Biomarkers in breast and colorectal cancer

Discussion: 171O and 172O

Christoph Zielinski

Vienna, Austria

Disclosure

- I have received honoria and research support from Roche, GlaxoSmithKline, Merck, Pfizer and Boehringer Ingelheim

What are we talking about?

- Prognostic: predict outcome irrespective of treatment
  - Does she need treatment?
- Predictive: predict outcome with a specific treatment
  - Which treatment will be best for her?

  HER2 and ER are prognostic *and* predictive
- Monitoring disease during treatment
  - Is her treatment (still) working?

Presentations for discussion

1. ER+/HER2+ and ER-/HER2+ breast cancers are molecularly distinct but immune gene signatures are prognostic and predictive in both groups: Takayuki Iwamoto, Japan
2. Monitoring of metastatic breast cancer using circulating tumour DNA: a comparison with circulating tumour cells; Sarah-Jane Dawson et al, UK

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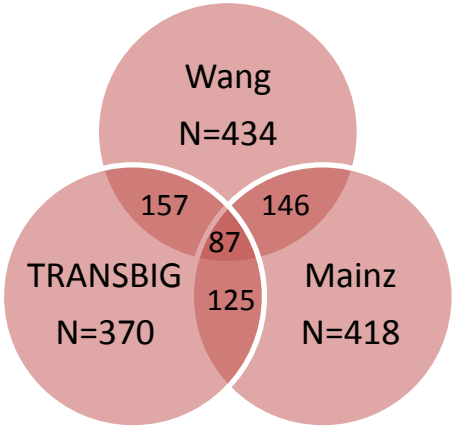
Multigene parameters in BC

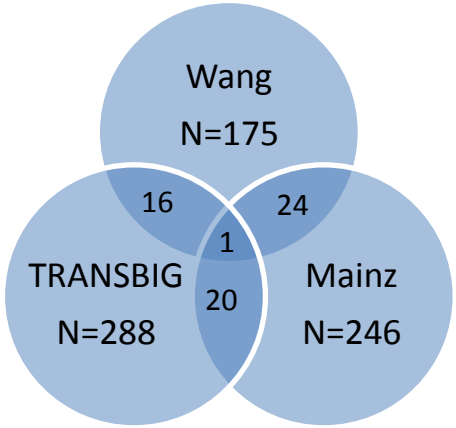
Gene signature	No. of genes assessed	Tissue	Application	Trials
MammaPrint	70	Fresh frozen	Prognostic for recurrence within 5 years in all node-negative and -positive patients	MINDACT
Oncotype DX	21	FFPE	Residual risk of distant recurrence in ER-positive patients treated with tamoxifen or AIs; and predictive of chemotherapy benefit in node-negative ER-positive patients	TAILORx
Genomic-grade index	97	Originally fresh frozen, validated for FFPE	Prognostic, prediction of relapse in endocrine-treated ER-positive BC	
Molecular grade index	5	FFPE	Predicts poor outcome despite endocrine therapy in ER-positive BC	
Rotterdam signature	76	Fresh frozen	Prognostic for development of distant metastases within 5 years	

Weigel & Dowsett. Endocrine-related Cancer 2010

Foundation of this research: HER2-normal BC

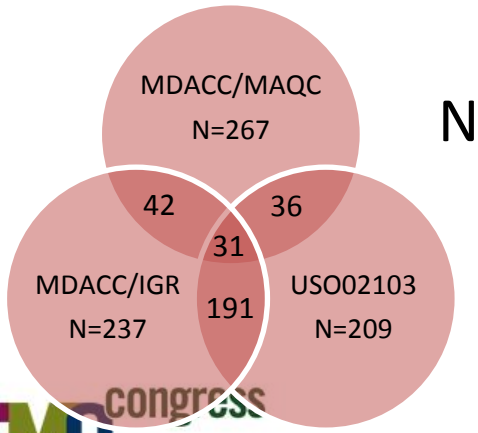


Prognostic datasets

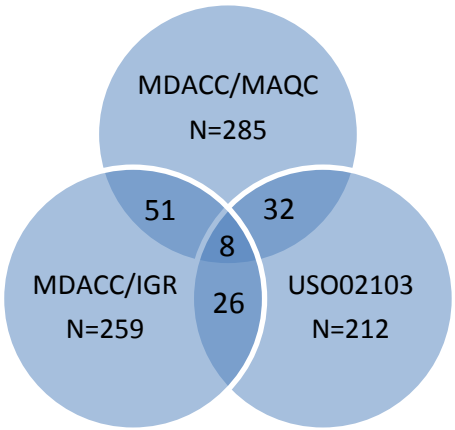


ER positive

ER negative



Neoadjuvant datasets



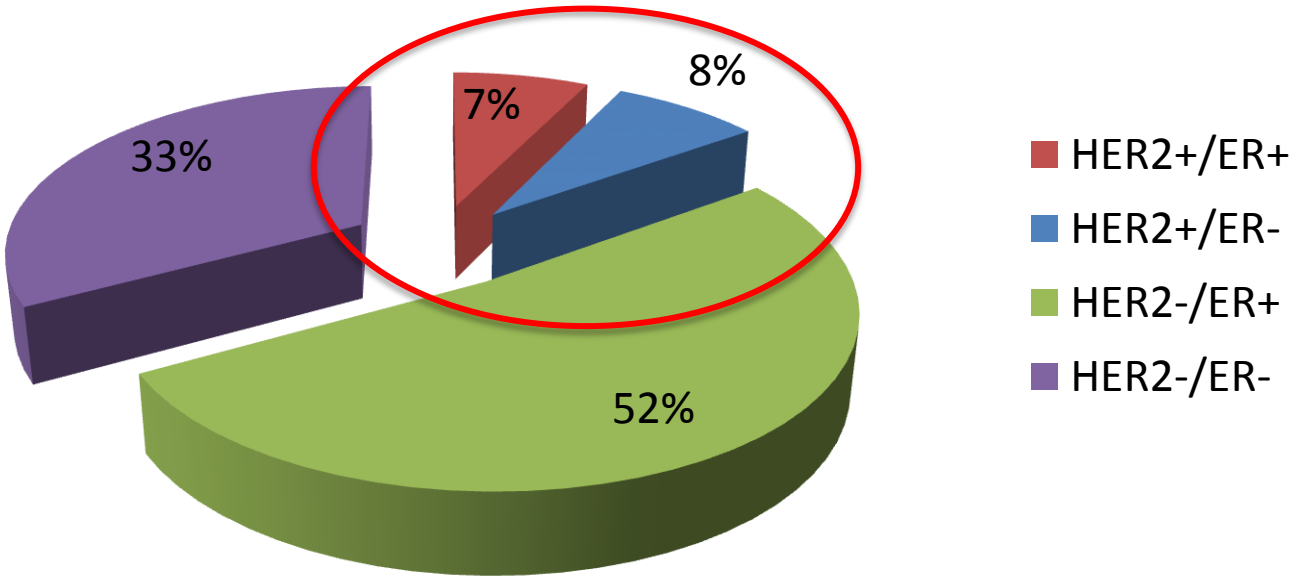
Iwamoto et al. JNCI 2011

Prognostic and predictive gene pathways in HER2-normal BC

	HER2 normal	
Gene sets	ER positive	ER negative
Prognostic	131 Poor: ↑ expression of cell cycle-related gene sets Good: B-cell immunity-related gene sets	14 Good: sphingolipid and glycolipid metabolism
Predictive (pCR)	69 Microtubule motor activity and cell cycle regulation	23 Base excision repair, cell aging, microtubule spindle regulation

- More prognostic and predictive gene sets with ER+ vs ER- BC
- Little overlap between ER+ vs ER- gene sets with prognostic or predictive value

Focus on HER2-positive setting



- Retrospective analysis of samples from a large dataset
- Rigorous evaluation and validation

Similar findings in HER2-positive and HER2-negative BC

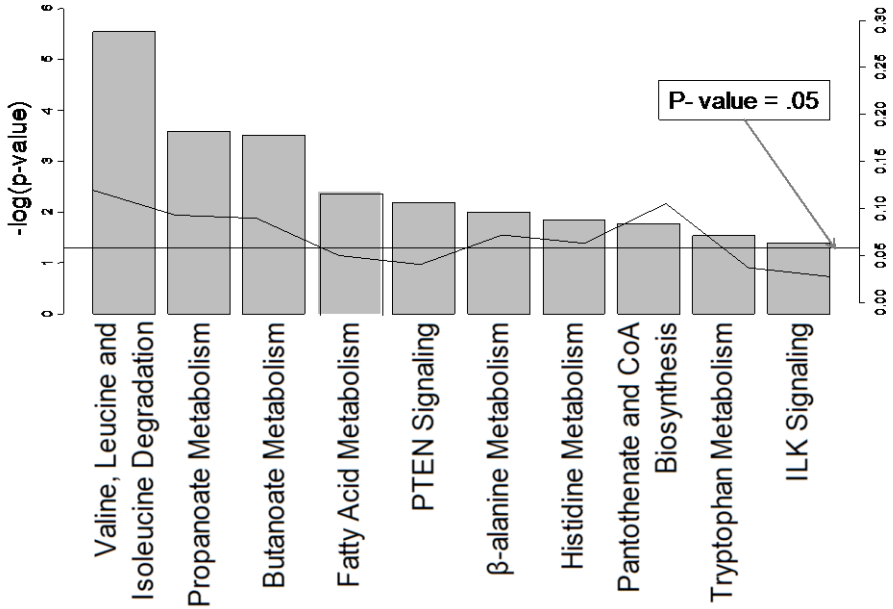
Prognostic gene sets	HER2 negative		HER2 positive	
	ER positive	ER negative	ER positive	ER negative
By HER2 status	3637	3077	113	81
By ER status	101	431	141	769

- More prognostic gene sets with ER+ vs ER- BC
- High (84%) overlap between HER2+ and HER2- prognostic gene sets
- Biologically consistent with previous findings in HER2-normal BC
  - Immunity-related gene sets associated with good prognosis
  - Cell-cycle related gene sets associated with poor prognosis

ER+ vs ER– subtypes

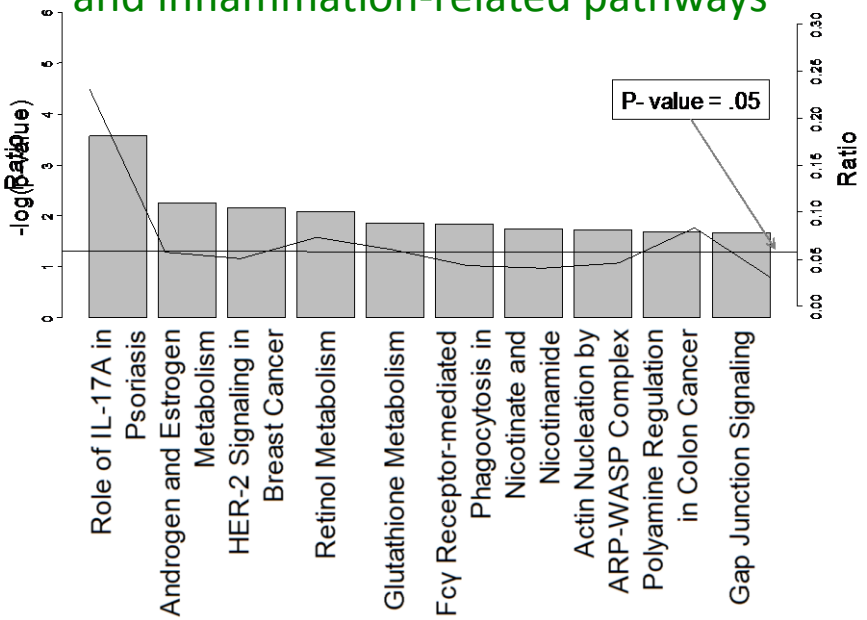
ER+/HER2+

Amino acid and fatty acid metabolism, PTEN signaling



ER–/HER2+

Androgen, estrogen, HER2 and gap junction signaling; antioxidant activity- and inflammation-related pathways



Conclusions

- Within HER2-positive BC, ER+ and ER– BC represent distinct molecular subtypes
- However, compared with HER2– BC, HER2+ BC exhibits fewer differences between ER+ and ER– subsets
- When stratified by ER status, there were significant differences between HER2+ and HER2– cancers
- Immune signatures predict for good prognosis and higher chemotherapy sensitivity in HER2+ cancers, regardless of ER status

Implications and next steps

- Gene signatures (especially those relevant to immune signatures) may open up a further predictive characteristic and generate an additional subset in BC
- Subsets of HER2-positive patients with a poor prognosis and worse chemosensitivity can be characterised by biosynthetic and metabolic processes, warranting further research
- Can potentially predictive gene sets be validated with new HER2-targeted therapies?

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Circulating tumour cells (CTCs) vs circulating tumour DNA (ctDNA)

CTCs	ctDNA
Minimally invasive method of obtaining biomarkers	
High CTC count associated with poor prognosis	Nuclear or mitochondrial origin
Sustained high CTC count on treatment associated with high likelihood of progression	Increased nuclear circulating free DNA levels associated with malignancy and tumour size
	Possibility to screen for PIK3CA mutations

Adapted from Weigel & Dowsett. Endocrine-related Cancer 2010

Study overview

- Heterogeneous cohort of women receiving sequential single-agent therapies (capecitabine, epirubicin, ememestane, paclitaxel, vinorelbine, carboplatin, letrozole, tamoxifen)
- Direct comparison of ctDNA with two alternative methods
- ctDNA measured on average every 2–3 months throughout the follow-up period
- Average duration of follow-up across the series: 350 days
- Average number of serial blood samples per participant: 5

Monitoring mBC using ctDNA

- Key findings and strengths of the technique:
  - Minimally invasive
  - Potential to identify changes in women with BC that is not measurable using other techniques (CA 15-3, CTCs)
  - Evidence that ctDNA provides an early indicator of response
    - ctDNA elevation detected ~5 months before other techniques identify PD
- Limitations:
  - Paired samples from only 30 women (114–126 samples)
  - Heterogeneous treatment regimens and settings

Unanswered questions

- Are the results/reliability influenced by the regimen?
  - Are there data for this technique with 'targeted' agents?
- Have dynamic changes in ctDNA vs CTCs been compared in other tumour types?
- Is there any benefit from tracking multiple mutations?
- Is there any interaction between the impact of treatment/response on ctDNA and the prognostic role?
- Might ctDNA have predictive value?
  - How should/will this be investigated?

What now?

- Is prospective evaluation/validation of prognostic potential planned?
- Should these findings be tested in monitoring patients after adjuvant therapy?
- Should an early indication of PD influence treatment decisions and trigger a change of treatment?
  - Parallel with ovarian cancer: rise in CA-125 is an early indication of progression but early treatment impairs QoL without improving OS[1]

Rustin et al. Lancet 2010

Thank you