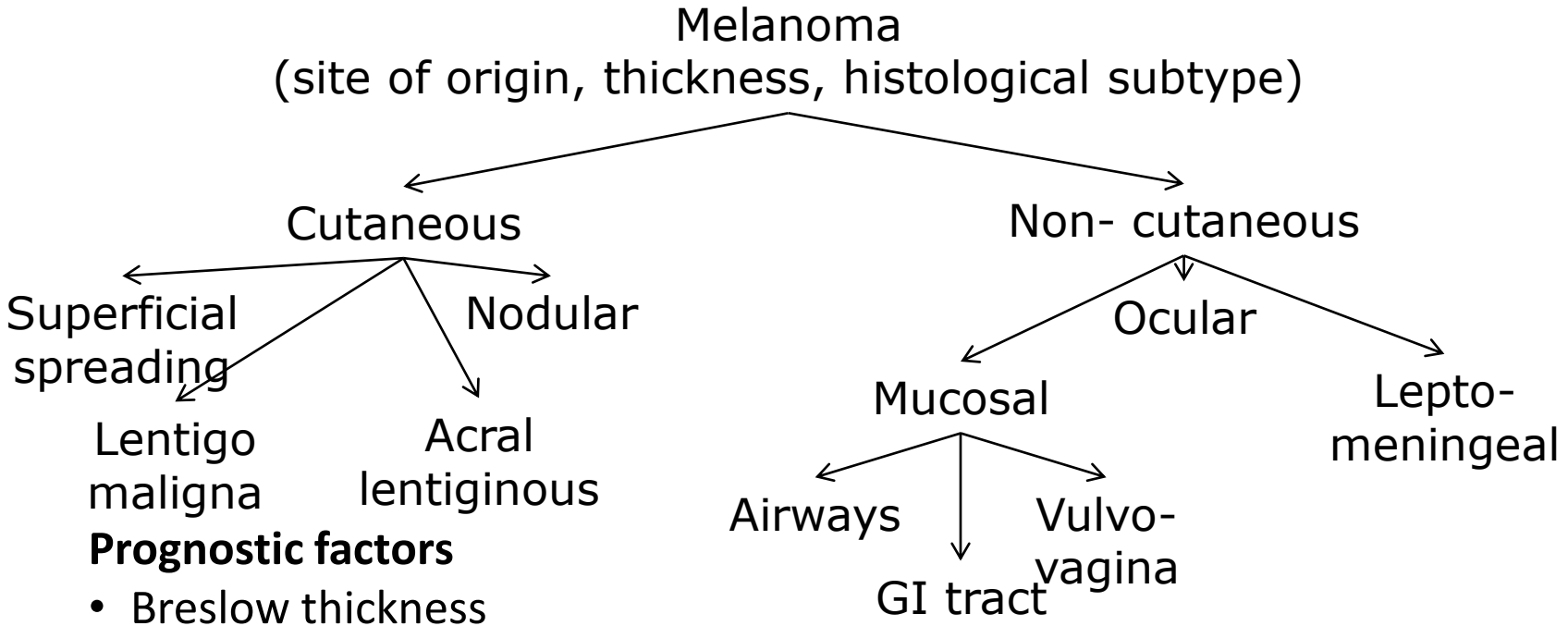
Rare melanoma: Are the options improving?

Dr Neil Steven
Consultant in Medical Oncology
University Hospital Birmingham
University of Birmingham

Classifying melanoma



Prognostic factors

- Breslow thickness
- Ulceration
- Nodal involvement

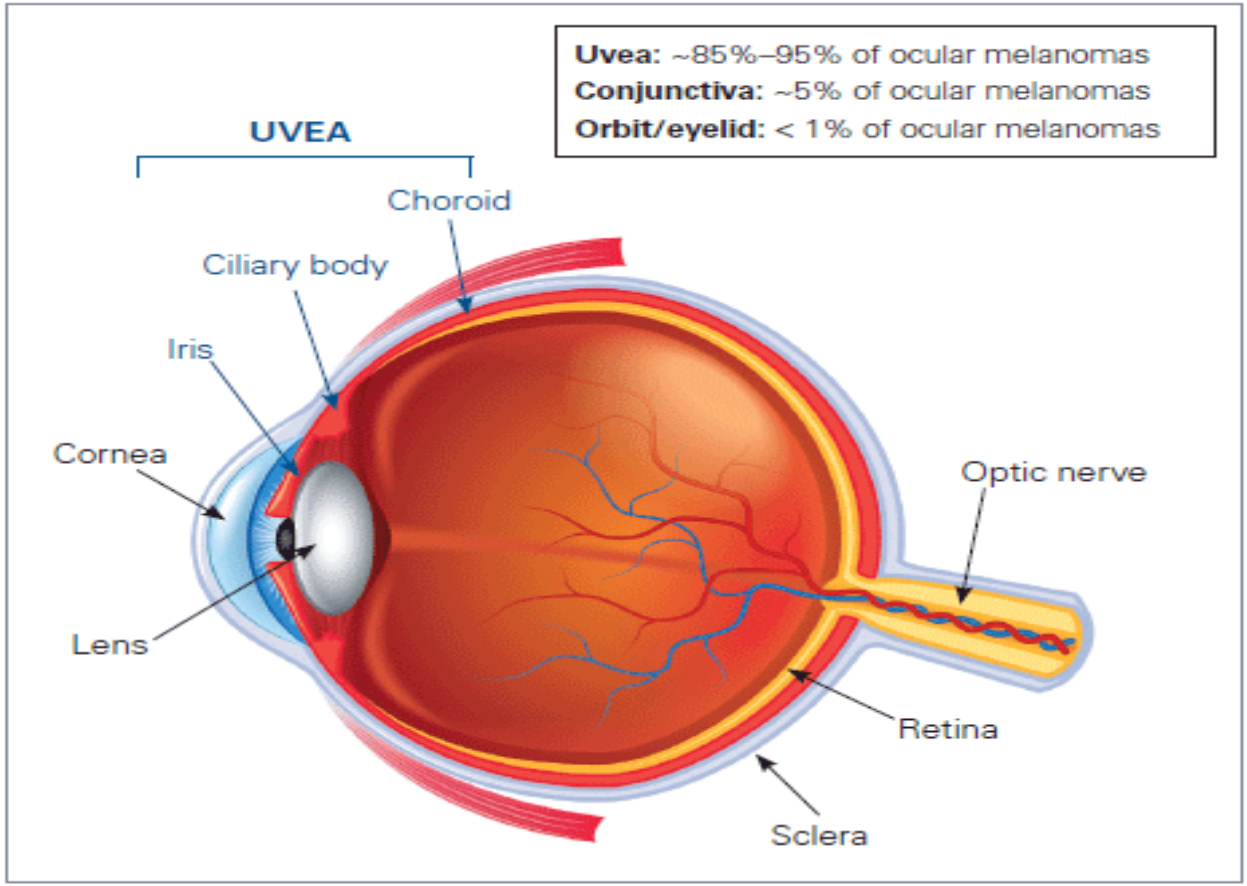
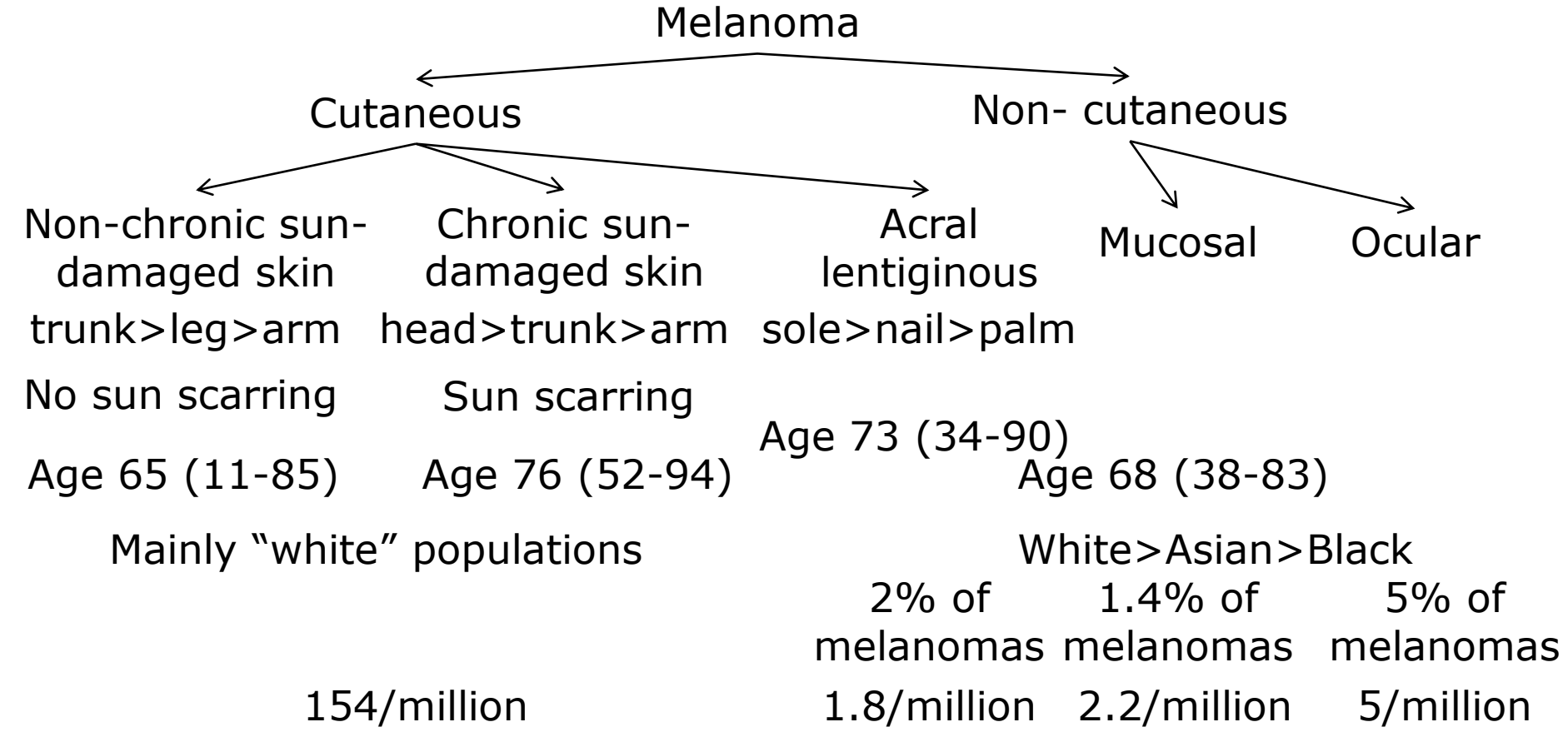


Figure 1. Anatomy of Ocular Melanoma—The uveal tract is comprised of the choroid, the ciliary body, and the iris. The majority of ocular melanomas arise within the uvea. Tumors can also arise in the conjunctiva (in approximately 5% of cases), and more rarely in the orbit/eyelid.

Oncology (Williston Park). 30(1):29-43.

Classifying melanoma



Ocular melanoma

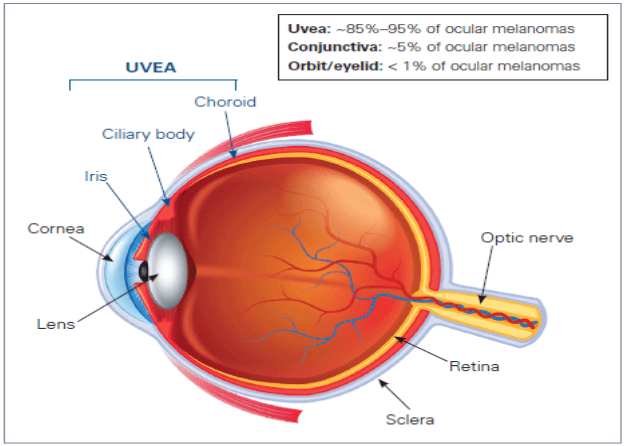


Figure 1. Anatomy of Ocular Melanoma—The uveal tract is comprised of the choroid, the ciliary body, and the iris. The majority of ocular melanomas arise within the uvea. Tumors can also arise in the conjunctiva (in approximately 5% of cases), and more rarely in the orbit/eyelid.

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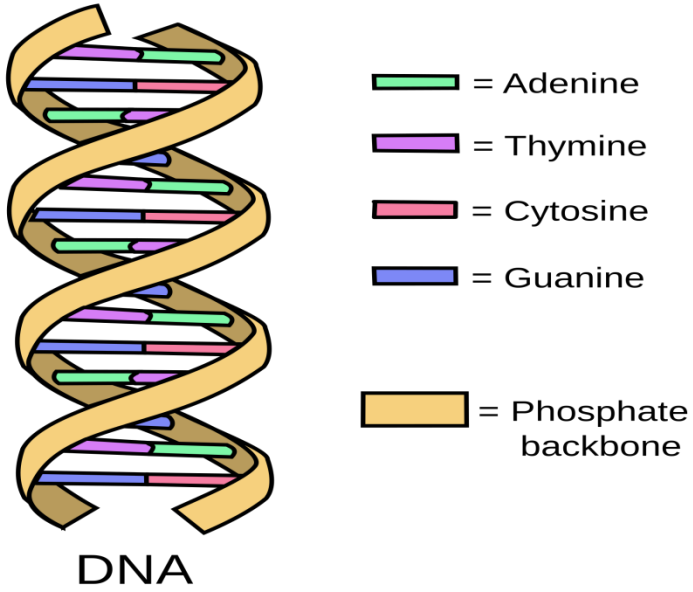
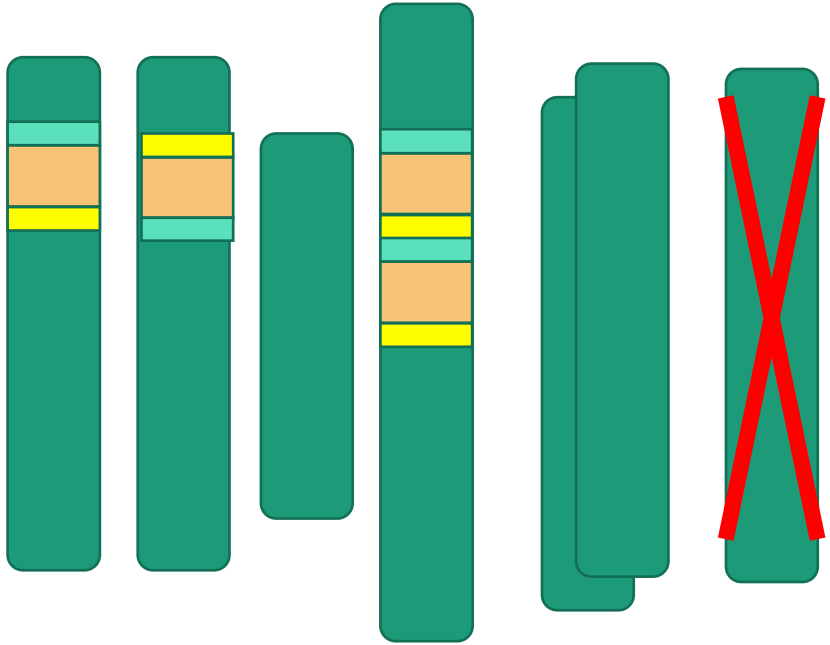
Krantz et al Clinical Ophthalmology 2017 11 279-289.

- Excellent rates local control
- Up to 50% develop metastases
- Initial sites liver > lung > skin / soft tissue > bone
- Overall survival
  - 69% a 5 years
  - 55% at 15 years
  - 51% at 25 years
- After development metastases
  - Median survival 13.4 months
  - 2-year survival 8%

The variable biology of melanomas

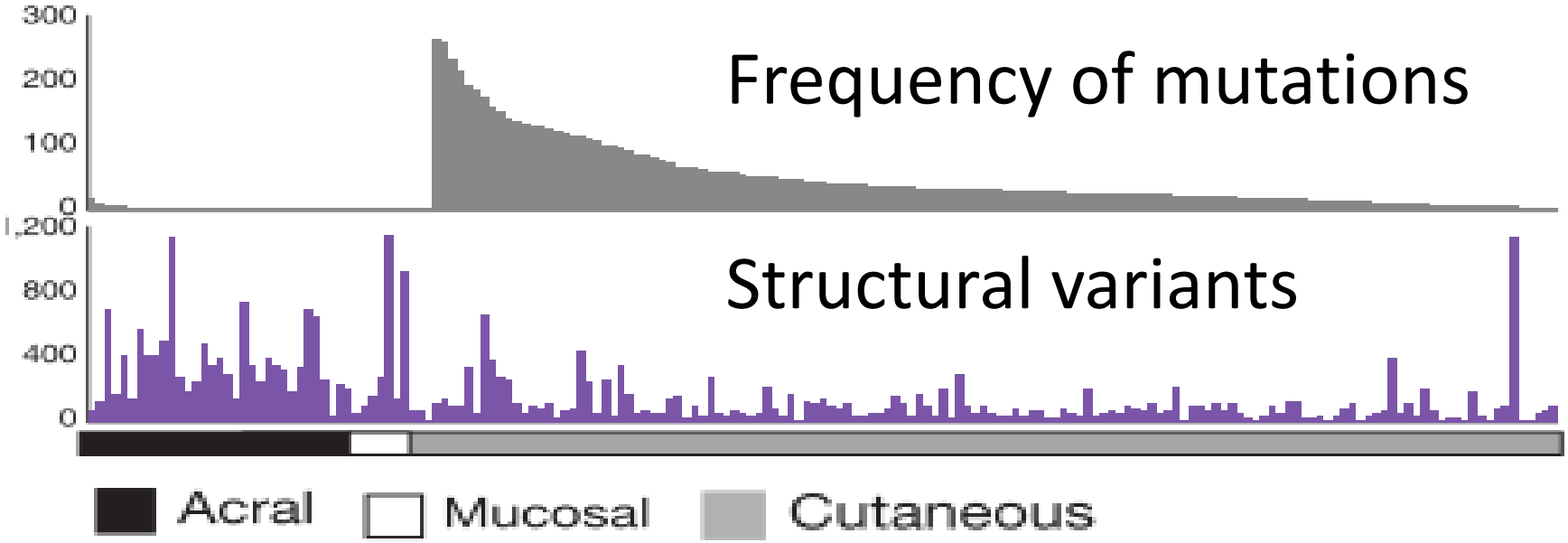




Single nucleotide variant – swaps one coding letter for another

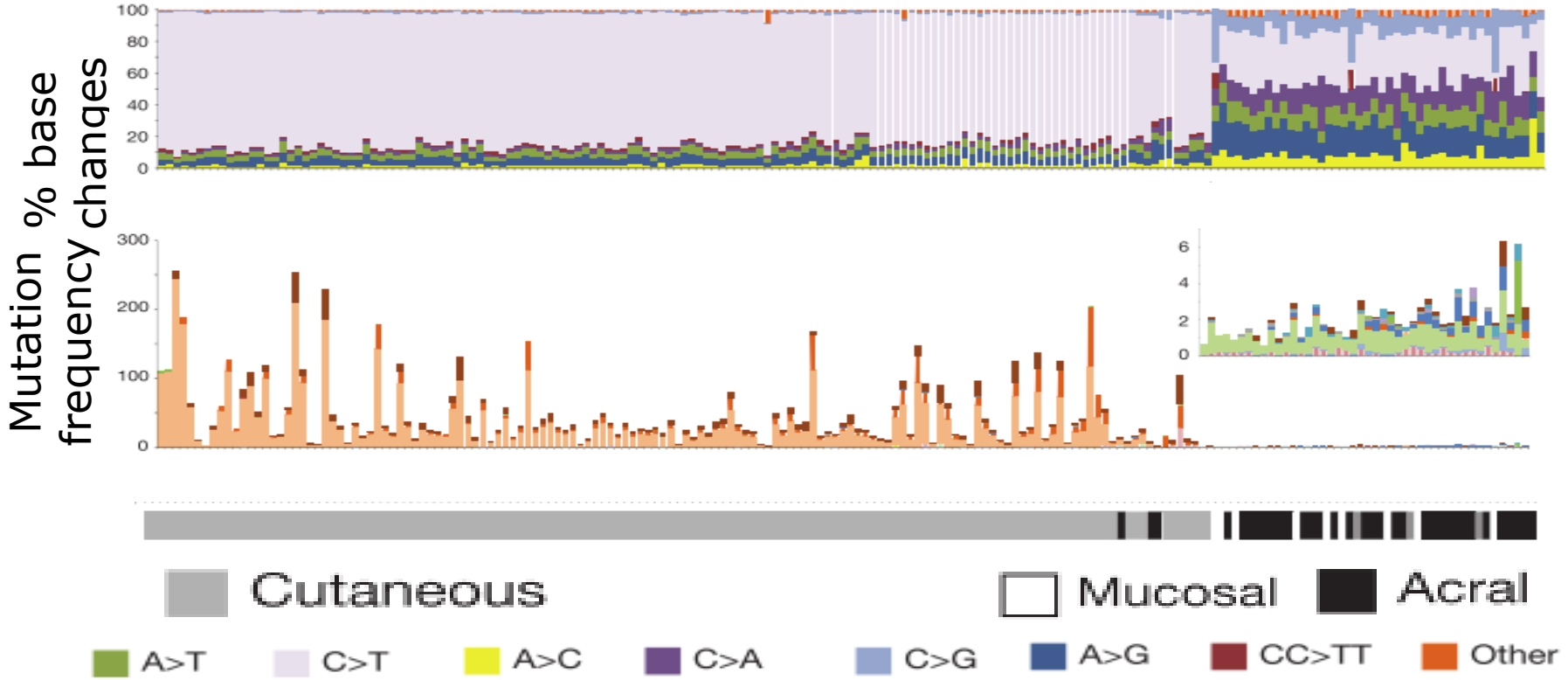
Structural variation – inversions, deletions, duplications etc of chromosomes, extra or loss of chromosomes

Comparing mutation patterns



Haywood et al Nature 2017 175-180

Overview of mutation patterns

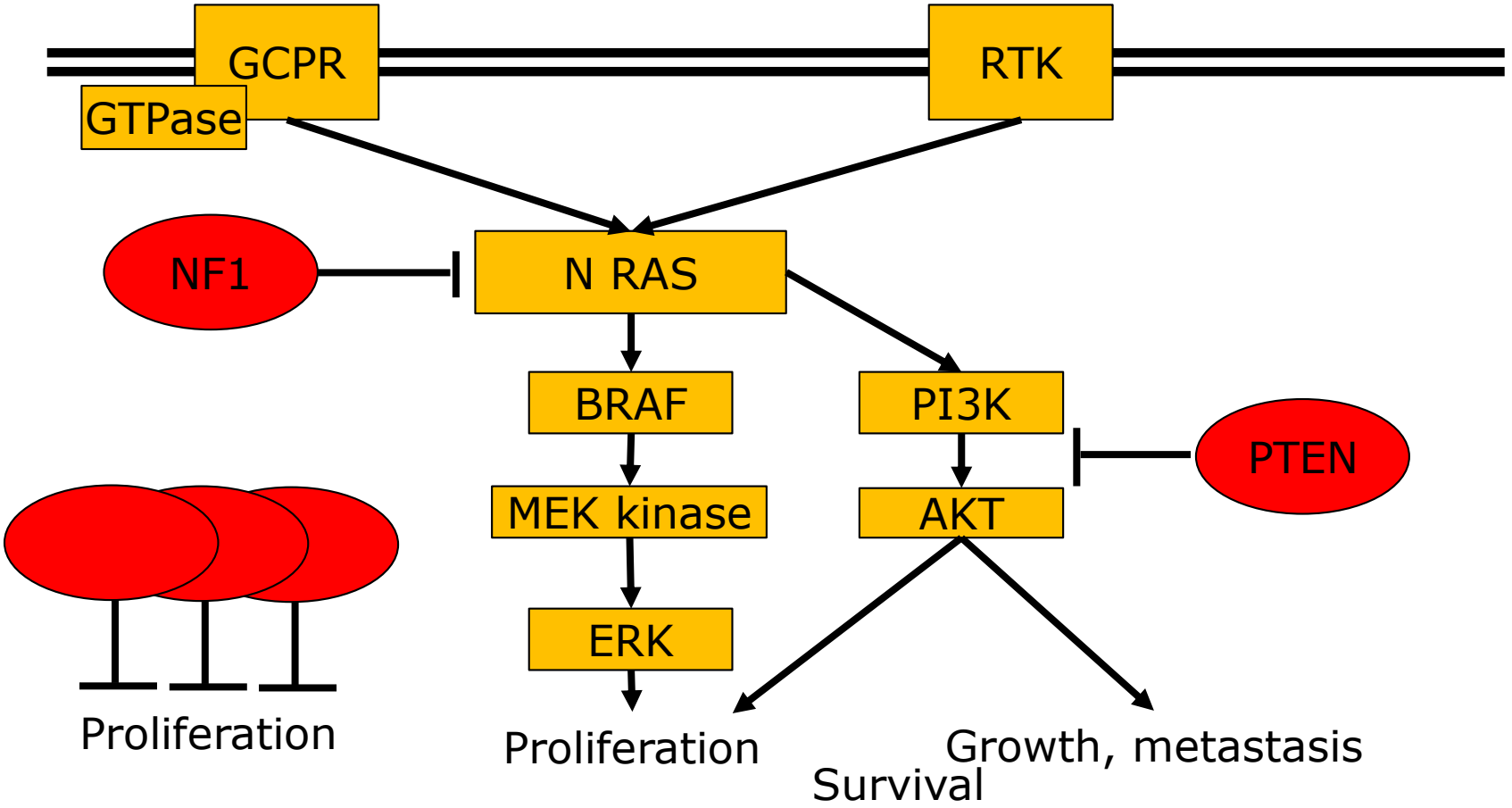


Haywood et al Nature 2017 175-180

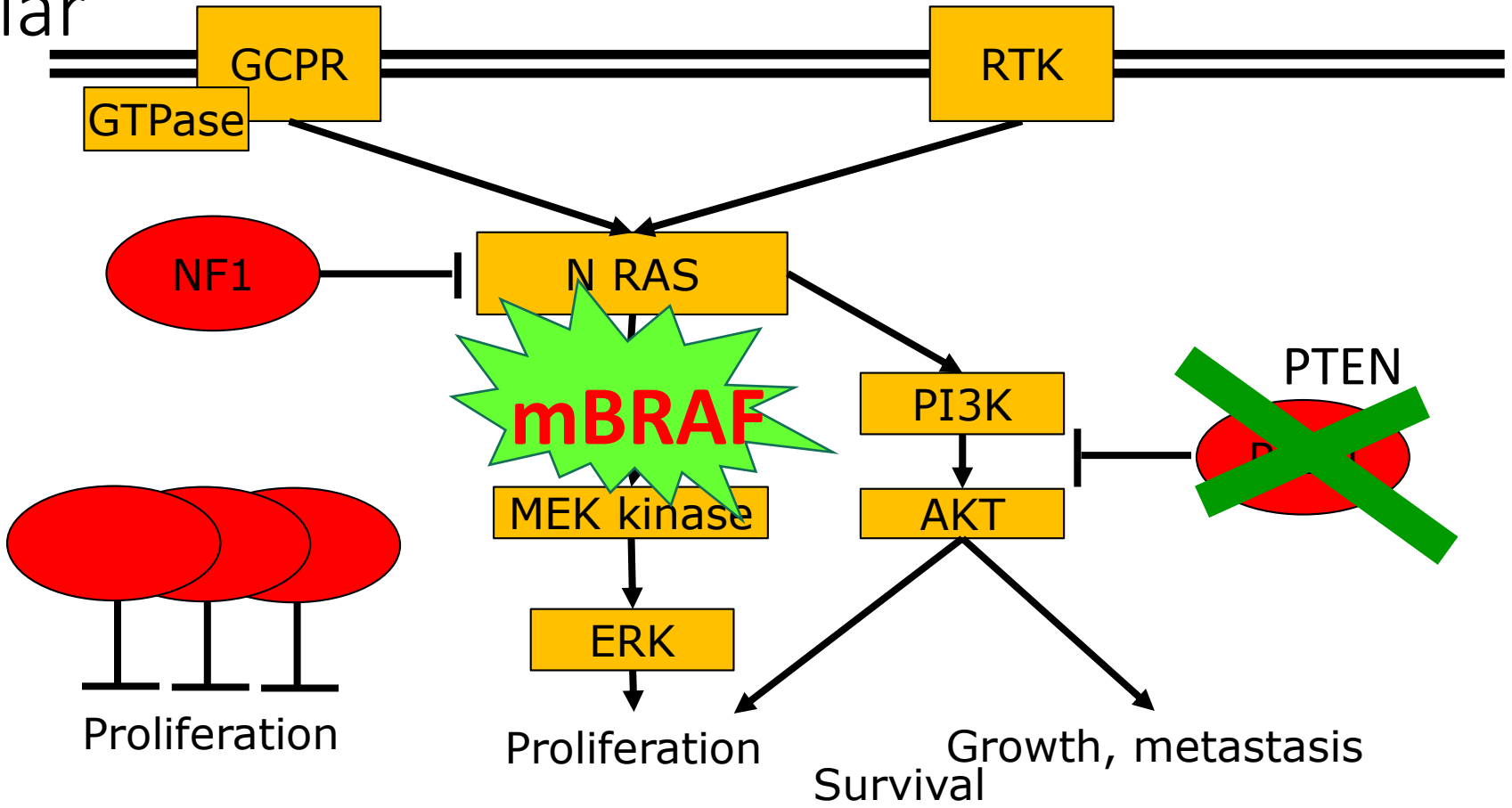
Ocular melanoma

- low mutation burden
- no enrichment for C>T transitions typical of UV damage found in most cutaneous melanoma
- UV induced mutations in TERT promoter common in CM rare in UM
- Structural variations in UM
  - Monosomy 3 (loss or partial loss of one of two copies of chromosome 3) – strongest predictor of metastasis
  - Chromosome 1p loss – poorer prognosis
  - Chromosome 6p gain – better outcome
  - Chromosome 6q losses and gains
  - Chromosome 8q loss
  - Chromosome 8p losses and gains

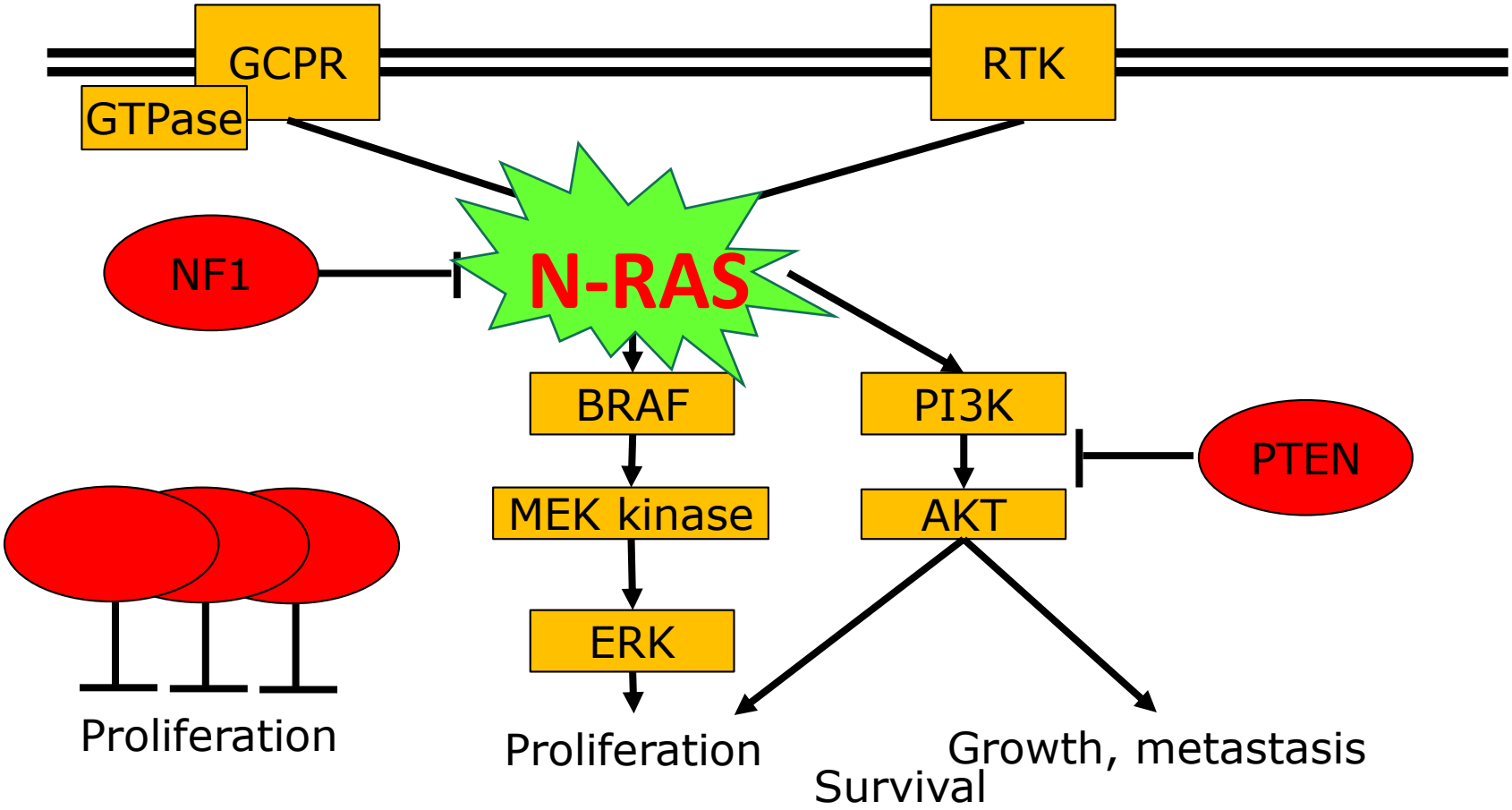
The signalling bucket chain



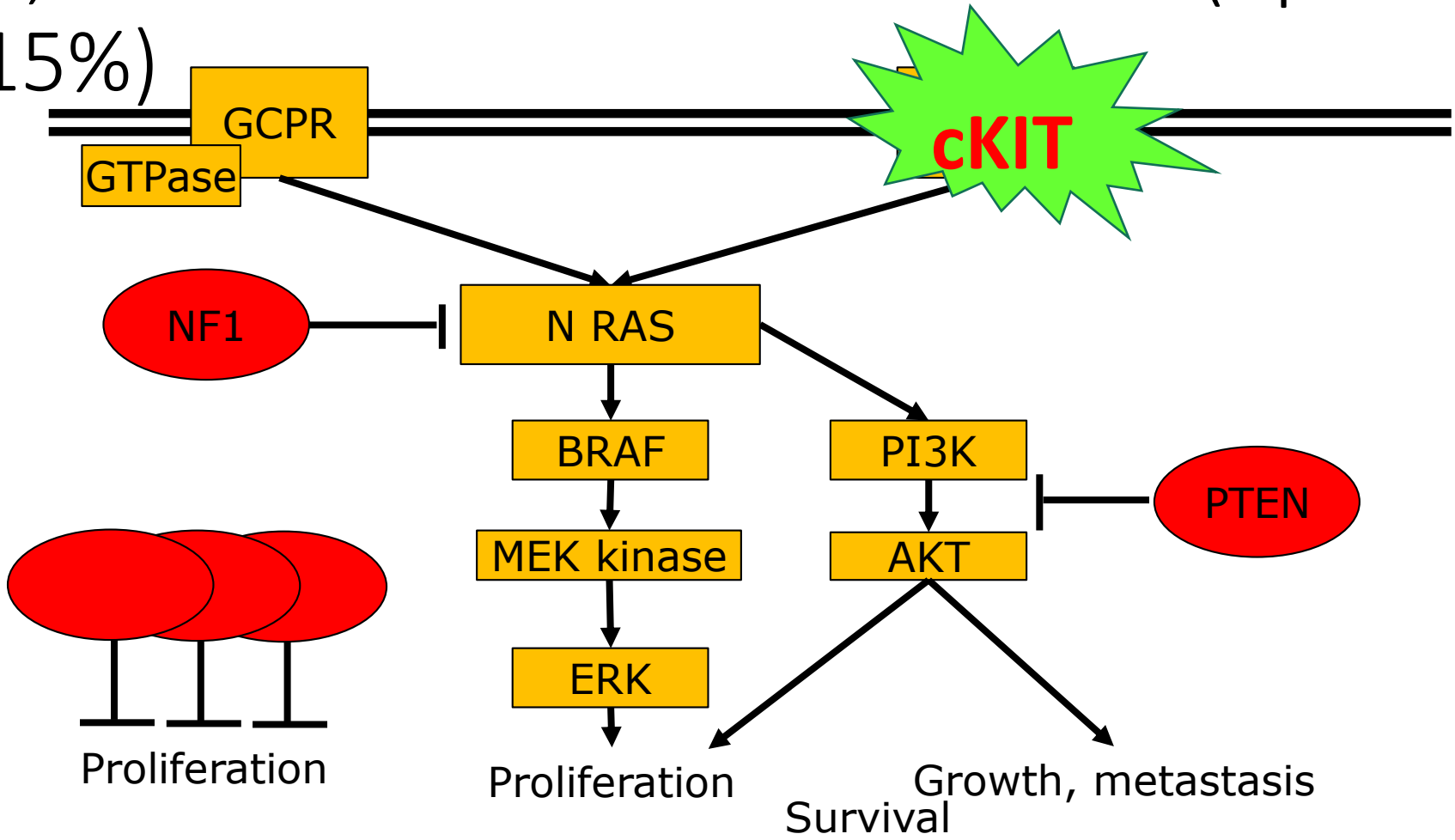
Skin melanoma, few acral, few mucosal, no ocular



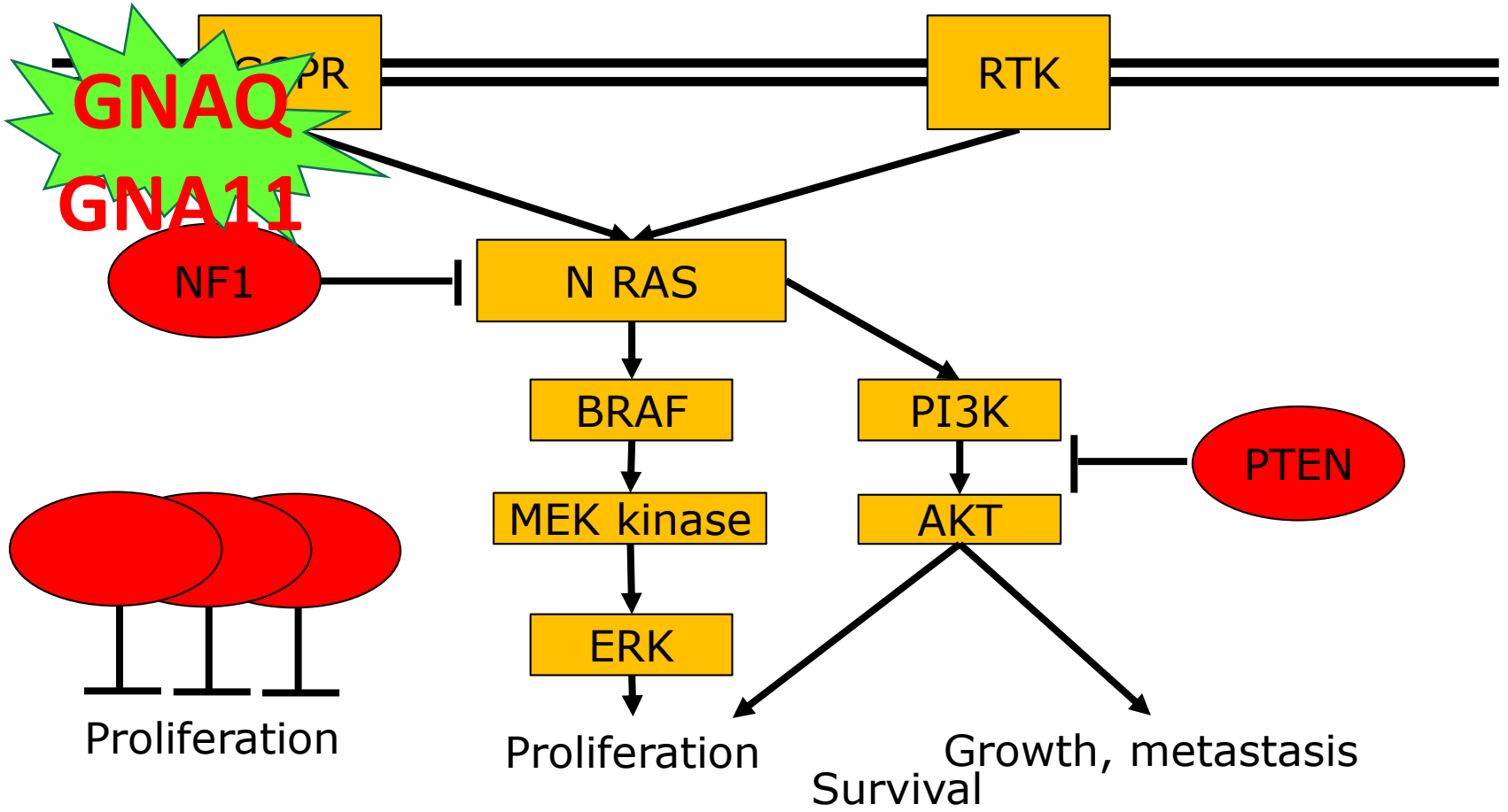
Skin, acral and mucosal melanoma



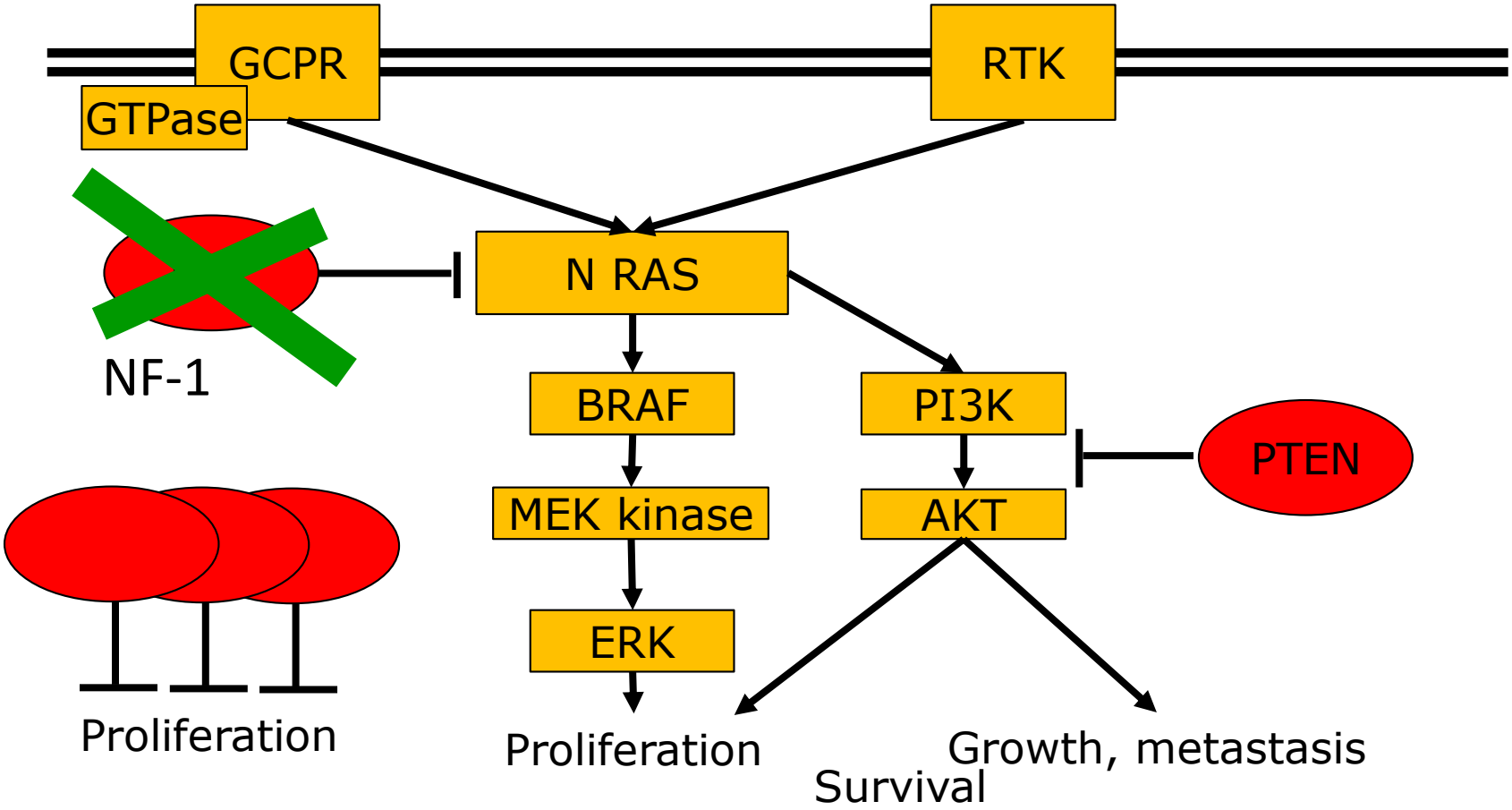
Skin, acral and mucosal melanomas (up to 15%)



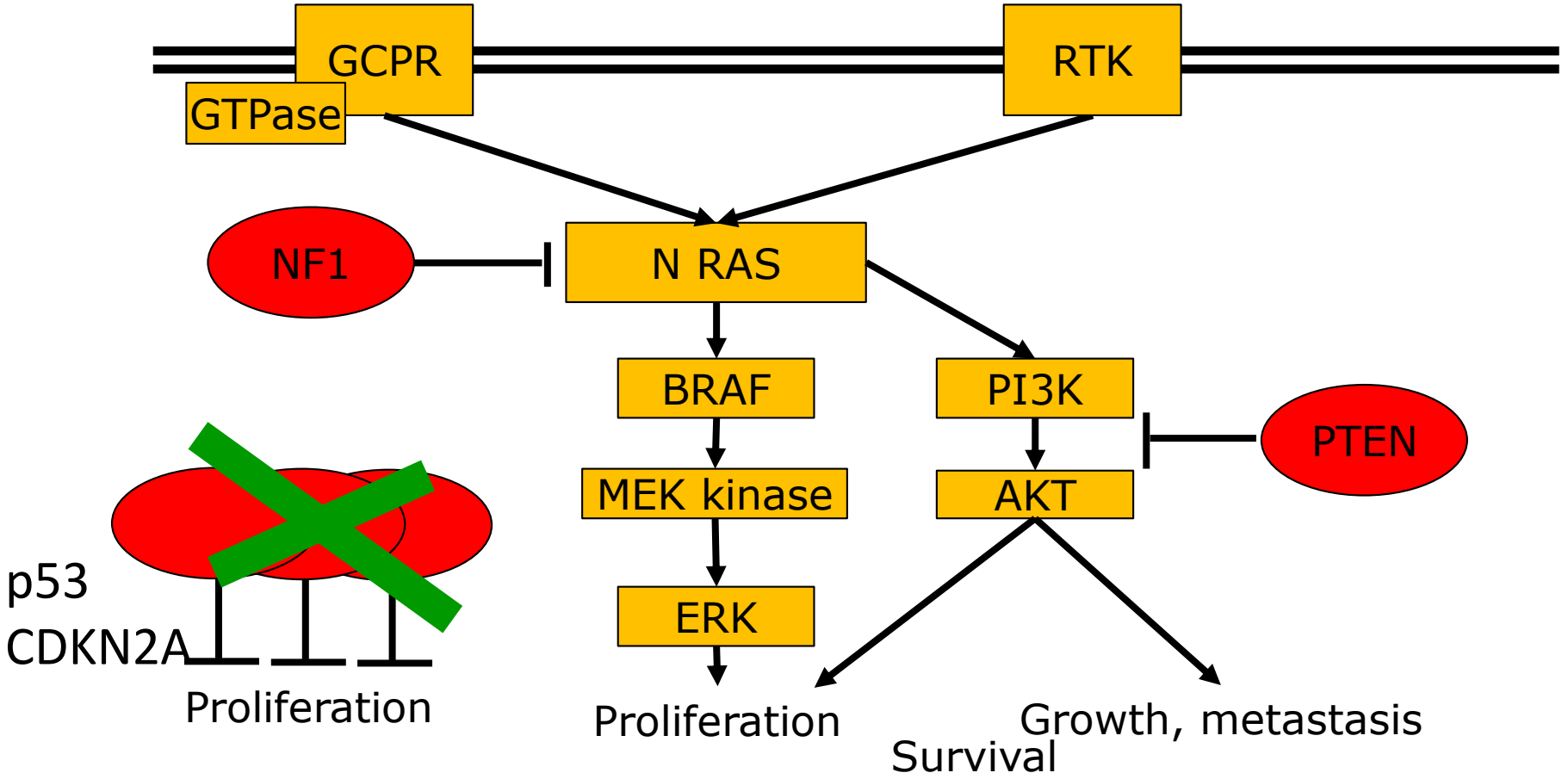
Ocular melanoma (>80%)



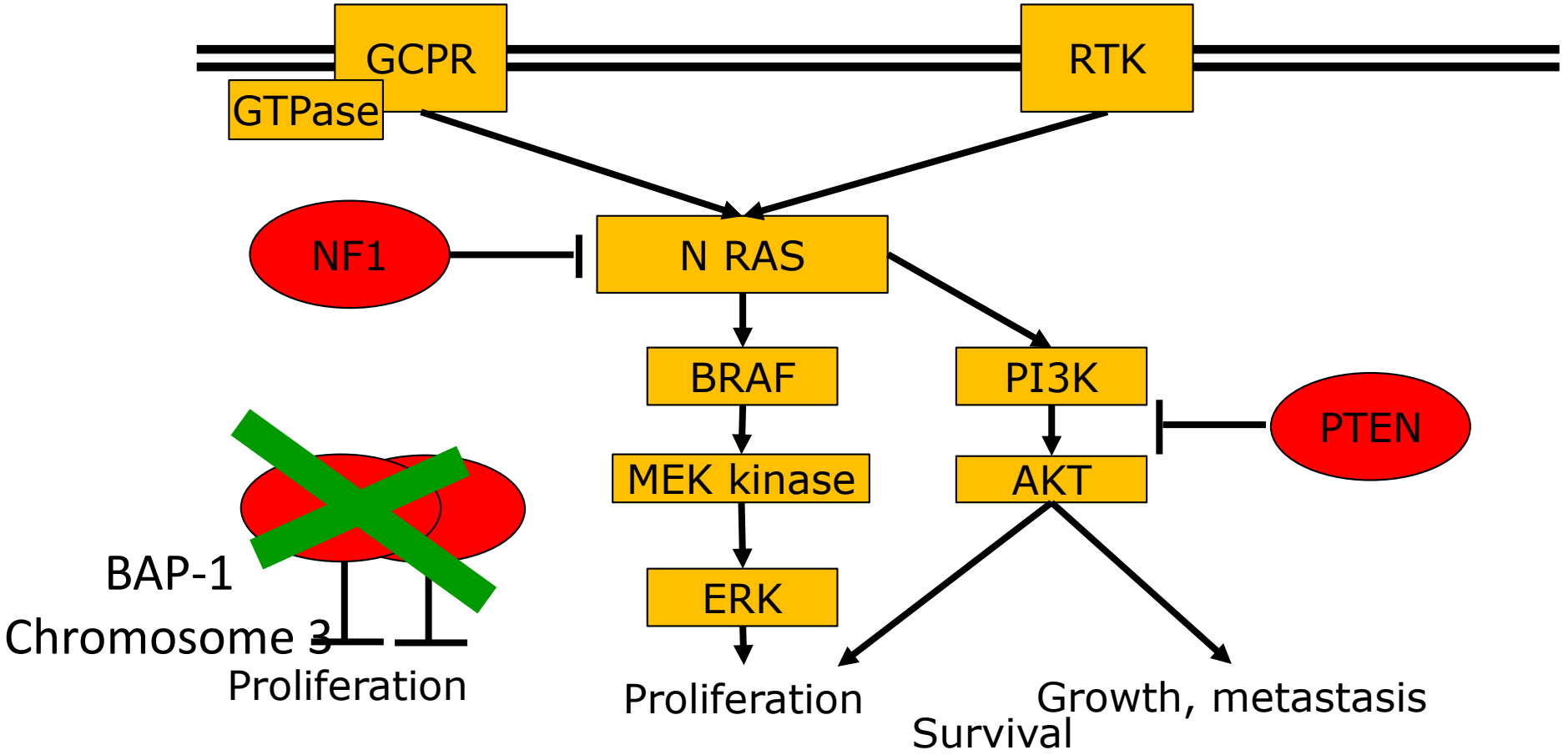
Loss of function skin and acral



Cutaneous melanoma



Ocular melanoma



Ocular melanoma – practice guideline

Suspected primary

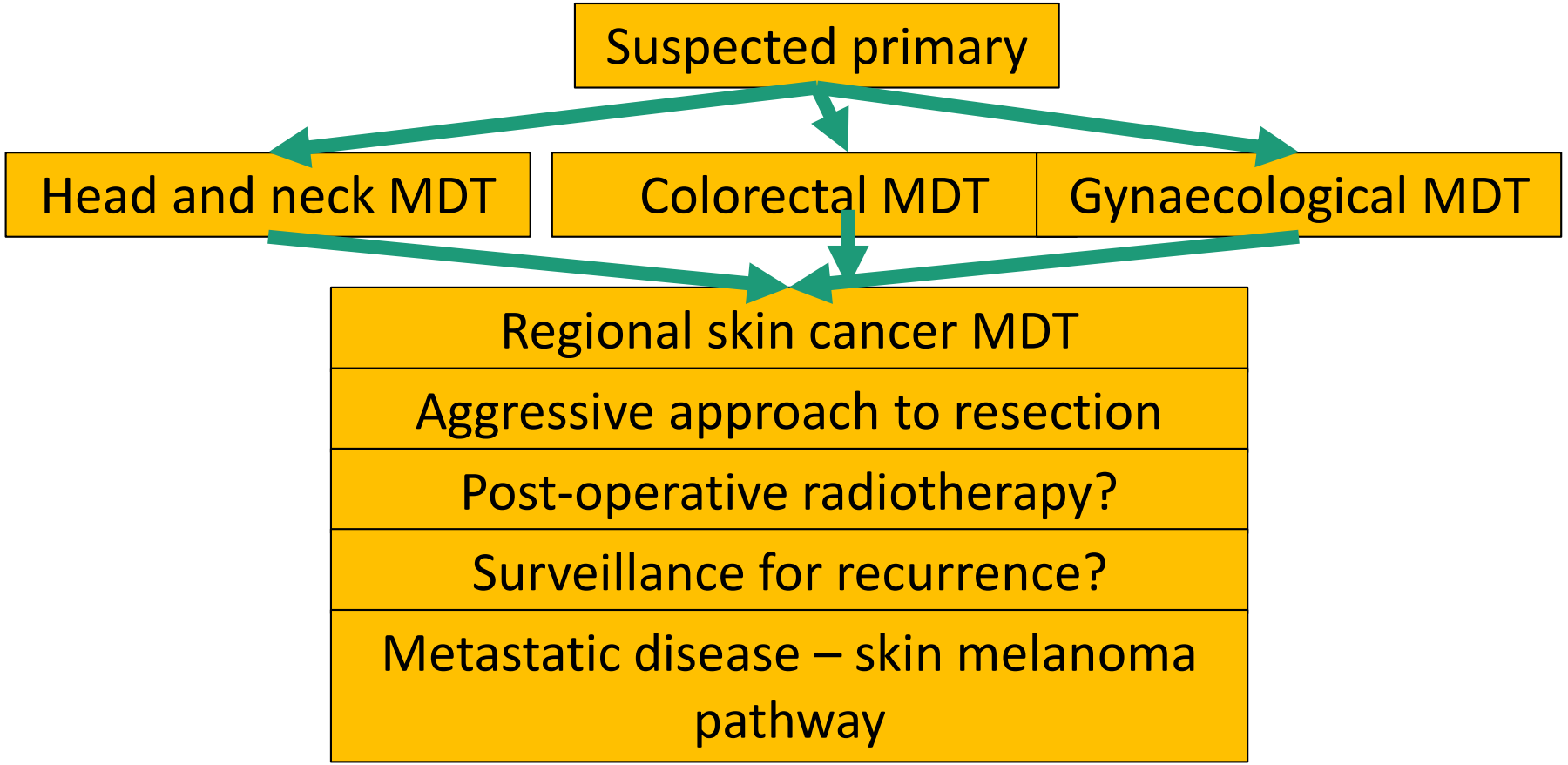
REFER – 3 specialist units
- Diagnosis
- Prognosis (LUMPO)
- Staging – MRI + / - US
- Follow up for primary

SURVEILLANCE for metastases
High risk – 6-monthly life long review with liver imaging

Metastases

REFER – networked regional melanoma / liver centres
Resection hepatic disease
Ablation isolated metastases
Clinical trials
Regional hepatic therapies
Dacarbazine based chemotherapy
Immune therapy

Mucosal melanoma



Immune therapy – mucosal melanoma

- Compared outcome of people treated for advanced mucosal therapy pooled from 6 trials – 10-15% of patients
- Nivolumab versus ipilimumab versus combination
- 5-10% BRAF mutations
- Lower proportion PD-L1 +

D'Angelo J Clin Oncol 2017 Jan 10;35(2):226-235

Immune therapy – mucosal melanoma

All	Nivolumab		Combination		Ipilimumab	
	Mucosal	Skin	Mucosal	Skin	Mucosal	Skin
Response	23%	41%	37%	60%	8%	21%
Complete response	6%	7%	3%	14%	0	3%
PFS	3m	6m	6m	12m	3m	4m

Mucosal	Nivolumab		Combination		Ipilimumab	
	PDL1+	PDL1-	PDL1+	PDL1-	PDL1+	PDL1-
Response	53%	12%	60%	33%	14%	10%
PFS	12m	<3m	NR	<3m	3m	<3m

D'Angelo J Clin Oncol 2017 Jan 10;35(2):226-235

Immune therapy – ocular melanoma

56 patients

90% liver metastases

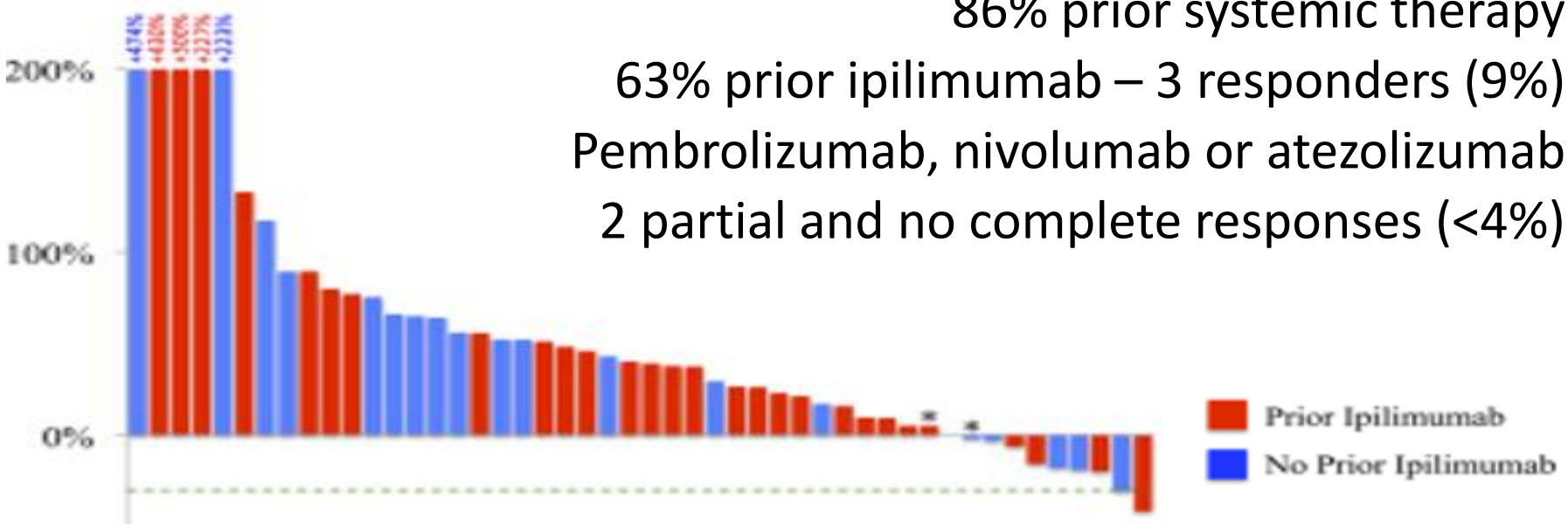
23% prior liver directed therapy

86% prior systemic therapy

63% prior ipilimumab – 3 responders (9%)

Pembrolizumab, nivolumab or atezolizumab

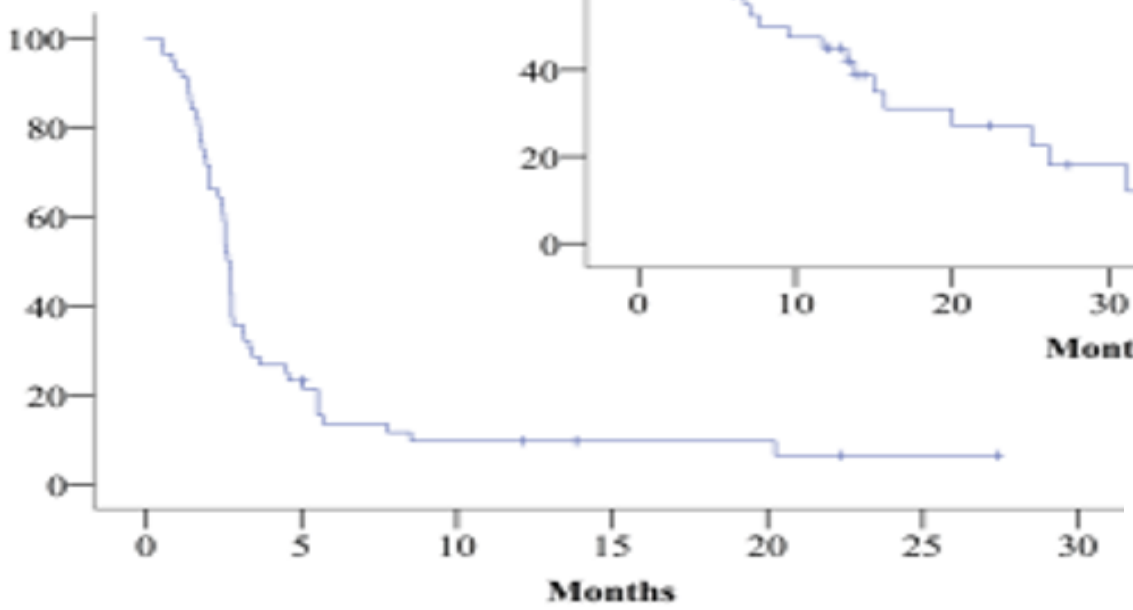
2 partial and no complete responses (<4%)

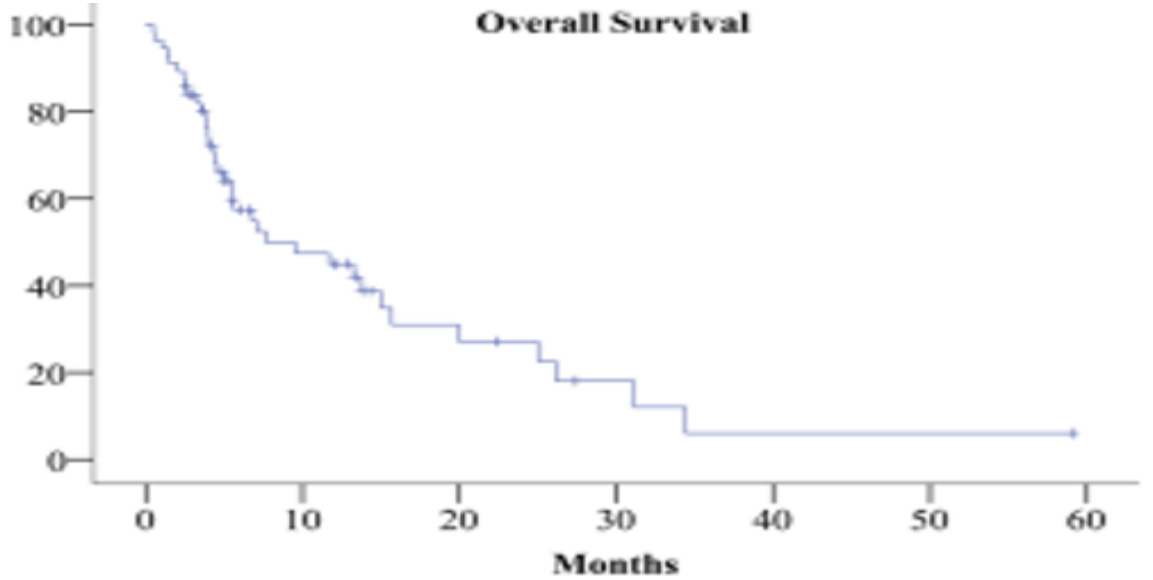


Algazi 2016 Nov 15;122(21):3344-3353

Immune therapy – ocular melanoma

Progression free survival





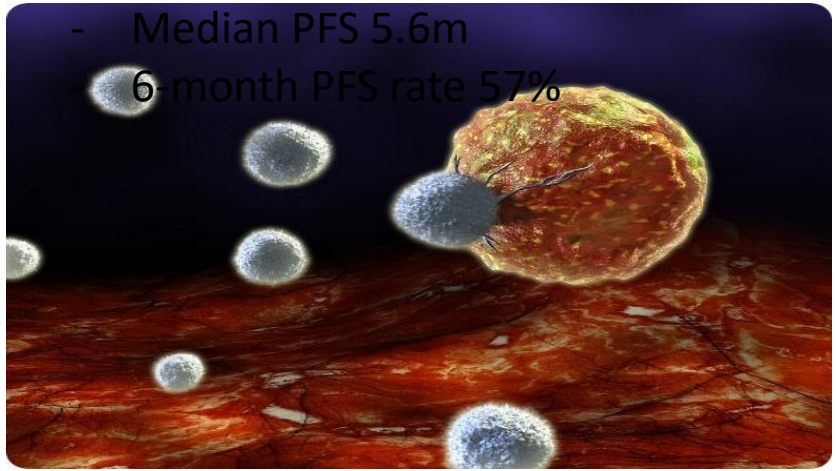
IMCgp100

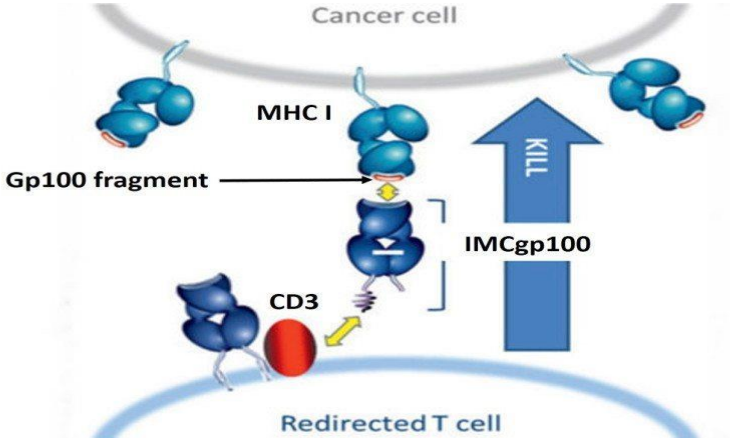
NCT01211262

- Response in 4 (2 uveal) / 26 treated
- Stable disease in 1 patients

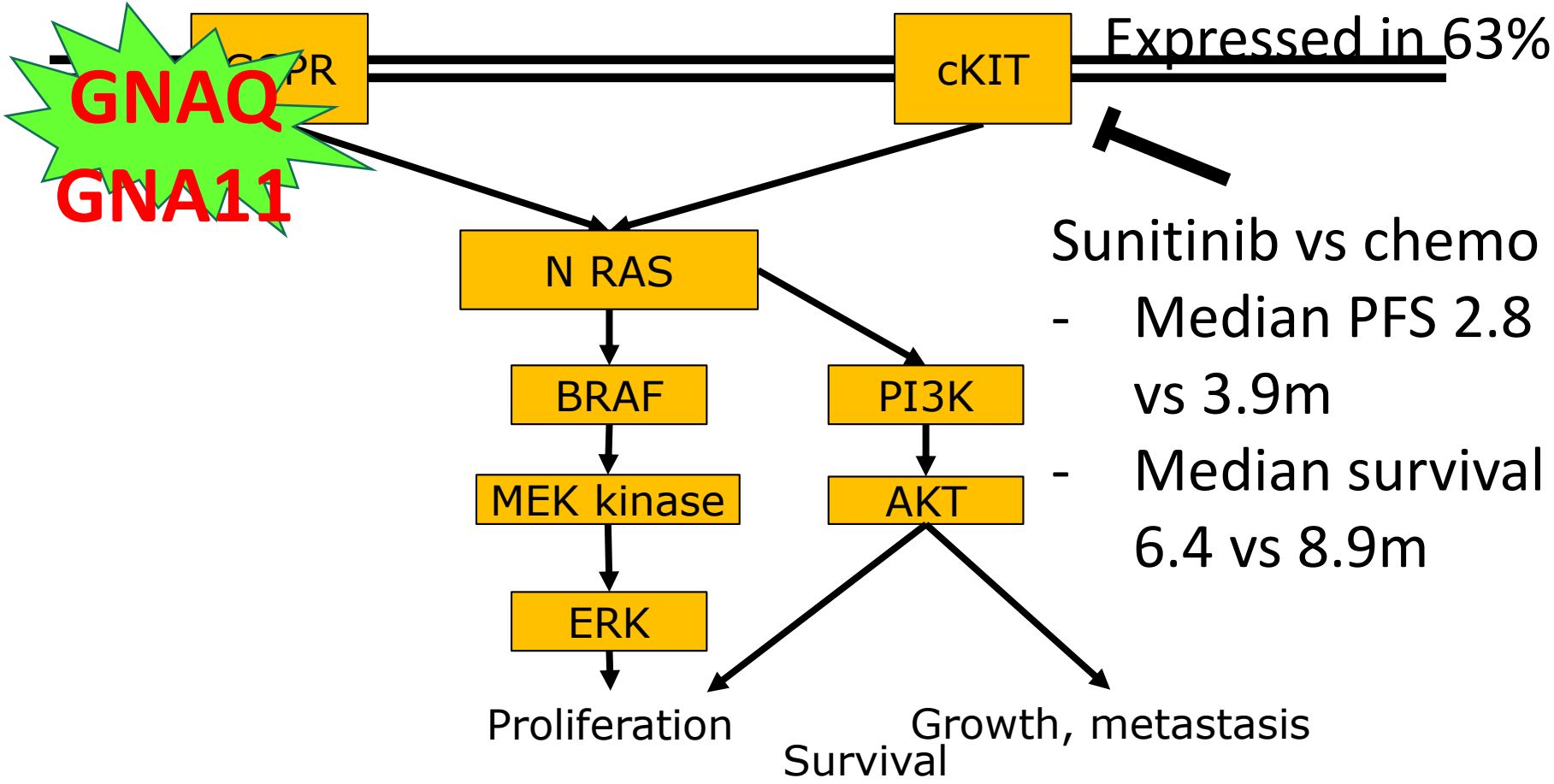
NCT02570308

- Best overall response rate – 12/17 stable disease 63% including 4 with >= 10% reduction in tumour
- Median PFS 5.6m
- 6-month PFS rate 57%





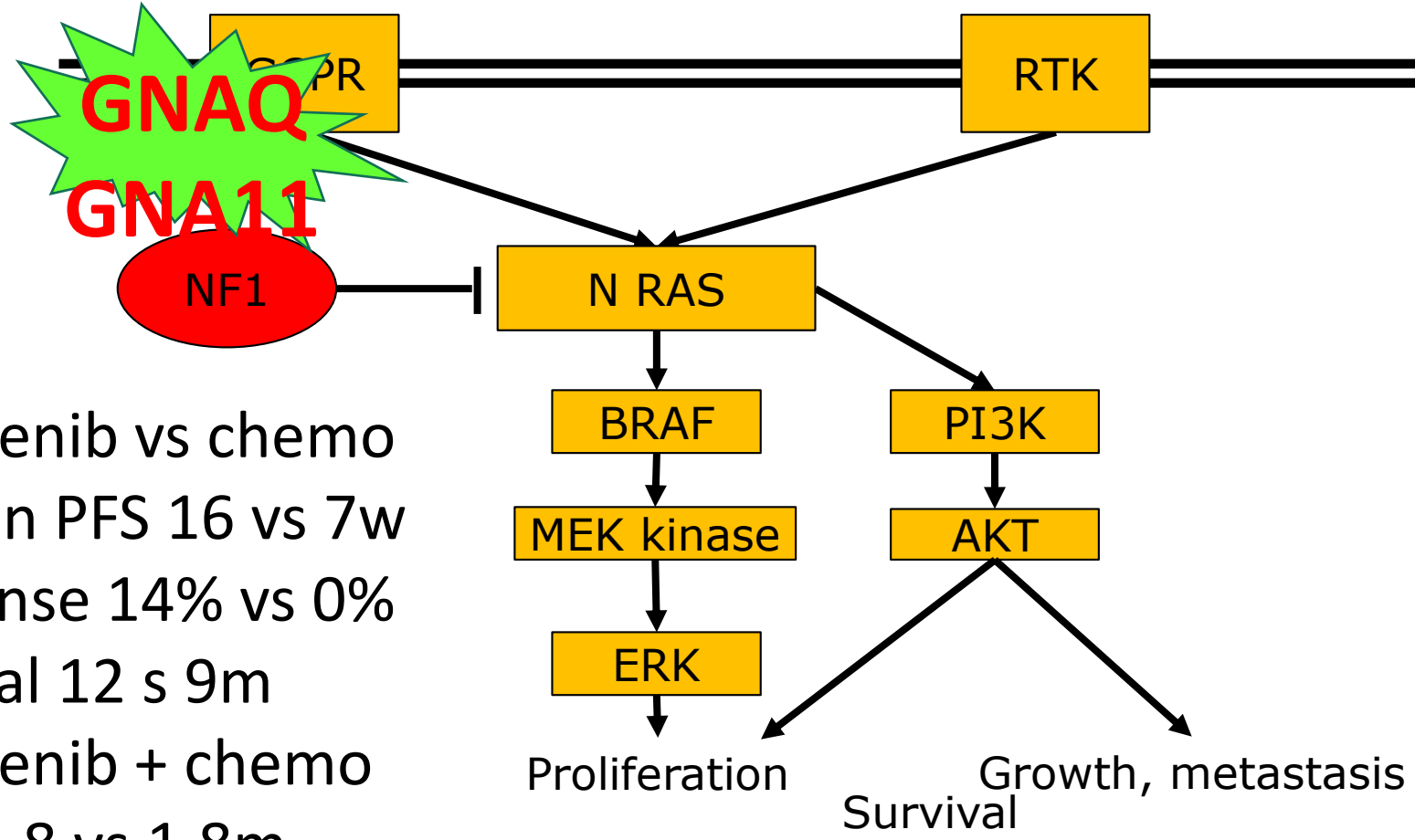
Ocular melanoma experimental treatments



Sunitinib vs chemo

- Median PFS 2.8 vs 3.9m
- Median survival 6.4 vs 8.9m

Ocular melanoma experimental treatments



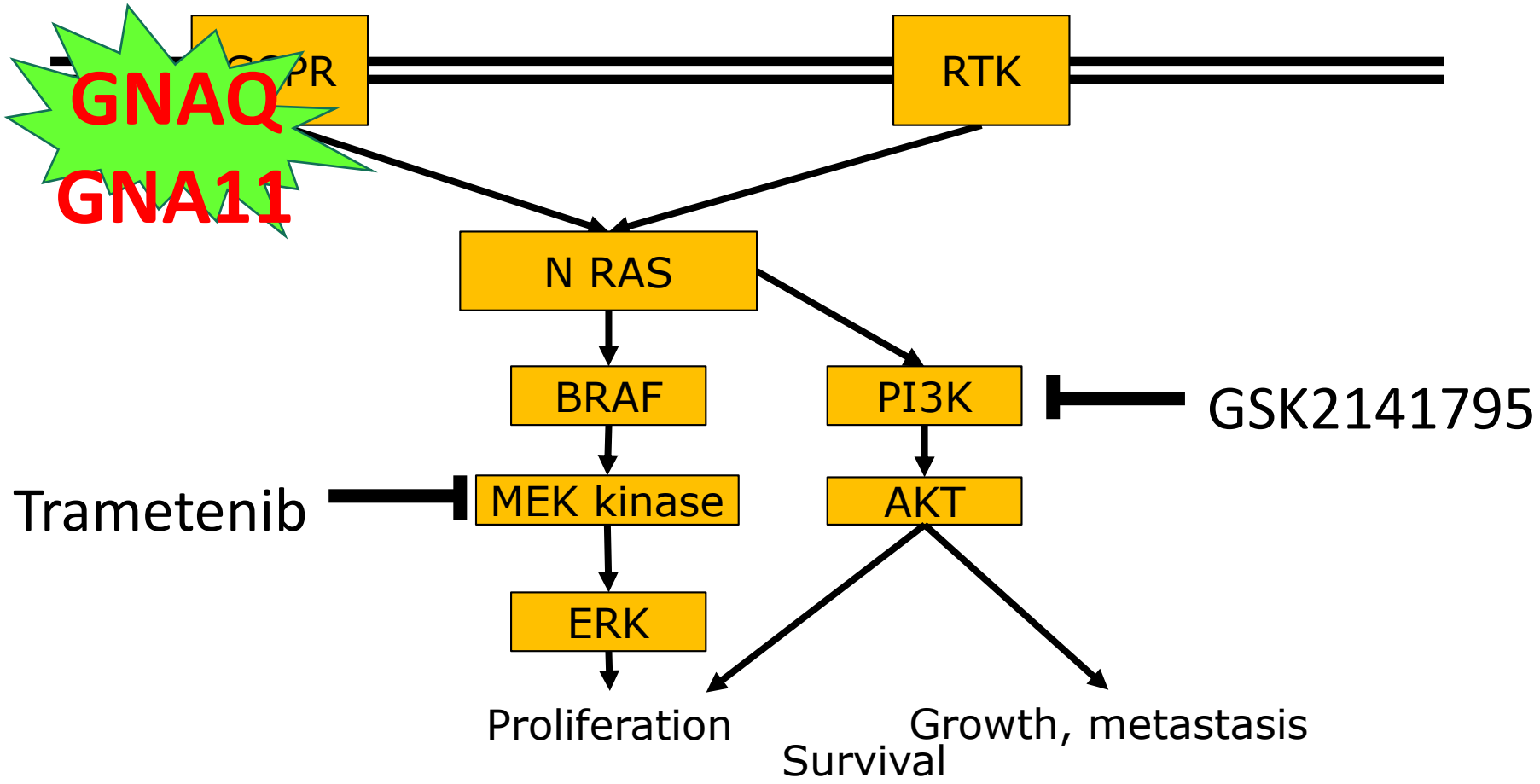
Selumetenib vs chemo

- Median PFS 16 vs 7w
- Response 14% vs 0%
- Survival 12 s 9m

Selumetenib + chemo

- PFS 2.8 vs 1.8m

Ocular melanoma experimental treatments



Rare melanomas - challenges

- Concentration of expertise
- Need for multidisciplinary management
- Critical role of surgery and (ocular melanoma) radiotherapy
- Clear management pathways
- Less intrinsically druggable
  - Low mutation burden – lower probability of immune recognition
  - Limited opportunity to target a “simple” common activating mutation
- Better molecular understanding is the best hope for more effective treatment