Developmental Therapeutics Case Studies Resistance in drug development – two scenarios

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Outline

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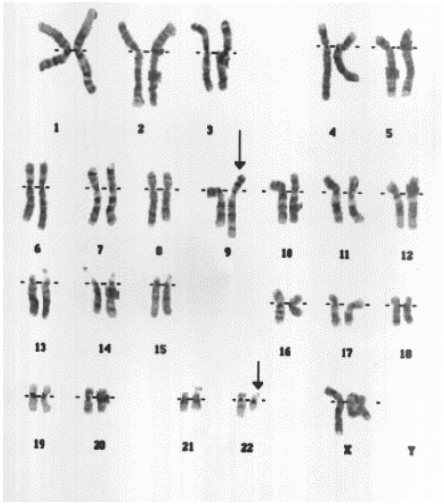
Northern Institute for Cancer Research

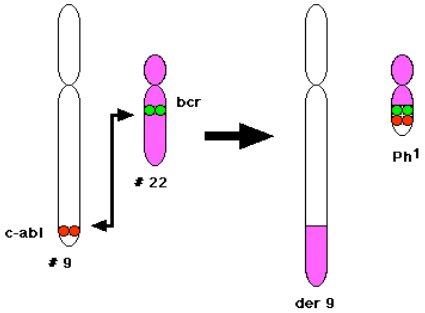
- Imatinib in CML and GIST – late emergence of resistance
- BRAFi in melanoma – rapid resistance
- Two very different clinical scenarios driving drug development?

Imatinib in CML and GIST
– late emergence of resistance

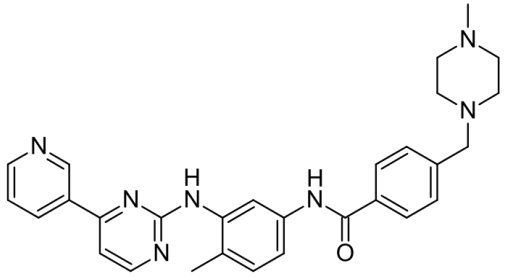
Disease defining mutation
Philadelphia Chromosome

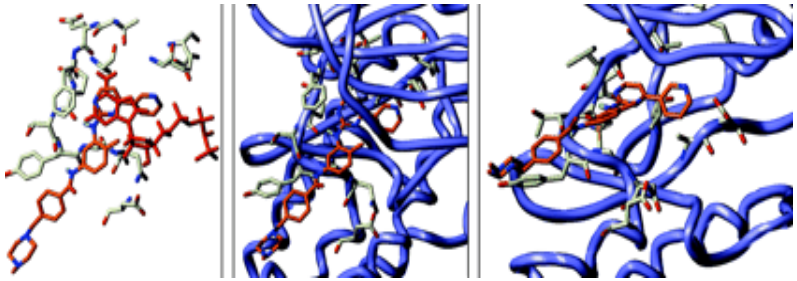
- Present in 95% of chronic myeloid leukaemia and 5-10% acute lymphoblastoid leukaemia, BcrAbl re-arrangement leading to an active kinase
- Imatinib competes at ATP binding site and inhibits phosphorylation by the kinase





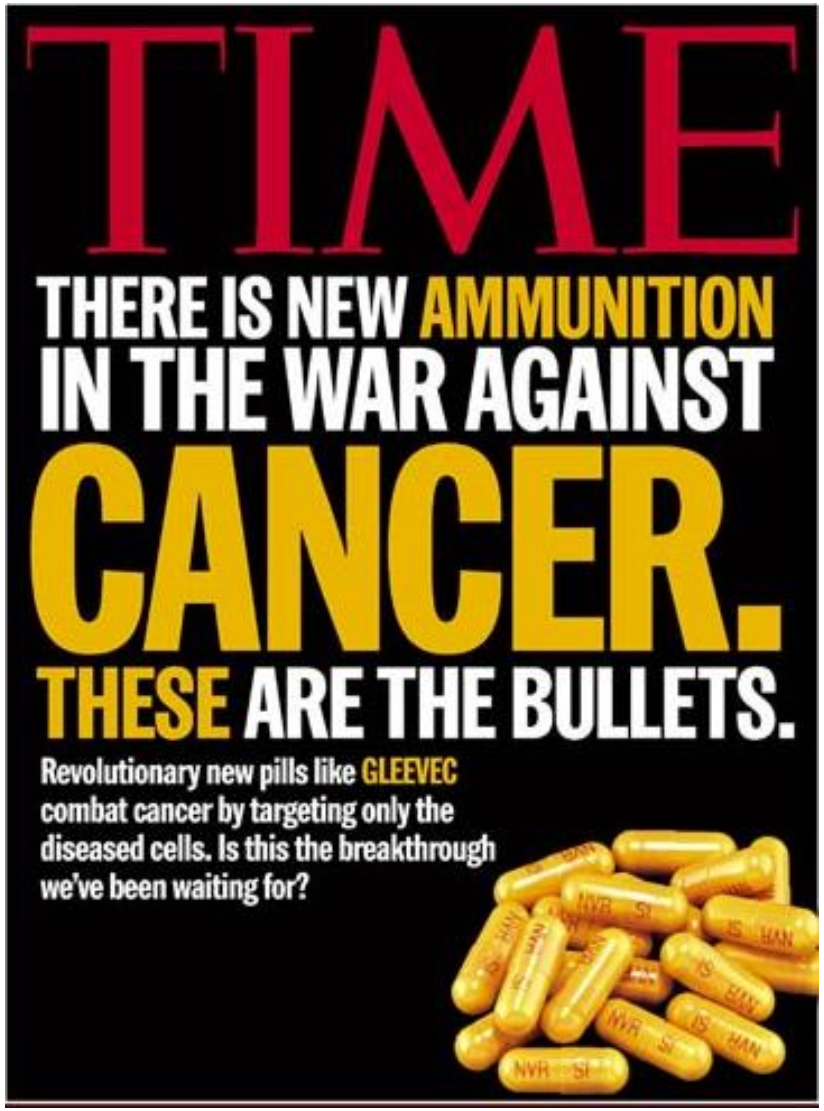
Reciprocal translocation between one # 9 and one #22 chromosome forms an extra-long chromosome 9 ("der 9") and the Philadelphia chromosome (Ph^1) containing the fused abl-bcr gene. This is a schematic view representing metaphase chromosomes.





The poster child of targeted therapy

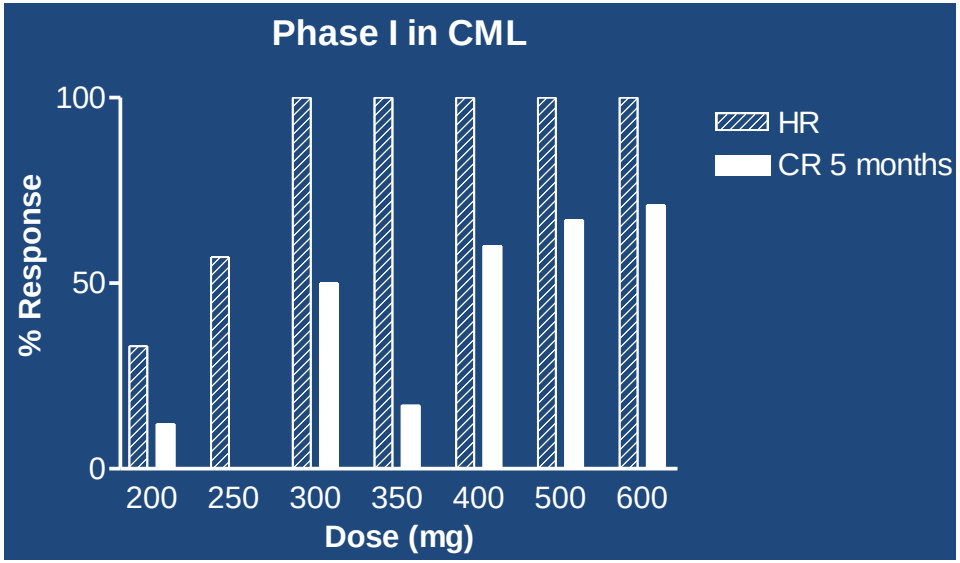
2001



Early trials in CML

- Phase I study in chronic, IFN refractory CML
- 25 to 600mg daily (n=61)
- Side effects
  - Anaemia
  - Nausea/indigestion
  - Cramps/arthralgia/oedema
- No MTD
- Haematological response
- In 31/31 >300mg

Drucker, ASH 1999
Buchdunger, AACR 2000



Duration of response in CML

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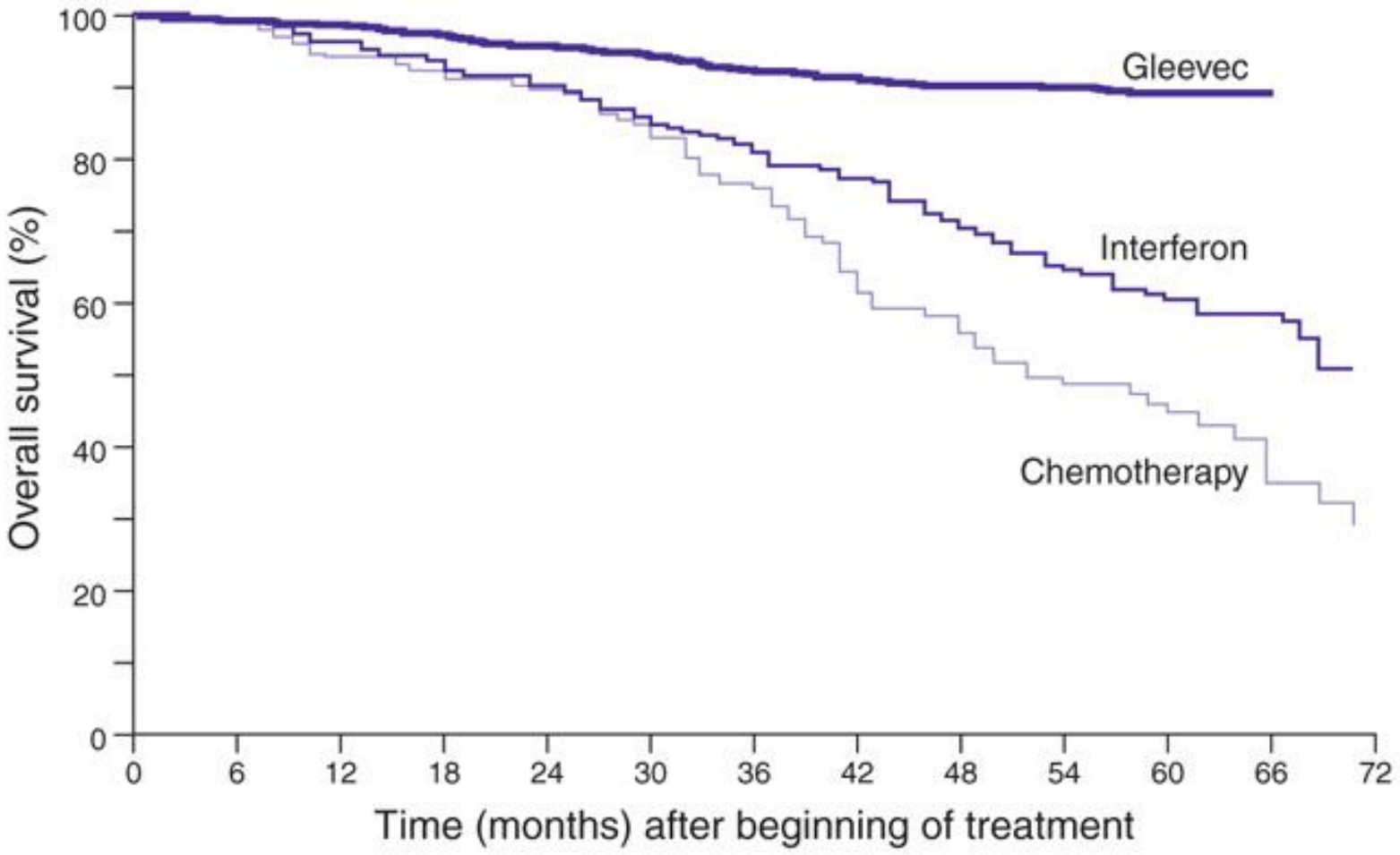

Resistance is due to acquired mutations in BCR-ABL

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- Treatment options as resistance emerges
  - Increase imatinib dose from 600 mg to 800 mg
  - Dasatinib (TKI) licenced 2006 for imatinib resistant CML
  - Nilotinib (TKI) licenced 2007 for imatinib resistant CML
  - Neither has activity if tumour acquires T315I mutation

GIST

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- Rare STS with incidence of 15 per million, median age at diagnosis ~60, most commonly found in the stomach but can be anywhere in GI tract
- Most GISTs have a mutation in the *KIT* proto-oncogene (*cKIT*) that translates into a gain-of-function constitutive activation of the KIT kinase
- Overexpress the KIT protein, a transmembrane tyrosine kinase receptor for stem-cell factor (SCF). Immunohistochemical detection of cKIT overexpression (CD117 antigen) considered diagnostic
- Small proportion have mutations in PDGFR

EORTC Early Clinical Studies

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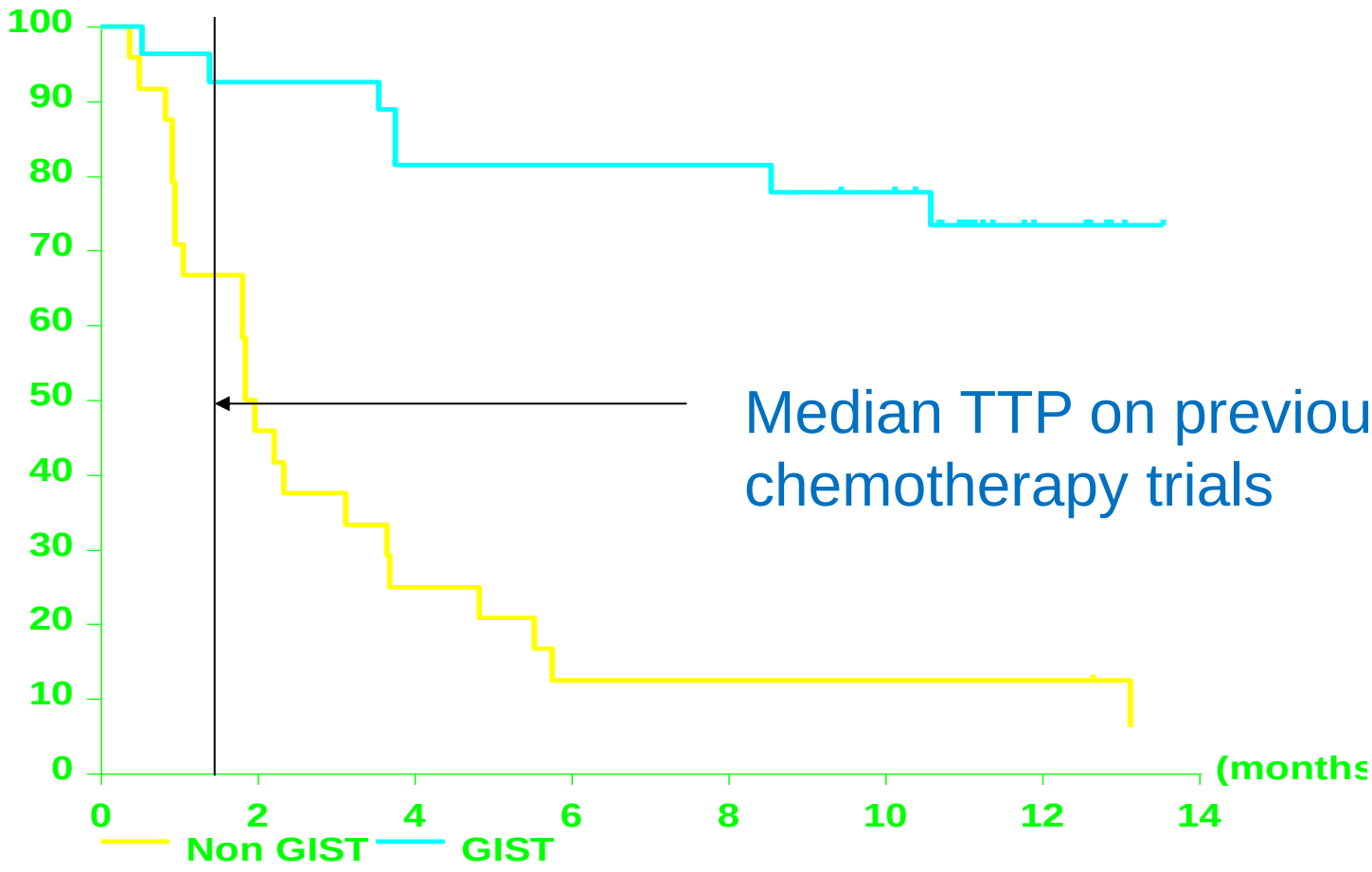
- Phase I
  - Dose escalation in STS (range 400mg to 1000 mg)
  - 36/40 patients in study had GIST
  - 69% objective response,
  - 81% progression free at a year.
- Phase II
  - 800 mg o.d.
  - 24 patients with GIST, 24 other STS
  - 71% objective response rate in GIST
  - 73% GISTs were progression free at 12 months
- No activity in non-GIST STS
- Few severe or very severe side effects

- **No phase III study required for registration**

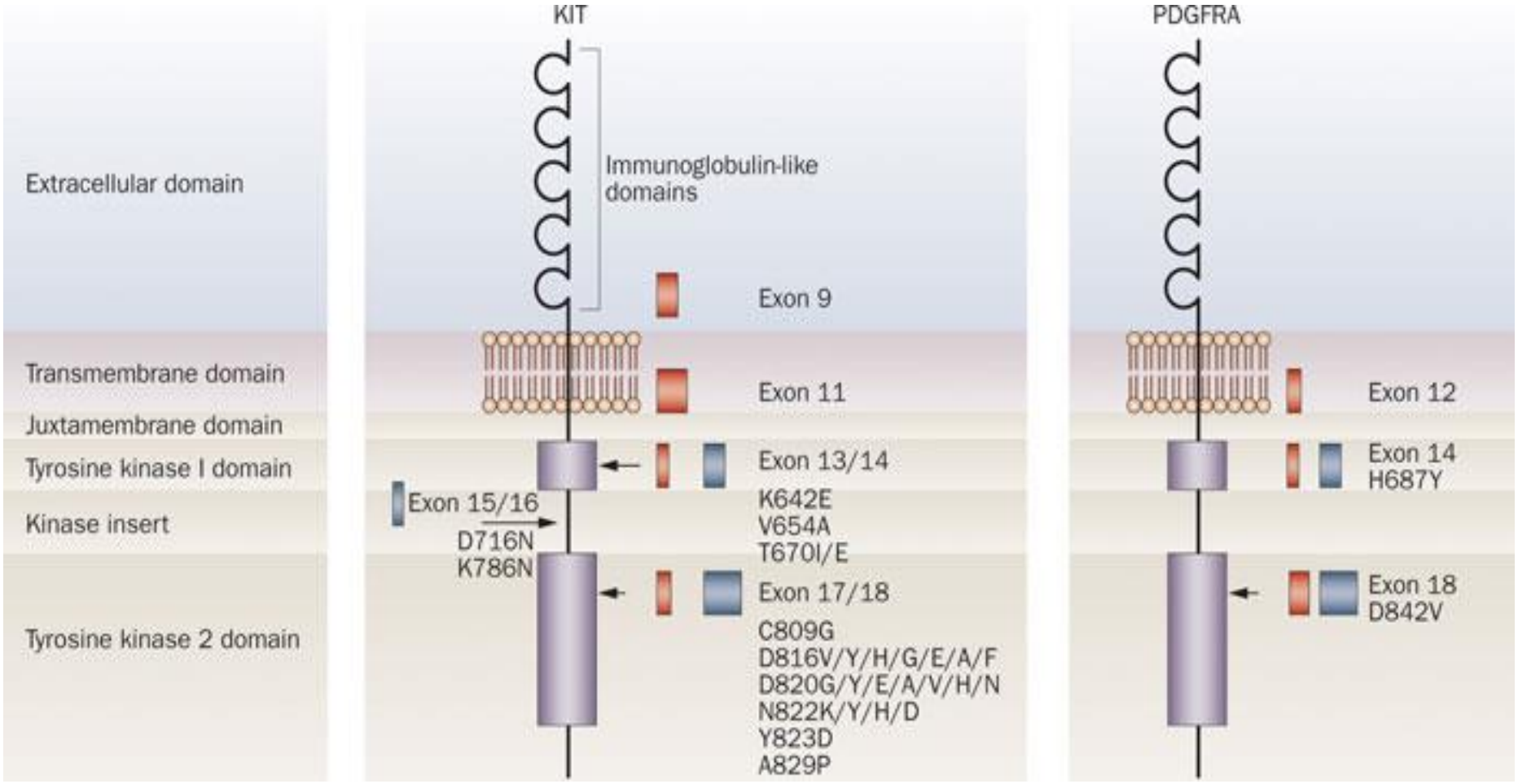
Van Oosterom et al. Lancet - October 2001
Judson et al. Proc ASCO 2002

EORTC Phase II: Time to Progression



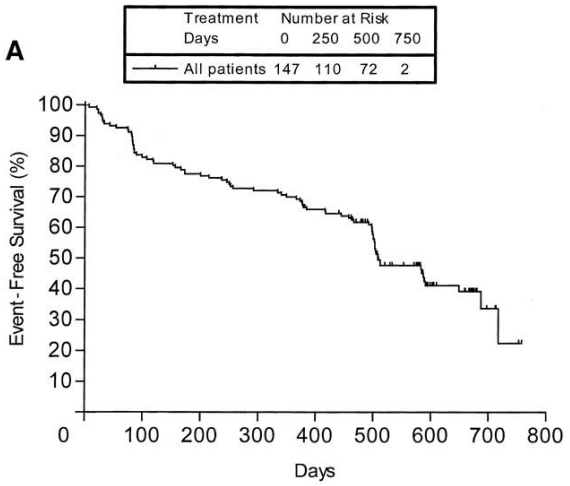
Judson et al. Proc ASCO 2002

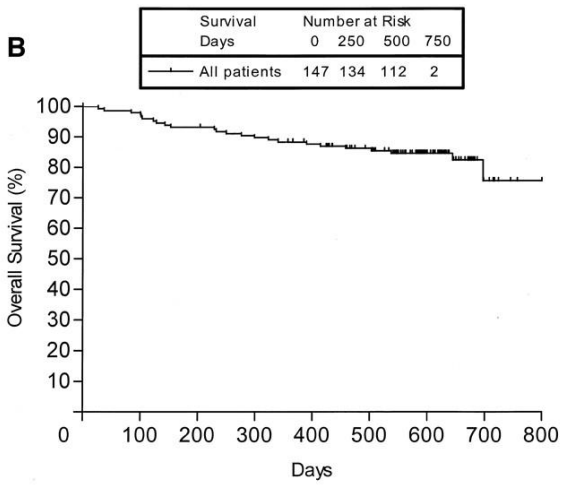
KIT and PDGRF structures and mutation sites



Gastrointestinal stromal tumor (GIST) kinase genotype correlates with event-free survival and overall survival.

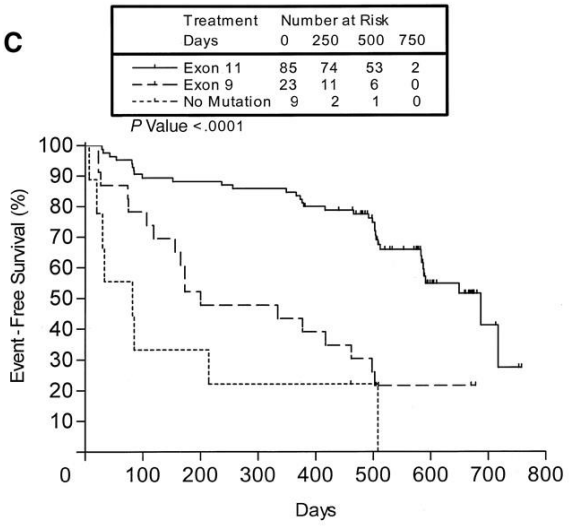
Overall PFS

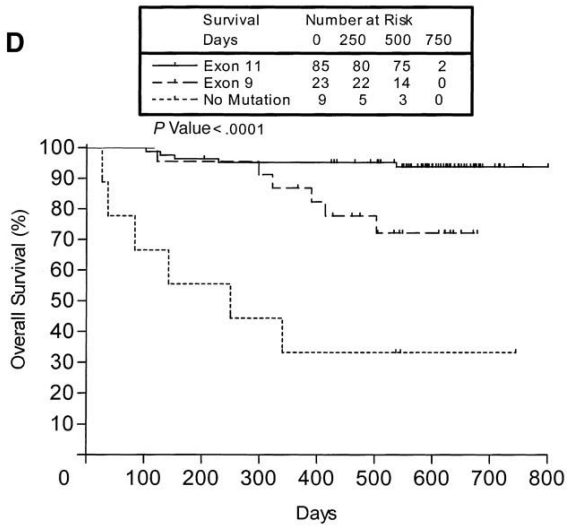




Overall OS

PFS by mutation





OS by mutation

Heinrich M C et al. JCO 2003;21:4342-4349

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Resistance in GIST

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- Development of mutations in the driver kinase
  - Increase the dose 400 mg to 800 mg
  - Sunitinib licensed in GIST 2006
  - Nilotinib effective against Exon 17 mutation
  - Dasatinib not FDA approved in this indication
- Development of further agents
  - anti-KIT MAB
  - HDACi, Hsp90i, mTORi

Conclusion

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Very effective first in class agent for both diseases

Slow emergence of resistance (years)

Second generation drugs emerged after 5 years

No significant clinical advances in targeting any other aspect of tumour biology

BRAFi in melanoma

– rapid resistance and subsequent drug sequencing research

RAS-RAF-MEK-ERK pathway

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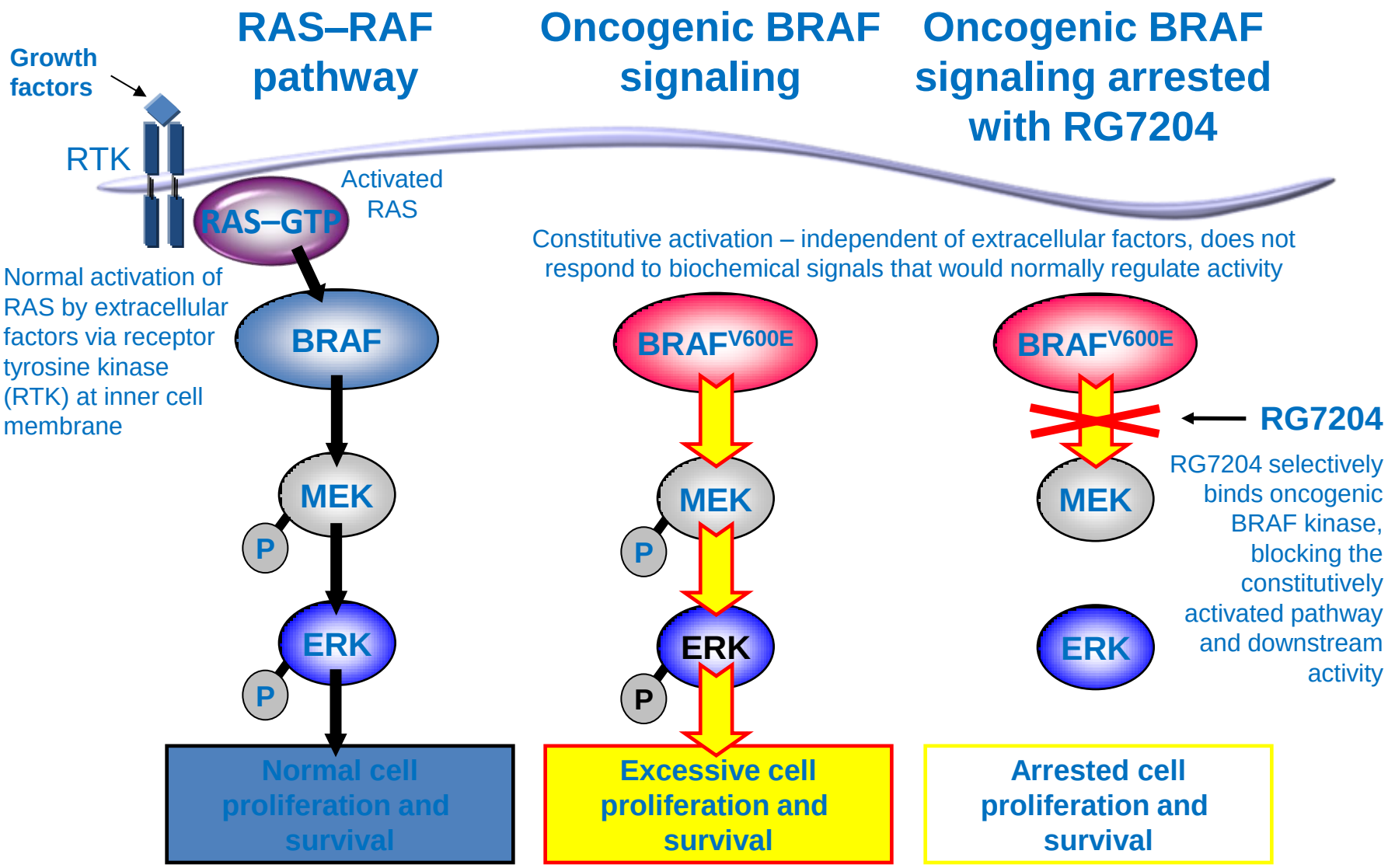

Dramatic advance in melanoma treatment

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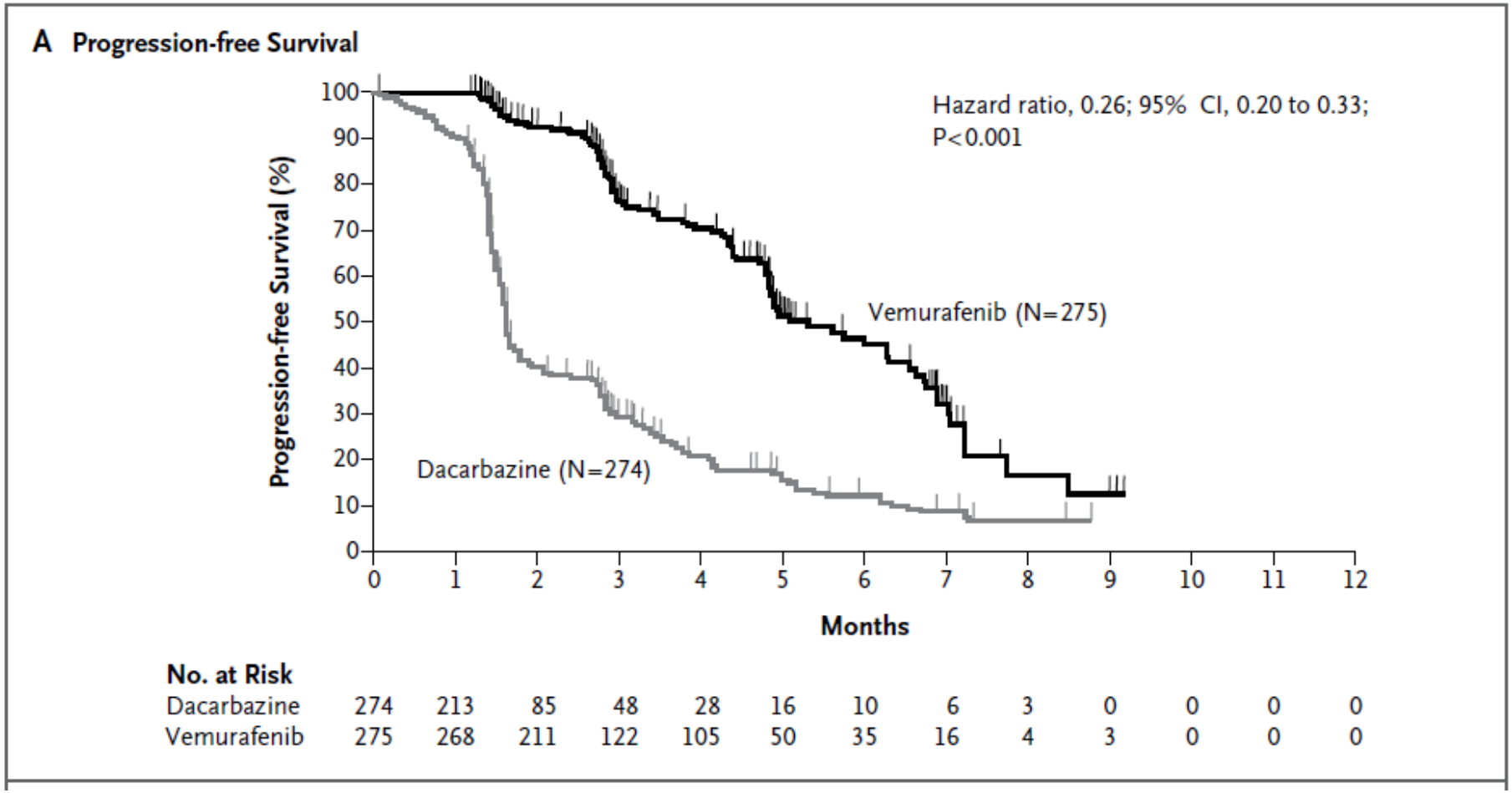
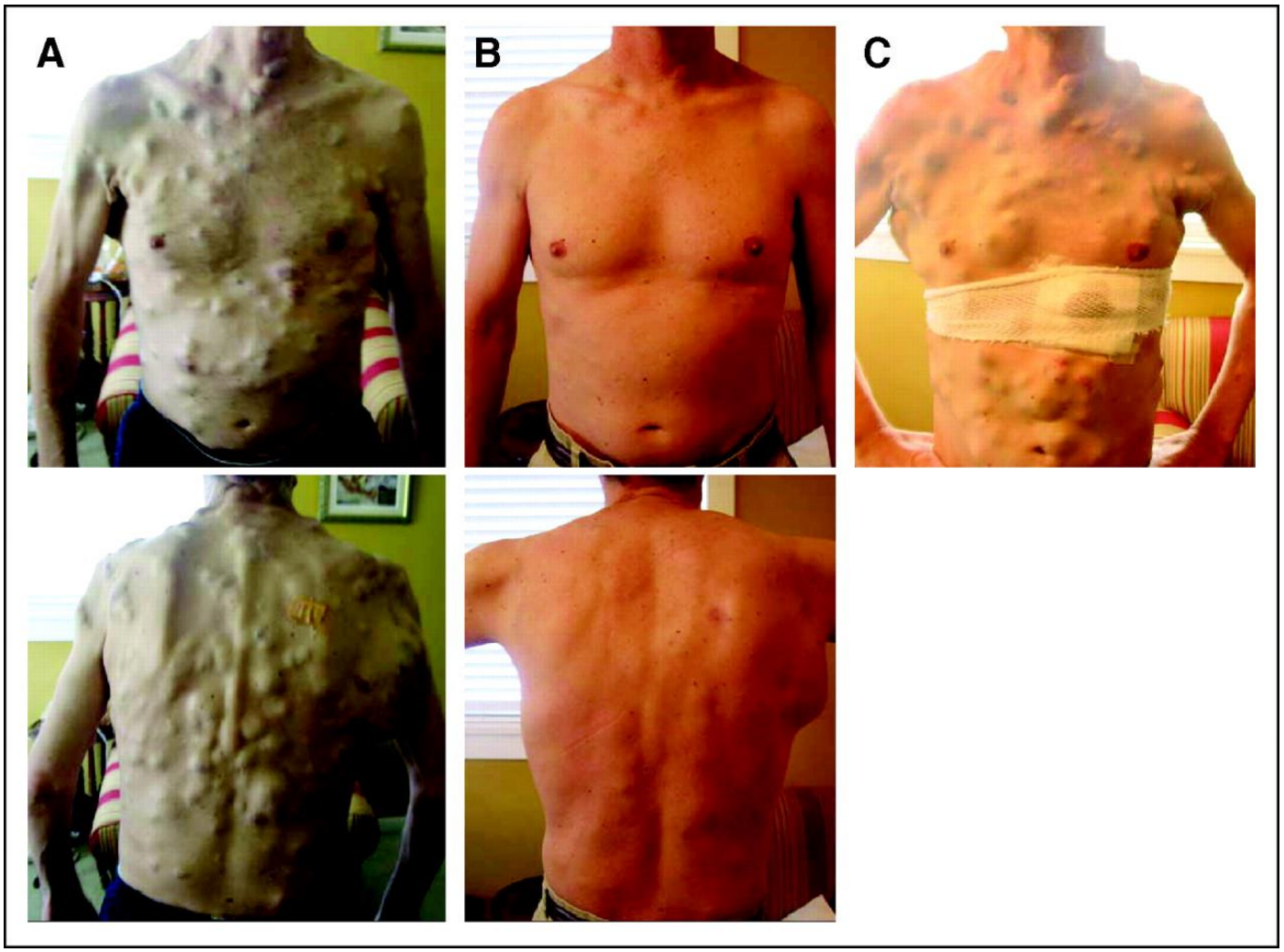


Vemurafenib licence 2011, dabrafenib licence 2013

A 38-year-old man with BRAF-mutant melanoma and miliary, subcutaneous metastatic deposits.

Baseline 15 weeks 23 weeks



Wagle N et al. JCO 2011;29:3085-3096

Targeting RAS/RAF/MEK and PI3K to overcome resistance

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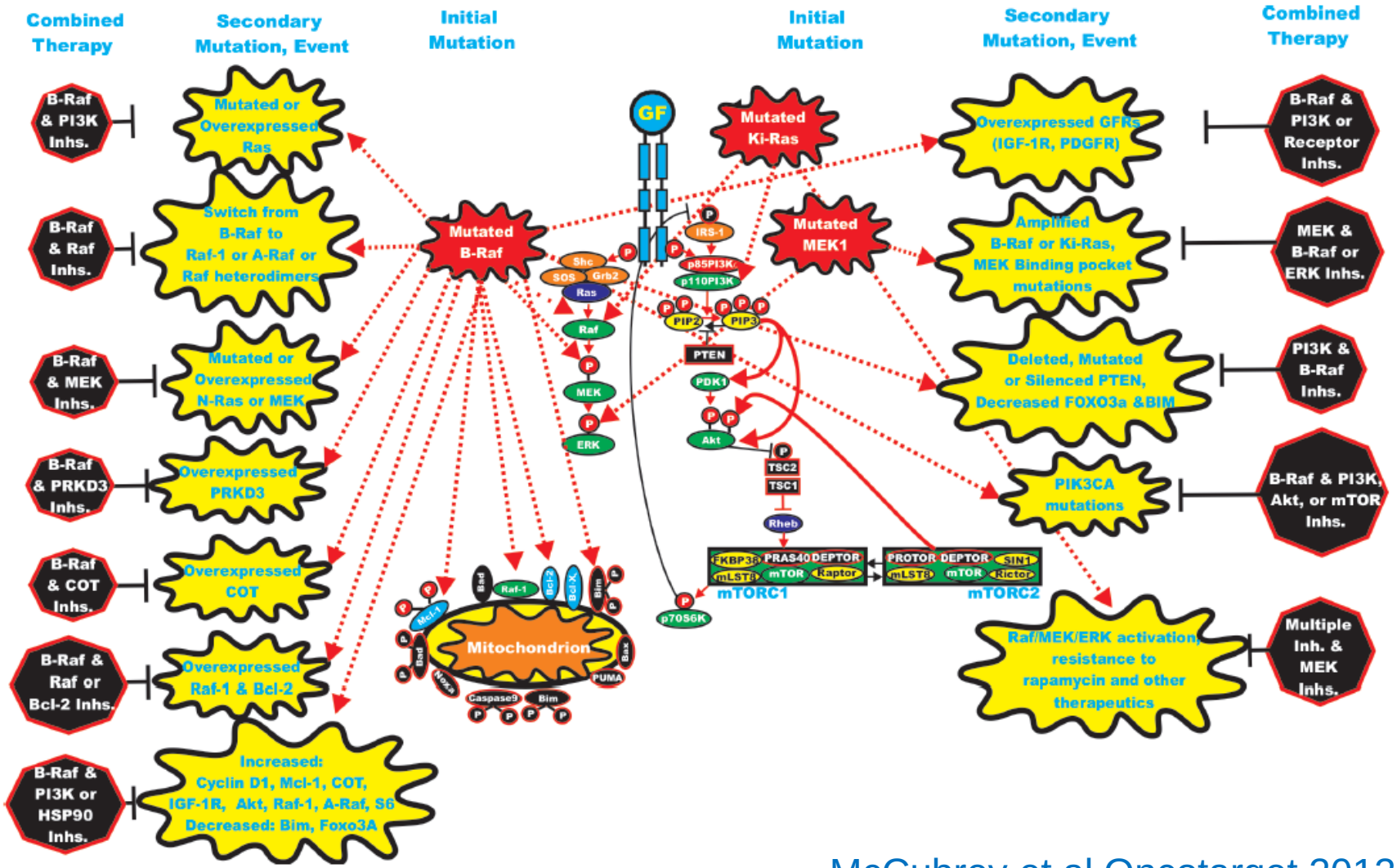

McCubrey et al Oncotarget 2012

Sequencing MEKi *with* rather than *after* BRAFi (dabrafenib)

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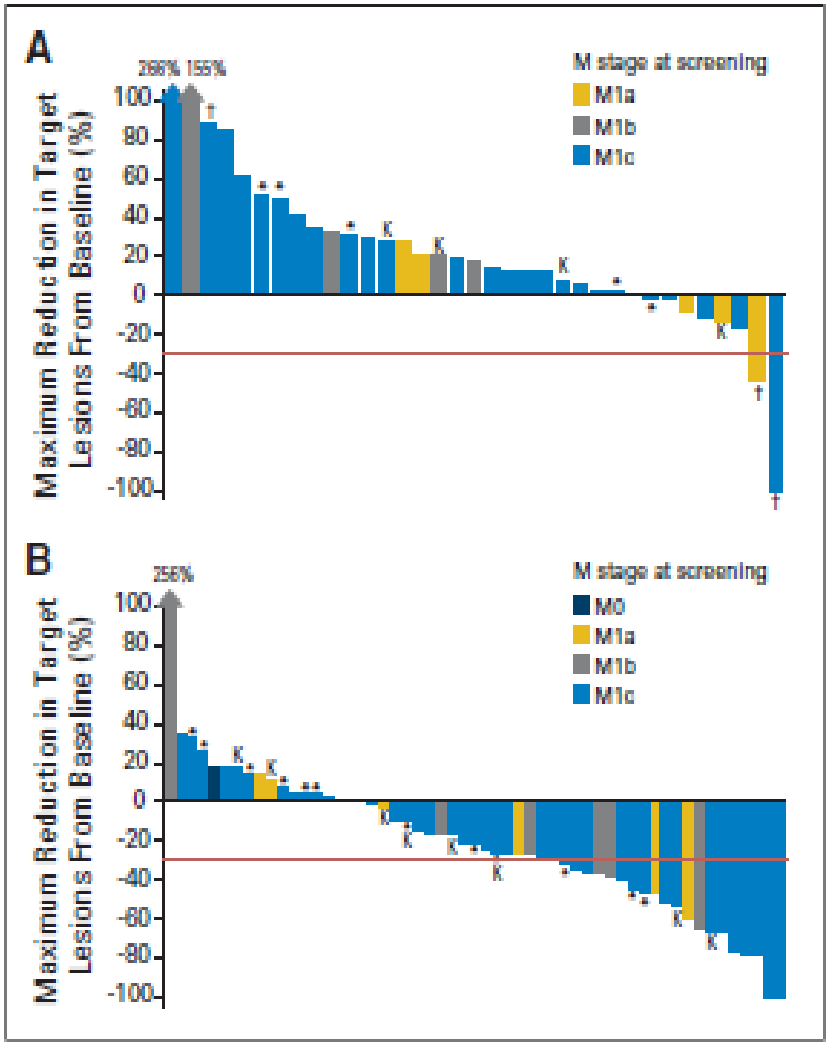
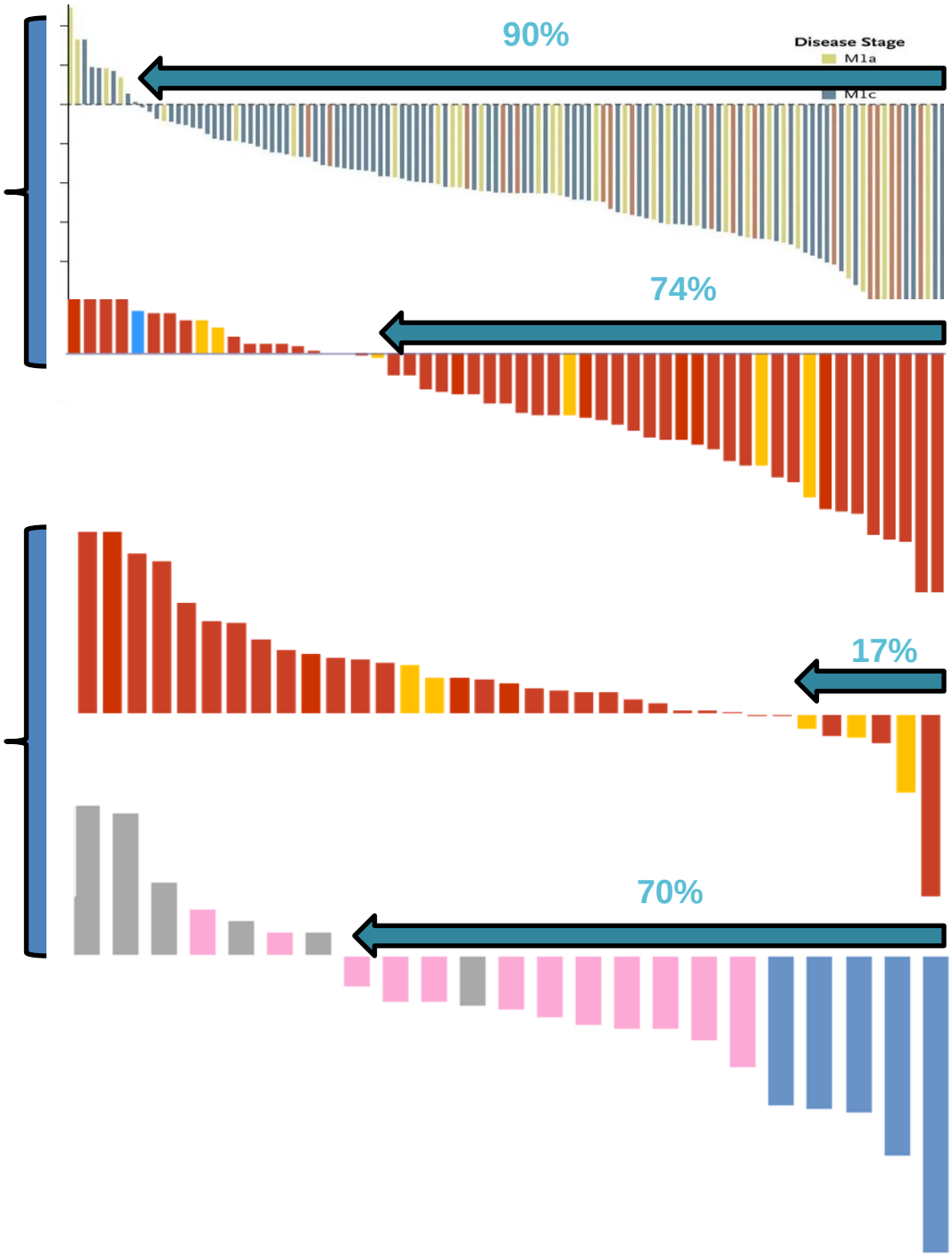
Group A – after BRAF1

Arm closed as too low RR

Group B – BRAFi naïve





BRAFi (Vem) Vs DTIC
BRAFi Naïve Pts
Chapman (BRIM 3) NEJM 2011

MEKi (Trametinib) v Chemo
BRAFi Naïve Pts
Flaherty NEJM 2012

MEKi (Trametinib)
BRAFi **RESISTANT** Pts
Kim, Kefford, Pavlick, J Clin Oncol

MEKi (Trametinib)+BRAFi (Dabraf)
BRAFi **RESISTANT** Pts
Flaherty Soc Melanoma Res 2011

Slide courtesy of Dr Paul Donnellan

Rapid emergence of resistance

– has this driven rapid development of new treatments?

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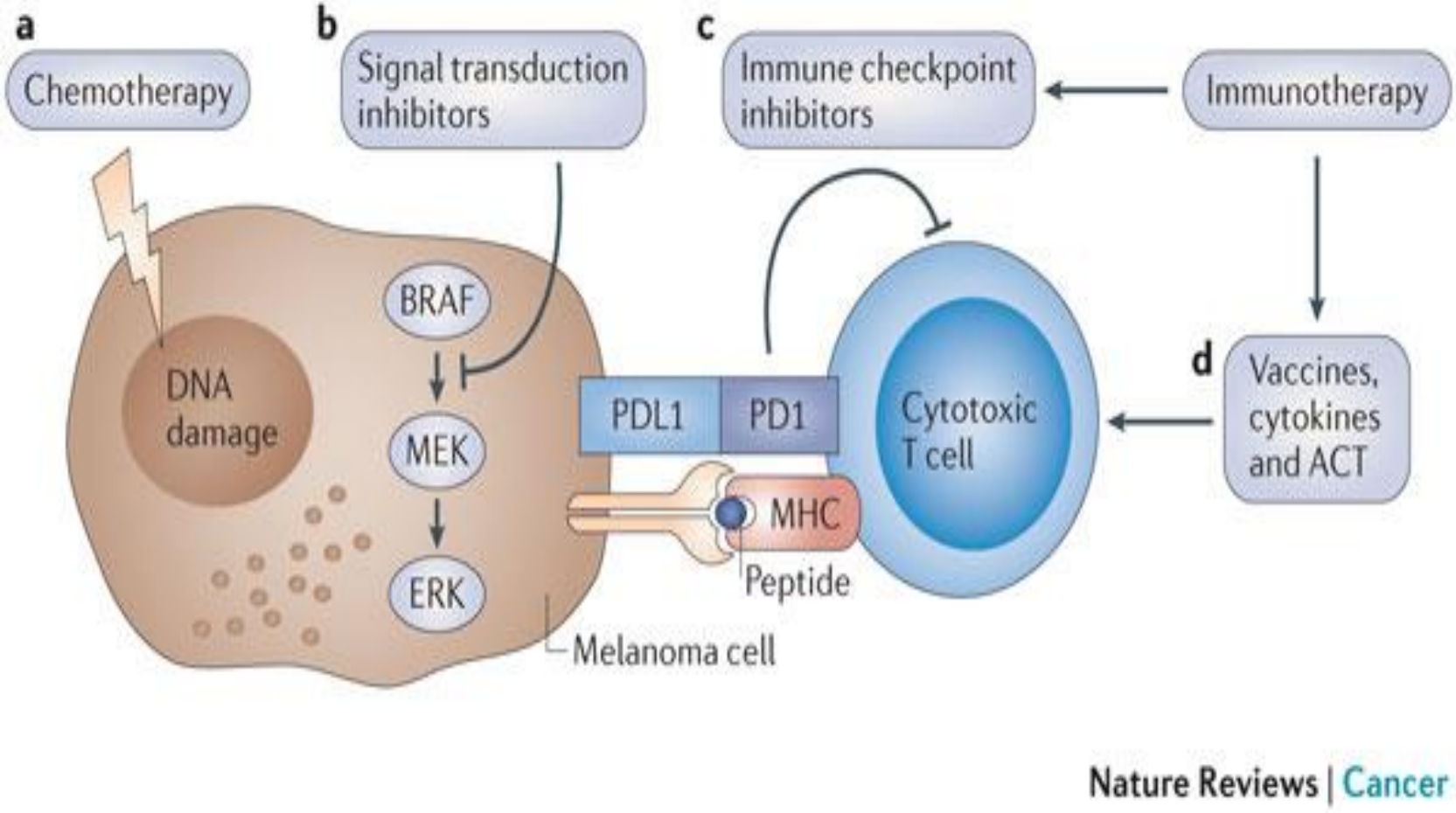

Conclusion

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- Understanding tumour biology has revolutionised treatments in last decade
- Resistance seems inevitable!
- Speed of resistance development appears to have been a key driver in further drug discovery

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Thank you

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- Targeting cancer metabolism dysfunctions
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