**EZH2:** Histone methylation and transcriptional repression

- Mutations in EZH2 result in pro-cancer epigenetic changes.
- Inhibition of EZH2 results in increased chromatin accessibility and transcription of tumor suppressor genes.

**MDM2:** Negative regulator of P53

- Mutations result in MDM2 result in evasion of apoptosis and sustained cell proliferation.
- Inhibition of MDM2 results in increased P53 tumor suppressor functions (e.g., induction of apoptosis, cell cycle arrest).

**CD47:** A tumor’s “don’t eat me” signal

- CD47 is overexpressed in some tumors and enables evasion of the immune system.
- Inhibition of CD47 enables immune destruction of tumor cells.

### Key Considerations

**EZH2:**
- EZH2 is an attractive target for anti-cancer therapy because it helps cancerous cells divide and proliferate by turning off tumor suppressor genes.
- Relevant pediatric indications include: neuroblastoma, ATRX-driven tumors, and MYC-N-driven tumors.
- May require combination strategies with other therapeutic classes.
- Inhibitors with different targets (e.g., embryonic ectoderm development inhibitors) can also inhibit EZH2 activity.

**MDM2:**
- MDM2 is an attractive target for anti-cancer therapy because it helps cancerous cells proliferate and evade apoptosis.
- Serious toxicity concerns
- Safe MDM2 inhibitor dose may sensitize tumors to other therapies
- Consider mechanisms of MDM2 inhibitor resistance

**CD47:**
- CD47 is an attractive target for anti-cancer therapy because it helps cancer cells evade destruction by the patient's immune system.
- May improve efficacy in combination with chemotherapy, immunotherapy, and/or monoclonal antibody therapy.
- Prioritize pediatric indication preclinical research based on results from adult indication research.
- Macrophage expression of SIRPα may alter anti-CD47 efficacy.

### Recommendations

**EZH2:**
- Expand preclinical testing to relevant pediatric indications.
- Perform preclinical research to understand the effects of EZH2 on the immune system.
- Use immunocompetent preclinical models to study EZH2 inhibitor combinations, especially immunotherapies.
- Identify biomarkers that predict EZH2 inhibition sensitivity through further molecular characterization of tumors.

**MDM2:**
- Test MDM2 inhibitor treatment combinations with chemotherapy or radiation.
- Evaluate efficacy of second-generation MDM2 inhibitors in relevant preclinical models.
- Identify predictive biomarkers for sensitivity to MDM2 inhibition.

**CD47:**
- Use immune-competent pediatric central nervous system preclinical models to study the mechanisms by which anti-CD47 monoclonal antibodies exert effects across the blood-brain barrier.
- Assess preclinical efficacy of CD47 inhibition in models of sarcoma and acute lymphoblastic leukemia.
- Determine whether SIRPα expression patterns can provide insight into CD47 inhibitor sensitivity.
- Conduct preclinical research to identify CD47 inhibitor combination treatments.

### Clinical Development Status

**EZH2:**
- 1 approved drug (adult and pediatric [1 indication])
- 12 drugs in active development, but 0 in Phase III clinical trials

**MDM2:**
- 0 approved drugs
- 8 drugs in active development, with 1 in Phase III clinical trials

**CD47:**
- 0 approved drugs
- 70 drugs in active development, with 3 in Phase III clinical trials