Critical Issues in Immunotherapy Clinical Trials Session

Design issues in the immunotherapy combinatorial trials

15 min

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How to rationally combine therapies and chose the best endpoints?

- Design the clinical development plans of future agents through:
  - Deeper understanding of the mechanism of action in early clinical testing
  - Pivotal trials that focus on the strengths of the new agents and the potential benefits demonstrable in clinical trials

Perspective

Clinical Cancer Research

New Challenges in Endpoints for Drug Development in Advanced Melanoma

Antoni Ribas[1], Peter Hersey[2], Mark R. Middleton[3], Helen Gogas[4], Keith T. Flaherty[5], Vernon K. Sondak[6], and John M. Kirkwood[7]

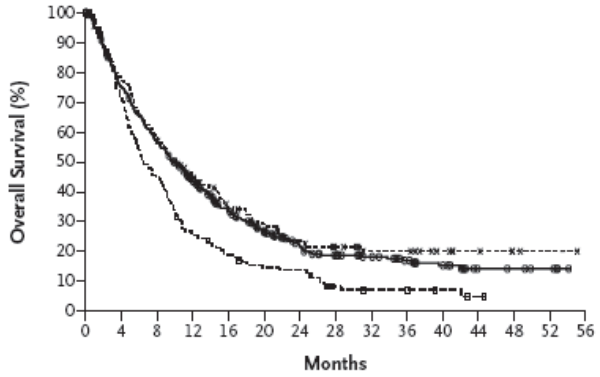
Clin Cancer Res; 18(2) January 15, 2012

Different effects of immunotherapy and targeted therapy for melanoma in randomized clinical trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma



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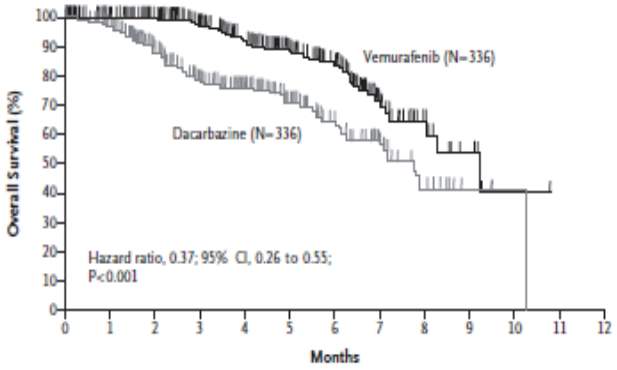
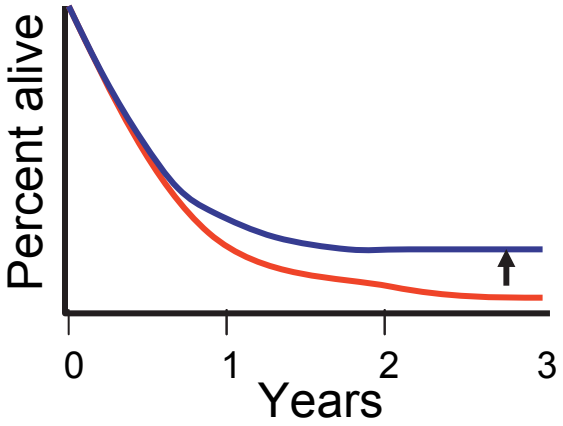
ORIGINAL ARTICLE

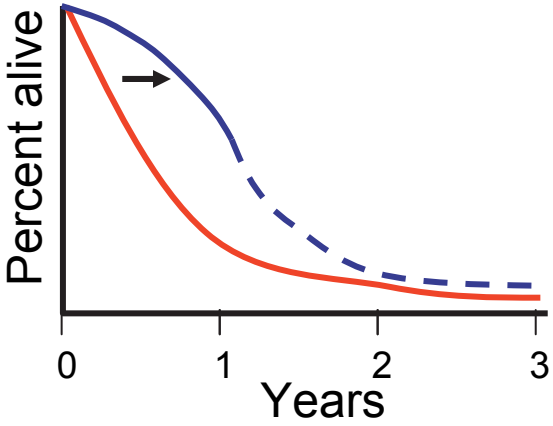
Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation



Immunotherapy



Targeted therapy

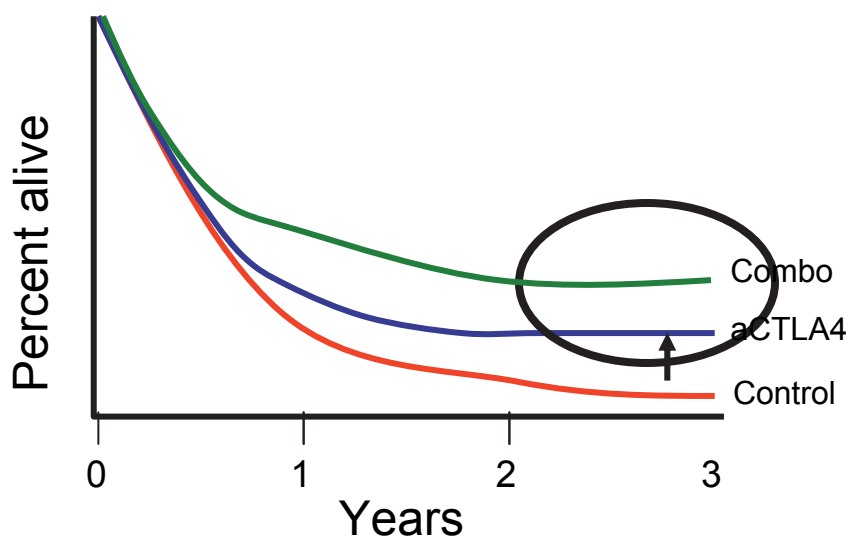


Relative merits of different endpoints in melanoma clinical trials

Endpoint	Advantages	Limitations
Overall Survival	Gold standard	Quality of life not necessarily considered. Will be difficult to achieve when control groups have high survival. High patients numbers then needed. Symptom relief not taken into account. Cross over designs make overall survival outcomes difficult to achieve. Long term outcomes confounded by the clinical availability of other agents with similar mechanism of action.
Progression Free Survival	Outcome more rapid and allows rapid selection of agents. If very prolonged may be an endpoint of merit in its own right.	Not necessarily related to overall survival. Quality of life not necessarily considered.
Response Rate	Valuable in single arm studies if "unprecedentedly" high	Not necessarily a surrogate endpoint for overall survival benefit. Difficult to achieve when developing new agents with similar mechanism of action with already high response rates.
Quality of Life	May be a valid endpoint irrespective of effects of other endpoints.	No information about benefits based on time-to-event endpoints.

Examples of adapted clinical development plans (1)

- Combination of two non-antigen specific immunotherapies:
  - Anti-CTLA4 + IL-2, IL-21, IFN



- In early clinical testing, focus on detecting an increased frequency of durable tumor responses
- Focus on OS instead of PFS for pivotal clinical trials
- Long term follow up of patients to detect changes at the tail

PFS vs OS in the pivotal ipilimumab clinical trials

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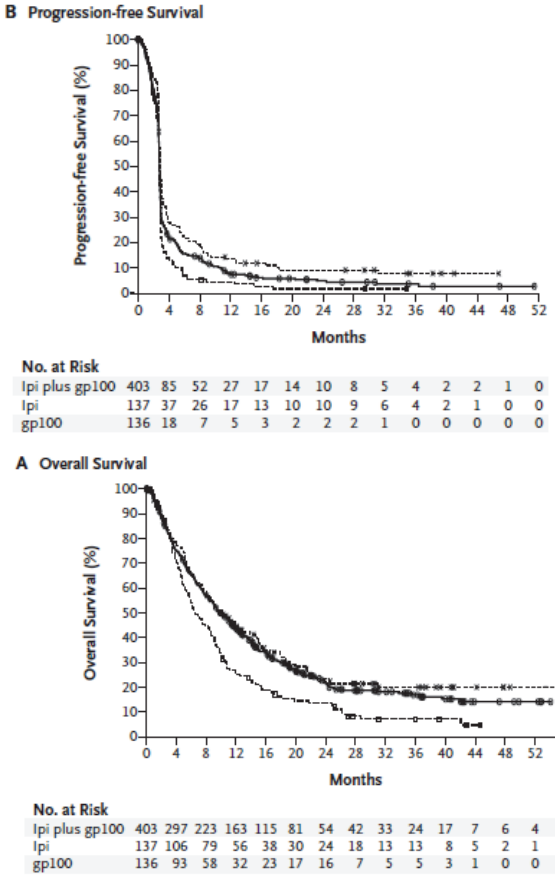
ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.D., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.



PFS

OS

HR = 0.66 > 3 years

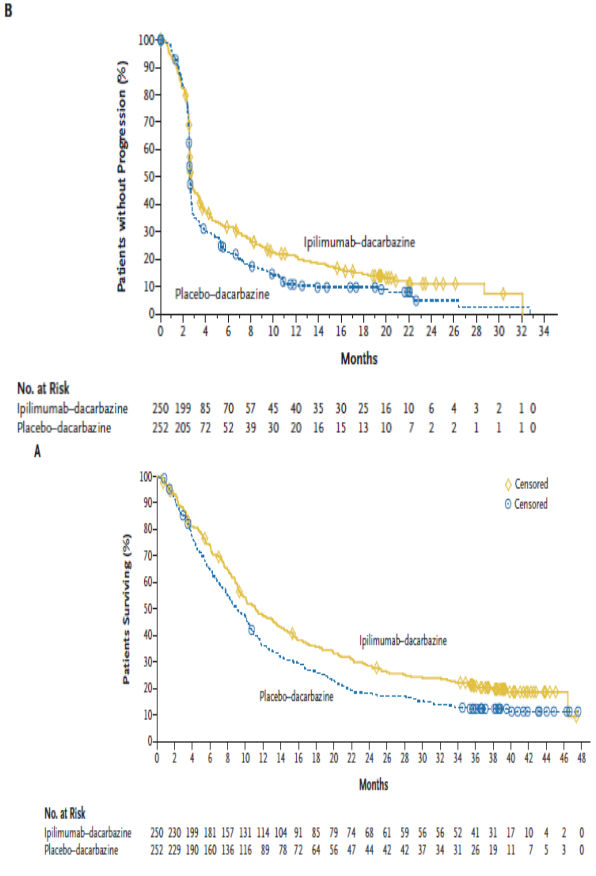
HR = 0.72 > 3 years

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

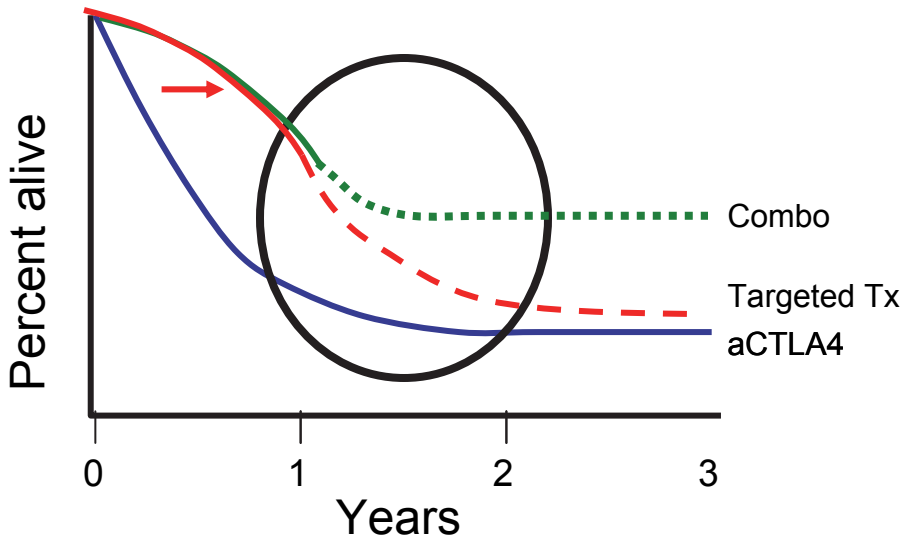
Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D.,



Examples of adapted clinical development plans (2)

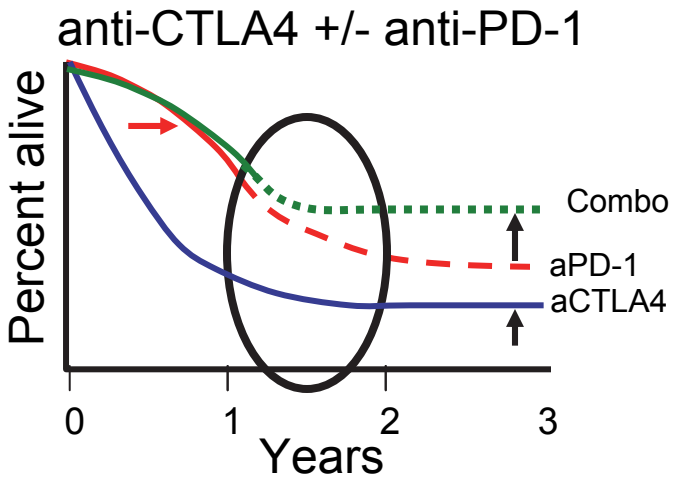
- Combination of immunotherapy and oncogene-targeted therapy:
  - Anti-CTLA4 + targeted oncogene inhibitors

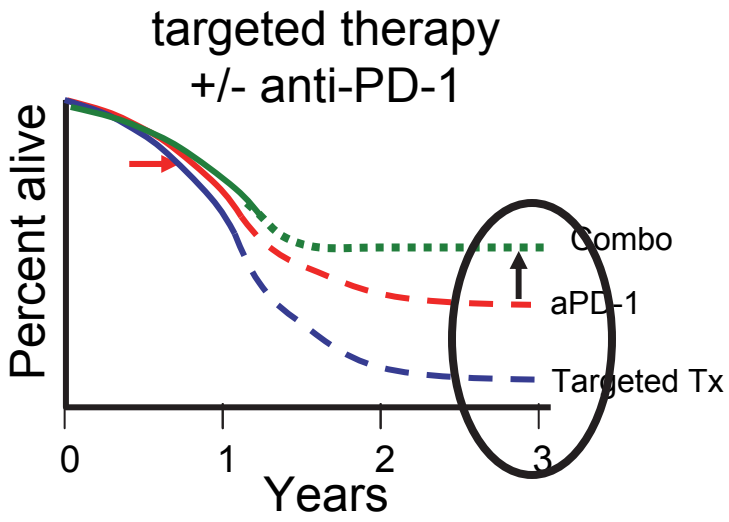


• In early clinical testing, focus on detecting if the immunotherapy results in increased duration of the targeted therapy-mediated tumor responses
• Focus on PFS for pivotal clinical trials
• No need for very long follow up of patients to detect changes at the tail

Examples of adapted clinical development plans (3)

- Combination with anti-PD-1 antibodies:
  - Anti-PD-1 + anti-CTLA4
  - Anti-PD-1 + oncogene inhibitors





• Focus on PFS if compared to anti-CTLA4
• Focus on longer term OS if compared to targeted therapies