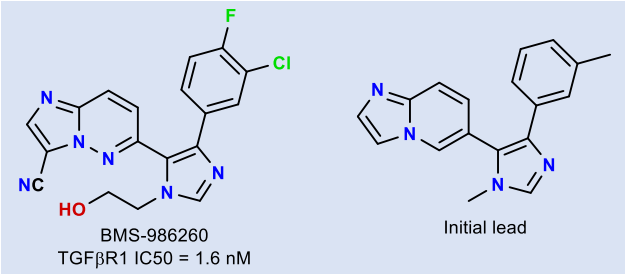
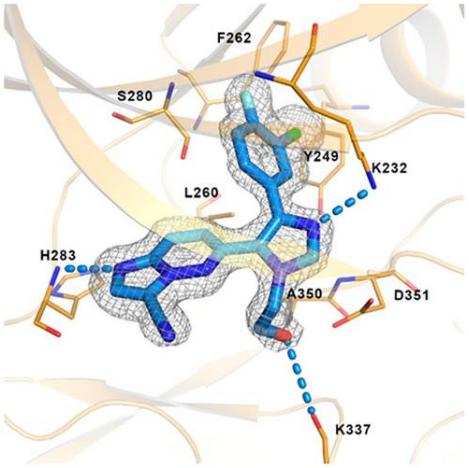
DRUG of the week

BMS-986260

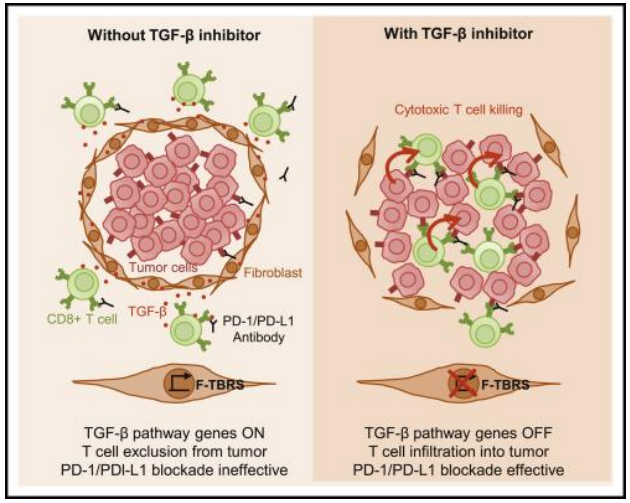
The SARLAH Group



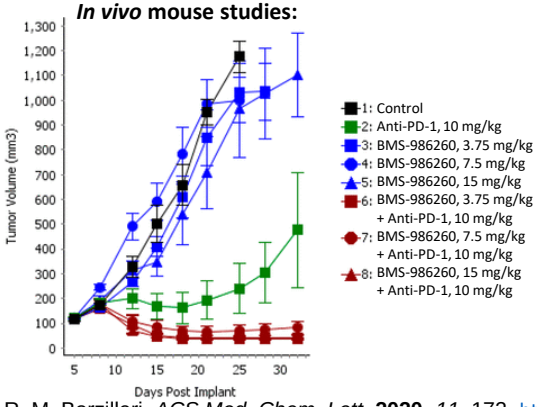
- BMS-986260 is an imidazole based TGFβR1 inhibitor that when used in combination with a programmed cell death protein 1 antibody displayed curative *in vivo* efficacy in colorectal cancer models
- Screening efforts provided the initial imidazo-pyridine lead and extensive SAR studies led to BMS-986260.
- Changing the core to an imidazo-pyridazine and installing the nitrile and fluoride functionalities increased metabolic stability while incorporating a hydroxyethyl group and a chloride improved aqueous solubility.



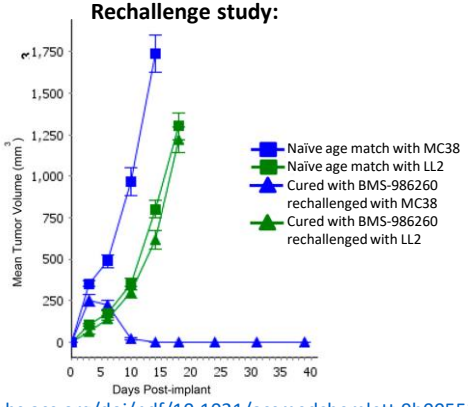
- Antibodies that target immune checkpoints such as programmed cell death protein 1 (PD-1), elicit impressive long-term durable remissions in multiple tumor types. However, limitations exist as only a fraction of patients respond to therapy
- Expression of F-TBRS in peritumoral fibroblasts can lead to T cell sequestration away from the tumor mass, leaving it unharmed.
- Pharmacological inhibition of TGF-β reverses such immune exclusion and facilitates T cell infiltration into tumors.
- Unfortunately, TGFβ pathway inhibitors are associated with considerable on-target cardiotoxicity, requiring holiday dosing to reduce these side effects



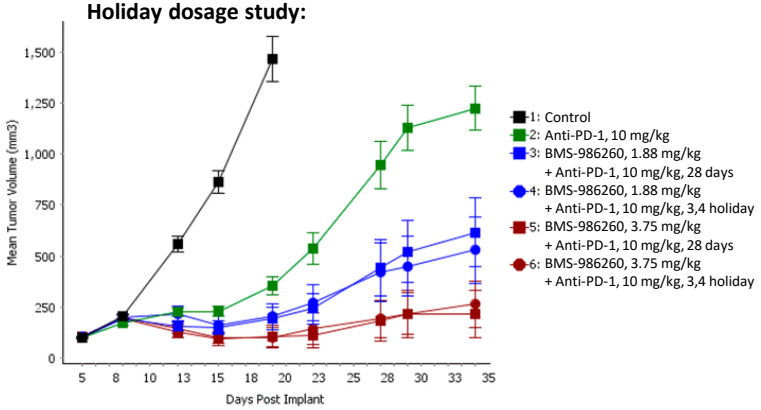
***In vivo* mouse studies:**



Rechallenge study:



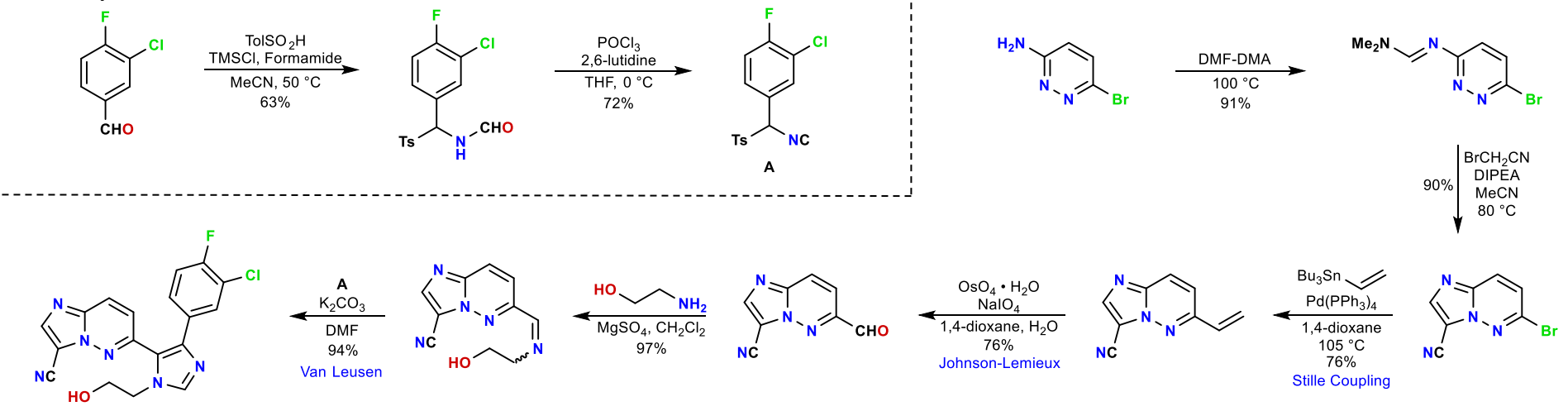
Holiday dosage study:



R. M. Borzilleri, *ACS Med. Chem. Lett.* **2020,** *11*, 172, https://pubs.acs.org/doi/pdf/10.1021/acsmedchemlett.9b00552

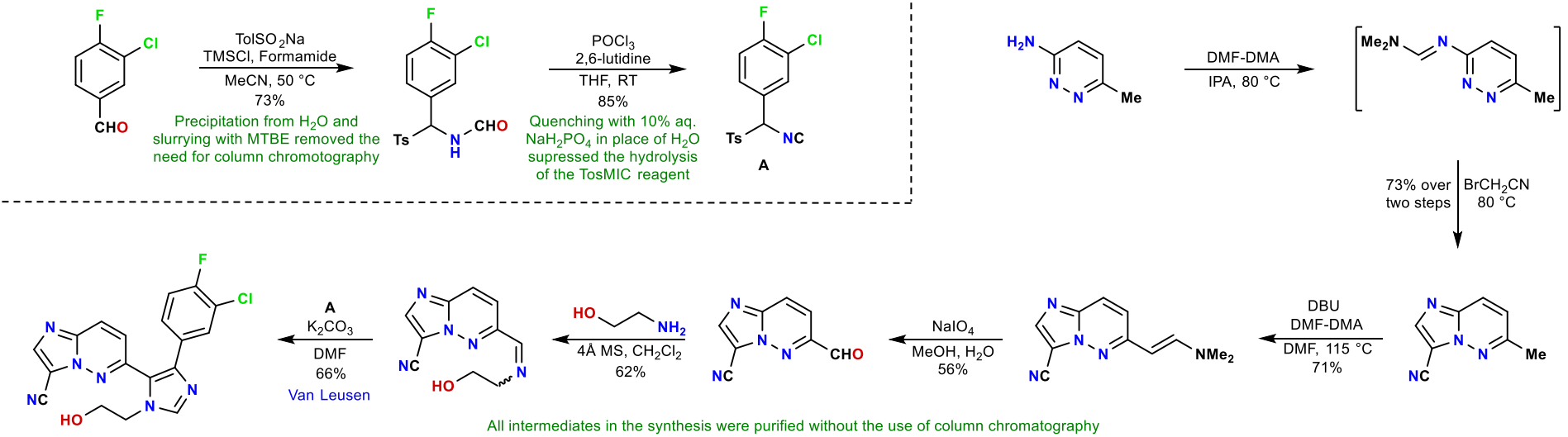
BMS-986260

Discovery Route:



R. M. Borzilleri, *ACS Med. Chem. Lett.* **2020,** *11*, 172, https://pubs.acs.org/doi/pdf/10.1021/acsmedchemlett.9b00552

Process Route:



All intermediates in the synthesis were purified without the use of column chromatography

R. Vaidyanathan Org. Process Res. Dev. **2020**, *24*, 1310 https://pubs.acs.org/doi/pdf/10.1021/acs.oprd.0c00232