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Phase I and II clinical trials

The clinician view

A Tale of two eras in Immunotherapy

Initiated in 1996

- **Morse MA**, Deng Y, Hull S, Coleman D, Nair S, Schlom J, Ryback ME, Gilboa E, Lyerly HK. A phase I study of active immunotherapy with carcinoembryonic antigen peptide (CAP-1)-pulsed, autologous human cultured dendritic cells in patients with metastatic malignancies expressing carcinoembryonic antigen. *Clin Cancer Res* 5: 1331-1338, 1999.

Study Design

- 3+3 design
- Dose: 1 x 10(7), 3 x 10(7), and 1 x 10(8) cells IV x 4
- A subset of the patients in the last group also received intradermal injections of 1 x 10(6) DCs.
- Subset received In111 labeled DCs IV, ID, SQ

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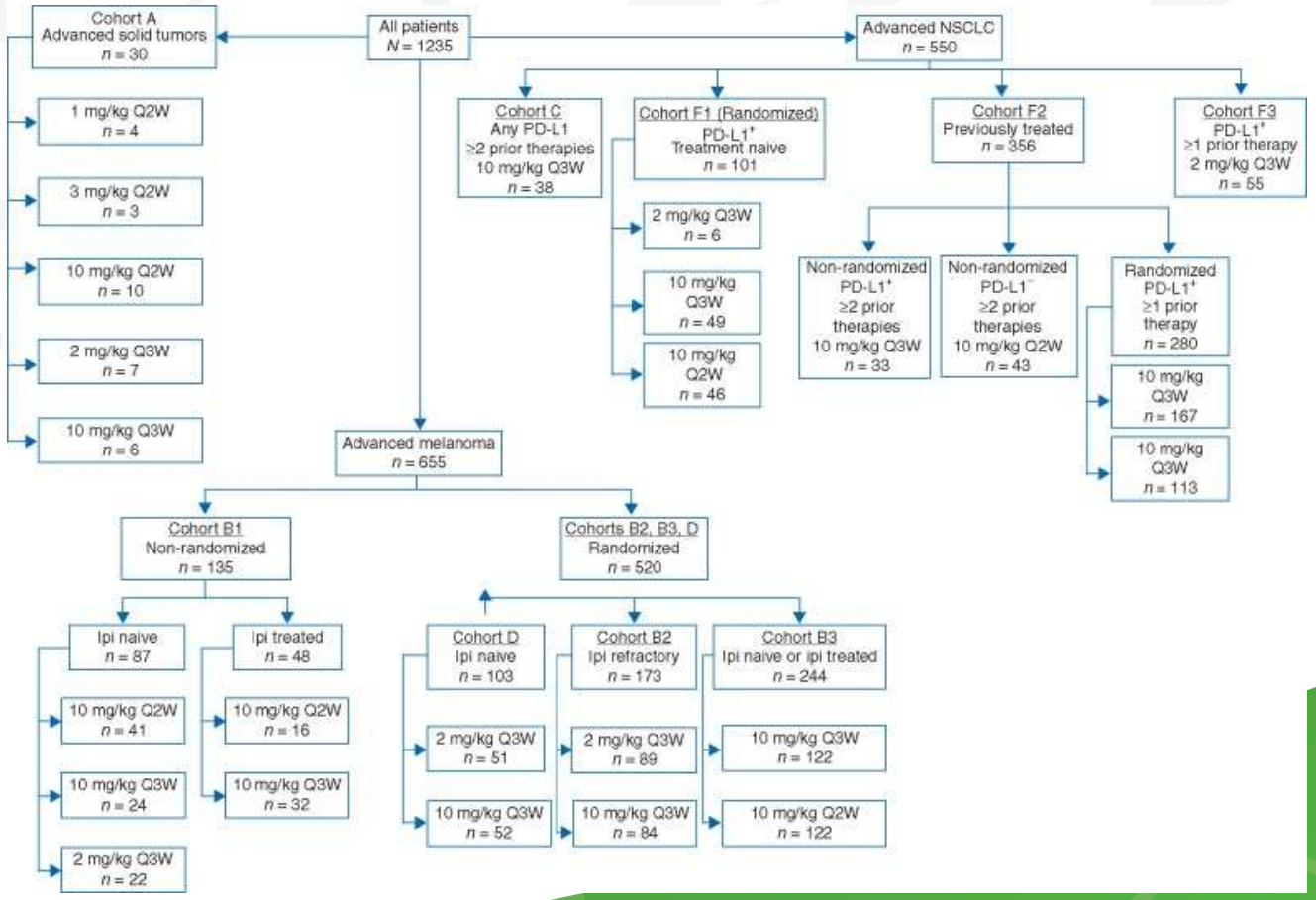
KEYNOTE-001



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Kang SP, Ann Oncol. 2017 Jun 1;28(6):1388-1398.

What's different

- Classic drug-development pathway:
  - Phase 1 (MTD, DLTs, safety, and tolerability) →
  - Phase 2 (efficacy assessment/dose refinement)→
  - Phase 3 (RCT to demonstrate efficacy/safety vs standard to support regulatory Kapproval in a single indication

- KEYNOTE-001
  - After standard 3+3 →
  - 6 randomized dose/schedule-comparison sub-studies
  - Nested phase-2-like studies in two oncologic indications—melanoma and NSCLC
  - training and validation sets for the development of the PD-L1 IHC companion diagnostic assay.

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Why is it different?

- Breakthrough designation
  - Intended to treat a serious or life threatening disease or condition
  - Preliminary clinical evidence that drug may give a substantial improvement in clinically significant endpoints

  - Expedited approval process
    - rolling reviews, smaller clinical trials, and alternative clinical trial designs

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Traditional Definitions

- **21 CFR § 312.21 - Phases of an investigation.**
- (a)Phase 1.

- (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

- (2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

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Traditional Definitions

- **21 CFR § 312.21 - Phases of an investigation.**
- (b)Phase 2. Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

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Identify MTD and recommended Phase II dose (RP2D)

Learn more about the drug before phase II

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What is happening in immunotherapy studies now?

- Phase Ia: for cancer therapies, generally multiple doses are given
  - Adaptive designs utilize real time data to make decisions on dosing
- Phase Ib:
  - Combinations of agents (established and experimental) are given
  - Expansion cohorts designed to study clinical activity in specific patient groups, study different dosing schemas, study other formulations, study relationship of biomarkers to outcome
    - Data from expansion cohorts may inform dosing recommended for later studies
    - Breakthrough designation-→FDA approval from earlier studies

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General challenges for PH1 clinical trials of immunotherapy

Immunotherapy

- Vast array of biologic products
  - MAbs, cells and cell derivatives, viruses, bacteria, cytokines, proteins/peptides, DNA, RNA
  - ADME/PK concepts may be less well understood or irrelevant
    - Quantifying the immunotherapy more challenging
- Efficacy and toxicity often indirect (require immune response) and may be unusual

Non-immunotherapies

- Well defined chemical entities and some Mabs and biologics not modulating immune response
  - Well established understanding of ADME/PK
  - Quantifying drug well understood (mol, mg)
- Efficacy and toxicity more direct and well characterized

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Using preclinical data to inform dose/schedule

- Was relevant animal model used ?
  - Human version of biologic may have no function in certain animal models
  - AA sequence of the extracellular domain of mouse PD-1 is only 62% identical to human; human PD-1 is 96% identical with Rhesus and Cynomolgus monkey PD-1
  - Pembrolizumab binds to Cynomolgus monkey, but not mouse PD-1
- Human immune response may vary from that of available models
  - Toxicities may not be observed in animal models (ex: TGN1412)
  - Use Minimal Anticipated Biological Effect Level (MABEL) rather than no observed adverse effect level (NOAEL) to predict starting dose?
- Allometric scaling may be irrelevant/may require different models (Lymphocytes in mice and humans are similar size, so cannot deliver as many lymphocytes to a mouse)
- Target of human therapy may not be found in animal models
  - Vaccine targeting CEA-→ are CEA transgenics the answer?
- Implanted tumors in animal models do not recapitulate spontaneously developing human tumors
- Rapid tumor growth in animal models results in administration schedules that could differ from human planned studies

Dose-efficacy/dose-toxicity relationships for immunotherapeutic agents may be different than drugs

- No MTD may exist-all feasible doses may be tolerated
  - May be limited by how much of drug can be produced or delivered
  - Preferred endpoint may be optimal biologic dose
    - Anti-PD-1 Abs fully saturate PD-1: No utility for escalating dose above this amount
    - Flat dosing may be acceptable
- Pre-administration may affect tolerability
  - Single dose of IL-12 protected against subsequent severe IL-12 toxicity (Leonard, Blood 1997 90:2541-2548)
- Pre-existing immunity may affect dose that can be delivered (ex: immunity against vaccinia or adenovirus reduce ability to administer viruses later)
- Does 3+3 design capture the full extent of toxicities?
  - Stay tuned for statistician lecture

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New considerations for toxicity assessment/management

- Toxicities not previously seen
  - irAEs are different than usual AEs seen with drugs
    - Recognition and aggressive management critical
  - Unexpected AEs due to cross reactivity (MAGE-TCR target cross reacts with Titin)
- Late onset toxicity
  - Immune related adverse events tend to develop at various delayed times.
  - Given durable efficacy, immunotherapies may be administered for very prolonged periods and patient tolerance for toxicity may change over time
  - Is there a need for very long term follow-up (if the immunotherapeutic is potentially called a gene therapy).
  - Live therapeutic could have toxicity years later (Listeria vaccine)

Complexities of escalating multiple agents

- Drugs with independent efficacy or toxicity versus drugs with synergistic efficacy or toxicity
- Biologic rational for combination versus pragmatic combination
- Studies combining novel agents versus established agent + novel agent
- Expansion cohorts of different combinations (Drug A + B, A+C, A+D, etc.)
  - Using data from one expansion cohort to inform another cohort
    - Administrative complexity for CRO or sponsor

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Usual endpoints may not apply

- May not have tumor regression;
  - rather delay progression and prolong survival without significant tumor shrinkage
  - Durability of response in the few responders may be important
- PFS may not be prolonged but OS may be
- Biologic endpoints are critically important
  - Vaccines: induction of antigen-specific immune response
  - Tumor infiltration with T cells
  - Changes in cytokine profile within tumor tissue

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Biomarker challenges

- Deciding whether enrollment should be based on biomarker
  - Potential for greater efficacy if biomarker used
  - Limiting group of patients who might benefit from drug
- Are there toxicity biomarkers?
  - Does toxicity differ in subgroups (e.g., hepatitis B/C + HCC patients)
  - Could toxicity events be biomarkers (hypothyroidism)
  - Could toxicity vary between people with different underlying diseases or extent of tumor
  - Is toxicity different depending on sites of tumor (such as pulmonary sites).

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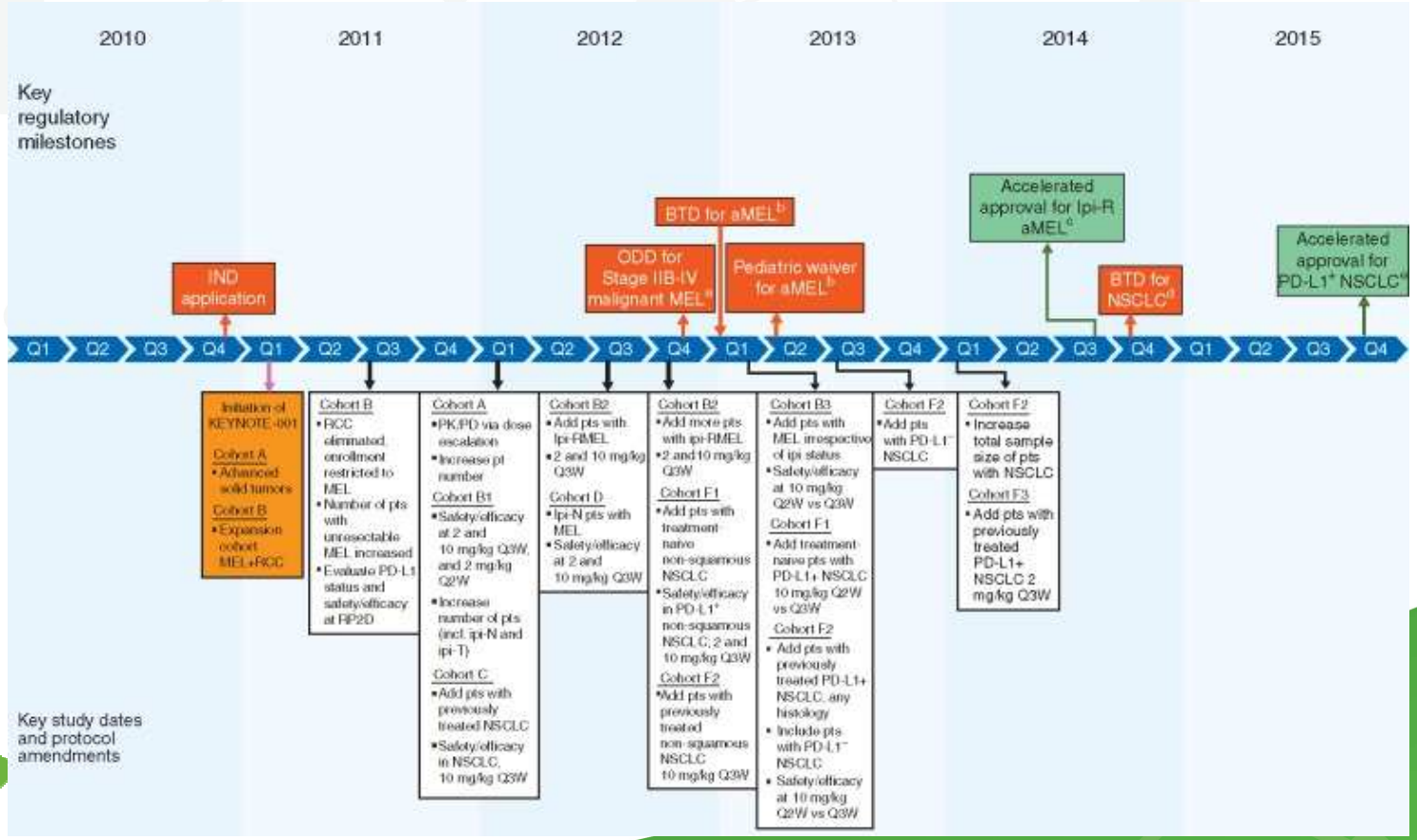
Successful example: KEYNOTE-001



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Cautionary example:
CD28 superagonist TGN1412

- 3/13/2006:
  - 6 healthy volunteers received IV TGN1412 around same time
  - all developed life-threatening cytokine-release syndrome
  - All treated in ICU and survived
- What happened?
  - Preclinical models did not predict this toxicity
  - Mice housed in clean rooms have few CD4+ effector memory T cells which release the cytokines that caused CRS
  - Cynomolgus macaques' effector memory T cells lose CD28 after activation
  - Human PBMC do not release cytokine with TGN1412 but when in close contact as they would be in tissues, then secrete cytokine

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Summary

- Blurring of phase I/II lines
- Trying to speed up a determination of MTD and recommended dose for further testing
- Understand imitations of preclinical testing:
  - Chose MABEL vs NOAEL?
- Learn as much as possible about drug in early phase: Expand cohorts aggressively?
- Look for opportunities for regulatory approvals early in course
- Do expansion cohorts (nested phase II) take the place of formal phase II now?

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