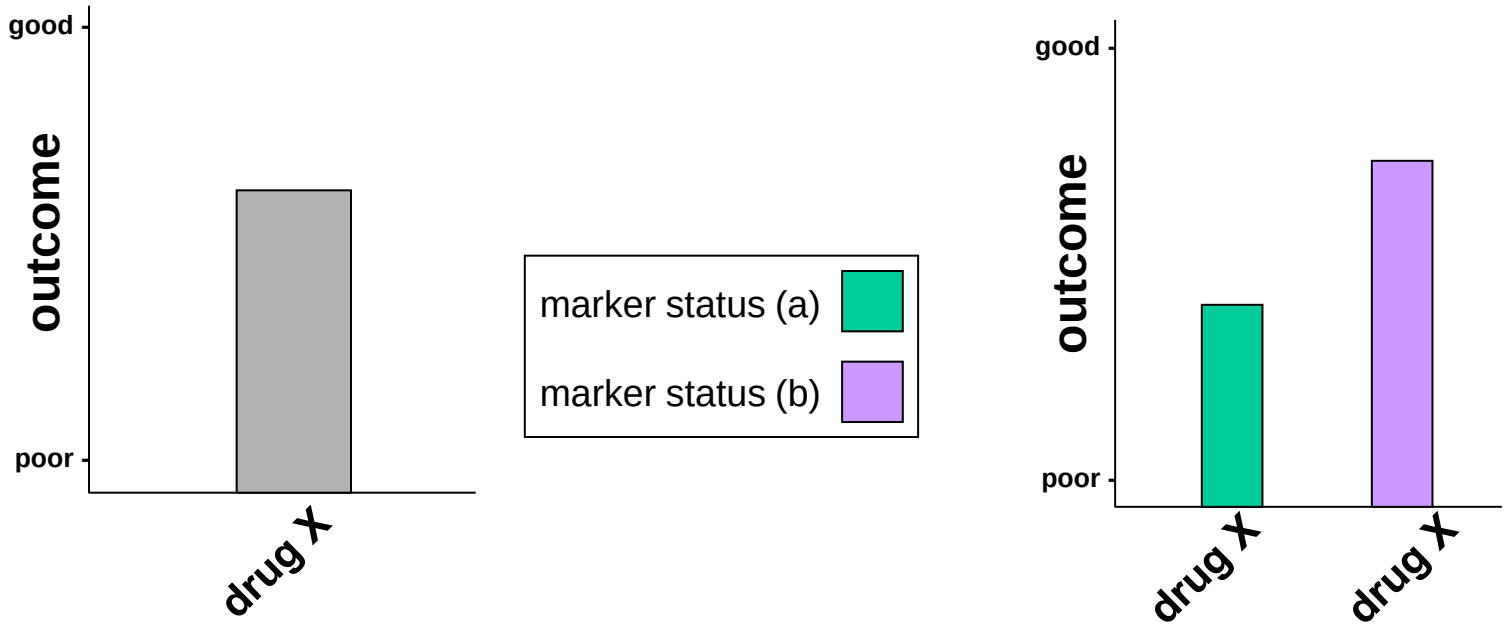
Poster Discussion:

525PD	Hsa-miR31-3p Expression as a Predictor of Anti-EGFR response in wild-type KRAS Patients with metastatic Colorectal Cancer	Pierre Laurent-Puig, FR
526PD	Development of a predictive score using amphiregulin (AREG), epiregulin (EREG) and EGFR-FISH expression levels to determine treatment efficacy in mCRC patients receiving cetuximab-based therapy. Analysis of the German AIO CRC-0104 trial	Volker Heinemann, DE
527PD	Pharmacogenetic predictors of severe chronic peripheral neuropathy in stage II-III colon cancer (CC) patients treated with oxaliplatin-based adjuvant chemotherapy (CT). A GEMCAD study	Ana Custodio, ES

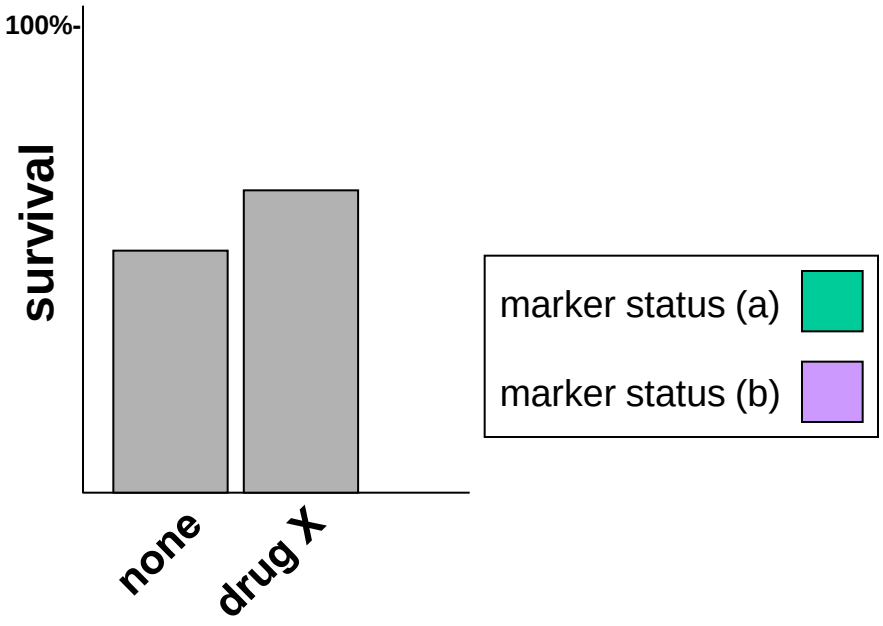
Discussant: Matt Seymour,

University of Leeds & NCRN, UK

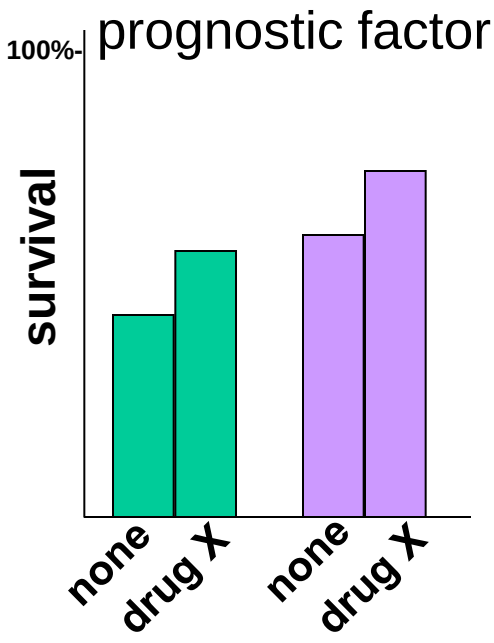


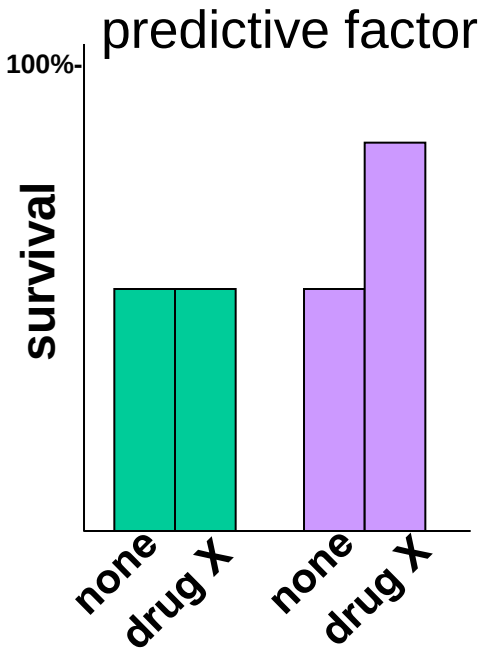
we may have a **prognostic marker** – correlates with underlying cancer biology

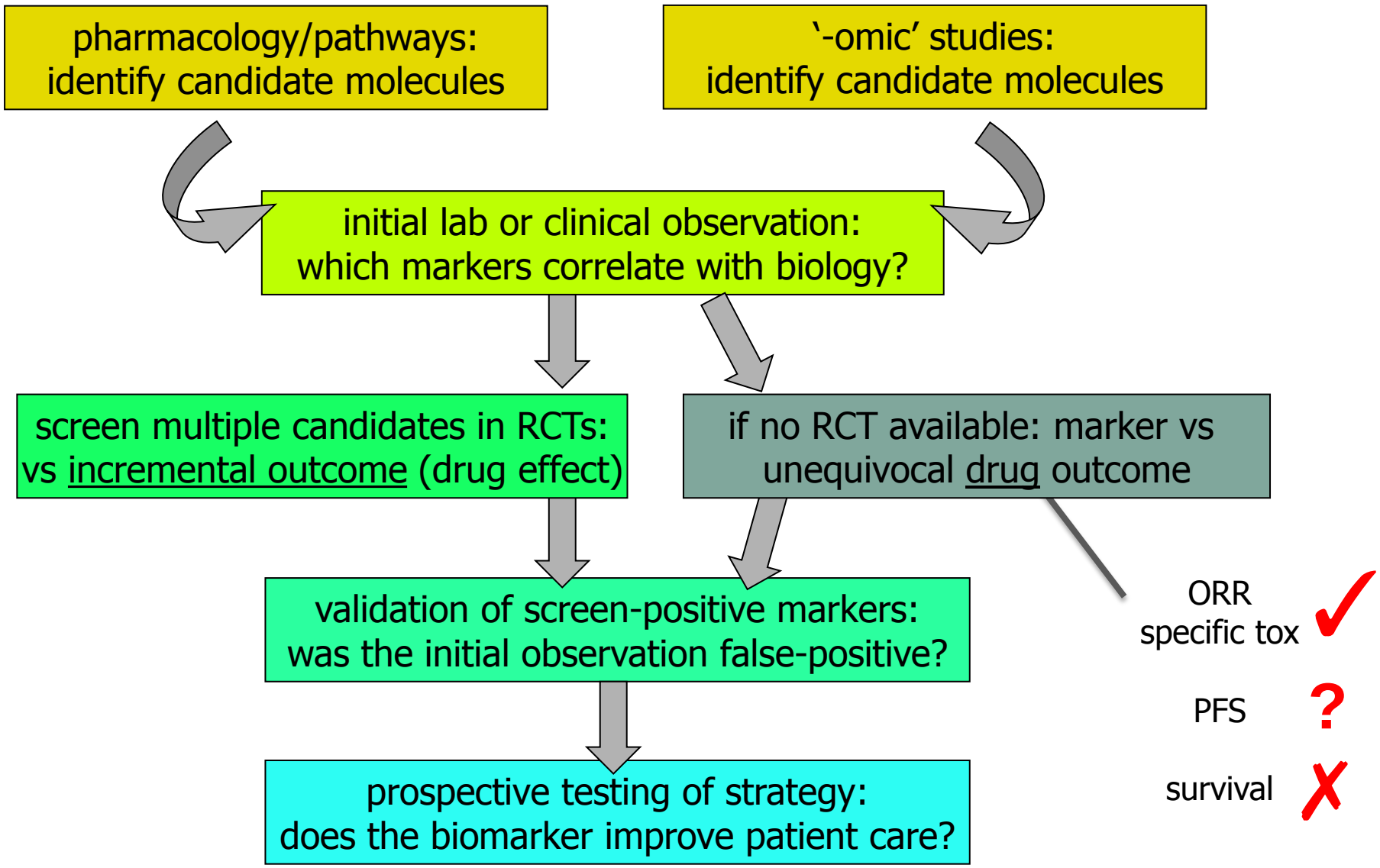
we may have a **predictive marker** – correlates with response to drug X



randomised trial






pharmacology/pathways:
identify candidate molecules
'-omic' studies:
identify candidate molecules
initial lab or clinical observation:
which markers correlate with biology?
screen multiple candidates in RCTs:
vs incremental outcome (drug effect)
if no RCT available: marker vs
unequivocal drug outcome
validation of screen-positive markers:
was the initial observation false-positive?
prospective testing of strategy:
does the biomarker improve patient care?
ORR
specific tox
PFS
survival

hsa-mir31-3p Expression as a Predictor of Anti-EGFR response in WT KRAS Patients with mCRC

G. Manceau, JB. Bachet, B. Chibaudel, F. Liebaert, O. Bouché, F. Penault-Llorca, MD. Diebold, T. André, S. Imbeaud, P. Laurent-Puig

microRNA

- ~22-base RNAs
- bind to and regulate mRNA
- more stable than mRNA
- profiling arrays (e.g. Illumina);
- specific assays (e.g. qPCR - Taqman)

hsa-mir31-3p Expression as a Predictor of Anti-EGFR response in WT KRAS Patients with mCRC

G. Manceau, JB. Bachet, B. Chibaudel, F. Liebaert, O. Bouché, F. Penault-Llorca, MD. Diebold, T. André, S. Imbeaud, P. Laurent-Puig

Global miRNA expression profiling of 43 WT KRAS CR tumor frozen tissue samples using the Illumina Human microRNA Expression Profiling Assay v2® : **1145 miRNAs**

Survival information is associated with miRNA hsa-mir-31-3p expression.

Predictive ability of hsa-miR31-3p

- Training group: retrospective series of 33 patients treated with cetuximab and irinotecan:

  → hsa-miR31-3p exhibits significant different expression levels* between tumor samples from patients with bad or good PFS (25 weeks PFS)

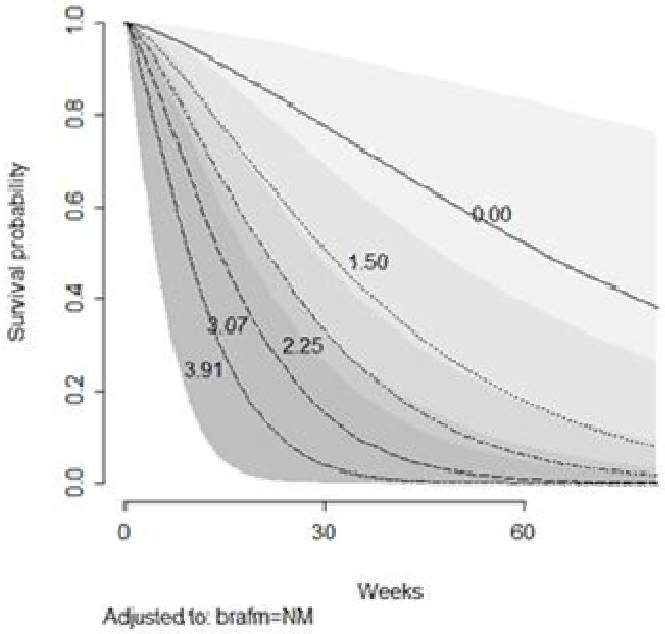
- Validation groups*: 2 prospective series of 19 patients treated with cetuximab and of 19 patients treated with panitumumab

  → Predictive ability of hsa-miR31-3p expression is validated on the 2 series

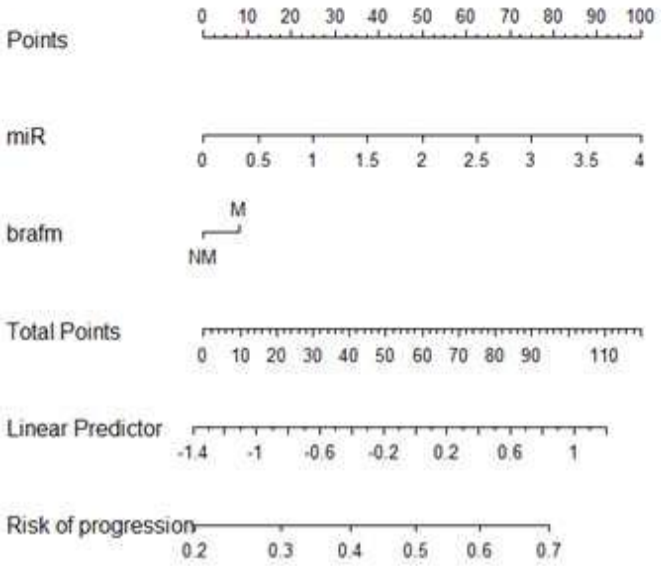
* Taqman technology

Nomogram

- Construction of a nomogram for PFS to predict the likelihood of progression



Multivariate Cox proportional hazards models with BRAF mutational status and has-miR31-3p expression as covariates.



Nomogram for PFS constructed based on BRAF mutational status and log. miR expression (miR). For each patient, points are allocated to each of the variable by selecting the corresponding points from the points scale.

525PD

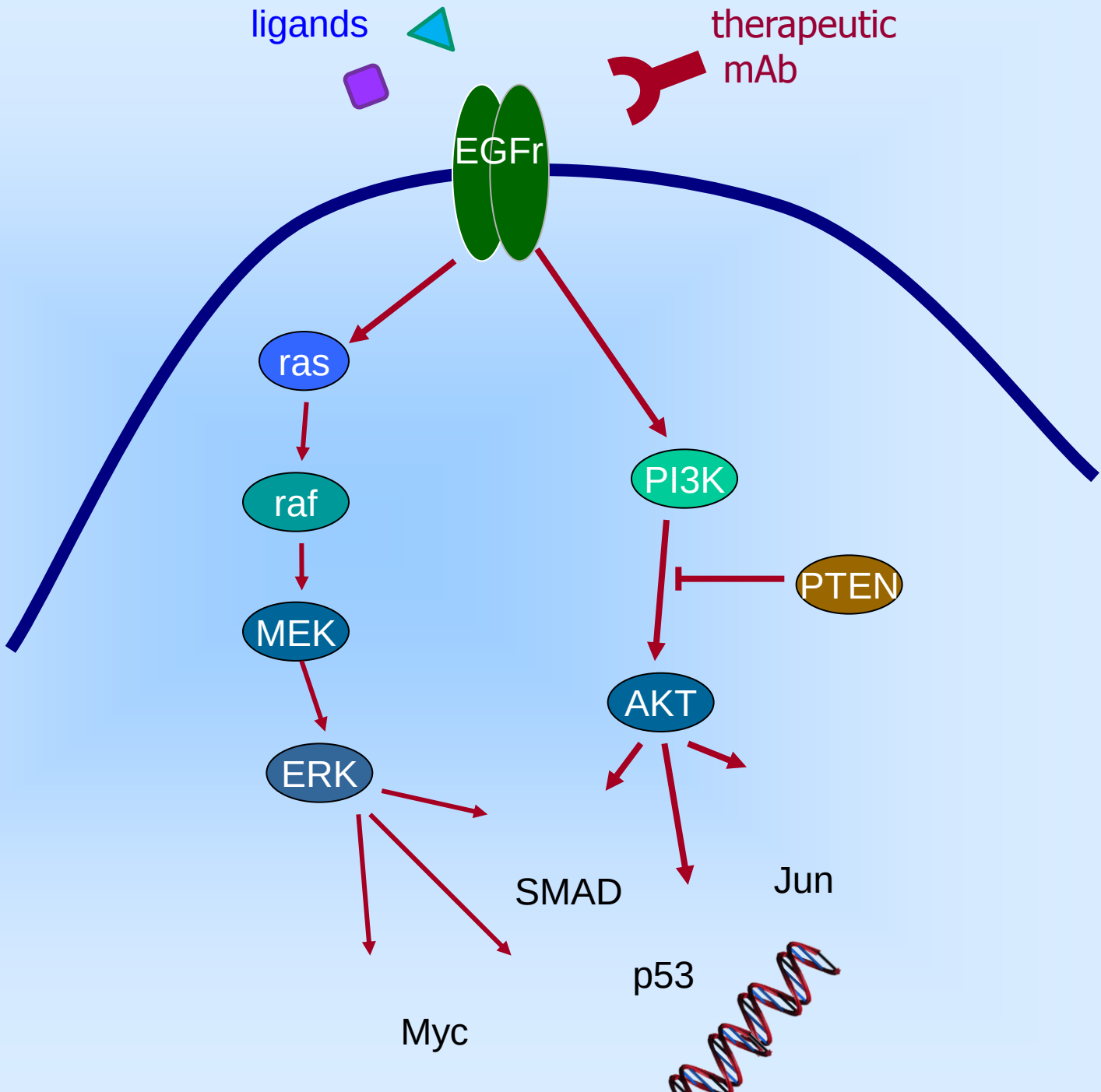
- What have we learned?
  - miRNAs are promising new markers
  - miR31-3p is prognostic for PFS in *KRAS*-wt patients receiving chemo+EGFRmAb

- What next?
  - use RCT material to see if miR31-3p predicts which KRAS-wt patient benefit or do not benefit from the addition of EGFR-mAb

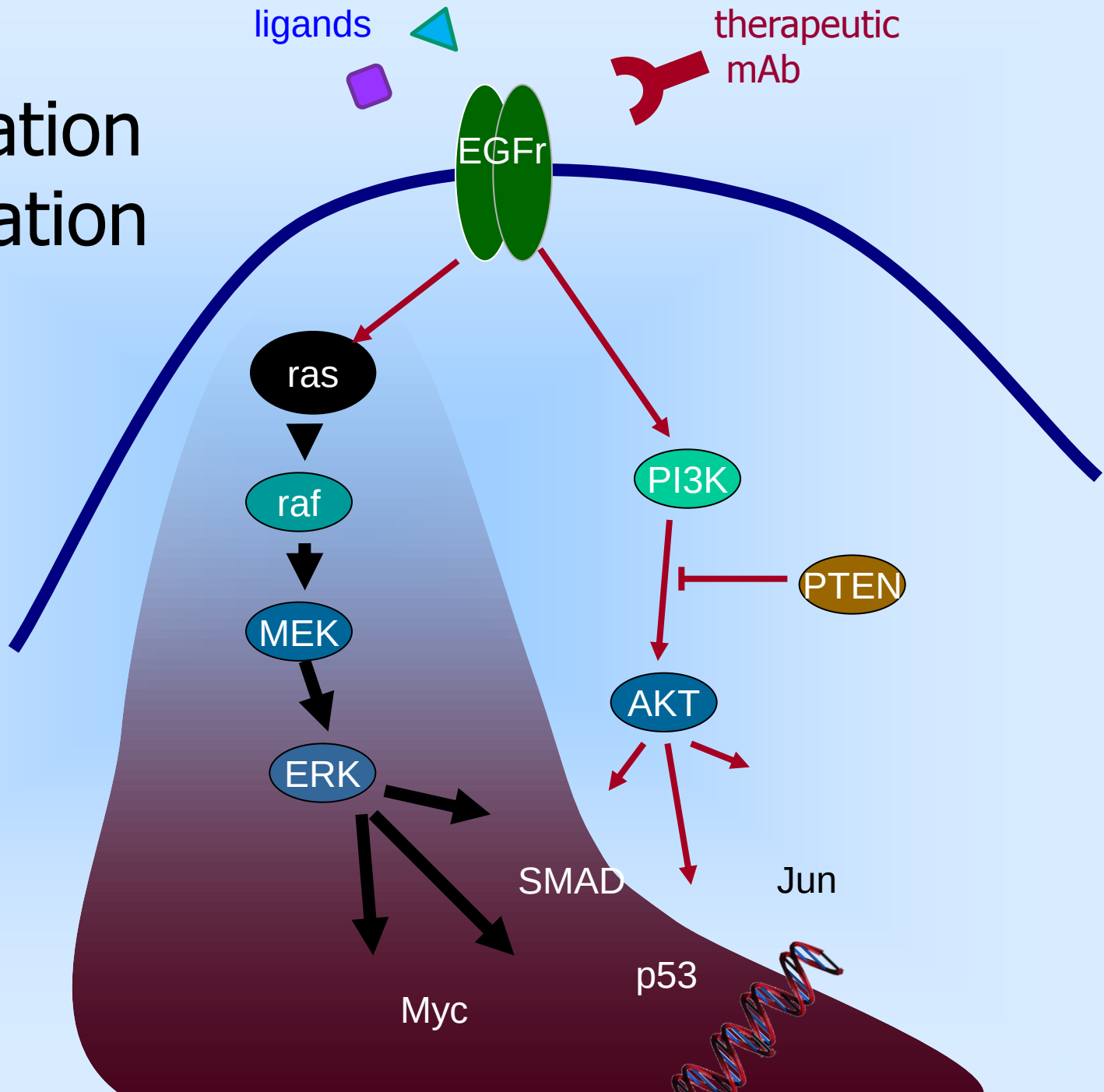
Development of a predictive score using amphiregulin (AREG), epiregulin (EREG) and EGFR-FISH expression levels to determine treatment efficacy in mCRC patients receiving cetuximab-based therapy. - Analysis of the German AIO CRC-0104 trial -

S. Stintzing1, R.P. Laubender2, D.P. Modest1, C. Kapaun1, A. Jung3, L. Fischer von Weikersthal4, H.Hass5, U. Vehling-Kaiser6, C.Giessen1, T. Kirchner3, U. Mansmann2, V. Heinemann1

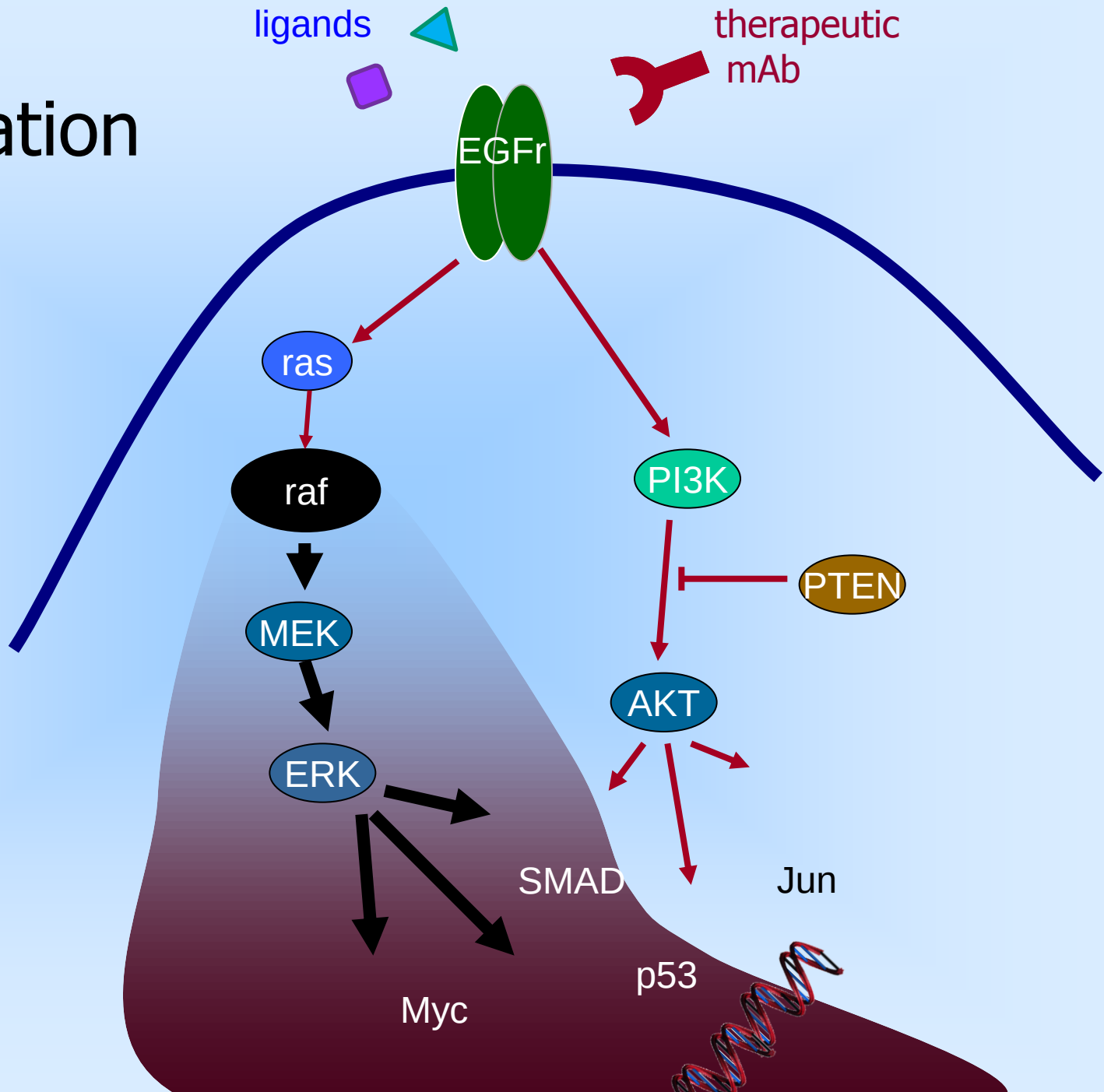
1Department of Medical Oncology and Comprehensive Cancer Center, Hospital Grosshadern, University of Munich; 2Institute of Medical Informatics, Biometry and Epidemiology, University of Munich; 3 Institute of Pathology, University of Munich; 4 Gesundheitszentrum St. Marien, Amberg; 5 Marienhospital Stuttgart; 6 Onkologische Praxis, Landshut


ligands
therapeutic
mAb
EGFr
ras
raf
MEK
ERK
PI3K
PTEN
AKT
SMAD
Jun
p53
Myc

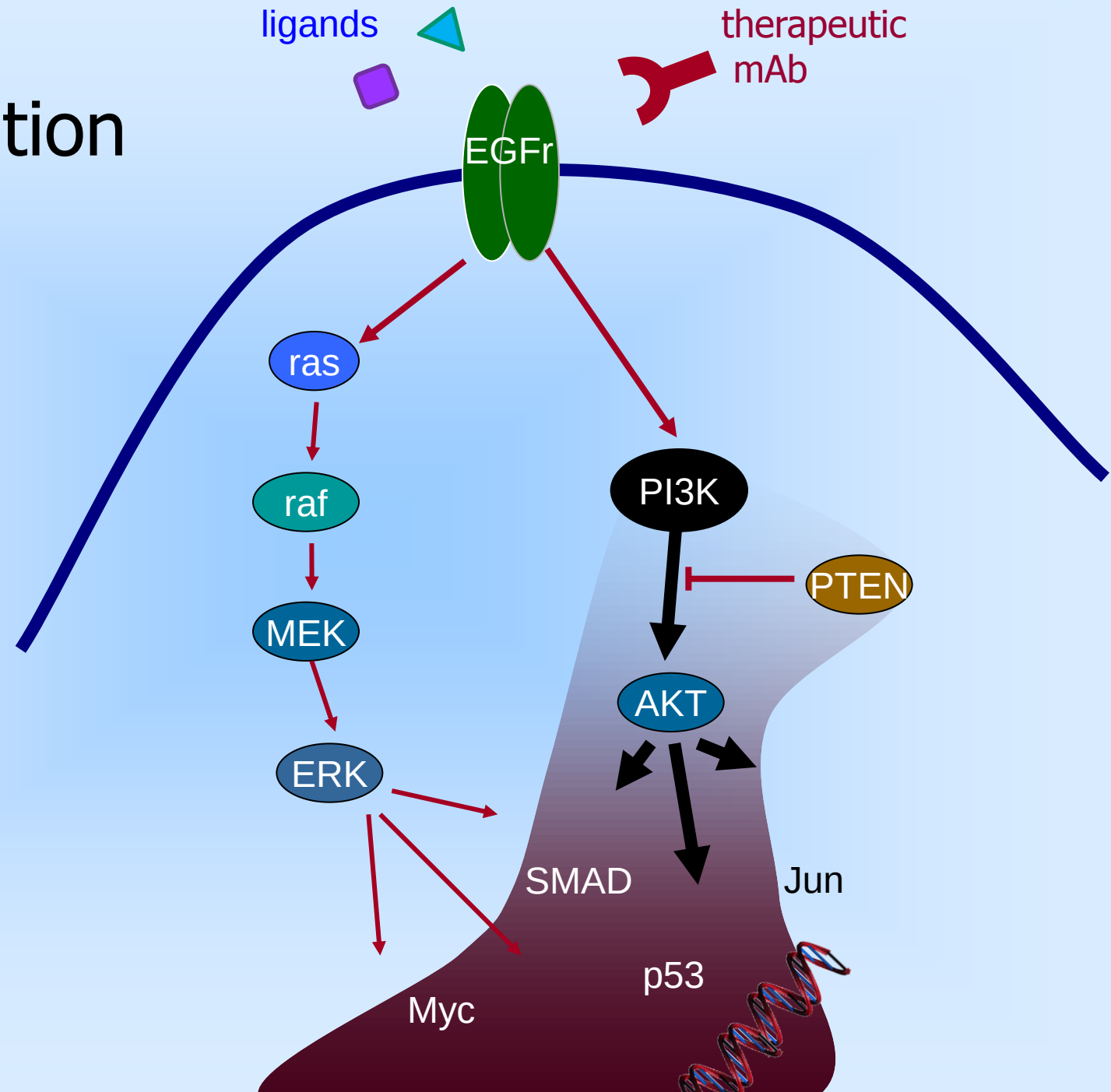
KRAS mutation
NRAS mutation

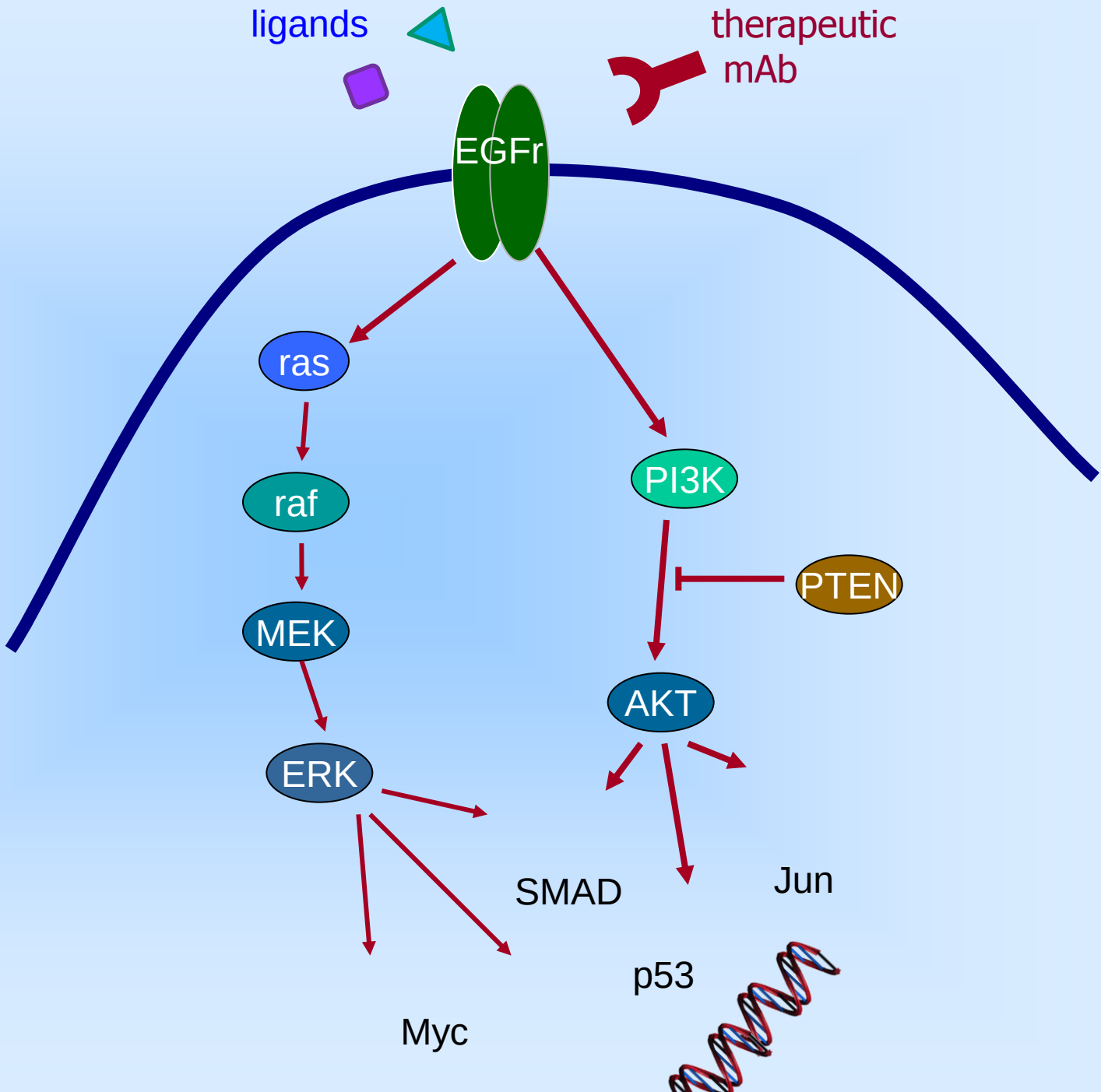


BRAF mutation

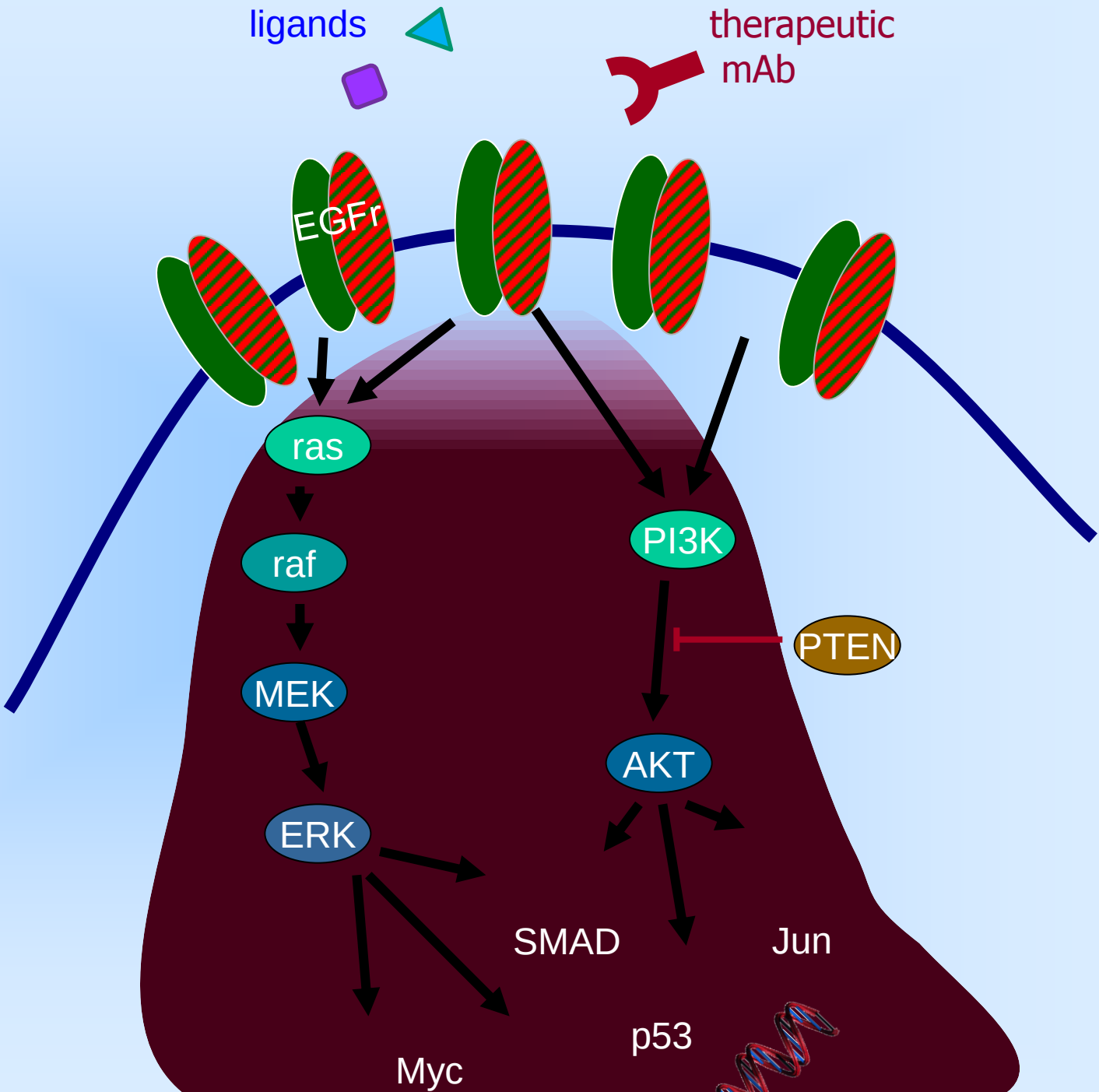


PI3K mutation
PTEN loss

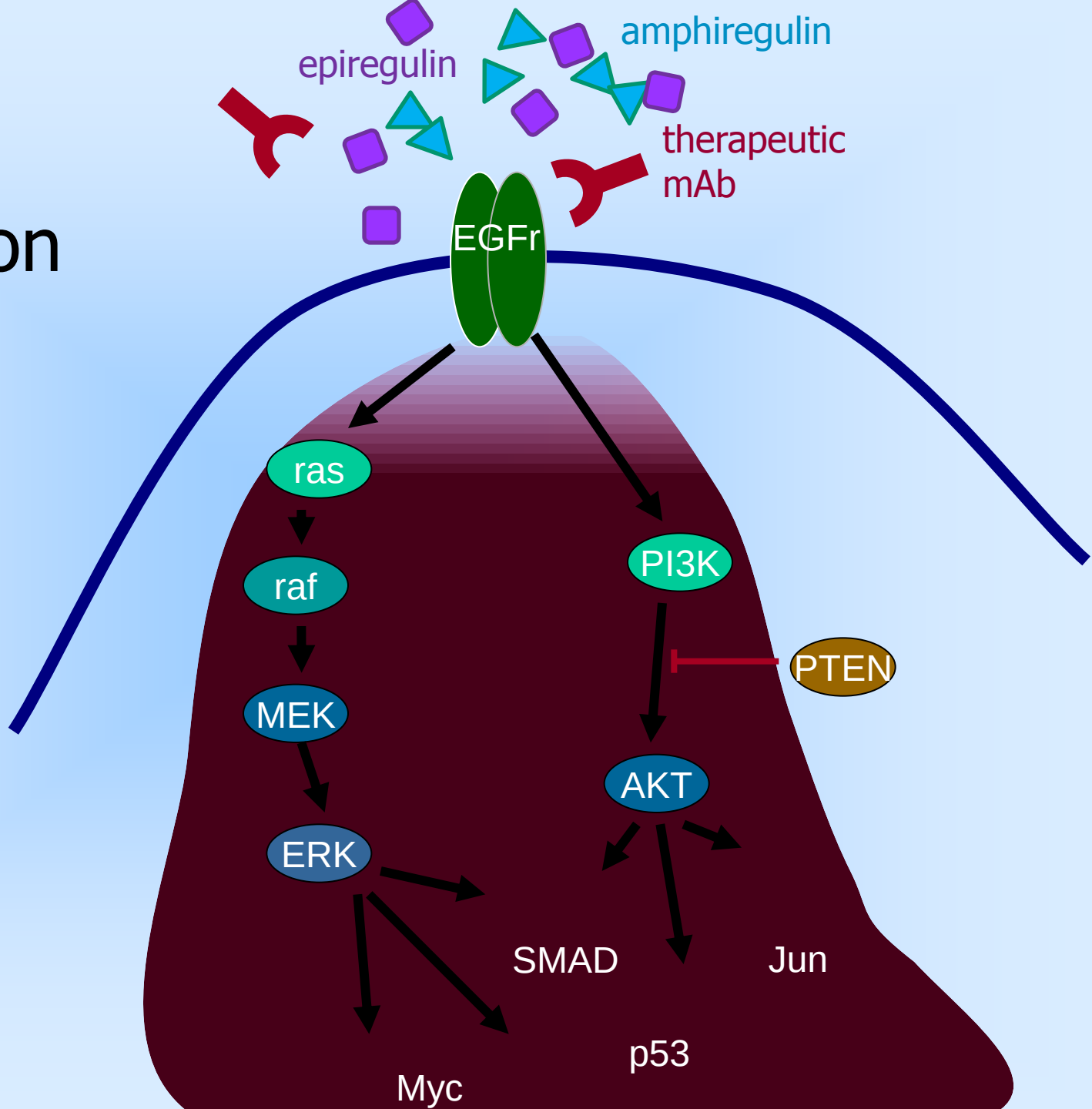



ligands
therapeutic
mAb
EGFr
ras
raf
MEK
ERK
PI3K
PTEN
AKT
SMAD
Jun
p53
Myc

Receptor increase



Ligand upregulation



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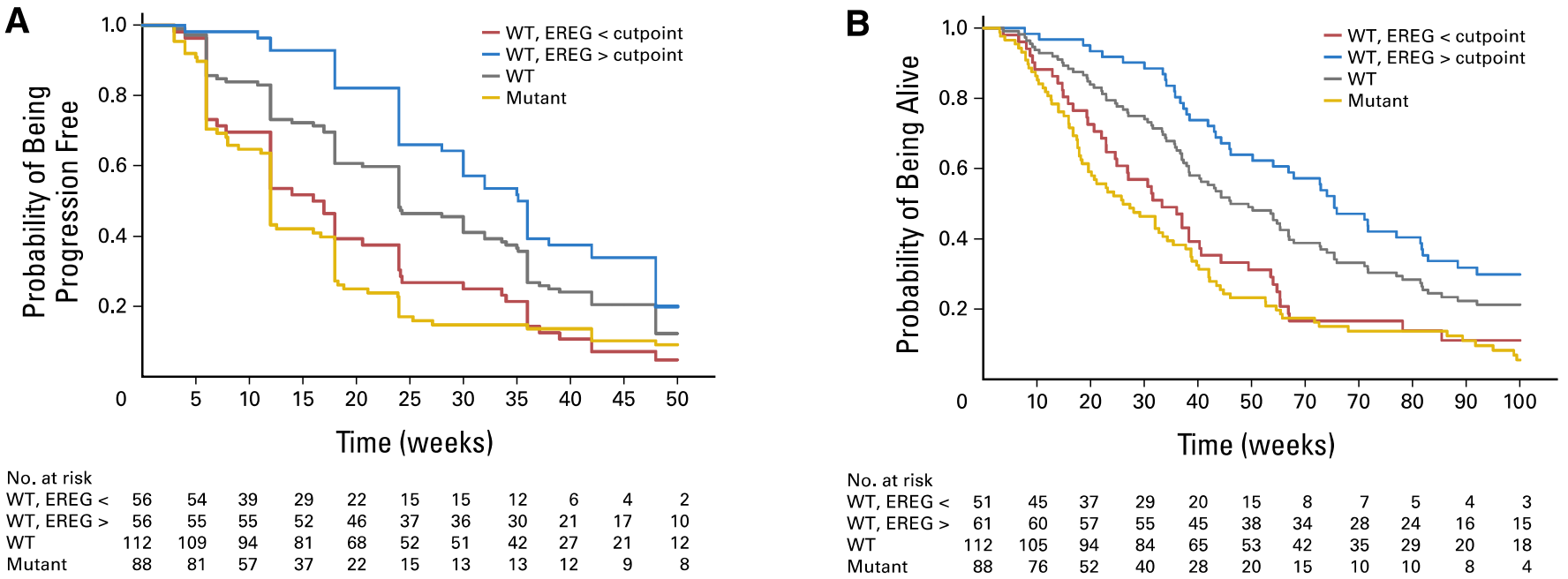
JOURNAL OF CLINICAL ONCOLOGY

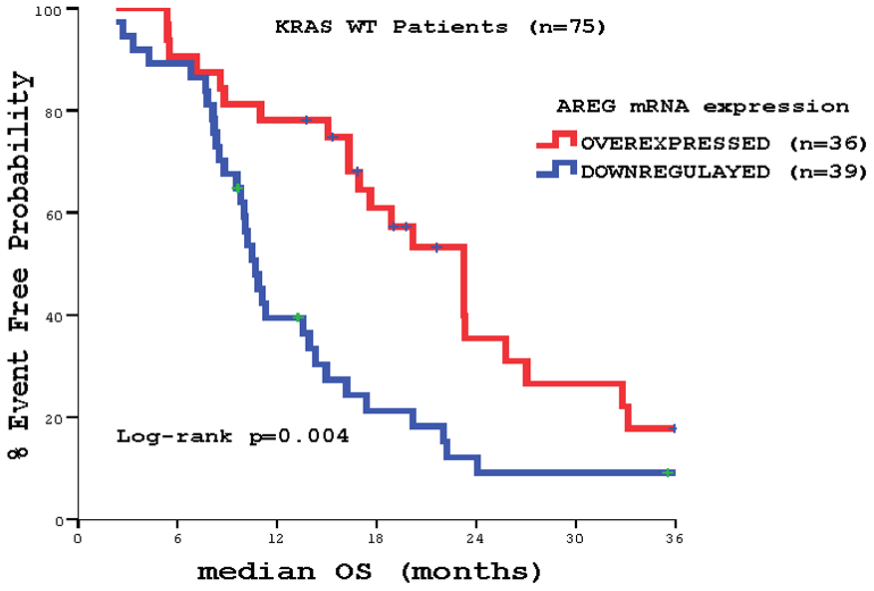
ORIGINAL REPORT



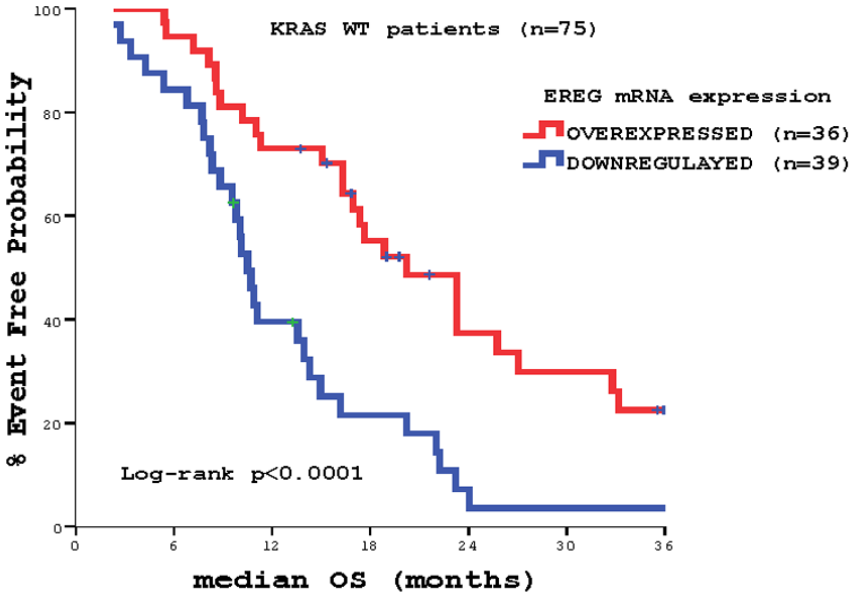
PFS (A) and OS (B) according to EREG expression (blue, red) in KRAS-wt patients receiving cetuximab (n=112), and compared with KRAS-mut patients (yellow)

Jacobs B, deRook W, et al and Tejpar S. JCO 27:5068-74, 2009

Amphiregulin



Epiregulin



Overall Survival according to AREG and EREG expression in KRAS-wt patients receiving cetuximab (n=75)

Saridaki Z. Tzardi M. et al and Souglakos J. PLoS ONE 6(1):e15980, 2011.

CiOx Study Design

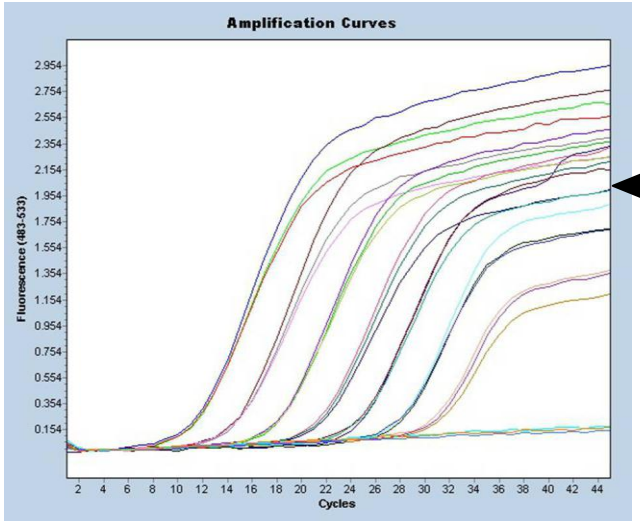
Metastatic colorectal cancer
61 pts (of 185 in trial)

→ **R**

→ **CAPIRI + Cetuximab**

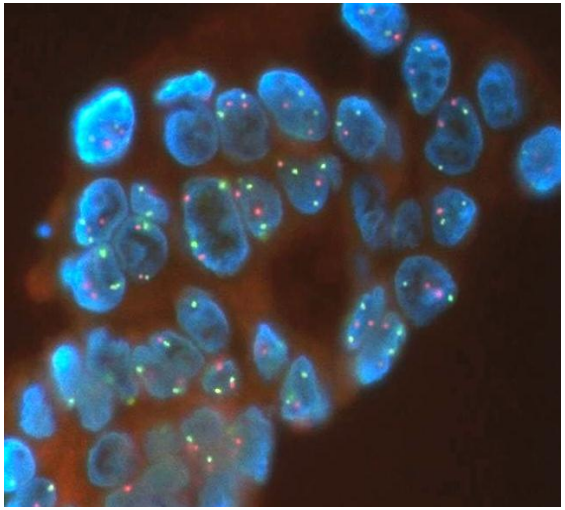
→ **CAPOX + Cetuximab**

Endpoints:
ORR, PFS, OS

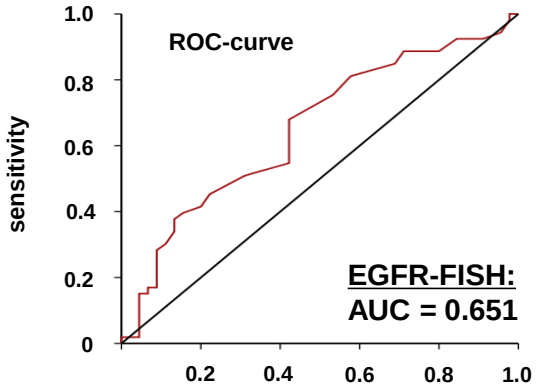


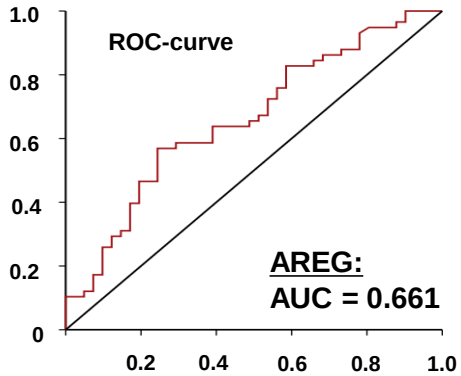
Multivariate analysis
for association with ORR

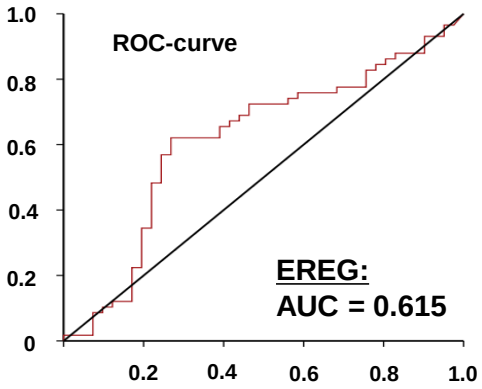
AREG & EREG
EGFR FISH
+
age
sex
BRAF-mut



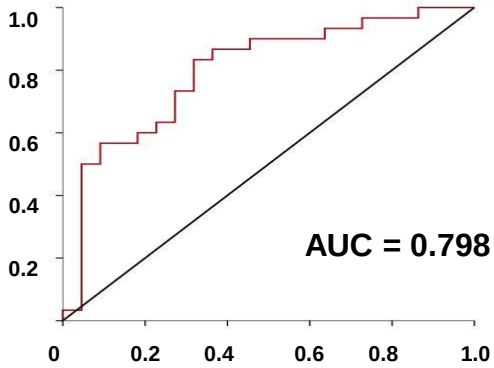
Single Markers







Combined Model (AREG+EGFR)



Model correctly identifies patients with better outcomes <u>in this test set</u> (as expected)

- ORR
- PFS
- OS

Conclusions

- In this retrospective and exploratory analysis it was possible to predict ORR probability with the help of molecular markers.
- There is an acceptable discriminatory performance as measured by the AUC for predicting ORR by AREG and EGFR-FISH.
- Both molecular markers might be promising candidates for predicting ORR under cetuximab-based treatment regimens.
- Prospective evaluation of these markers is needed for replicating and validating our findings.

526PD

- What have we learned?
  - the combined use of AREG and EGFR FISH may be useful
- What next?
  - validate the predictive model in independent dataset(s)
  - establish assays for FFPE material
  - consider alternative ways of combining data – e.g. [AREG⇧ or EREG⇧ or EGFR⇧] –vs– not
  - if still interesting, explore in RCT material

Pharmacogenetic predictors of severe chronic peripheral neuropathy in stage II-III colon cancer patients treated with oxaliplatin-based adjuvant chemotherapy: A GEMCAD study

A. Custodio, J. Moreno, J. Aparicio, J. Gallego Plazas, C.Fernández-Martos, J.Maurel, D. Ramos, P.Cejas, R.Madero, J. Feliu.

Grupo Español Multidisciplinar en Cáncer Digestivo

Toxicity predisposition

- Potential uses:
  - drug avoidance
  - dose reduction [and escalation]
  - targeted preventive measures

- Challenges:
  - pharmacological pathway led –vs– genomic approach to marker identification
  - wide and reliable risk discrimination needed to alter clinical management

The oxaliplatin problem

- High risk in relation to gain for many patients
- Extent of the problem under-estimated initially

original article

Annals of Oncology 21: 1657–1661, 2010
doi:10.1093/annonc/mdp594
Published online 20 January 2010

Capecitabine combined with oxaliplatin (CapOx) in clinical practice: how significant is peripheral neuropathy?

D. J. Storey[1,2*], M. Sakala[2], C. M. McLean[2], H. A. Phillips[2], L. K. Dawson[2], L. R. Wall[2], M. T. Fallon[1] & S. Clive[2]

"...Concerningly, while the majority (94%) experienced acute PN (43% with functional impairment), at least 11% (possibly up to 30%) of adjuvant patients still had unresolved chronic PN which impaired function 12 months after CapOx completion."

CLINICAL AND PATHOLOGICAL CHARACTERISTICS

Characteristics	All patients (n=379)	Training cohort (n=202)	Validation cohort (n=177)	Characteristics	All patients (n=379)	Training cohort (n=202)	Validation cohort (n=177)
Median age (range)	61.94 (23-85)	63.82 (23-85)	59.8 (23-76)	**Grade**			
				Grade 1	60 (15.8%)	19 (9.4%)	41 (23.2%)
				Grade 2	274 (72.3%)	160 (79.2%)	114 (64.4%)
				Grade 3	45 (11.9%)	23 (11.4%)	22 (12.4%)
Sex				**Stage**			
Men	194 (51.2%)	115 (56.9%)	79 (44.6%)	II	105 (27.7%)	60 (29.7%)	45 (25.4%)
Women	185 (48.8%)	87 (43.1%)	98 (55.4%)	III	274 (72.3%)	142 (70.3%)	132 (74.6%)
Tumour site				**Adjuvant CT**			
Cecum-right colon	115 (30.34%)	60 (29.7%)	55 (33.1%)	FOLFOX	173 (45.6%)	51 (25.24%)	77 (43.5%)
Transverse colon	23 (6.1%)	15 (7.4%)	8 (4.5%)	CAPOX	206 (54.4%)	151 (74. 75%)	100 (56.5%)
Left colon-sigma	52 (13.7%)	28 (13.9%)	24 (13.6%)				

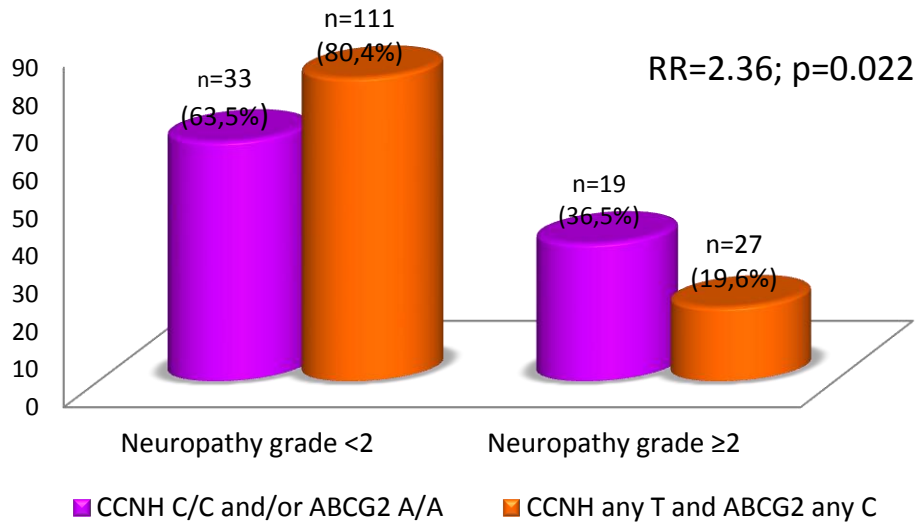
PERIPHERAL NEUROPATHY

All patients (n=279)	Training cohort (n=202)	Validation cohort (n=177)
No neuropathy	59 (29.2%)	23 (13%)
Grade 1	95 (47.02%)	82 (46.32%)
Grade ≥2	48 (23.76%)	72 (40.68%)

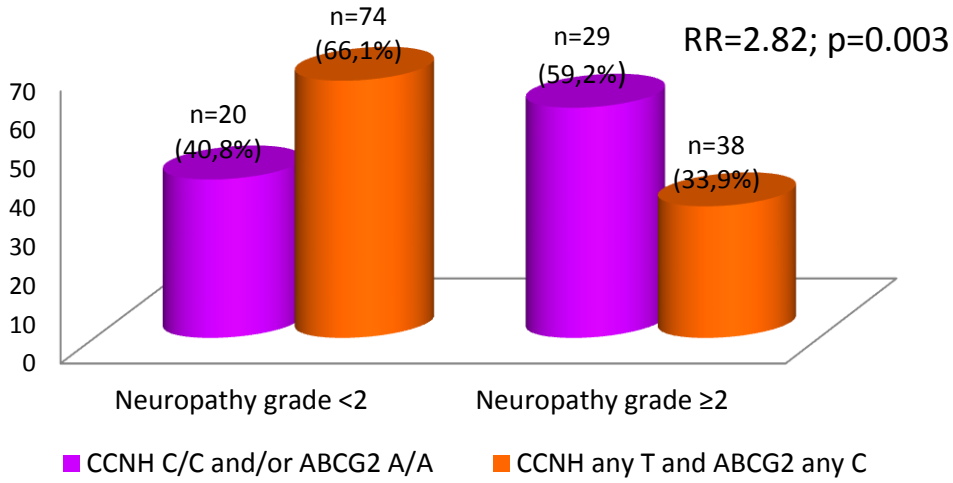
SELECTED GENES AND SNPs

Category	Gen	SNP	Category	Gen	SNP
Oxaliplatin sensibility/ resistance	ERCC1	rs11615, rs3212964	Drug transport	MDR1/ABCB1	rs1045642
	ERCC2/XPD	rs13181, rs1799793, rs238404		ABCG2	rs2231142
	ERCC5/XPG	rs4150279, rs4150360		SULT1A1	rs1968752
	ERCC6	rs2228527, rs7907557	Others	XPA	rs3176639, rs3176751
	XRCC 1	rs25489, rs12611088, rs3213255		XPC)	rs2607739, rs2733534
	XRCC2	rs3218536, rs3218408, rs3111471		E-selectine	rs3917412, rs3917436
	RAD23B	rs10759225, rs2147072		CCNH	rs2230641, rs3093816
	GSTP1	rs749174		MMP 1	rs498186
	MGMT	rs1803965, rs656639		mTOR	rs2295080, rs357278, rs6895953

CCNH rs2230641+ ABCG2 rs3114018 SNPs and NEUROPATHY (training cohort)



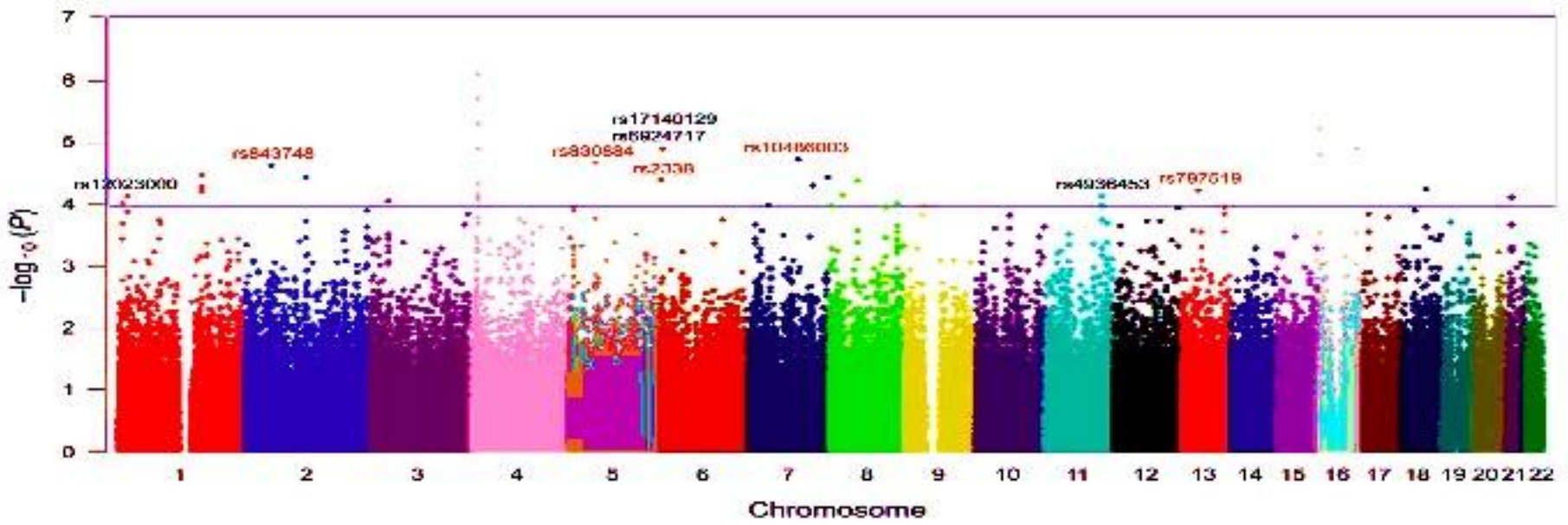
CCNH rs2230641+ ABCG2 rs3114018 SNPs and NEUROPATHY (validation cohort)



Polymorphic Markers Associated With Severe Oxaliplatin-Induced, Chronic Peripheral Neuropathy in Colon Cancer Patients

Hong-Hee Won, PhD[1,2]; Jeeyun Lee, MD, PhD[3]; Joon Oh Park, MD, PhD[3]; Young Suk Park, MD, PhD[3]; Ho Yeong Lim, MD, PhD[3]; Won Ki Kang, MD, PhD[3]; Jong-Won Kim, MD, PhD[4]; Soo-Youn Lee, MD, PhD[4,5]; and Se Hoon Park, MD, PhD[3]

Cancer 118:2828-36, 2012



Genes containing or adjacent to SNPs correlating with severe neuropathy in discovery and validation sets (n=96 discovery; 247 validation; 657K SNP profile)

- *TAC1*
- *FOXC1, GMDS*
- *ITGA1, PELO*
- *ACYP2, TSPYL6*
- *BTG4, POU2AF1*
- *CAMK2N1*
- *FARS2, LYRM4*
- *DLEU7*

527PD

- What have we learned?
  - convincing data: effect in validation cohort very similar to training set.
  - however CAUTION: hypothesis led SNPs but post-hoc combination of data from the best performing SNPs.

- What next?
  - risk discrimination not wide enough to be clinically applicable ‘as is’ (34% vs 60% grade ≥2)
  - combine with other risk factors (other SNPs, comorbidities)

Poster Discussion:

525PD	Hsa-miR31-3p Expression as a Predictor of Anti-EGFR response in wild-type KRAS Patients with metastatic Colorectal Cancer	Pierre Laurent-Puig, FR
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Discussant: Matt Seymour,

University of Leeds & NCRN, UK