Impact of New/Emerging Changes in Standard Cancer Treatments on Clinical Trial Enrollment

Advisory Council on Alzheimer's Research, Care, & Services Meeting
July 19, 2021

NIH NATIONAL CANCER INSTITUTE

Meg Mooney, MD
Associate Director
Cancer Therapy Evaluation Program
Division of Cancer Treatment & Diagnosis
National Cancer Institute

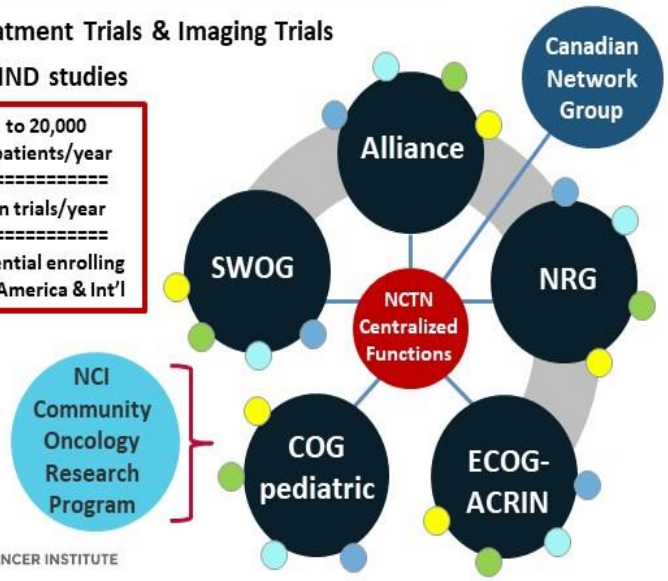
Overview

1. NCI National Clinical Trials Network (NCTN) Structure & Role in Cancer Tx Trials
2. Accrual Impact on NCTN Phase 3 Trials due to New/Emerging Cancer Treatments
3. Assessment Process for Evaluating Need for Changes in Ongoing Trials
   - Sources of New/Emerging Information
   - Components of Evaluation/Assessment
4. Examples (Past/Present) Affecting Existing Trials – Need to follow the science

NCI National Clinical Trials Network (NCTN)

- 5 US Trial Groups & 1 Canadian Partner
- Late-Phase Emphasis Network (Phase 2 & Phase 3)
- Cancer Treatment Trials & Imaging Trials
- IND & non-IND studies

≈18,000 to 20,000 enrolling patients/year
==========
≈ 200 open trials/year
==========
≈ 2,200 potential enrolling sites North America & Int'l



LEGEND:

- Central Functions:
  - NCI Central IRB
  - Cancer Trials Support Unit
  - Imaging & Radiotherapy Core
  - Common Data System/Hosting
  - Network Accrual Team
- 32 Lead Academic Sites
- Operations Centers
- Statistics/Data Centers
- Tumor Banks
- Member Sites

NIH NATIONAL CANCER INSTITUTE

3

Accrual Impact on NCTN Phase 3 Trials due to New/Emerging Cancer Treatments 2000-2007

Reasons for Enrollment to Trials Not Reaching Accrual Goals 2000-2017

(i.e., total enrollment to trial < 90% of protocol-specified accrual goal)

Category	%
Inadequate Accrual rate	22%
Interim Monitoring within trial	6%
Unacceptable toxicity	2%
External Information affecting trial (*)	**5%**
Drug supply issues	1%

(*) Results of another trial that answered current trial question/rendered it irrelevant
2 of the trials ended b/o external information & interim monitoring
Does not include trials requiring amendments b/o new information or trials in development

NIH NATIONAL CANCER INSTITUTE Korn EL, Freidlin B, Mooney M, & Abrams JS; J Clin Oncol. 2010 Dec 10; 28(35): 5197–5201

4

Assessment Process for Evaluating Need for Changes in Ongoing Trials Based on New Results

Sources of New/Emerging Information

- Clinical Trials Results (Publication / Scientific Meeting Presentations)
- Practice Guidelines changes
- Regulatory approvals

Primary Questions in Evaluating Impact

- Does equipoise still exist?
  - Trials still accruing and/or treating patients (& trials in development)
- What needs to be communicated to patients?
  - Patients on trial & patients that will be enrolled if trial continues

Considerations in Evaluating if New Trial Results Affect Equipoise of Existing Trials

- Primary Endpoint
  - Surrogate endpoint (Validated vs Non-validated/signal in disease & clinical setting; Possible change with new class of agents)
  - Consensus clinical benefit endpoint (survival, functional benefit, etc.)
  - Clinical relevance of magnitude of benefit regardless of endpoint type
- Patient Population
  - General patient characteristics (Demographics)
  - Local/Regional vs National vs Global participation
  - Biomarker Considerations

Considerations in Evaluating if New Trial Results Affect Equipoise of Existing Trials

- Trial Design
  - Trial phase
  - Clinical setting
  - Dose/schedule of Tx
  - Inclusion of QA/QC for Tx
  - Placebo vs active control
  - Similar assessment schedules
  - Statistical plan, interim monitoring, length F/U
- Trial Conduct
  - Design changes during trial; compliance issues
- Impact other endpoints
  - Toxicity / AEs
- Tx Feasibility/Availability
- Regulatory approvals
- Practice Guidelines changes

Decisions Based on Evaluation/Assessment

- Stop existing trial
- Temporary hold on new enrollments while trial is amended to address/incorporate new information and/or new agent(s) (e.g., design, treatments, statistical plan, informed consent)
- Continue existing trial

In all cases, there is communication to patients on study and to the trial investigators of new results & potential impact on study unless there is consensus that new results have no impact on existing trial (e.g., b/o significant differences in patient population, clinical setting, etc. between the new results and existing trial)

On-going Review, Dialogue, & Discussion on Regulatory Approvals (including Accelerated Approval)

A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics

Beaver JA, et al. *JAMA Oncol*. 2018;4(6):849-856

Review of all malignant hematology & oncology accelerated approvals (AAs) from 1992-2017.
64 products & 93 Indications: 55% verified benefit; 40% not yet complete/verified; 5% withdrawn.
"Only a small portion of indications under the AA program fail to verify clinical benefit."

Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval

Gyawali B et al. *JAMA Intern Med*. 2019;179(7):906-913.

"Confirmatory trials for one-fifth (19 of 93) cancer drug indications approved via FDA's AA pathway demonstrated Improvements in overall patient survival. Reassessment ....may be necessary to obtain more clinically meaningful information."

NIH NATIONAL CANCER INSTITUTE 9

Recent Withdrawals of FDA Accelerated Approvals (AAs) of Immunotherapy Agents in Cancer Treatment

Agent	Cancer Type for AA Pathway	Clinical Setting/Indication for AA Pathway	Date Withdrawal
Atezolizumab	Advanced/Metastatic Urothelial Cancer	Disease progression during/following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant/adj tx with platinum-containing chemo	3/7/2021
Durvalumab	Advanced/Metastatic Urothelial Cancer	Disease progression during/following platinum-based chemotherapy or within progression within 12 months of neoadjuvant/adj tx with platinum-containing chemotx	2/22/2021
Pembrolizumab	Metastatic Small Cell Lung Ca	Disease progression on/after platinum-based chemotherapy and at least 1 other prior line of therapy	3/1/2021
Nivolumab	Metastatic Small Cell Lung Ca	Disease progression after platinum-based chemotherapy and at least 1 other line of therapy	12/29/2020

FDA also held ODAC Meeting April 27-29, 2021, to discuss 6 indications granted accelerated approval that have since reported results from a confirmatory trial(s) that have not verified clinical benefit.

NIH NATIONAL CANCER INSTITUTE 10

NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®)

NCCN Guidelines are developed & updated by 60 individual panels, comprising > 1,660 clinicians & oncology researchers from the 31 NCCN Member Institutions. These panel members are multidisciplinary, disease- and issue-specific subspecialists who are clinicians, researchers, and advocates. https://www.nccn.org/

NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence; uniform NCCN consensus
Category 2A	Based upon lower-level evidence; uniform NCCN consensus
Category 2B	Based upon lower-level evidence; there is NCCN consensus
Category 3	Based upon any level evidence, major disagreement intervention is appropriate

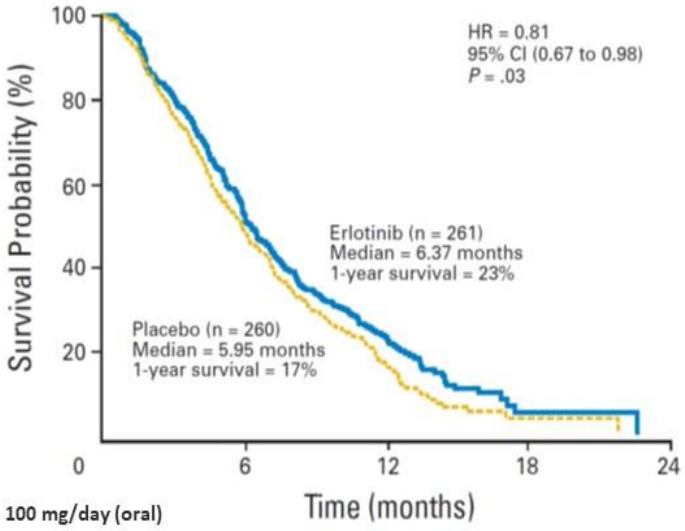
NCCN Categories of Preference

Preferred Intervention
Other Recommended Intervention
Useful in Certain Circumstances

2 Examples (Past/Present) of New Clinical Trial Results/Regulatory Approvals Affecting Existing Trials

- Most changes in standard of care reflect strong clinical trials results (with regulatory approval if a new agent/new indication is involved)
- Purpose here is to provide cautionary examples of how uncertainty exists in some situations & how that might be handled with respect to on-going trials & those in development
- These examples illustrate concerns regarding the clinical benefit of the new information due to its magnitude in overall or particular patient populations
  - Erlotinib in Combination with Gemcitabine in Advanced/Metastatic Pancreatic Cancer (FDA Approval 2005)
  - Nivolumab in Advanced/Metastatic Gastric, GEJ, Esophageal Adenocarcinoma (FDA Approval 2021)

Erlotinib w/ Gemcitabine in Advanced Pancreatic Cancer



100 mg/day (oral) Erlotinib Cohort

Moore MJ, Goldstein D, Hamm J, et al. JCO 2007 25:15, 1960-66

NIH NATIONAL CANCER INSTITUTE

ASCO Presentation – May 2005
FDA ODAC – Sept 2005 (10 to 3 vote)
FDA Full Approval – Nov 2005

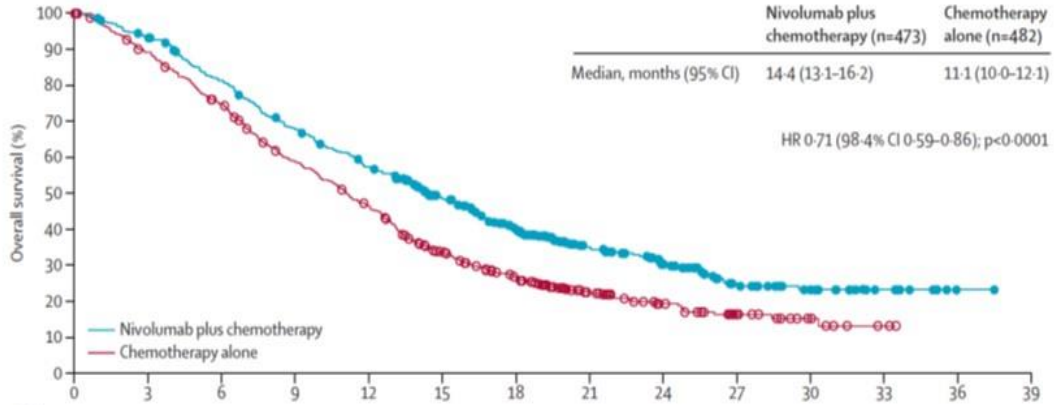
Despite this finding, subsequent trials conducted in same setting against gemcitabine alone & showed greater benefit:

- Celgene trial: nab-paclitaxel/gemcitabine vs gem alone – FDA approval Sept 2013
- French gov. trial: FOLFIRINOX vs gemcitabine – NEJM May 2011

NCCN Guidelines Feb. 25, 2021, for Erlotinib for Pancreatic Cancer: Under Other Recommended Regimens (Category 1). *"However, the panel notes that although this combination significantly improved survival, the actual benefit was small, suggesting only a small subset of patients benefit."*

13

Nivolumab + Chemo in Adv. Gastric/GEJ/Esoph Adenoca



	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)
Median, months (95% CI)	14·4 (13·1–16·2)	11·1 (10·0–12·1)

HR 0·71 (98·4% CI 0·59–0·86); p<0·0001

Number at risk (number censored)														
Nivolumab plus chemotherapy	473 (0)	438 (3)	377 (9)	313 (11)	261 (14)	198 (39)	149 (55)	96 (91)	65 (110)	33 (133)	22 (142)	9 (155)	1 (163)	0 (164)
Chemotherapy alone	482 (0)	421 (10)	350 (13)	271 (19)	211 (21)	138 (37)	98 (50)	56 (78)	34 (93)	19 (103)	8 (113)	2 (118)	0 (120)	0 (120)

For Patients with a PD-L1 CPS ≥ 5

NIH NATIONAL CANCER INSTITUTE

Janjigian YY, Shitara K, Moehler M, et al. Lancet 2021; 398: 27-40. Published Online June 5, 2021.

14

Concern About Benefit in Different Biomarker Populations

- Large, international, randomized phase 3 trial in patients with previously untreated, unresectable, non-HER2-positive disease regardless of PD-Ligand 1 (PD-L1) expression
- Dual primary endpoints of overall survival (OS) & progression-free survival
- Statistical plan tested OS first in patients with tumors with a PD-L1 combined positive score (CPS) ≥ 5, & if positive, then in those with PD-L1 CPS ≥ 1 tumors
- Trial investigators recognized "Relatively large % of patients in the study had tumors CPS ≥ 5 affects the magnitude of the benefit observed in patient with a CPS ≥ 1 & all randomized patients" – other exploratory analyses done that "suggests the magnitude of survival could improve…with longer follow-up."
- FDA approval in April 2021 without limitation based on PD-L1 biomarker

Patient Population Cohorts: Biomarker Cut-offs (PD-L1 CPS)

- Overall survival significance in Patient Cohort with PD-L1 ≥ 5 and all randomized patients irrespective of PD-L1 CPS level. However, concern around exploratory analyses on Patient Cohorts with PD-L1 <5.

Current Full Prescribing Information (FDA Label) - Exploratory Analyses:					
Patient Cohort	**Treatment Arm**	**Median Overall Survival**	**95% Confidence Interval**	**Stratified Hazard Ratio**	**95% Confidence Interval**
PD-L1 CPS<1	Nivolumab + Chemotherapy	13.1 months	95% CI: 9.8, 16.7		
	Chemotherapy Alone	12.5 months	95% CI: 10.1, 13.8	0.85	95% CI: 0.63, 1.15
PD-L1 CPS<5	Nivolumab + Chemotherapy	12.4 months	95% CI: 10.6, 14.3		
	Chemotherapy Alone	12.3 months	95% CI: 11.0, 13.2	0.94	95% CI: 0.78, 1.14

Concern About Benefit in Different Biomarker Populations

- Current NCCN guidelines (June 22, 2021): Category 1 for those with CPS ≥ 5 and Category 2b for those with CPS 1-4
- How would trials be affected by concerns about benefit in different patient populations? Will assessment by NCCN/others issue change over time?
- Approach under consideration in current randomized NCTN trial evaluating chemo +/- radiotherapy (RT) for oligometastatic esophagogastric cancers
  - Not to change drug regimen to I/O therapy (nivolumab) + chemotherapy for all
  - For patients with CPS ≥ 5, change control arm to I/O therapy + chemo
  - For patients with CPS 1-4, allow patients to receive I/O therapy + chemo or chemo alone, but stratify the patients at time of randomization
  - Amend trial design and informed consent

Impact of New/Emerging Changes in Standard Cancer Txs on Clinical Trial Enrollment

- Evaluation of new trial results, regulatory approvals, practice guidelines is by broad community of investigators, patients, healthcare providers & others
- Need to continue to follow the science & impact of new information, especially given the complexity of underlying biology of diseases
- Continuation or modification of existing trials requires in-depth evaluation of the equipoise of the research question as well as feasibility
- Design of new trials often includes plans to adjust design given potential future information from other trials
- Commitment to changing trials (including temporary accrual hold) to ensure patients are fully informed of new information & potential impact on care


NIH
NATIONAL
CANCER
INSTITUTE
www.cancer.gov
www.cancer.gov/espanol