Phase II and III Immunotherapy Clinical Trials

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Disclosures

I work for a non-profit (ASCO)

I am the primary statistician for the TAPUR study, a precision medicine phase II basket trial with 17 different treatment regimens, including “Nivolumab and Ipilimumab” and “Pembrolizumab”

I serve on a DSMB for Deciphera Pharmaceuticals (although have not received or requested compensation for my DSMB service in >2 years).

No other conflicts to report

Topics

Levels of Evidence

Endpoints

Trial types

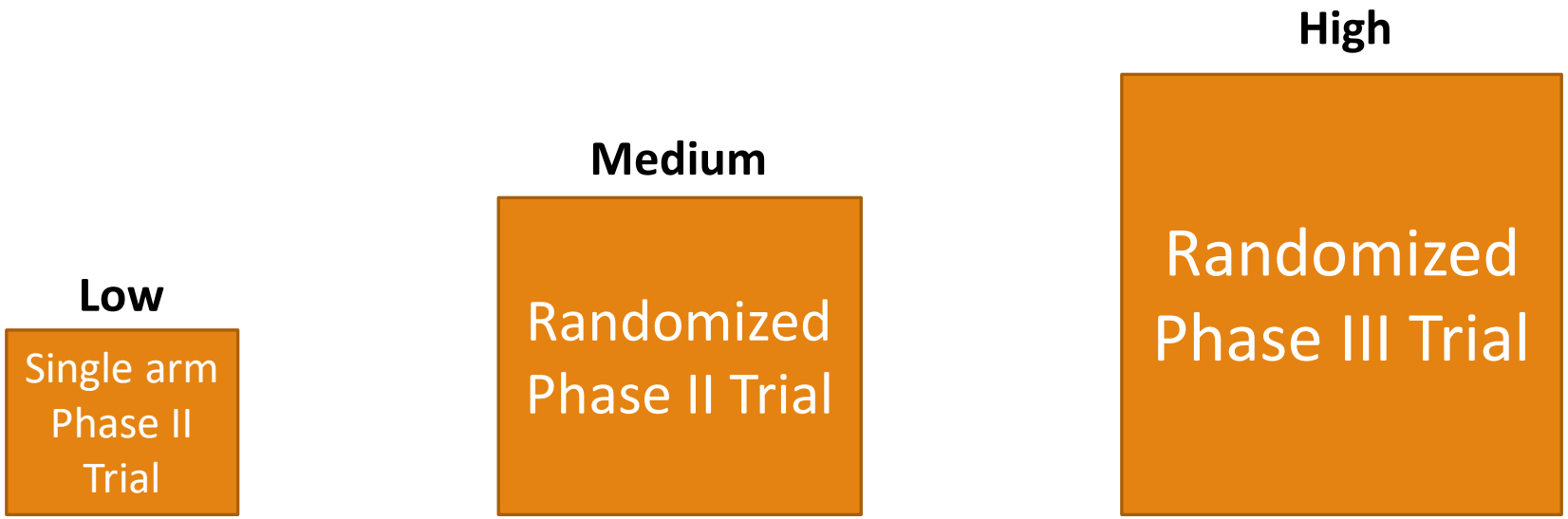
- Single Arm Phase II trials
- Randomized Phase II Trials
- Randomized Phase III Trials

Data display and interpretation

Challenges and Considerations for Immunotherapy Trials

- Interpreting trials with cross-over
- Comparing to traditional therapies

Levels of Evidence of Efficacy



What makes a cancer therapy “efficacious”?

It delays time to death, compared to other available treatments

It maintains or improves quality of life

Assumptions regarding tumor burden:

- Shrinking tumor burden **should** lead to longer survival
- Delayed progression **should** lead to longer survival

Minimizing toxicities (adverse events, especially serious ones) is important

Common Efficacy Endpoints in Phase II and III trials

Objective Response (OR):

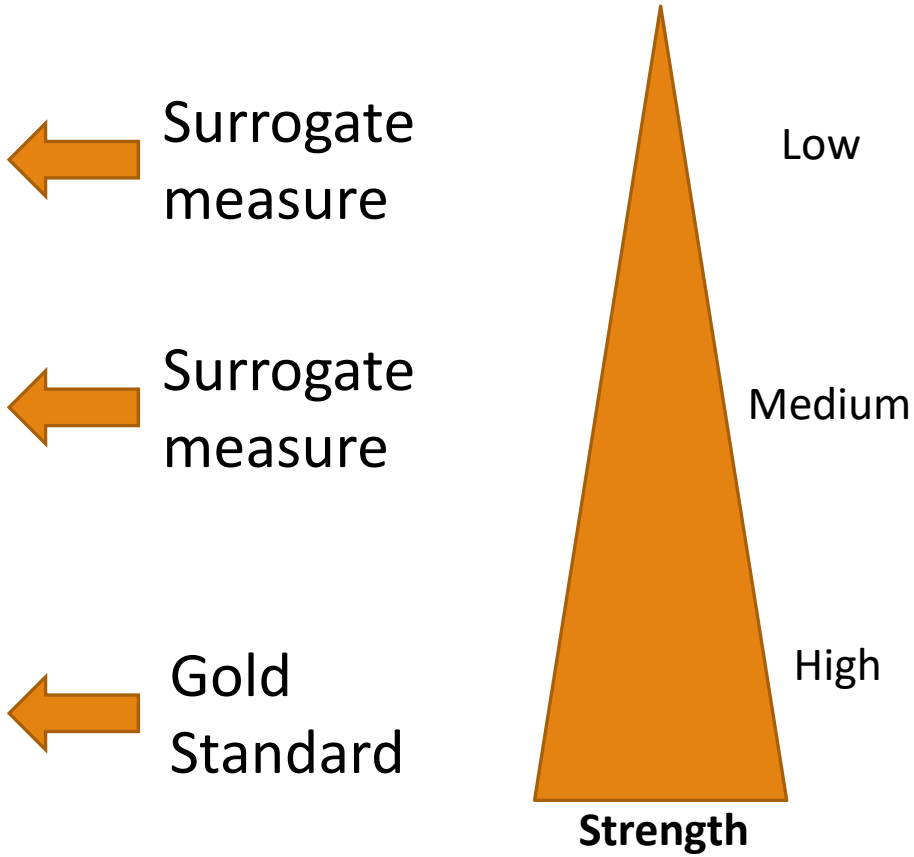
- Partial or complete tumor response
- Significant shrinkage of 'target lesions' and no new lesions.
- **RECIST criteria**: Response Evaluation Criteria in Solid Tumors
- **ir-RECIST criteria:** Immune-related Response Evaluation Criteria In Solid Tumors

Progression-Free Survival (PFS, or ir-PFS):

- Time from treatment initiation (or randomization) until PROGRESSION or DEATH from any cause
- Progression based on **RECIST** or **ir-RECIST**

Overall Survival (OS):

- Time from treatment initiation (or randomization) until DEATH



Common Endpoint in Cancer Immunotherapy Trials

Duration of Response (DOR)

- Time from Objective Response (OR) to disease progression
- Can only be measured in patients who have an objective response

Why **DOR** in cancer immunotherapy trials?

- Some patients have an exceptional response with long duration.
- Different than in chemotherapy which tends to delay progression in patients with metastatic disease
- Look for ‘swimmer plots’ and ‘spider plots’

Durable Response Rate (DRR)

- Objective response (partial or complete response) lasting at least 6 months (or other length of time)
- Short term responses often do not translate into meaningful improvements in survival
- More practical for immunotherapy trials

Swimmer Plot

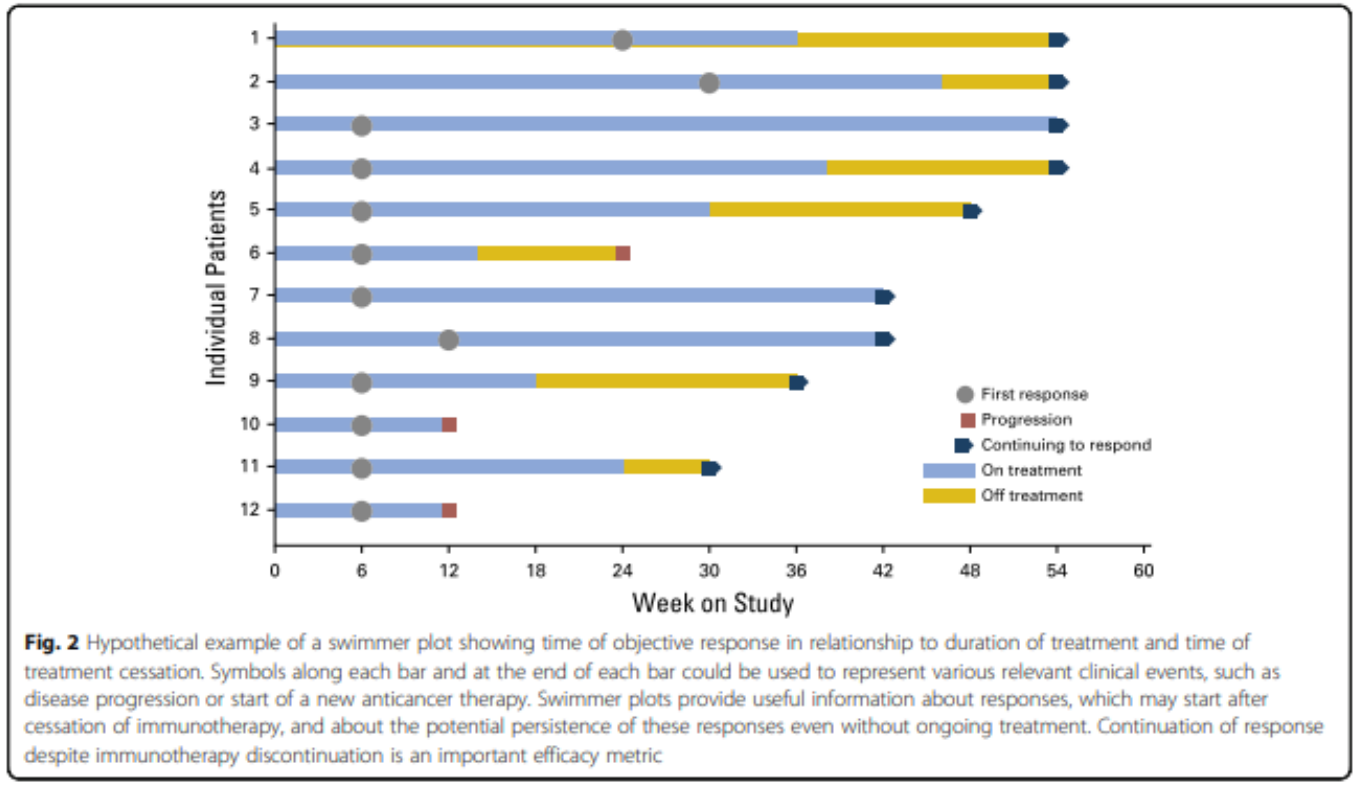


Fig. 2 Hypothetical example of a swimmer plot showing time of objective response in relationship to duration of treatment and time of treatment cessation. Symbols along each bar and at the end of each bar could be used to represent various relevant clinical events, such as disease progression or start of a new anticancer therapy. Swimmer plots provide useful information about responses, which may start after cessation of immunotherapy, and about the potential persistence of these responses even without ongoing treatment. Continuation of response despite immunotherapy discontinuation is an important efficacy metric

Tsimberidou, Levit, Schilsky, et al. "Trial Reporting in Immuno-Oncology (TRIO): an American Society of Clinical Oncology-Society for Immunotherapy of Cancer statement", Journal for Immunotherapy of Cancer, 2019: 6(108).

Spider Plot

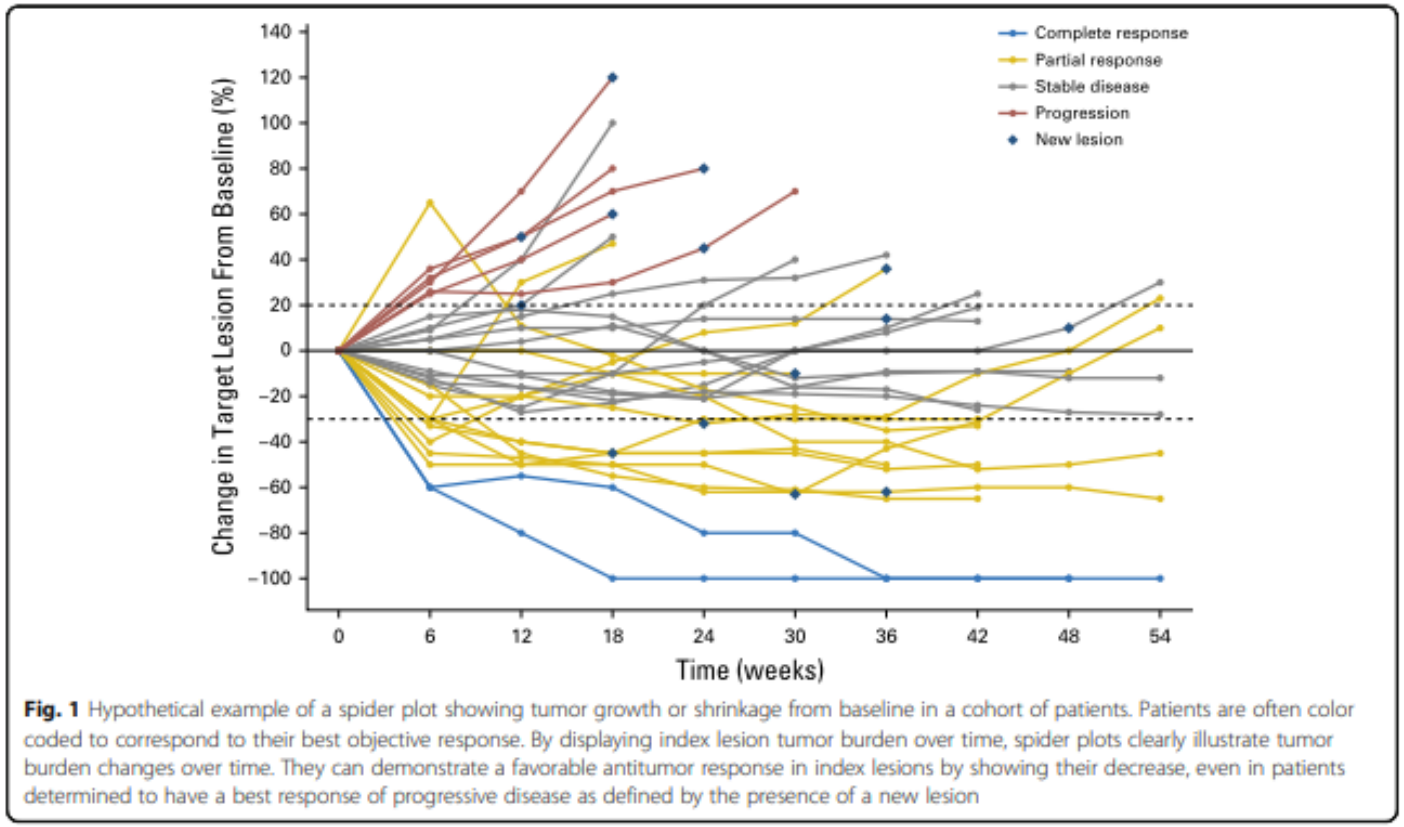


Fig. 1 Hypothetical example of a spider plot showing tumor growth or shrinkage from baseline in a cohort of patients. Patients are often color coded to correspond to their best objective response. By displaying index lesion tumor burden over time, spider plots clearly illustrate tumor burden changes over time. They can demonstrate a favorable antitumor response in index lesions by showing their decrease, even in patients determined to have a best response of progressive disease as defined by the presence of a new lesion

Tsimberidou, Levit, Schilsky, et al. "Trial Reporting in Immuno-Oncology (TRIO): an American Society of Clinical Oncology-Society for Immunotherapy of Cancer statement", Journal for Immunotherapy of Cancer, 2019: 6(108).

Single Arm Phase II

Follows Phase I, initial look at efficacy

Enroll all patients on a SINGLE treatment arm

- Sample size usually around 20 to 50 patients
- Common endpoint is **Objective Response** (RECIST or ir-RECIST)
- Can be combination therapy

Common when the target patient population is relatively RARE

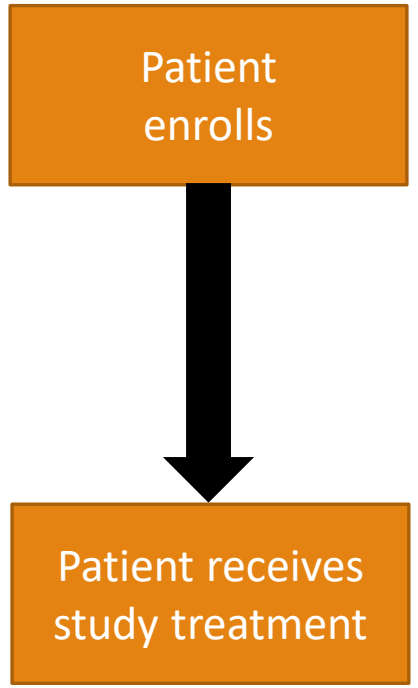
- Biomarker required for eligibility
- Rare cancer

Benefits

- Relatively small sample size

Limitation

- Without a comparator arm, difficult to conclude “success”



Lancet Oncology, May 2020, 21(5):655-663

Primary objective: To estimate the proportion of patients who have a brain metastasis response.

Endpoint: brain metastasis response

Sample size: Target N = 44 (actual N = 37)

25% response rate considered “success”

Results: 30% response rate observed

Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial

Sarah B Goldberg, MD • Kurt A Schalper, MD • Prof Scott N Gettinger, MD • Amit Mahajan, MD • Prof Roy S Herbst, MD • Anne C Chiang, MD • Prof Rogerio Lilenbaum, MD • Frederick H Wilson, MD • Sacit Bulent Omay, MD • Prof James B Yu, MD • Lucia Jilaveanu, PhD • Thuy Tran, MD • Kira Pavlik, MPH • Elin Rowen, MSN • Heather Gerrish, BSN • Annette Komlo, MBA • Richa Gupta, BS • Hailey Wyatt, BS • Matthew Ribeiro, BS • Prof Yuval Kluger, PhD • Geyu Zhou, BSc • Wei Wei, PhD • Prof Veronica L Chiang, MD

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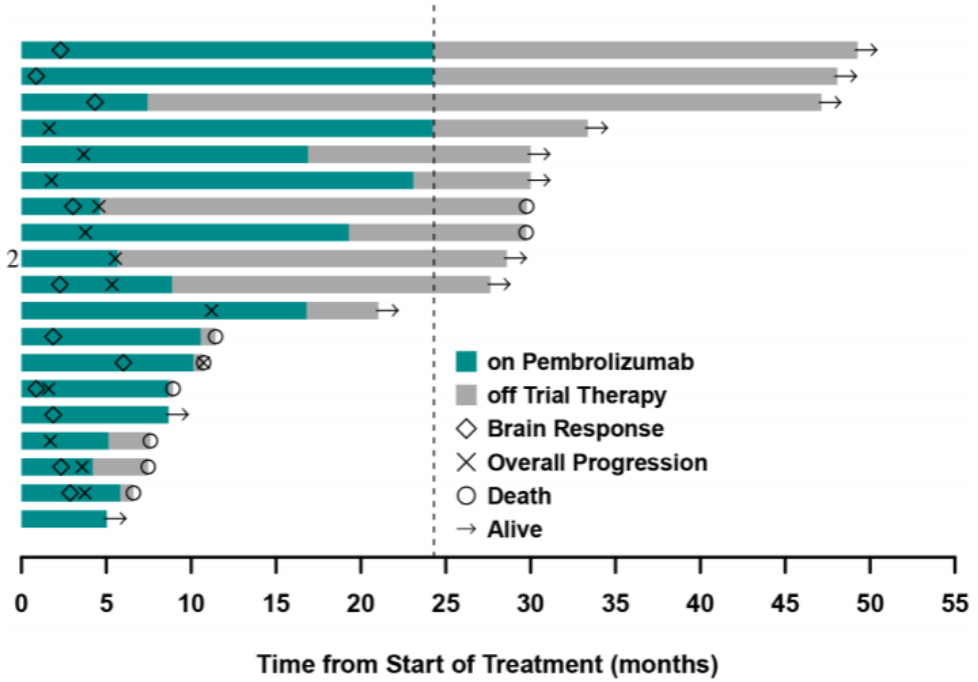

Swimmer plot including patients who had a brain metastasis response or remained on trial for at least 4 months (19 patients).

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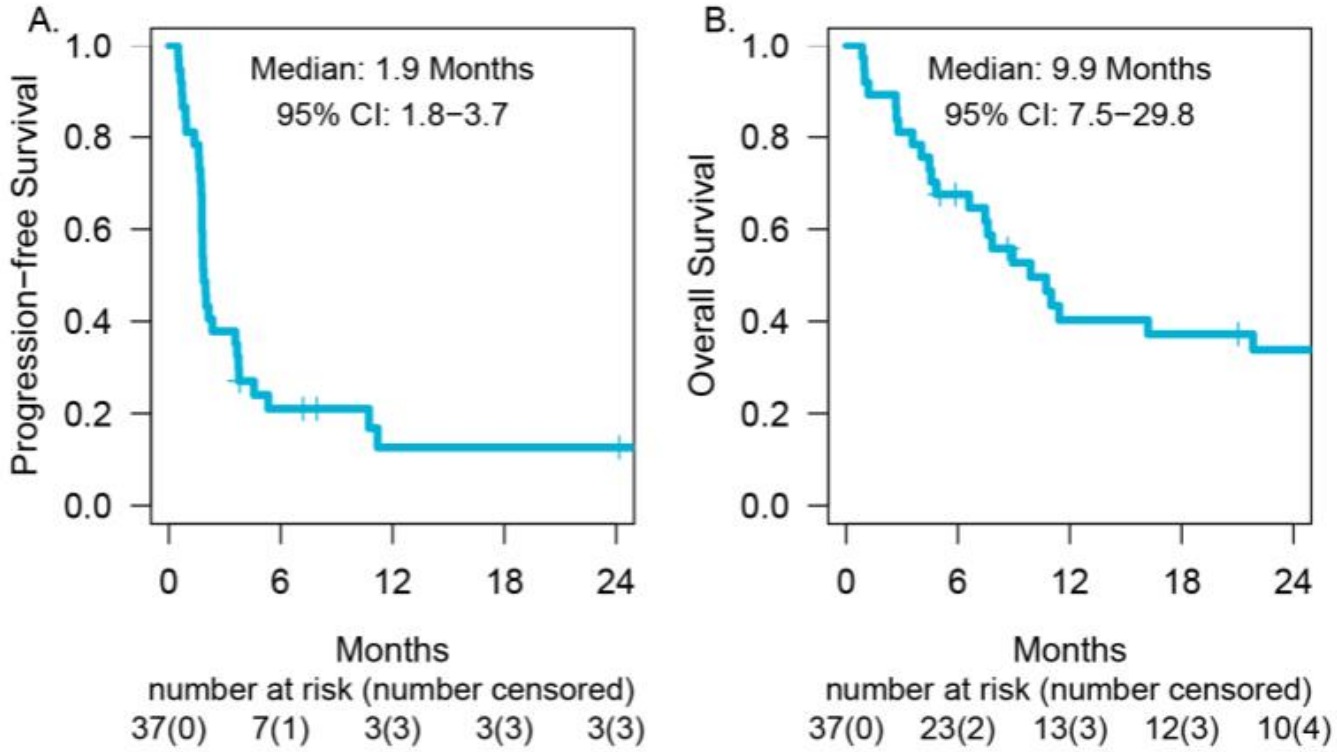


Figure 3. Progression-free survival
(A) and overall survival (B) for patients with NSCLC and brain metastasis treated with pembrolizumab in cohort 1 (PD-L1 expression ≥ 1%).

Phase II Basket Trials

Precision medicine

Tests how well a new drug or other substance works in patients who have different types of cancer that all have the same mutation or biomarker. (NCI, www.cancer.gov)

Focus is more on the genetic/genomic make-up of the tumor than on the site of the tumor

Example: TAPUR (Targeted Agent and Profiling Utilization Registry) Trial

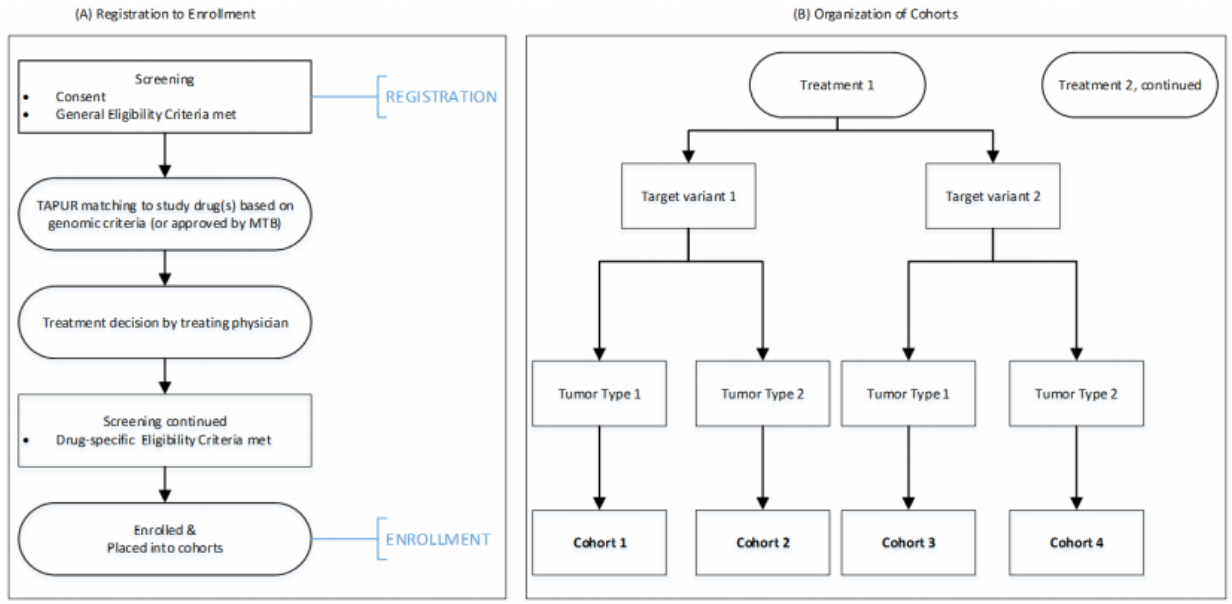


Figure 1:
Participant registration, enrollment and cohort assignment process. Panel A displays the process by which participants are registered and enrolled into the study. Panel B displays the organization of the cohorts for analysis which are grouped by treatment, targeted variant and tumor type.

Mangat, Halabi, Bruinooge et al., JCO Precision Oncology, 2018

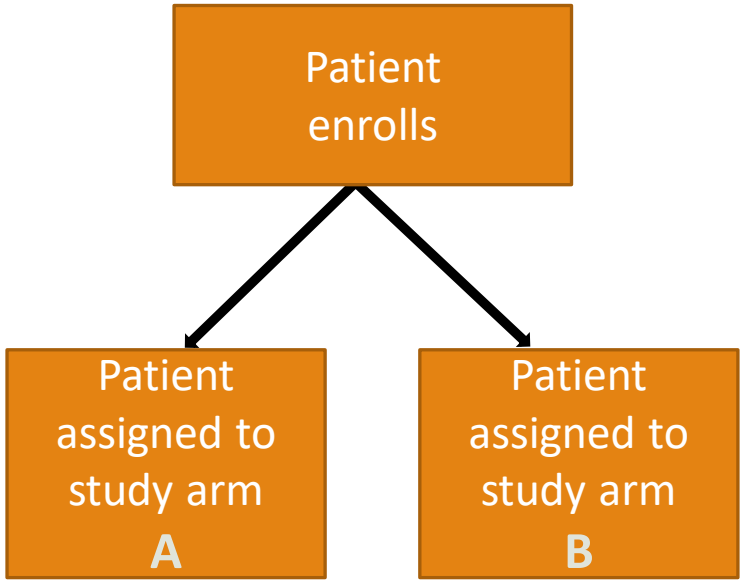
Randomized Phase II Trials

At least two treatment groups

Patients are randomly assigned to groups
- Might be masked (i.e., arm assignment is unknown)

Comparison arms can take different forms
- Combination vs. single agent
- Two different doses or schedules of same treatment
- Experimental agents vs. standard of care

What makes it phase II vs. phase III?
- Endpoint choice
- Sample size (~50 to several hundred patients)



Phase III usually still required after a “successful” randomized phase II trial.

Randomized Phase II example

Annals of Oncology. 2013 Jan;24(1):75-83

Design: Patients with chemotherapy-naïve ED-SCLC were randomized 1: 1: 1 to receive paclitaxel/carboplatin with either (A) placebo or (B) concurrent ipilimumab or (C) phased ipilimumab

Objective: Compare ir-PFS in ipilimumab groups vs. placebo

Sample size: Target N = 130 (~ 43 per group)

Primary endpoint: ir-PRS

Randomized Phase

Annals of Oncology. 2013 Jan;24(1):75-83

Design: Patients with chemotherapy-naïve ED-SCLC were randomized 1: 1: 1 to receive paclitaxel/carboplatin with either (A) placebo or (B) concurrent ipilimumab or (C) phased ipilimumab

Objective: Compare ir-PFS in ipilimumab groups vs. placebo

Sample size: Target N = 130 (~ 43 per group)

Primary endpoint: ir-PRS

Result: ir-PFS in phased ipilimumab has longer ir-PFS than placebo

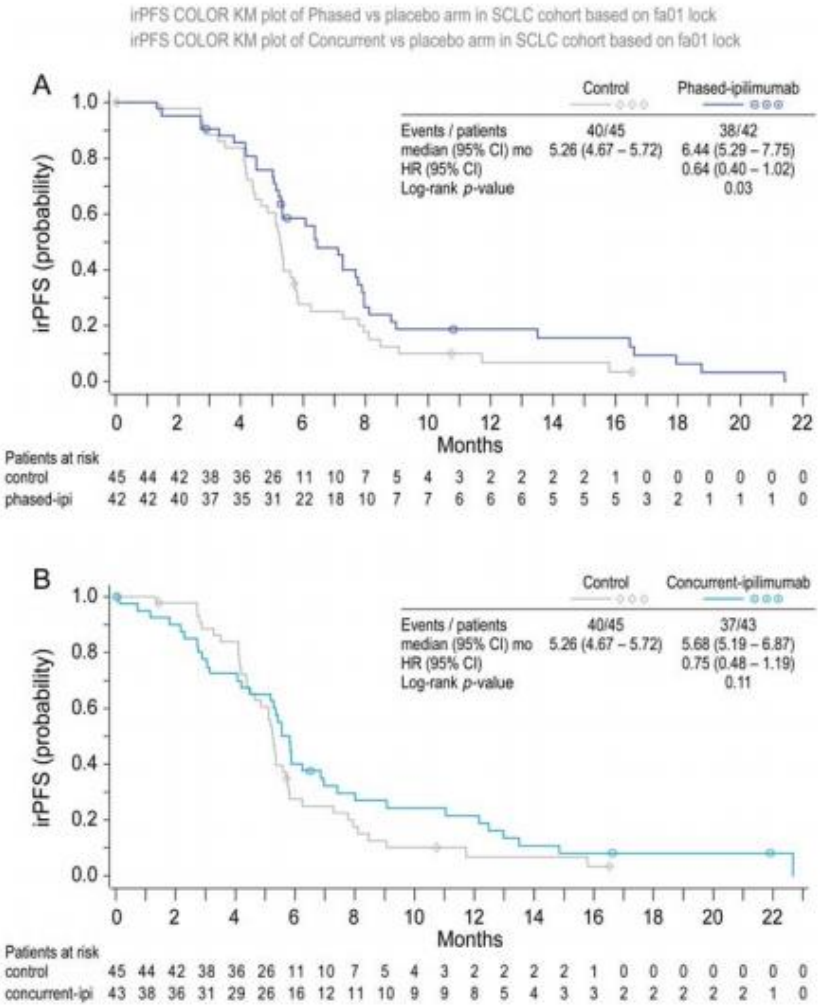


Figure 2. Kaplan–Meier plots for progression-free survival (PFS) per immune-related (ir) response criteria (irPFS). To account for the unique tumor response patterns to ipilimumab, immune-related response criteria (irRC) was proposed. Per irRC, new lesions, whether measurable or not, were not considered progression. Measurable new lesions were rather added to the index lesions to obtain total tumor burden, and a ≥25% reduction in this total tumor burden from nadir was defined as immune-related progression. irPFS was defined as the time from the randomization to immune-related progression [as determined by an Independent Radiologic Review Committee (IRRC)] or death. As indicated by symbols, patients who neither progressed nor died were censored on the date of last tumor assessment. *P*-values are based on an unstratified log-rank test with a one-sided α of 0.1.

Considerations for Trial Designs

Evaluability of patients:

- Patients who leave the study for reasons unrelated to treatment or disease?
- Patients who enroll but receive no therapy or just a small amount (< 1 cycle) of treatment?

Timing of measurements

- When OR or PFS is endpoint, how often to assess disease?
- Needs to be consistent with other trials in same population
- Should be convenient for patients (i.e., time it with treatment visit)

Quality of Life and/or Patient Reported Outcomes

- Important to ensure patient well-being is captured, assessed, compared.

Challenges in Immunotherapy Trials

Pseudo-progression

- "Pseudo-progression is a phenomenon in which an initial increase in tumor size is observed or new lesions appear, followed by a decrease in tumor burden; this phenomenon can **benefit patients receiving immunotherapy but often leads to premature discontinuation of treatment owing to the false judgment of progression**."
- Use ir-RECIST to help mitigate issue

Delayed responses

- Different than cytotoxics
- Challenging for adaptive trial designs using OR as endpoint

Non-specific or heterogeneous adverse event (AE) profile

- Traditional anti-cancer agents have predictable and/or consistent toxicities
- Immunotherapies affect patients in various ways.
  - Attribution of AEs affected
  - Patterns of AEs harder to discern

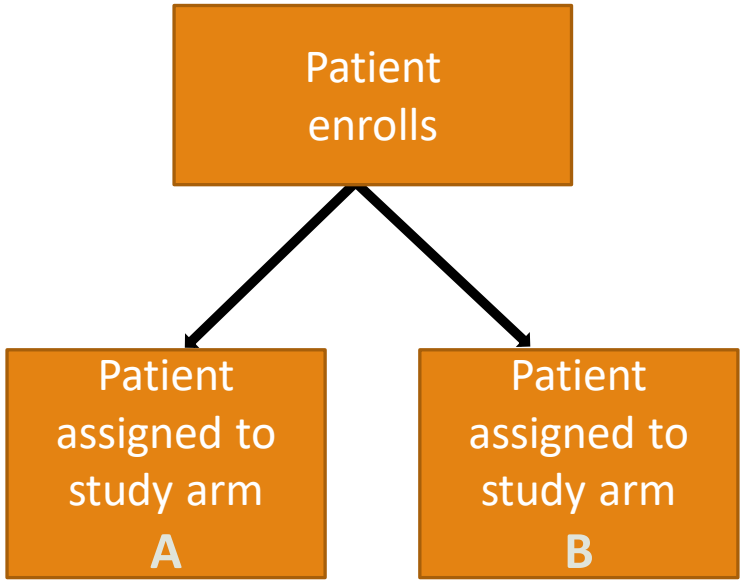
Randomized Phase III Trials

Similar to randomized phase II, but designs include:
- More relevant endpoint
- Larger sample size
- Inferences are more definitive; less exploratory

Often have overall survival as the primary endpoint
- More challenging as more treatment options are available
- “Cross-over” can confound inferences

“Powered” to detect a clinically meaningful difference
- That is, sample size is sufficiently large.

Designed to change treatment paradigm
- Limited comparisons considered
- Usually, experimental regimen vs. standard of care



Randomized Phase III Trial Example

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial

James Larkin, David Minor, Sandra D'Angelo, Bart Neyns, Michael Smylie, Wilson H. Miller Jr, Ralf Gutzmer, Gerald Linette, Bartosz Chmielowski, Christopher D. Lao, Paul Lorigan, Kenneth Grossmann, Jessica C. Hassel, Mario Sznol, Adil Daud, Jeffrey Sosman, Nikhil Khushalani, Dirk Schadendorf, Christoph Hoeller, Dana Walker, George Kong, Christine Horak, and Jeffrey Weber

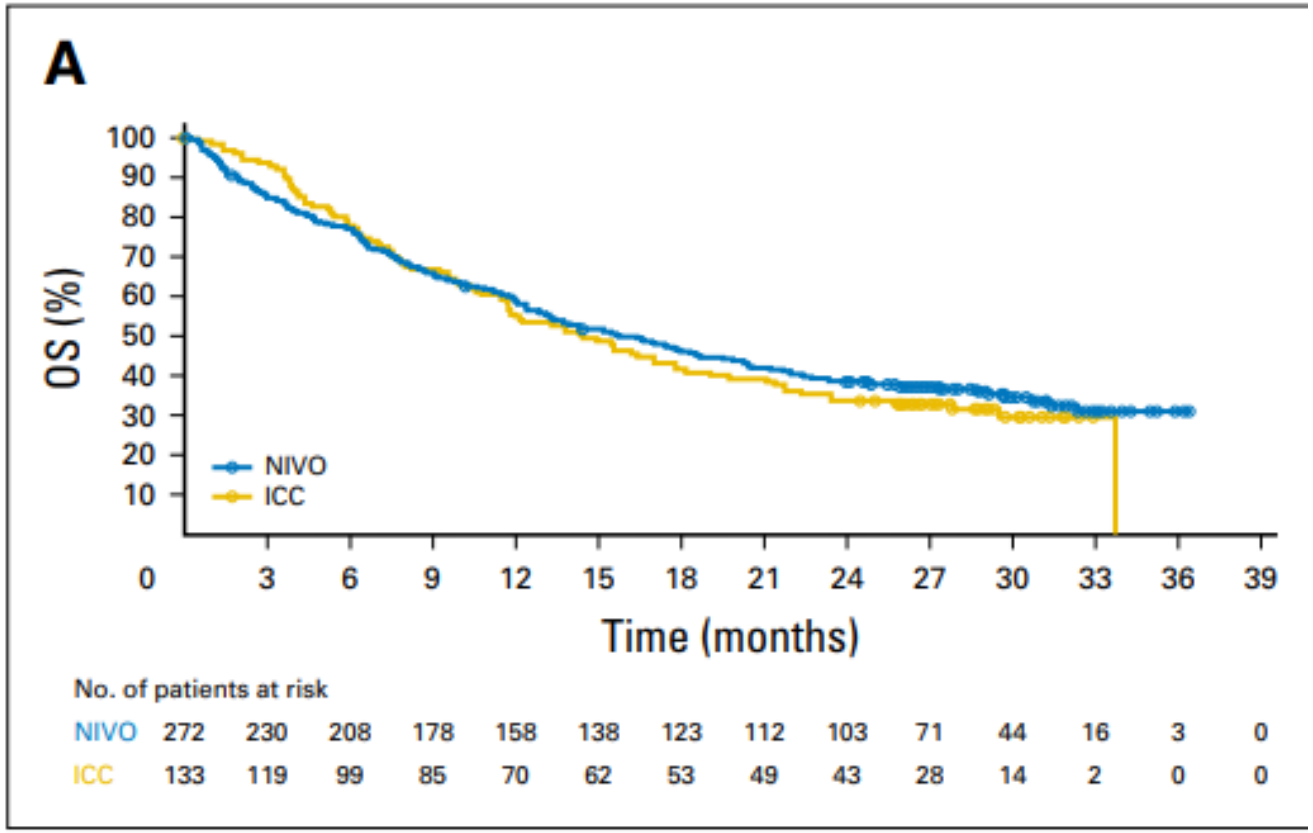
Design: Patients with advanced melanoma randomized (2:1) to nivolumab vs. investigator's choice chemotherapy

Objective: Compare OS in two treatment arms

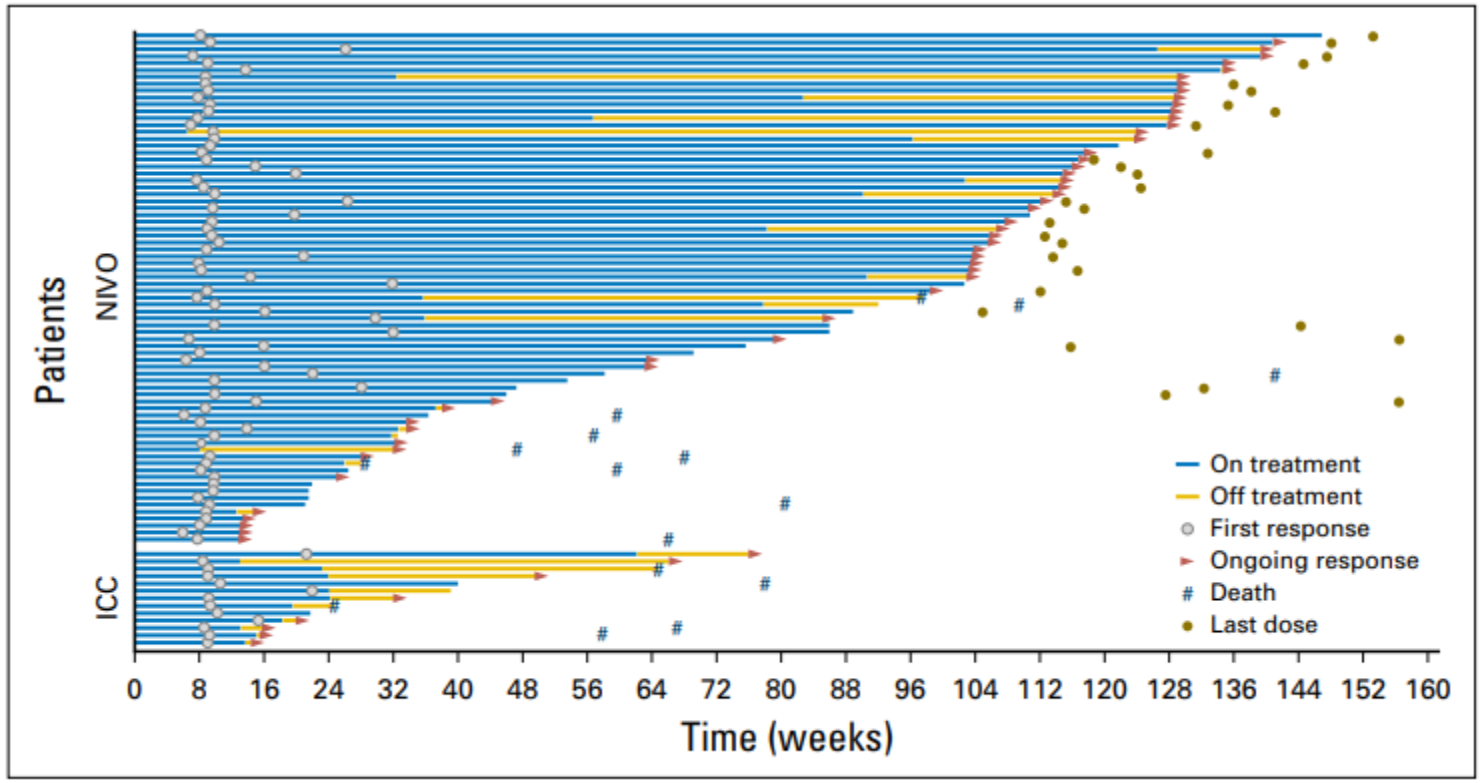
Sample size: N = 405

Primary endpoint: Overall survival

Result: Higher, more durable responses with longer DOR in nivolumab arm, but no difference in OS



Swimmer plot
(remember—2:1 randomization)



27% response rate in Nivo (N=74)
10% response rate in ICC (N=13)

Fig 3. Duration of response per independent radiologic review committee. Swimmer plots show time to first response and duration of response, as defined by RECIST v1.1, for responders who received nivolumab (NIVO) or investigator's choice chemotherapy (ICC).

Issues with Cross-Over

Upon progression, patients will receive another treatment (maybe ICI).

"Given the higher number of ICC patients who received subsequent systemic treatment, OS was investigated in a sensitivity analysis by censoring at the start of the PD-1/PD-L1 therapy that was received after assigned therapy in the ICC group."

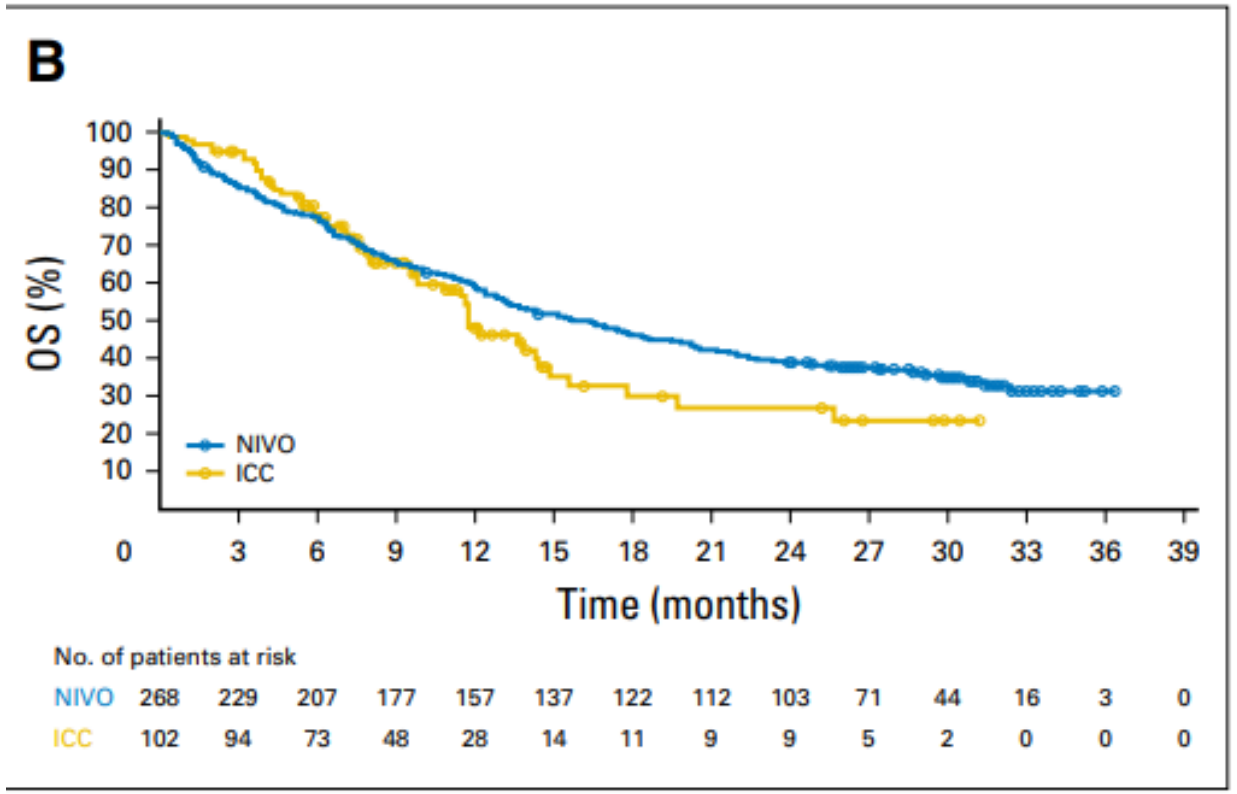
Cross-over **within** protocol: Ethical approach, encourages enrollment.

However, groups become:

- Nivolumab, or Nivolumab followed by ICC
- ICC, or ICC followed by ICI (or something else)

What happens if we 'censor' death times for patients who cross-over to Nivolumab?

- Looks like Nivolumab has better survival
- But…selection bias!



“Long tail”

Common measure of overall treatment effect is the **hazard ratio.**

Assumes “proportional risk” of events over time.

Shapes of the Kaplan-Meier curves for traditional agents and immunotherapies are different:

- Proportionality is violated
- Hazard ratio is not valid

New measures are needed to quantify treatment effect which has multiple components.

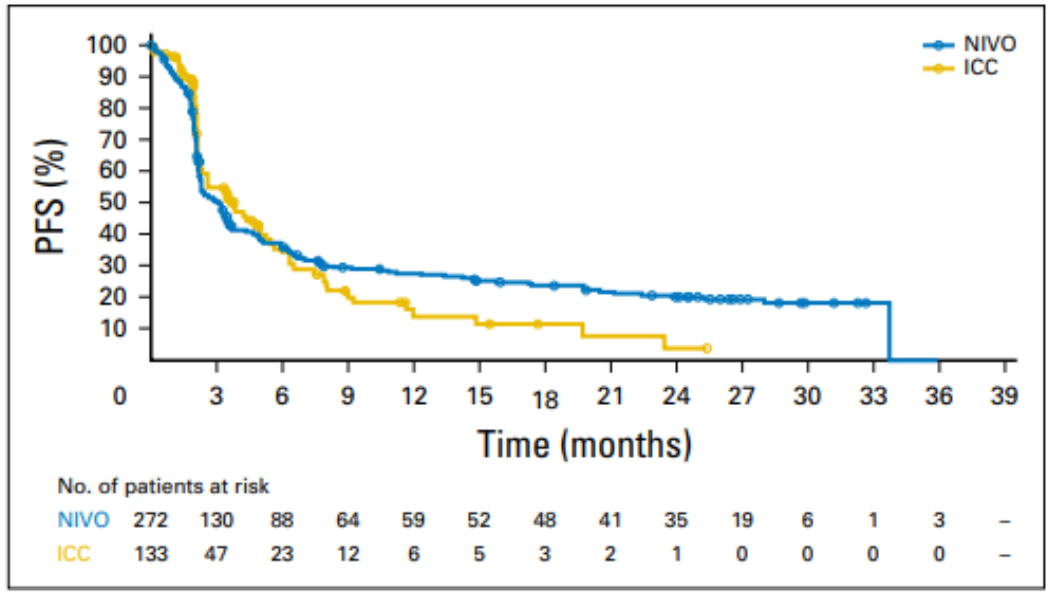


Fig 4. Progression-free survival (PFS) by independent radiologic review committee (IRRC) assessment. Kaplan-Meier curves for PFS in all randomly assigned patients by IRRC assessment. Median PFS was 3.1 months (95% CI, 2.3 to 3.5) in the nivolumab (NIVO) group and 3.7 (95% CI, 2.3 to 5.3) in the investigator’s choice chemotherapy (ICC) group (hazard ratio for death or disease progression, 1.03; 95.1% CI, 0.78 to 1.436).

Future of trials for cancer immunotherapy

- Dose optimization is a major issue

  → Current dose finding paradigm does not focus on the optimal dose or minimally effective dose

- Traditional endpoints are not as useful for determining efficacy

  → expect a shift towards efficacy outcomes that incorporate durable and duration of response

- Survival distribution has a different shape than traditional therapies, making comparisons more complex

  → Statisticians and trialists are working on novel methods to aid in inferences and to replace/revise traditional measures (e.g., hazard ratios)


Questions
?
?
Answers
?