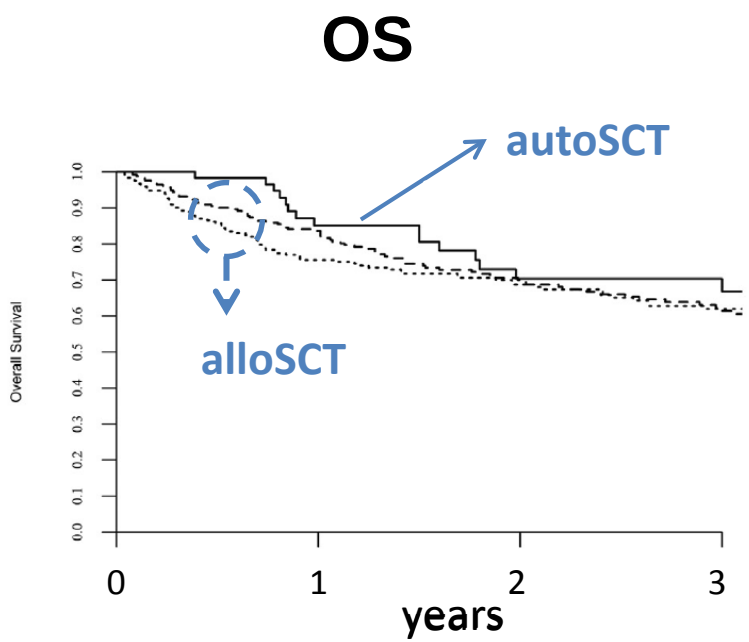

autoSCT (n = 67)
alloSCT
(n= 502)
Overall Survival
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
1
2
3
years

auto vs. allo in Molecular CR Ph+ ALL

no detectable MRD (with sensitivity of at least 0.01%)



- retrospective
- age 18 – 65 years
- 2007 – 2014
- myeloablative (>70% TBI)

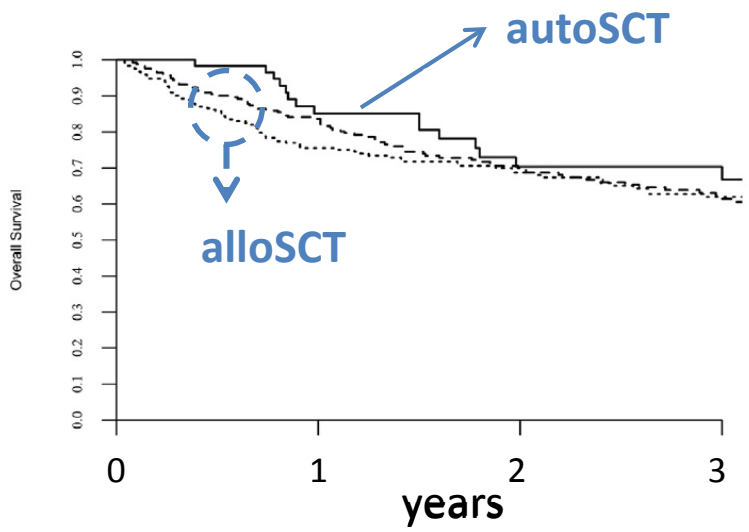
- incomplete info on
  - TKI use before and after SCT
    - mostly imatinib
  - induction schemes

Giebel, et al. European Journal of Cancer 2018, p. 73

EBMT
European Society for Blood and Marrow Transplantation

role of TKI ? 4 scenario's

OS



1. what if

- none in ***auto***SCT had TKI before and after ?

- **adding TKI will improve OS**

Giebel, et al. European Journal of Cancer 2018, p. 73

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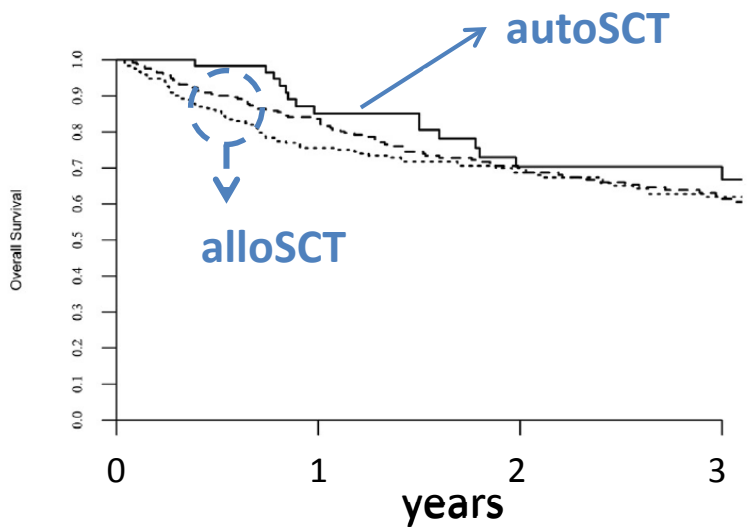
role of TKI ? 4 scenario's

OS



2. what if

- all in ***auto***SCT had TKI before and after ?
- **result is fine**

Giebel, et al. European Journal of Cancer 2018, p. 73

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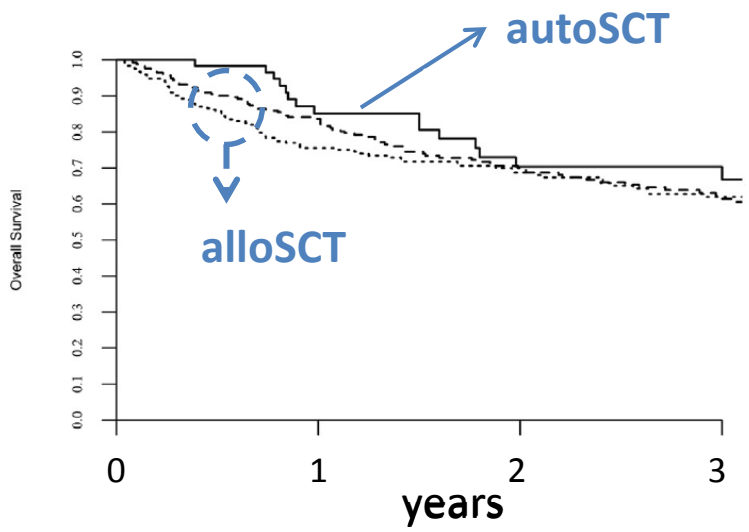
role of TKI ? 4 scenario's

OS



3. what if

- none in ***allo***SCT had TKI before and after ?

- **adding TKI improves outcome**
  - Brissot, Haematologica 2015
  - this alloSCT OS curve is superior to Brissot's study

Giebel, et al. European Journal of Cancer 2018, p. 73

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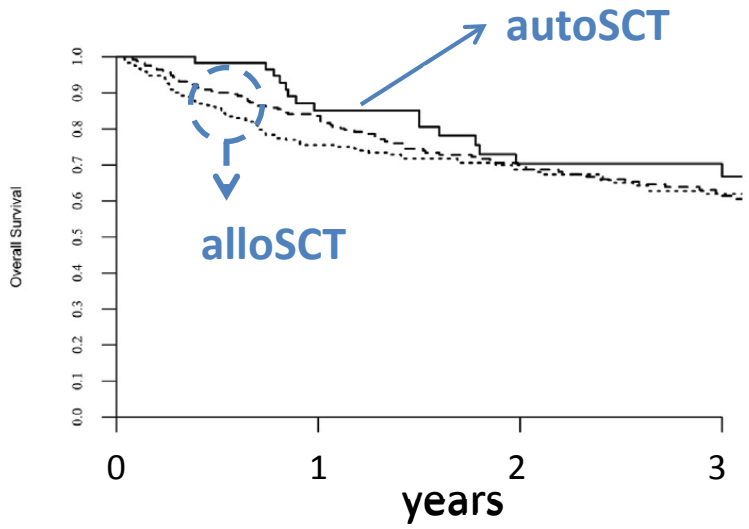
role of TKI ? 4 scenario's

OS



4. what if

- all in ***allo***SCT had TKI before and after ?
- **autoSCT +/- TKI at least equivalent**

Giebel, et al. European Journal of Cancer 2018, p. 73

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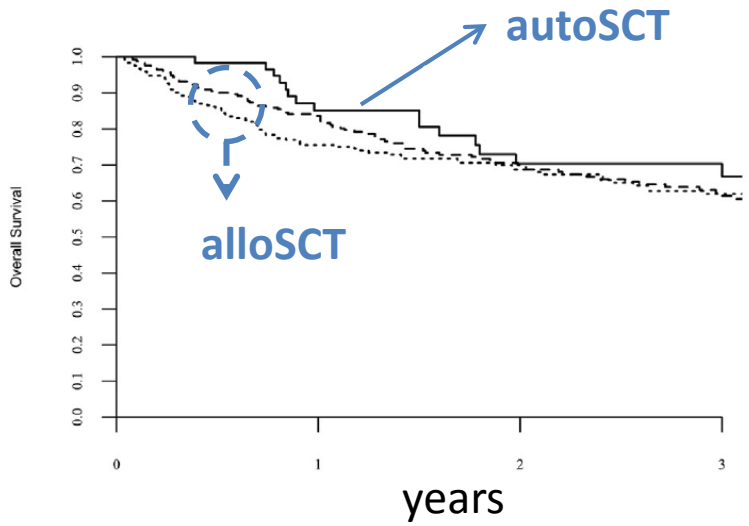
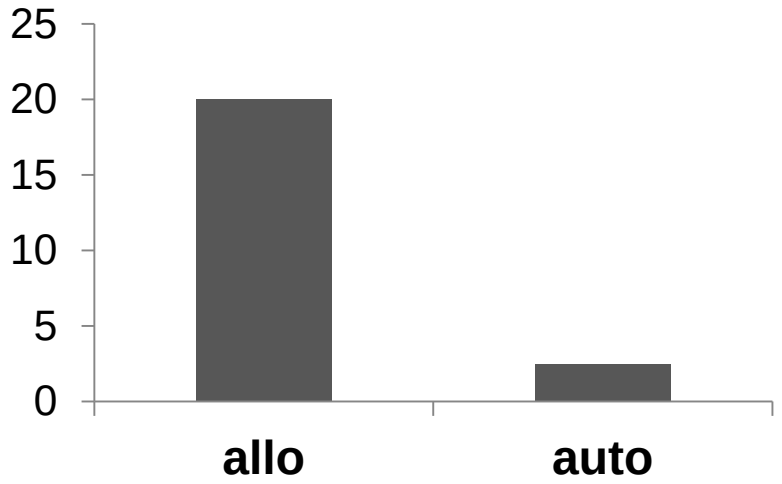
non-relapse mortality

os



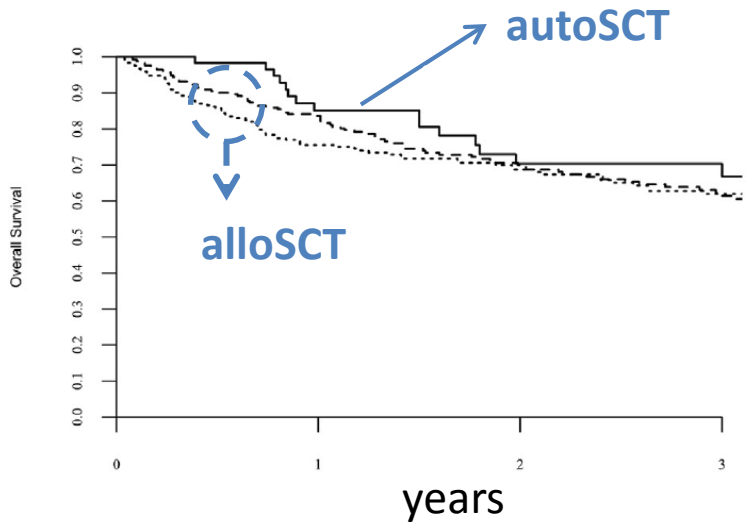
% dead for sure



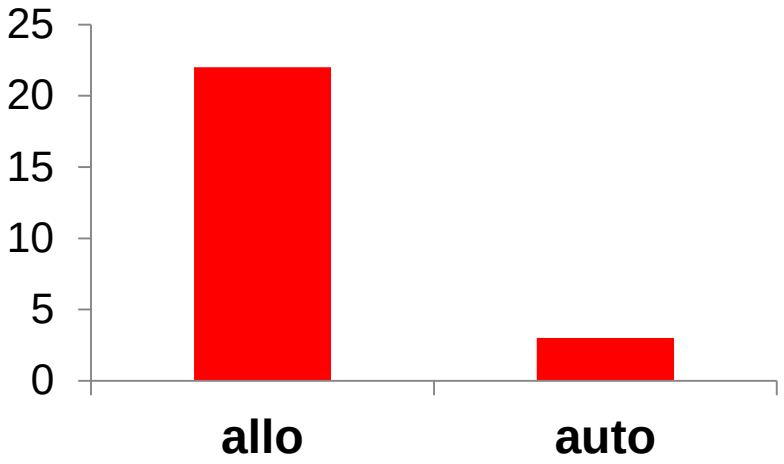
Giebel, et al. European Journal of Cancer 2018, p. 73

extensive chronic GVHD

OS



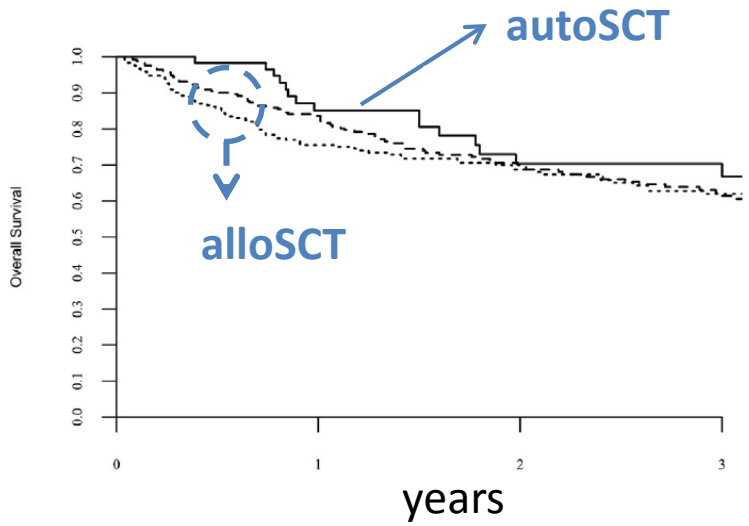
% long-term discomfort



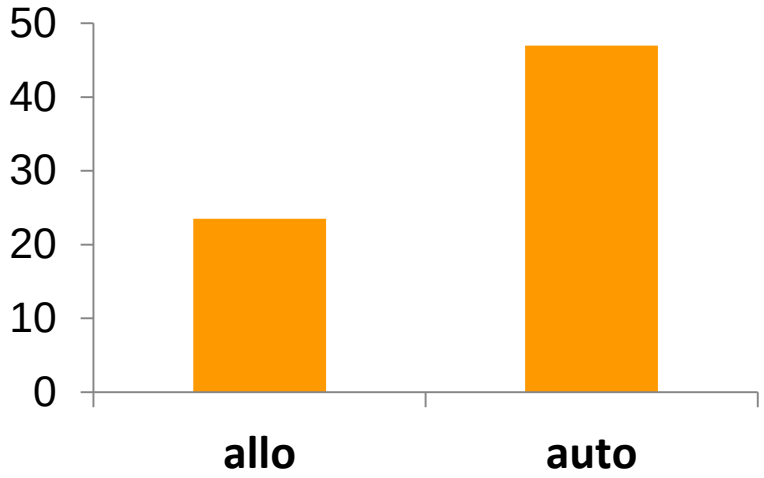
Giebel, et al. European Journal of Cancer 2018, p. 73

Relapse

OS

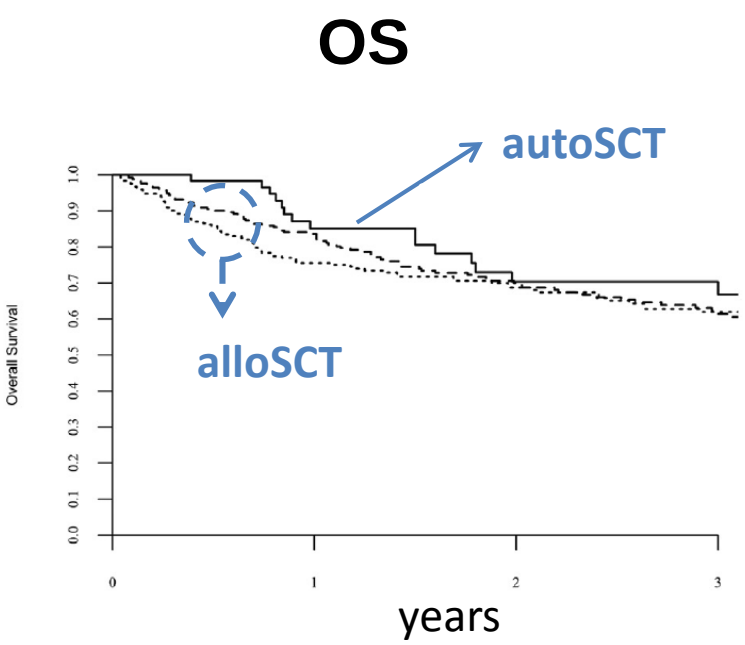


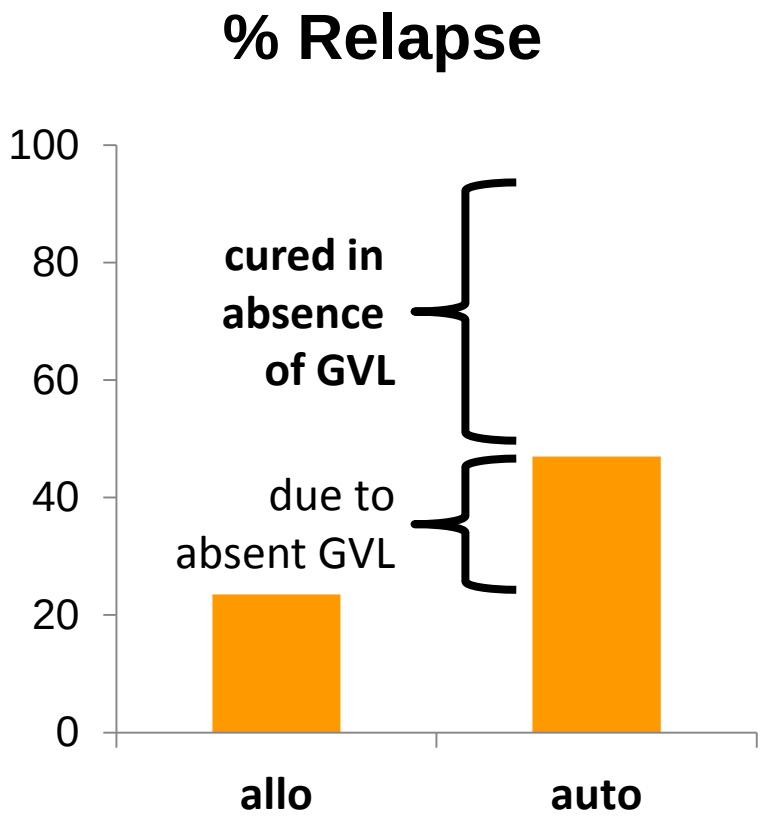
% potentially salvagable



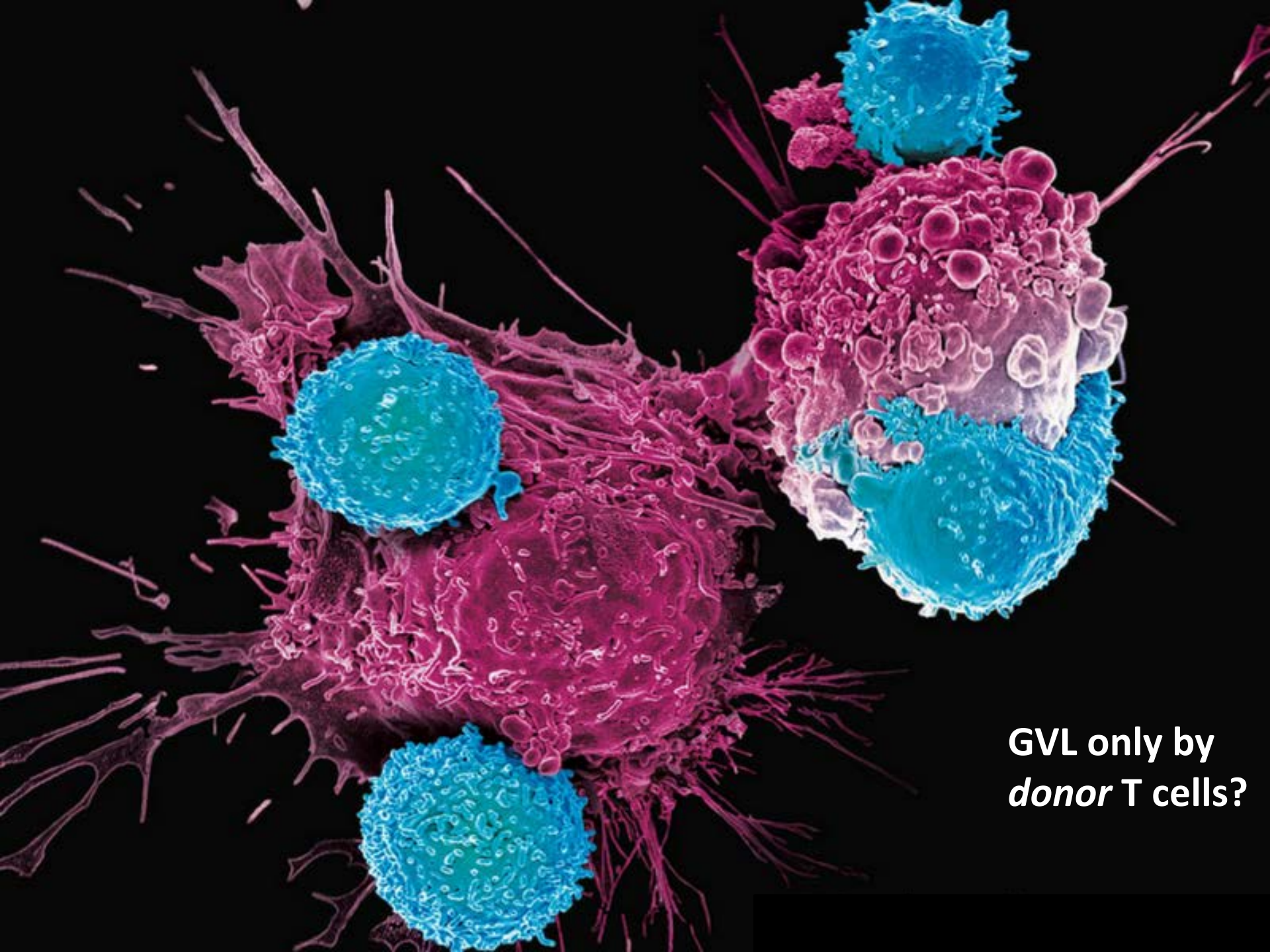
Giebel, et al. European Journal of Cancer 2018, p. 73

Graft-versus-Leukemia





20% needs to die (NRM) & 22% needs to suffer long-term discomfort for a 25% profit from GVL , without an OS difference


GVL only by
donor T cells?

GVL is not exclusively accomplished by donor lymphocytes in Ph+ ALL

Emergence of BCR-ABL–specific cytotoxic T cells in the bone marrow of patients with Ph$^+$ acute lymphoblastic leukemia during long-term imatinib mesylate treatment

*Giovanni Riva,[1] *Mario Luppi,[1] *Patrizia Barozzi,[1] Chiara Quadrelli,[1] Sabrina Basso,[2,3] Daniela Vallerini,[1] Eleonora Zanetti,[1] Monica Morselli,[1] Fabio Forghieri,[1] Monica Maccaferri,[1] Francesco Volzone,[1] Cinzia Del Giovane,[1] Roberto D'Amico,[1] Franco Locatelli,[2,3] Giuseppe Torelli,[1] †Patrizia Comoli,[2,3] and †Leonardo Potenza[1]

International Journal of Hematology
https://doi.org/10.1007/s12185-019-02789-6

CASE REPORT

Nilotinib treatment induced large granular lymphocyte expansion and maintenance of longitudinal remission in a Philadelphia chromosome-positive acute lymphoblastic leukemia

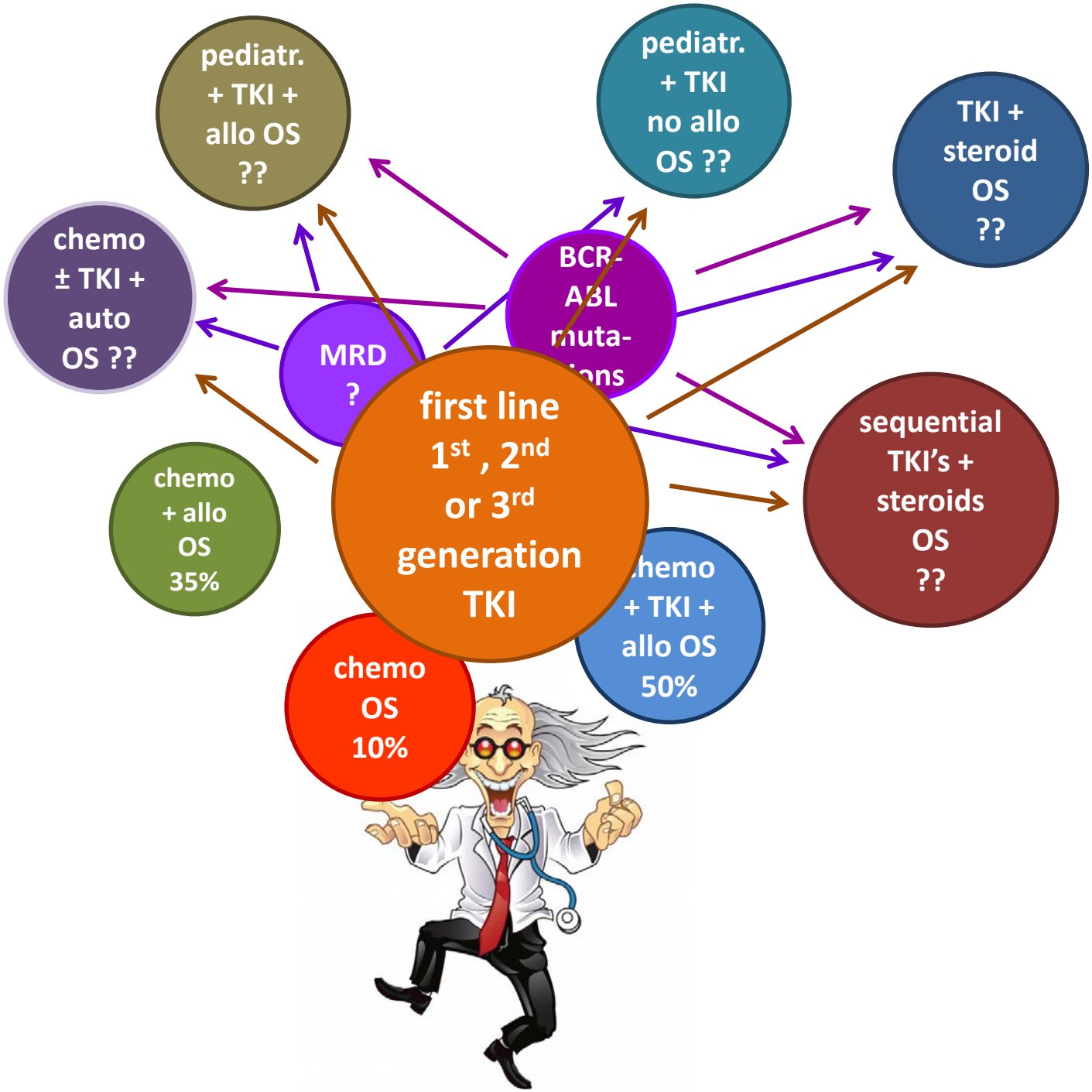
Masao Hagihara[1] · Jian Hua[1] · Morihiro Inoue[1] · Tomoyuki Uchida[1] · Shiro Ide[1] · Shin Ohara[1] · Tomoiku Takaku[2]

REVIEW

Cancer Biology & Therapy 15:3, 247–255; March 2014;

Large granular lymphocytosis during dasatinib therapy

Zhi-Yuan Qiu, Wei Xu*, and Jian-Yong Li*


pediatr. + TKI + allo OS ??
pediatr. + TKI no allo OS ??
TKI + steroid OS ??
chemo ± TKI + auto OS ??
MRD ?
BCR-ABL muta-
first line 1st , 2nd or 3rd generation TKI
sequential TKI's + steroids OS ??
chemo + allo OS 35%
hemo + TKI + allo OS 50%
chemo OS 10%

How to achieve Complete Molecular Remission ?

- impact of chemo intensity?
- impact of TKI choice?

RCT

reduced vs. intense chemo + imatinib

age 18 - 59

Chalandon et al., Blood 2015, p. 3711

RCT

reduced vs. intense chemo + imatinib

reduced intensity

- n = 135

hyperCVAD

- n = 133

Chalandon et al., Blood 2015, p. 3711

RCT

reduced vs. intense chemo + imatinib

reduced intensity

- n = 135
- 66% *BCR-ABL/ABL* ≤ 0.1%

hyperCVAD

- n = 133
- 65% BCR-ABL/ABL ≤ 0.1%

Chalandon et al., Blood 2015, p. 3711

RCT

reduced vs. intense chemo + imatinib

reduced intensity

- n = 135
- 66% *BCR-ABL/ABL* ≤ 0.1%
- 29% *BCR-ABL/ABL* ≤ 0.01%

hyperCVAD

- n = 133
- 65% BCR-ABL/ABL ≤ 0.1%
- 23% BCR-ABL/ABL ≤ 0.01%

Chalandon et al., Blood 2015, p. 3711

RCT

reduced vs. intense chemo + imatinib

reduced intensity

- n = 135
- 66% *BCR-ABL/ABL* ≤ 0.1%
- 29% *BCR-ABL/ABL* ≤ 0.01%
- 2% NRM (day 60)

hyperCVAD

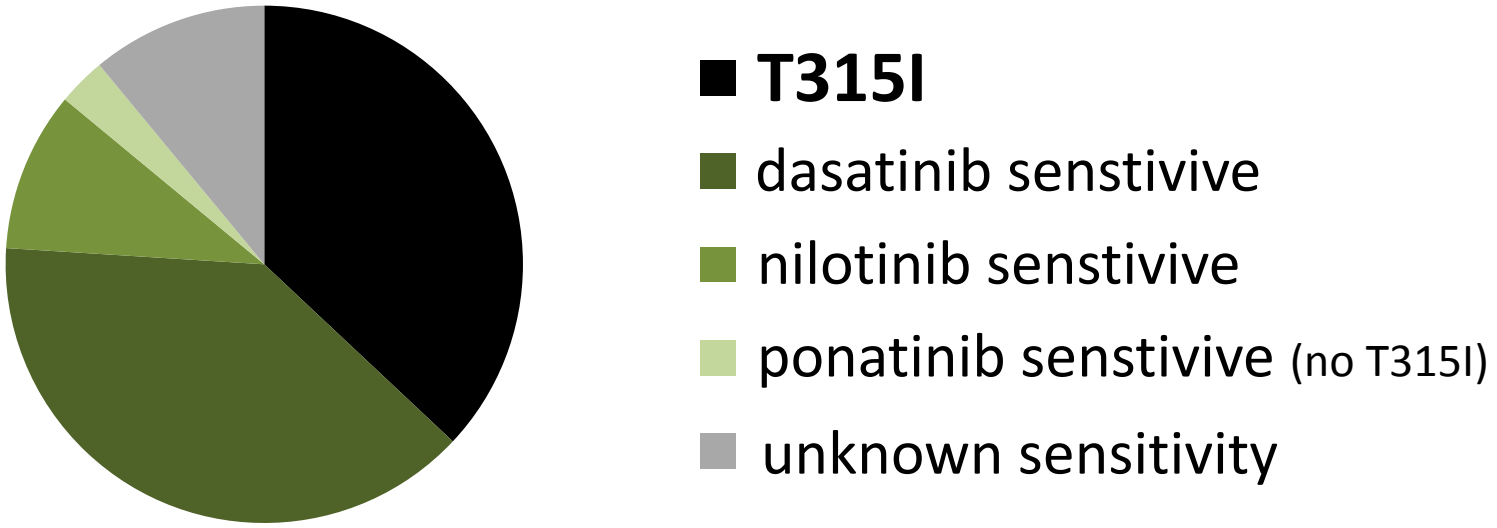
- n = 133
- 65% BCR-ABL/ABL ≤ 0.1%
- 23% BCR-ABL/ABL ≤ 0.01%
- 9% NRM (day 60)

Chalandon et al., Blood 2015, p. 3711

TKI resistance

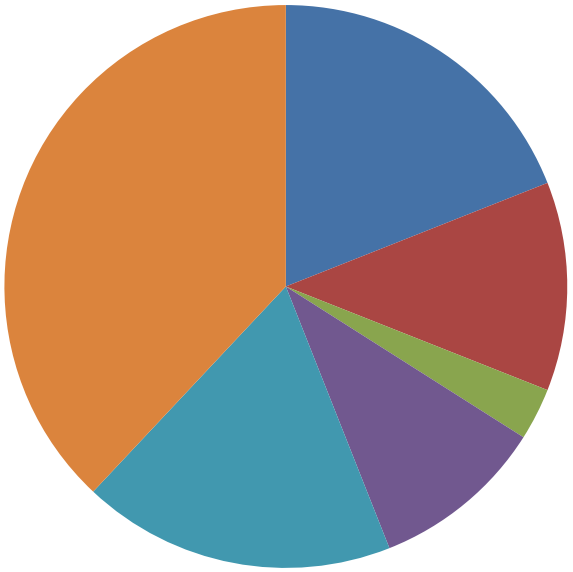
- BCR-ABL mutations
- other mechanisms

BCR-ABL mutations in 189 imatinib resistant Ph+ ALL patients



Soverini, Cancer, 2014

BCR-ABL mutations in 68 imatinib & dasatinib resistant Ph+ ALL patients



- wt → wt
- wt → new mutation
- mutation → wt
- mutation → same mutation
- mutation → new mutation
- mutation → new + pre-existing mutation

30% T315I

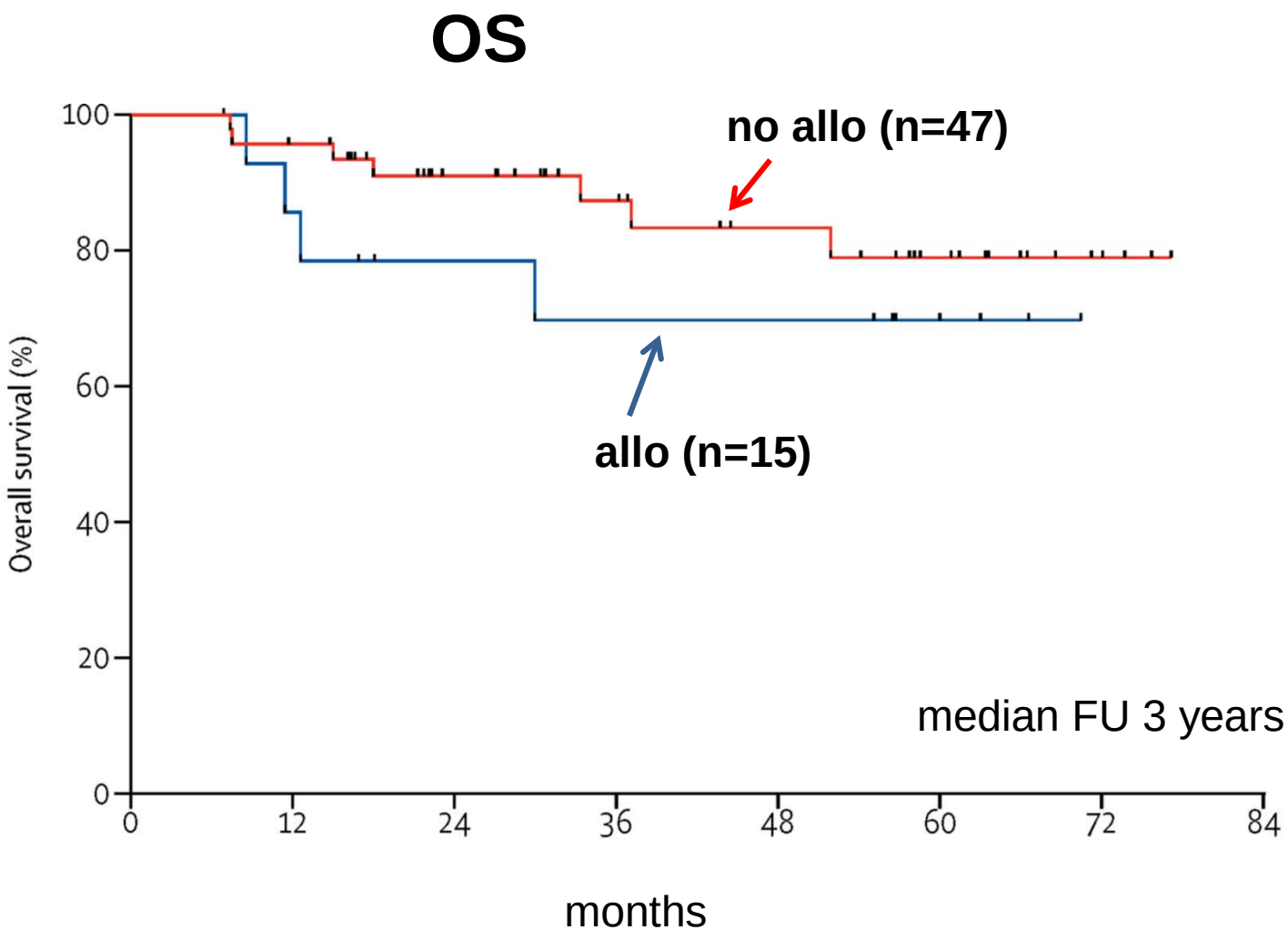
Soverini, Cancer, 2014

how to improve Complete Molecular Remission rate?

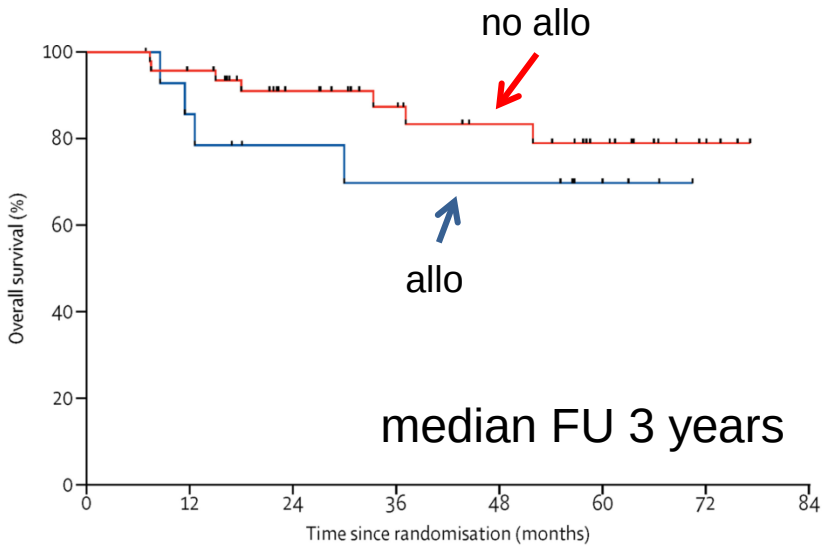
- imatinib +/- chemo
  - around 20%
- dasatinib +/- chemo
  - around 20%
- nilotinib + chemo
  - 60%
- ponatinib
  - 60-80%

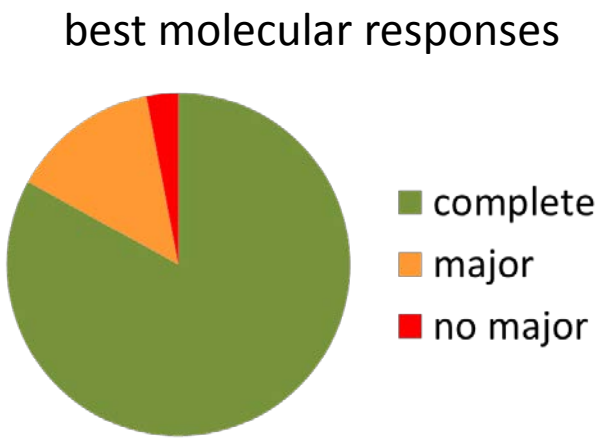
Soverini, Bassan, Lion, review, J Haematol & Oncol 2019

would you propose alloSCT?



hyperCVAD + ponatinib





ponatinib handling

- risk-adapted dosing
  - no cardio-vascular deaths
  - all non-relapsed patients remained on ponatinib

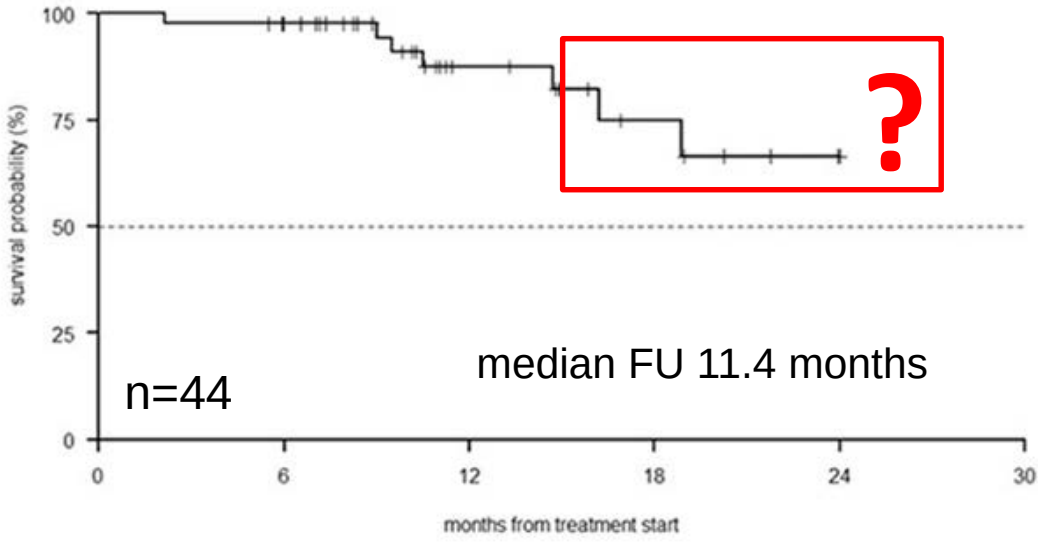
8 relapses (1 after allo)

- 3 while on ponatinib
  - 2x Q255K mutation
  - no T315I
- 4 after switch to other TKI
  - 2x T315I
- 1 while off TKI

Jabbour et al., Lancet Haematol 2018

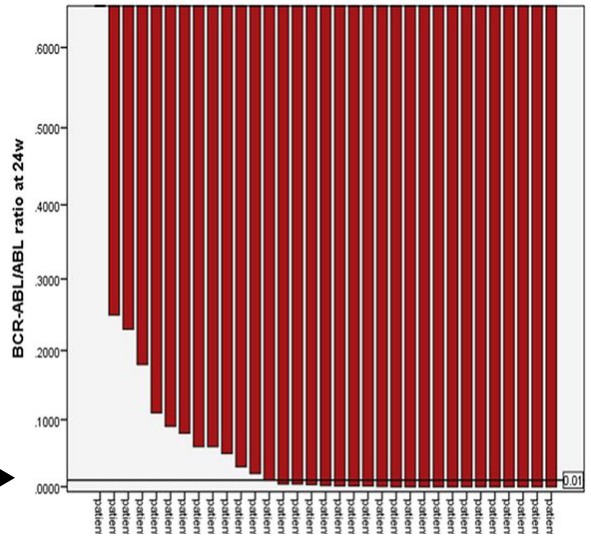
chemotherapy needed?
only steroids with Ponatinib

OS



BCR-ABL/ABL ratio

0.01% →



at 24 weeks

Median age 68 years (range 27-85)

Martinelli et al., ASH 2017 abstract

Conclusions

- highest CMR rates with ponatinib or nilotinib in 1st line
  - how applicable in NL?
- early Complete Molecular Remission seems relevant
  - early switch from 1st via 2nd to 3rd generation TKI ?
- no allo in 1st line Complete Molecular Remitted Ph+ ALL
  - chemo + TKI ?
  - autoSCT + TKI ?
  - what TKI?