Developmental Therapeutics 449PD & 450PD

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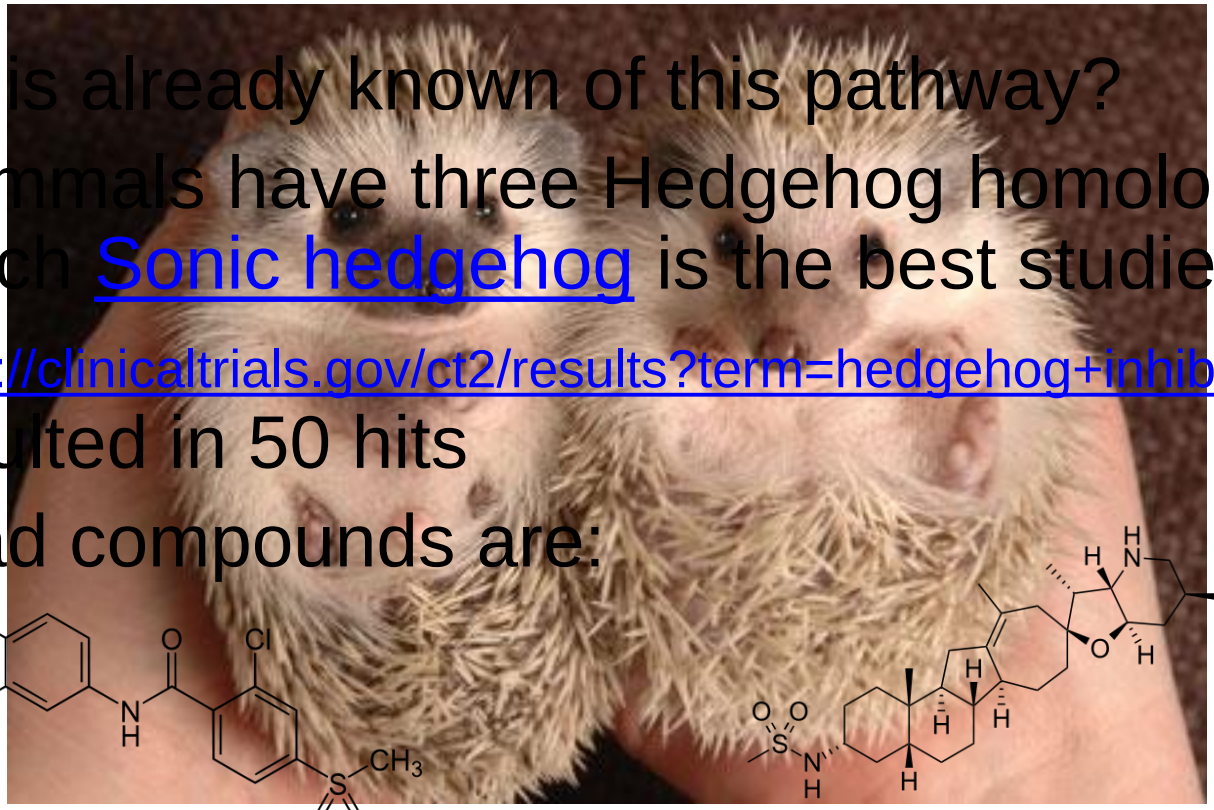
Disclosure

- Research grants to NKI from:
  - Roche, Novartis, GSK, Eisai
- Investigator on ~30 phase I, II studies
- Member Dutch Medicines Evaluation Board
- Member SAG-Oncology EMA

Phase I study of Hegdehog (Hh) pathway inhibitor TAK-441 (449PD)



What is already known of this pathway?

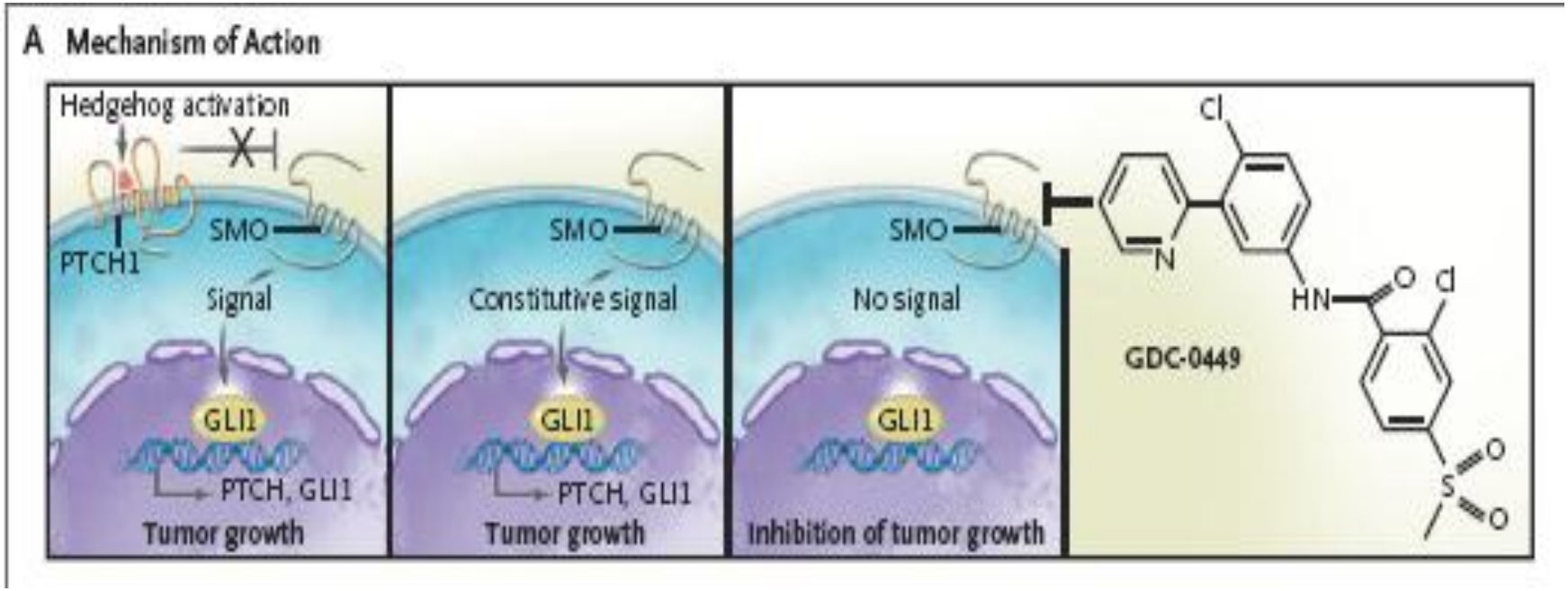
- Mammals have three Hedgehog homologues, of which Sonic hedgehog is the best studied
- http://clinicaltrials.gov/ct2/results?term=hedgehog+inhibitor&pg=2 resulted in 50 hits
- Lead compounds are:

Vismodegib (GDC-0449)

Saridenib (IPI-926)

- Vismodegib is FDA approved for metastatic BCC and under review by EMA

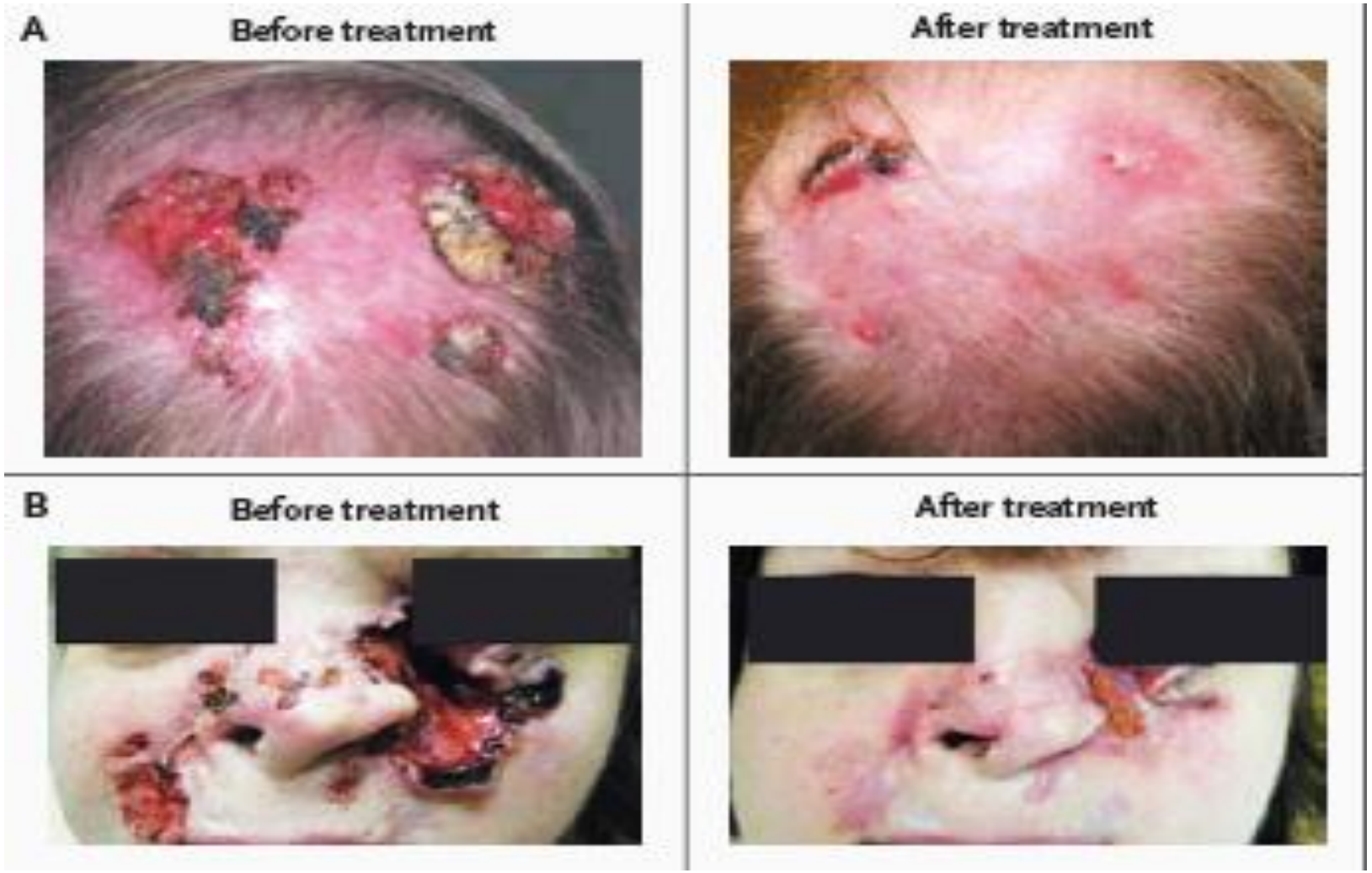
Hedgehog signaling pathway



- Hedgehog is a regulator of cell growth, controls epithelial and mesenchymal interactions (embryogenesis)
- Hedgehog pathway is inactive in adult tissue (PTCH1 inhibits SMO)
- Most basal cell tumors have mutations in hedgehog (a.o. PTCH1) → constitutively active SMO pathway → unrestrained proliferation of basal cells

New Eng J Med 2009;361:1164 -1173

Vismodegib (GDC-0449) in patients with locally advanced basal-cell carcinoma



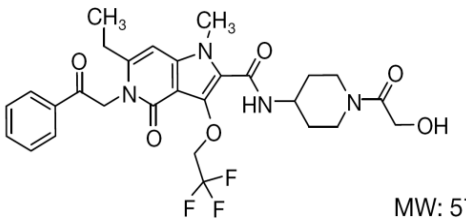
New Eng J Med 2009;361:1164-72

Current developmental strategies Hedgehog inhibitors

- Single agent or chemotherapy combination
- Tumor types:
  - Medulloblastoma
  - GI: pancreas, gastric, CRC, HCC
  - Gyneacological: ovarian cancer
  - Urology: UCC
  - Heamatology: AML, myelodysplasia
  - H/N cancer
  - Lung: SCLC
  - Sarcoma: chondrosarcoma
- Uncertainties exist about biomarker(s) and rational combinations

Poster 449 of Goldman et al.

- TAK-441 is an orally available inhibitor of G protein-coupled Smoothened
- Phase I study to determine safety & MTD
- 3 + 3 design
- Advanced non-heamatologic malignancies
  - Single-dose and multiple-dose plasma pharmacokinetics (PK) of TAK-441
  - Pharmacodynamic effect of TAK-441 on *Gli1* expression in skin and tumors
- TAK-441 PO daily doses: 50, 100, 200, 400, 800, 1600 mg in continuous 21-day cycles



MW: 576.56

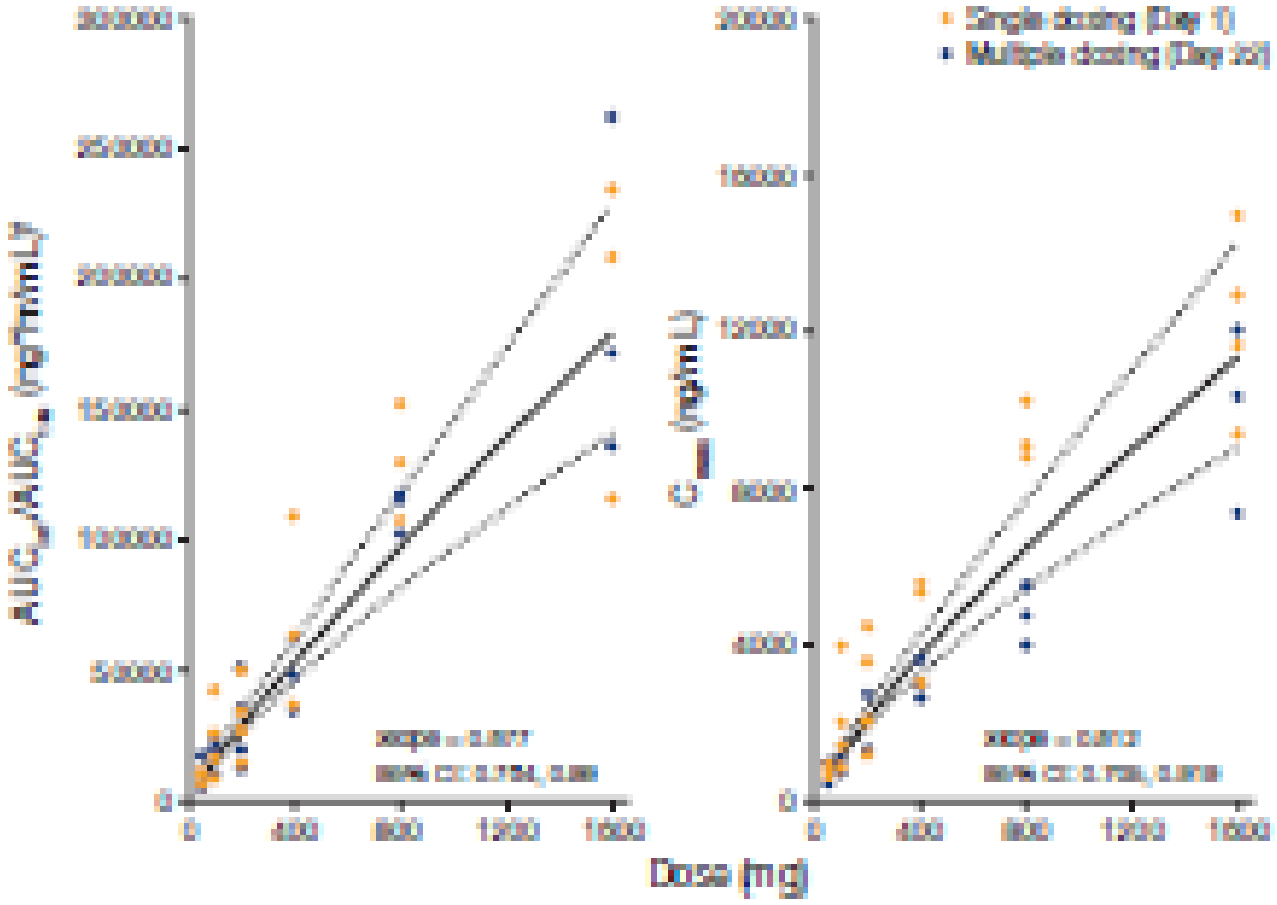
Results & Discussion phase I TAK-441

- DLTs Grade 3 fatigue and muscle spasms (N=1, 1600 mg)
- The MTD has not been reached yet
- Most common treatment-emergent AEs: muscle spasms (44%), dysgeusia (41%), nausea (41%), fatigue (38%), and constipation (28%)
- Six subjects discontinued due to AEs including a fatal cerebral hemorrhage possibly related to TAK-441
- C_{max} for TAK-441 was ~3h, median $t_{1/2}$ 12.5h; both AUC and C_{max} were less than dose-proportional

Non-linear AUC & Cmax of TAK-441

AUC

Cmax



Conclusions

- TAK-441 is well tolerated with dysgeusia, fatigue, nausea and constipation as main AEs
- PK is non-linear
- The MTD needs to be determined
- Skin and tumor Gli1 mRNA inhibition at the MTD and/or RP2D will need to be done

Perspectives Hh-inhibitor TAK-441

- What this poster adds is preliminary phase I data about a novel Hedgehog pathway inhibitor
- Currently no comparison is possible with other inhibitors of the Hedgehog pathway
- Target engagement needs to be shown:
  - Is there specificity for any of the three Hh homologues?

Future

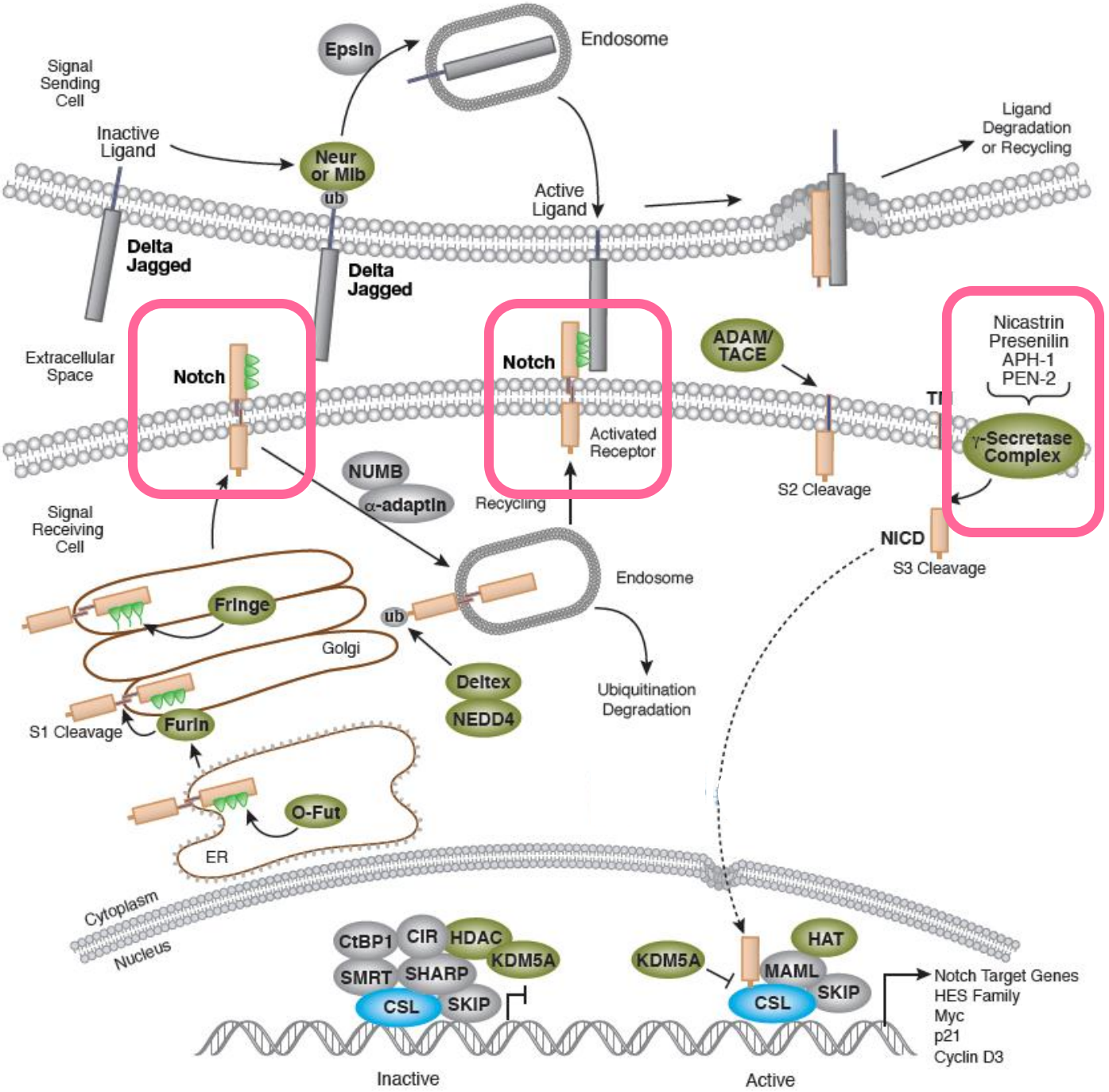
- In designing rational combination studies implementing validated biomarkers is pivotal
- Mechanism and relevance of the non-linear PK need to be addressed

Phase IB study of γ-secretase inhibitor RO4929097 + temsirolimus (450PD)

What is already known about this pathway?

- Notch pathway mediates cell differentiation, proliferation and apoptosis
- Mammalian cells possess 4 notch receptors (NOTCH1-4)
- Two ligand families (Jagged1,2; Delta-like 1,3,4): role as biomarker?
- Cross talk with a.o. PI3K/AKT/mTOR, MAPK and Bcl-2 pathways
- Activity of Notch is controlled by γ-secretase complex
- Notch pathway mutations in a.o.:
  - Heamatology: B-cell CLL, CML, T-cell ALL
  - Solid tumors: a.o. Cutaneous SCC & BCC; H/N, oesophageal & Lung SCC; pancreatic, breast ca, RCC
- γ-secretase inhibitors (γ-Si) under development a.o.:
  - RO4929097; MRK-003; PF-03094014;
- http://clinicaltrials.gov/ct2/results?term=notch+inhibitor : 39 trials

Leukemia 2006: 20: 537-9; Nature 2011; 473: 230-33; BJC 2012; 106: 1953-9


Signal Sending Cell
Epsin
Endosome
Inactive Ligand
Neur or Mib
ub
Active Ligand
Ligand Degradation or Recycling
Delta Jagged
Delta Jagged
Extracellular Space
Notch
Notch
Activated Receptor
ADAM/ TACE
Nicastrin
Presenilin
APH-1
PEN-2
γ-Secretase Complex
S2 Cleavage
NICD
S3 Cleavage
NUMB
α-adaptin
Recycling
Signal Receiving Cell
Endosome
Fringe
Golgi
ub
Deltex
NEDD4
Ubiquitination Degradation
S1 Cleavage
Furin
O-Fut
ER
Cytoplasm
Nucleus
CtBP1
CIR
HDAC
KDM5A
SMRT
SHARP
CSL
SKIP
KDM5A
HAT
MAML
CSL
SKIP
Notch Target Genes
HES Family
Myc
p21
Cyclin D3
Inactive
Active

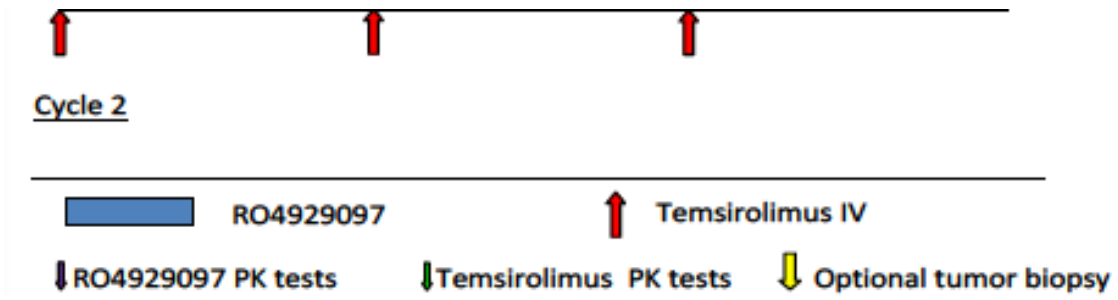
Experience with γ-Si RO4929097

- Phase I: fatigue, nausea, emesis, diarrhea upon intermittent or continuous QD dosing
- Phase II: no relevant activity in unselected Pt-resistant ovarian cancer (ASCO 2012 Diaz-Padilla et al.)
- Phase II ongoing: RCC, pancreatic ca, GBM, CRC, breast, NSCLC (single agent or combination)
- Biomarkers evaluated: o.a. intracellular Notch, JAG1 protein expression, IL-6, IL-8, notch targets (HES1)

Poster 450 of Diaz-Padilla et al.

- Phase IB: safety, MTD RP2D, PK & PD
- 3+3 design of three planned dose-levels

Dose Level	RO Dose (mg)	TEM Dose (mg)	No. of pts treated	No. of pts with DLT
1†	10	25	8	1‡
2	20	25	3	0
3^	20	37.5	6	0



Results & Discussion phase IB RO4929097 + temsirolimus (1)

- Common AEs: fatigue, mucositis, neutropenia, anemia, hypertriglyceridemia
- RP2D: RO 20 mg day 1-3/week+ tem 37.5 mg weekly
- PD: Jagged-1, Notch-3, Notch intracellular domain (NICD) on paraffin-embedded archival tumor tissue – no correlation with outcome

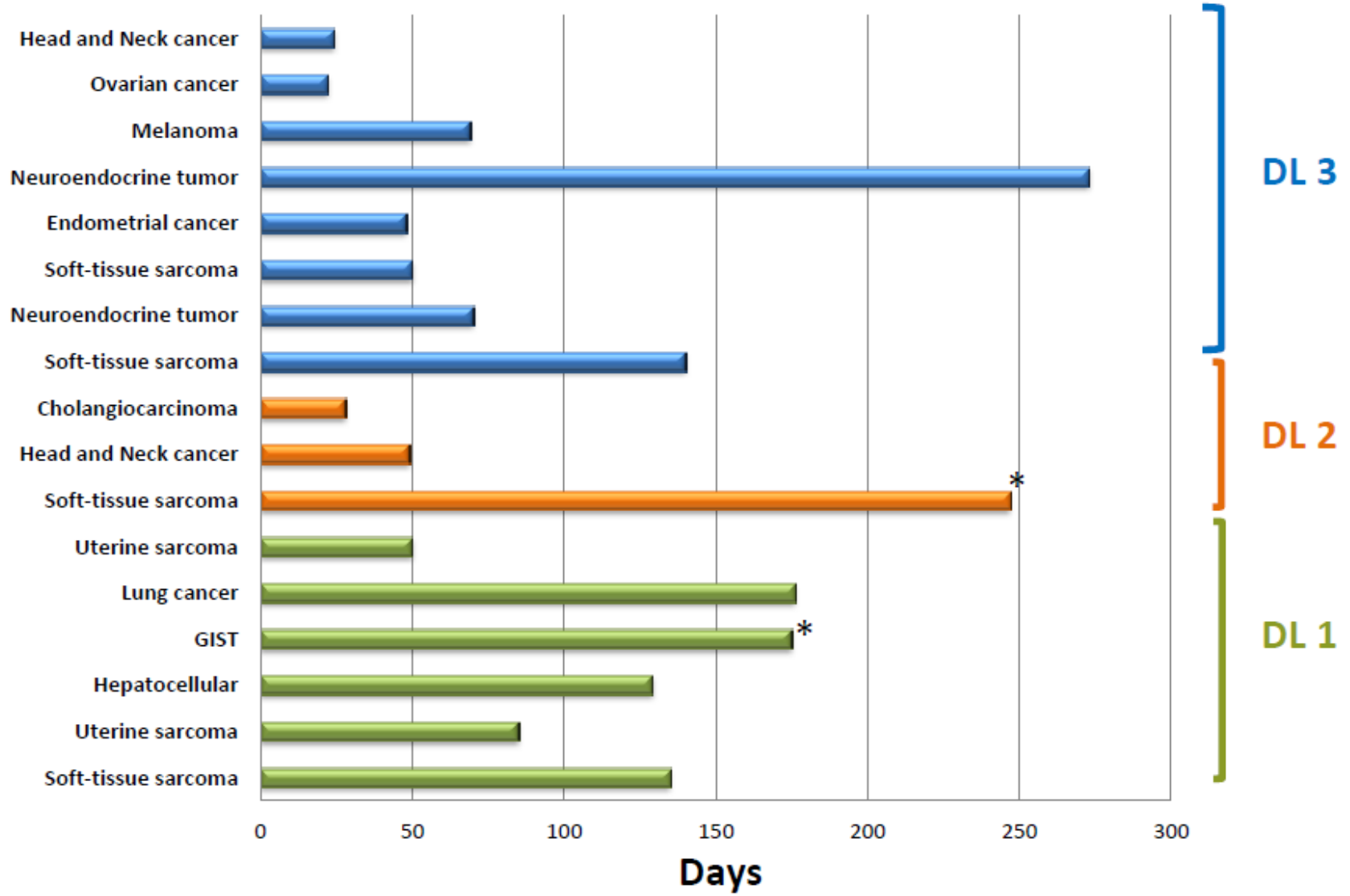
Table 4. Notch-pathway protein expression and outcome (N=14)*

Protein	HR (95% CI)	P value
Jagged-1	1.2 (0.7-2.1)	0.4
NCID	0.9 (0.6-1.2)	0.4
Notch-3	1.1 (0.8-1.4)	0.7

Anti-tumor activity

Response assessment: 6 weeks

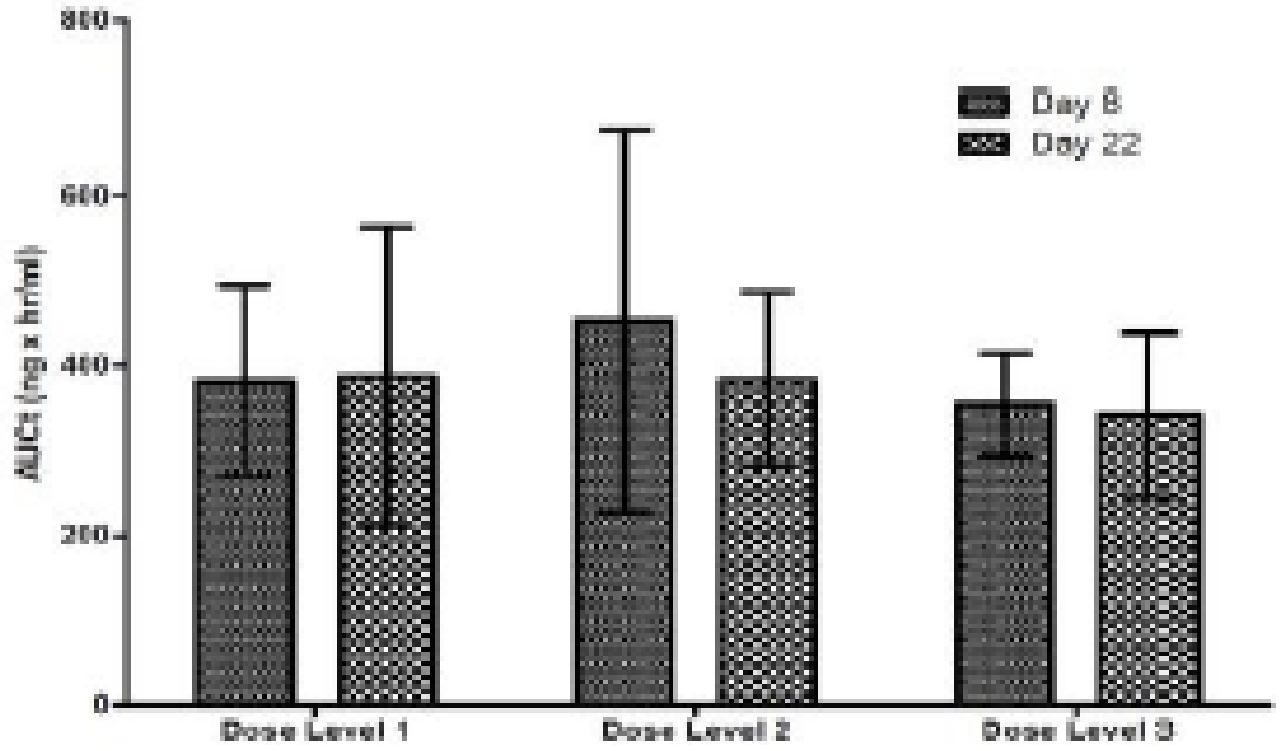
0 PR, 11 (73%) SD, 4 (23%) PD



Results & Discussion phase IB RO4929097 + temsirolimus (3)

- No increase in AUC of RO from 10 to 20 mg

Figure 1. Plasma exposure of RO4929097 (area under the curve [AUC]) at day 8 and day 22, at the different dose levels.



Conclusions & Perspectives

- There is preclinical rational for combining a γ-secretase & mTOR inhibitor
- This study revealed a safe dose for phase II-III
- In unselected patients this combo was ~inactive
- PK of RO4929097 from 10 to 20 mg was not linear; DDI with temsirolimus not excluded

Future

- Without proper patient selection in ph II-III studies development of this concept is high-risk
- Identification of predictive biomarkers is pivotal