

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma



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6th - 9th February 2019
Verona, Italy

Decrease in p-PRAS40 plays a role in the synergy between erlotinib and crizotinib in an *EGFR* and *cMET* wild-type squamous NSCLC cell line

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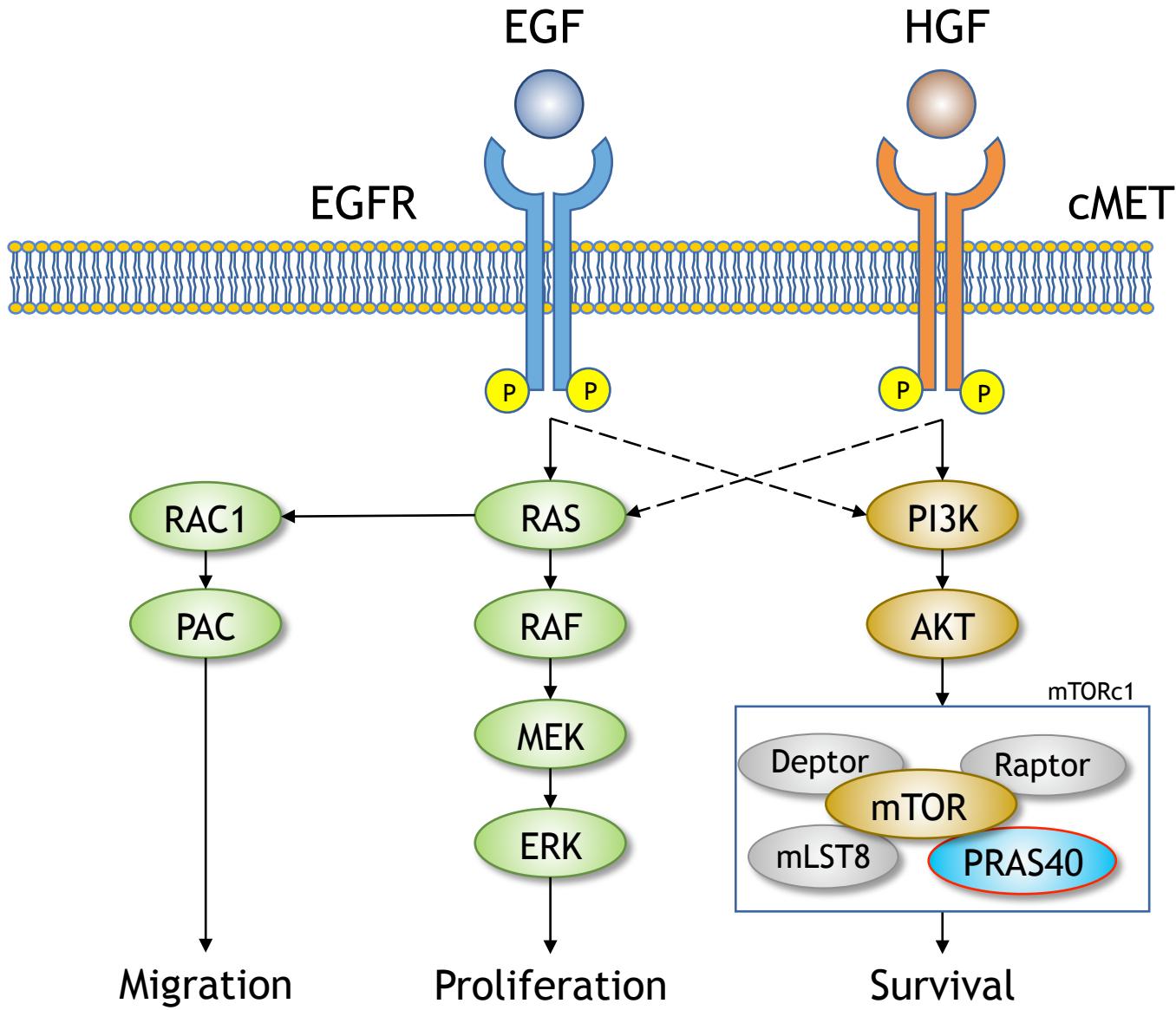


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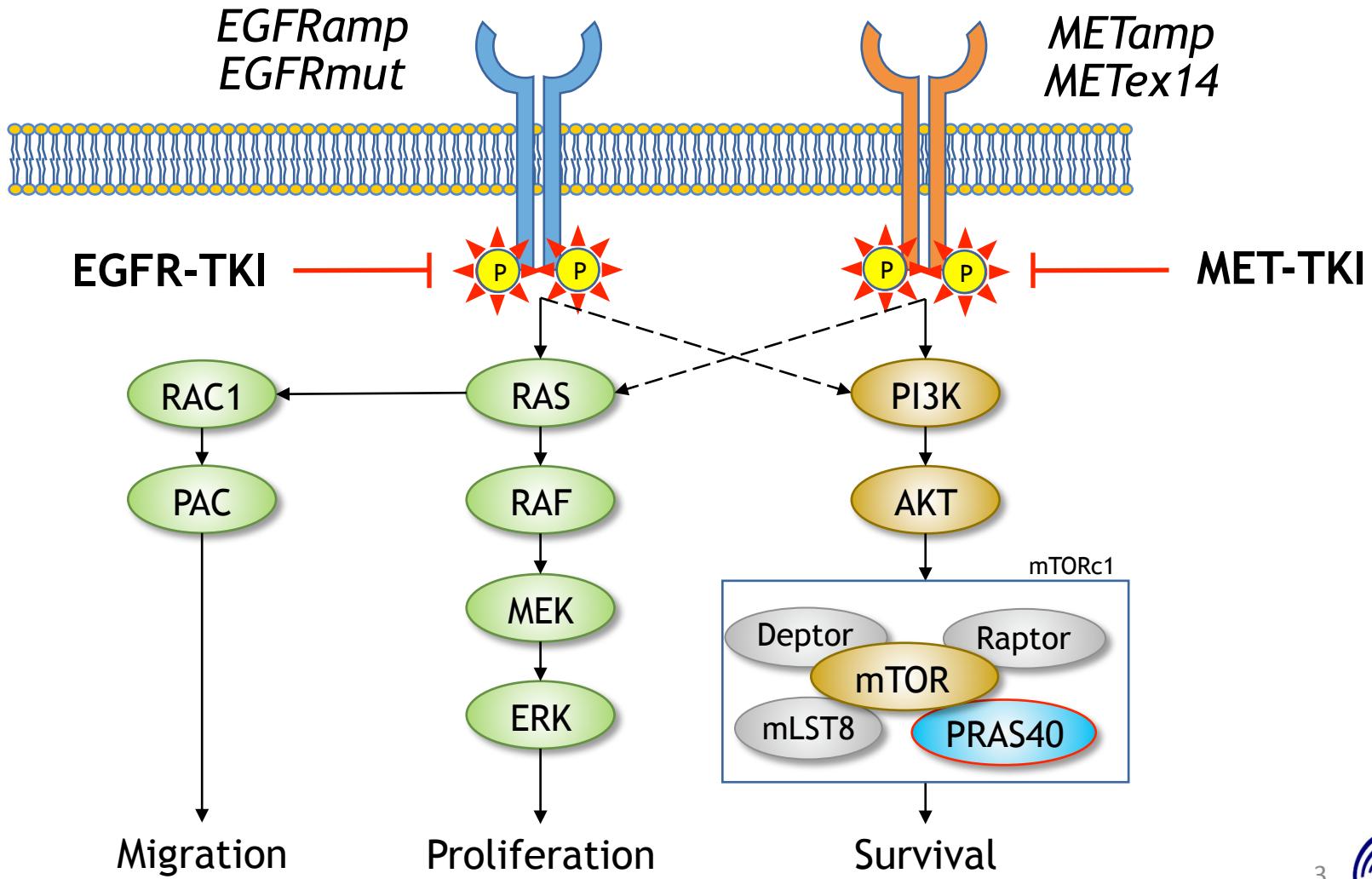
8th of February, 2019



Background



Background



Rationale

- EGFR is overexpressed in squamous NSCLC (~80%)¹
- EGFR-TKIs granted a modest benefit over placebo in unselected squamous NSCLC²⁻⁴
- cMET activation is a common resistance mechanism to EGFR-TKIs⁵

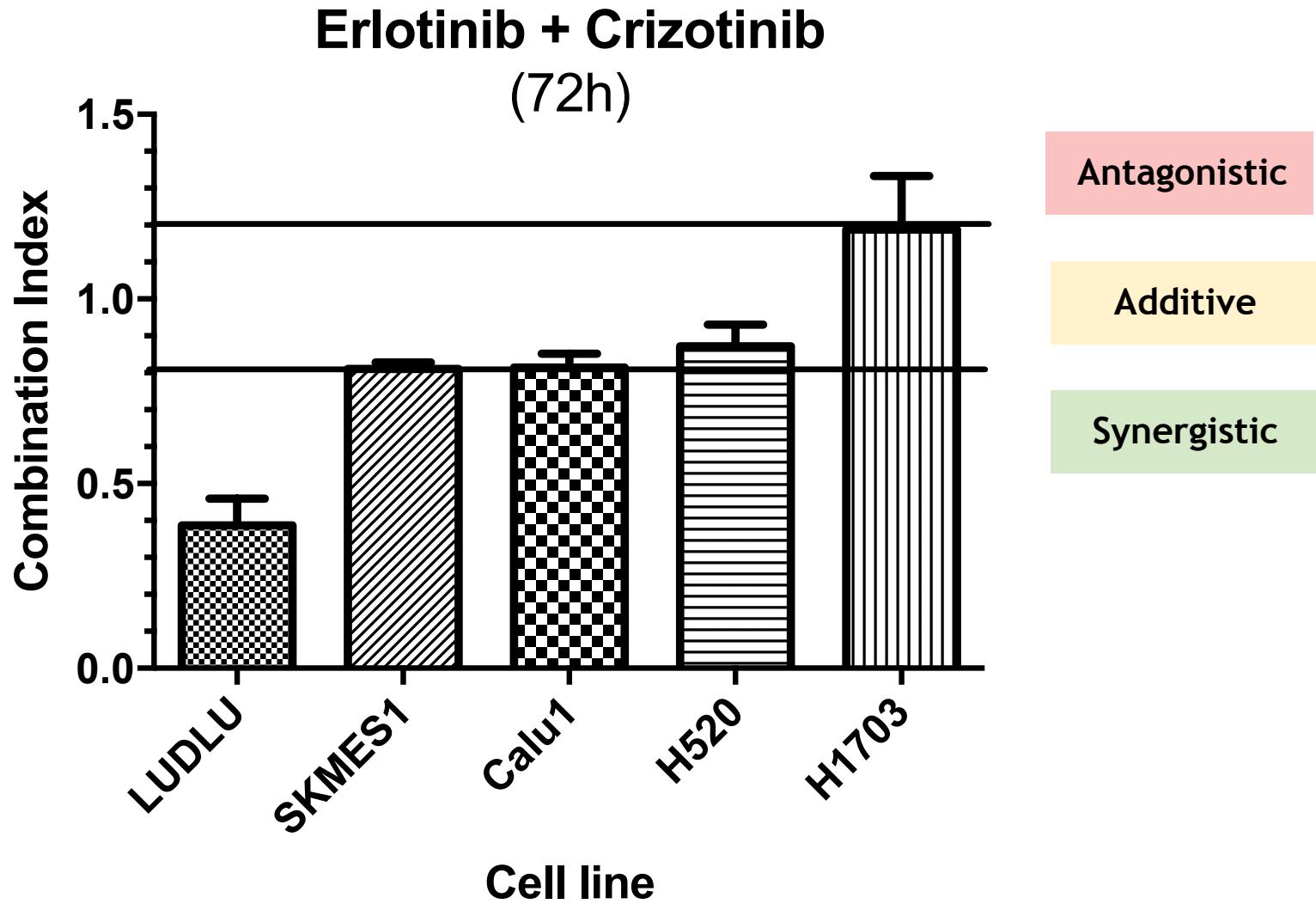


**Erlotinib + Crizotinib
in squamous NSCLC cell lines**

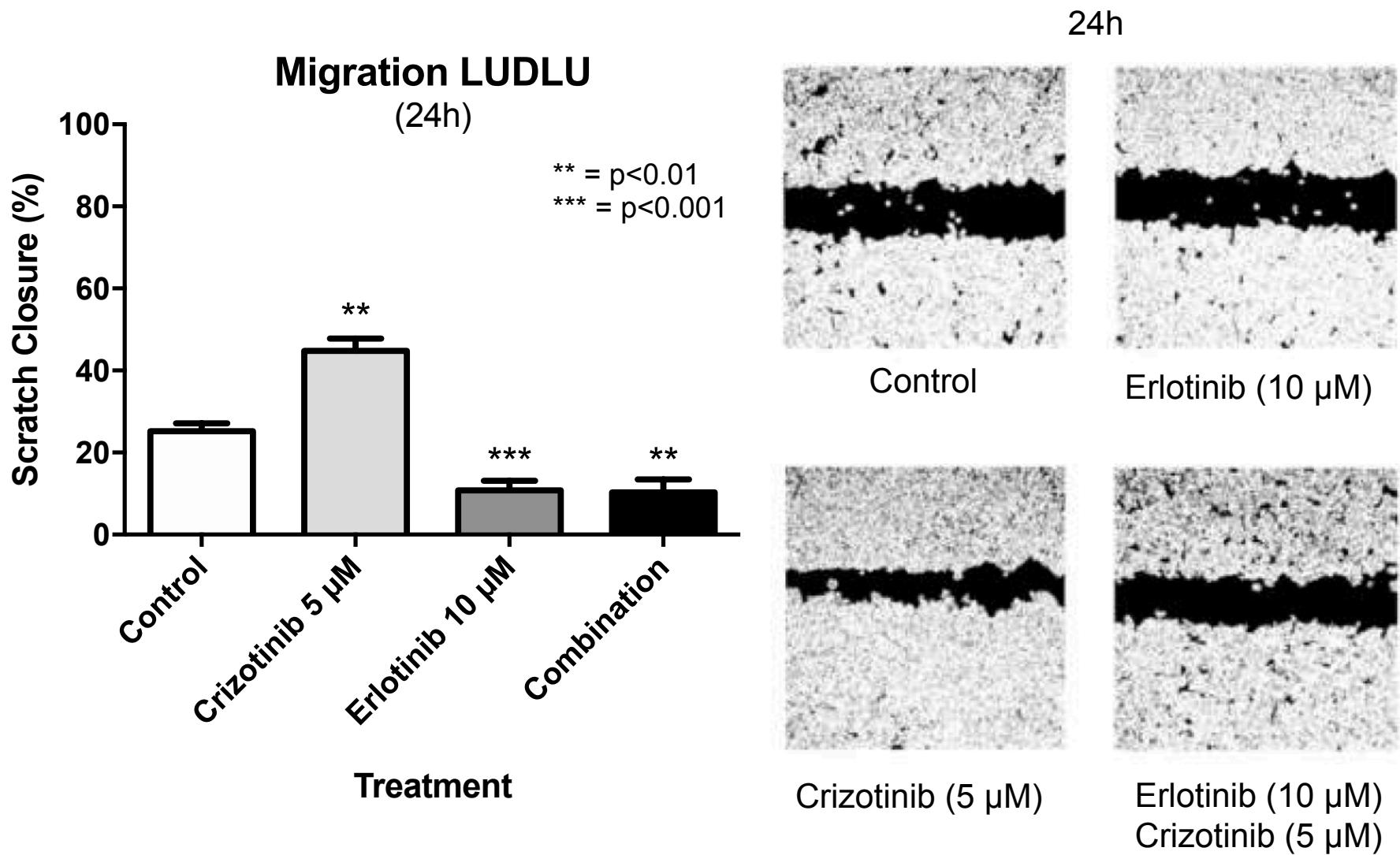
¹Hirsch, J Clin Oncol 2003; ²Wojtowicz-Praga, Ann Oncol 2012; ³Ameratunga, Asia Pac J Clin Oncol 2014; ⁴Soria, Lancet Oncol 2015; ⁵Van Der Steen, Cancer Drug Resist 2018



Erlotinib combined with crizotinib showed strong synergy in LUDLU cell line



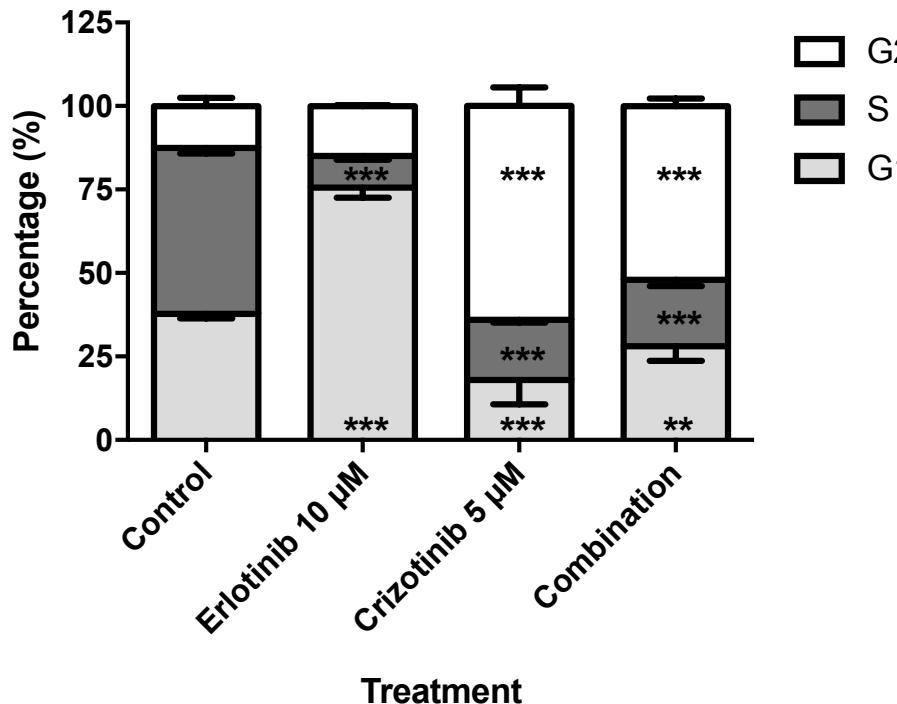
Erlotinib combined with crizotinib reduced LUDLU migration



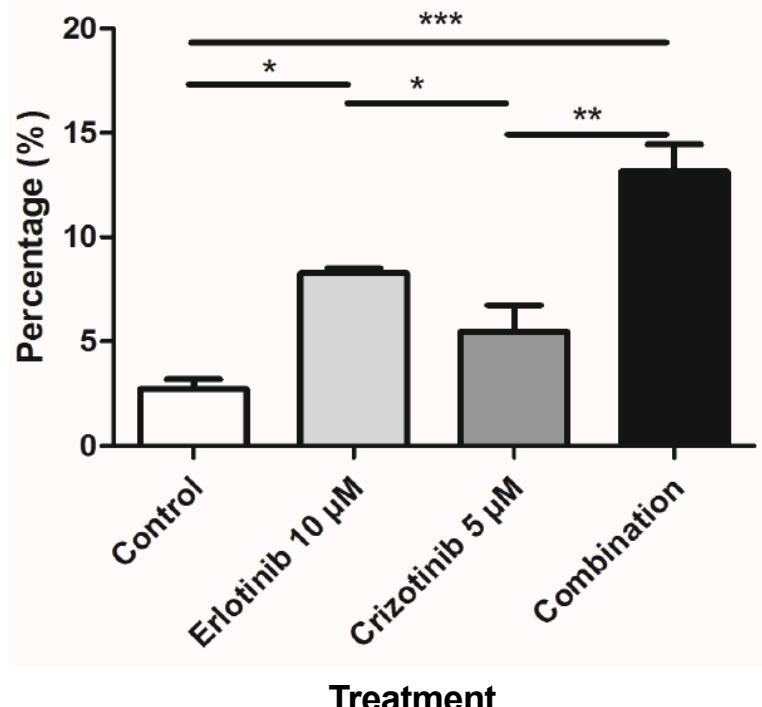
Erlotinib combined with crizotinib induced G2/M arrest and apoptosis

**Cell cycle distribution LUDLU
(24h)**

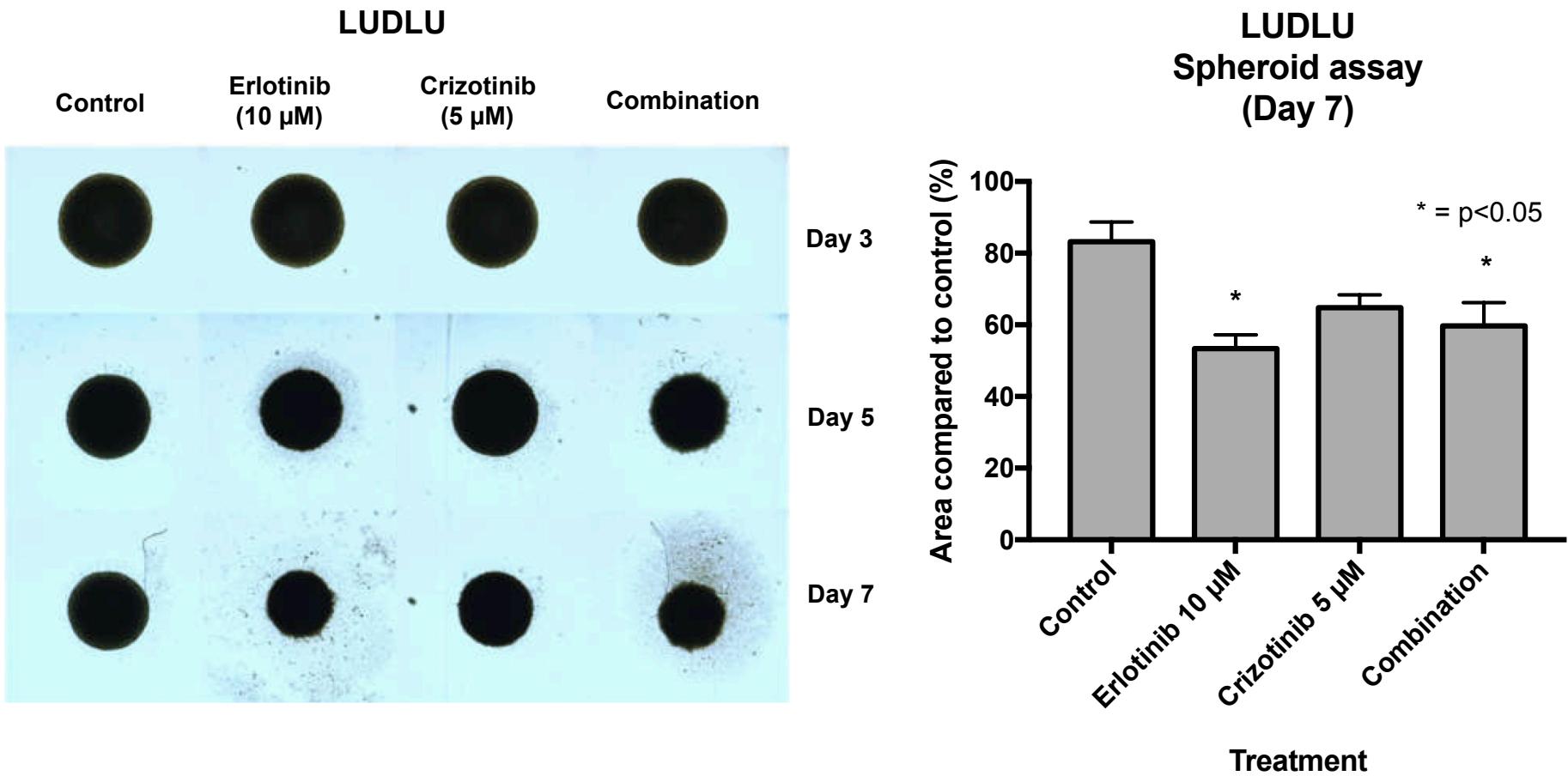
* = $p < 0.05$
** = $p < 0.01$
*** = $p < 0.001$



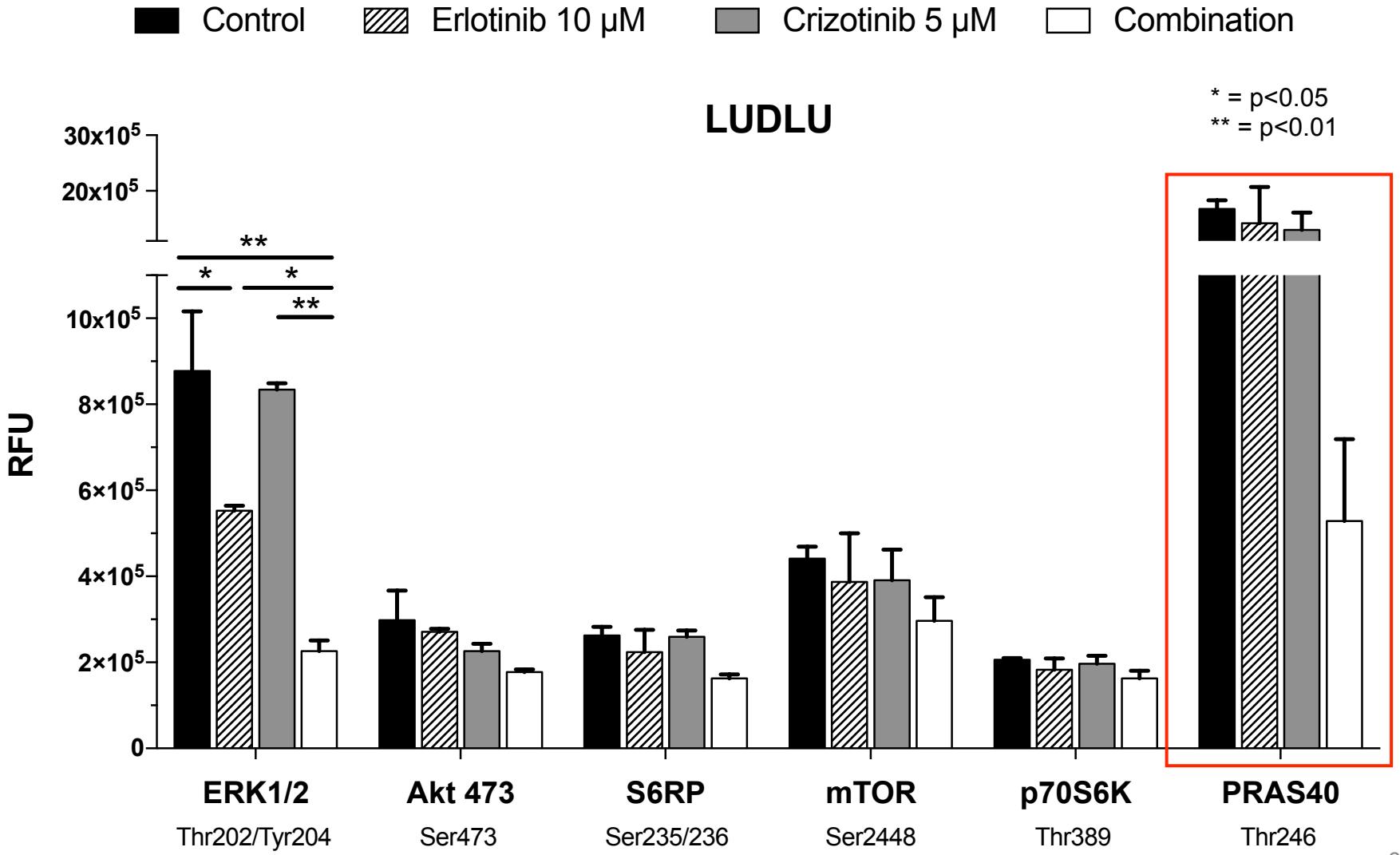
**Apoptosis LUDLU
(48h)**



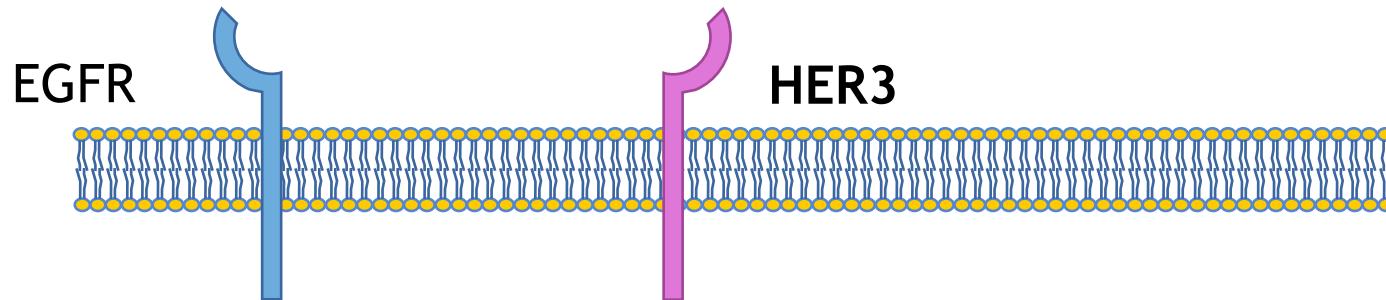
Erlotinib combined with crizotinib reduced the area of spheroids



Erlotinib combined with crizotinib decreased the phosphorylation of PI3K/AKT/mTOR pathway proteins



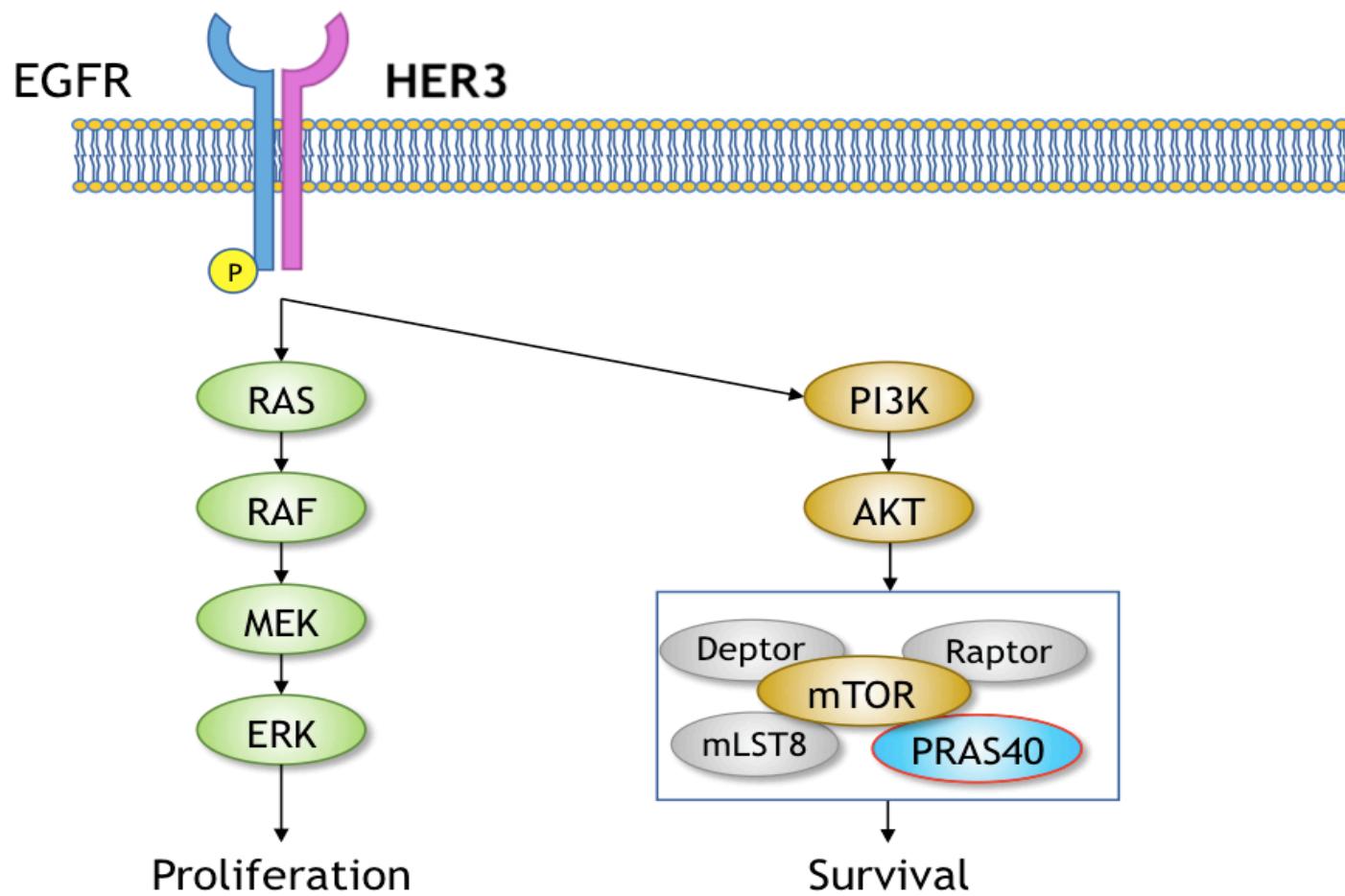
HER3: a link between RAS/MAPK and PI3K/AKT/mTOR pathways



30% of squamous
NSCLC
overexpress **HER3**



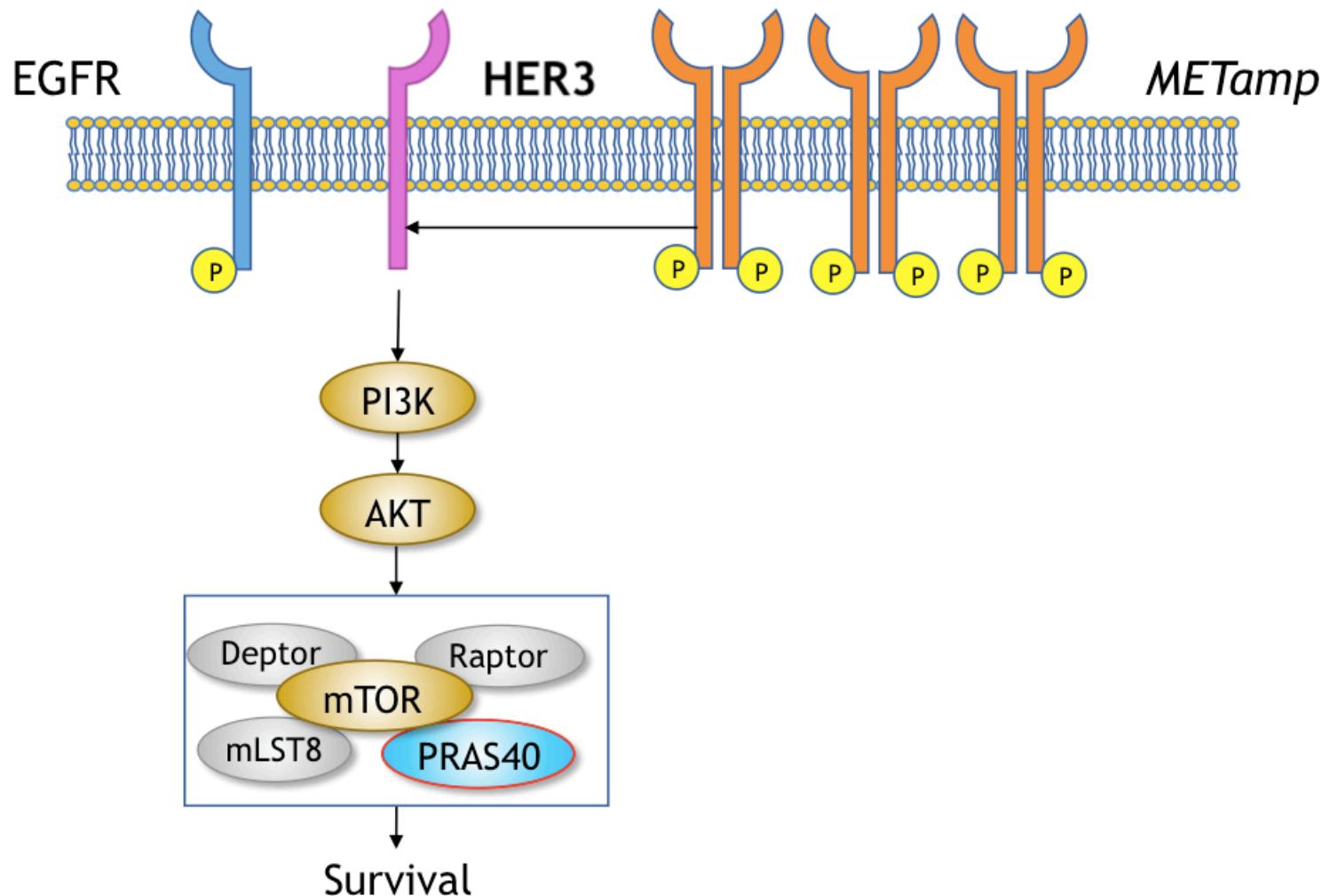
HER3: a link between RAS/MAPK and PI3K/AKT/mTOR pathways



Engelman, *Science* 2007; Arteaga, *Nat Med* 2007; Mishra, *Oncol Rev* 2018

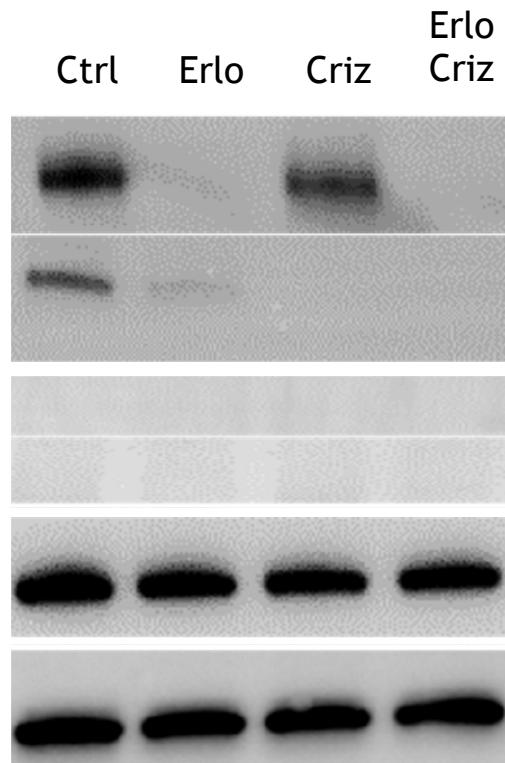


HER3: a link between RAS/MAPK and PI3K/AKT/mTOR pathways

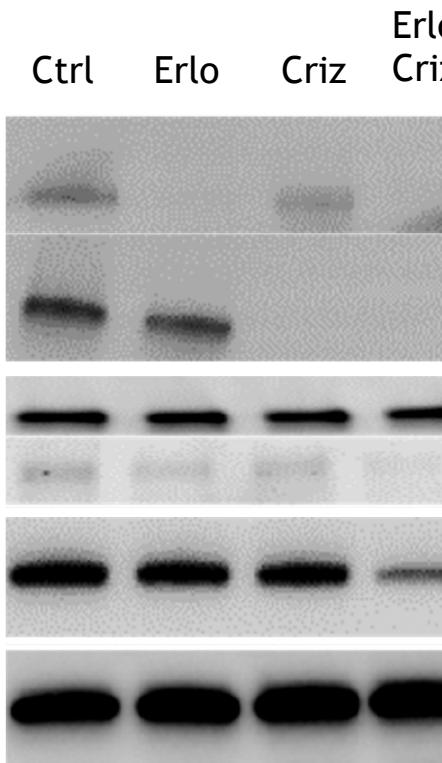


p-HER3 and p-PRAS40 expression decreased in LUDLU following the combination treatment

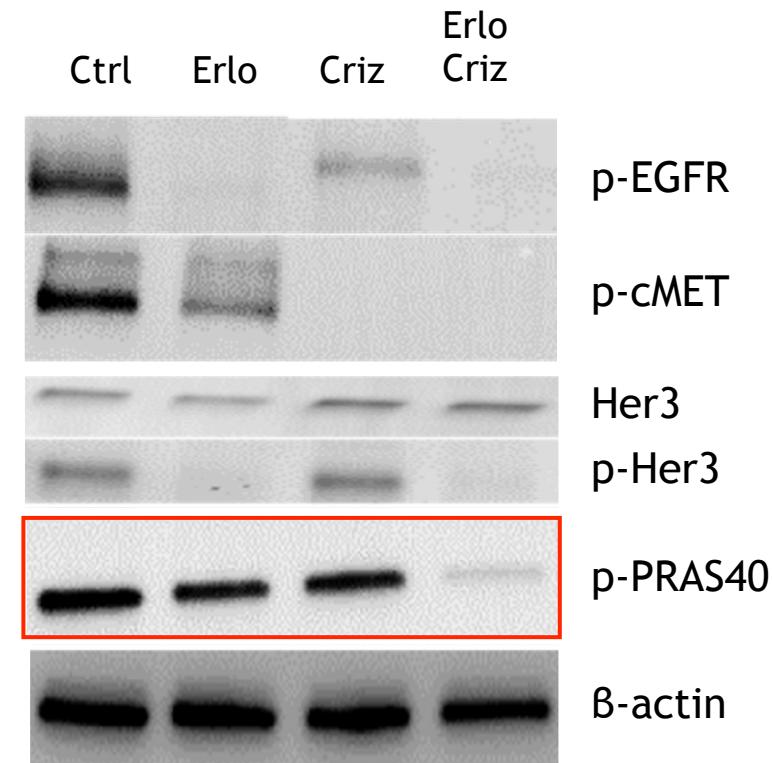
H1703: antagonistic



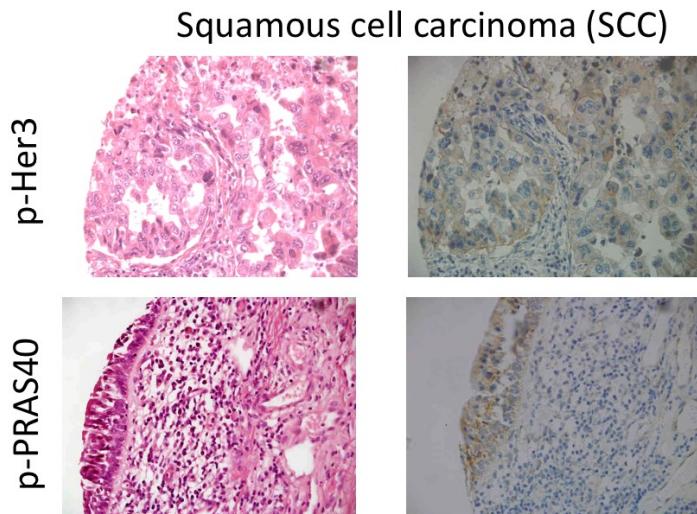
SKMES-1: additive



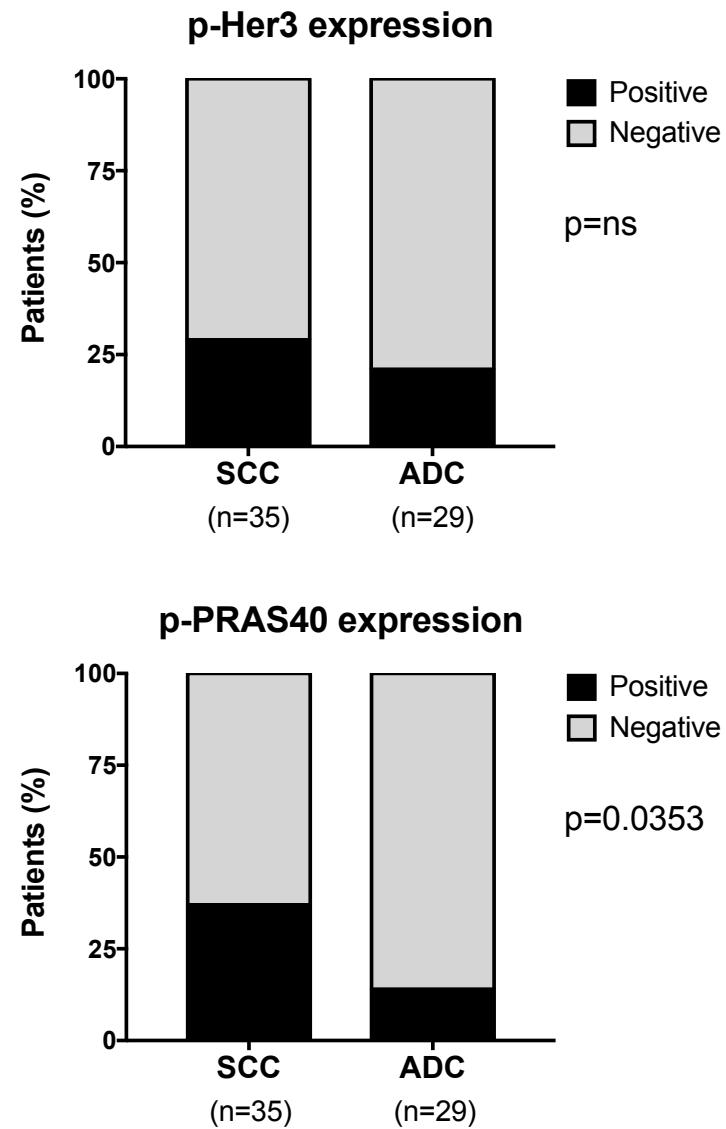
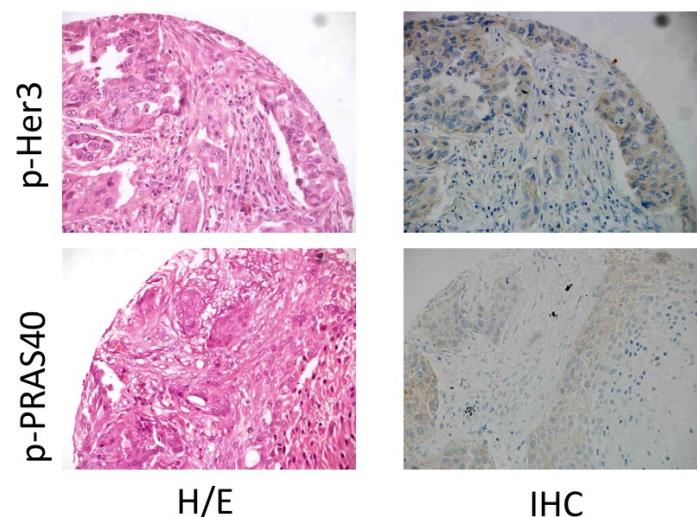
LUDLU: synergistic



p-HER3 and p-PRAS40 are differently expressed in SCC and ADC



Adenocarcinoma (ADC)



Conclusions

- Erlotinib combined with crizotinib showed remarkable synergy in the LUDLU squamous NSCLC cell line (*EGFRwt, cMETwt*)
- p-Her3 and p-PRAS40 have a role in the synergistic effect of erlotinib and crizotinib in LUDLU
- p-Her3 and p-PRAS40 might be used as biomarkers for selecting potential candidates for the combination treatment

