Expansion Cohorts in Early Phase Clinical Trials: Valuable or Not?

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Phase I Current/unpublished CCC Studies

PhI-76: Phase I Study of TRC102 in Combination with Cisplatin and Pemetrexed in Patients with Advanced Solid Tumors, with Expansion Cohort in Mesothelioma / Phase II Study of TRC102 with Pemetrexed in pts refractory to cis/pem [PI Koczywas, Traditional 3+3]

2 Expansion cohorts:

To confirm tolerability of RP2D: TRC102+Cis+Pemetrexed in a total of 14 chemotherapy-naïve patients with advanced malignant mesothelioma to obtain additional safety data, PK data, and a preliminary indication if the combination might be effective

To see activity: TRC102+Pemetrexed in 14 response evaluable patients who recently failed cis+Pemetrexed (treated at DL1 once it passed safety assessment.)

Phase I Current/unpublished CCC Studies

PhI-77:A Phase I Trial of AZD9291 (Osimertinib) and Necitumumab in EGFR-Mutant Non-Small Cell Lung Cancer After Progression on a Previous EGFR TKI [PI Riess, Trad 3+3]

Multiple Expansion cohorts:

To confirm the RP2D (combined across expansion cohorts) and provide an initial estimate of activity and biological correlatives within each 18 patient expansion cohort. Cohorts differed by EGFR mutation and prior treatment, where most expansions had failed Osi or 3rd generation TKI

Phase I Current/unpublished CCC Studies

PhI-79:A Phase I Trial of the Combination of Lenalidomide and Blinatumomab in Patients with Relapsed or Refractory Non-Hodgkins Lymphoma (NHL) [PI Tuscano, IQ 3+3]

1 Expansion cohort:

The expansion cohort will be expanded to a total of 12 patients with informative courses of therapy to better evaluate the toxicity, tolerability and clinical activity on the expansion dose and schedule (see below), with the additional rule that if 3 patients experience a DLT during the expansion phase the study will hold accrual pending review of the toxicities and consultation with CTEP.

Phase I Current/unpublished CCC Studies

PhI-92:A Phase 1B Study of AMG-232 in Combination with Decitabine in Acute Myeloid Leukemia [PI Kelly, Trad 3+3]

1 Expansion cohort:

The MTD/RP2D will be expanded to enroll an additional 10 patients to further characterize the safety and toxicity of this regimen, to assess the PK properties and biological changes, and to obtain preliminary information regarding the overall response rate (ORR) and PFS to this combination in patients with refractory AML unfit for intensive chemotherapy.

Phase I Current/unpublished CCC Studies

PhI-96:A Pilot Phase I Study of Atezolizumab (MPDL3280A) in Combination with Immunogenic Chemotherapy (Gemcitabine-Oxaliplatin) and Rituximab for Transformed Diffuse Large B-Cell Lymphoma [PI Herrera, Trad 3+3]

Expansion cohorts:

With 24 patients at the RP2D (14 in transformed from FL, 10 from other), the probability of a DLT or any specific AE will be estimated and exact 95% confidence intervals will be constructed. Using the large sample approximation, the 95% CI half-width will be no larger than 0.20.

Phase I Current/unpublished CCC Studies

PhI-103:A Phase I Study of M3814 in Combination with MEC in Patients with Relapsed or Refractory Acute Myeloid Leukemia [PI Jonas, Traditional 3+3, w/PK etoposide]

Expansion Cohorts: With respect to clinical activity, with 12 patients on cohorts A2 and A4, if the better response cohort has a response rate of 40% and the inferior response cohort has a response rate of 20% (using CR/CRi), the chance of response favoring the inferior cohort based on response is less than 10% (based on 10,000 simulations). Similar comparison of toxicity.

Phase I Current/unpublished CCC Studies

PhI-113: A Phase 1 Trial of MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl in Advanced NSCLC Patients [PI Riess, IQ 3+3]

Expansion Cohorts: There are 4 expanded cohorts of 14 patients for a total of 56 patients in expanded cohorts. From this pool of patients, we expect to accrue 16-20 patients for repeat PET imaging to show an increase in tumor uptake of radio-labelled glutamine (18FGln). Cohorts of mutated *NFE2L2* LSCC, *KEAP1* LSCC, *KRAS/KEAP1* NSCLC, and *KEAP1/NFE2L2* WT LSCC

Phase I Current/unpublished CCC Studies

PhI-115:A Phase 1b Study with Expansion Cohort of Escalating Doses of KRT-232 (AMG 232) Administered in Combination with Standard Induction Chemotherapy (Cytarabine and Idarubicin) in Newly Diagnosed Acute Myelogenous Leukemia (AML) [PI Kelly, IQ 3+3]

Expansion:The MTD/RP2D will be expanded, to enroll up to 18 total patients, to further characterize the toxicity of this regimen, to assess the PK properties and biological changes, and to obtain preliminary information regarding the overall response rate (ORR) and PFS to this combination in patients with previously untreated AML fit for intensive chemotherapy.

Phase I Current/unpublished CCC Studies

PhI-117:A Phase 1 Trial of the ATR Inhibitor BAY 1895344 in combination with cisplatin and with cisplatin plus gemcitabine in advanced solid tumors with an emphasis on urothelial carcinoma [PI Parikh, IQ 3+3]

Expansion: Additional patients will be added at the MTD/RP2D planning to achieve 12 patients at the RP2D, for each combination.

Phase I Current/unpublished CCC Studies

PhI-124:A Phase 1/1a Study of Venetoclax, MLN9708 (ixazomib citrate) and Dexamethasone for Relapsed/Refractory Light Chain Amyloidosis. [PI Rosenzweig, BOIN design targeting 25% DLT rate]

Expansion: We plan to enroll a total of 12 patients at the RP2D including those treated at the RP2D in the dose escalation stage. A sample of size 12 produces a two-sided 80% confidence interval with a CI width 0.27 when the sample DLT rate is 0.17.

Phase I Current/unpublished CCC Studies

PhI-141:A Phase 1 Study of Mosunetuzumab with Polatuzumab Vedotin and Lenalidomide (M+Pola+Len) in Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL) [PI Tuscano, IQ 3+3]

Expansion: We seek a total of 12 evaluable patients at the RP2D for each of the expansion cohorts: cohort A that have < complete response (CR) or Deauville score of 3 or worse at D90 (or before) after standard of care chimeric antigen receptor (CAR) T-cell therapy; cohort B - other patients who have failed prior treatment (e.g. relapse after Day 90 from CAR-T, or relapsed after other therapies and were not considered candidates for CAR-T). As cohort A is expected to have residual CAR-T cells present, both the toxicity (expected to be higher in cohort A) and activity may differ.

Summary of Expansion Cohorts for Phase 1 studies:

11/11 of recent studies have expansion cohorts:

All expansion cohorts will increase confidence in the dose determined to the RP2D. Why? You can rule out a 40% DLT rate with 0 of 6 DLTs ($p<0.05$), but not much lower. With a 25% DLT rate, there is a 17.7% chance of observing no DLTs.

Some expansion cohorts are in settings where any response is encouraging. If 0/14 responders, you can rule out a 20% response rate ($p<0.044$). In other settings, very high response rates can add motivation for future studies

Some expansion cohorts provide enhanced opportunity for correlatives

Summary of Expansion Cohorts for Phase 1 studies:

Where we do not see expansion cohorts:

1. Asian vs non-Asian in anthracyclines (2012, Bourdeneau et al)
2. To explore height and dosing for paclitaxel or neurotoxic drugs (2005, Openshaw, et al)
3. Other Minorities

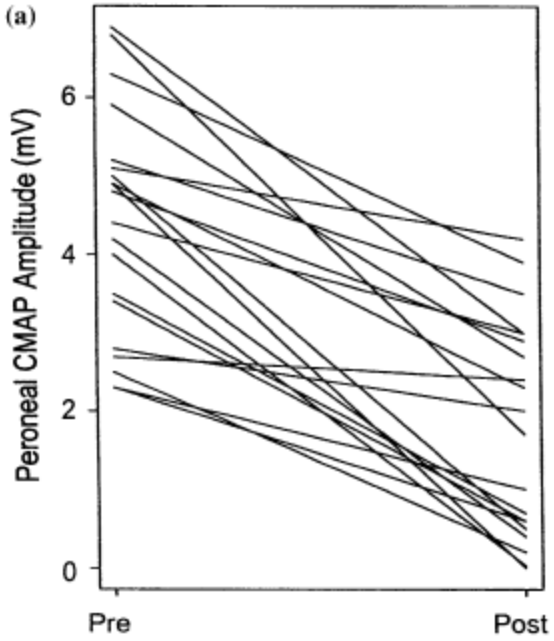
Asian vs non-Asian in anthracyclines (2012, Bourdeneau et al)

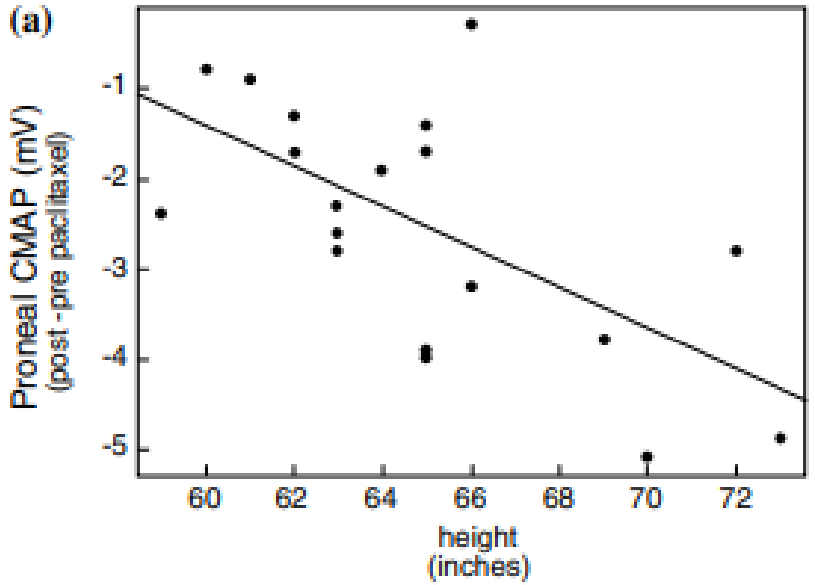
For the purpose of this study, CINV was graded as “clinically important” if other antiemetics were added to the current antiemetic regimen, the patient had a reduction in chemotherapy dose, or the treatment was delayed or discontinued due to CINV only.

Relative Risk of CINV was 2.44 ($p<0.01$), 95% 1.4-4.2 (univariate)

Relative Risk of CINV was 2.12 ($p<0.05$), 95% 1.18-3.81 (multivariate adjusted for age<=50, GERD, insurance (private).

Height with respect to neuropathy in paclitaxel drugs (2005, Openshaw, et al)



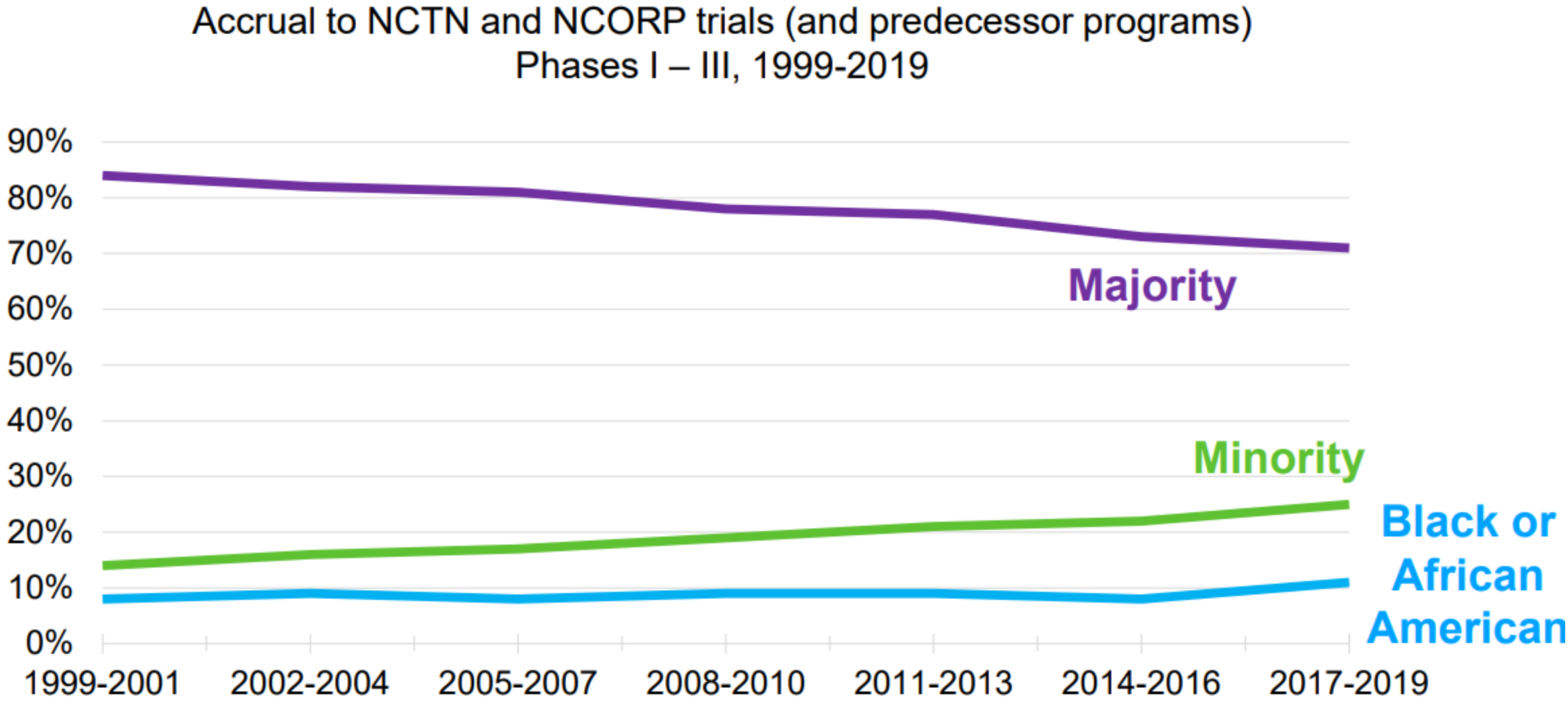


From UNC Bioethics. Senior author Jill Fisher, J. of Law Medicine, and Ethics 2023

General Phase 1 studies

	n	%
Gender		
Women	47	26.4%
Men	131	73.6%
Race/Ethnicity		
Non-Hispanic white	57	32.0%
Black / African American	72	40.4%
American Indian	2	1.1%
Asian	6	3.4%
Hawaiian / Pacific Islander	2	1.1%
More than one race	13	7.3%
Hispanic[1]	38	21.3%
Born Outside of the U.S.	35	19.7%
Age		
18-21	6	3.4%
22-29	34	19.1%
30-39	58	32.6%
40-49	54	30.3%
50+	26	14.6%
Household Income[2]		
Less than $10,000	30	16.9%
$10,000 to $24,999	52	29.2%
$25,000 to $49,999	71	39.9%
$50,000 to $74,999	13	7.3%
$75,000 to $99,999	7	3.9%
$100,000 or more	4	2.2%

Minority accrual to clinical trials



Conclusion

- Expansion cohorts are ubiquitous.
- Primary benefit is to confirm tolerability. Especially important with DLT targeting designs.
- In some settings, helps select between two candidate doses (Project Optimus)
- Can provide added motivation for future evaluation and the opportunity for correlatives