Using TCGA data to inform on precision medicine in late-stage cancer settings

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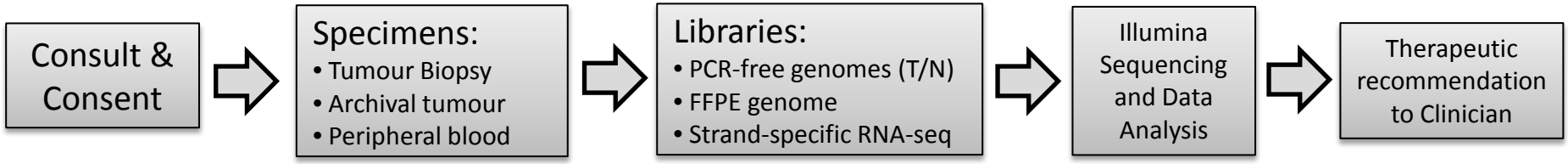
Personalized Oncogenomics

- BC Cancer Agency – Cancer Care and Research
- Provincial population-based cancer control program
  - Prevention, Screening, Diagnosis and Treatment
- Scope:
  - POG aims to bridge divide between genomics research and clinical practice
  - identify tumour-specific therapeutic targets in cancer patients with late stage disease



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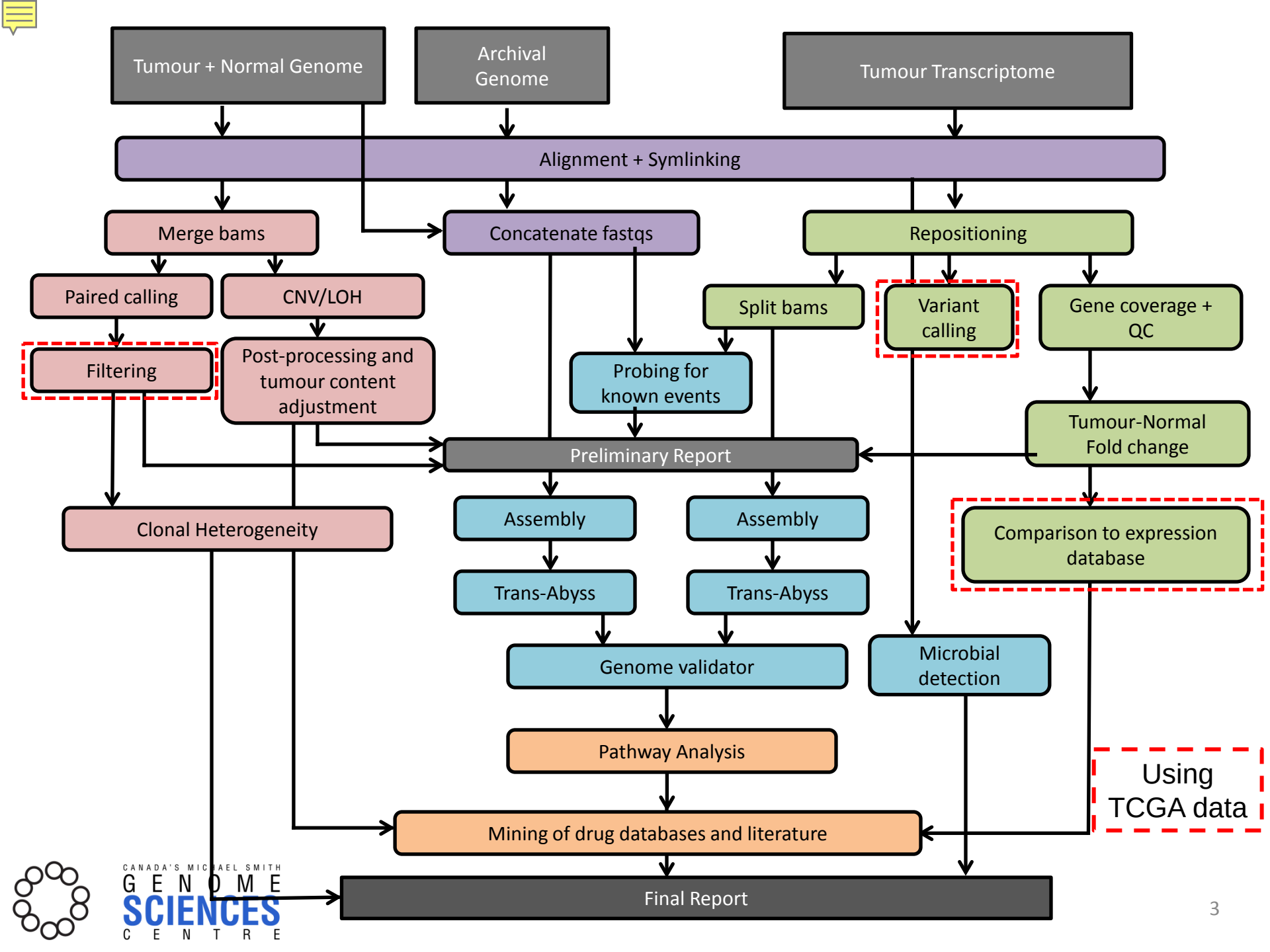

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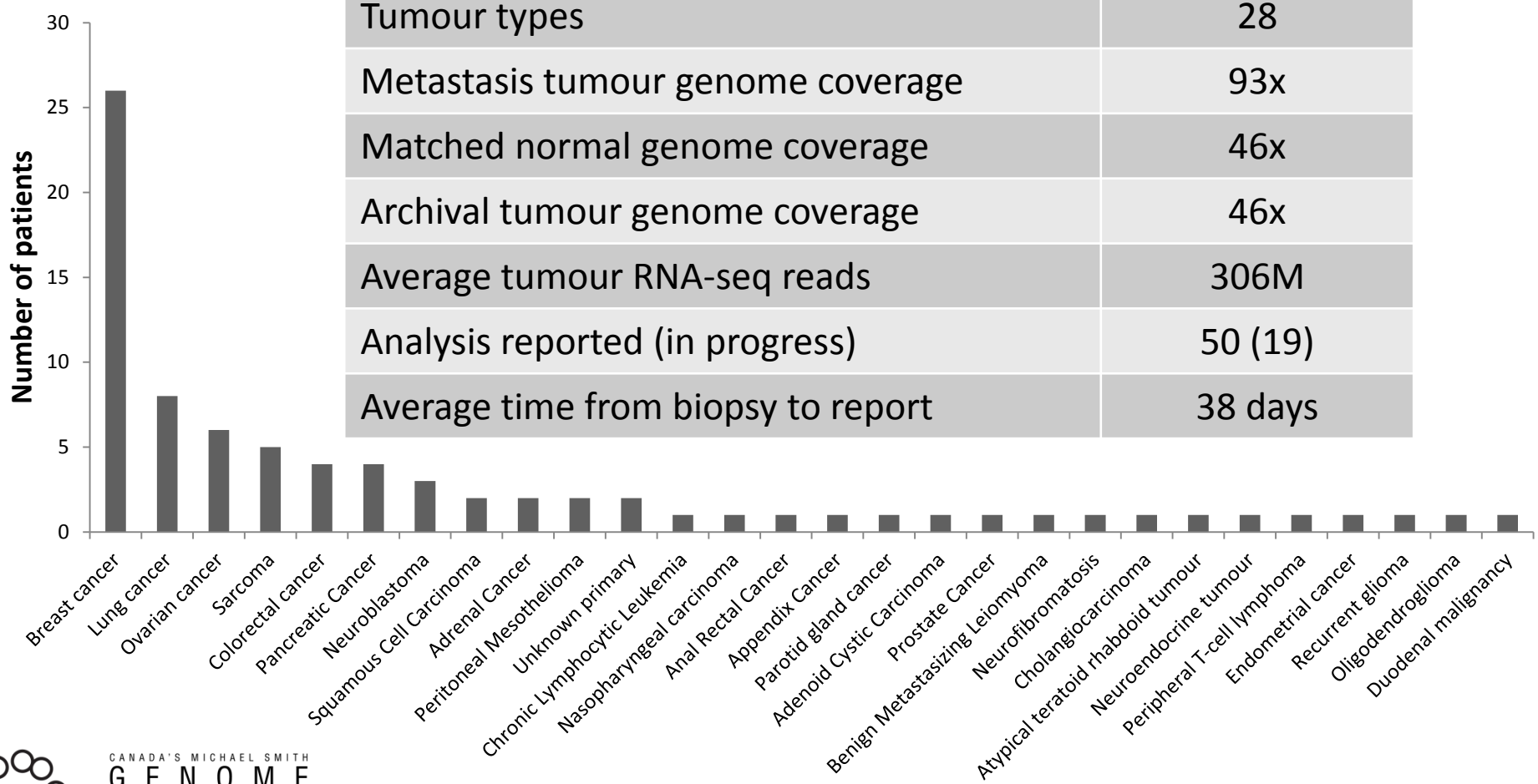
Patients enrolled and data generated

Patients enrolled since July 2012 (pediatric)	83 (8)
Biopsies performed	69
Tumour types	28
Metastasis tumour genome coverage	93x
Matched normal genome coverage	46x
Archival tumour genome coverage	46x
Average tumour RNA-seq reads	306M
Analysis reported (in progress)	50 (19)
Average time from biopsy to report	38 days



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How POG guides treatment decision making

1) Providing directed cytotoxic chemotherapy choices & targeted therapeutic options
2) Complemented/corrected clinical tests
3) Changed diagnosis
4) Identifying primary tumour sites when previously unknown

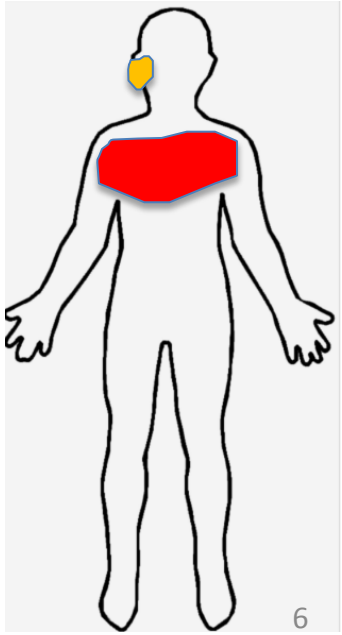
1) Case POG 003 – SCC
Provided targeted therapeutic options

2007 2008 2009 2010 2011 2012 2013 2014

"red rash" on chest
Developed bleeding ulcerations
Diagnosed with Squamous cell carcinoma

Three lines of chemotherapy and multiple rounds of radiotherapy started in 2007

- Jan 2012 – new preauricular node
- Jun – Aug 2012 node and chest mass growing (pain and hearing loss)
- Sep 2012, preauricular and chest lesions biopsied for POG



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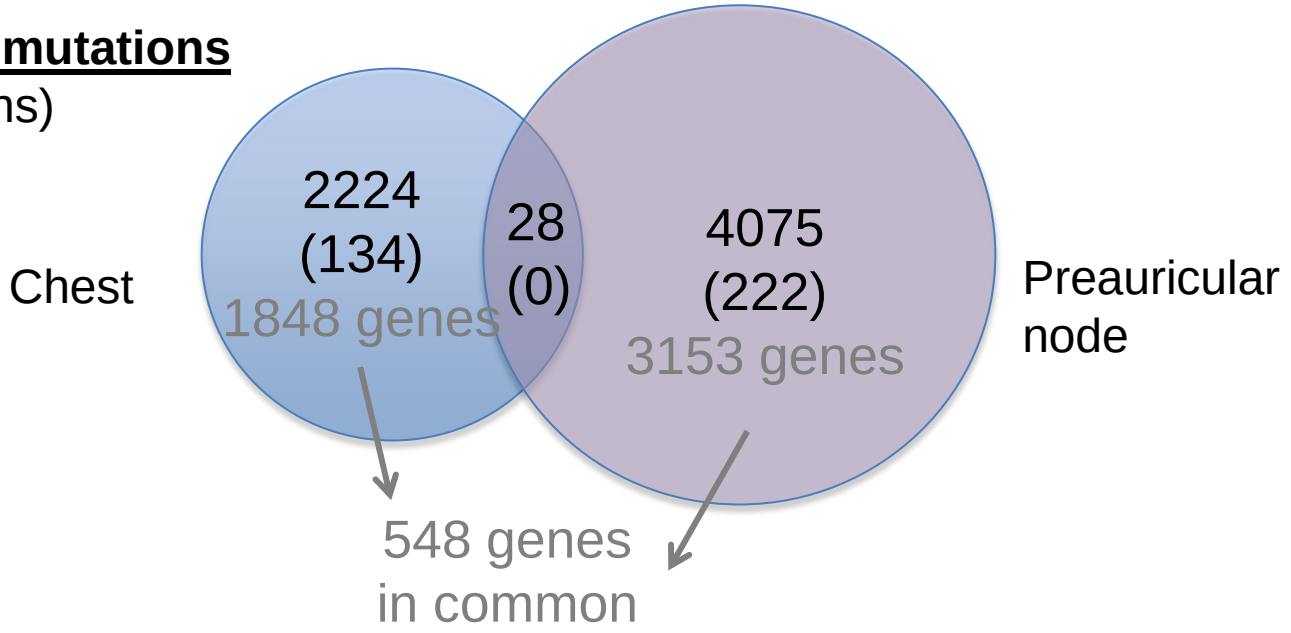
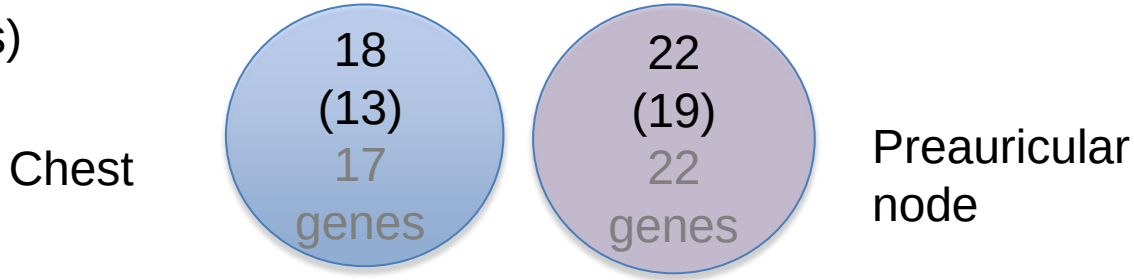
POG 003: Squamous cell carcinoma of skin

Single nucleotide mutations
(truncating mutations)



Small indels
(frameshift mutations)



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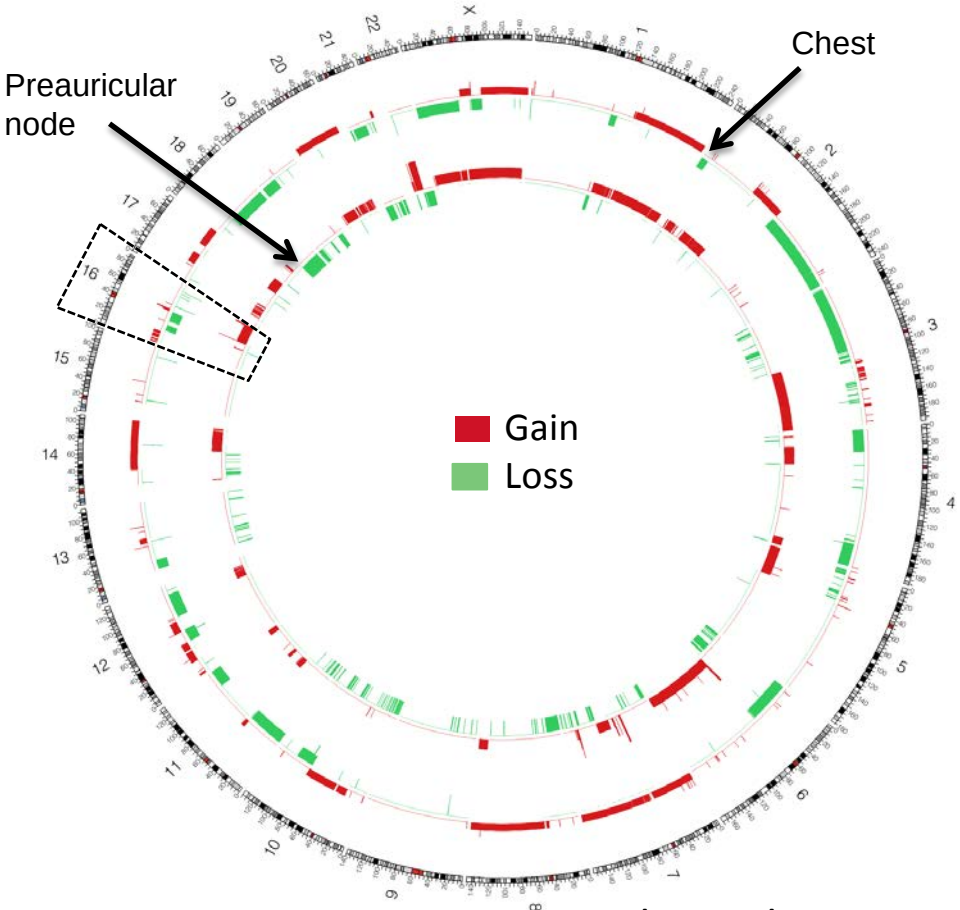
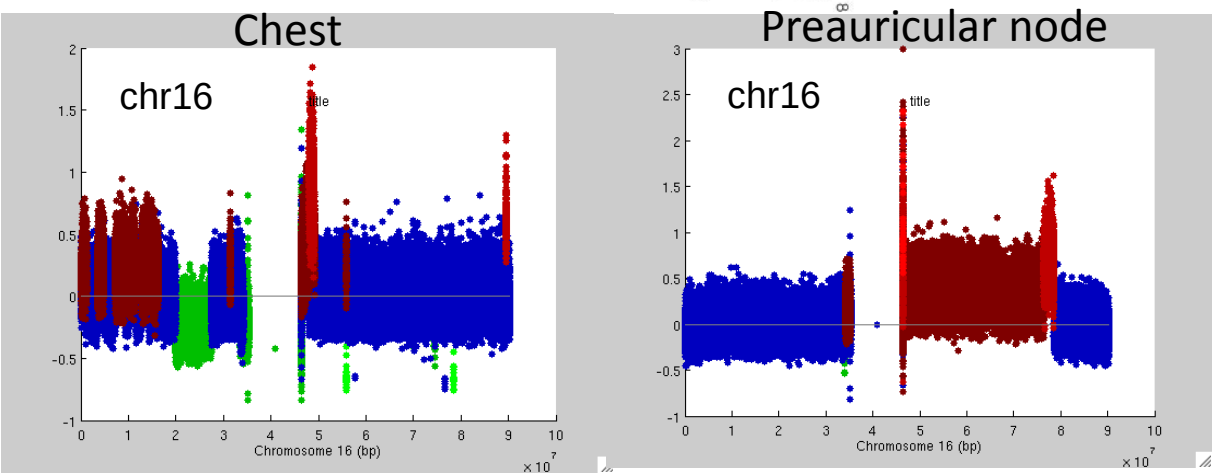
POG 003 – Copy number variants

- Samples almost completely distinct
- Very few common breakpoints





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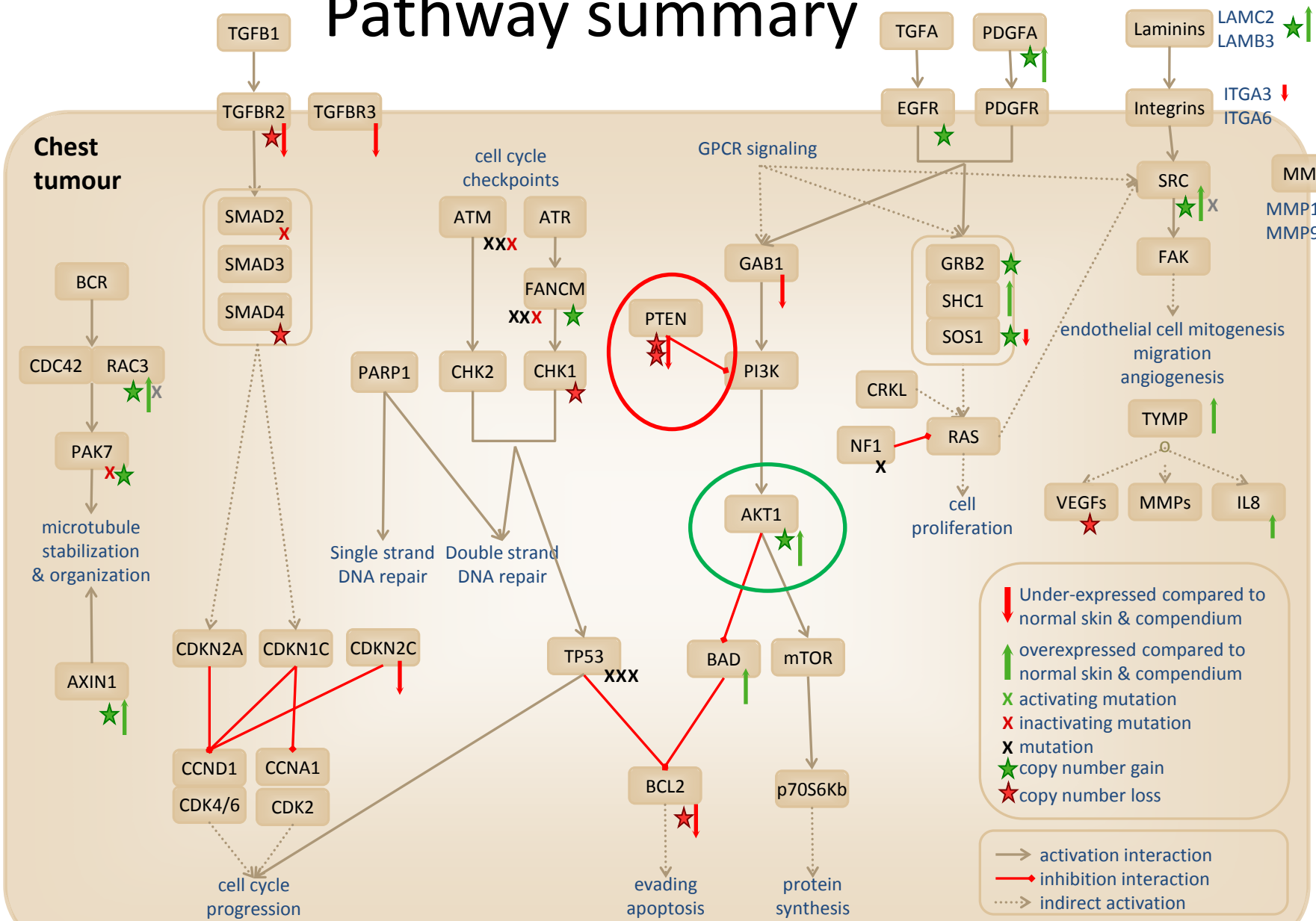
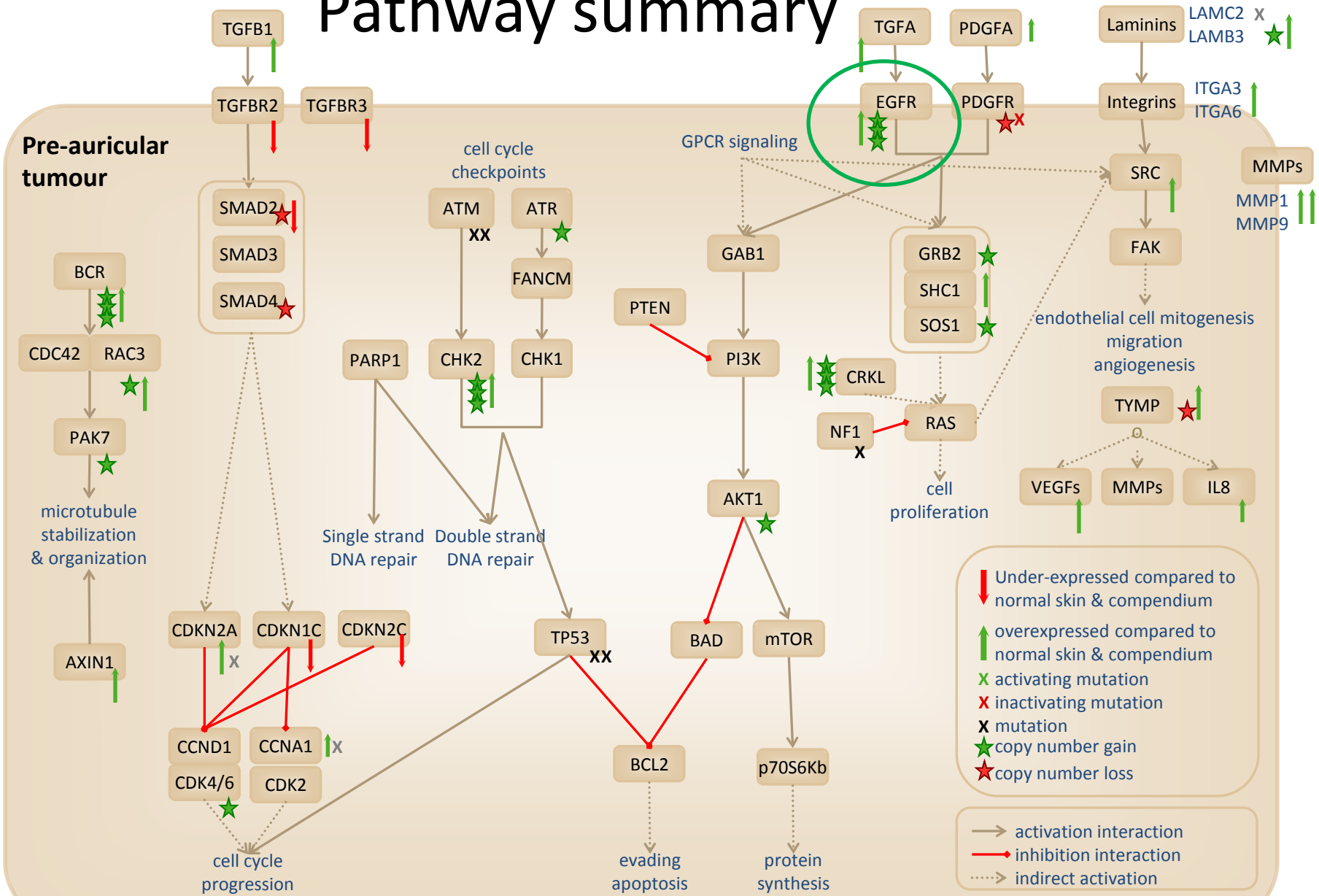
Pathway summary



DNA repair defects, PTEN loss, AKT1 gain

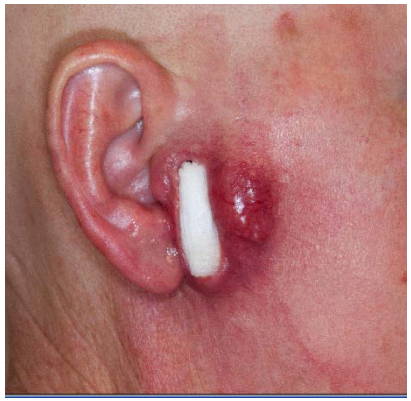
Pathway summary



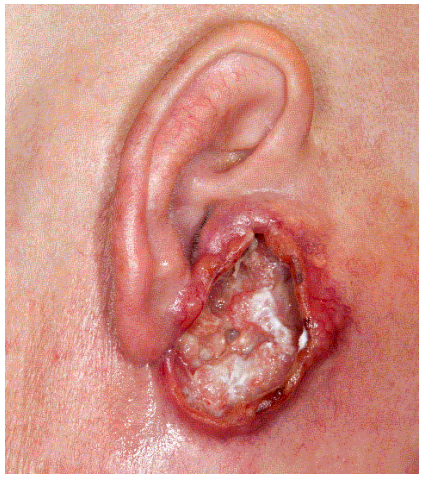
DNA repair defects, EGFR amplicon, MMPs

Therapeutic options, treatment and response

- Treatment:
  - High-level amplification and over-expression of *EGFR* in the **preauricular tumour** suggested **erlotinib**
  - PTEN homozygous loss and AKT gain and over-expression in the **chest** lesion suggested **everolimus**
- Response:
  - Dramatic reduction in the size and extent of his tumours
  - Hearing returned to his right ear
  - Dramatically reduced use of pain medications
  - After a few months, the pre-auricular tumour progressed, so we re-biopsied and sequenced this tumour



Dec 6, 2012



Jan 15, 2013

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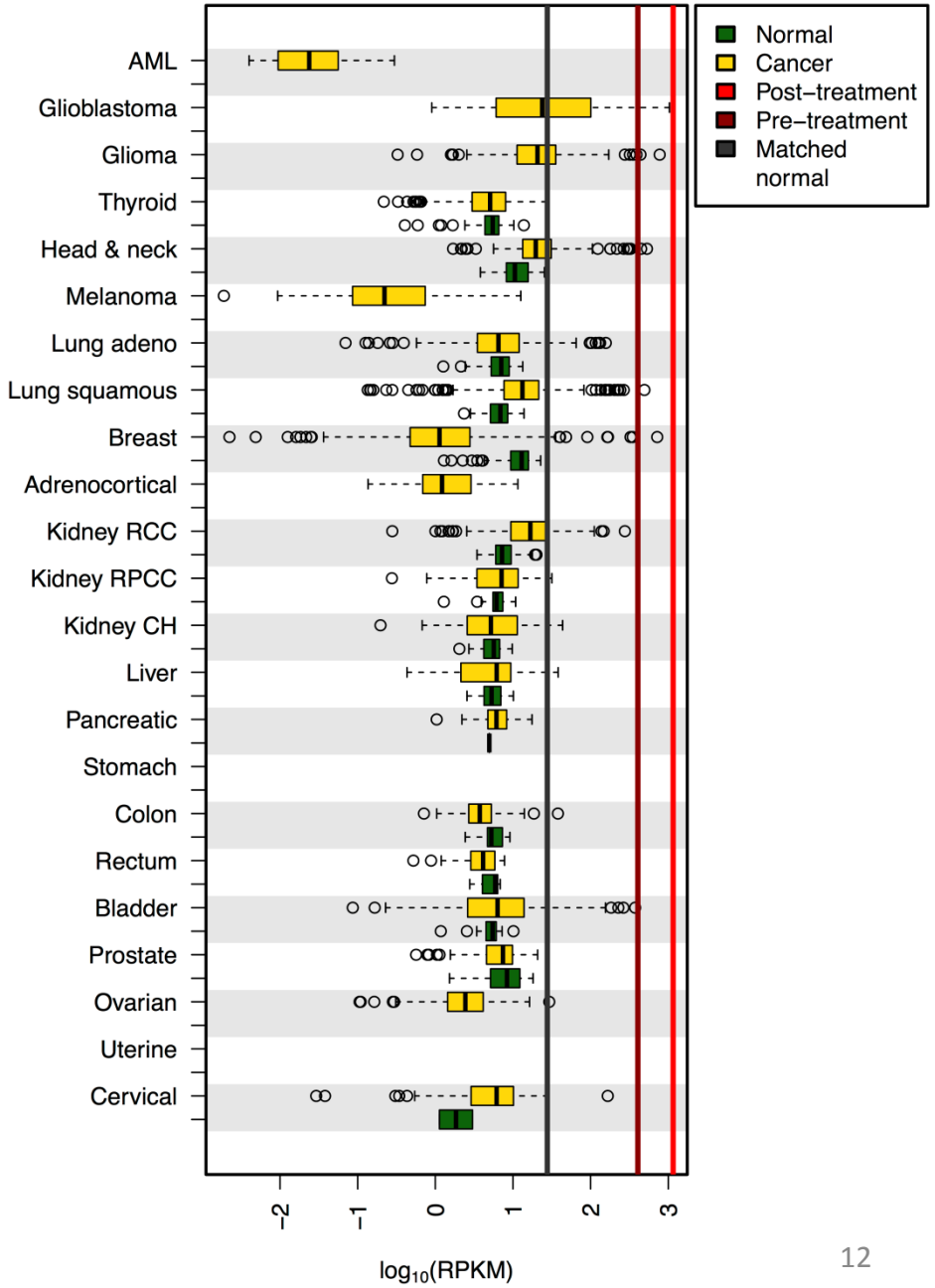
Progressed preauricular tumour

- Further *EGFR* amplification and over-expression observed
  - Higher copy number (55) than in the 2012 biopsy (32)
  - Highest expression level in all TCGA samples



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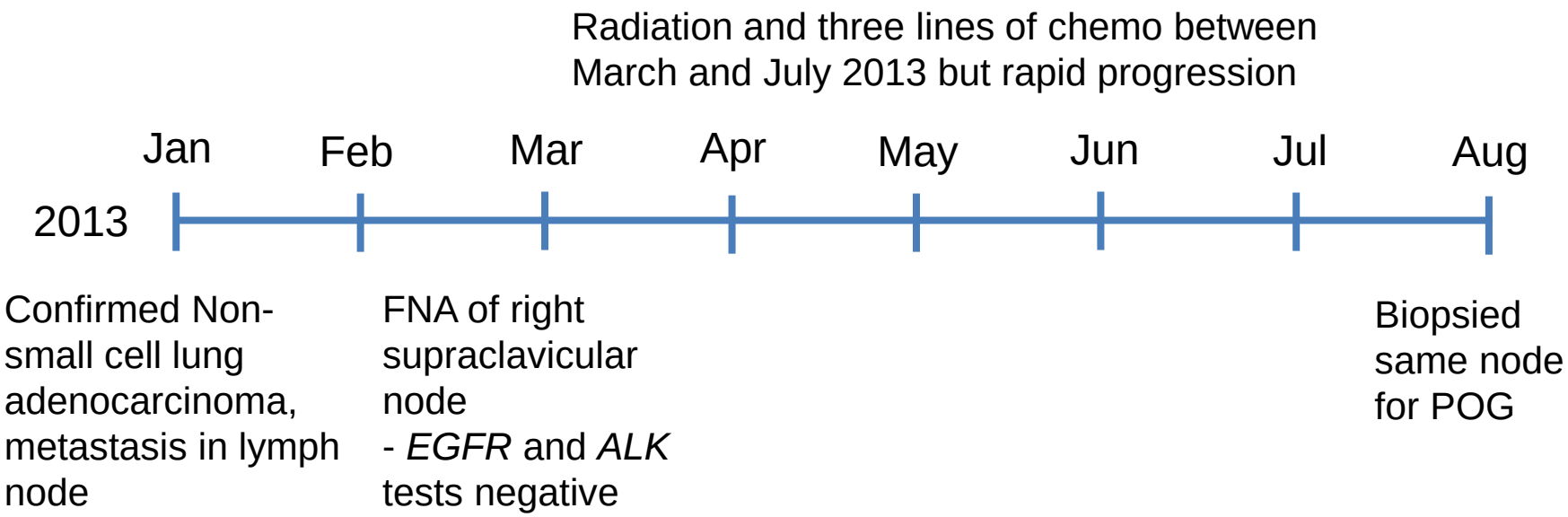
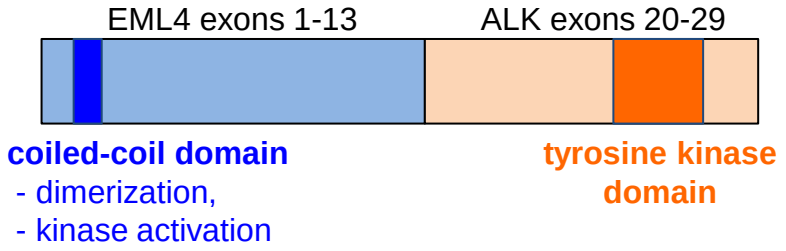
2) Case POG 030 - NSCLC
Complemented/corrected clinical tests

- 68 yo male lifelong never smoker diagnosed with non-small-cell lung adenocarcinoma

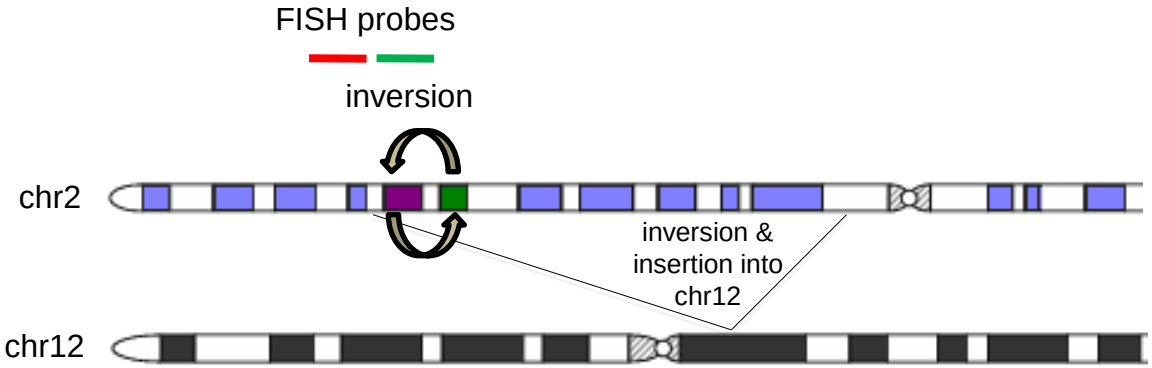


EML4-ALK fusion found in this patient

- Transcriptome and genome sequencing revealed chr2 inversion fusing *EML4-ALK* genes

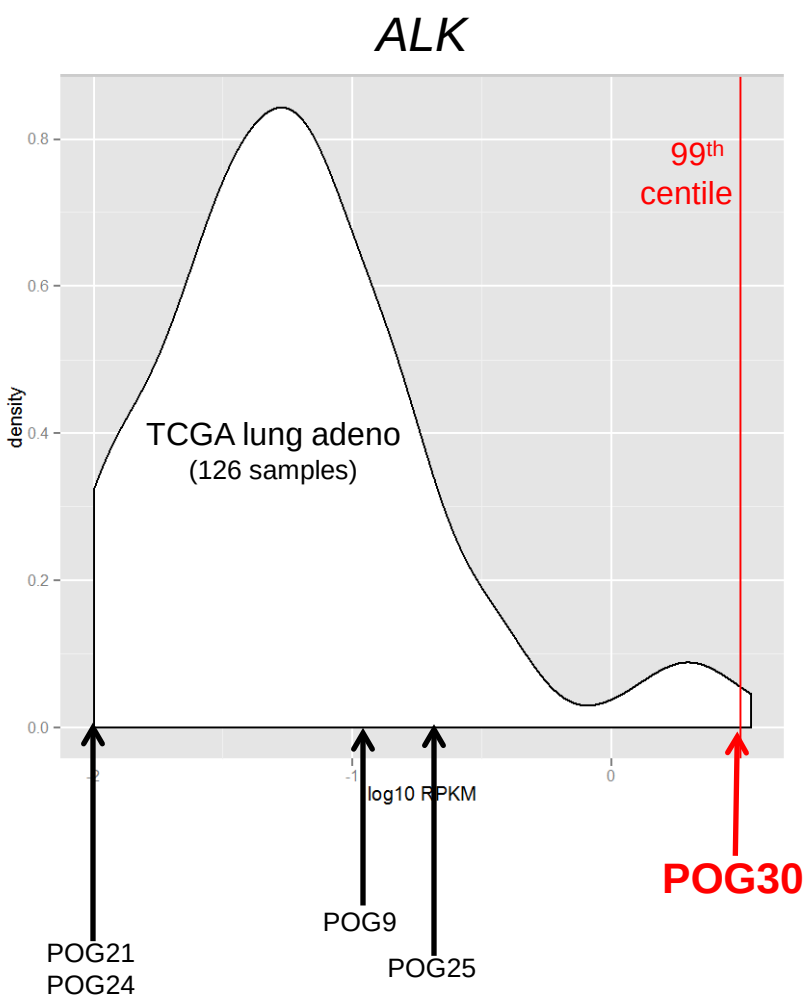


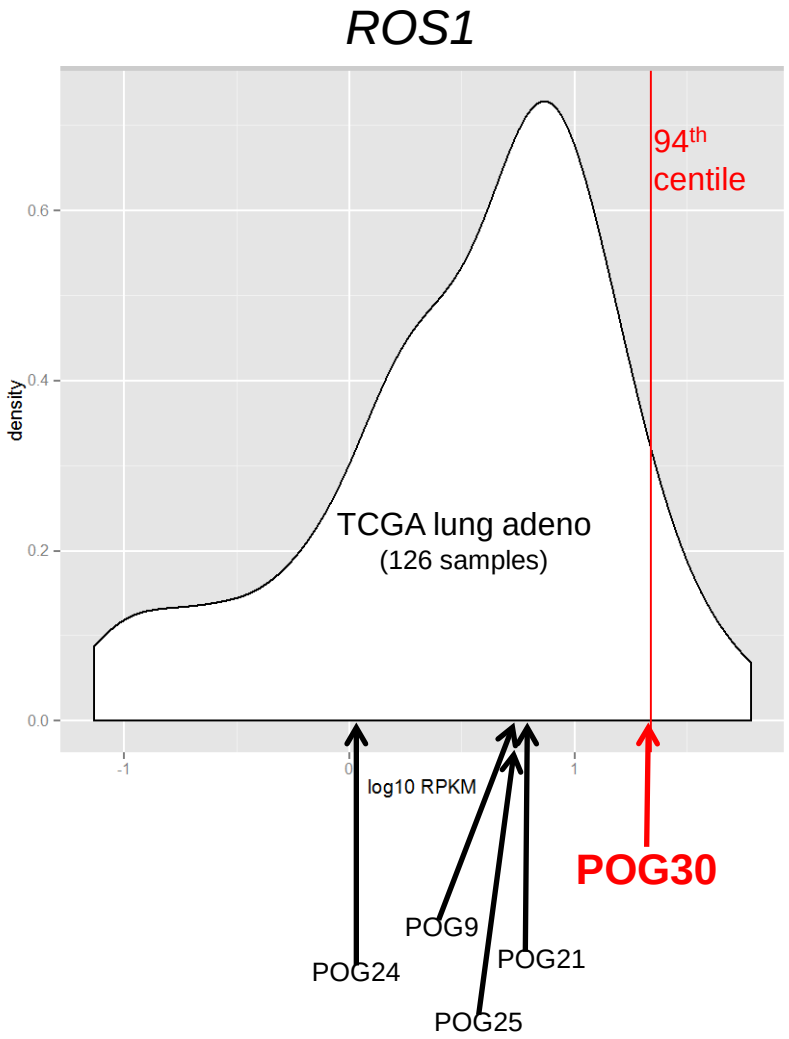
- Sequence analysis at chr2 breakpoints identified a further inversion and insertion into chr12 that appears to prevent Vysis dual-colour break-apart probe from hybridizing



ALK and ROS1 are highly expressed in POG 030

(compared with TCGA lung adenocarcinoma and other POG lung cases)





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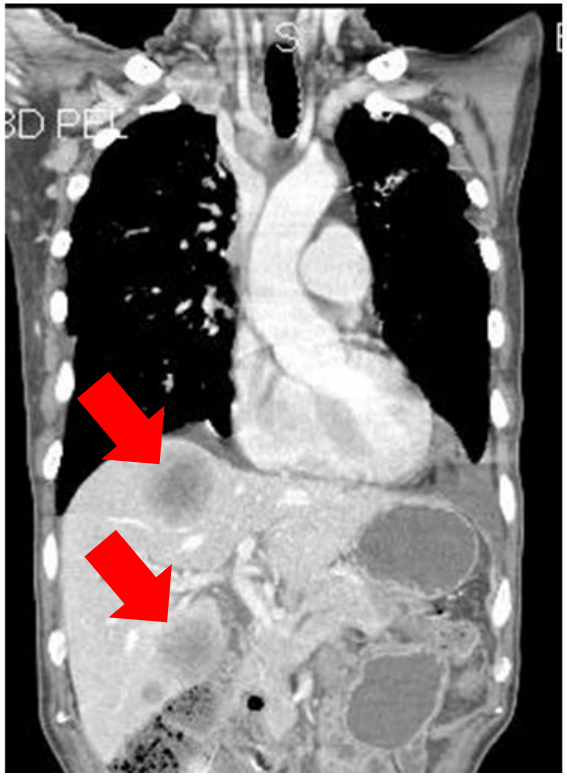
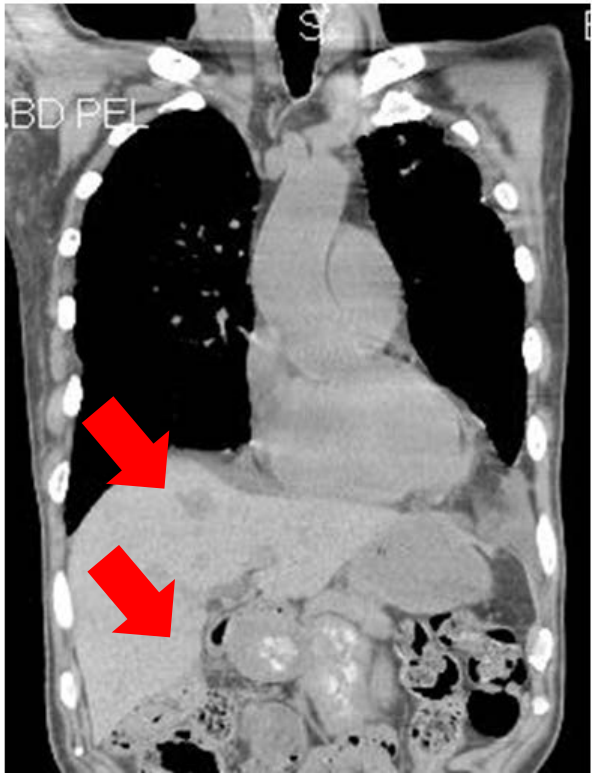
Response to ALK inhibition (Crizotinib)

- *EML4-ALK* fusion, with high overall expression of *ALK* together with *ROS1* over-expression
- TKI Crizotinib was immediately administered
- The tumour responded dramatically



Sept 4 2013 – before Crizotinib



Crizotinib started Sept 25
Scan from Dec 12, 2013

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Evaluation of POG Results

- For each patient, sequenced ≥3 genomes (normal, archival, tumour) and 1 transcriptome (tumour)
- 82 consented patients with advanced cancer
  - 74 biopsies attempted
    - 3 biopsies failed, 2 patients withdrew consent
  - Full data available for 50 patients
    - 9 in progress, 6 on hold, 4 patients died during analysis phase
  - Clinically evaluated in 38 cases
- POG informative or actionable for treatment: 33/38 (87%)
- Treatment available and offered: 18/33 (55%)
  - ≥ 6 (18%) patients died during or shortly after analysis, precluding treatment

Personalized Oncogenomics - Phase II

- REB approval for 5,000 cases (in 5yrs)
- Move from ~1 pt / week to >1 pt / day
- Emphasis on genome + transcriptome sequencing
- Include the “oncopanel” for a rapid TAT “first look”
- Emphasis will expand beyond end stage patients
- Increase speed and accuracy of sequence analysis & report generation
- Verifying “actionable” results in clinical lab. prior to treatment

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Poster #10

THANK YOU!