In June 2023, COACH convened its fifth meeting with representatives from the National Cancer Institute (NCI), Food and Drug Administration (FDA), European Medicines Agency (EMA), advocacy groups, the Pediatric Preclinical Testing Program (PPTP), and the International Proliferation of Cancer (IPIC) to discuss the potential for development of life-saving drugs for pediatric indications. All three targets are BCL-2, BCL-xL, and MCL-1.

**BCL-2: Cell Death Inhibitors**

- BCL-2, BCL-xL, and MCL-1 are not cancer drivers. BCL-2 expression can inhibit apoptosis to facilitate tumor development and resistance to apoptosis.
- The BCL-2 inhibitor venetoclax has shown efficacy in adult leukemias and pediatric solid tumors, especially when used in conjunction with other therapies associated with hematological toxicities.
- Further preclinical development is needed to establish strategies for mimicking inhibitor activity, such as venetoclax, in pediatric indications.
- Venetoclax enhances chemotherapy toxicities in adults and should be used with caution in children, as it may impede bone growth.
- In acute myeloid leukemia (AML) preclinical studies, MCL-1 inhibitors maintain mitochondrial homeostasis and are inhibited by NOXA, which frees BAX and BAK to initiate subsequent caspase-dependent apoptotic signals.
- Both splicing dysregulation of the BCL-xL gene, which increases BCL-xL expression, and overexpression of BCL-xL are broadly implicated in cancer.
- MCL-1 inhibition exhibited strong synergistic effects in ALL and mixed activity among various AML preclinical models.
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**MCL-1: Cell Death Inhibitor and Regulator of Mitochondrial Homeostasis**

- MCL-1 is an essential mitochondrial homolog and is inhibited by NOXA, which frees BAX and BAK to initiate subsequent caspase-dependent apoptosis.
- MCL-1 is required for T and B cell survival, as well as when used in conjunction with other therapies associated with hematological toxicities.
- In acute myeloid leukemia (AML) preclinical studies, MCL-1 inhibitors maintain mitochondrial homeostasis and are inhibited by NOXA, which frees BAX and BAK to initiate subsequent caspase-dependent apoptotic signals.
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**BCL-xL: Cell Death Inhibitor**

- BCL-xL is a key regulator of cell death. BCL-xL inhibition may require administration in combination with other therapies associated with hematological toxicities.
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