

Sym004: a novel synergistic anti-EGFR antibody mixture with superior anti-cancer efficacy

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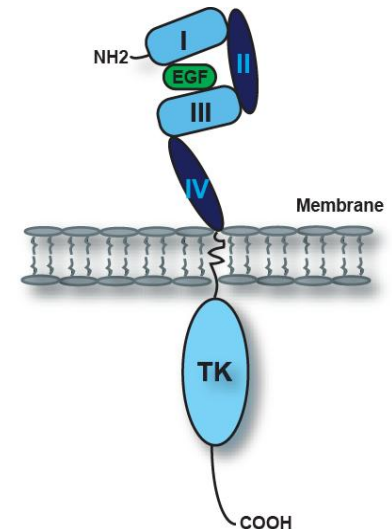
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No conflicts of interest to declare.

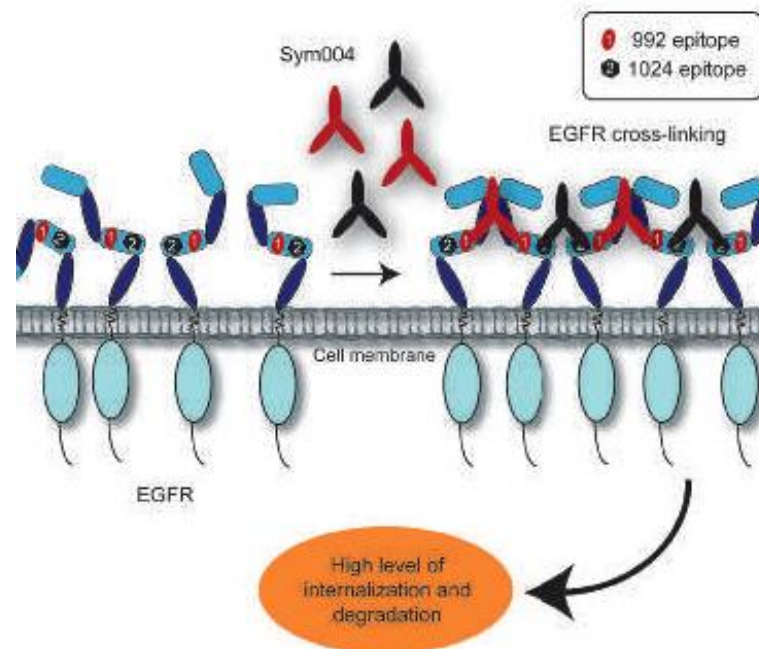
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- EGFR is a validated therapeutic target in cancer.
- Mechanisms of action of mAbs:
 - inhibition of ligand binding and receptor dimerization;
 - inhibition of downstream signaling;
 - ADCC and CDC;
 - receptor internalization.
- Combinations of mAbs can be considerably more potent at inducing downregulation of RTK.

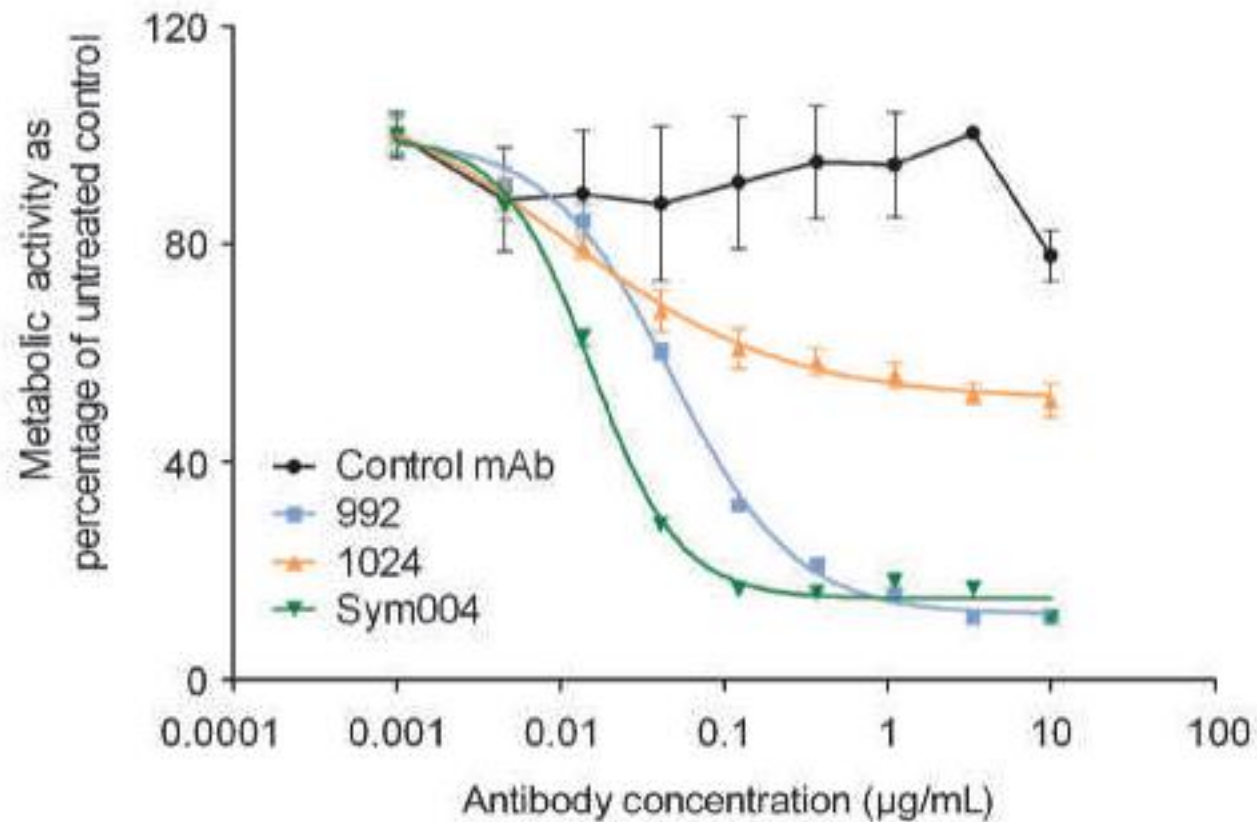


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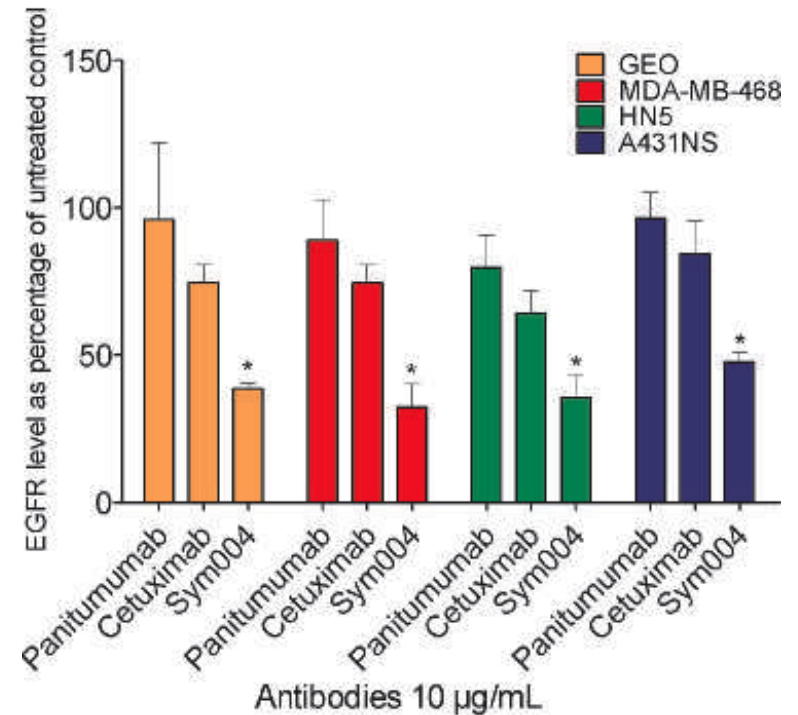
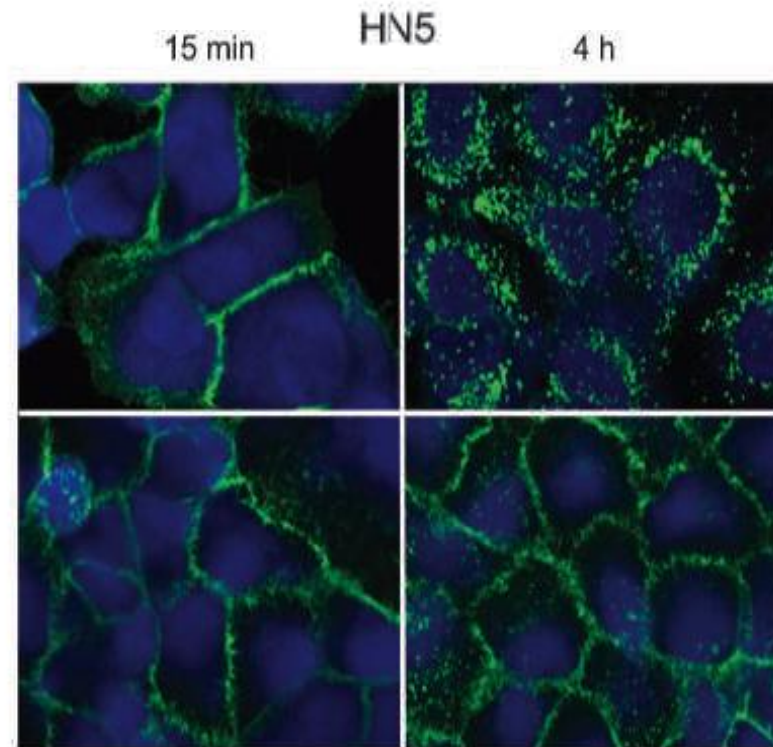
- Sym004 is a 1:1 mixture of two chimeric IgG 1 anti-EGFR mAbs directed against distinct non-overlapping epitopes in EGFR extracellular domain III.
- mSymplex technology: PCR-based method for cloning of Abs from single-sorted murine plasma cells
 - combination of Abs 992 and 1024 was the most potent and with the highest efficacy both *in vitro* and *in vivo*



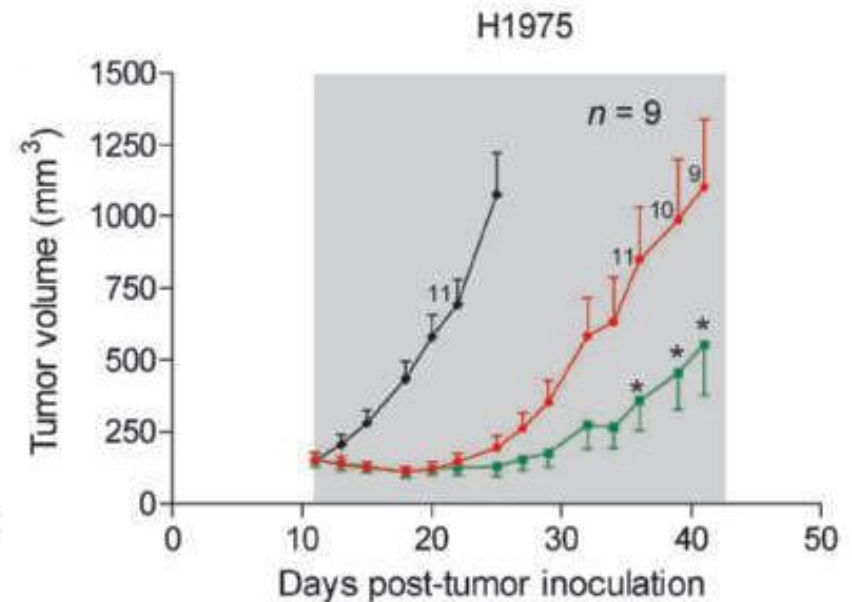
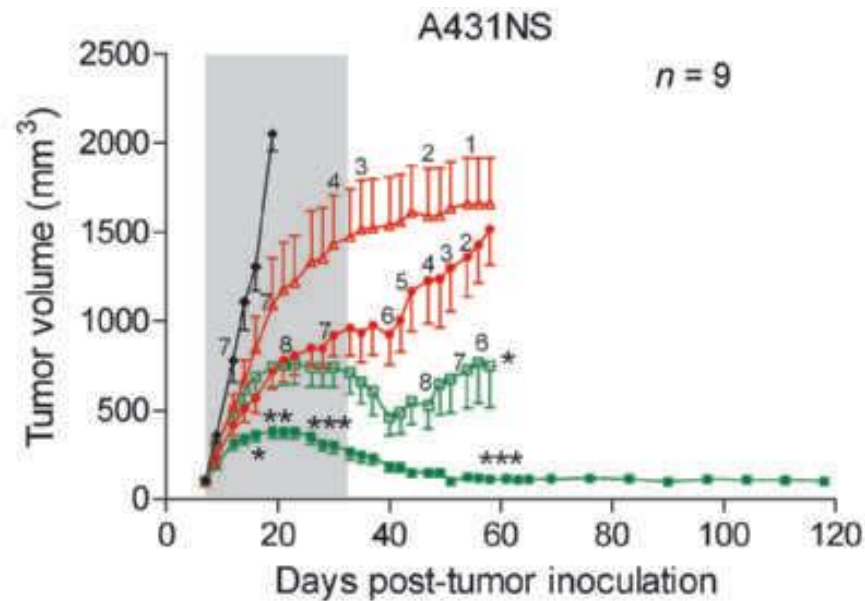
Sym004 synergistically inhibits cancer cell growth *in vitro* (HCC827 cells)



Sym004 induces efficient internalization of EGFR on cancer cells

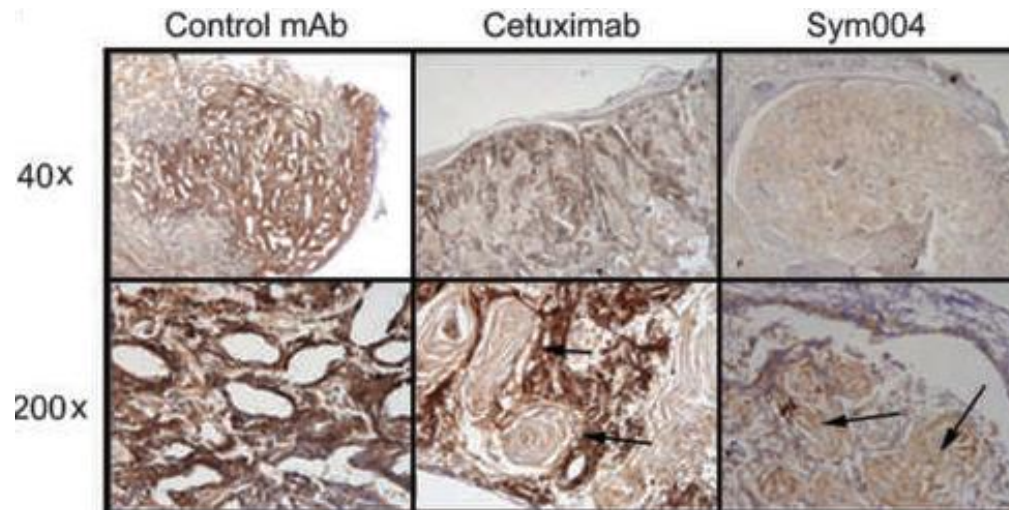
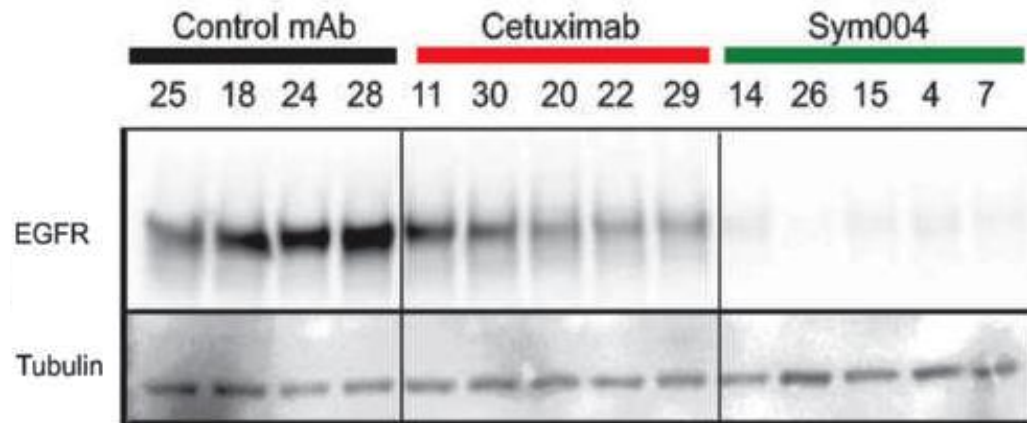


Sym004 is a potent inhibitor of tumor growth in a range of xenograft models

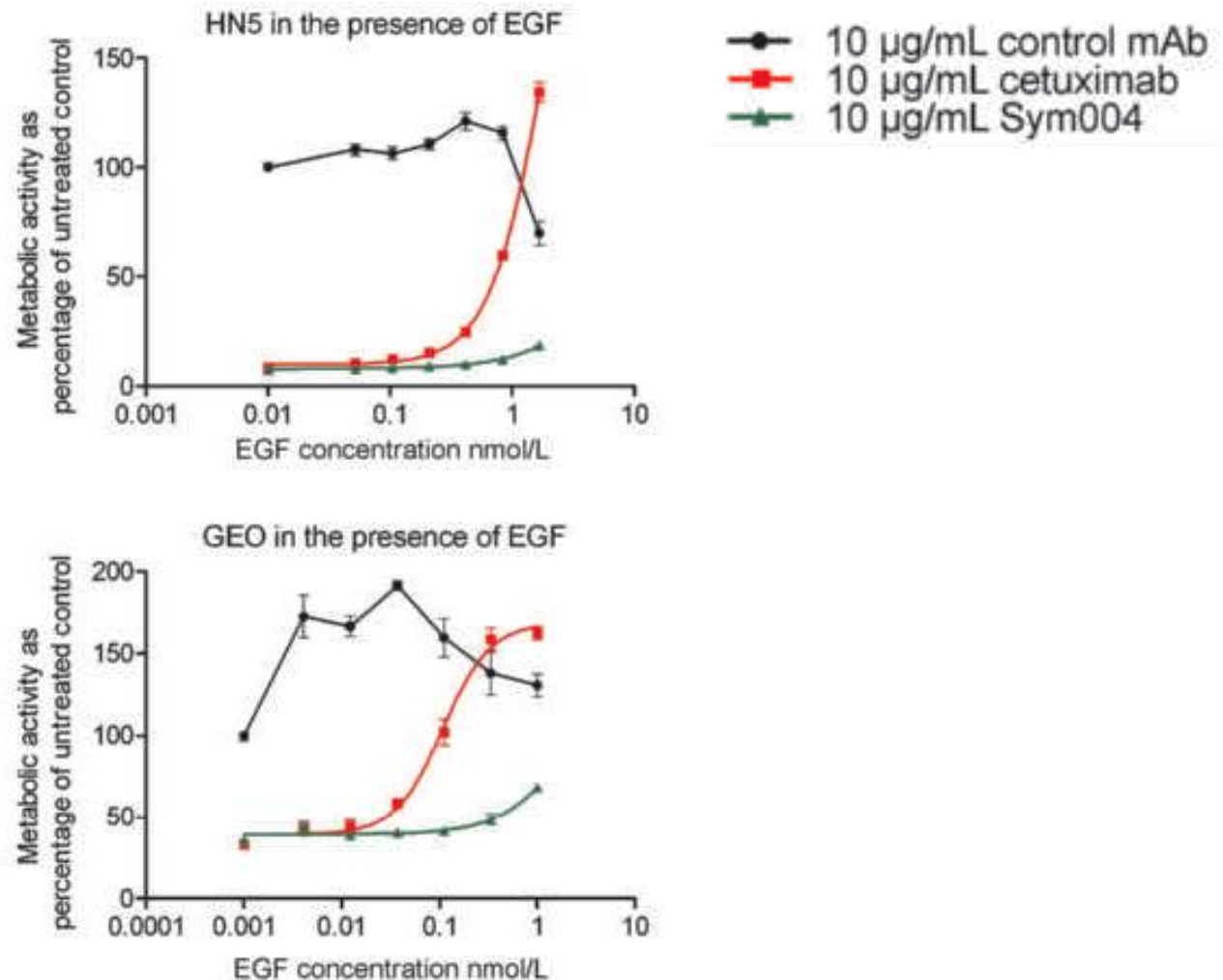


- ◆ Control mAb, 50 mg/kg i.p. twice weekly
- Sym004, 50 mg/kg i.p. twice weekly
- Sym004, 25 mg/kg i.p. twice weekly
- Cetuximab, 50 mg/kg i.p. twice weekly
- ▲ Cetuximab, 25 mg/kg i.p. twice weekly

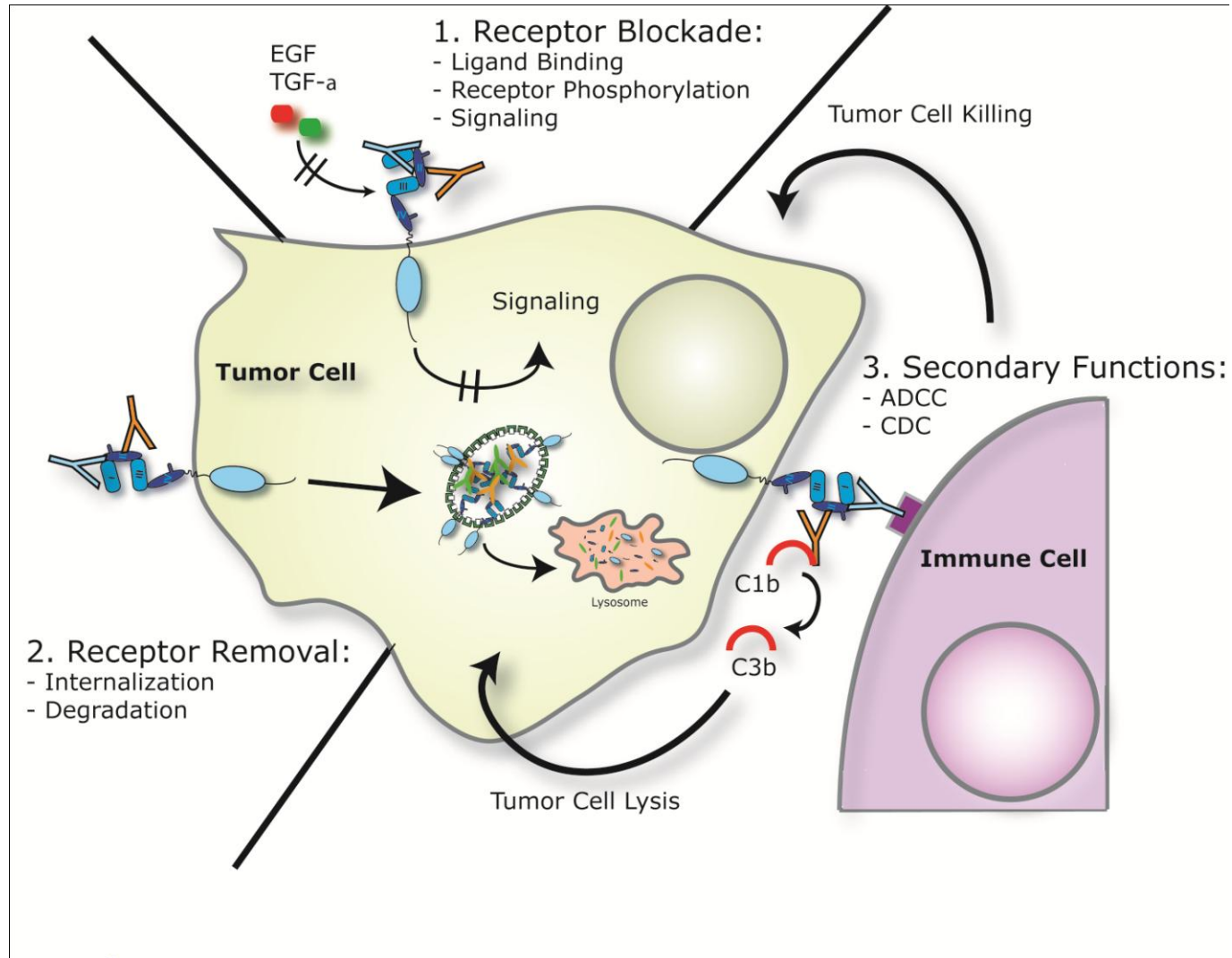
Sym004 causes complete removal of EGFR *in vivo* (A431NS tumors)



Sym004 treatment is less sensitive to ligand-dependent resistance



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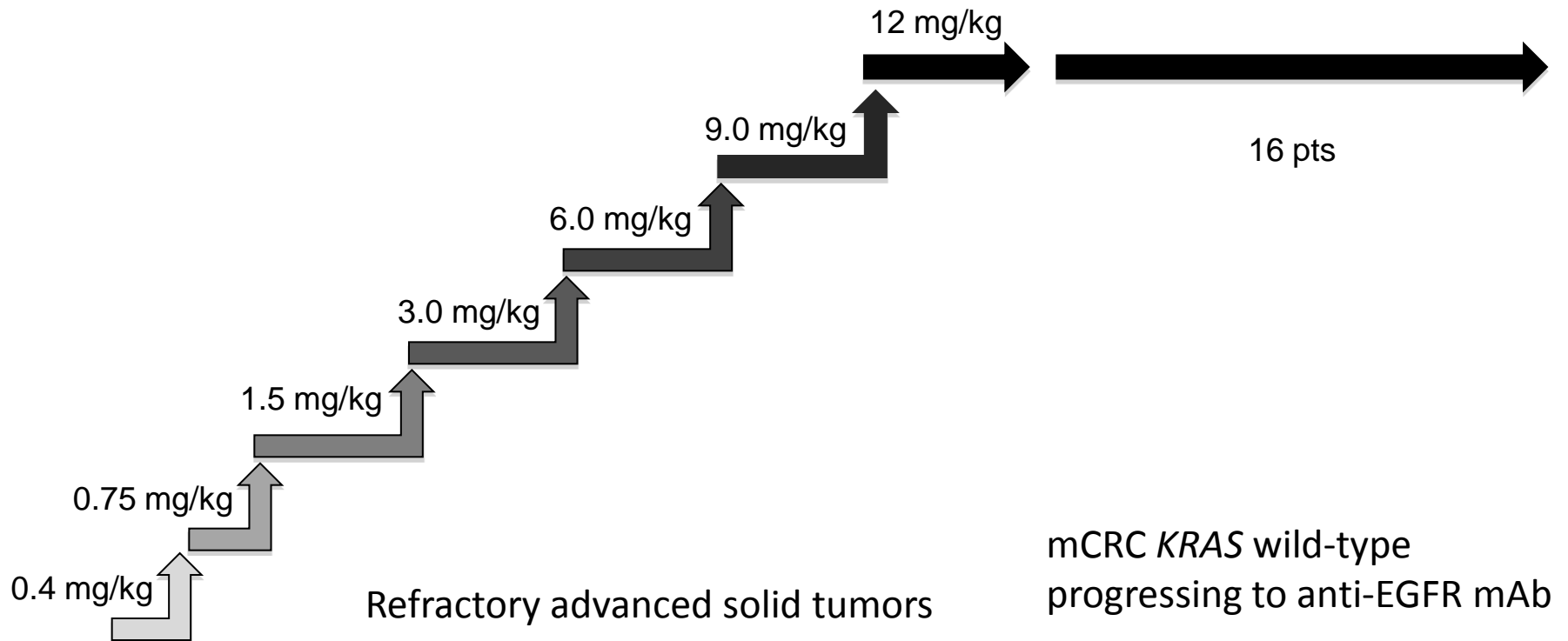


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Phase 1 first-in-human dose escalation trial:

- evaluate safety and tolerability
- define MTD (based on the first 4 **weekly** infusions)
- plasma PK
- biomarker assessment: skin and tumor tissue biopsies
- MTD cohort expansion: preliminary anti-tumor activity

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DLT definition standard to phase 1 trials in addition to:

- Grade 3 skin rash not improved to grade ≤ 2 in 2 weeks
- Grade ≥ 3 infusion reaction

Phase 1 first-in-human dose escalation trial: preliminary toxicity data (part A)

Median age: 60 years

Common tumor types: colorectal, pancreatic and head & neck

<i>Dose level</i>	<i>Number of pts</i>	<i>Grade ≥ 3 toxicity first 4 weeks</i>	<i>Number of infusions</i>
0.4 mg/kg	1	No	6
0.75 mg/kg	1	No	41 [#]
1.5 mg/kg	3	No	6, 6, 21
3.0 mg/kg	3	No	3, 5, 6
6.0 mg/kg	3	Rash (no DLT)	3, 13, 20 [#]
9.0 mg/kg	6	Infusion reaction (DLT)*	1, 5, 9 [#] , 10 [#] , 10, 11 [#]
12.0 mg/kg	3	No	5 [#] , 6 [#] , 6 [#]

* intensified pre-medication scheme with steroids, antihistamines and paracetamol before the first 4 infusions and lower infusion rate

[#] ongoing

9 mg/kg Sym004 - Week 4



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Phase 1 first-in-human dose escalation trial

PK data: Weeks 1 and 3 (24 h)

Other weeks (pre and post-infusion)

PD analysis: skin Bx screening and week 5 (all pts)

tumor Bx screening and week 5 (dose expansion cohort)

IHC: pEGFR, p-MAPK, p-AKT, PTEN, Ki67 levels

Mutation status: *KRAS*, *BRAF*, *PIK3CA*

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Phase 1 first-in-human dose escalation trial

- Sym004 is well tolerated with no unexpected toxicities
- Accrual in the dose expansion cohort at 12 mg/kg ongoing

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Thank you

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