Cancer Prevention Strategies

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Foundations of Cancer Therapeutics
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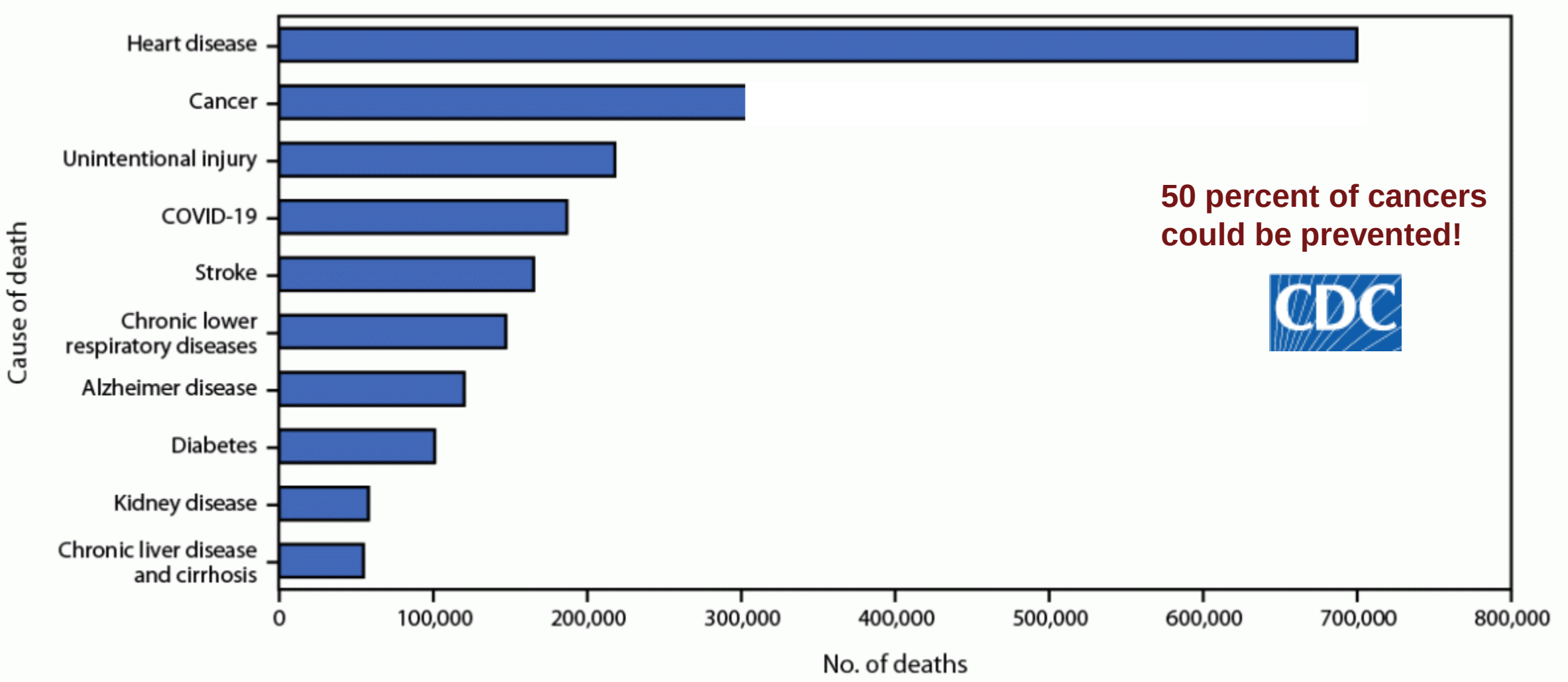
Topics

1) Introduction to Cancer Prevention

2) Cancer Prevention Strategies

3) Case study

Cancer is one of the leading causes of death



50 percent of cancers could be prevented!

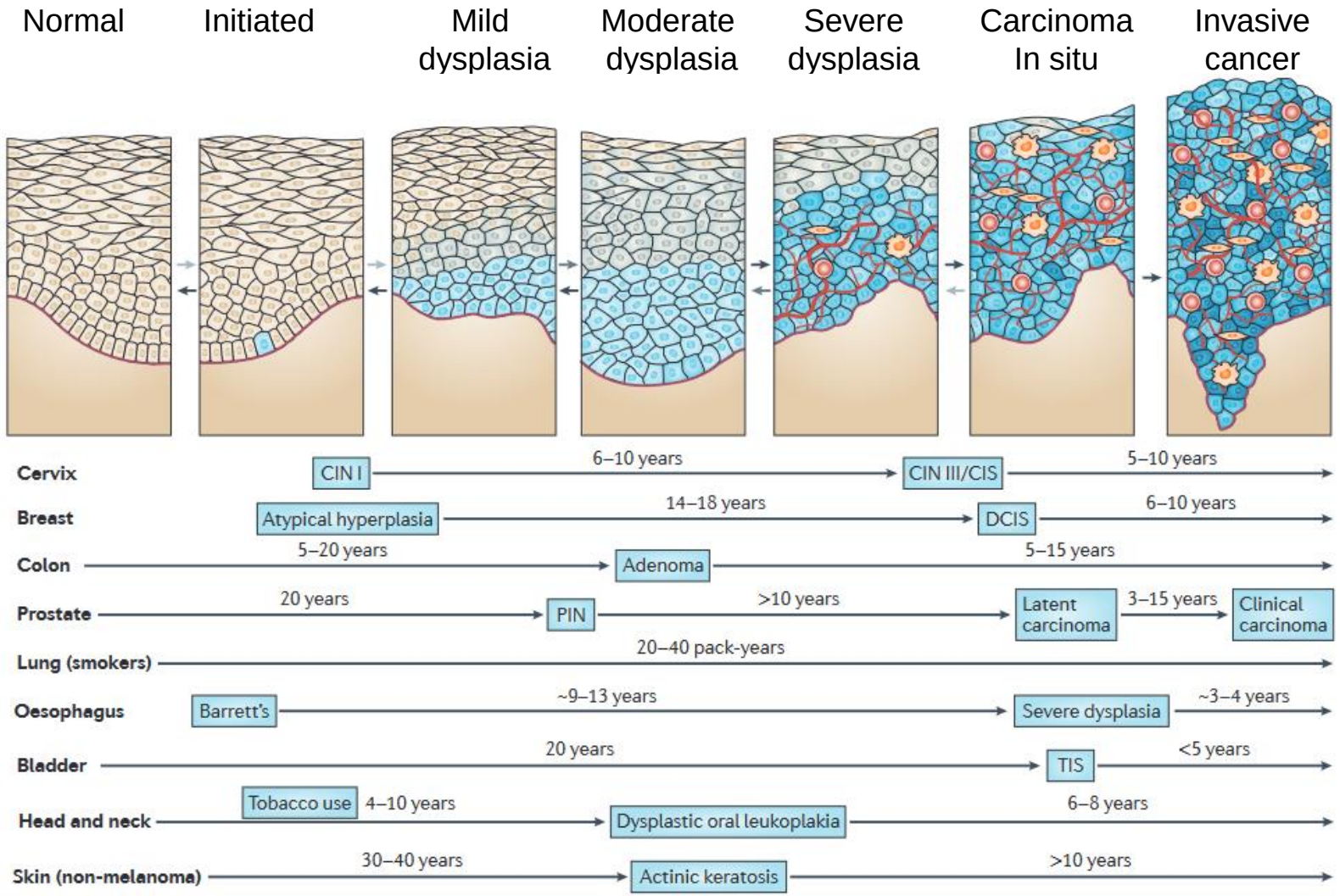
CDC

“An ounce of prevention is worth a pound of cure”

“Prevention is the protection of health by personal and community-wide efforts”

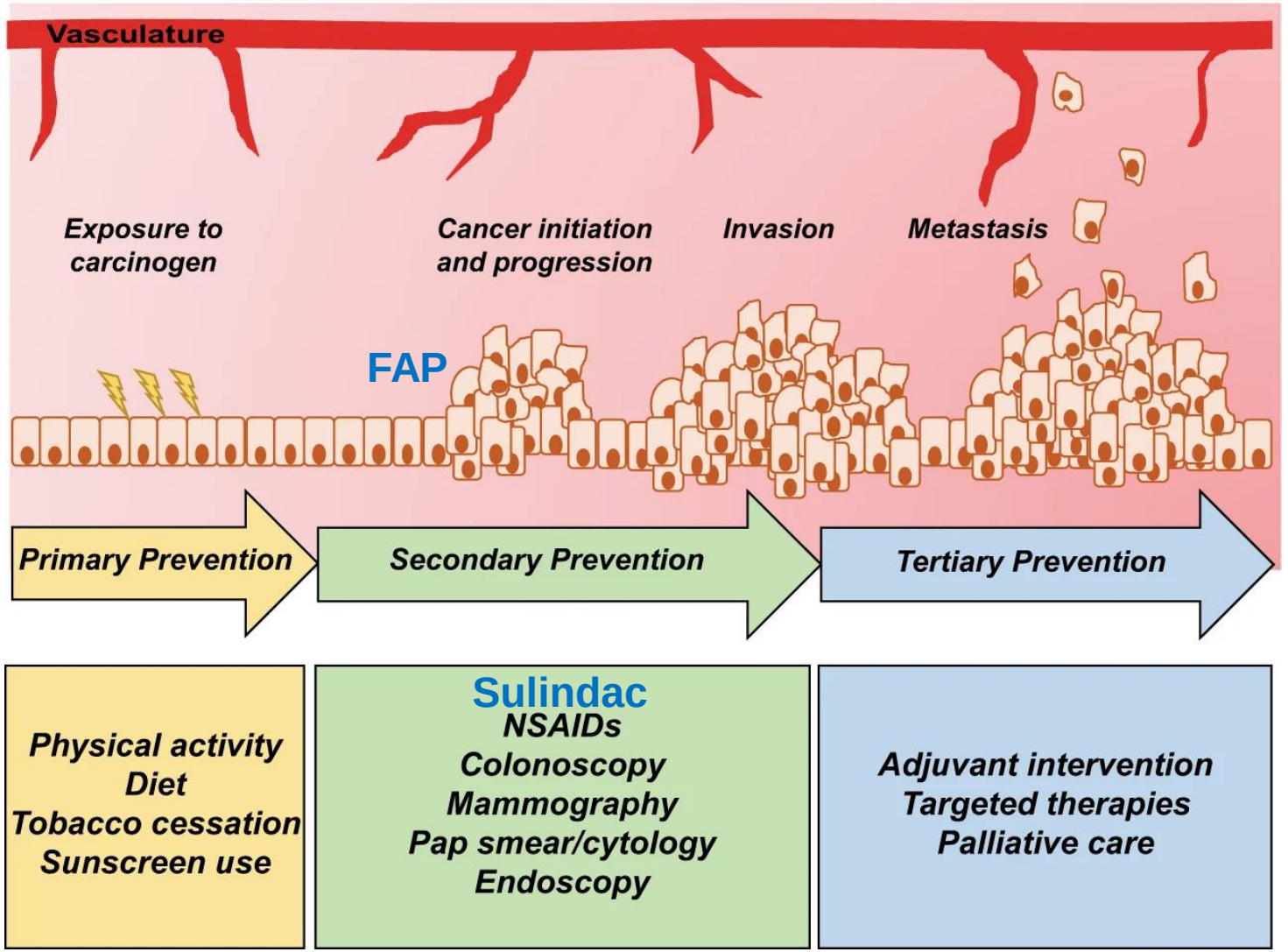
Opportunities for Cancer Prevention

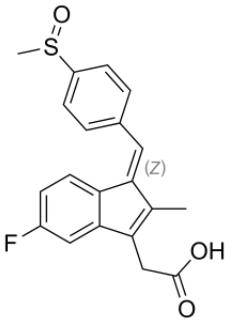
- Long incubation time is required for the development of cancer giving ample opportunity to detect and intervene.
- Major technological advances in cancer screening and prevention are making it possible to intervene early.



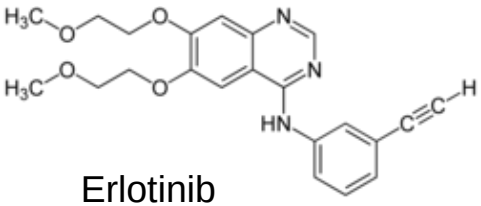
Umar, Nature Reviews Cancer, 2012

Cancer Prevention Strategies





Sulindac
(COX1/2 inhibitor)

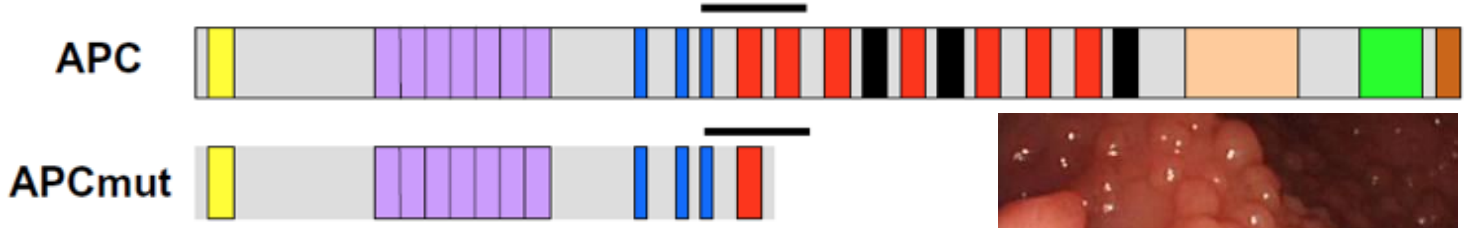


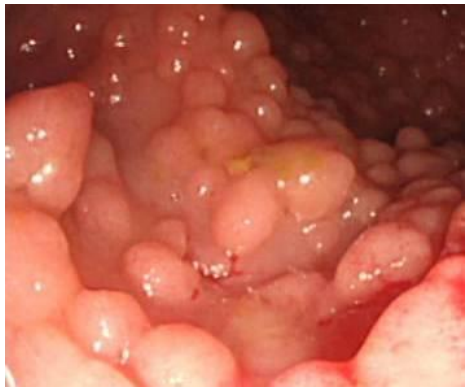
Erlotinib
(EGFR inhibitor)

Umar, Nature Reviews Cancer, 2012

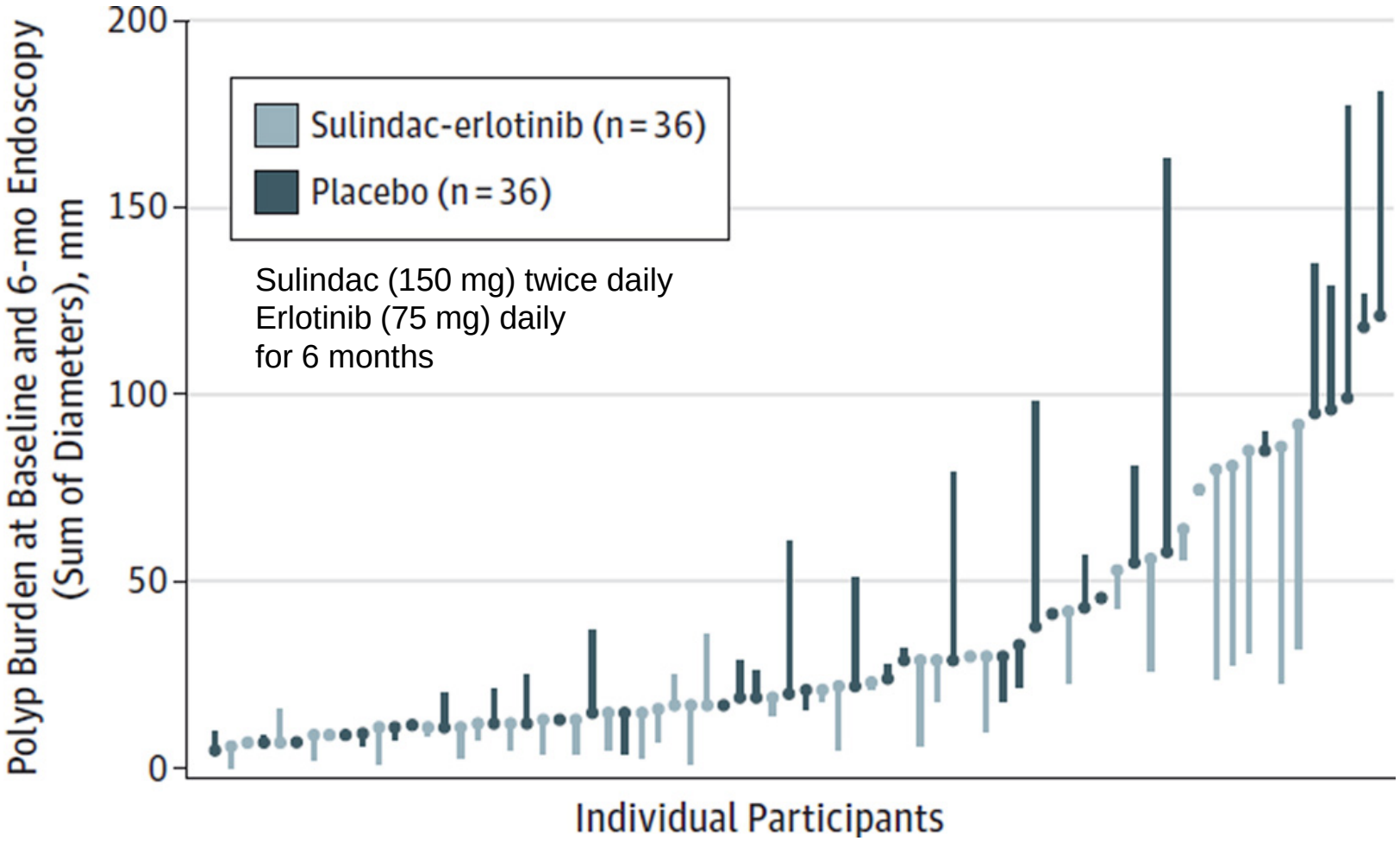
Colorectal Cancer and Familial Adenomatous Polyposis

- Familial Adenomatous Polyposis (FAP) is an autosomal dominant, inherited condition.
- FAP causes numerous GI polyps with malignant transformation.
- Mutations in Adenomatous Polyposis gene (*APC*) are responsible for the formation of adenomatous polyps in FAP.





Effect of Sulindac and Erlotinib vs Placebo on Duodenal Neoplasia in Familial Adenomatous Polyposis: A Randomized Clinical Trial



CONCLUSIONS AND RELEVANCE

SUL+ERL, compared with placebo, resulted in >30% lower duodenal polyp burden after 6 months. Adverse events (skin rash in 87% of FAP patients) may limit the use of these medications at the doses employed here.

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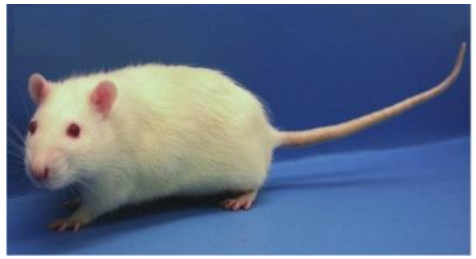
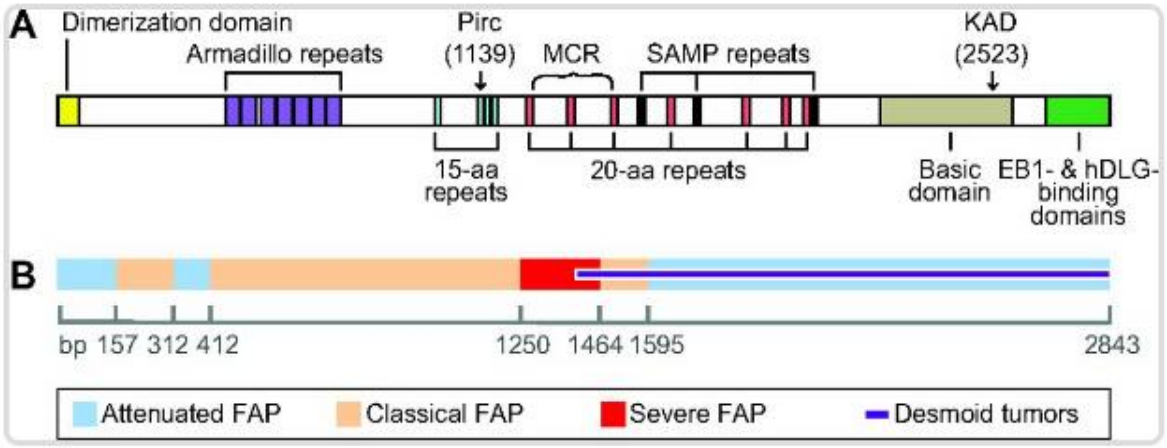
Samadder et. al. JAMA 2016;315:1266-75

Polyposis in rat colon (Pirc)





Adenomatous polyposis coli (Apc) protein

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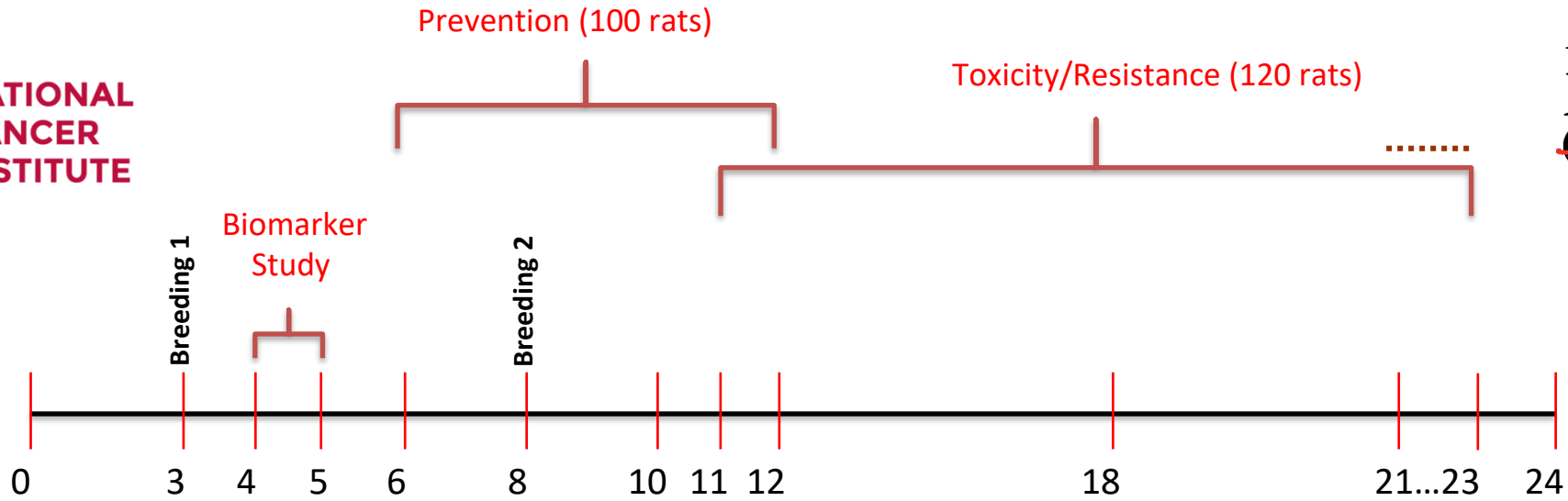
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center



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Biomarker study

SUL 250 ppm diet = 300 mg human dose

ERL 6 mg/kg rat = 75 mg human dose

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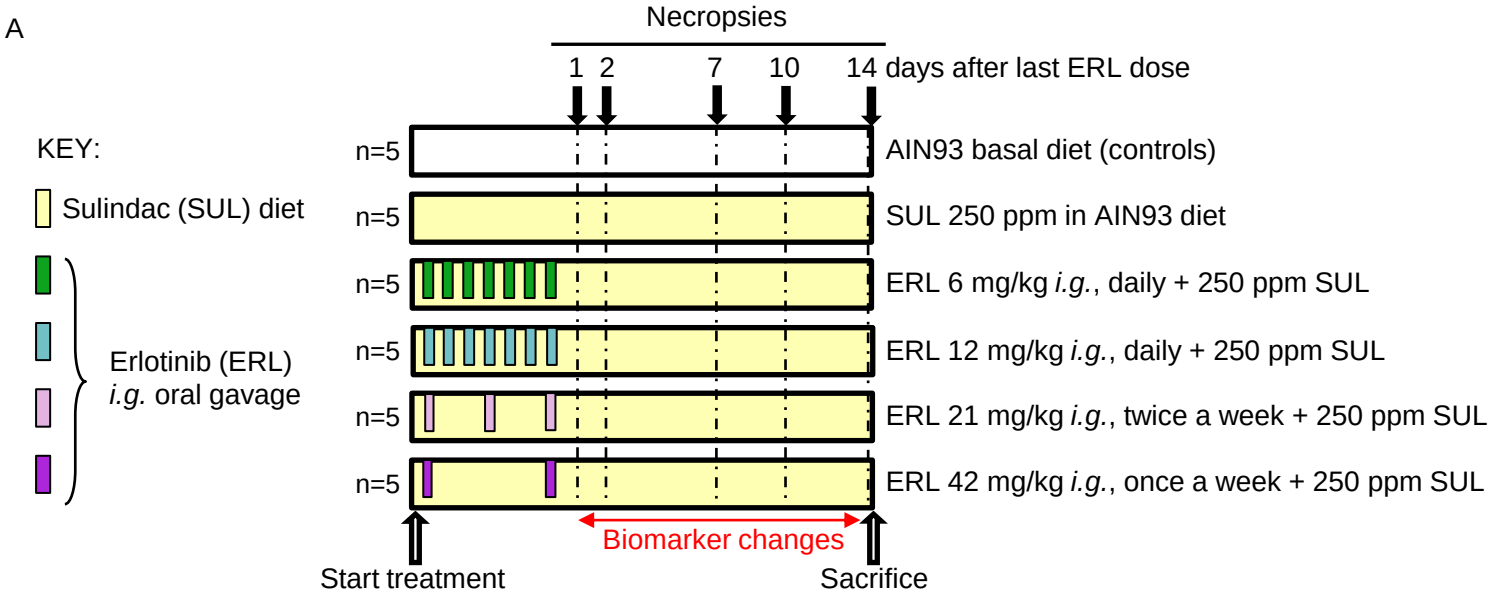

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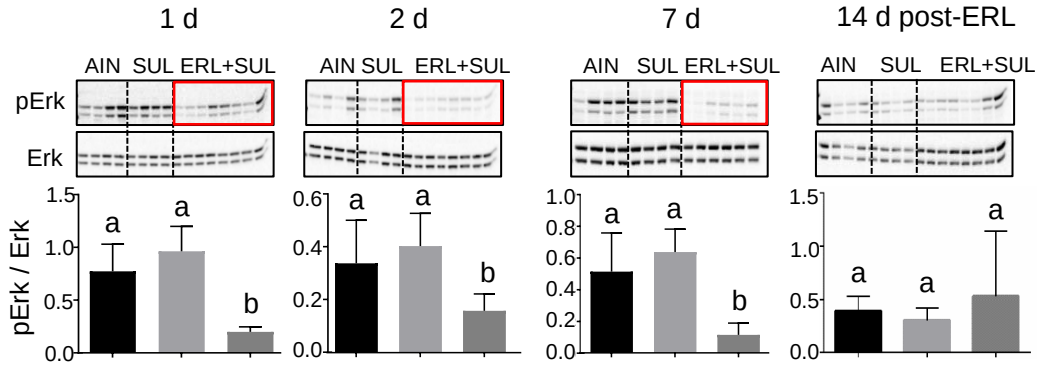

ERL 6 mg/kg daily

Efficacy and Toxicity study

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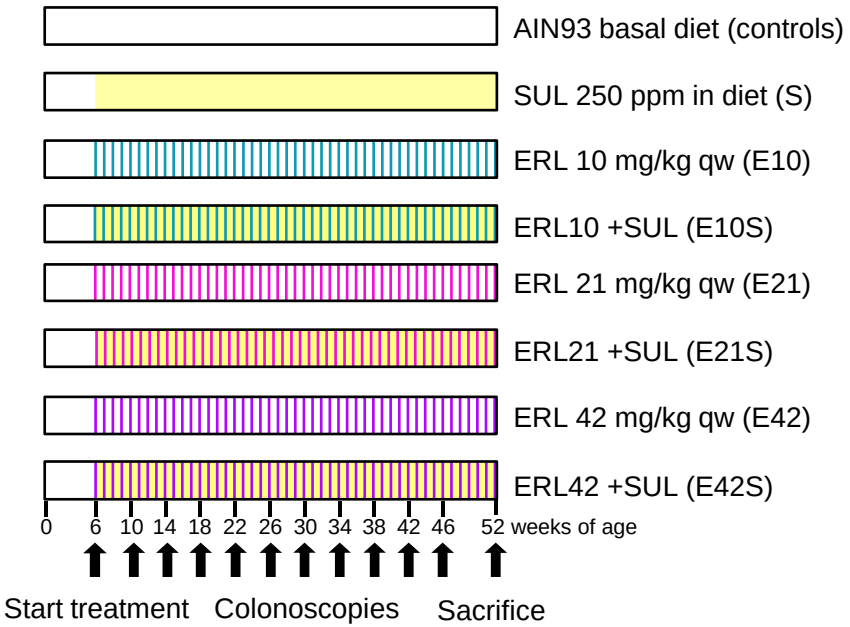

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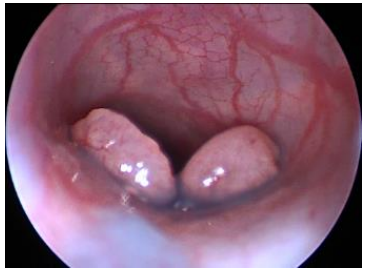
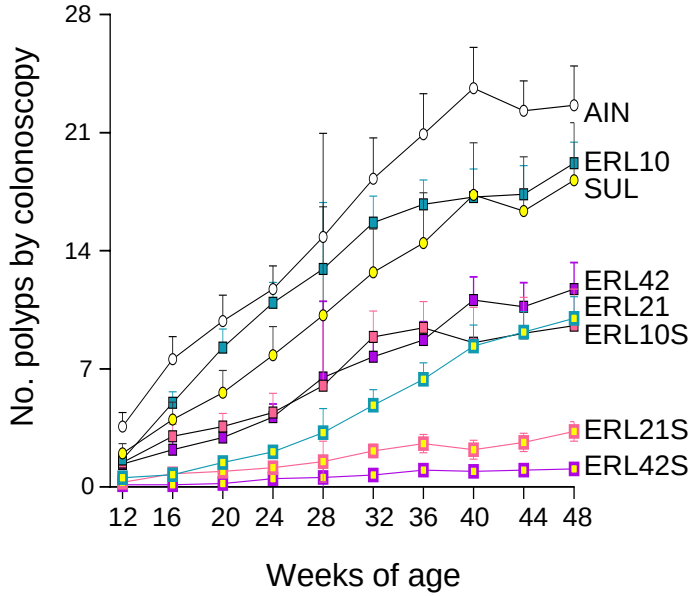
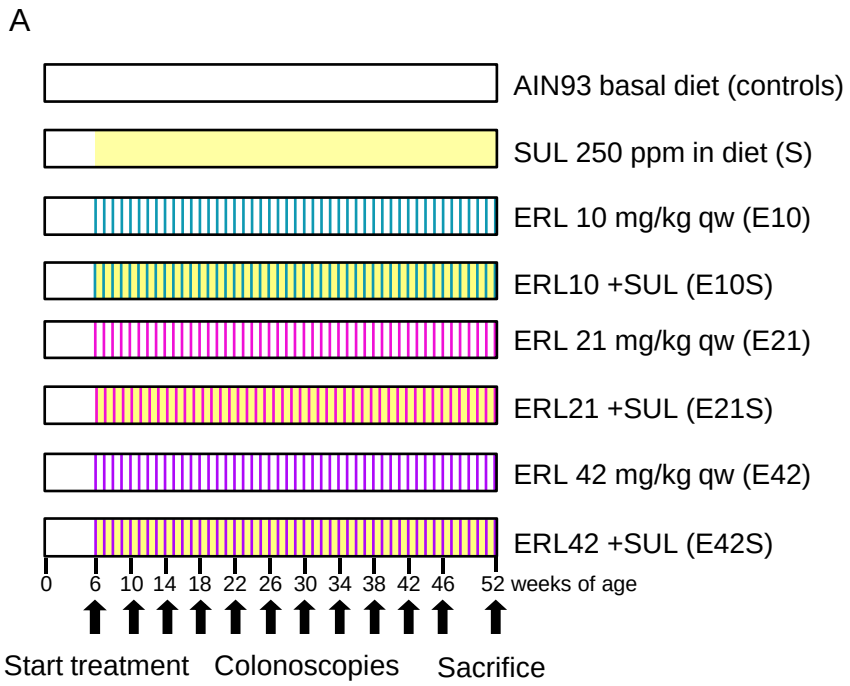
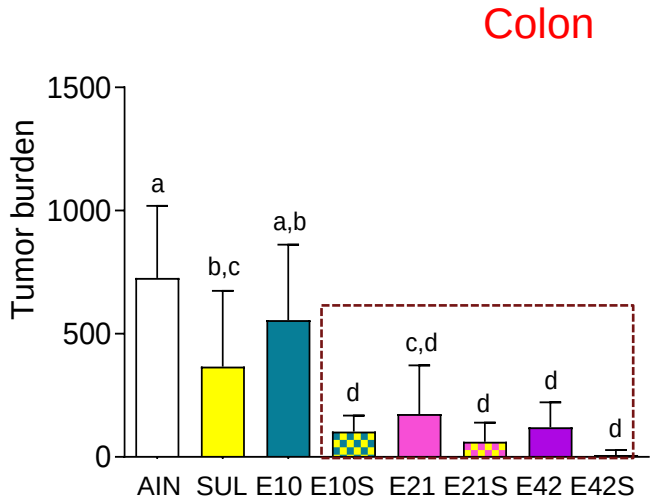


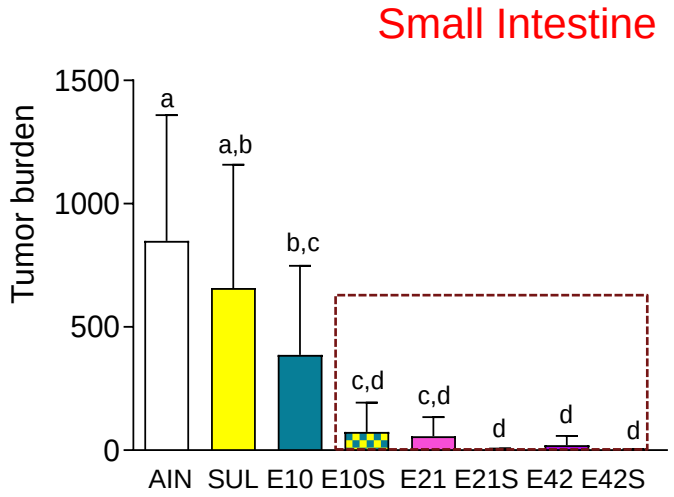
Colonoscopy



Efficacy and Toxicity study





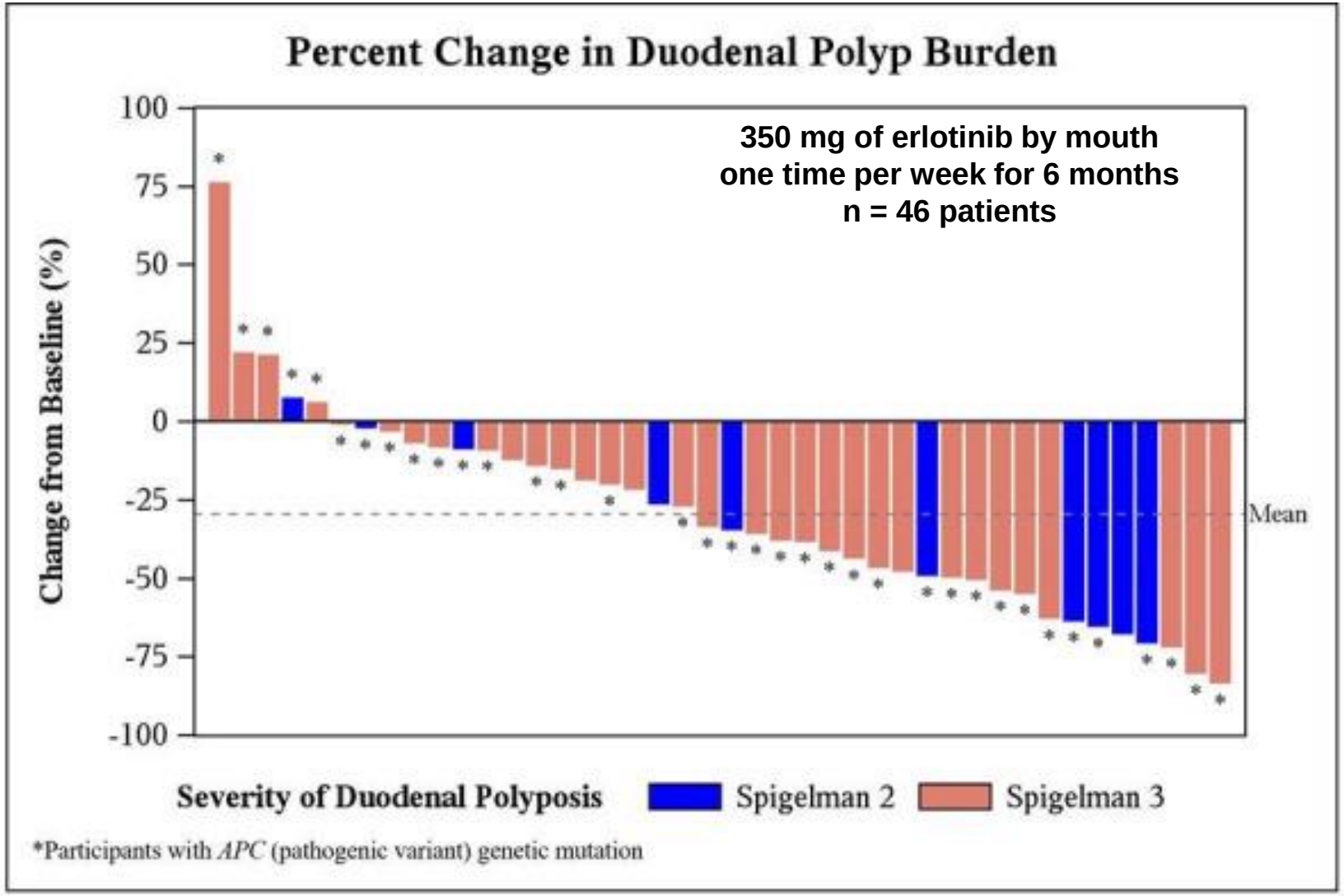


Summary cage-side observations

Group	Rats in study	Rats at 1 yr	Eye/skin phenotype	Diarrhea	Blood in rectum	Weight loss (>10%)	Mortality
AIN	14	7	0	4	7	7	7
SUL	14	10	0	2	7	5	4
E10	14	10	0	2	6	1	1
E10+SUL	13	10	0	1	3	1	1
E21	13	9	**1**	1	2	0	1
E21+SUL	14	14	**5**	0	3	0	0
E42	14	12	**2**	1	2	1	1
E42+SUL	14	13	**4**	0	3	0	0

We concluded that switching from continuous to once-per-week ERL, given at one-quarter of the current therapeutic dose, will exert good efficacy with standard of care SUL against adenomatous polyps in the colon and in the small intestine, with clinical relevance for FAP patients.

Phase II trial of weekly erlotinib dosing reduces duodenal polyp burden associated with familial adenomatous polyposis

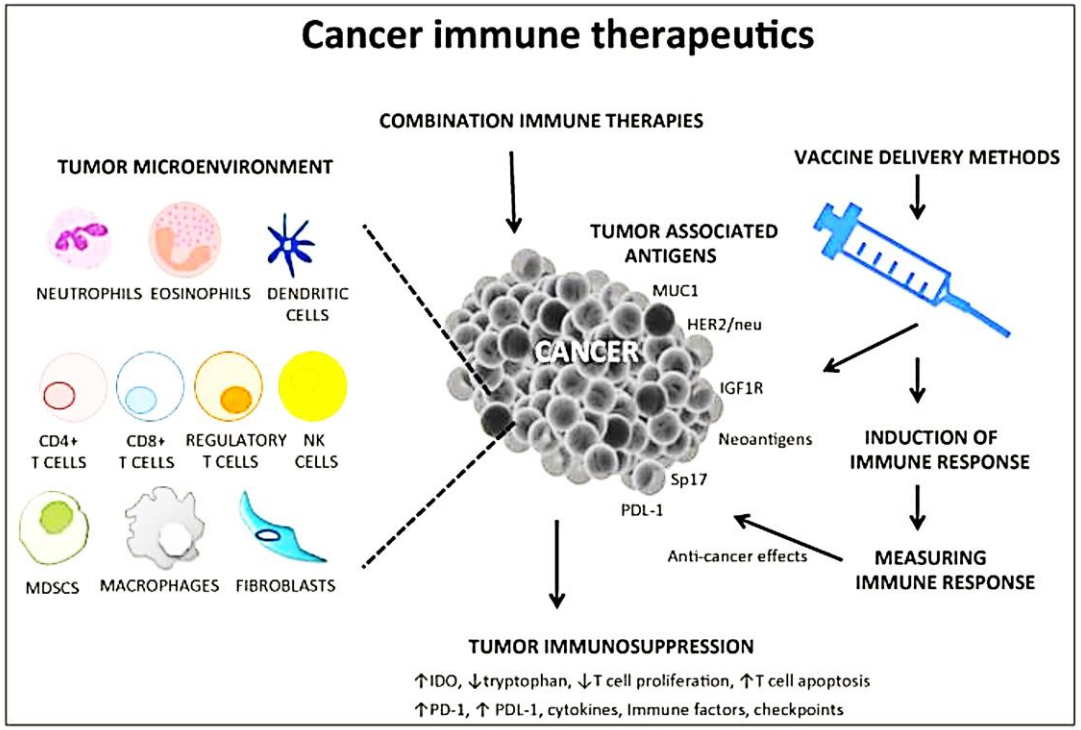


- In this single-arm, multi-centre trial of participants with FAP, erlotinib one time per week resulted in markedly lower duodenal polyp burden, and modestly reduced lower GI polyp burden, after 6 months of intervention. Mean per cent change of −29.6%.
- While AEs were still reported by nearly three-quarters of all participants, these events were generally lower grade and well-tolerated.

Samadder et. al. Gut 2023

Translational Advances in Cancer Prevention Agent Development

- A focus on identifying high-risk populations with targetable lesions (e.g., FAP, Lynch Syndrome).
- Investigate cancer progression from normal to cancer cells.
- Focus on improving the safety profiles of known (repurposing drugs) and novel agents by designing novel delivery methods or improved formulations and dosing strategies.
- Utilizing strategies that alter the precancer immunosuppressive microenvironment and promote immune responses.
- Development of multi-antigen targeted vaccines that can target a variety of dysfunctional signaling and immune pathways.
- Focus on the development of biomarkers predictive of cancer interception-prevention efficacies in clinical trials.
- Design appropriate clinical trials that target the population(s) most likely to harbor the lesion(s).



Apostolopoulos, Cancers, 2019

Miller et. al., J Cancer Prev 2023