FDA Experience Reviewing Single Arm Trials of Combination Oncology Therapies

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Disclaimer

- The views expressed in this presentation are those of the author and not necessarily the views of FDA.


Many Moving Parts
Novel-Novel Combinations

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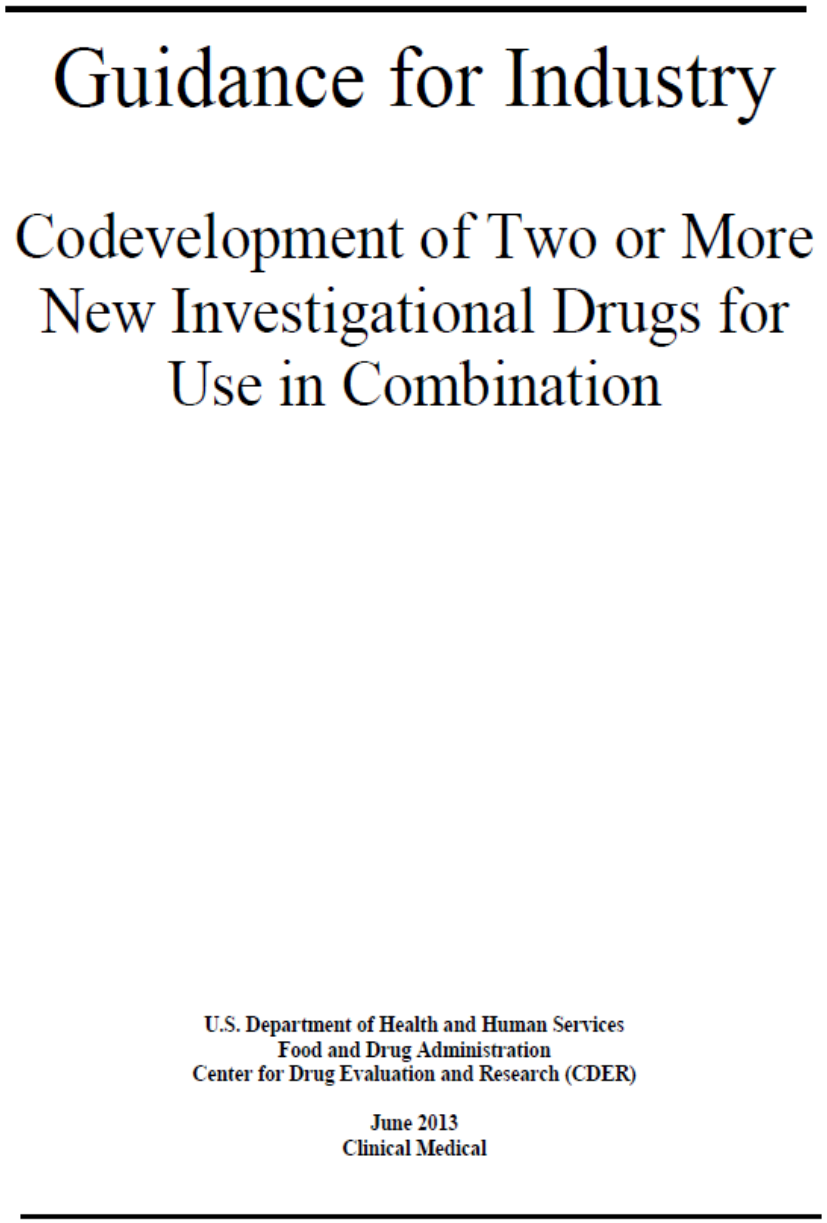
Combination Therapies for Oncology Indications

- FDA Guidance (2013)
- Review of recent experience
  - Melanoma example
  - Multiple myeloma example
- Challenges
- Considerations
  - Adaptive designs
  - Complex Innovative Designs

FDA Guidance

- Two or more new drugs that have not been previously developed for any indication to be used in combination to treat a disease or condition

- Theme: demonstrating the contribution of the individual new investigational drugs to the effect(s) to the combination



Guidance for Industry

Codevelopment of Two or More New Investigational Drugs for Use in Combination

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2013
Clinical Medical

Combination Therapy Approvals

- Overview of Hematology/Oncology Approvals & Safety Notifications
- From 2013-2020
- 381 entries
- 80 approvals for combinations

Less Information

- Guidance assumes the combination is more thoroughly studied than each of its components.
  - Codevelopment goal implies limited independent study of components
- Challenge: Laws & regs seem geared toward specific products
- Drugs are approved from marketing if they are safe and effective if used according to their label
  - Many products labeled for “use in combination with…”
  - FDA regulates drug marketing, not the practice of medicine
  - Don’t want to approve a “toxic placebo”…. is one along for the ride?
  - How much information on the component drugs is adequate?

Appropriateness of Codevelopment

- Combination is to treat a serious disease or condition
- Strong biological rationale
- Available information* suggests combination may provide significant therapeutic advance over available therapy and is superior to the individual agents
    - *Non-clinical
    - *Short-term biomarker study
- Compelling reason against independent development
    - Monotherapy leads to resistance
    - One or more of the agents would be expected to have limited activity when used as monotherapy

Early Information: Non-Clinical

- Biologic rationale for codevelopment
- Compare activity of components to that of combination
- Additional safety information may be needed if clinical studies of components will be limited
- ICH M3(R2) Nonclinical safety studies for the conduct of human clinical trials and marketing authorization
- ICH S9 nonclinical evaluation for anticancer pharmaceuticals

Early Information: Clinical

- Characterize safety and pharmacokinetics of individual components
  - Whenever possible: safety profile characterized in p1 in same manner as for single drugs
  - MTD, DLT, bioavailability, mass balance, PK parameters
  - individual component dose response to inform combination dose (if feasible)
    - If not feasible: approaches for varied dose combinations
  - Healthy volunteers, patients
- Characterize safety and pharmacokinetics of the combination

Later Clinical Phases

- Each new drug has activity and can be admin separately
  - AB vs A vs B vs SOC
  - Consider add on design if SOC is known effective (not solely palliative)
  - Adaptive Designs- dropping treatments when information indicates
- Each new drug cannot be admin separately
  - AB vs SOC
  - Examine possible flexibilities (short duration of mono therapy?)
- One drug active, one inactive in monotherapy
  - A vs AB vs SOC

Examples

Melanoma Example

- BRAFTOVI (encorafenib) is a kinase inhibitor indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

- MEKTOVI (binimetinib) is a kinase inhibitor indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

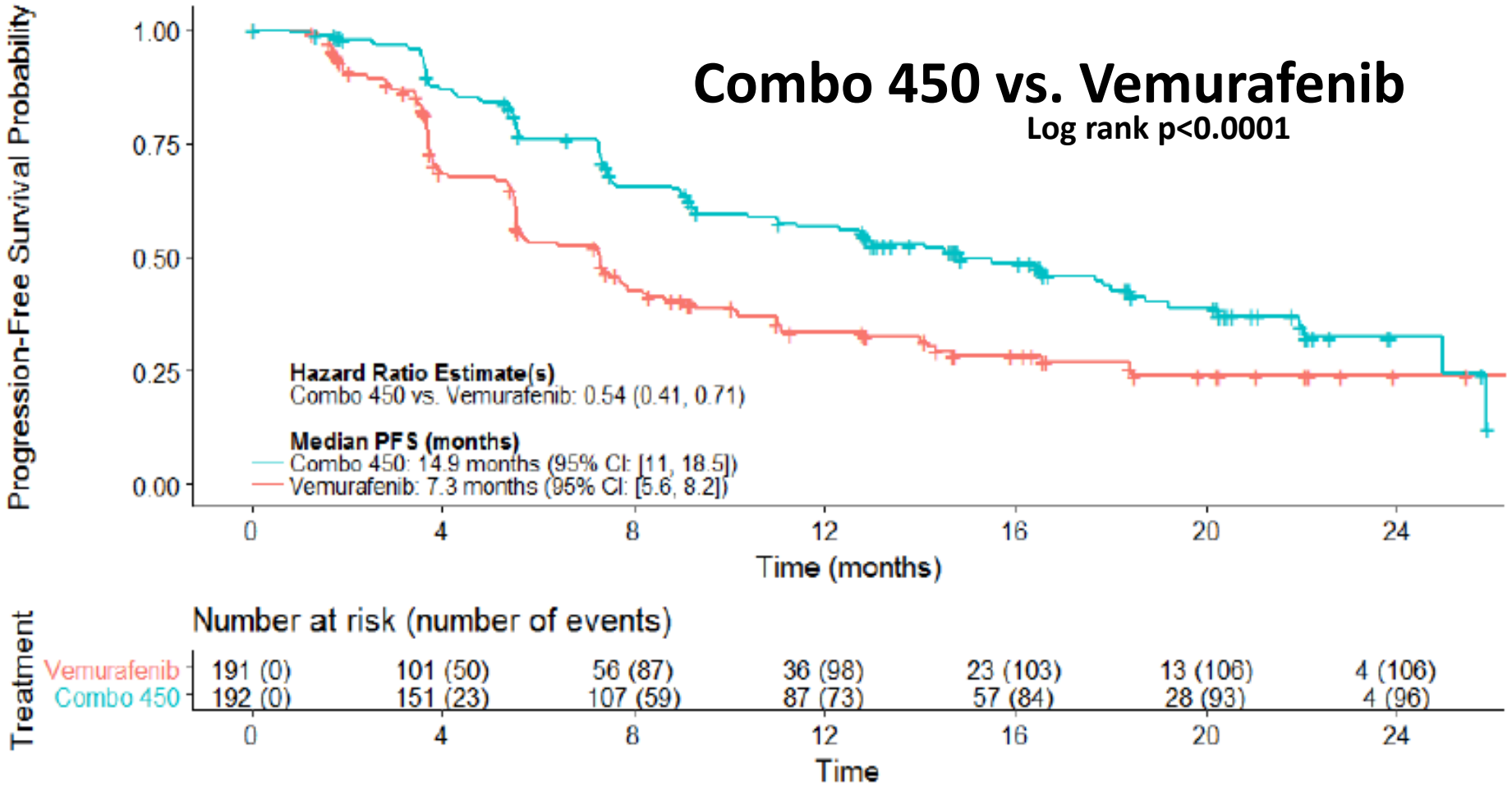
Synergy

- Encorafenib Mechanism of Action
  - Inhibition of mutant and wild-type BRAF enzyme by encorafenib prevents activation of MEK1, leading to reduced cellular proliferation.
- Binimetinib Mechanism of Action
  - Inhibition of MEK1 and MEK2 enzyme by binimetinib prevents phosphorylation of ERK, leading to reduced cellular proliferation.
- Impact pathway at different points
- Similar combination:
  - dabrafenib (BRAF inhibitor)
  - trametinib (MEK inhibitor)

COLUMBUS

- Open-label, randomized, multicenter, two-part clinical trial
- encorafenib in combination with binimetinib for adults with unresectable or metastatic melanoma harboring a V600E or V600K mutation.
- Part 1: patients were randomized 1:1:1
  - “Combo 450” [encorafenib (450 mg daily) with binimetinib (45 mg twice daily)]
  - encorafenib alone (300 mg daily)
  - vemurafenib (960 mg twice daily)

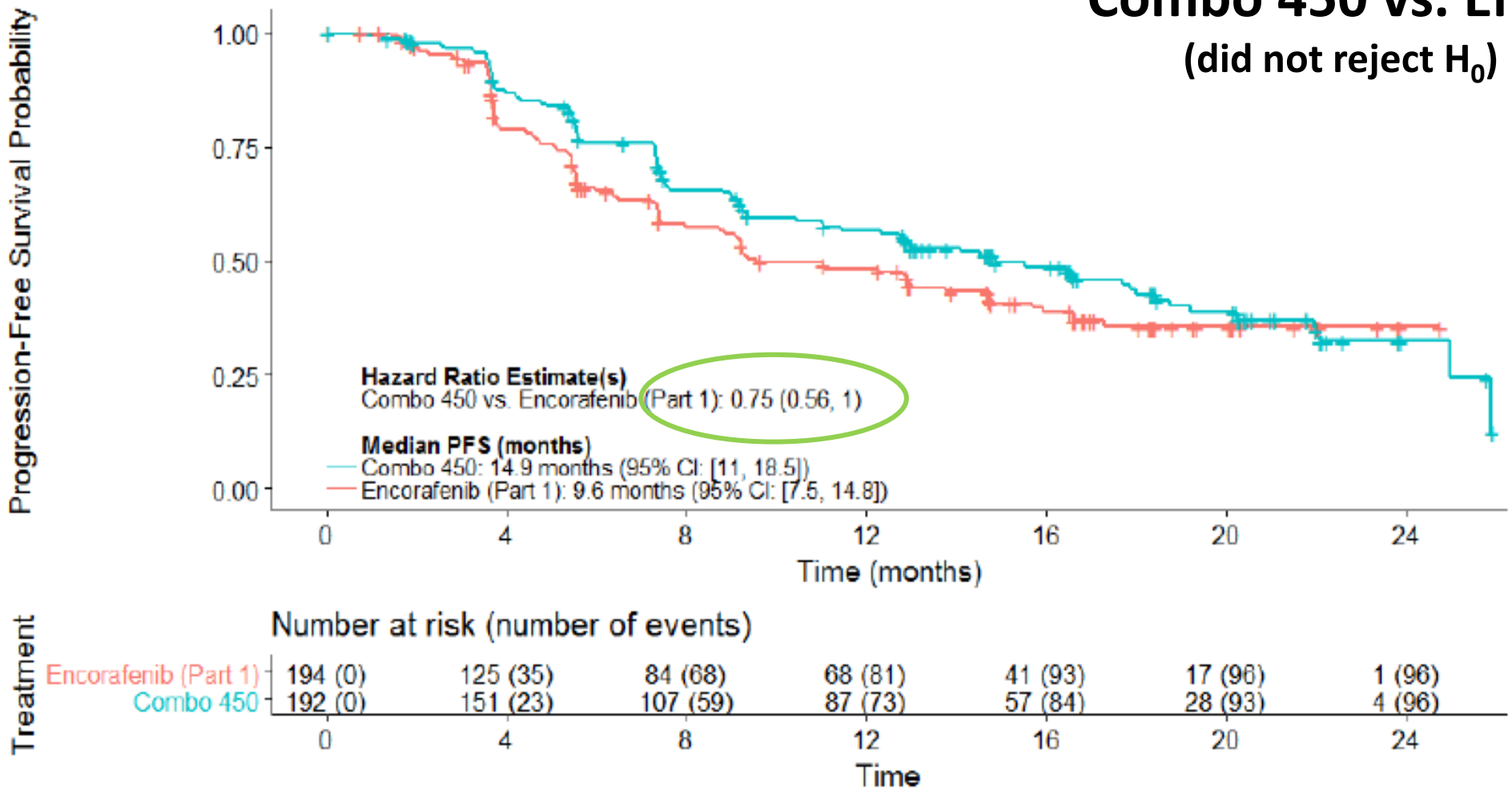
Part 1 of COLUMBUS
Progression-Free Survival (ITT)



Source: FDA Analysis

Part 1 of COLUMBUS
Secondary Endpoint (ITT)

Combo 450 vs. Encorafenib
(did not reject H_0)

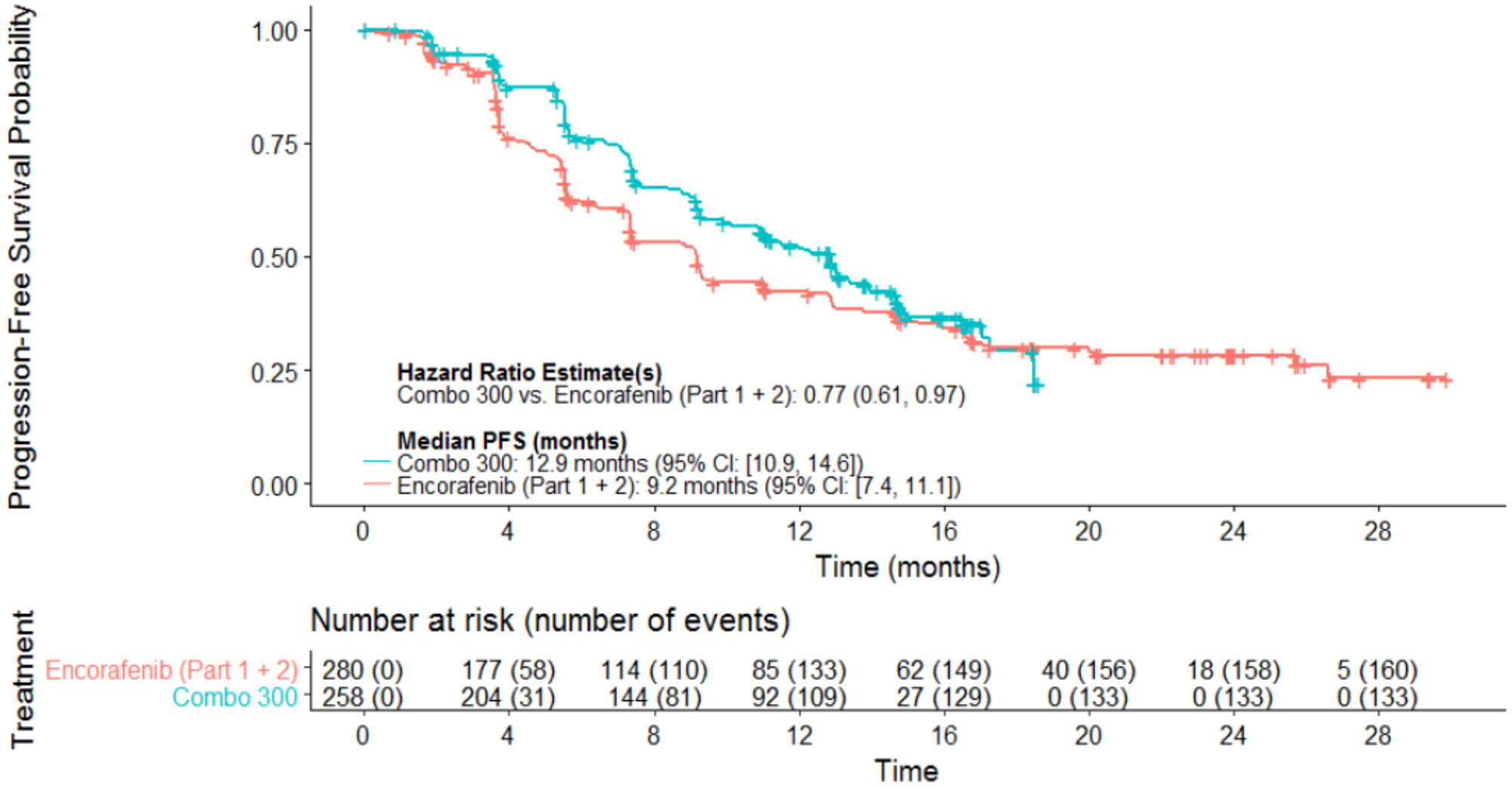


Source: FDA Analysis

Part 2: Contribution of Binimetinib

- Estimate the contribution of binimetinib to the effect of the Combination.*
- Patients were randomized in a 3:1 ratio to one of the two treatment arms:
  - 1) Encorafenib 300 mg by mouth once daily plus binimetinib 45 mg by mouth twice daily continuously in 28-day cycles (Combo 300 arm)
  - 2) Encorafenib 300 mg by mouth once daily continuously in 28-day cycles (Encorafenib arm)
    - Encorafenib arm also included patients from the encorafenib arm of part 1.

Part Two Analysis



Source: FDA Analysis

Multiple Myeloma Example
Study MMY1001

- Single arm, open label study
- Daratumumab
  - (In combination with pomalidomide and dexamethasone)
- N=103
- multiple myeloma
  - Patients who had received two prior lines of therapy
  - Including prior Proteasome Inhibitor (PI) and an immunomodulatory (IMID) agent
- Overall response rate (ORR) by Independent Review Committee (IRC) using International Myeloma Working Group (IMWG) criteria

MMY1001

Primary Endpoint: overall response rate as determined by Independent Review Committee using IMWG criteria

	N=103
Overall response rate (ORR) 95% CI (%)	61 (59.2%) (49.1, 68.8)
Stringent complete response (sCR)	8 (7.8%)
Complete response (CR)	6 (5.8%)
Very good partial response (VGPR)	29 (28.2%)
Partial response (PR)	18 (17.5%)

ORR = sCR+CR+VGPR+PR

Assurance of Contribution to Effect

- Daratumumab as monotherapy was evaluated in a population that had at least three prior lines of therapy including a PI and IMiD or who were double-refractory to a PI and IMiD.
  - Daratumumab monotherapy cohort (n=106)
  - ORR: 29% (20.8%, 38.9%)
    - Lonial, et al 2016/FDA review

- Pomalidomide had been approved “in combination with dexamethasone (Pd) for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.”
  - From USPI information
    - The ORR for Pom-dex was 23.5% (95% CI: 18.7, 28.3)
    - The CR rate was 0.3% and VGPR rate was 2.6%.

Complex and Innovative Designs Pilot Program

- Sponsors
  - submit designs
  - have the opportunity to engage with regulatory staff on designs via two meetings
- Agency
  - will select up to 2 submissions per quarter
  - uses the design as a case study for continuing education and information sharing
- Meetings led by the Office of Biostatistics at CDER
  - All relevant disciplines participate
- Five year duration

Summary

- Estimating effects of components: important, complicated
- FDA guidance
  - 2013 Guidance on codevelopment
  - 2019 Adaptive designs guidance
- Complex Innovative Designs Pilot

References

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