



Plerixafor Improves Local Control and Reduces Metastases in Cervical Cancer Treated with Radiotherapy

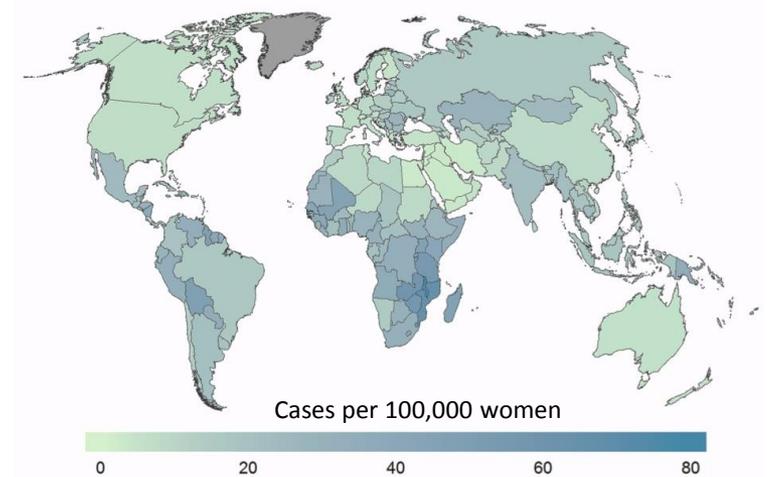
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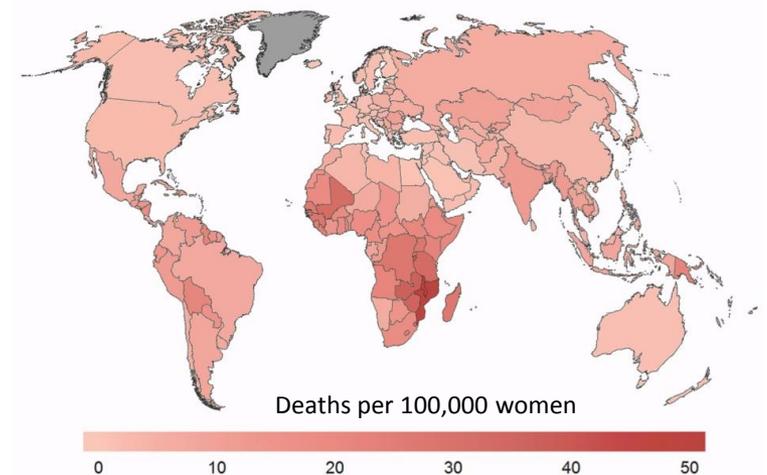
Cervical Cancer

- Major global health problem
- Developed nations
 - Failure of screening programs
 - Immigration
- Curable with radiotherapy
- 11M deaths globally in the next 20 years due to lack of RT
- Model for innovation in radiation medicine

Incidence

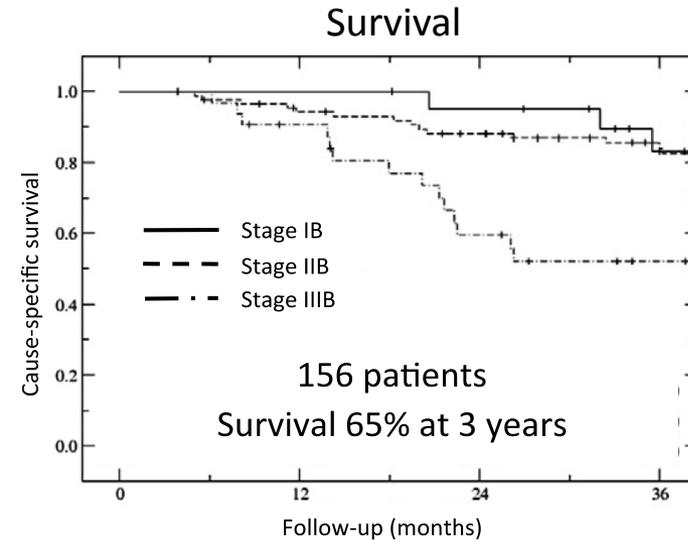
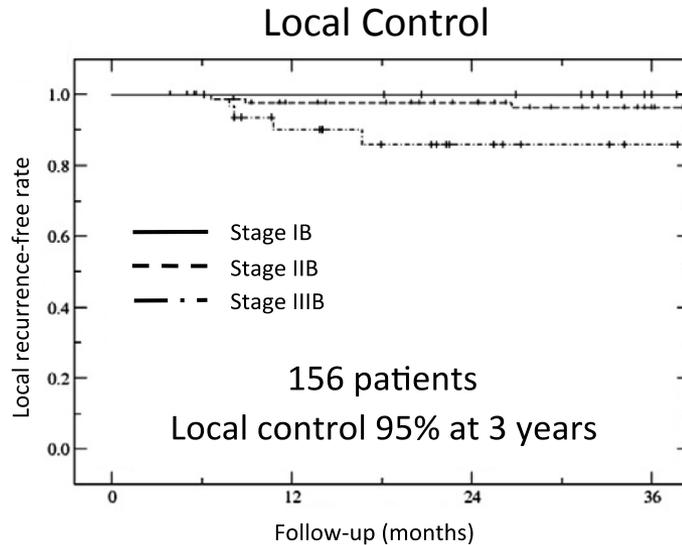


Mortality

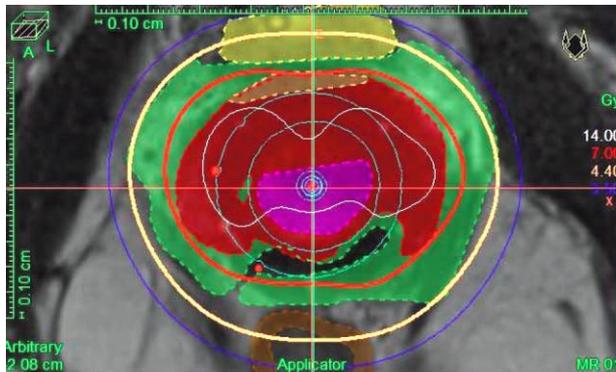


Cervical Cancer

Local control and survival with best-practice radiotherapy

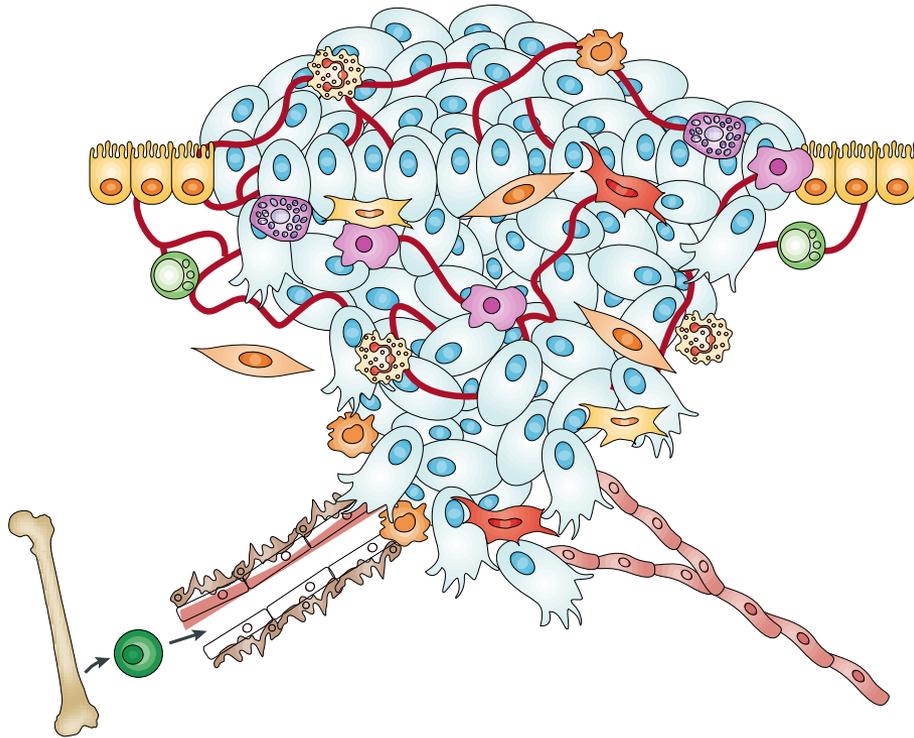


Potter, 2011



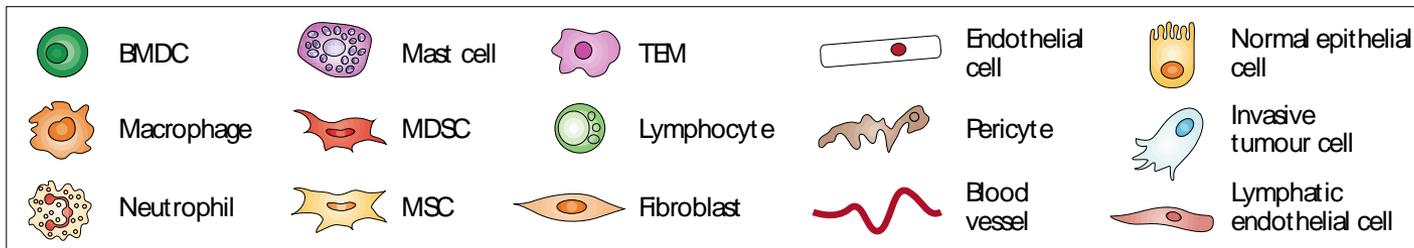
- External beam radiotherapy
- Concurrent cisplatin
- MR-guided brachytherapy

Tumor-Stromal Interplay



Functional Consequences

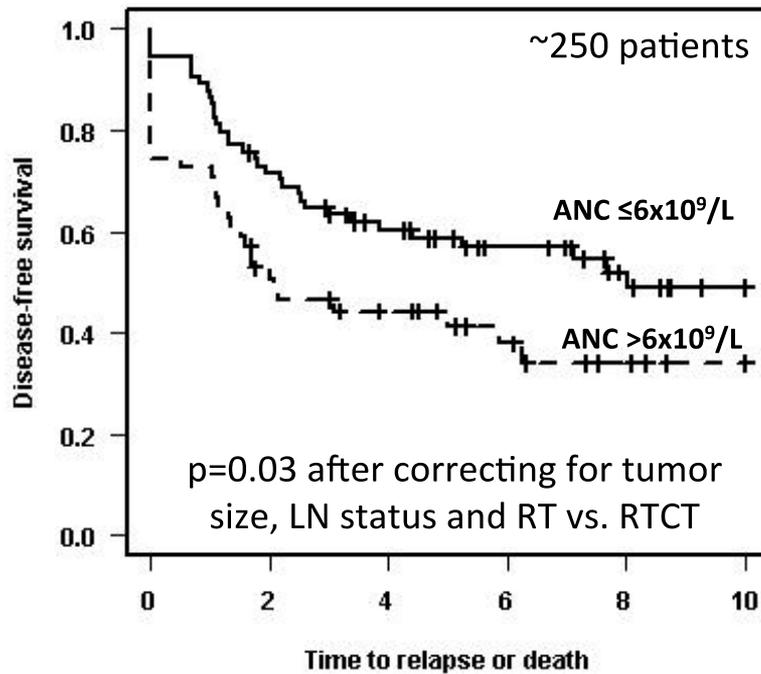
- Angiogenesis
- Hypoxia
- High IFP
- Immune effects



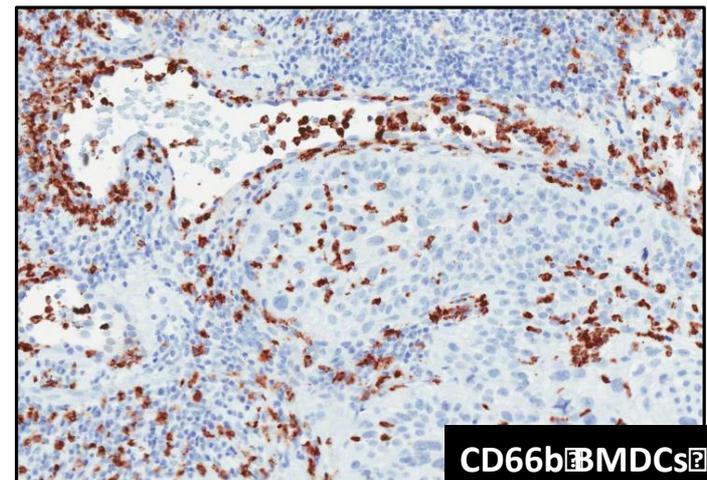
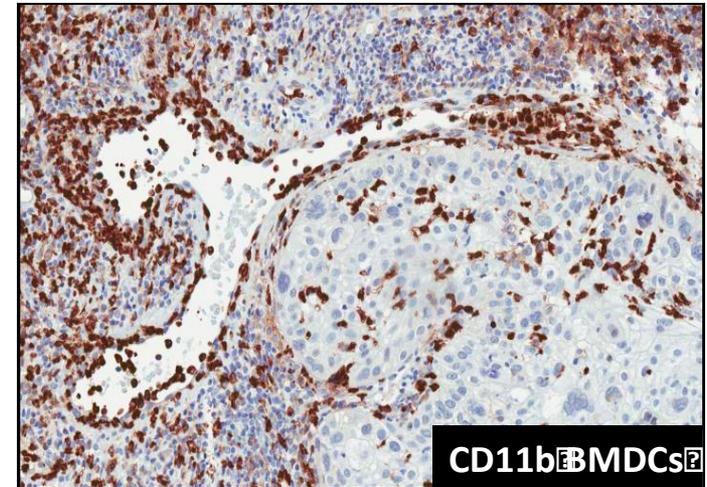
Myeloid Cells in Cervical Cancer

Circulating neutrophils

Baseline Neutrophil Count

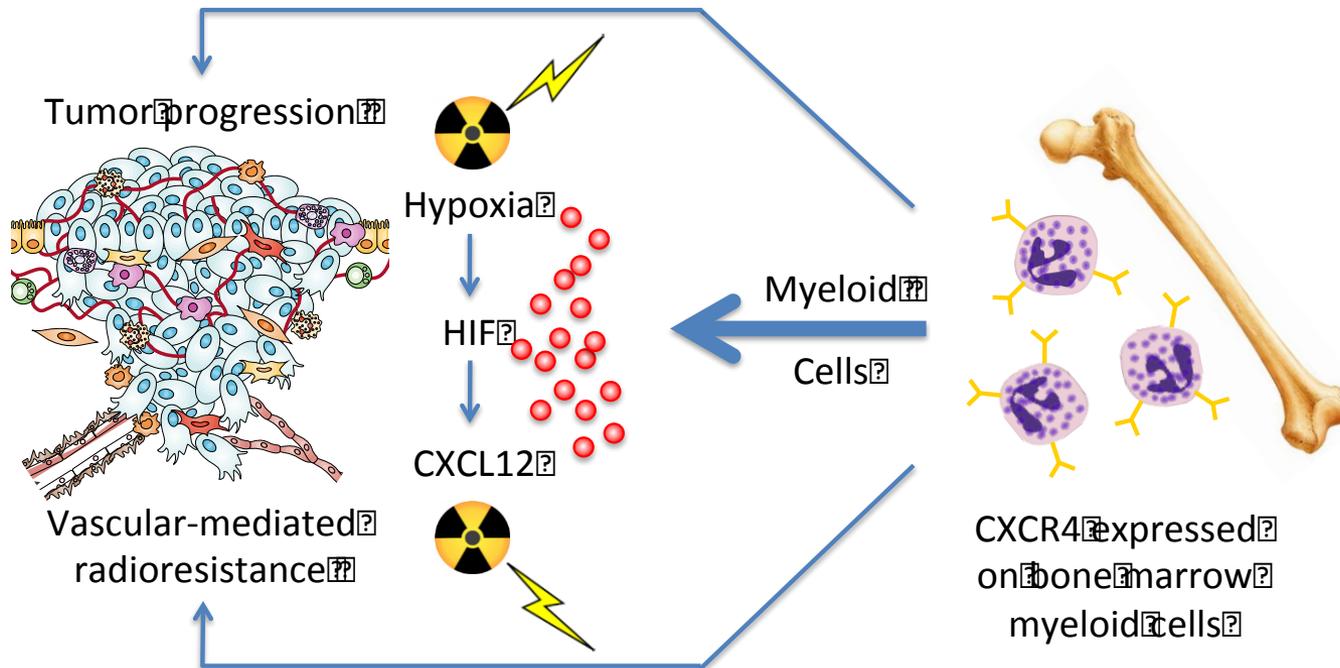


Tumor-infiltrating neutrophils



CXCL12 Pathway

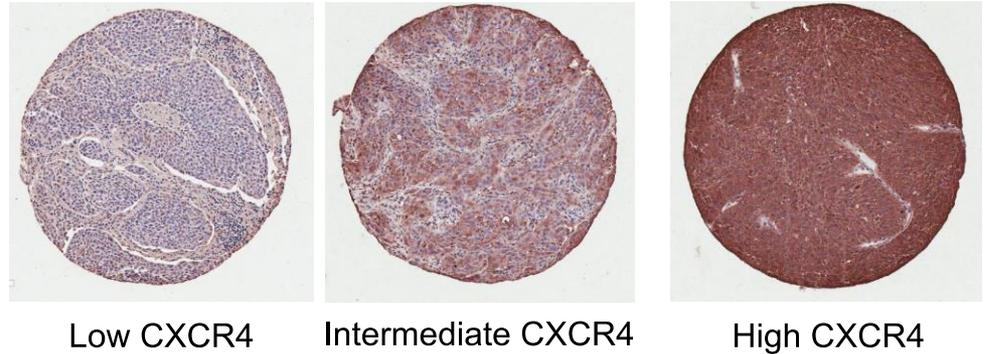
Tumor hypoxia increases expression of CXCL12 and CXCR4, leading to myeloid cell recruitment and radioresistance



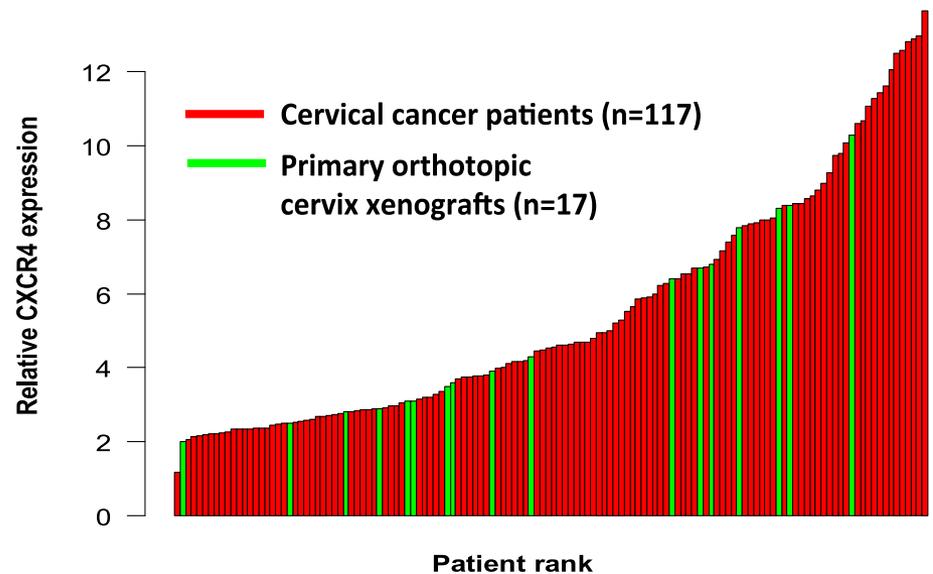
Plerixafor (AMD3100) is a commercially available CXCR4 receptor inhibitor

CXCR4 in Cervical Cancer

58% of 132 patients with high CXCR4 protein expression



5-fold range in CXCR4 mRNA expression in 117 patients



Hypothesis and Aims

Hypothesis: Plerixafor, when added to standard RTCT for cervical cancer will improve local tumor control and reduce metastases.

Aims: Evaluate tumor growth delay, toxicity and CXCL12 pathway inhibition with RTCT + Plerixafor compared to RTCT alone in orthotopic cervical cancer xenografts derived from patients.

Primary Orthotopic Cervical Xenografts

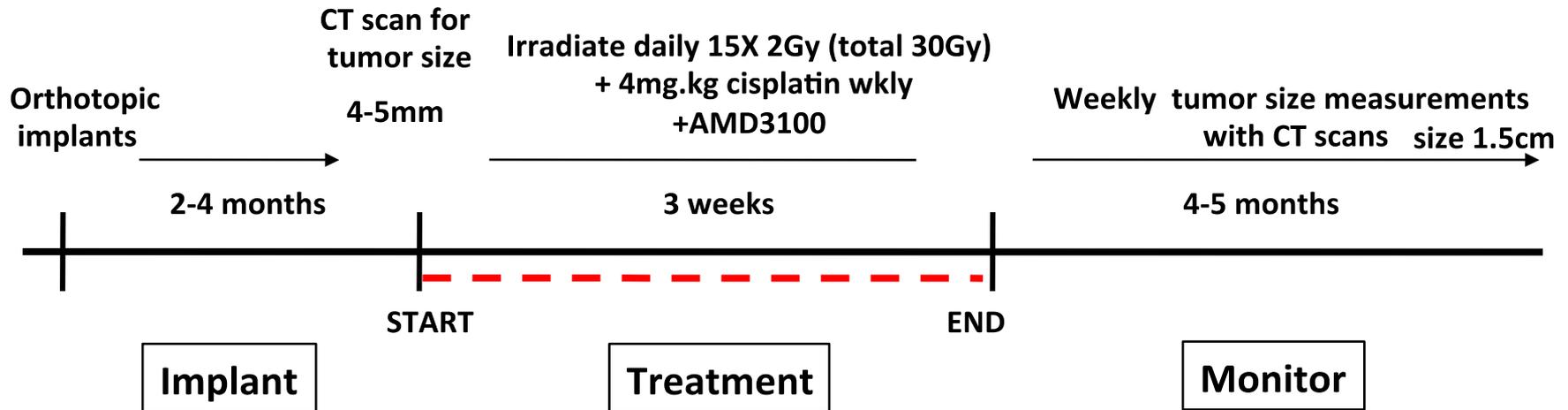
Primary cervical tumor



Lymph node metastases



Treatment Schedule



Endpoints:

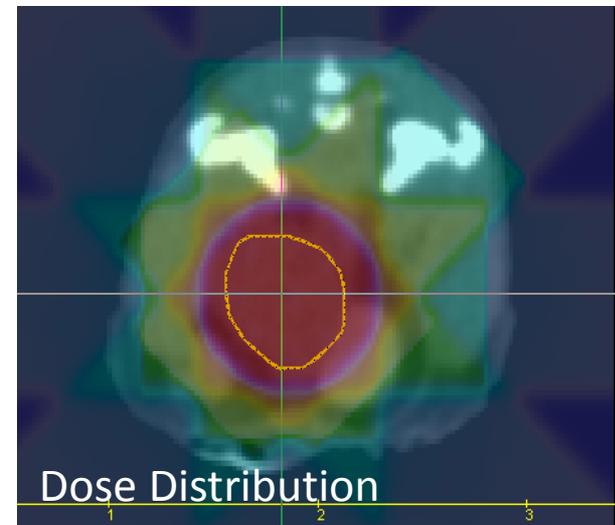
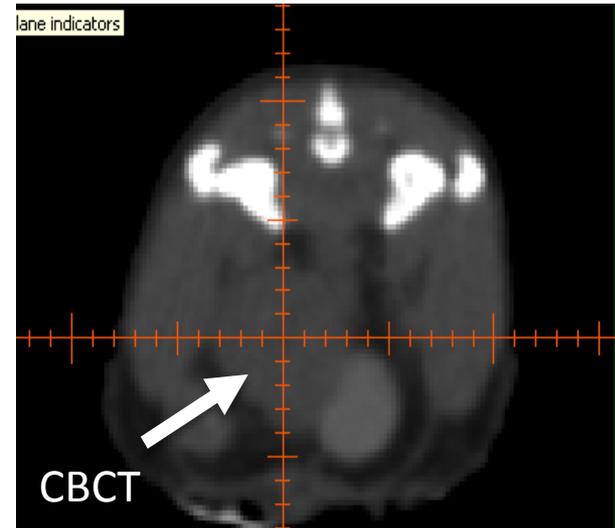
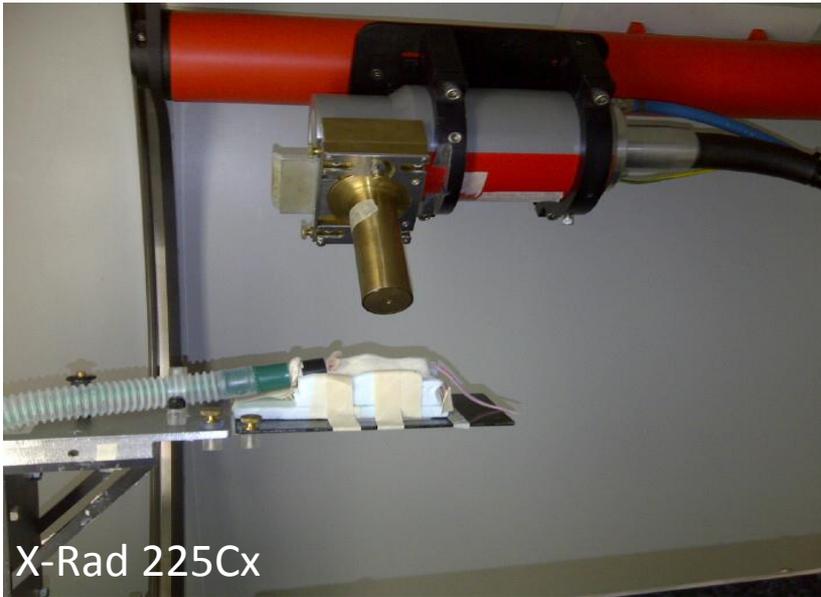
- Tumor growth delay
- Metastasis
- Survival
- Toxicity: Mouse weight
Gut



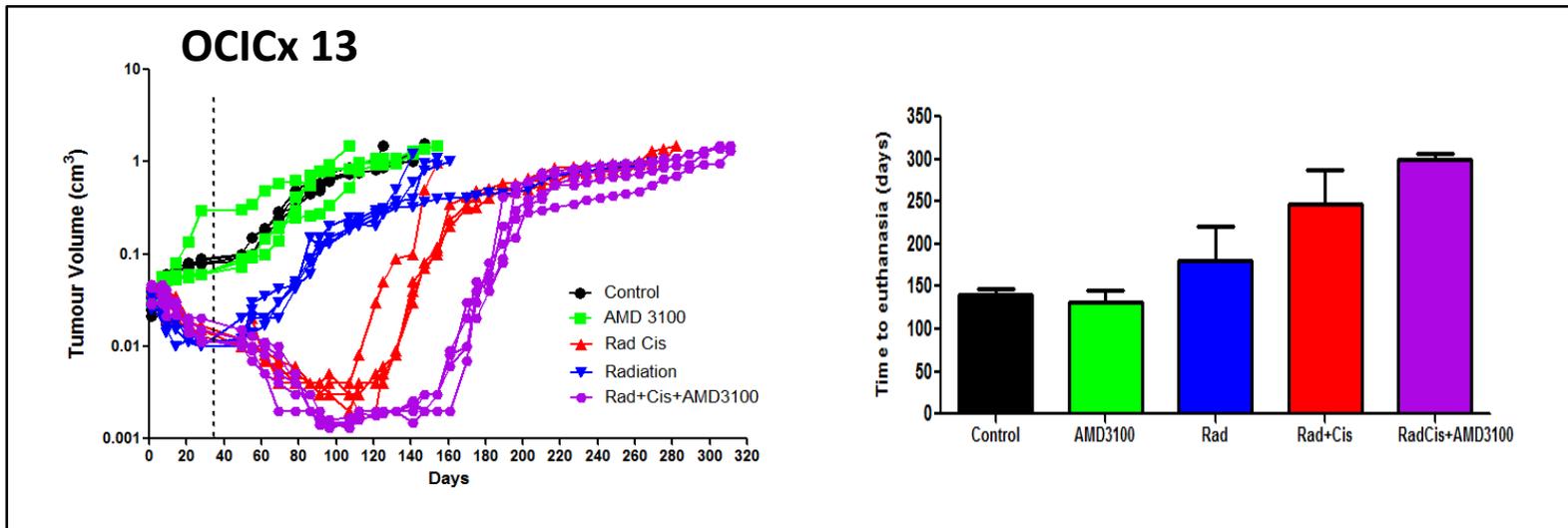
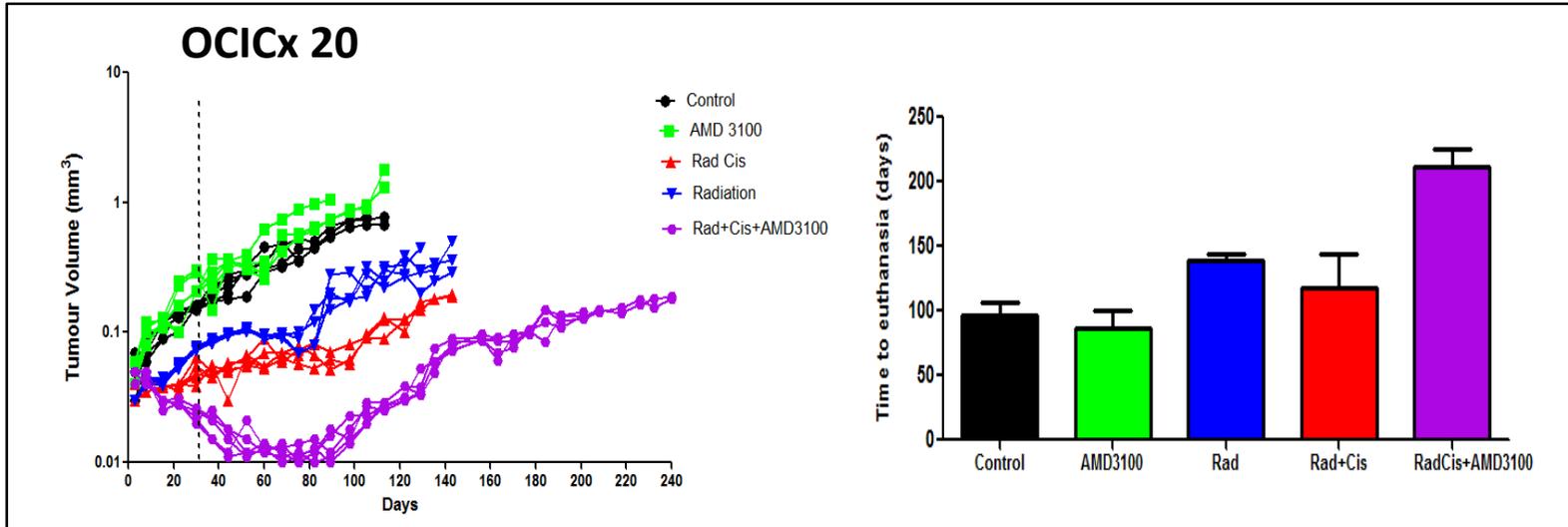
Primary, orthotopic cervical xenografts (OCICx 20 and OCICx 13) in NRG mice

CT Imaging and Treatment

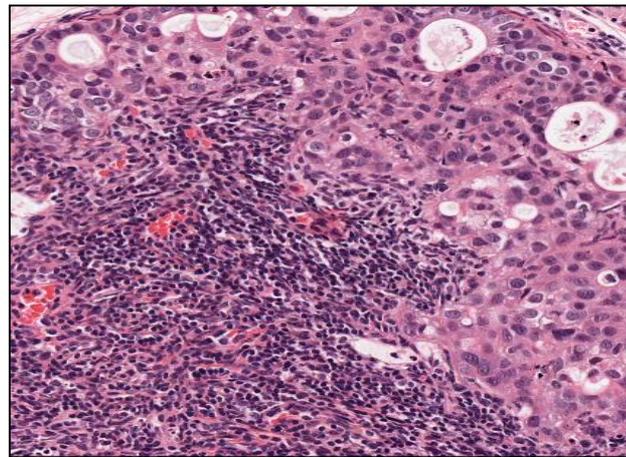
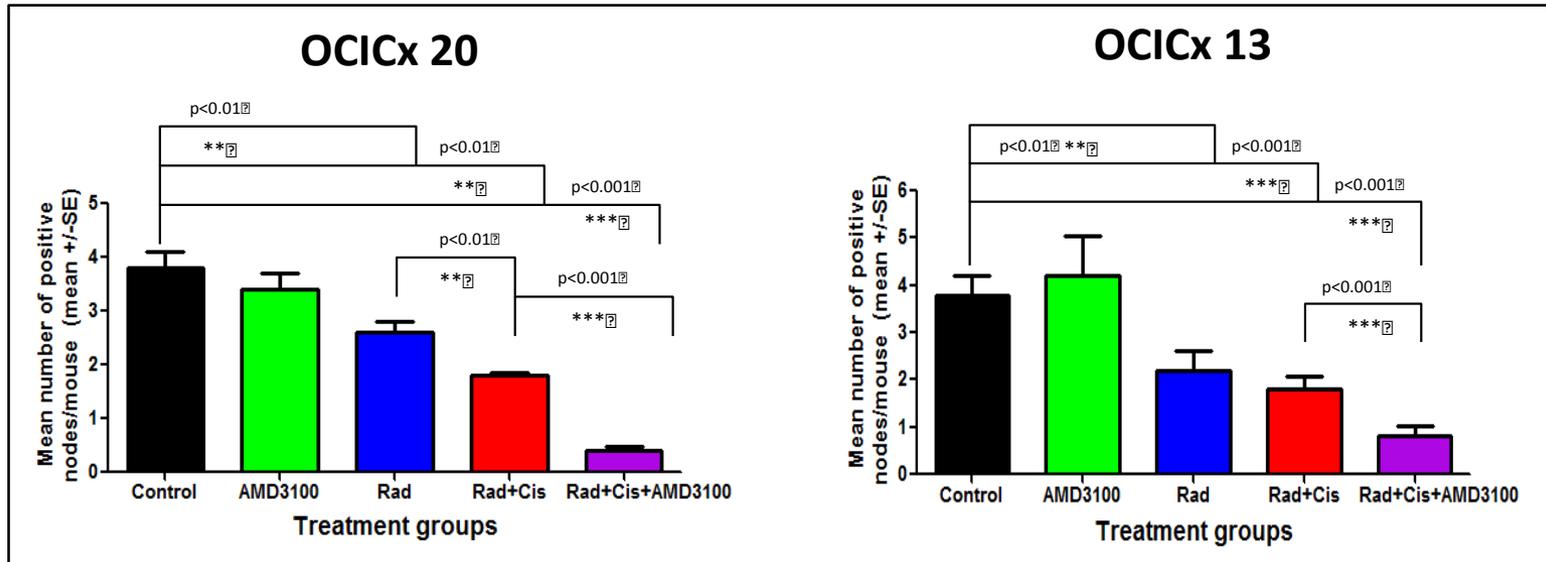
Fractionate image-guided radiation (30 Gy in 15 f) with weekly cisplatin (4 mg/kg)



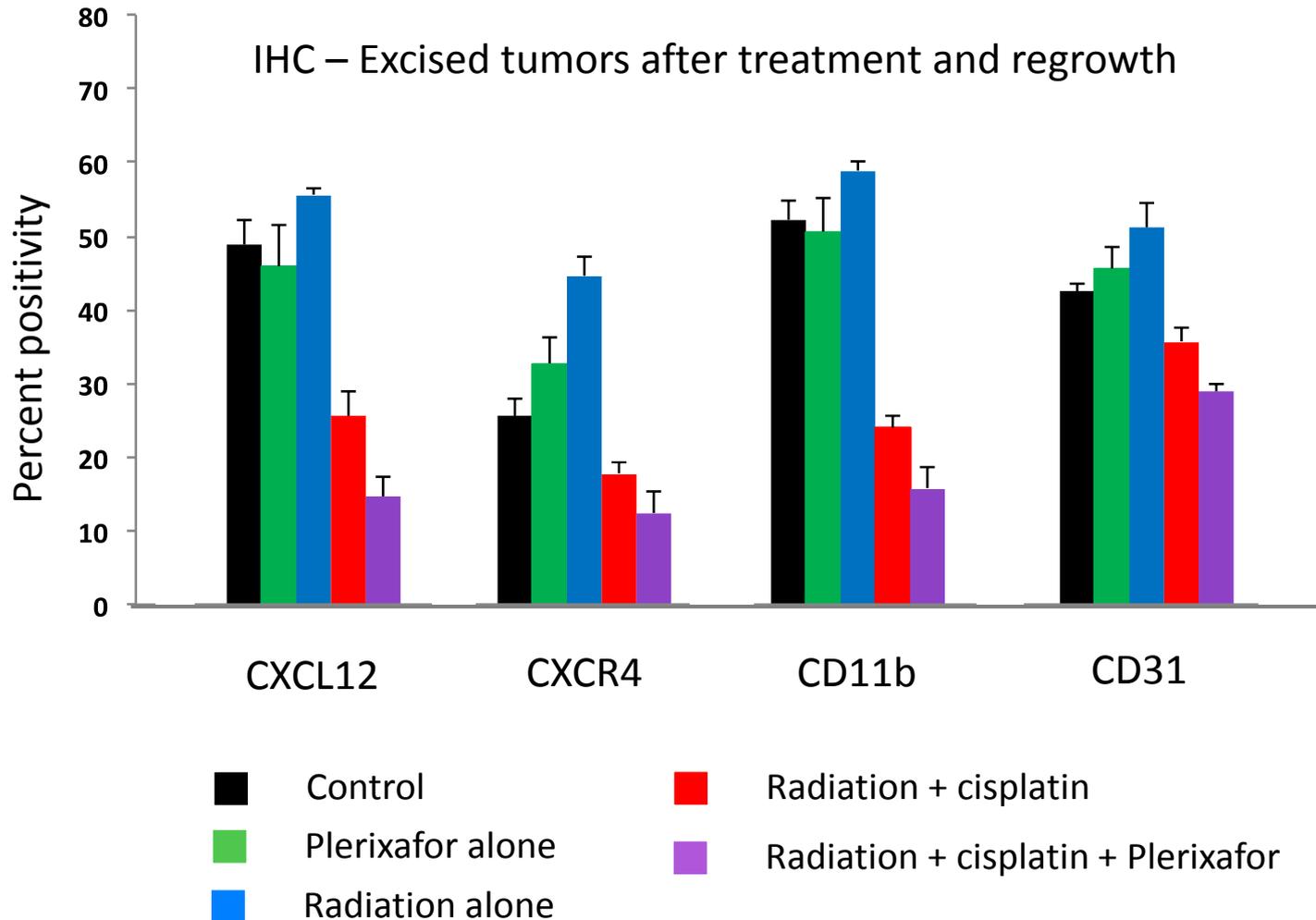
Tumor Growth Delay



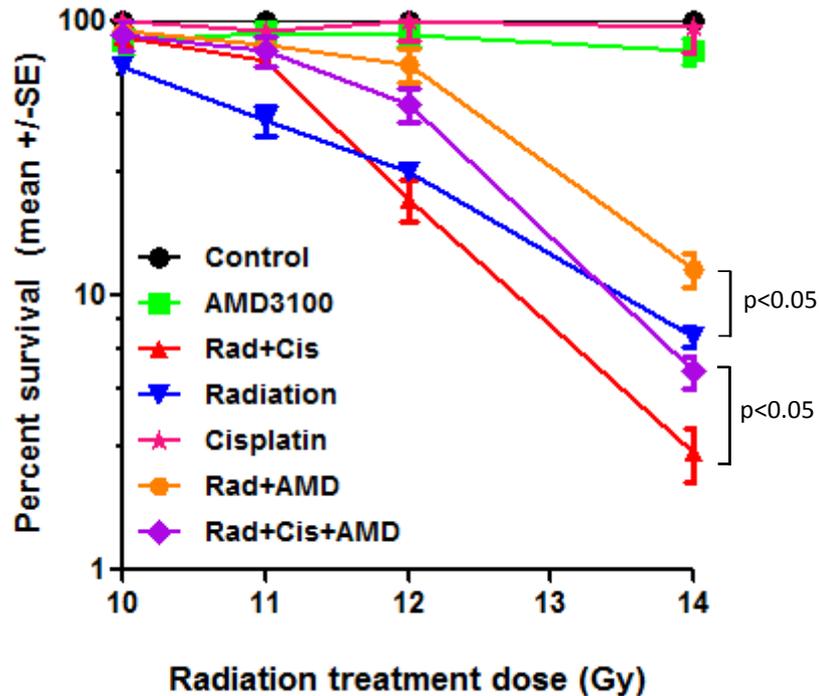
Lymph Node Metastases



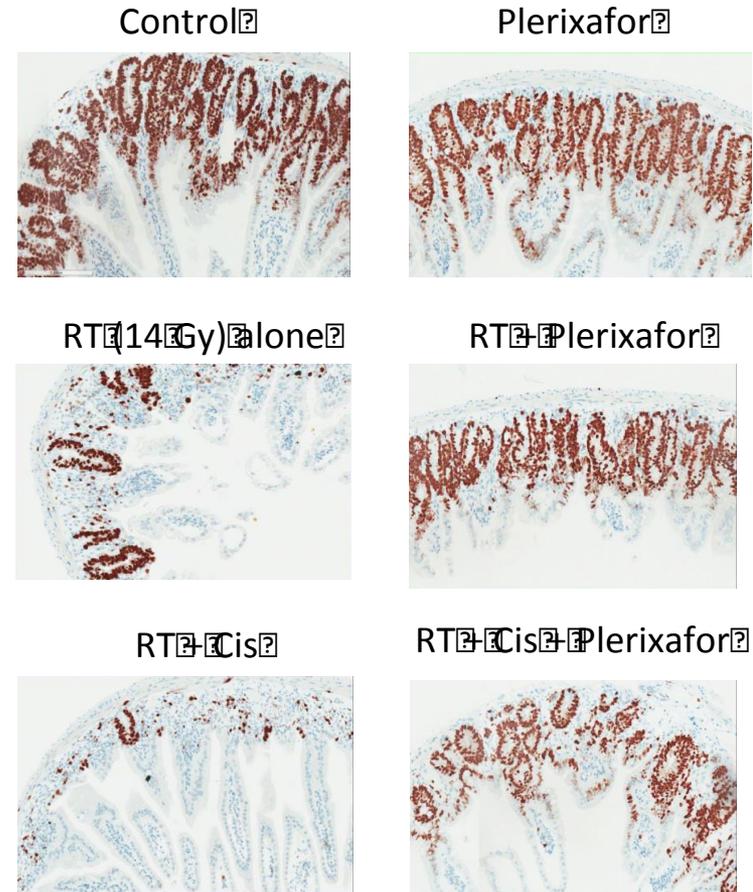
CXCL12 Pathway Inhibition



Acute GI Toxicity



No difference in animal weight, blood counts or normal organ morphology among the treatment groups



Late GI toxicity?

Conclusions

- Plerixafor, when added to standard RTCT for cervical cancer, improves tumor control and reduced metastasis with no increase in toxicity.
- The optimal sequencing of Plerixafor with RTCT requires further investigation.
- This study provides support for a phase I/II clinical trial in patients with cervical cancer.

Acknowledgements

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