Early Phase Combination Drug Studies in Pediatric Oncology

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Coalition Against Childhood Cancer (CAC2) Conference

June 20, 2023

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Objective

To provide an overview of the strategy for development and design of early phase combination drug studies in pediatric oncology

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Key Points

- Combinations should be developed based on the following:
  - Biology of childhood (not adult) cancers
  - Mechanism of action of the drugs (rather than adult indication)
  - Robust preclinical evaluation from *in vivo* models (genomically characterized)
  - Clinical activity for the agent (when known)
- Trials should be dose and schedule confirmatory, rather than exploratory, and move seamlessly to expansion cohorts or phase 2 in tumor or target of interest (efficiency is key!)
- Novel trial designs and randomization should be considered to improve efficiency and isolate effects (toxicity and anti-tumor) of novel agent
- Strategy should consider agent or combination's ultimate role in frontline therapy
- Early engagement of regulators and regulatory requirements for all drugs in essential
- Involving parent and patient advocates early and throughout development is critical

Moreno, et al. *Nat Rev Clin Oncol*. 2017; Pearson, et al. Eur J Cancer. 2016; Pearson, et al. Lancer Oncol. 2017; Moreno, et al. *J Clin Oncol*. 2023

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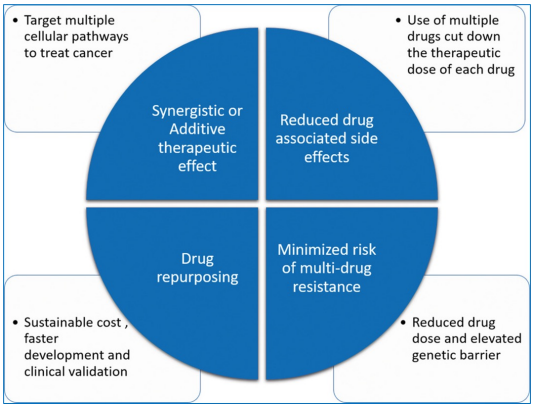
Why Test Combinations in Early Phase Studies?

- Cornerstone of curative therapy
- Numerous benefits
  - Minimize risk of drug resistance
  - Target multiple cellular pathways
  - Reduce toxicity if non-overlapping
- Combination approaches more efficacious than the same agents used alone
  - Single agent activity predicts activity in combination trials
- Goals are to efficiently determine safe dose/schedule and identify early signals of activity



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Shrestha, et al. Adv. Ther. 2019; Foster, et al. ESMO Open. 2020

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General Principles of Peds Early Phase Trials

Early-Phase Clinical Trial

Component	Recommendations	Rationale
Dose-finding or dose-confirmation phase	Starting dose: If a drug has neither serious dose-related toxicities nor a narrow therapeutic index: Adult RP2D (if known) corrected for patient size (BSA or weight) Objectives: Confirm toxicity profile, RP2D, and preliminary PK parameters with minimal dose ranging Extrapolation from data in adults should be considered, when possible[22]	Pediatric RP2D of most molecularly targeted drugs range between 90% and 130% of the BSA-adjusted RP2D for adults and, in the absence of DLT, is often based on PKs[20,21]
Expansion cohorts	Early signals of antitumor activity Additional PK, PD, and safety data including young children and infants Opportunity to evaluate a child-friendly oral formulation that was not available at the start of trial	Generate activity data to inform potential late-phase trials in target population of interest

- Seamless transition between dose-finding/confirmation and efficacy (Phase 1/2)
- Age-specific cohorts discouraged for majority of cohorts
  - No differences in PK of cytotoxic drugs between younger and older age cohorts
  - Additional PK/PD in kids ≤ 2 years can be obtained during PK expansion
- Age-appropriate (liquid) formulations are important, but shouldn't delay opening
- Incorporating correlative trials is a crucial (biomarkers of response/non-response)

Moreno, et al. *J Clin Oncol*. 2023; Doz, et al. *Br J Cancer*.2011; Mosse, et al. *Lancet Oncol*. 2013. Vassal, et al. *J Clin Oncol*. 2003

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Begin with the End in Mind

- Early engagement of regulators
  - Consider regulatory requirements along a full development pathway
  - Allows fewest number of patients be enrolled to obtain sufficient evidence
- Early involvement of patient/parent advocacy groups
- Consider where combination might fit into current treatment paradigms

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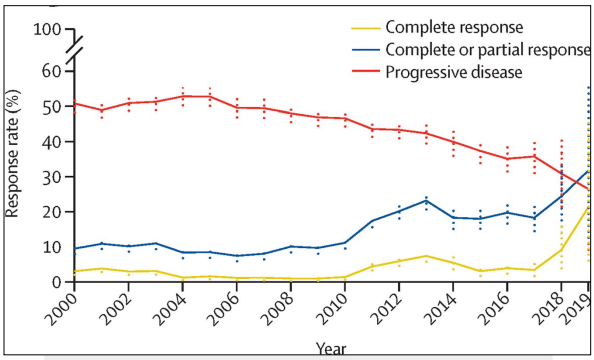
Therapeutic Misconception or Therapeutic Intent?

- Perception that phase 1 trials offer no potential benefit should be challenged
- Combination trials increase the likelihood for therapeutic benefit
- Therapeutic intent should guide early phase trial design considerations
  - Minimize single-agent evaluations
  - Avoid subtherapeutic doses, consider intra-subject dose escalation
  - Limit # of dose levels
  - Rapid assessment of agent efficacy, moving to disease specific cohorts early
  - Randomization when feasible
  - Use of novel trial designs (e.g. platform trials) to improve efficiency



Historical dogma: A phase 1 is a phase 1 is a phase 1

Statistically significant improvement in response rate (18.0% vs. 9.6%) in adult patients with solid tumors enrolled in CTEP-sponsored phase 1 trials (2000–2019).

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Chihara, et al. *Lancet*. 2022; Moreno, et al. *J Clin Oncol*. 2023

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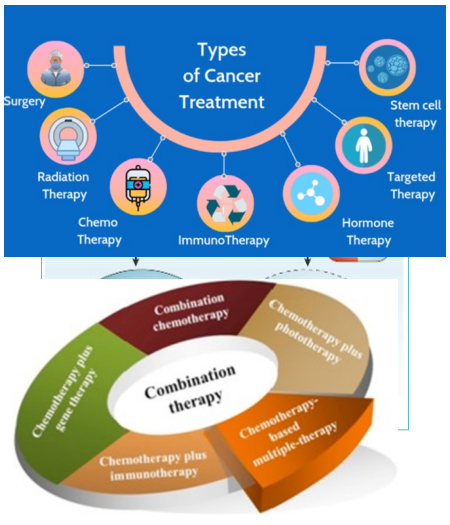
So Many (Potential) Combos, So Few Patients

- Combinations with cytotoxics vs. novel agents vs. other?
- How much preclinical data required? Adult data?
- Prioritization of agents should consider:
  1. Knowledge of tumor biology
  2. Molecular drivers of disease
  3. Drug's mechanism of action
  4. Activity of combo in relevant *in vivo* preclinical models (additive or synergistic); synthetic lethality?
  5. Therapeutic unmet needs
- Is there single agent activity?



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Brunen, et al. *Nat Rev Clin Oncol*. 2017; Pearson, et al. *Eur J Cancer*. 2016

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Design Considerations: Who to include?

- All-comers vs. enriched population (histology, molecular) vs. all comers in dose-finding/confirmation with enrichment in efficacy phase/expansions
  - Enrichment is the prospective use of any patient/tumor characteristic to select a study population in which detection of a drug effect is more likely than in an unselected population
- Antitumor activity should be evaluated in enriched populations, by disease or biomarker, to determine future clinical development
- Patients with prior exposure to single-agent therapy may (should?) be included

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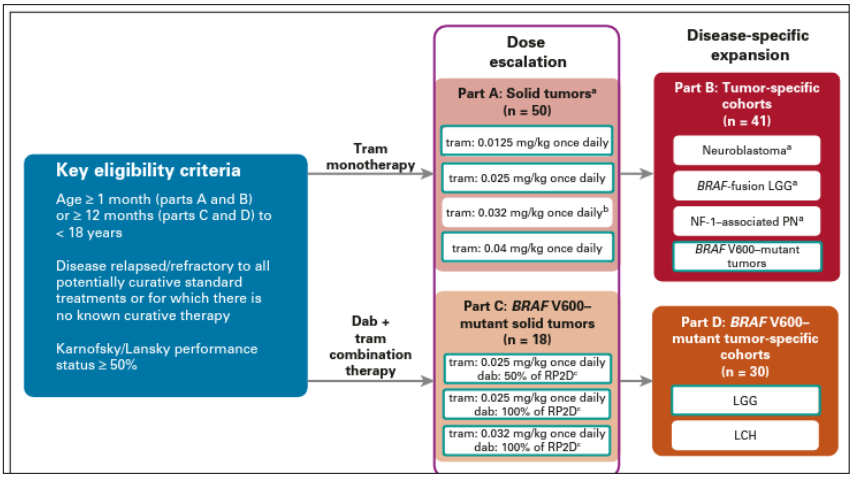
original reports

Efficacy and Safety of Trametinib Monotherapy or in Combination With Dabrafenib in Pediatric *BRAF* V600–Mutant Low-Grade Glioma

Eric Bouffet, MD[1]; Birgit Geoerger, MD, PhD[2]; Christopher Moertel, MD[3]; James A. Whitlock, MD[1]; Isabelle Aerts, MD[4]; Darren Hargrave, MD[5]; Lisa Osterloh, PhD[6]; Eugene Tan, PhD[7]; Jeea Choi, PhD[7]; Mark Russo, MD, PhD[7]; and Elizabeth Fox, MD[8]



J Clin Oncol 2022;41:664-674

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NCI Pediatric Early Phase Clinical Trials Network

ADVL1412: Phase 1/2 of Nivolumab +/- Ipilumumab

- Part A: Nivolumab Monotherapy dose confirmation (R/R solid tumors)
- Part B: Nivolumab Phase 2 (disease specific cohorts: rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, neuroblastoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and melanoma)
- Part C: Dose Confirmation Nivolumab (1 or 3 mg/kg) + Ipilumumab (1 mg/kg) (R/R solid tumors)
- Part D: Disease Expansion Nivolumab (3 mg kg) + Ipilumumab (1 mg/kg) in EWS, OS, RMS
- Part E: Selected Histologies Nivolumab (1 mg kg) + Ipilumumab (3 mg/kg)

Slide courtesy of Elizabeth Fox, MD

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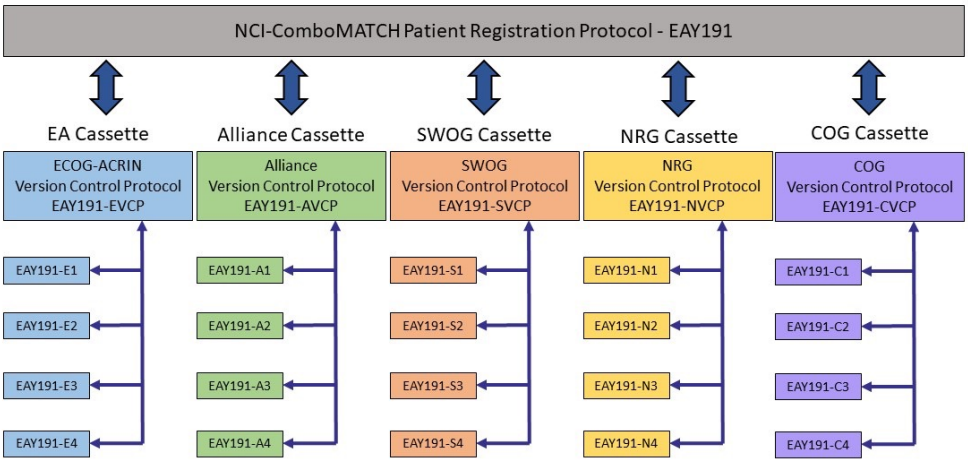
NCI-ComboMATCH Protocol Organization



Prototype as of February 19, 2020. Number of studies in each cassette likely to vary.

Slide courtesy of Elizabeth Fox, MD

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Design Considerations: What to Combine and How?

- **Is the pediatric monotherapy recommended phase 2 dose (RP2D), PK and safety profile known?**
  - **If no, a limited monotherapy, dose confirmation phase should be included**
    - Start at 100% of BSA-adjusted adult monotherapy RP2D (few exceptions)
    - Allow for transition to combination in same patient ASAP (1 or 2 cycles)
    - Fewest number of patients possible should receive monotherapy
- **Combining novel drug with standard of care (SOC) chemo is most common**
  - Dosing depends on availability of pediatric RP2D and adult combo data
  - Confirmation of BSA-adjusted adult combination RP2D preferred, but can start 20%-30% lower if concerns for safety, overlapping toxicities, or drug-drug interactions
  - Limited sample size that allows for PK estimation and determination of combo dosing
- **Novel-novel combinations considered when strong biologic rationale with robust preclinical data**
  - Considerations: 1) pediatric and adult PK/safety profiles; 2) metabolism that is expected to contribute to PK interactions?; and (3) expected interactions or overlapping toxicities

Lee, at al. *J Clin Oncol*. 2005; Place, et al. *Future Oncol*. 2018; Moreno, et al. *J Clin Oncol*. 2023

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Design Considerations: Dose Escalation and Toxicity

- Multiple approaches to escalate novel agent vs. SOC chemo vs. other novel
  - Novel agent typically escalated/de-escalated first, goal is fewest dose levels possible
  - Rolling six or 3+3 designs common
  - Newer designs (POCRM) allow for more efficient and accurate identification of combination dose/schedule and allow for tailoring which drug is modified in each cohort
- Pre-specified rules for which drugs will be escalate/de-escalated if excess toxicity or exposure below what's predicted to be needed from adult studies
- Toxicity considerations
  - Mechanism-based synergistic toxicity
  - Acceptable vs. unacceptable toxicity
  - Class effects and known toxicities should usually be excluded as DLTs
  - QOL and PRO measures, advocates' input, important to assess tolerability

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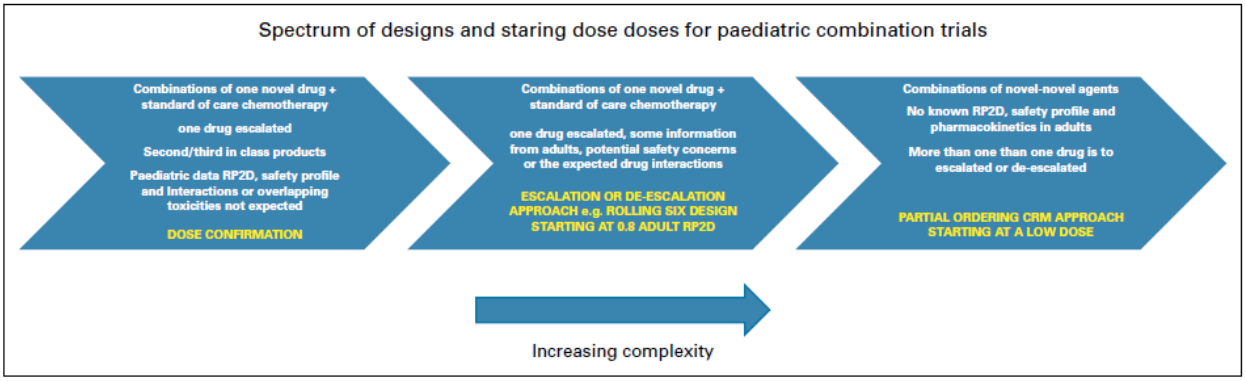
special articles

Combination Early-Phase Trials of Anticancer Agents in Children and Adolescents

Lucas Moreno, MD, PhD[1]; Steven G. DuBois, MD, MS[2]; Julia Glade Bender, MD[3]; Audrey Mauguen, PhD[3]; Nick Bird, MSc[4]; Vickie Buenger, PhD[5]; Michela Casanova, MD[6]; François Doz, MD[7,8]; Elizabeth Fox, MD[9]; Lia Gore, MD[10,11]; Douglas S. Hawkins, MD[12,13]; Shai Izraeli, MD[14,15]; David T.W. Jones, PhD[16,19]; Pamela R. Kearns, MB ChB, PhD[20,21]; Jan J. Molenaar, MD, PhD[22,23]; Karsten Nysom, MD, PhD[24]; Stefan Pfister, MD[16,17,18]; Gregory Reaman, MD[25]; Malcolm Smith, MD, PhD[26]; Brenda Weigel, MD, MSc[27]; Gilles Vassal, MD, PhD[28,29,30]; Christian Michel Zwaan, MD, PhD[22,31]; Xavier Paoletti, PhD[32]; Alexia Iasonos, PhD[3]; and Andrew D.J. Pearson, MBBS, MD, DCH[28,29]



J Clin Oncol. 2023 Apr 4;JCO2202430. doi: 10.1200/JCO.22.02430

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New Agents Combined with Cytotoxic Therapy

ADVL1514

Nab-sirolimus is albumin-bound mTOR inhibitor (sirolimus)

Primary Endpoint: DLTs in Cycle 1 and 2 to determine MTD

- Cycle 1 Monotherapy: nab-Sirolimus IV Days 1 and 8 of cycle 1 (cycle=21d),
- Cycle 2+ Combination: nab-Sirolimus administered IV on day 1, 8 in with Temozolomide (TMZ) +Irinotecan (IRN) day 1-5

Dose Level	Nab Sirolimus Dose	TMZ/IRN PO daily x 5	# patients DLT/Course	DLT
DL1 (n=5)	35 mg/m^2	125/90 mg/m^2	N=2 in Cycle 1	Thrombocytopenia
	35 mg/m^2	125/90 mg/m^2	N=1 in Cycle 2	Thrombocytopenia
DL -1 (n=6)	20 mg/m^2	125/90 mg/m^2	N=3 in Cycle 1	Thrombocytopenia
DL -2 (n=6)	15 mg/m^2	125/90 mg/m^2	N=1 in Cycle 1	Thrombocytopenia
PK DL-2 (n=4)	15 mg/m^2	125/90 mg/m^2	N=1 in Cycle 1	Mucositis

- RP2D: nab Sirolimus 15 mg/m^2 day 1 and 8, TMZ 125 mg/m^2 + IRN 90 mg/m^2 day 1-5 PO, q 21d
- One patient with EWS had PR received 35 cycles

NCI Pediatric Early Phase Clinical Trials Network

Cramer, et al. ASCO 2022

Slide courtesy of Elizabeth Fox, MD

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New Agents on a Cytotoxic Backbone

- Maintain the doses of the known active agents required reduced dose of nab-sirolimus
- DLT evaluation period used for determination of RP2D
  - Evaluate toxicity and PK of single agent and in combination (drug interactions)
  - Determination of single agent activity, however, if tumor progressed in cycle 1 may proceed to combinations
  - Many patients (50%) did not proceed to cycle 2, therefore not evaluable for the primary toxicity endpoint and had to be replaced.
- Does not address if nab-sirolimus/TMZ/IRN better than TMZ/IRN
- No Pharmacodynamics: Did not address if RP2D of nab-sirolimus inhibited target (4EBP1, S6K1)
- Future development
  - Bone tumor and CNS committees interested further development
  - PRECISON 1 - biomarker selected (TSC1/2) tumors (NCT05103358) or PEComa (NCT02494570)

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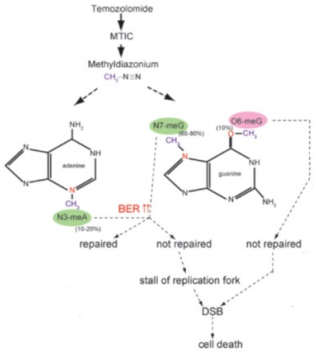
Synergistic Combinations

- PARP family of proteins are critical in DNA repair (esp. base excision repair mechanism)



- Talazoparib (BMN 673) is a novel, oral, highly potent, inhibitor of PARP 1/2
- PARP1 has been described as a key cofactor in ETS positive tumors (e.g. Ewing sarcoma, prostate carcinoma)
- PARP inhibitors synergize with temozolomide by inhibiting repair of TMZ-induced N^7 guanine and N^3 adenine methyl adducts → cell death

Slide courtesy of Elizabeth Fox, MD

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NCI Pediatric Early Phase Clinical Trials Network

ADVL1411: Talazoparib + Temozolomide

Talazoparib (mcg/m^2)	TMZ (mg/m^2) d2-6	# Entered/ Evaluated	# patients with DLTs	DLT Detail
400 daily d1-6	20	3/3	0	
400 twice daily d1 Then daily d 2-6	20	3/3	0	
600 twice daily d1 Then daily d 2-6	20	3/3	0	
600 twice daily d1 Then daily d 2-6	30	7/6	1	•Neutropenia (Grade 4 x ≥7 days)
600 twice daily d1 Then daily d 2-6	40	6/6	1 (2)	•intra-abdominal hemorrhage (Grade 4) •neutropenia (Grade 4 x ≥7 days) •ALT (prolonged Grade 3) •*≥2 platelet transfusions x 7 days*
600 twice daily d1 Then daily d 2-6 (PK)	55	3/3	2	•≥2 platelet transfusions x 7 days •neutropenia (Grade 4 x ≥7 days) •sepsis
600 twice daily d1 Then daily d 2-6 (PK)	30	6/5	0	

Slide courtesy of Elizabeth Fox, MD

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Synergy

- Activity of the combination of two drugs is more than additive
- Mechanism of action of talazoparib indicated synergy with temozolomide
  - Trial demonstrated that toxicity was synergistic (very low doses of TMZ)
  - No objective responses in 10 patients with EWS
- ONITT (Onyvide + Talazoparib or temozolomide NCT04901702) in patients with relapsed EWS
- Other DNA damage repair inhibitors (PARP, ATR, ATK) being evaluated as single agents

Slide courtesy of Elizabeth Fox, MD

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Recommended Dose for Combination (RDC)

- Maximum tolerated dose (MTD) based only on dose-limiting toxicity (DLT) observed during cycle 1 of dose-escalation phase
- RDC should also incorporate:
  - Cumulative toxicity after cycle 1 (DLTs and persistent toxicities impacting QOL)
  - PK and pharmacodynamic (PD) data
  - Dose modifications
- Dose optimization might also include intra-patient dose escalation (after achieving steady-state drug exposure, completion of DLT period, and response evaluation)
- Leverage optimal dosage- and exposure-response relationships for efficacy identified in adult studies

Serritella, et al. Clin Pharmacol Ther. 2020; Moreno, et al. *J Clin Oncol*. 2023

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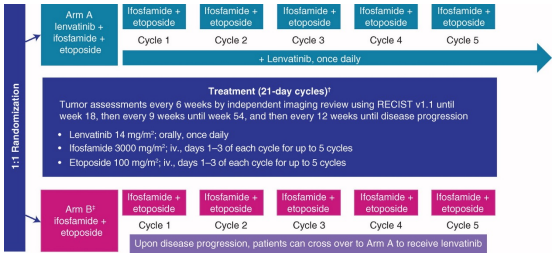
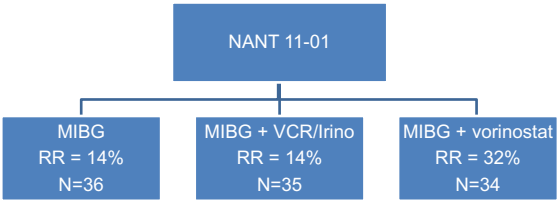
Evaluation of Anti-Tumor Activity

- Goal = identify promising regimens to take forward to later-stage trials
- Randomization is the most effective way to isolate effect of addition of novel agent
  - Randomized expansion phases, randomized selection, or screening designs (e.g. pick-the-winner)
  - Goal is to ensure that if one regimen is superior there is a high probability it will be selected (relaxed alpha)
  - Success defined by clinically acceptable response rate or progression-free survival
- Patients in dose-confirmation/escalation can be included in efficacy evaluation if they received the pediatric RDC

Gaspar, et al. *Future Oncol*. 2021; DuBois, et al. *J Clin Oncol*. 2021. Rubinstein, et al. *J Clin Oncol*. 2005

OLIE, ITCC-082: A Phase II trial of lenvatinib plus ifosfamide and etoposide in relapsed/refractory osteosarcoma (NCT04154189)





RR= response rate; VCR = vincristine; Irino= irinotecan

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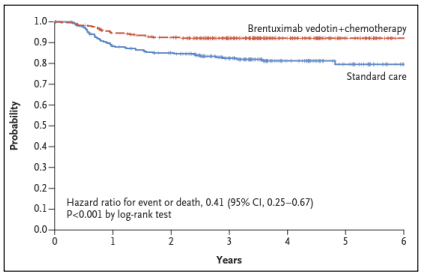
Begin with the End in Mind

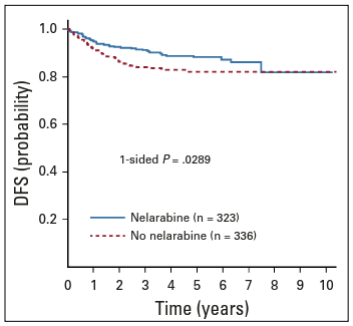
AHOD1331: Randomized Phase 3 Study of **Brentuximab Vedotin** for Newly Diagnosed High-Risk Classical Hodgkin Lymphoma (cHL) in Children and Young Adults



3-Year EFS: 92% vs. 83%; p<0.001

Castellino, et al. *N Engl J Med*. 2022

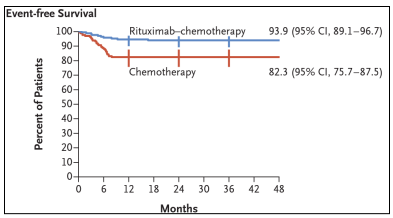
AALL0434: Intensified MTX, **Nelarabine** and Augmented BFM Therapy for Children and Young Adults with Newly Diagnosed T-cell ALL



3-Year DFS: 88% vs. 82%; p=0.03

Dunsmore, et al. J Clin *Oncol*. 2020

Rituximab for High-Risk, Mature B-Cell Non-Hodgkin's Lymphoma in Children: European Intergroup for Childhood NHL and COG



3-Year EFS: 94% vs. 82%; p<0.001

Minard-Colin, et al. *N Engl J Med*. 2020

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Conclusions (Key Points Revisited)

- Combinations should be developed based on the following:
  - Biology of childhood (not adult) cancers
  - Mechanism of action of the drugs (rather than adult indication)
  - Robust preclinical evaluation from *in vivo* models (genomically characterized)
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