ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

PERSONALISED MEDICINE SYMPOSIUM

SIGNALLING PATHWAYS SYMPOSIUM

Targeting the PI3K/AKT/ mTOR pathway in cancer

Sitges, Barcelona **28 February - 1 March 2014**

Signalling Pathways Symposium

Targeting the PI3K/AKT/mTOR pathway in cancer

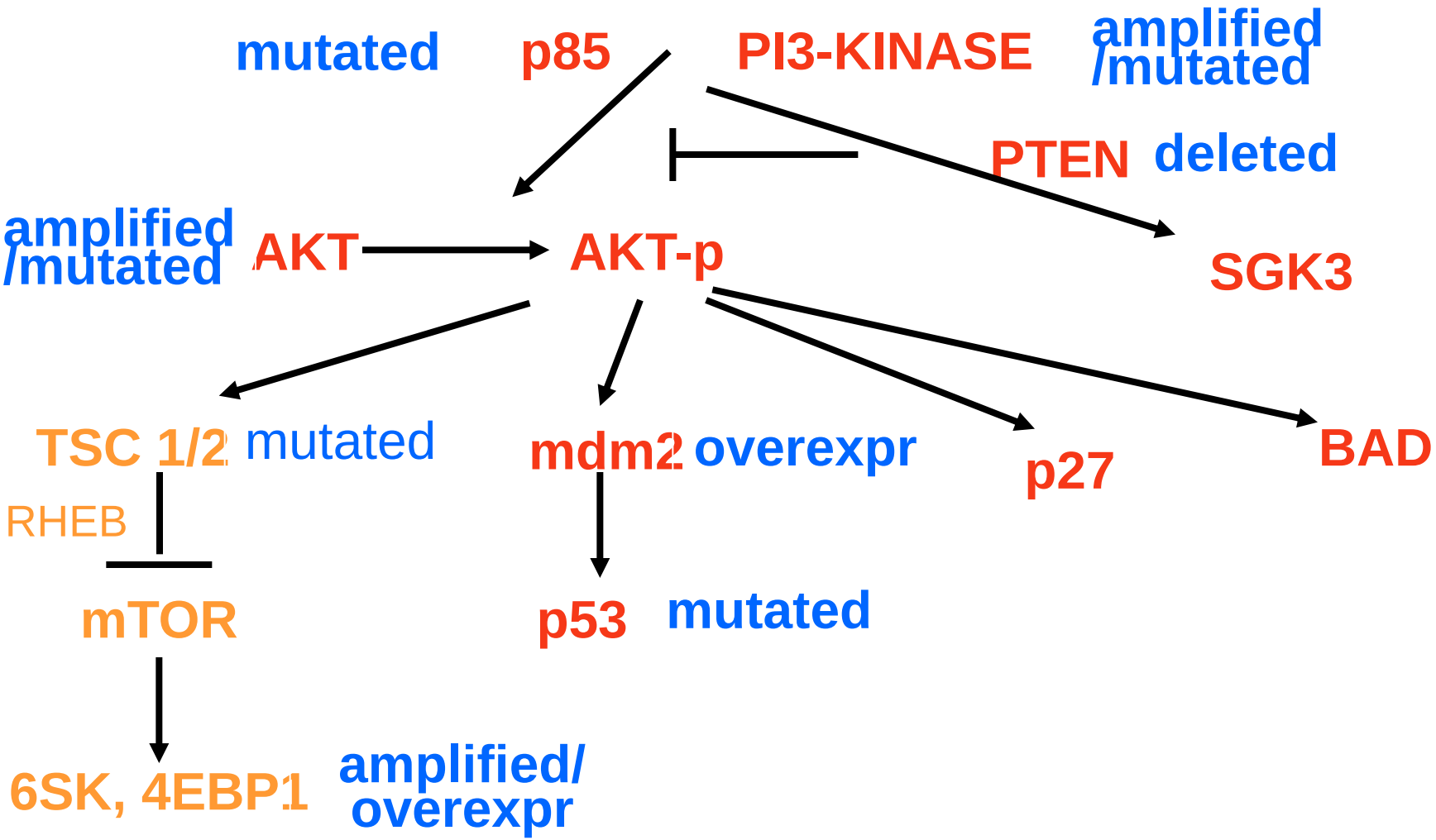
Take home messages

PI3K/AKT/mTOR inhibitors

The Devil is in the Details

Drugs with “unique” properties

The PI3K/Akt pathway



The PI3K/AKT pathway

The PI3K pathway plays a central role in driving and sustaining cancer cell growth.

Several activating mutations/deletions/amplifications converge to the activation of this pathway.

PI3K pathway alterations are associated with targeted and cytotoxic therapy resistance.

The PI3K/AKT/mTOR pathway in combination

Several other pathways interact with the PI3K pathway are the basis for the design of rational combination strategies.

Clinical trial design and correlative studies are needed to select the optimal PI3K pathway inhibitors, the specific biomarkers and the suitable patients.

Toxicities of PI3K/AKT/mTOR inhibitors

Common: stomatitis, metabolic, skin rash, GI, fatigue, AST/ALT elevation

Class effects for mTOR inhibitors – infection and NIP

Class effects for PI3K inhibitors – mood alteration, hyperglycemia

Strategies for effective managing include:

- Patients education
- Early recognition and practical management recommendations
- Dose and schedule modifications

PI3K/mTOR inhibitors in breast cancer

mTOR inhibitors improve outcome in patients with ER-positive or HER2-positive breast cancer

PI3K inhibitors are being investigated in phase III trials

There is a rationale for combining PI3K inhibitors and other targeted therapies

Biomarkers are lacking

In the future, combinations will be rationalized based on genomic profile

PI3K/AKT/mTOR inhibitors in RCC

mTORi active in RCC but less (on average in unselected patients) than anti-VEGF therapy

No predictive biomarkers for drugs in RCC

mTOR pathway aberrations not infrequent

Further study, particularly of metastatic sites / non-invasive technologies needed

PI3K/AKT/mTOR inhibitors in pNET

The PI3K/AKT/mTOR pathway is activated in pNET

Mutations of the PI3K/AKT/mTOR pathway are rare; no genotype phenotype correlations yet

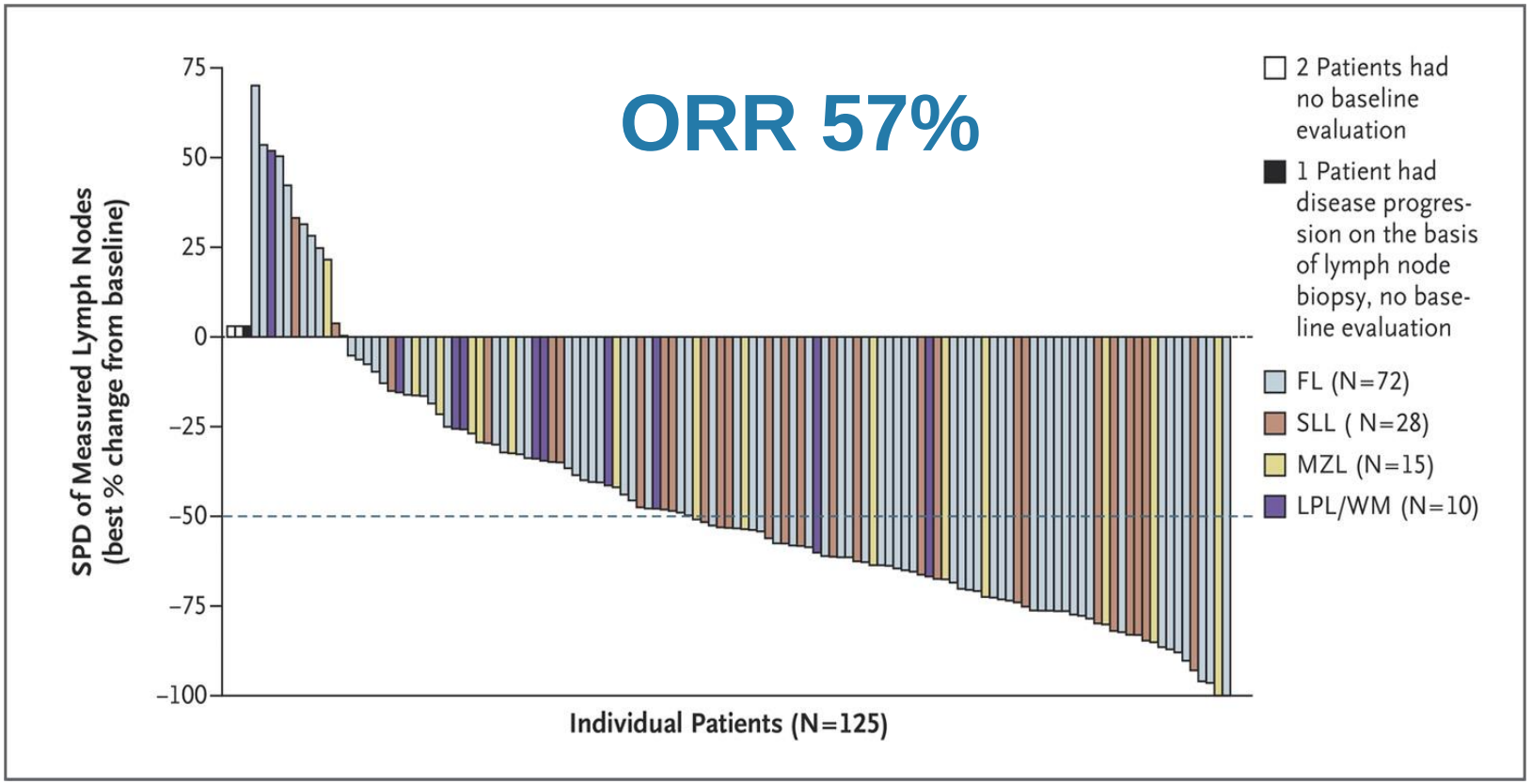
ORR with mTOR inhibitors are low, prolongation of PFS with everolimus by 6 months vs placebo in pNET

Some patients may have a durable benefit

Everolimus is one of several therapeutic optiions in pNET; the place in the treatment algorithm remains unclear

Molecular markers are lacking

Phase II study single agent Idelalisib in 125 pts with r/r (rituximab and alkylating) iNHL



Gopal AK et al. NEJM 2014

Open questions

Advantages and disadvantages of pan versus selective inhibitors

Advantages of inhibitors against mutated isoforms

Feasibility of developing mutant specifics

Advantages of AKT inhibitors

PI3K inhibitors

Still no conclusive results

Dual PI3K/mTOR inhibitors: a great concept but a disappointing clinical outcome

Only positive results with specific inhibitor in target specific expression (PI3Kδ)

Look at PI3K specific inhibitor in selected patients

MADRID 2014 ESMO congress

ESMO 2014

SEE YOU THERE!

Madrid, Spain

26-30 September 2014

PRECISION MEDICINE IN CANCER CARE

IMPORTANT DEADLINES

7 May 2014	Abstract submission
18 June 2014	Early registration
20 August 2014	Late-breaking abstract
20 August 2014	Late registration

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology

PERSONALISED
MEDICINE SYMPOSIUM

Signalling Pathways Symposium in Cancer

MET pathway as a target or a mechanism of resistance

2015 – Sitges, Barcelona