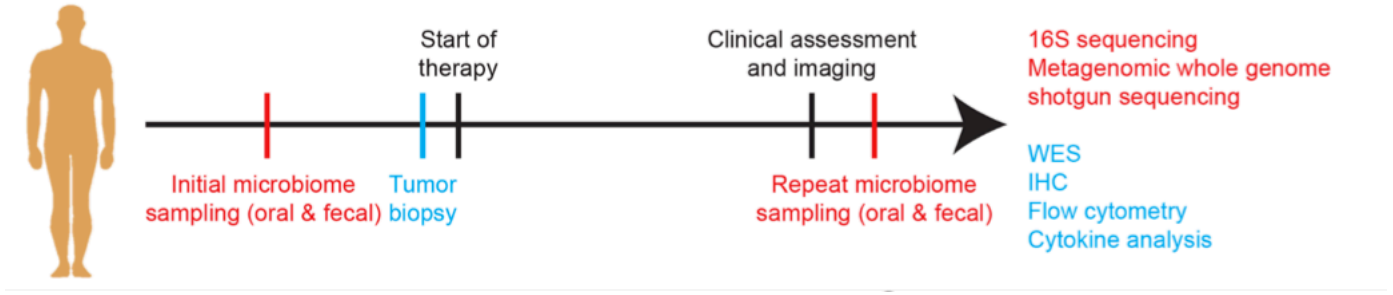
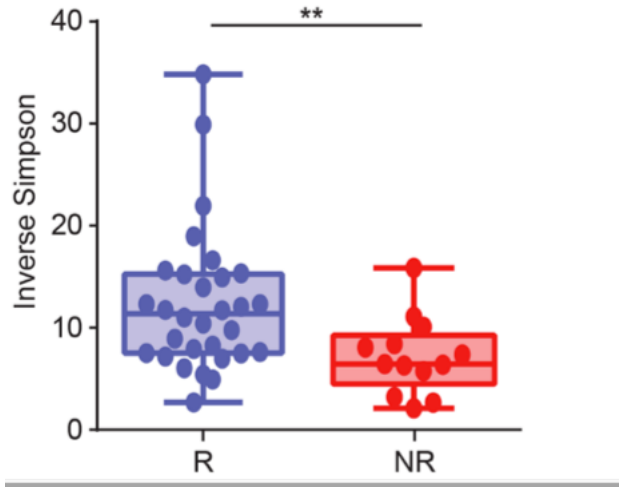
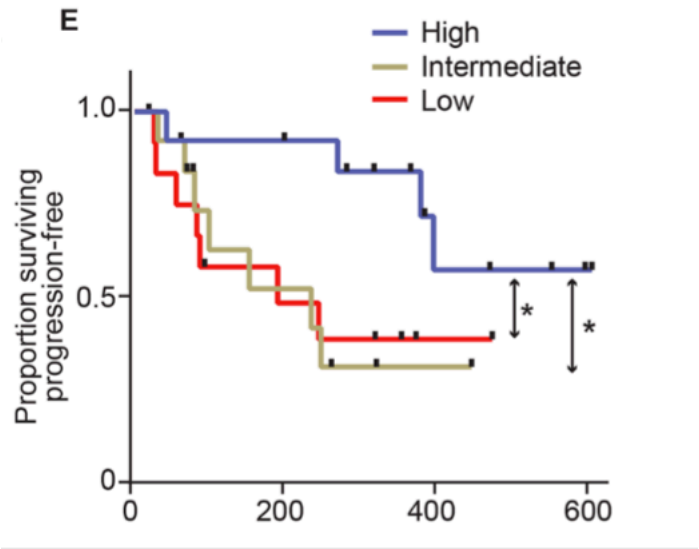
Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

V. Gopalakrishnan,[1,2*] C. N. Spencer,[2,3*] L. Nezi,[3*] A. Reuben,[1] M. C. Andrews,[1] T. V. Karpinets,[3] P. A. Prieto,[1†] D. Vicente,[1] K. Hoffman,[4] S. C. Wei,[5] A. P. Cogdill,[1,5] L. Zhao,[3] C. W. Hudgens,[6] D. S. Hutchinson,[7] T. Manzo,[3] M. Petaccia de Macedo,[6‡] T. Cotechini,[8] T. Kumar,[3] W. S. Chen,[9] S. M. Reddy,[10] R. Szczepaniak Sloane,[1] J. Galloway-Pena,[11] H. Jiang,[1] P. L. Chen,[9§] E. J. Shpall,[12] K. Rezvani,[12] A. M. Alousi,[12] R. F. Chemaly,[11] S. Shelburne,[3,11] L. M. Vence,[5] P. C. Okhuysen,[11] V. B. Jensen,[13] A. G. Swennes,[7] F. McAllister,[14] E. Marcelo Riquelme Sanchez,[14] Y. Zhang,[14] E. Le Chatelier,[15] L. Zitvogel,[16] N. Pons,[15] J. L. Austin-Breneman,[1||] L. E. Haydu,[1] E. M. Burton,[1] J. M. Gardner,[1] E. Sirmans,[17] J. Hu,[18] A. J. Lazar,[6,9] T. Tsujikawa,[8] A. Diab,[17] H. Tawbi,[17] I. C. Glitza,[17] W. J. Hwu,[17] S. P. Patel,[17] S. E. Woodman,[17] R. N. Amaria,[17] M. A. Davies,[17] J. E. Gershenwald,[1] P. Hwu,[17] J. E. Lee,[1] J. Zhang,[3] L. M. Coussens,[8] Z. A. Cooper,[1,3¶] P. A. Futreal,[3] C. R. Daniel,[4,2] N. J. Ajami,[7] J. F. Petrosino,[7] M. T. Tetzlaff [6,9] P. Sharma,[5,19] J. P. Allison,[5] R. R. Jenq,[3#] J. A. Wargo,[1,3#**]

Enhanced gut microbiome diversity is associated with improved response to anti-PD-1 immune therapy

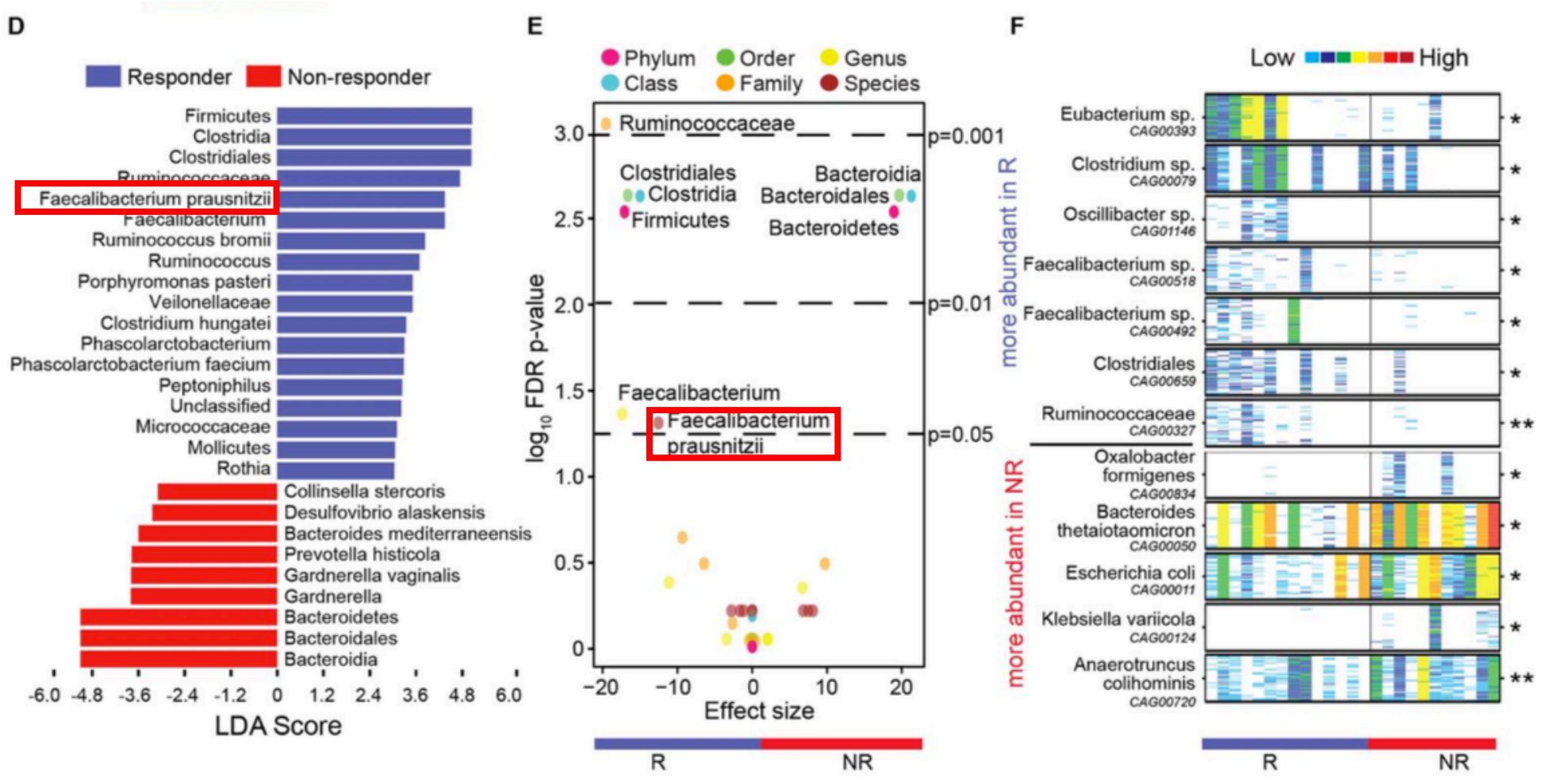




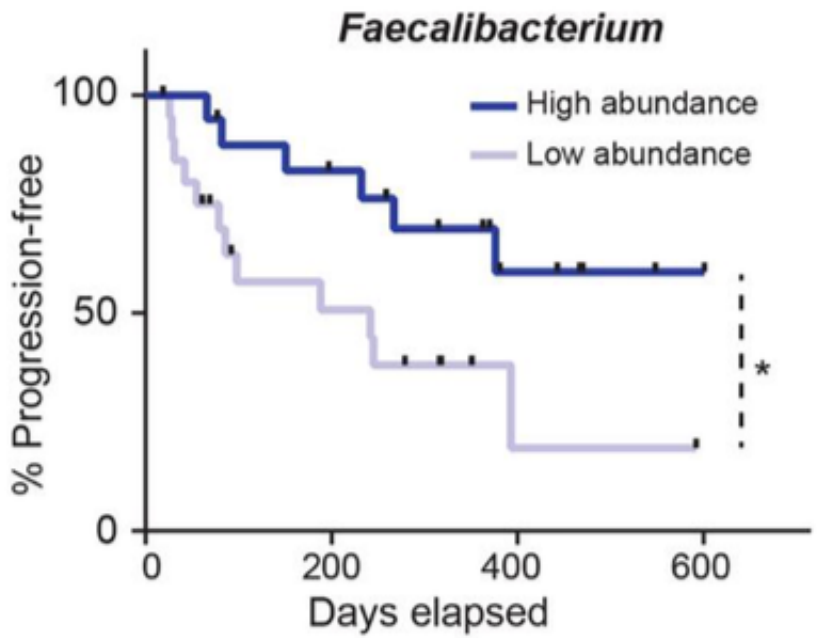


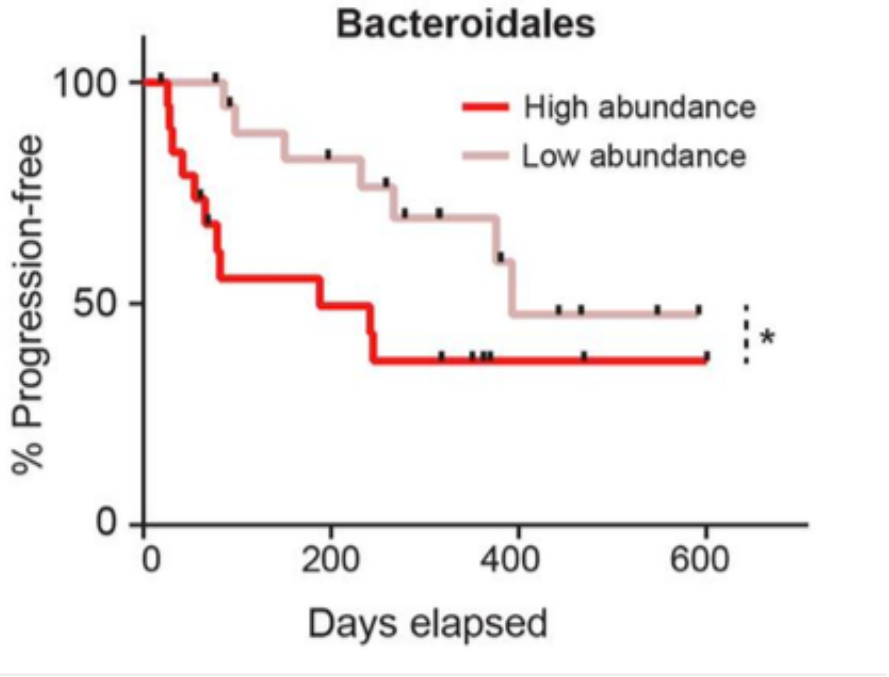
- No information about the initial sampling and repeat sampling ????
- Limited longitudinal samples… (n=3)

Taxa that are associated with responses to anti-PD-1 immune therapy

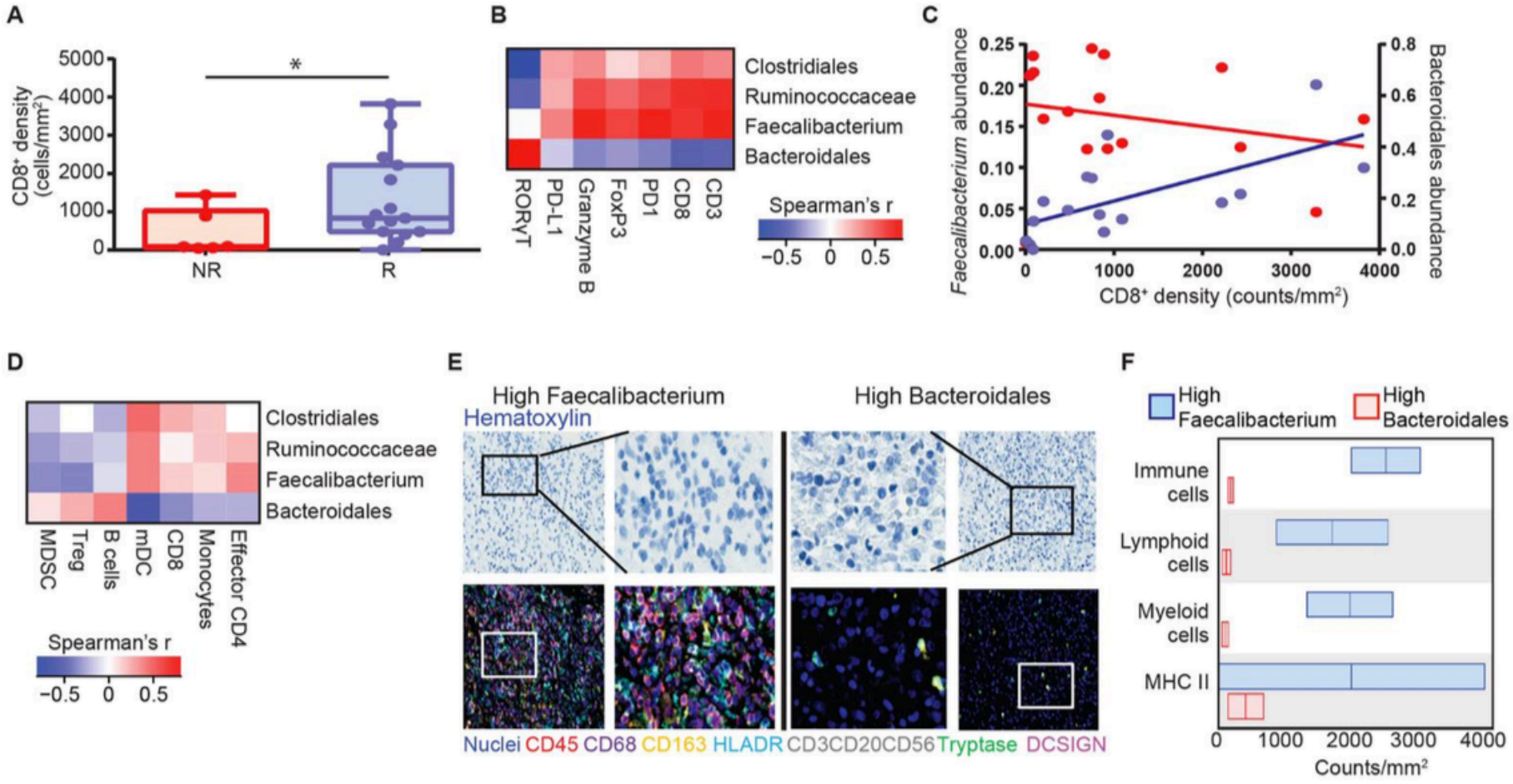


Abundances of two taxa are predicative of responses to anti-PD-1 therapy

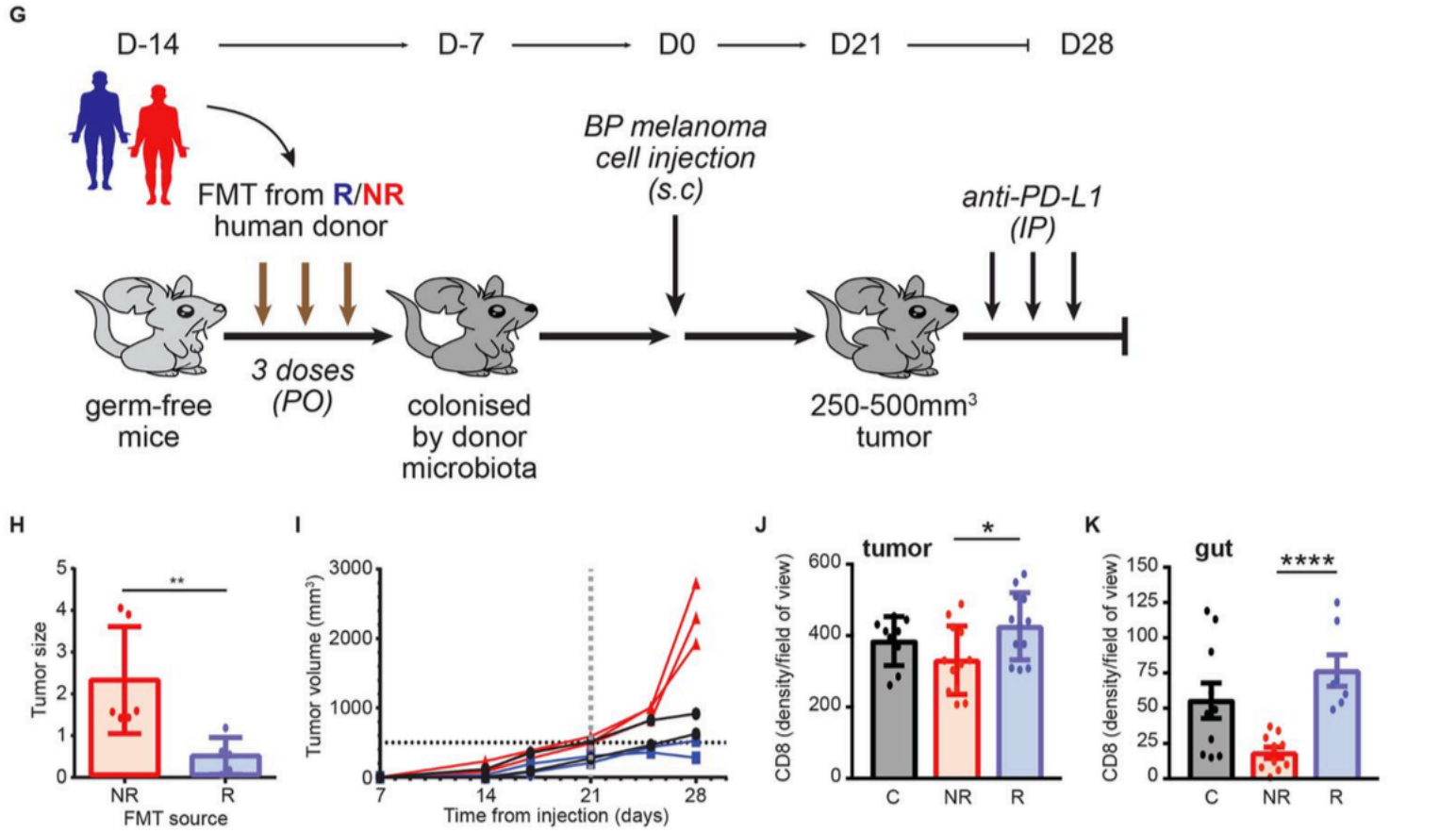




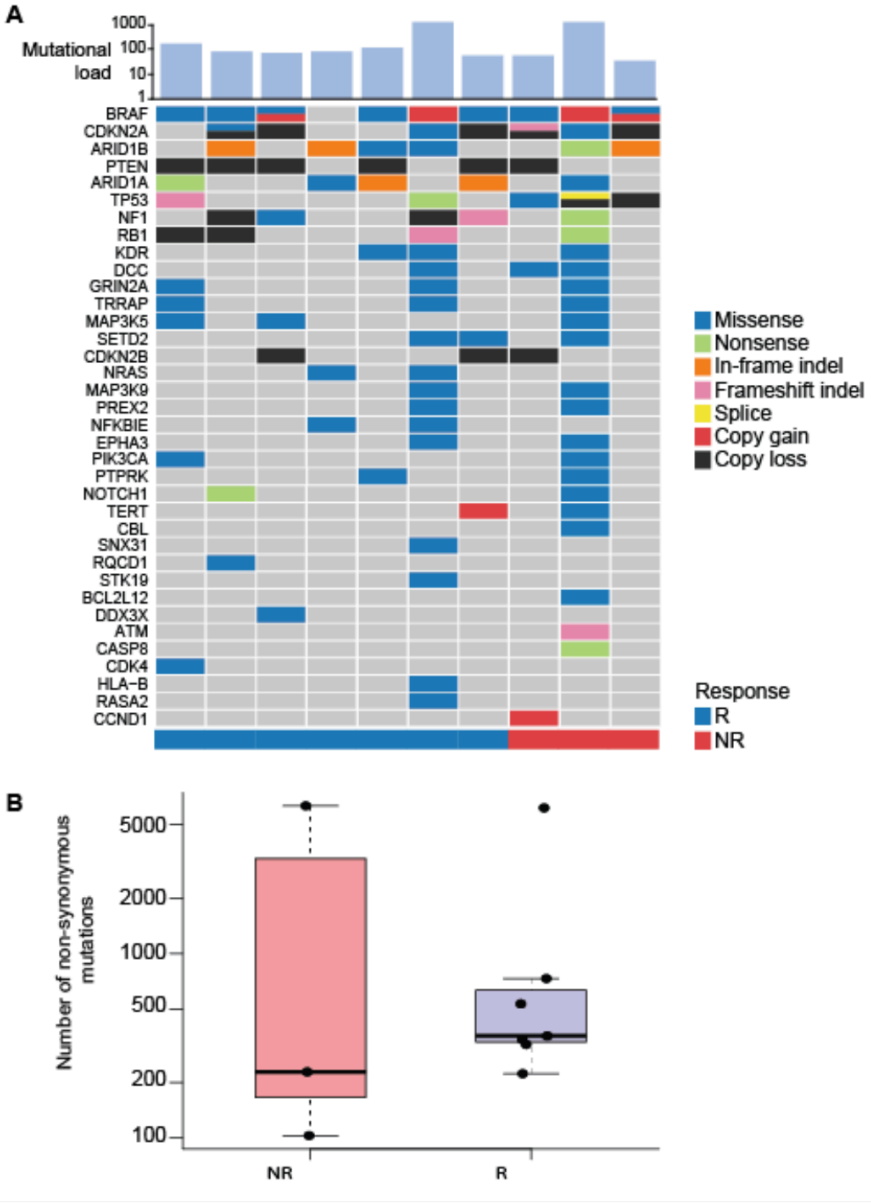
Favorable taxa are associated with enhanced systemic and anti-tumor immunity



FMT to mice with favorable taxa is associated with reduced tumor growth



Some issues



- Confounding factors
- Small cohort size
- Diversity or favorable taxa?

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

Immune checkpoint inhibitors (ICI) targeting the PD-1/PD-L1 axis induce sustained clinical responses in a sizeable minority of cancer patients. Here, we show that primary resistance to ICI can be due to abnormal gut microbiome composition. Antibiotics (ATB) inhibited the clinical benefit of ICI in patients with advanced cancer. Fecal microbiota transplantation (FMT) from cancer patients who responded to ICI (but not from non-responding patients) into germ-free or ATB-treated mice ameliorated the antitumor effects of PD-1 blockade. Metagenomics of patient stools at diagnosis revealed correlations between clinical responses to ICI and the relative abundance of *Akkermansia muciniphila*. Oral supplementation with *A. muciniphila* post-FMT with non-responder feces restored the efficacy of PD-1 blockade in an IL-12-dependent manner, by increasing the recruitment of $CCR9^{+}CXCR3^{+}CD4^{+}$ T lymphocytes into tumor beds.