State of the art and new targets in the treatment of small cell lung cancer:

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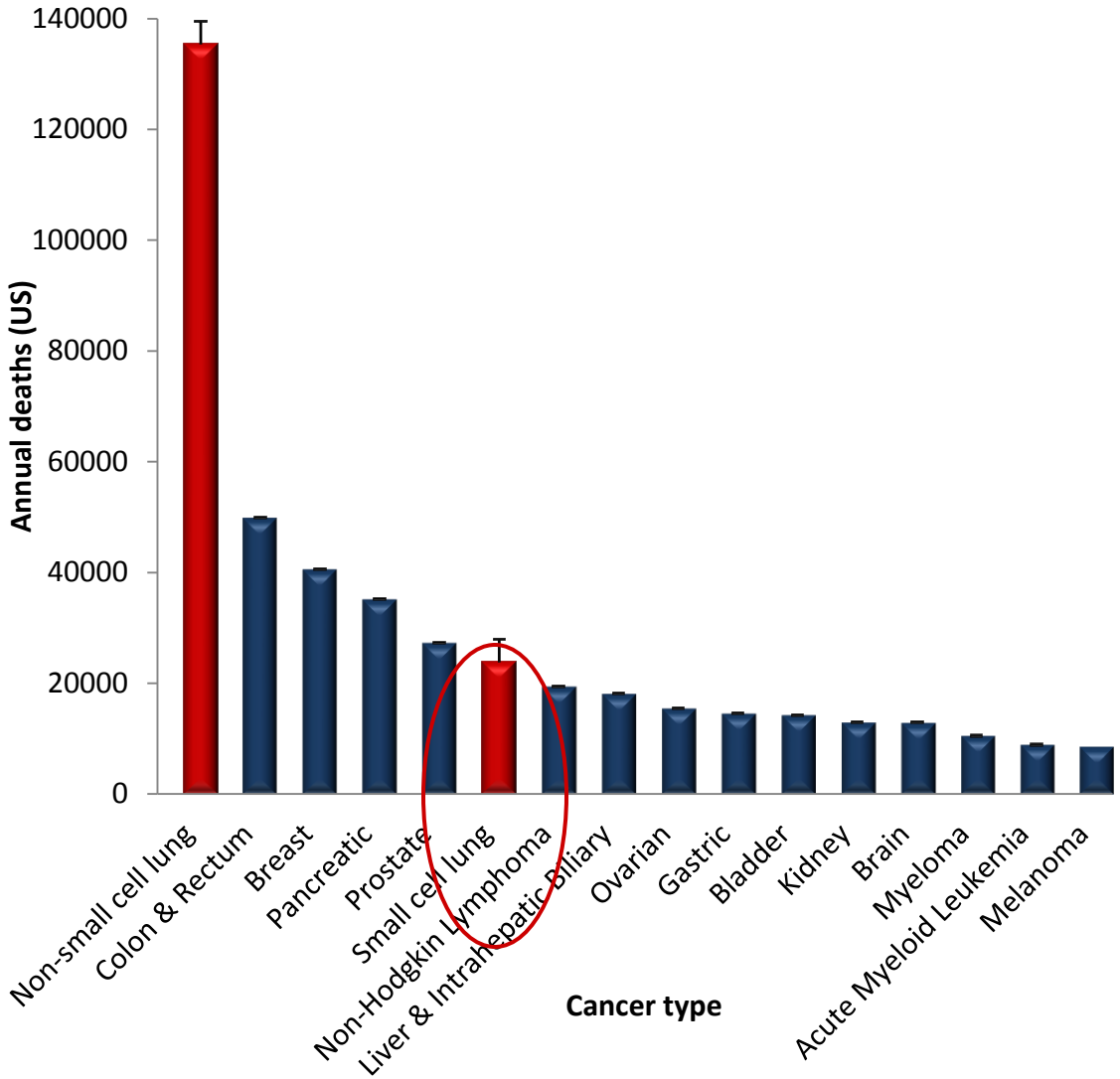
Disclosures

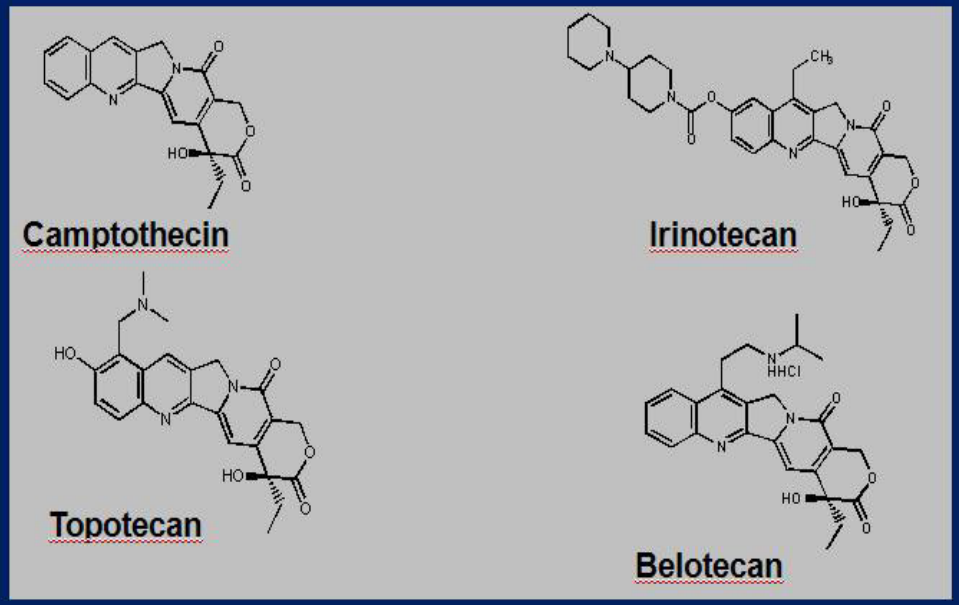
- None for this talk
- Ad boards for BI, MSD, Pierre Fabre Biomarin
- Research grants from Roche
- Meeting support

US cancer deaths

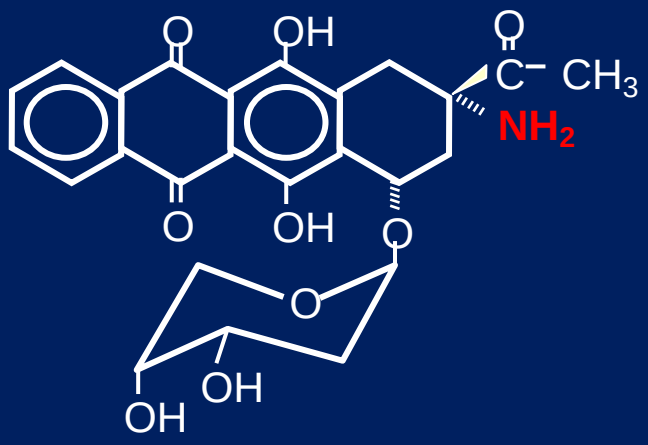


Cytotoxics

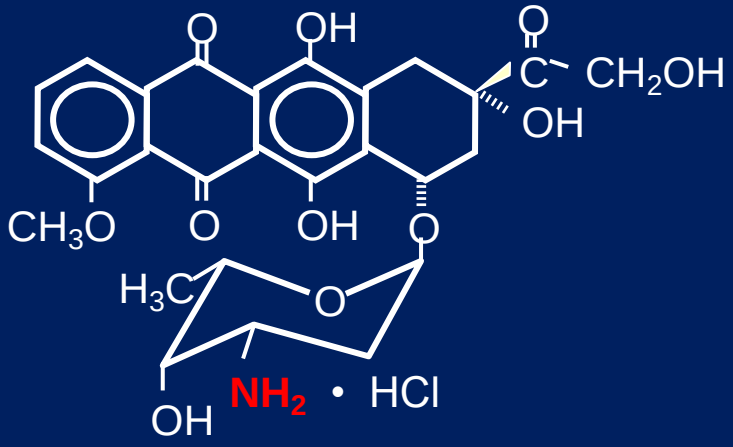
- Irinotecan – topo 1 inhibitor
- Topotecan – topo 1 inhibitor
- Amrubicin – topo 2 inhibitor



Amrubicin (AMR)

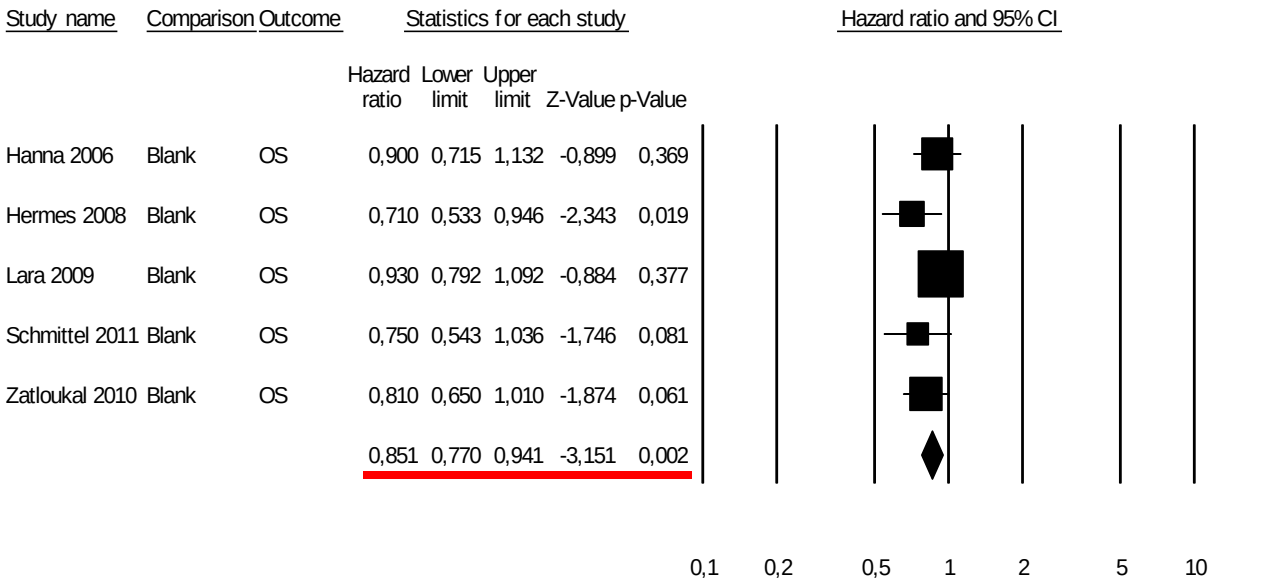


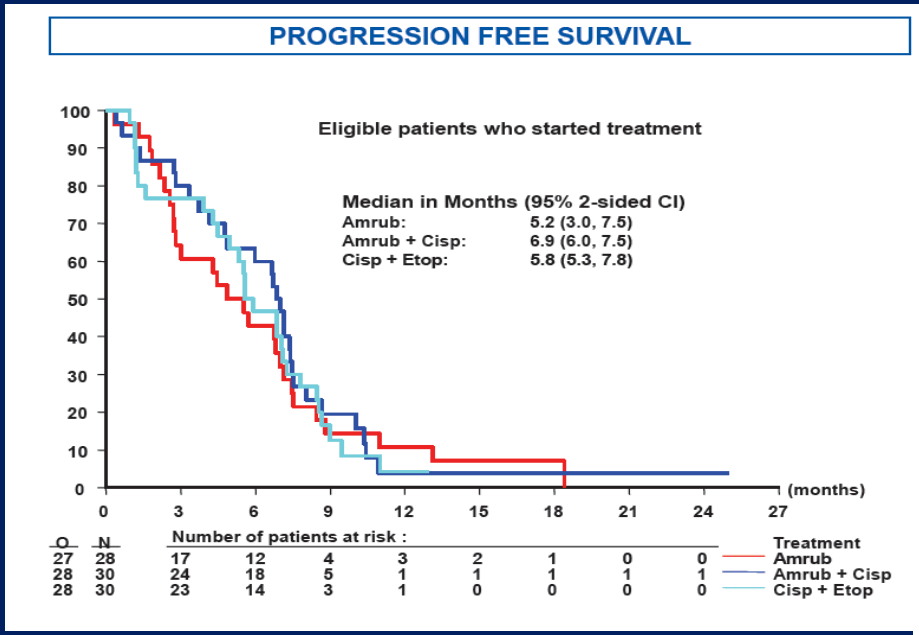
Doxorubicin (DXR)



Irinotecan East vs West – meta

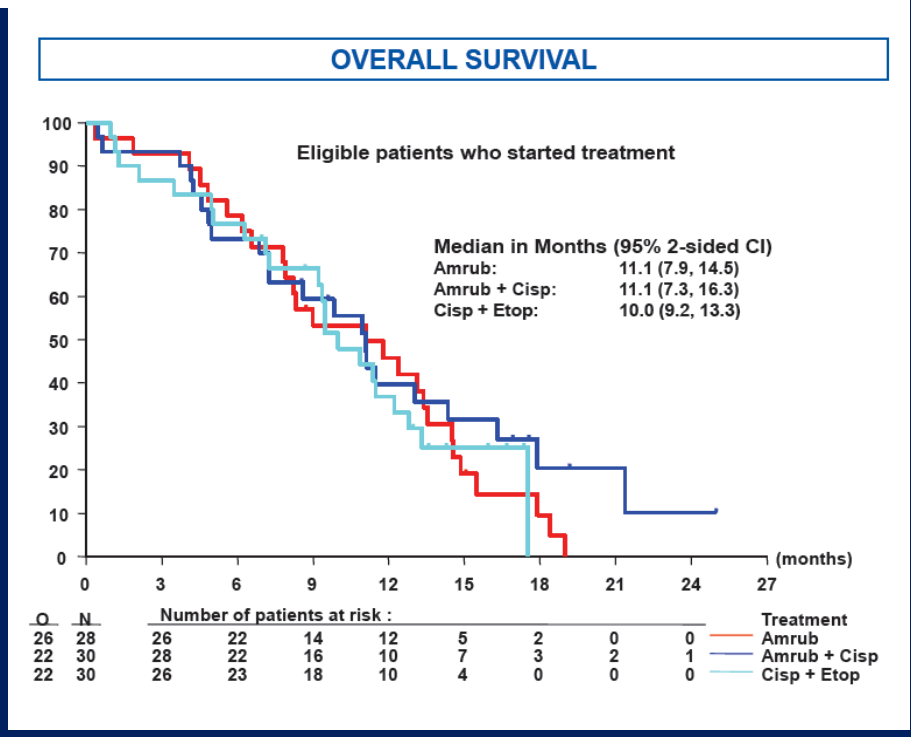
- OS positive in both but magnitude greater in the eastern 40% v 15%
- Snap shot of world Tx





First line

Amrubinin not better than PE in first line



Amrubicin and cisplatin (AP) with irinotecan and cisplatin (IP) for the treatment of extended-stage small cell lung cancer (ED-SCLC): JCOG0509 – *Kotani Y et al*

- aged 20 to 70, and ECOG PS 0–1:
- IP: I (60 mg/m^2) iv on days 1, 8, and 15, and P (60 mg/m^2) iv on day 1, every 4 weeks; or
- AP: A (40 mg/m^2) iv on day 1–3, and P (60 mg/m^2) iv day 1, 3 weeks
  - Dose of A was decreased from 40 mg/m^2 to 35 mg/m^2 due to increased FN

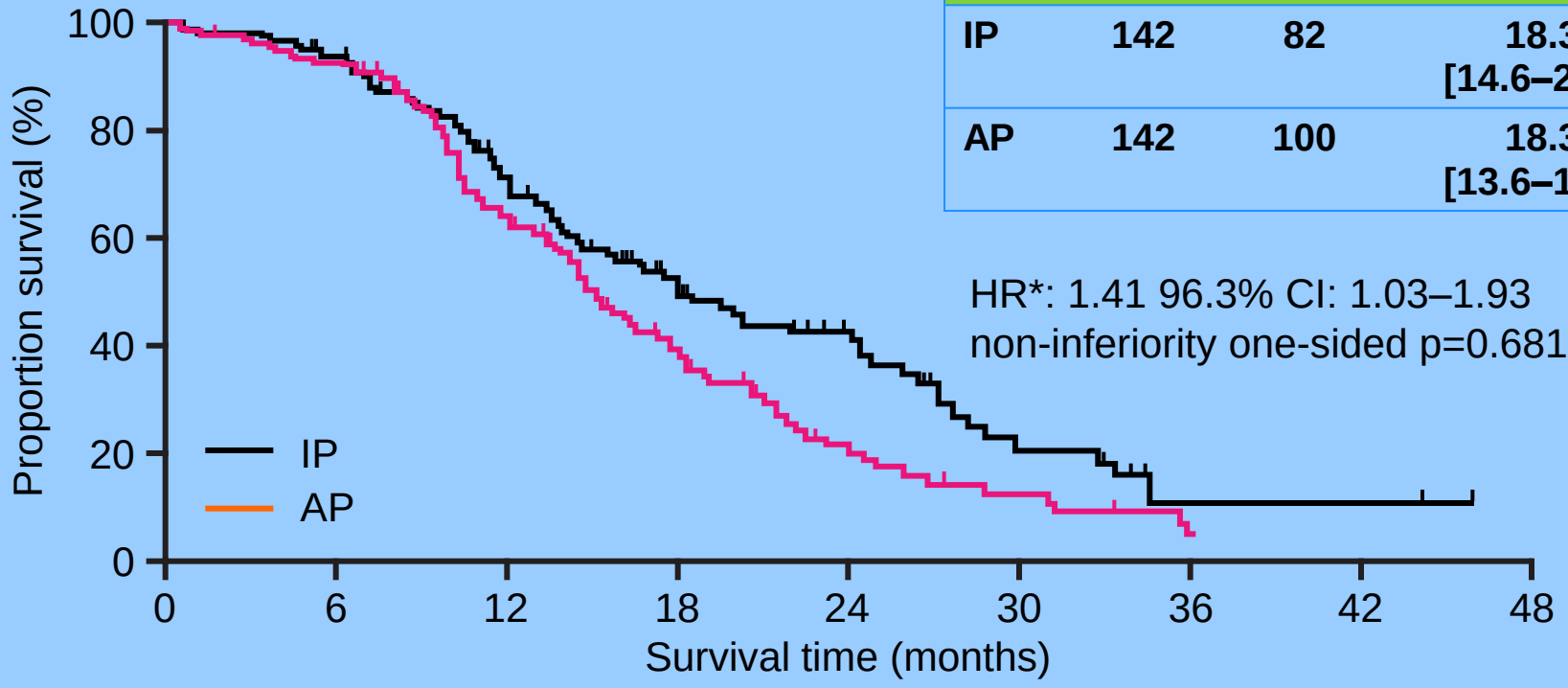
Patient characteristics	IP	AP
Patients enrolled	142	142
Male/Female	120/22	119/23
Age yrs, median (range)	63 (39–70)	63 (29–70)
Performance status: 0/1	78/64	80/62
Measurable lesion +/-	1/141	2/140
Metastasis (overlapped): lung/bone/brain/liver/others	9/25/32/35/68	14/31/41/45/64

FN, febrile neutropenia

Kotani et al. J Clin Oncol 30, 2012 (suppl; abstr 7003)

Key efficacy and safety data

	Pts	Event	Median (mo) [95% CI]
IP	**142**	**82**	**18.3 [14.6–24.3]**
AP	**142**	**100**	**18.3 [13.6–17.5]**



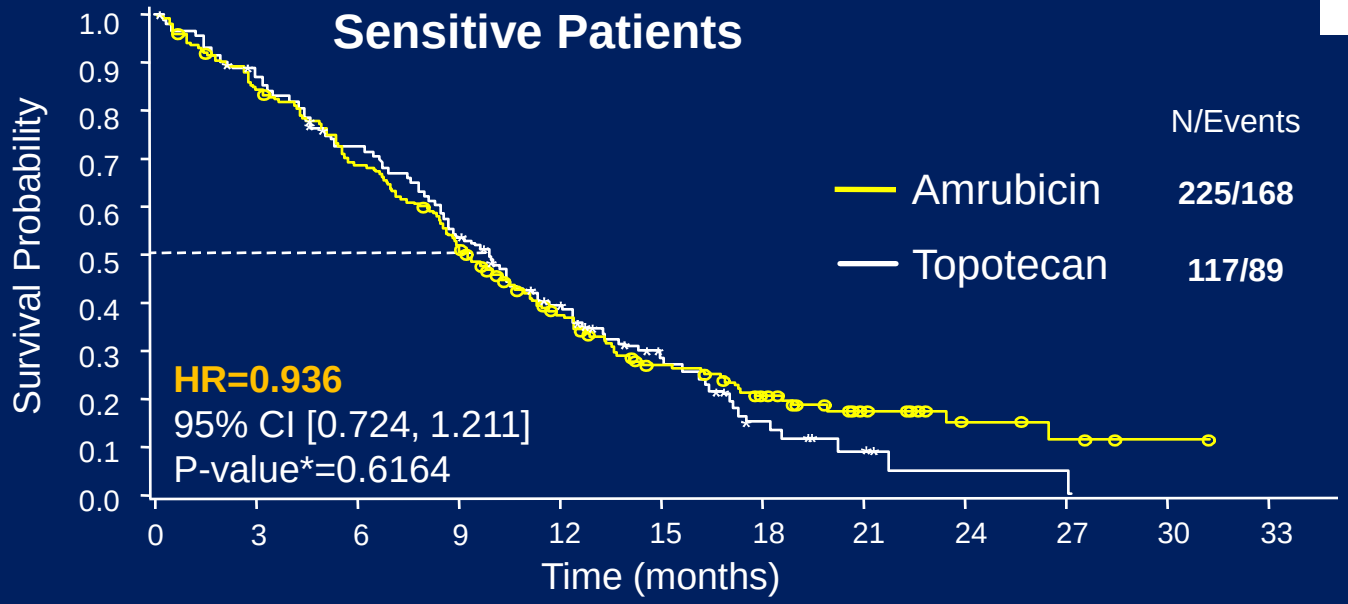
HR*: 1.41 96.3% CI: 1.03–1.93
non-inferiority one-sided p=0.681

- **Median PFS: 5.7 (IP) vs 5.1 months (AP) (HR 1.44, 95% CI: 1.13–1.83)**
- **Grade 4 neutropenia (22.5% vs 79.3%) and Grade 3–4 febrile neutropenia (10.6% vs 32.1%) was higher in the AP arm, while Grade 3–4 diarrhoea (7.7% vs 1.4%) was higher in IP arm**

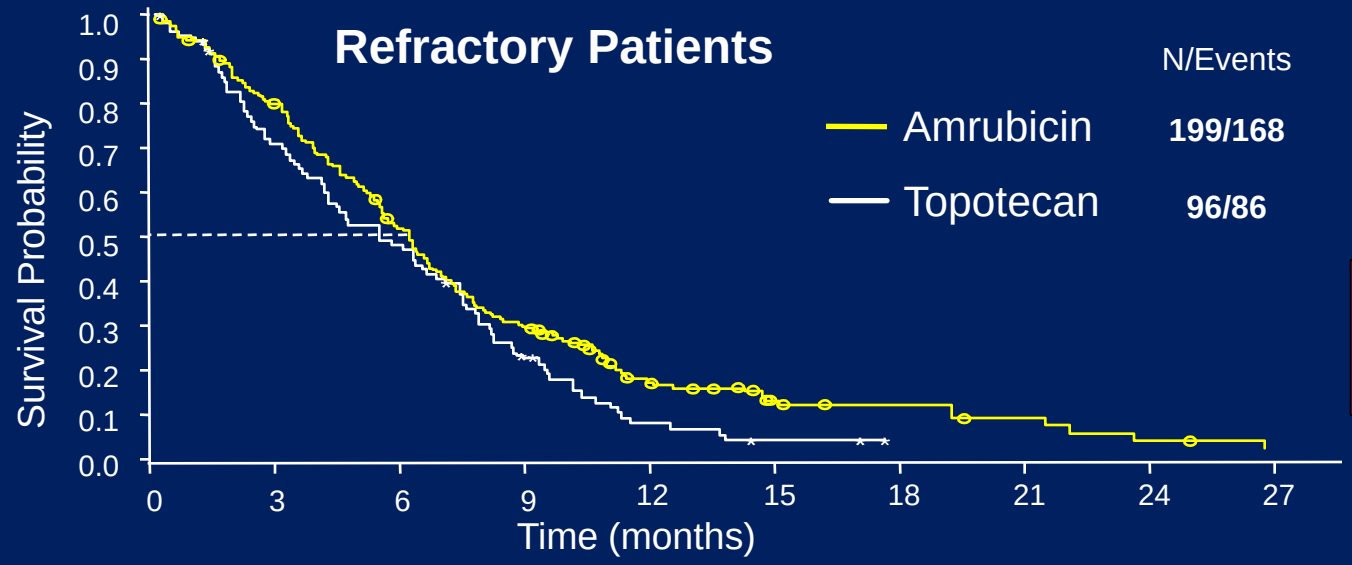
Amrubinin not better than IP in first line

Kotani et al. J Clin Oncol 30, 2012 (suppl; abstr 7003)

2nd line: amrubicin not better than topo



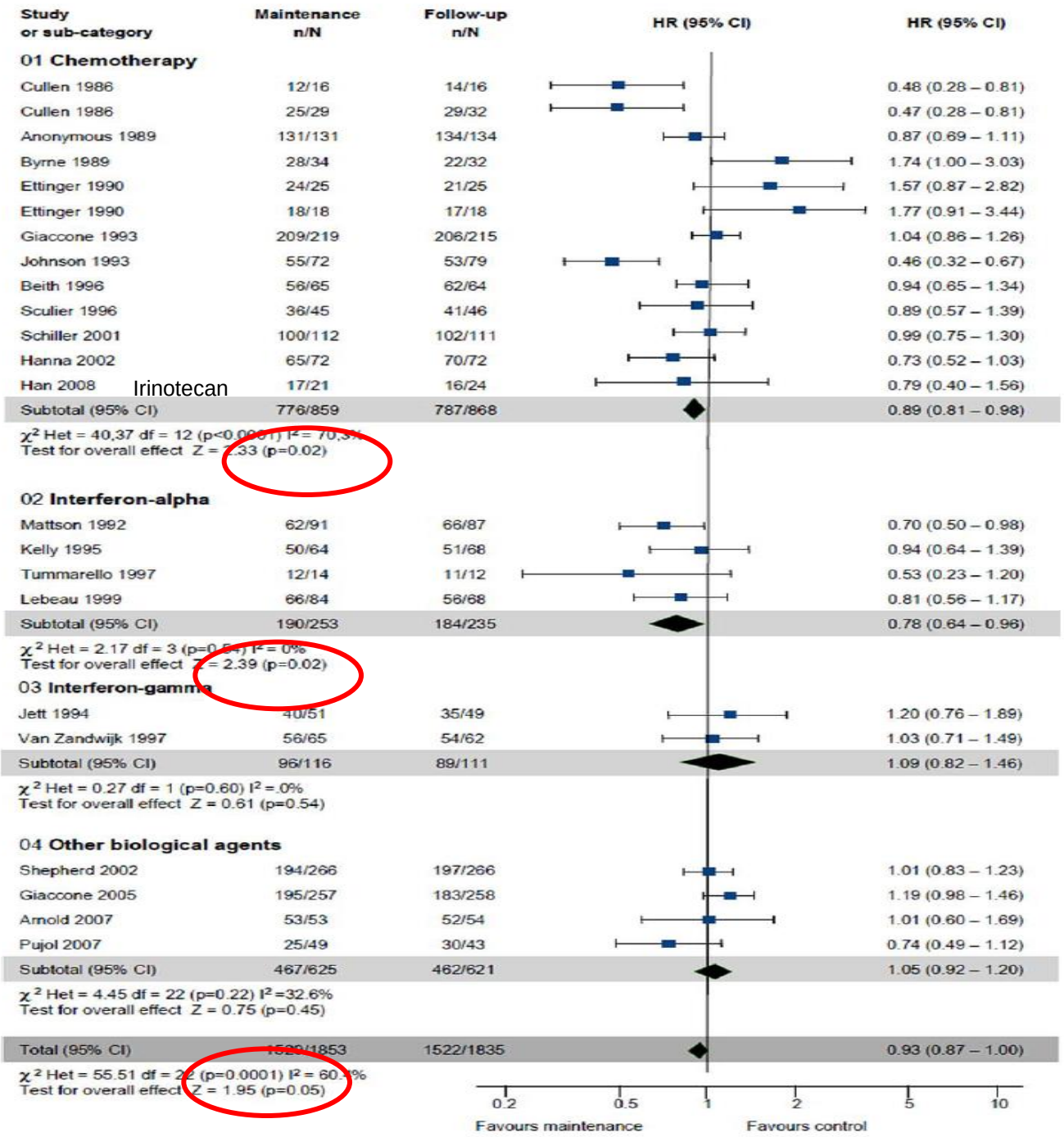
	N/Events	Median OS	95% CI
Amrubicin	**225/168**	**9.2 months**	**8.5-10.6**
Topotecan	**117/89**	**9.9 months**	**8.5-11.5**



	N/Events	Median OS	95% CI
Amrubicin	**199/168**	**6.2 months**	**5.5-6.7**
Topotecan	**96/86**	**5.7 months**	**4.1-7.0**

HR=0.766
95% CI [0.589, 0.997]
P-value*=0.0469

* Unstratified log-rank test



Maintenance chemotherapy

21 RCTs
PFS neg
OS +

Rossi et al

Maintenance sunitinib for untreated ext SCLC: A randomized, placebo controlled phase II study CALGB 30504 (ALLIANCE)

4-6 cycles of CT (cis 80 mg/m^2/carbo AUC5 plus etop 100 mg/m^2 d1-3 q3w)

Maintenance sunitinib 150 mg/day loading then 37.5 mg/day/placebo

Primary endpoint: PFS

- 144 patients; 138 patients received CT;
- 95 randomised to maintenance; 85 received (44 sunitinib, 41 placebo)
- PFS on maint: **2.3 vs. 3.8** mths p v sunit (HR 1.53; 90% CI 1.03–2.27; **p=0.037**)
- OS: **6.9 v 9.0** mths p v sunitinib (HR 1.17; 90% CI 0.77–1.78; p=0.27)
- 40% crossover

- G 3/4 tox in ≥5% with sunitinib: fatigue, neuts, platelets and hyponatremia

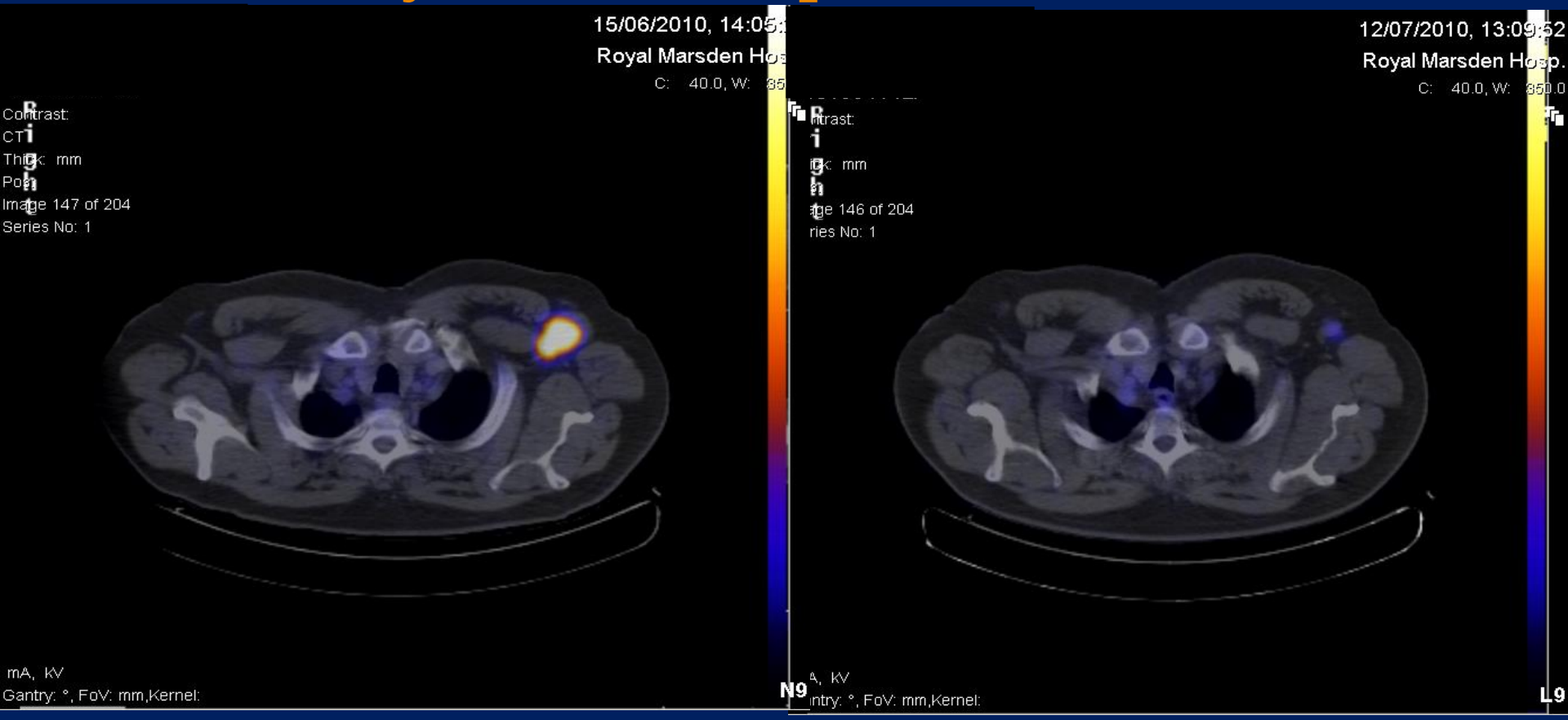
Ready et al. J Clin Oncol 31, 2013 (suppl; abstr 7506)

VEGF inhibitors – EORTC sunitinib

Drug Name	Target	Stage of Development
Bevacizumab	VEGF	Phase III
IMC-1121b	VEGFR-2	Phase I
IMC-18F1	VEGFR-1	Preclinical
Aflibercept	VEGF-A, PlGF	Phase III
Sorafenib	B-RAF, C-RAF, VEGFR2, VEGFR3, PDGFR-β, Kit	Phase III
Sunitinib	VEGFR1, VEGFR2, PDGFR-β, c-Kit	Phase III
Vandetanib	VEGF, EGFR	Phase III
Cediranib	VEGFR1, VEGFR2, VEGFR3	Phase II
Axitinib	VEGFR1, VEGFR2, VEGFR3, PDGFR-β, c-Kit	Phase II
Motesanib	VEGFR1, VEGFR2, VEGFR3, PDGFR-β, c-Kit	Phase I
Vatalanib	VEGFR1, VEGFR2, VEGFR3, PDGFR-β, c-Kit	Phase III
Pazopanib	VEGFR1, VEGFR2, VEGFR3, PDGFR-α, PDGFR-β, c-Kit	Phase I
CP-547,632	VEGFR2, PDGF	Phase II
BIBF 1120	VEGFR1, VEGFR2, VEGFR3, PDGFR, FGFR	Phase II
XL647	EGFR, HER2, EphB4, VEGF	Phase II
AEE788	EGFR, HER2, VEGF	Phase I
KRN951	VEGFR1, VEGFR2, PDGFR, c-Kit	Phase I
ABT-869	VEGF, PDGF	Phase I
OSI-930	Kit, KDR	Phase I
BMS-690514	pan HER, VEGF	Phase I
Thalidomide	BFGF	Phase III
Lenalidomide	BFGF	Phase I
Pomalidomide	BFGF	Phase I
Cilengitide	$\alpha v\beta 3$, $\alpha v\beta 5$	Phase I
TNP-470	Methionine aminopeptidase	Phase I
AMG 386	Angiopoietin, Tie2	Phase I
DMXAA	Vascular disrupting agent	Phase II

VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor.

Phase 2 sunitinib in SCLC – secondline with early PET for response



2nd line treatment: Sunitinib, to which he responded well and continued for 22 cycles.

Sudden death 20 months later – prob PE

After 4 weeks treatment with sunitinib

Case 2: Sunitinib Responder

- **70 years old Caucasian never smoker female.**
- **Presenting symptoms: breathlessness, cough and haemoptysis.**
- **PS = 1.**
- **History of malignant melanoma 20 years ago.**
- **Diagnosis:** *Pure SCLC, limited stage*.
- **1st line treatment: Concomitant chemoradiotherapy (6 cycles Carboplatin/Etoposide and 50 Gy radical radiotherapy) and PCI, with good response.**
- **Relapse: 2.5 years later.**
- **2nd line treatment: Sunitinib (10 cycles), with very good response.**
- **Sunitinib had to be discontinued after 10 months due to toxicities, followed by quick disease progression.**
- **Re-biopsy was performed**

After 4 weeks treatment with sunitinib

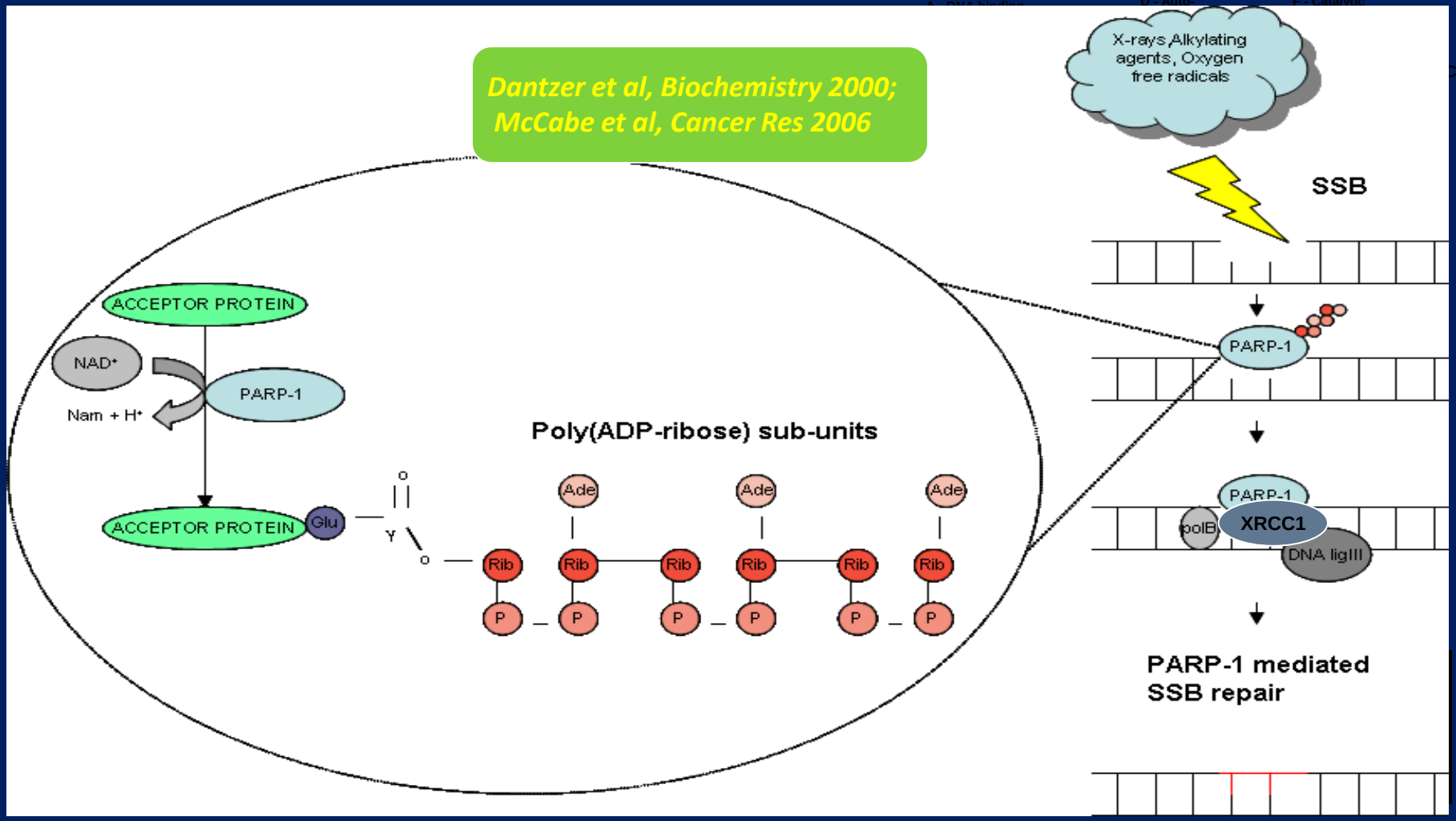
Other news

- Pravastatin may stop the growth of tumour cells and make tumour cells more sensitive to chemotherapy – phase III in UK negative
- enoxaparin in SCLC (Fragmatic)
- …..new agents

- At least 17 members of PARP family (PARP-1 and 2 are activated byDNA damage)
- PARP-1 localizes to the site of DNA damage and recruits proteins that mediate repair
- Double knockout of PARP 1 & 2 results in embryonal lethality to mice

Role of PARP-1 in BER/SSBR

PARP-1



Parp inhibitors

- **Olaparib**
- **Velaparib**
- **Niraparib**
- **BMN673 – PARP trap**

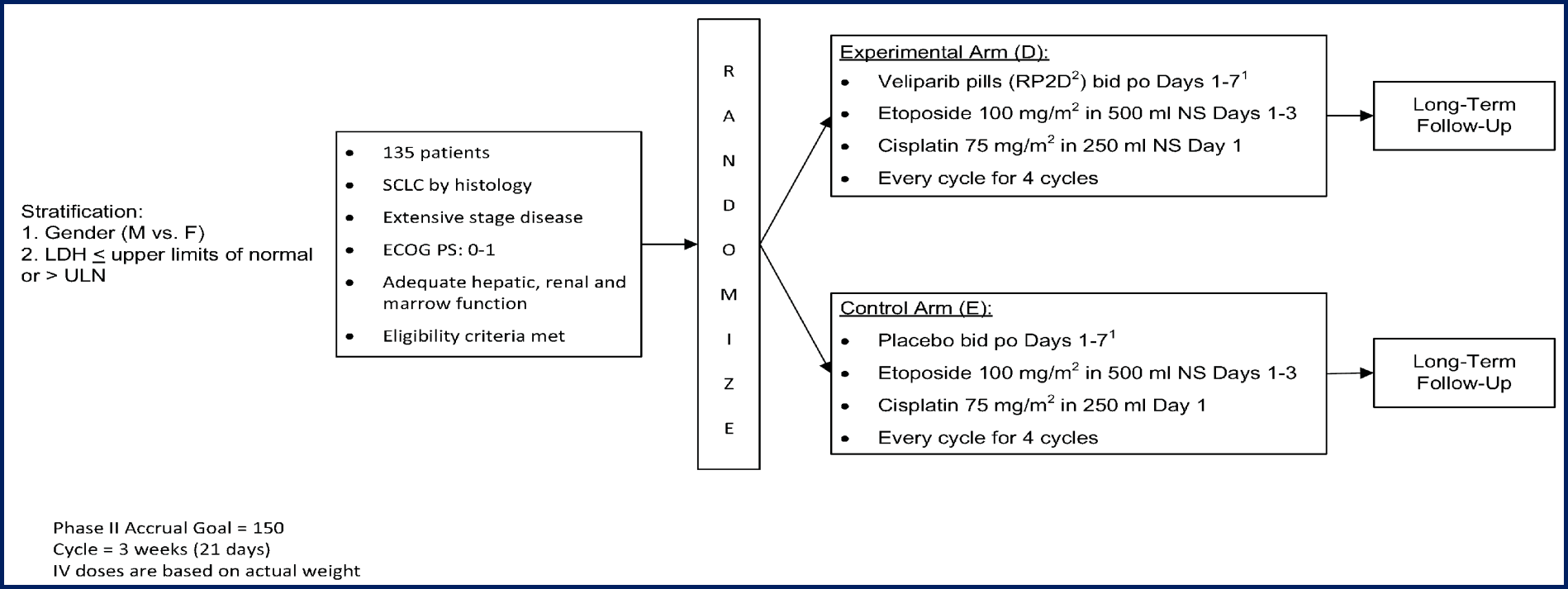
Stabilizing the PARP DNA complex

2/18 in SCLC in phase I

Biomarker is the BRCA 1 and 2 mutation, brcaness or protein expression
Not helpful in SCLC

ECOG 2511 - 3 arm
Phase I/II PE +/- veliparib (ABT-888)

- **Placebo-controlled first line randomized phase II study**



Study Chair: Taofeek Owonikoko MD PhD

Randomized phase II study of temozolomide with or without veliparib

Recurrent SCLC after 1 or 2 prior regimens
No chemotherapy or radiotherapy in prior 3 weeks
ECOG PS ≤1

Double blind

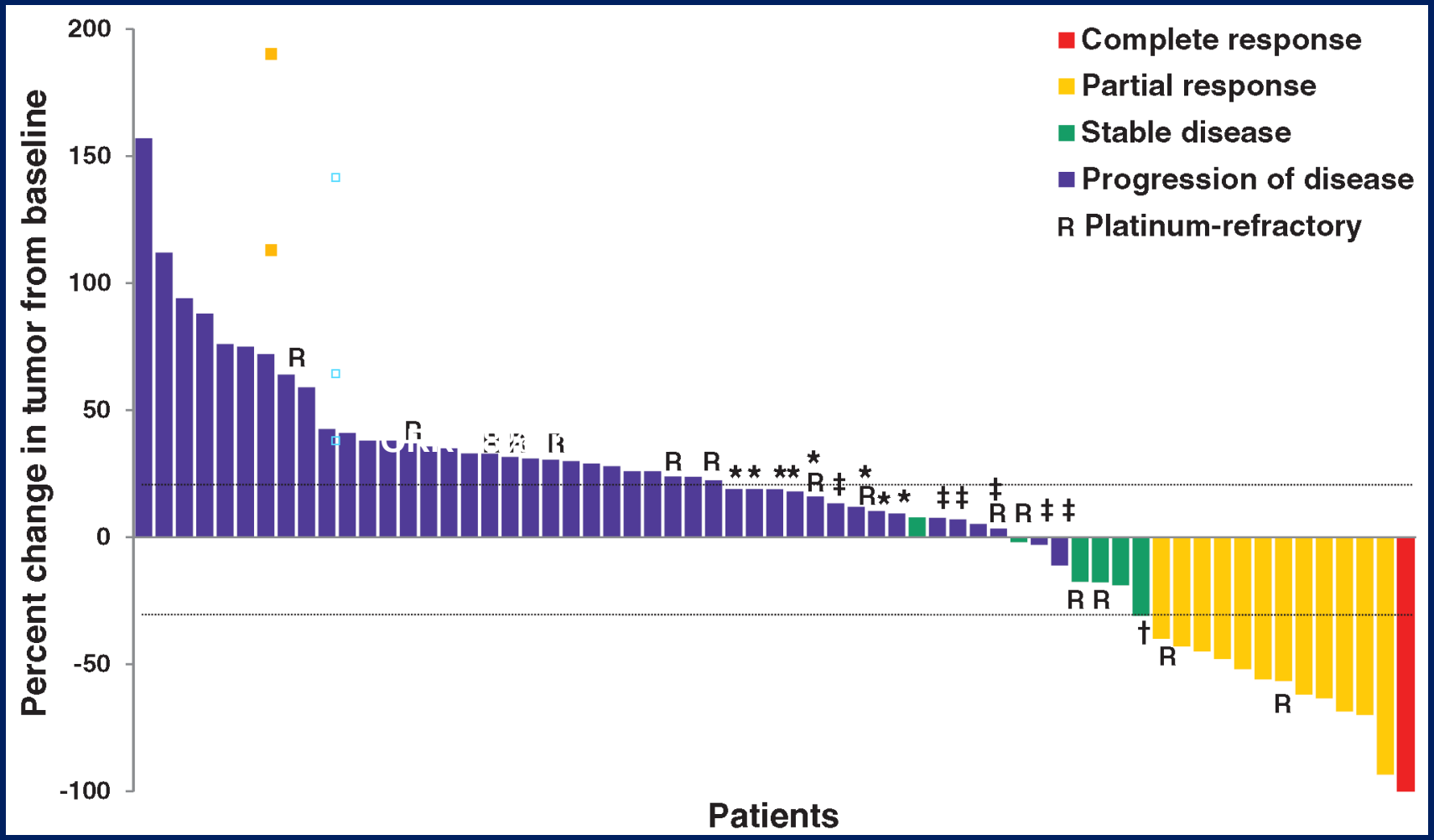
50	50
Veliparib 40mg PO BID × 7 days Temozolomide 200mg/m^2/d × 5 days 28 day cycle	Placebo 40mg PO BID × 7 days Temozolomide 200mg/m^2/d × 5 days 28 day cycle

Study Chair: Cathy Pietanza MD

Participating Sites:

MSKCC
SKCCC at JHU
MDACC
Seidman CC

Temozolomide – old (alkylating agent, cross BBB, - new - SCLC has aberrantly methylated *MGMT*



Pietanza et al., *Clin Cancer Res*, 2012

Startup

- Randomised trial of olaparib as maintenance chemotherapy in ext SCLC post 4-6 chemotherapy - STOMP
- Same design as French and UK NSCLC
- BMN 673

Aurora Kinases

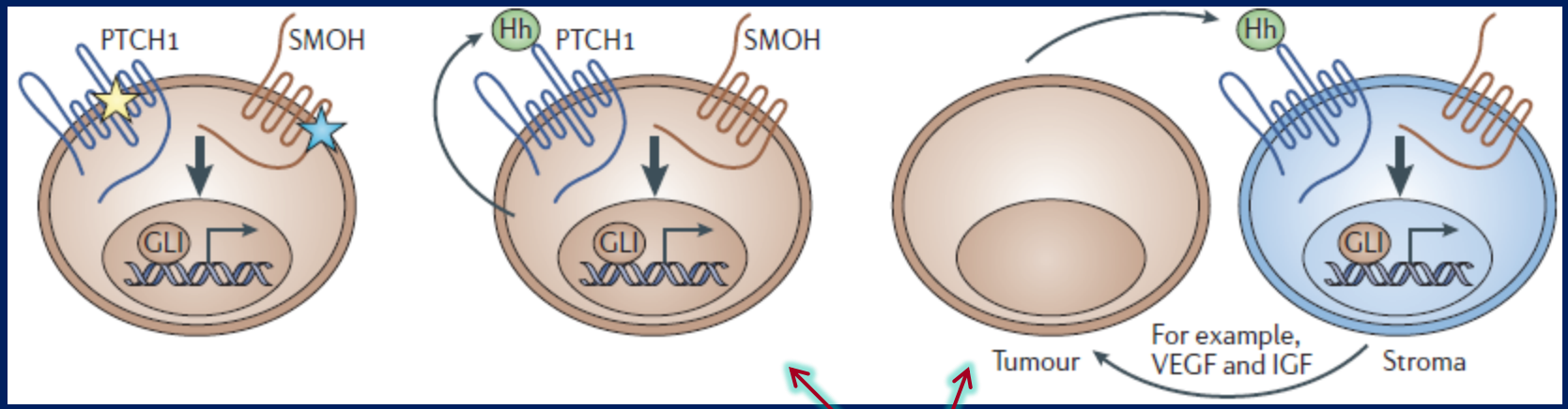
- Antimitotic agents ABC oral
- A MLN8237 – 2 responses
- B AZD1152 - alisertib

- 38% neutropenia, 39% alopecia
- 10/47 = 21%
- 3/11 responses in refractory 27%
- 7/36 19% in sensitive

- Alisertib + weekly paclitaxel
- C-Myc amplification and sensitivity

Models for Hedgehog activity in cancer - Hh sonic – required for lung development, upregulated in SCLC and inhibition delays recurrence in primary SCLC models – no mutation in sclc

Type-1	Type-2	Type-3
Cancers with mutations in Hh signaling	Cancers with autocrine requirement for Hh	Cancers with paracrine requirement for Hh



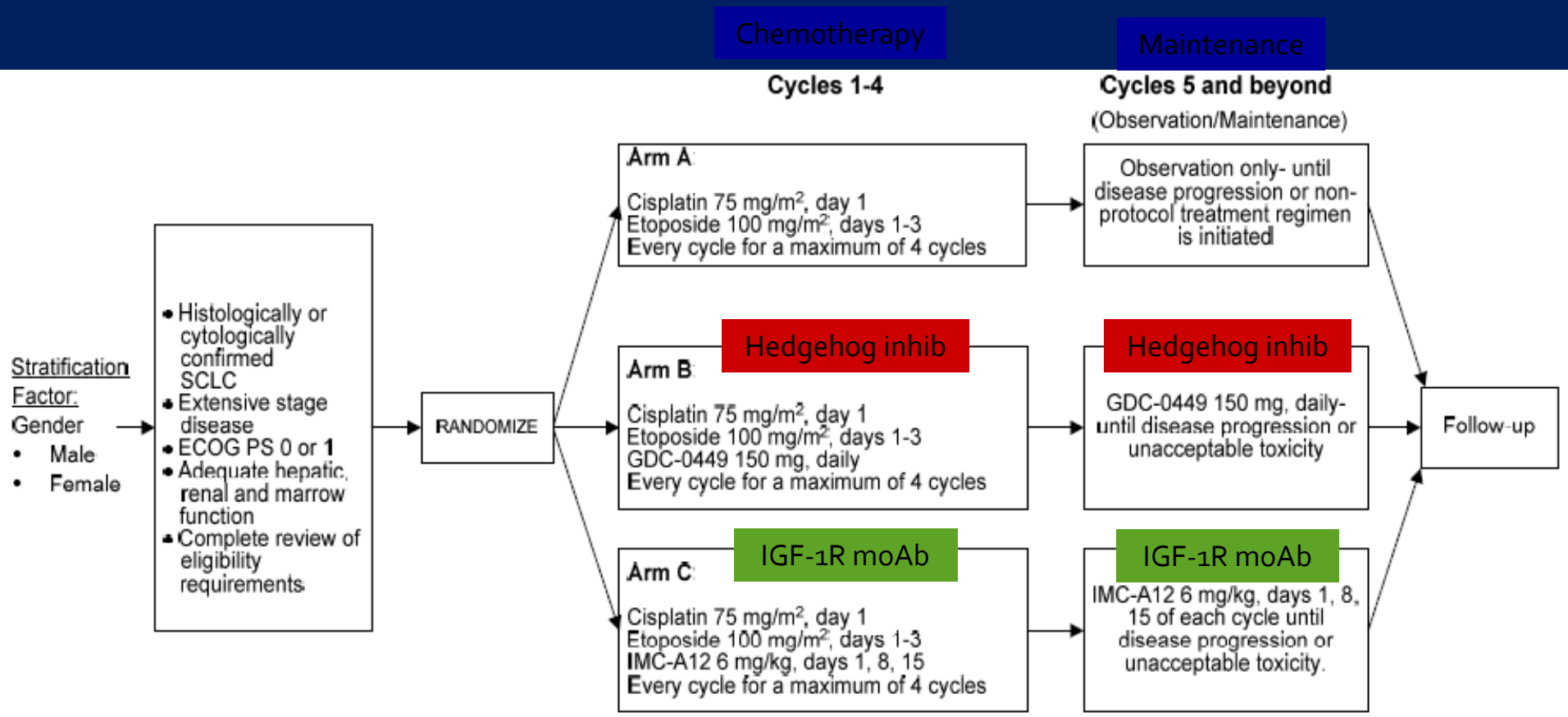
BCC
medulloblastoma

glioblastoma
myeloma

SCLC

pancreatic,
colon cancer

E1508: a randomized phase II study of chemotherapy +/- vismodegib or (IGF-1R mAb) A12



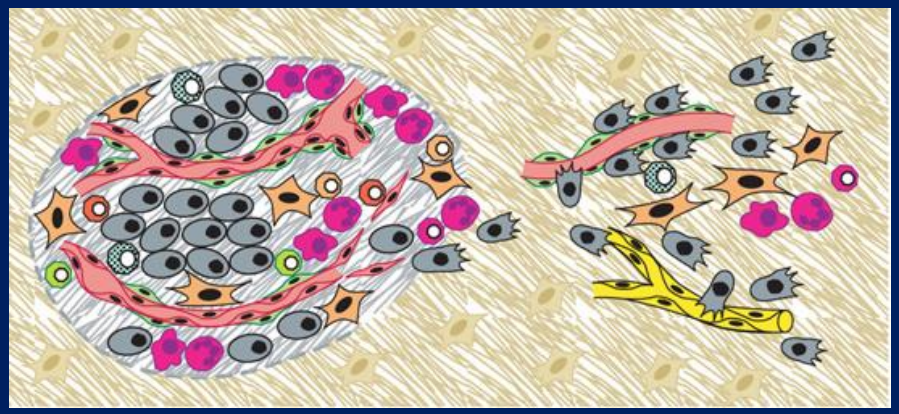
Belani & Rudin

T cell mediated immune rejection of tumours
Therapeutic intervention

Tumour vaccine

e.g. MAGE
or intrinsic (unknown)

Presentation of tumour-specific/associated Ag



Activation of Tumour-specific T cells

Other immunosuppressive factors environment

T regulatory cells
Myeloid suppressor cells
IL-10, TGFbeta

CD137

CD28

IL-2
IL-15

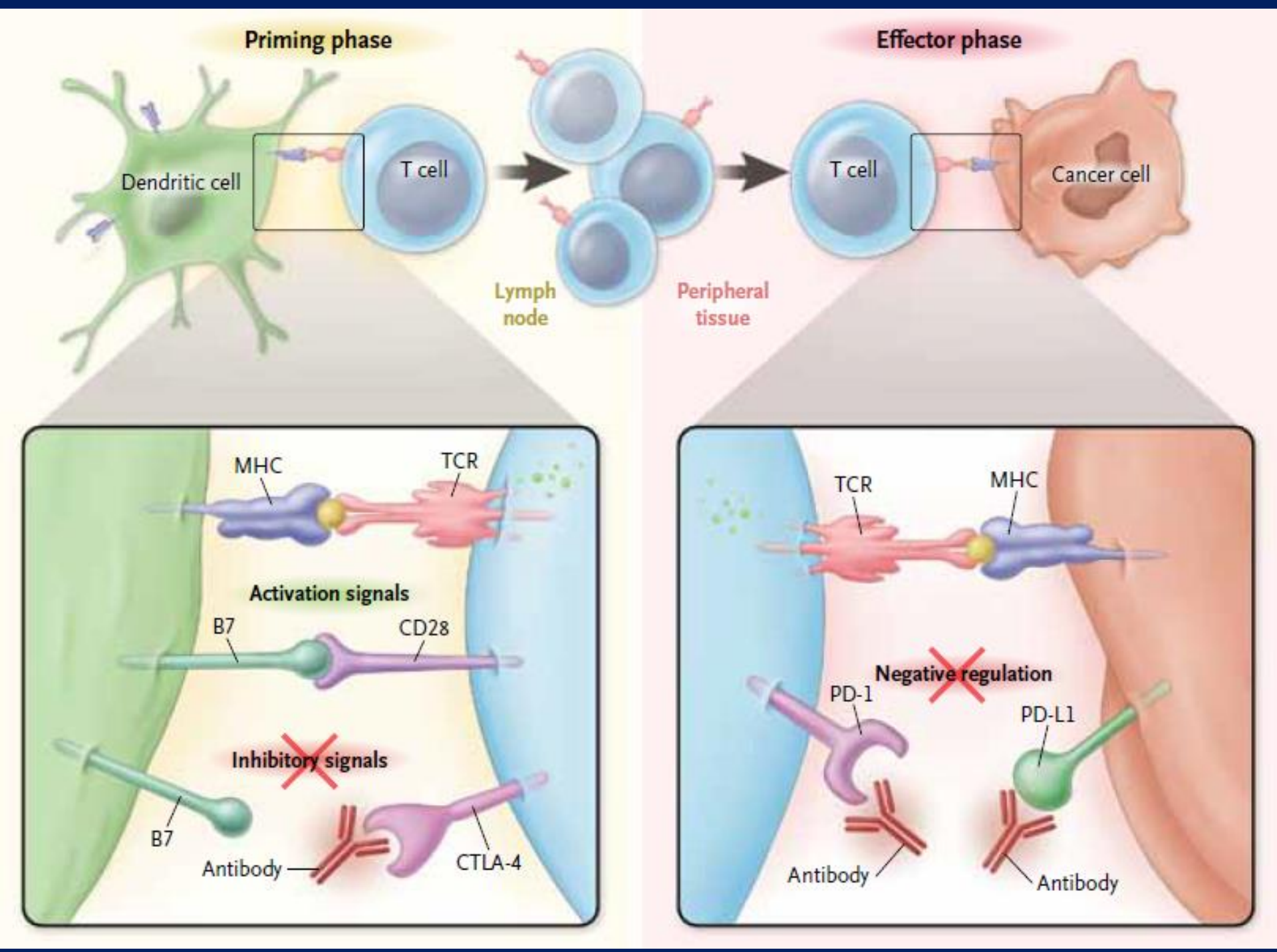
Co-stimulatory T cell Signals

Negative Regulatory signals (immune check-points)

CTLA-4
PD1
B7-1

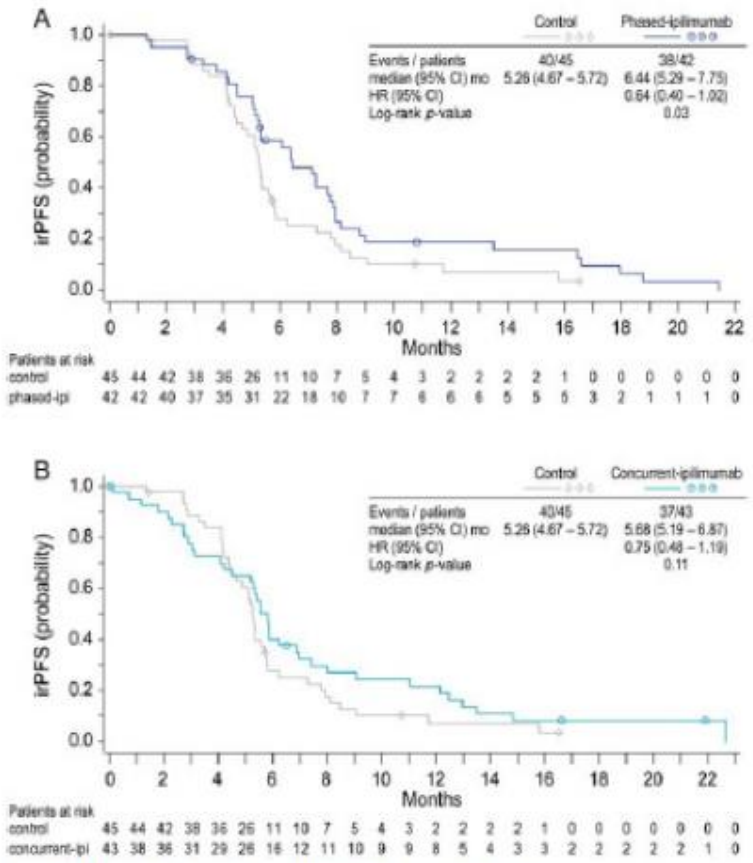
Agonists

Antagonists


Priming phase
Effector phase
Dendritic cell
T cell
Lymph node
Peripheral tissue
T cell
Cancer cell
MHC
TCR
Activation signals
B7
CD28
Inhibitory signals
B7
Antibody
CTLA-4
TCR
MHC
Negative regulation
PD-1
PD-L1
Antibody
Antibody

Sequential Ipilimumab Improves Irpfs In ED SCLC 1st Line Therapy With Paclitaxel / Carboplatin

CA209-032



Reck M et al., Ann Oncol. 2013 Jan;24(1):75-83

Being repeated as Ideate (CA 184-156), sequential ipi, Stimuli – limited stage

Immunotherapy and SCLC

- **Is it logical?? – very highly mutated – as is melanoma**
- Phase 2 randomized study, ipi TC v TC PFS 5.7m vs 4.6m, HR = 0.72, P = 0.05, no improvement when used concurrently Reck et al Ann Oncol 2013.
- **nivolumab (anti -PD1) v N + ipilumimab (CTL 4) followed by nivo maintenance**

Ongoing studies

- **Parp inhibitors/Temozolamide**
- **Aurora kinases/hedgehog/immuno**
- **2 studies French & Italian: recruiting**

Poster at meeting 2nd line paclitaxel weekly + bev

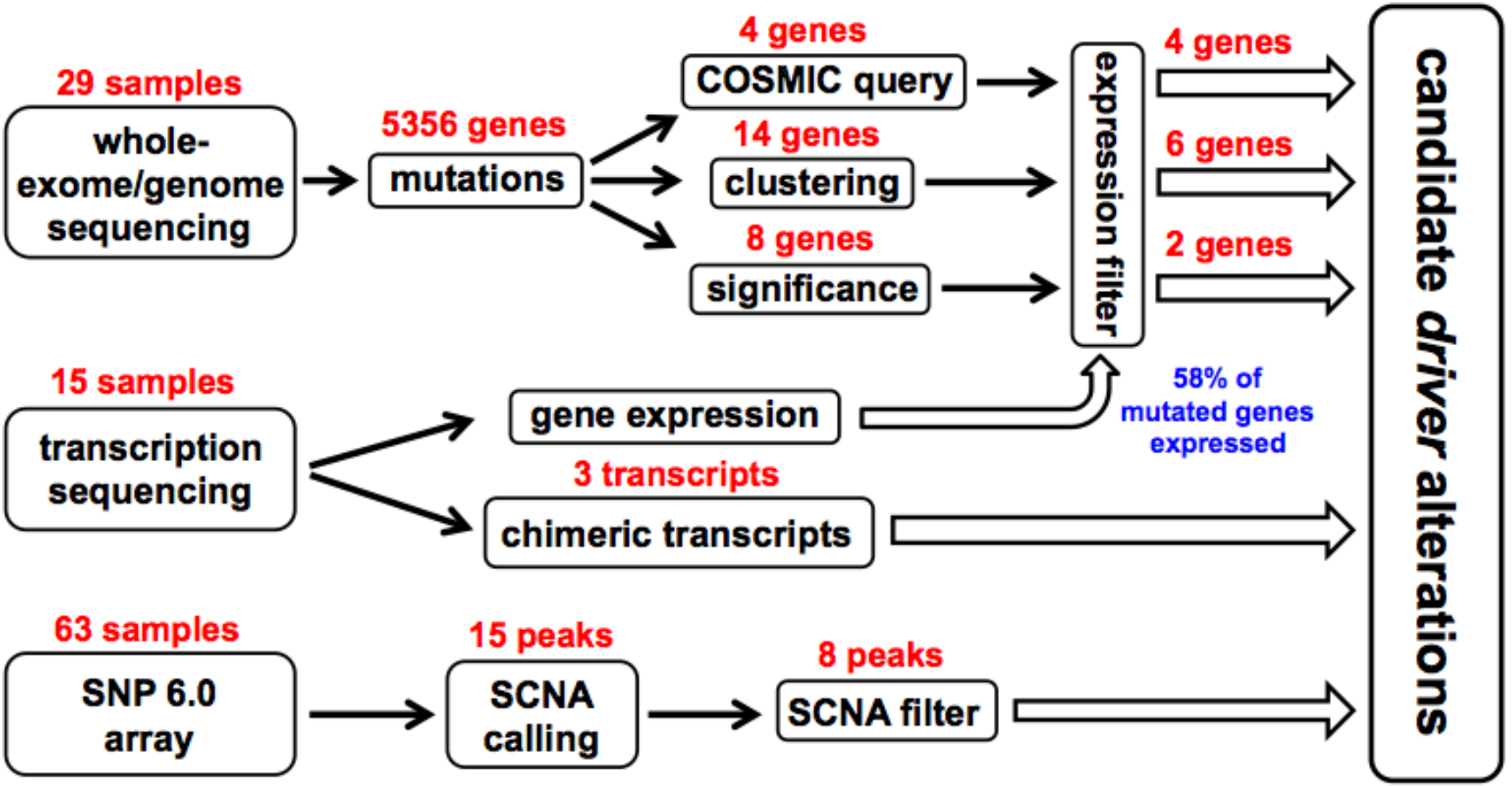
- **NGR-hTNF in Combination With Doxorubicin in Patients Affected by Metastatic Small Cell Lung Carcinoma (NGR007): MolMed**

- **Secondline +/- valproic acid**

Old drugs new indication

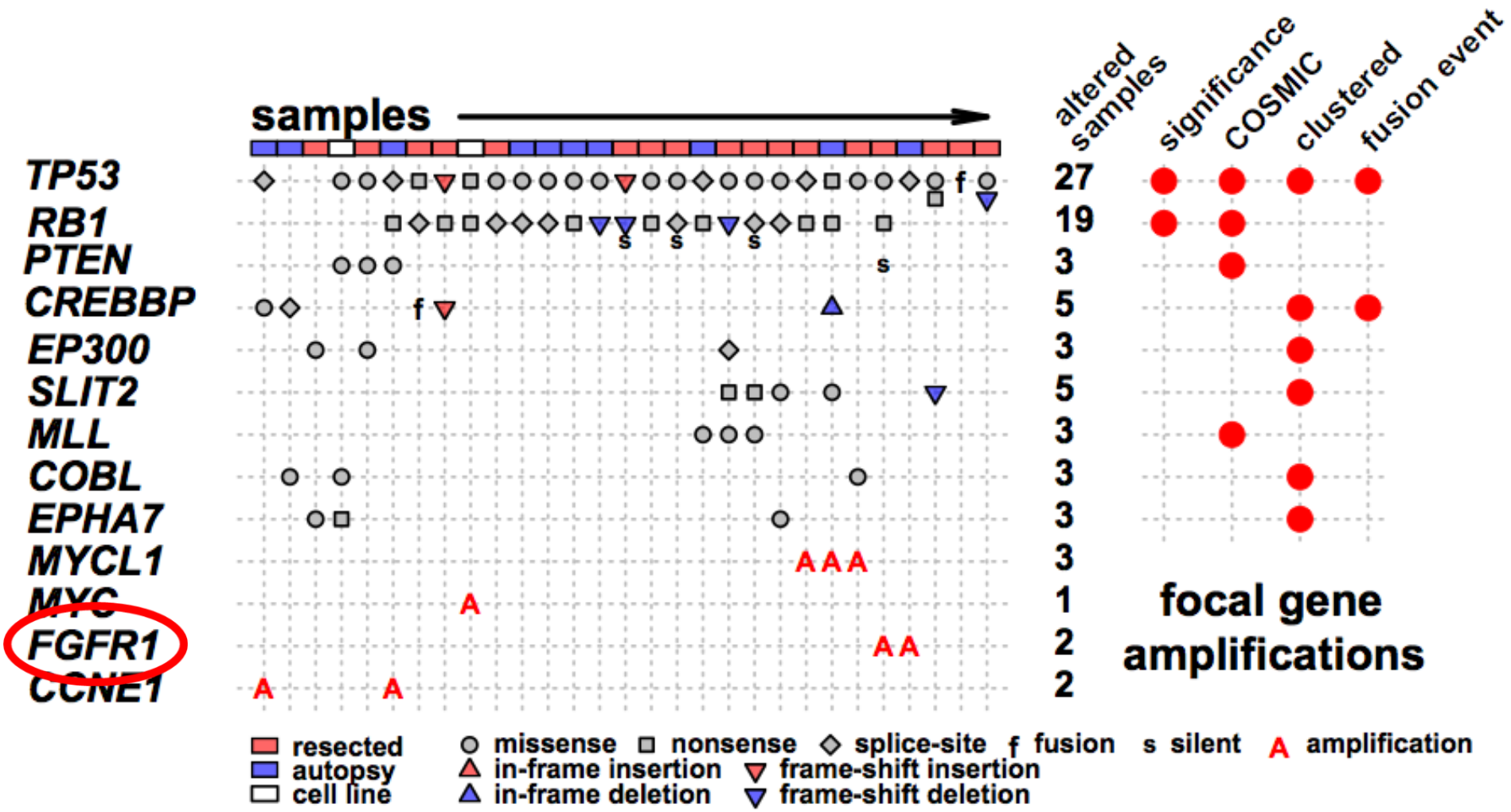
- **CE + anti-NCAM – anti CD 56 BB 10901 Immunogen NORTH study – closed toxicity**

Small-cell lung cancer sequencing project



Peifer M, Fernández-Cuesta L, et al. *Nature Genetics* 44 (2012).

Candidate *driver* genome alterations in SCLC

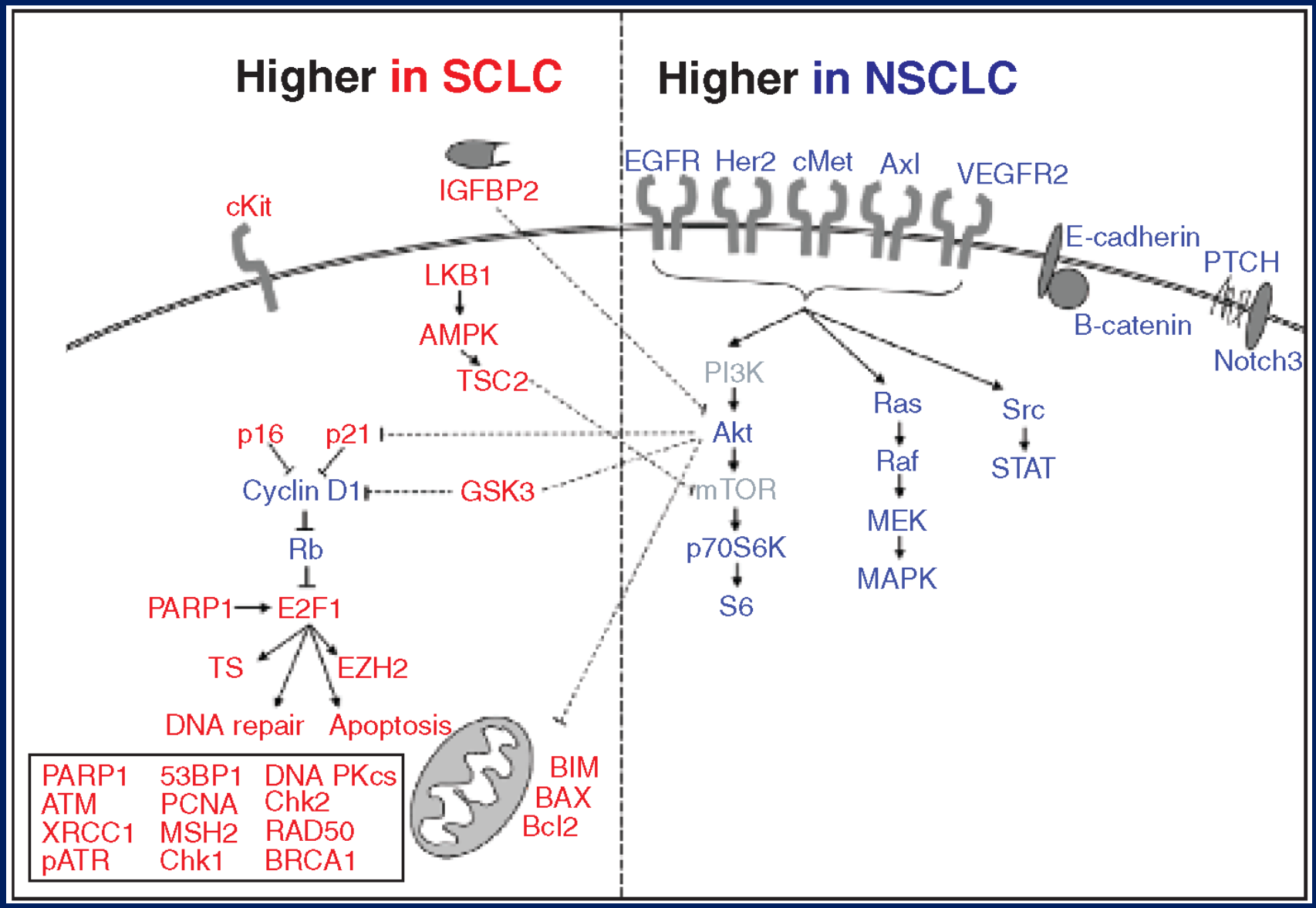


Some SCLC genes….

- **Hot spot mutations**
  - ***TP53, RB1, PIK3CA, CDKN2A, PTEN***
  - **RAS family regulators (*RAB37, RASGRF1, RASGRF2*)**
  - **Chromatin modifiers (*EP300, DMBX1, MLL2, MED12*, etc.)**
- **Hot spot mutations *PLUS* q-score**
  - ***RUNX1T1, CDYL, RIMS2***
- **Gene families and pathways**
  - **PI3K pathway, Notch and Hedgehog, glutamate receptor family, DNA repair/checkpoint, SOX family, histones**
- **Focal amplifications**
  - ***MYC, SOX2, SOX4, KIT***
- **Recurrent translocations and fusion genes**
  - **Recurrent: *RLF–MYCL1***
  - **Kinase fusions**

Rudin et al., *Nat Genet* 2012

Proteomic analysis of SCLC

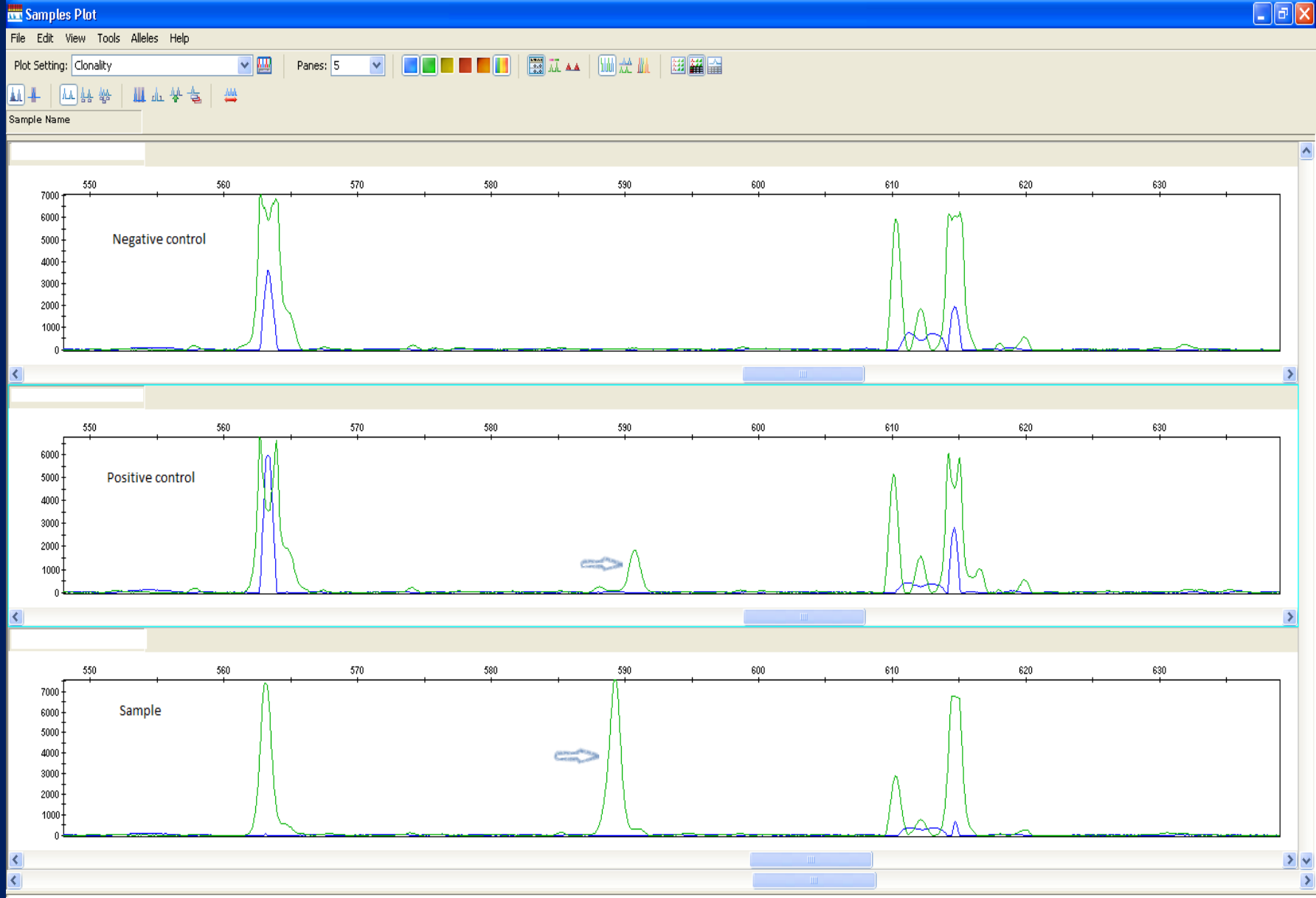


Byers et al., *Cancer Discovery*, 2012

SCLC – biomarker search

N= 60 patients

- BRAF **mutation:** 1 **positive** *(V600E mutation)*, 46 **wild type and 13 invalid.**
- EGFR **mutation:** 31 **wild type and 29 invalid.**
- KRAS **mutation**: 35 **wild type and 25 invalid.**
- ALK **gene rearrangement:** 58 **with no re-arrangements detected and 2 invalid.**
- MET **gene amplification: 40 no amplification, 18 invalid.**



exon 15 (including codon V600) (CE-SSCA)

capillary electrophoresis-single strand conformation analysis

A Case with Positive V600E BRAF Mutation

- **55 years old Caucasian male smoker.**
- **Presenting symptoms: increasing shortness of breath on exertion and dry cough.**
- **PS = 1**

- **A history of squamous cell carcinoma 6 months before the new diagnosis, treated by right lobectomy.**

- **Biopsy diagnosis:** *Pure SCLC, limited stage.*

- **Treatment: Radical chemoradiotherapy (4 cycles of Carboplatin/Etoposide and radiotherapy 36Gy in 12 fractions) and PCI.**
- **Sudden death 9 months from MI.**
- **Review pathology – mixed pathology in resected specimen**

Case 2 sunitinib: Whole Exome Sequencing of *initial* sample

- *68* ***somatic mutations*** **(50 substitutions and 18 indels) were detected in the relapsed sample that did not occur in the germline.** 28 **out of the 68 were predicted to alter protein sequences.**
- 311 **germline variants and** 2 **somatic mutations were enriched in the relapsed sample due to LOH and predicted to alter protein sequences.**
- **When compared to the Cancer Gene Census (CGC), a set of** 5 **genes in the CGC list were found to contain missense or splice site mutations that are either somatic or enriched in carcinoid cells due to LOH. These genes are:**

  MEN1**: essential splice site**

  PDGFRA **(a RTK target for sunitinib): missense**

  BCL6**: missense**

  MLH1**: missense**

  BRCA2**: missense**

- MLH1, BCL6, BRCA2 and PDGFRA **were predicted to be neutral with regard to the protein function.**

- **REPEAT biopsy …….**

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- MLH1, BCL6, BRCA2 and PDGFRA **were predicted to be neutral with regard to the protein function.**

- **REPEAT biopsy …….** **ATYPICAL CARCINOID**

Heterogeneity in SCLC

- SCLC - atypical carcinoid
- Adeno mutated – SCLC
- Squamous – SCLC – with bRAF

Words of warning

- One swallow does not make a summer
- Amrubicin in refractory
- Paclitaxel weekly + bevacuzimab

- Never smoking SCLC – think carcinoid
- Unexpected stable disease
- Sunitinib works for carcinoid

- Remember heterogeneity.
- Small biopsies are giving erroneous leads…….