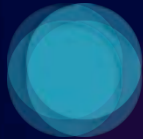




THE UNIVERSITY
of ADELAIDE



CANCER TREATMENT
TOXICITIES GROUP

Integrating the pathogenesis, prediction and prevention of cancer-related side effects

KR Secombe, IA Ball, J Shirren, AD Wignall, HR Wardill, YZA Van Sebille,
F Avogadri-Connors, D Martin, E Olek, S Moran, JM Bowen

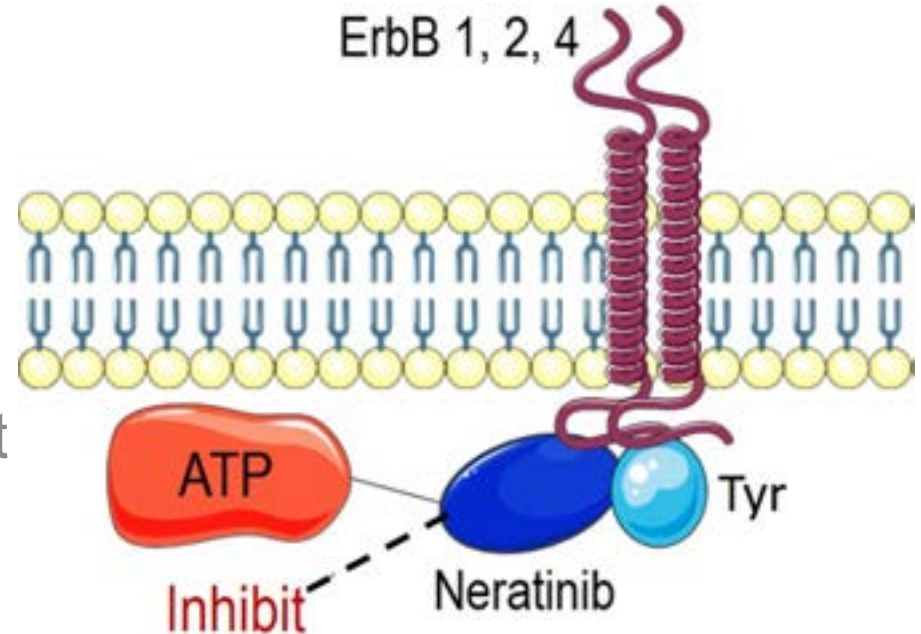
Budesonide reduces neratinib- induced diarrhea and intestinal inflammation in rats

adelaide.edu.au

seekLIGHT

Neratinib: cancer drug causing diarrhea

- Neratinib (Puma Biotechnology):
irreversible pan-ErbB tyrosine
kinase inhibitor
- FDA approved for extended
adjuvant treatment of HER2+ breast
cancer
- Severe diarrhea: 40% of patients
(no loperamide prophylaxis)¹



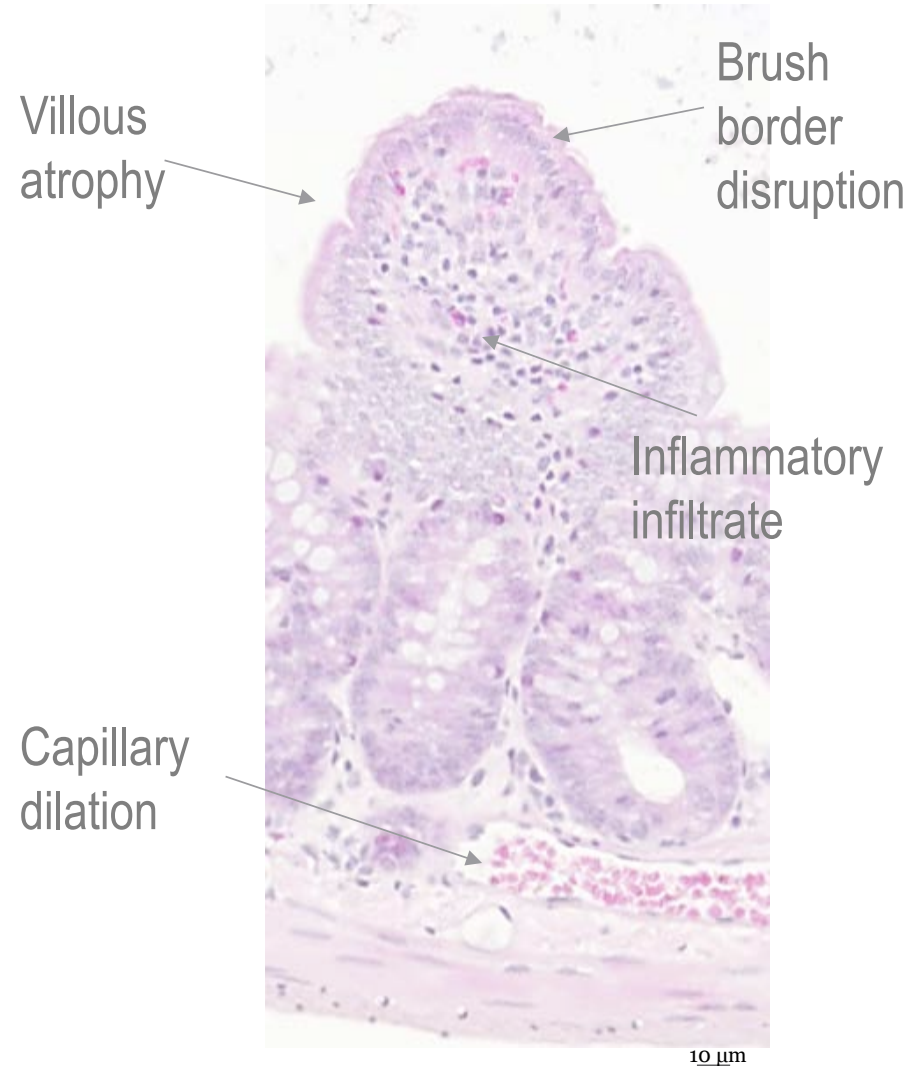
¹ Chan et al. (2016). *Lancet Oncol* 17:
367-77.

Our model

- Albino Wistar rats (90-100% of rats get diarrhea)
- Distal small intestine and colon
 - Anatomical derangement
 - Inflammation – linked with diarrhea

Budesonide

- Corticosteroid used to treat gastrointestinal disorders



Photomicrograph at 400x original magnification stained with Haematoxylin and Eosin (H&E)

Study design

- Male Albino Wistar rats (n=48); vehicle, neratinib only, neratinib + budesonide
- Collected intestinal tissue after 14 or 28 days treatment
- Clinical, histopathological and inflammatory measures

Budesonide
(1 mg/kg p.o.)

9 am
daily

Neratinib
(50 mg/kg p.o.)

11 am
daily

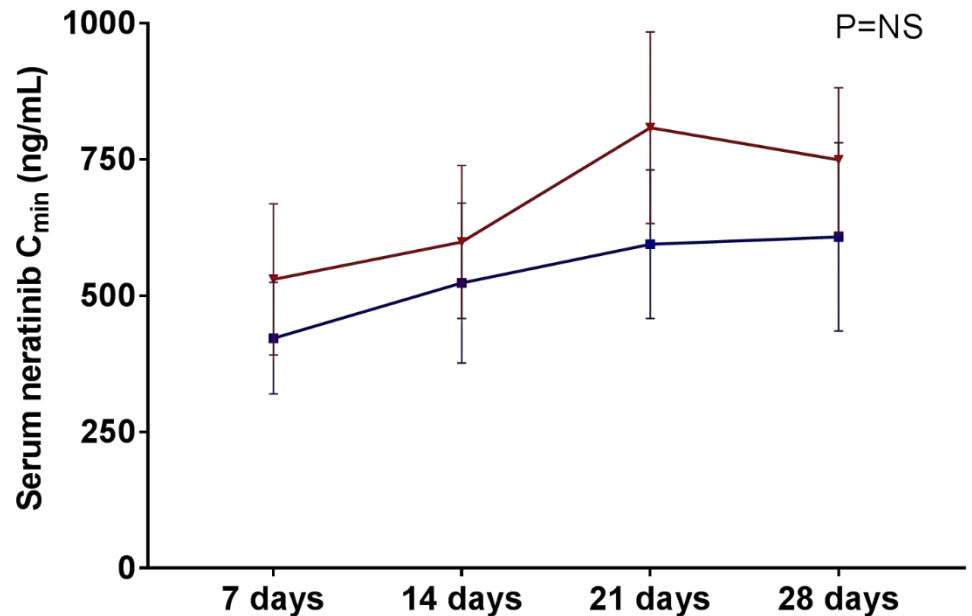
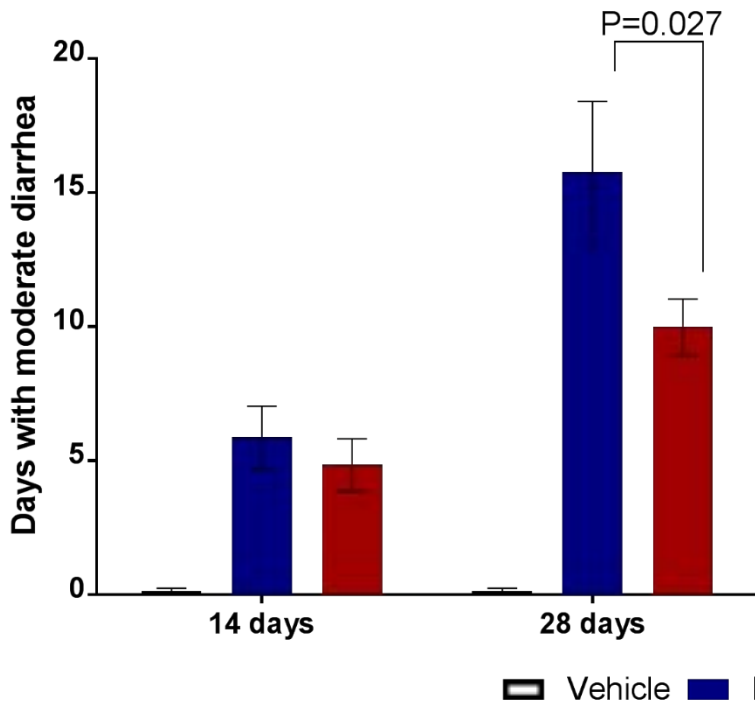
Acute damage

14 days

Chronic damage

28 days

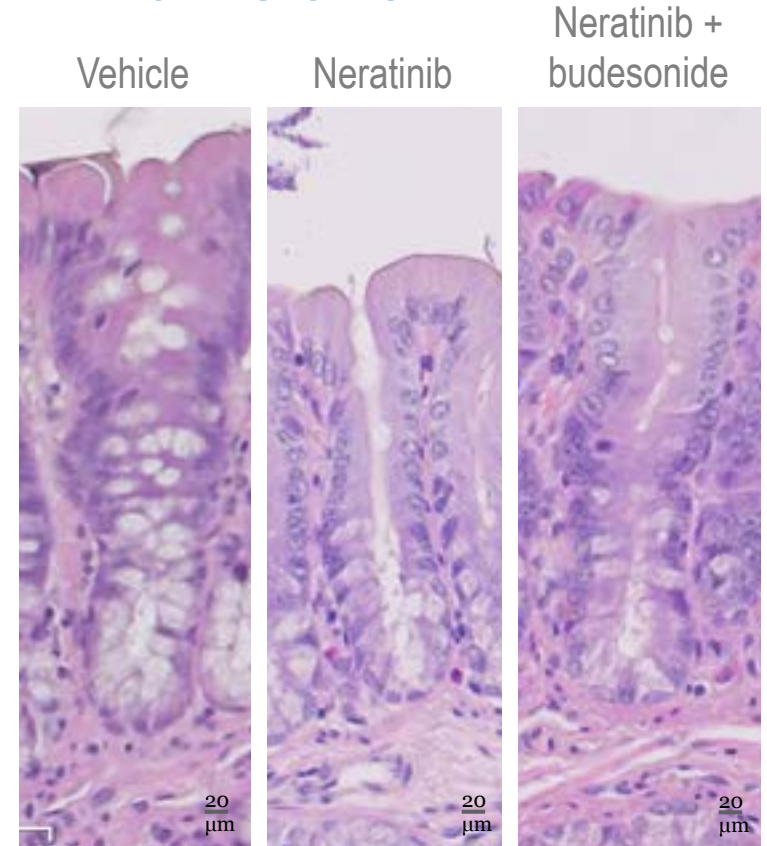
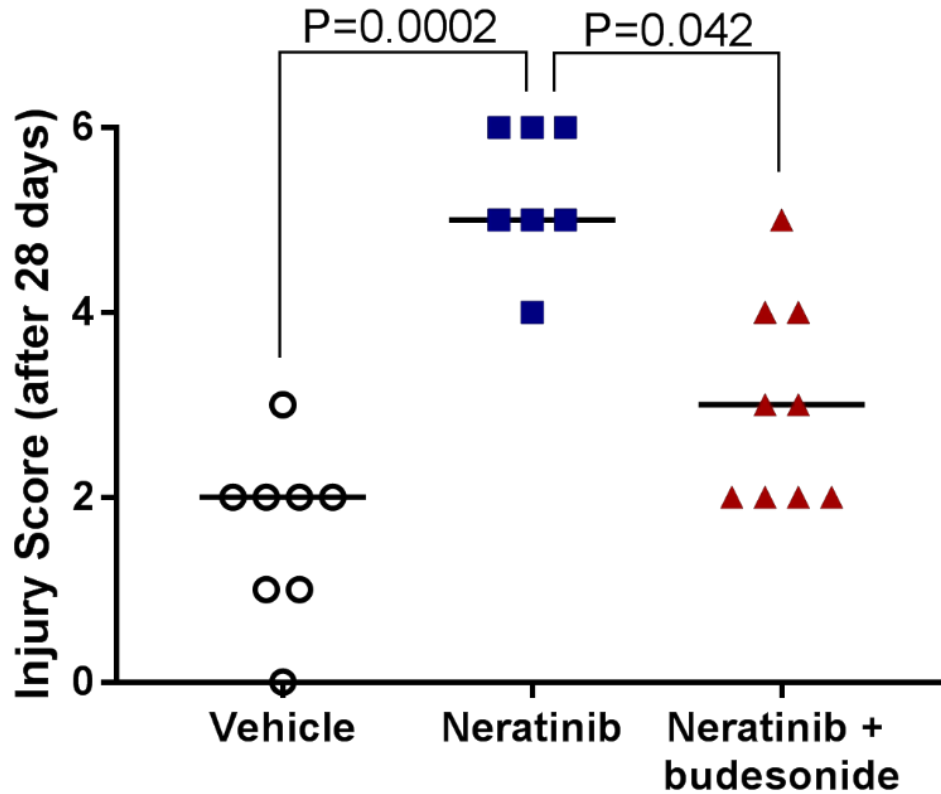
Diarrhea unrelated to serum neratinib concentration



Data shows mean ± SEM

- Budesonide significantly decreased mean number of days with moderate (grade 2) neratinib-induced diarrhea (10.0) vs. neratinib only (15.8)
- Budesonide did not significantly change serum neratinib concentrations

Budesonide decreased histological damage from neratinib in the proximal colon

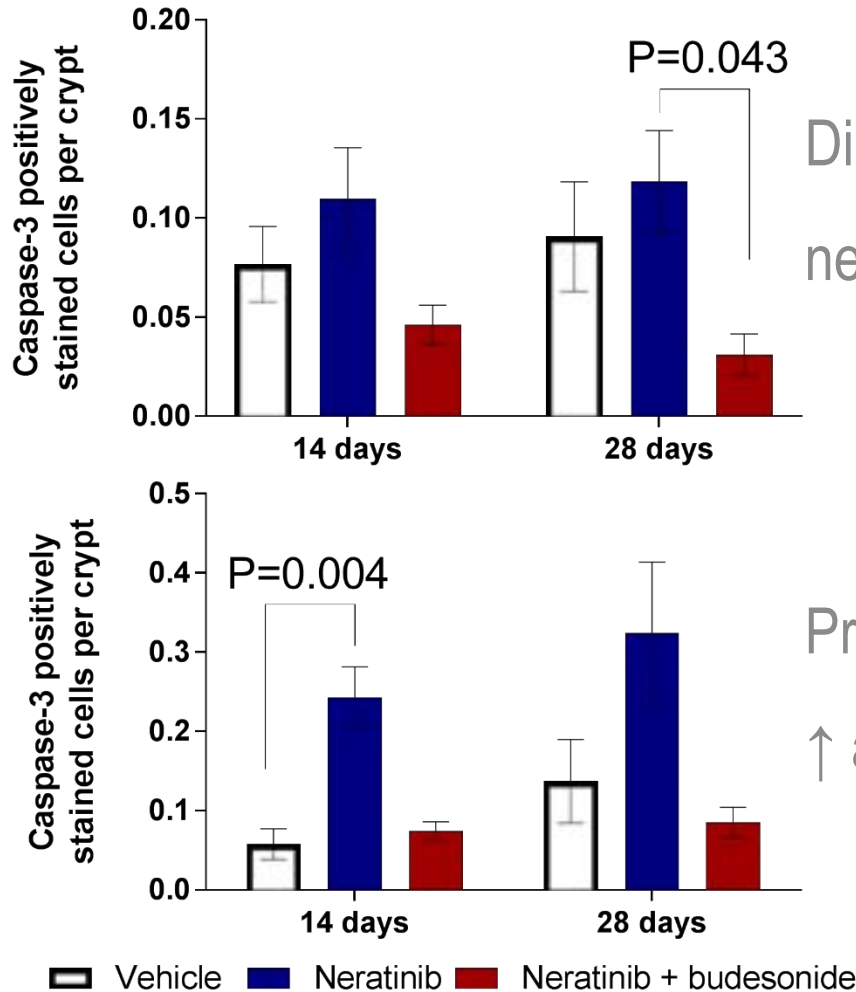


Photomicrographs at 200x original magnification stained with H&E

These results were also observed in the distal ileum

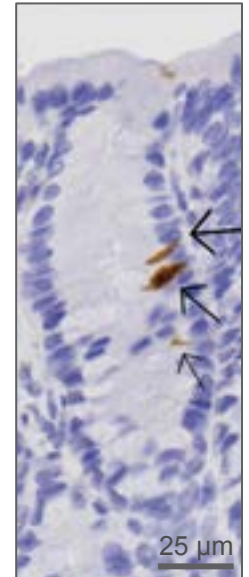
Budesonide reduces apoptosis in the distal ileum

Data shows mean \pm SEM



Distal ileum - 28 days: \uparrow apoptosis
neratinib vs neratinib + budesonide

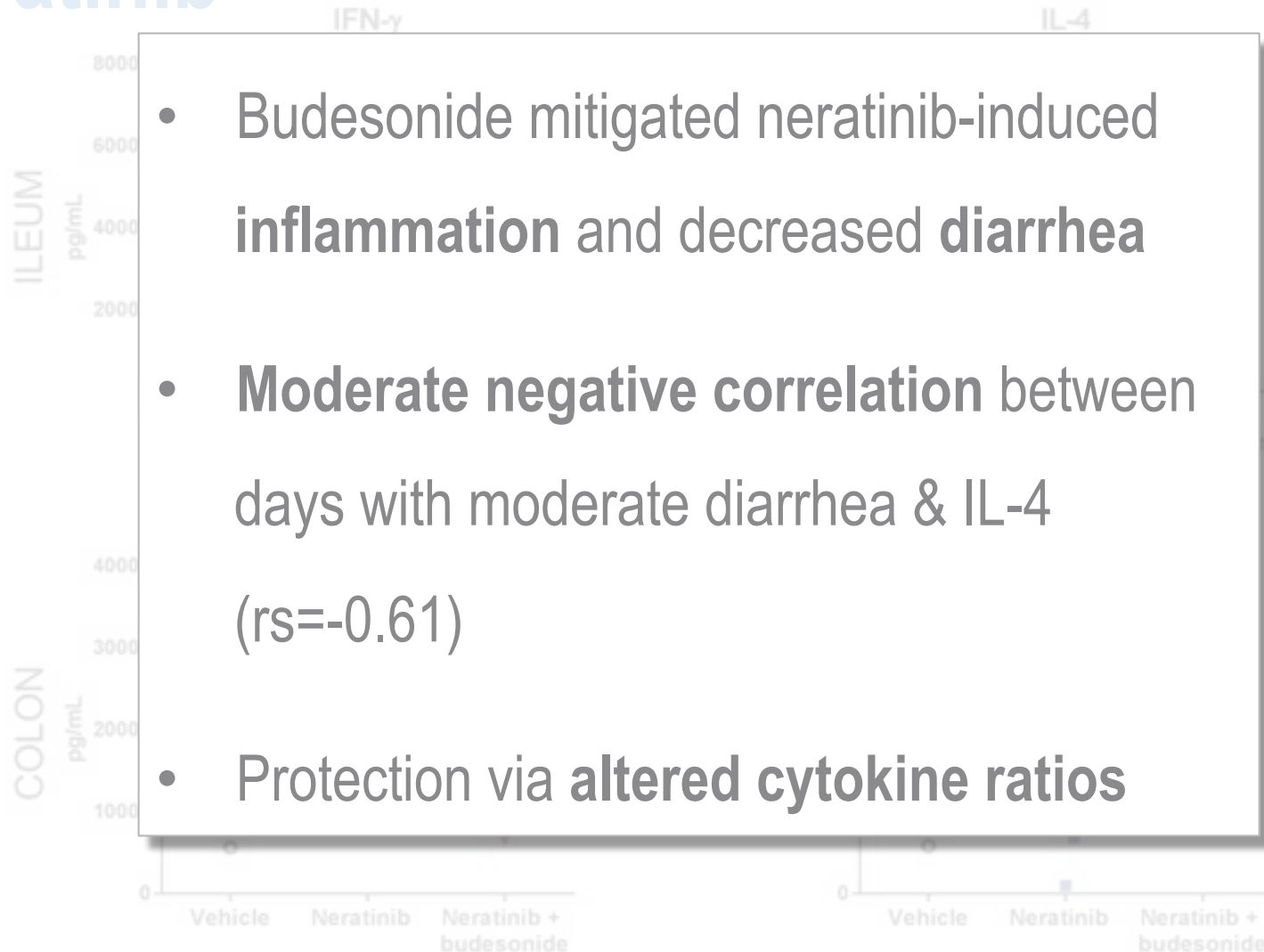
Proximal colon - 14 days:
 \uparrow apoptosis neratinib vs vehicle



*Neratinib 28 days colon
Example of positively stained cells*

Budesonide alters cytokine ratios following neratinib

Line shows median



- Budesonide mitigated neratinib-induced **inflammation** and decreased **diarrhea**
- **Moderate negative correlation** between days with moderate diarrhea & IL-4 ($r_s = -0.61$)
- Protection via **altered cytokine ratios**

Acknowledgements

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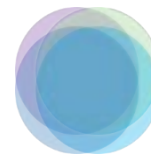
Puma Biotechnology

David Martin, Elizabeth Olek, Francesca Avogadri-Connors*, Susan Moran*, Irmina Diala

** At time of study*

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