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Estimand Framework – Are we asking the right questions?

A case study in the solid tumor setting

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Background

- Annually, ~338,000 persons are diagnosed with RCC, resulting in ~144,000 deaths[1]
- **Standard of care for adjuvant RCC:** Surgical resection followed by observation
  - Patients with a high risk of disease recurrence are in need of treatment options
- **Overarching scientific question of interest:** "Does the new treatment prolong patient's disease-free survival time?"
- **Fundamental issue:** How to define a patient as "disease-free"
  - Local recurrence
  - Metastatic recurrence
  - Contralateral kidney cancer
  - Second primary cancer
  - Death due to RCC
  - Death due to causes other than RCC
- Lack of harmonized endpoint definitions is recognized in the clinical community and has been discussed within the DATECAN[2] project

1. Ferlay, J. et al. Int J Cancer. 2015;136(5):E359–86. **2.** Kramer, A. et al. Ann Oncol. 2015;26(12):2392–8.

RCC=renal cell carcinoma

Variety of endpoint definitions in adjuvant RCC

Clinical Trial	Imaging-Related Endpoints	Events Included in the Endpoint Definition as Published
S-TRAC (2016)[1] Sunitinib vs Placebo	DFS*	Recurrence, second primary cancer, death from any cause
ASSURE (2016)[2] Sunitinib vs Sorafenib vs Placebo	DFS*	Recurrence, second primary cancer, death from any cause
PROTECT (2017)[3] Pazopanib vs Placebo	DFS*	Local recurrence, metastasis, death from any cause
PROSPER (2017)[4] Nivolumab vs Placebo	RFS*	Disease recurrence or death from any cause
IMmotion-010 (2017)[5] Atezolizumab vs Placebo	DFS*	Local recurrence of RCC, new primary RCC, distant RCC metastasis, death from any cause
	DMFS	Distant metastasis, death from any cause
KEYNOTE-564 (2017)[6] Pembrolizumab vs Placebo	DFS*	Local recurrence, distant metastasis, secondary systemic malignancy, death from any cause
	Local disease recurrence–specific survival	Local recurrence
	Local recurrence, distant metastasis, or secondary systemic malignacy with visceral lesions	Local recurrence, distant metastasis, secondary malignancy with visceral lesion presence

1. Ravaud, A. et al. N Engl J Med. 2016;375(23):2246-54. **2.** Haas, NB. et al. Lancet. 2016;387(10032):2008-16. **3.** Motzer, RJ. et al. J Clin Oncol. 2017;35(35):3916-23.
4. https://clinicaltrials.gov/ct2/show/NCT03055013; accessed May 3, 2019. **5.** https://clinicaltrials.gov/ct2/show/NCT03024996; accessed May 3, 2019.
6. https://clinicaltrials.gov/ct2/show/NCT03142334; accessed May 3, 2019.
*=primary endpoint
DFS=disease-free survival; DMFS=distant metastasis–free survival; RCC=renal cell carcinoma; RFS=recurrence-free survival

Intercurrent events (1)

- In addition to different endpoints and endpoint definitions, different methods of handling intercurrent events can further limit the interpretation of the primary question addressed by trial results
- “Intercurrent events” are events that occur after treatment initiation and either preclude observation of the variable of interest or affect its interpretation
  - Drop-out due to tolerability
  - Treatment not initiated
  - Initiation of systemic therapy prior to an event
  - ≥2 missed assessments just prior to an event (often referred to as “extended lost-to-follow-up” in oncology trials)
    - common censoring reason in some historical trials with the rationale it could affect interpretation
    - could be considered as missing data and utilized in sensitivity analyses within the estimand framework
  - If only considering time to RCC recurrence: Death or second primary malignancy

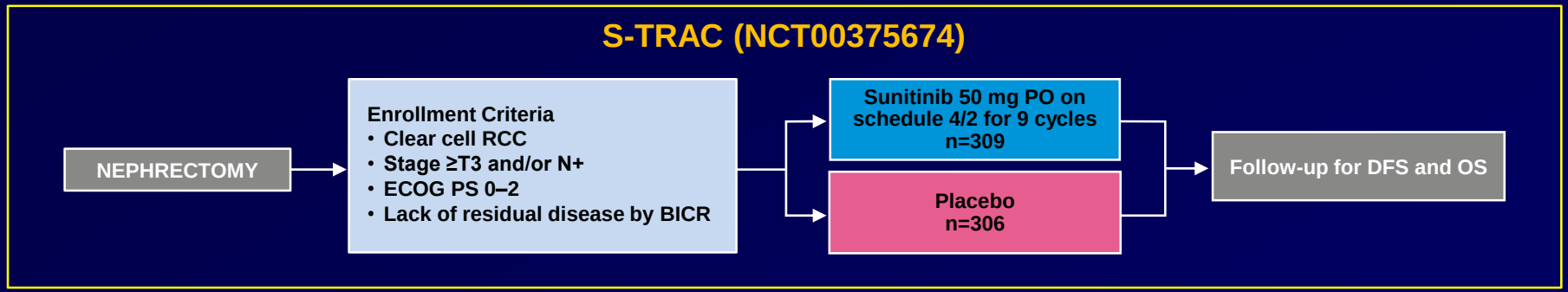
* RCC=renal cell carcinoma

Intercurrent events (2)

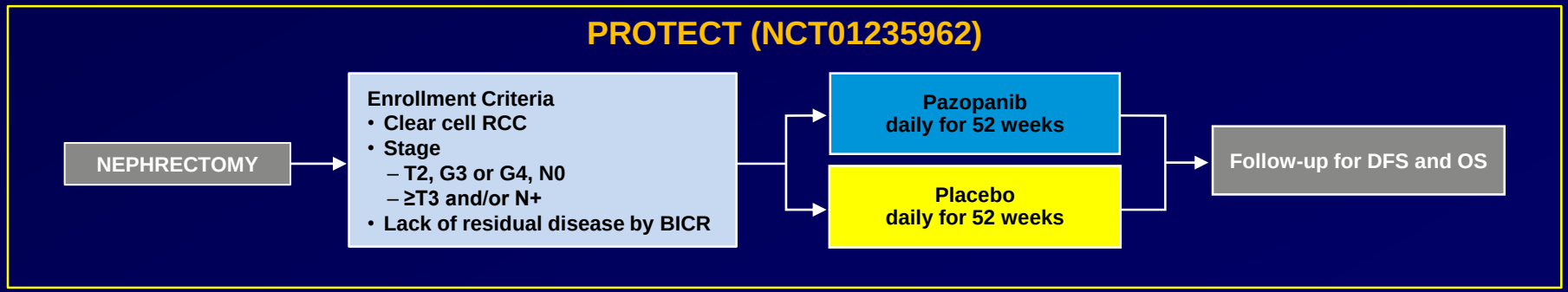
- NOT considered an intercurrent event for BICR endpoints: Investigator-declared relapse
  - Protocols often request continued follow-up until confirmation by BICR; however, this may not occur in all cases
  - Without further follow-up, relapse would likely be accounted for by one of the possible intercurrent events
- Different questions require different methods for handling intercurrent events
  - "Does the drug improve DFS if no patient had received new therapy" vs "Does the drug improve DFS and delay the start of new therapy"
    - Requires different censoring rules for start of new therapy
- Data from two recently completed studies in adjuvant RCC are used to consider common intercurrent events, illustrate the consequences of the estimand choice for analysis and interpretation, and review the importance of consistent terminology across trials

BICR=blinded independent central review; DFS=disease-free survival; RCC=renal cell carcinoma

Study designs: S-TRAC and PROTECT



- Primary endpoint: disease-free survival

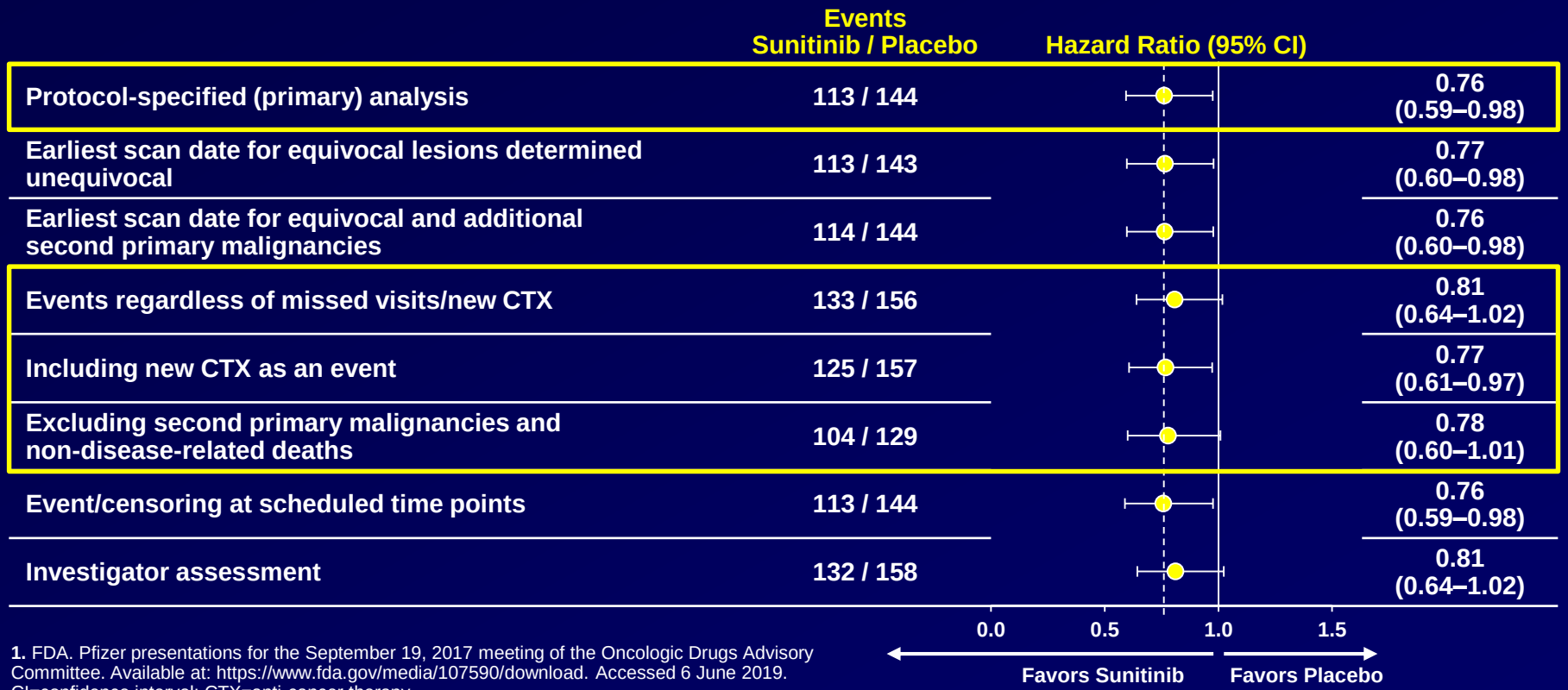


BICR=blinded independent central review; DFS=disease-free survival; ECOG PS=Eastern Cooperative Oncology Group performance status; OS=overall survival; PO=by mouth; RCC=renal cell carcinoma

Differences between S-TRAC and PROTECT

	S-TRAC	PROTECT
Endpoint definition	**Recurrence, second primary cancer,** death from any cause	**Local recurrence, metastasis,** death from any cause
Handling of intercurrent events: Primary analysis	Composite: Deaths and **second primary malignancy** Treatment policy: Tolerability/no treatment Hypothetical: New therapy/missed assessments	Composite: Deaths Treatment policy: Tolerability/no treatment and **second primary malignancy** Hypothetical: New therapy/missed assessments
Population: High risk of recurrence	Stage: ≥T3 and/or N+	Stage: **T2, G3 or G4, N0** ≥T3 and/or N+
Summary measure	Hazard ratio (**Cox Regression**)	Hazard ratio (**Pike estimator**)

Examples of common analyses in oncology trials: S-TRAC[1]



1. FDA. Pfizer presentations for the September 19, 2017 meeting of the Oncologic Drugs Advisory Committee. Available at: https://www.fda.gov/media/107590/download. Accessed 6 June 2019.
CI=confidence interval; CTX=anti-cancer therapy

Primary and secondary estimands: Common analyses mapped to the estimand framework

	Primary Estimand: Protocol-specified (Primary) Analysis	**Supplemental Estimand:** Events Regardless of Missed Visits/New CTX	**Supplemental Estimand:** Incl. New CTX as Event	**Supplemental Estimand:** Excl. Second Primary Malig. and Non-disease-related Deaths
Treatment effect of interest: Prolonging time to ...	**Relapse, second primary malig., or death** regardless of tolerability, if new Tx is not initiated, and extended loss to follow-up is not present	**Relapse, second primary malig., or death** regardless of tolerability, new Tx, or extended loss to follow-up	**Relapse, second primary malig., new Tx, or death** regardless of tolerability if extended loss to follow-up is not present	**Relapse or disease-related death** regardless of tolerability, second primary malig., and if new Tx is not initiated and extended loss to follow-up is not present
Population	Adjuvant RCC patients at high risk of recurrence			
Variable	DFS	DFS	DFS (+ new therapy)	RFS (only disease-related deaths)
Intercurrent event: Death not due to disease	Composite (event)			Hypothetical (censor)
Intercurrent event: second primary malignancy	Composite (event)			Treatment policy (no censoring/no event)
Intercurrent event: New therapy	Hypothetical (censor)	Treatment policy (no censoring/no event)	Composite (event)	Hypothetical (censor)
Intercurrent event: Extended loss to follow-up	Hypothetical (censor)	Treatment policy (no censoring)	Hypothetical (censor)	
Summary measure	Hazard ratio (Cox Regression)			

CTX=anti-cancer therapy; DFS=disease-free survival; excl=excluding; incl=including; malig=malignancy; RCC=renal cell carcinoma; RFS=recurrence-free survival; Tx=therapy

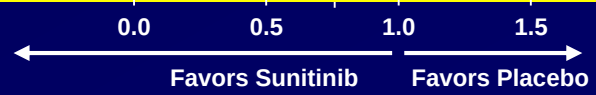
Additional differences between S-TRAC and PROTECT and impact on estimands

	S-TRAC	PROTECT
Investigator vs BICR DFS	**BICR-assessed DFS** primary analysis; additional analysis performed using investigator assessment	**Investigator-asssessed DFS** primary analysis; no BICR results
Earliest scan date vs latest scan date	**Latest** date used for primary analysis; additional analysis performed using earliest date	**Earliest** date used for primary analysis
Assessment schedule	Tumor imaging at baseline; every 12 weeks during first 3 years; then every 6 months thereafter until time of final analysis	Tumor imaging at baseline; Weeks 20, 36, and 52 during Year 1; every 6 months during Years 2–5; and yearly thereafter

BICR=blinded independent central review; DFS=disease-free survival

Sensitivity analyses to assess impact of event timing: S-TRAC[1]

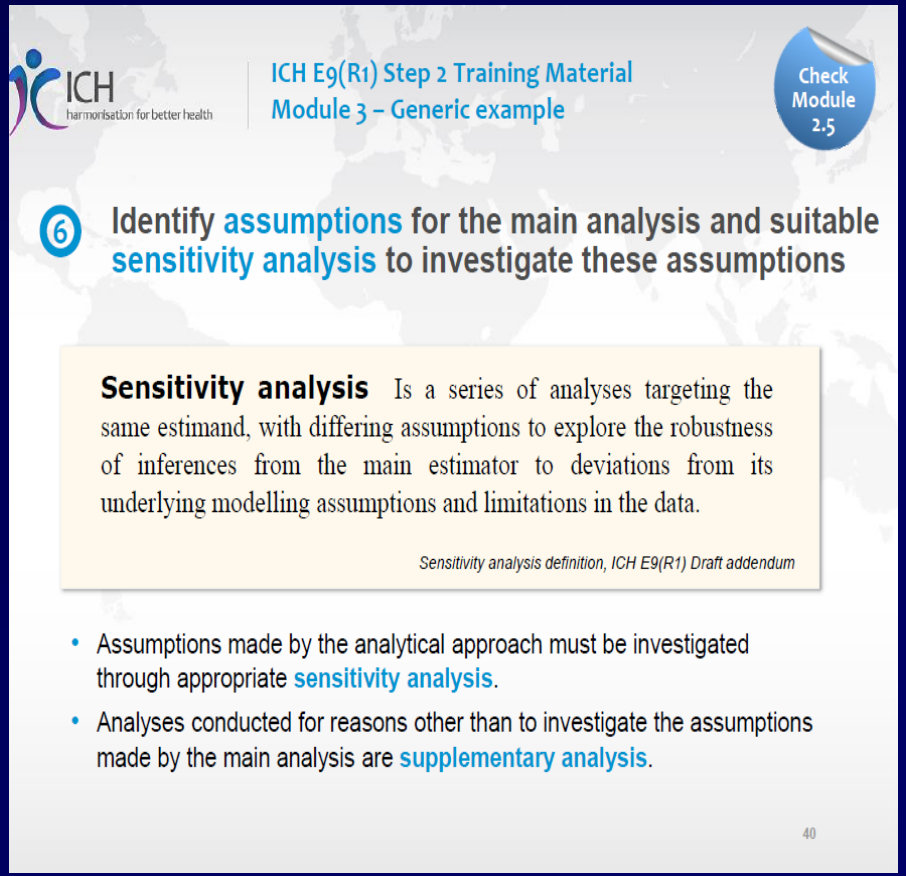
	Events Sunitinib / Placebo	Hazard Ratio (95% CI)
Protocol-specified (primary) analysis	113 / 144	0.76 (0.59–0.98)
Earliest scan date for equivocal lesions determined unequivocal	113 / 143	0.77 (0.60–0.98)
Earliest scan date for equivocal and additional second primary malignancies	114 / 144	0.76 (0.60–0.98)
Events regardless of missed visits/new CTX	133 / 156	0.81 (0.64–1.02)
Including new CTX as an event	125 / 157	0.77 (0.61–0.97)
Excluding second primary malignancies and non-disease-related deaths	104 / 129	0.78 (0.60–1.01)
Event/censoring at scheduled time points	113 / 144	0.76 (0.59–0.98)
Investigator assessment	132 / 158	0.81 (0.64–1.02)



1. FDA. Pfizer presentations for the September 19, 2017 meeting of the Oncologic Drugs Advisory Committee. Available at: https://www.fda.gov/media/107590/download. Accessed 6 June 2019.
CI=confidence interval; CTX=anti-cancer therapy

Sensitivity analyses

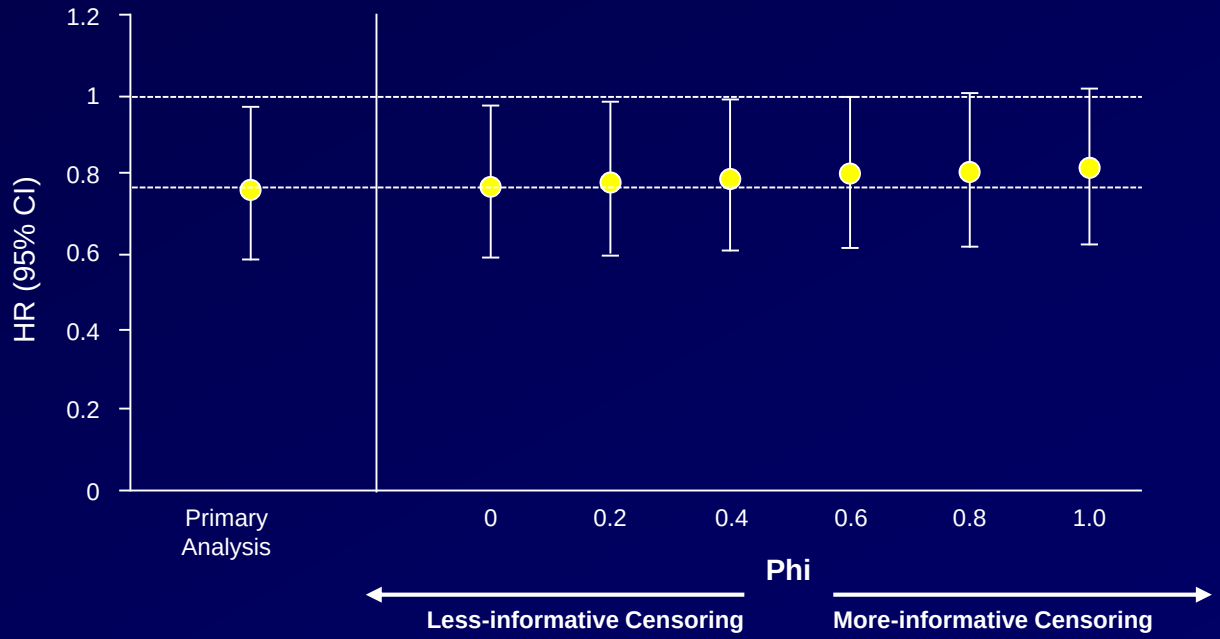
- "Spirit" of the ICH definition, with variations on the timing of progression to assess the impact of these assumptions
- Same methods for handling intercurrent events as the primary estimand
  - **Treatment effect of interest:** Prolonging time to relapse, second primary malignancy, or death regardless of tolerability, if new therapy is not initiated, and extended loss to follow-up is not present
  - **Population:** Adjuvant RCC patients at high risk of recurrence
  - **Variable:** DFS
  - **Intercurrent events:** Deaths/second primary malignancy (composite/events); new therapy or extended loss to follow-up (hypothetical/censor)
  - **Summary measure:** Hazard ratio



DFS=disease-free survival; ICH=International Council for Harmonisation; RCC=renal cell carcinoma

Additional analyses to consider: S-TRAC[1] imputation analysis

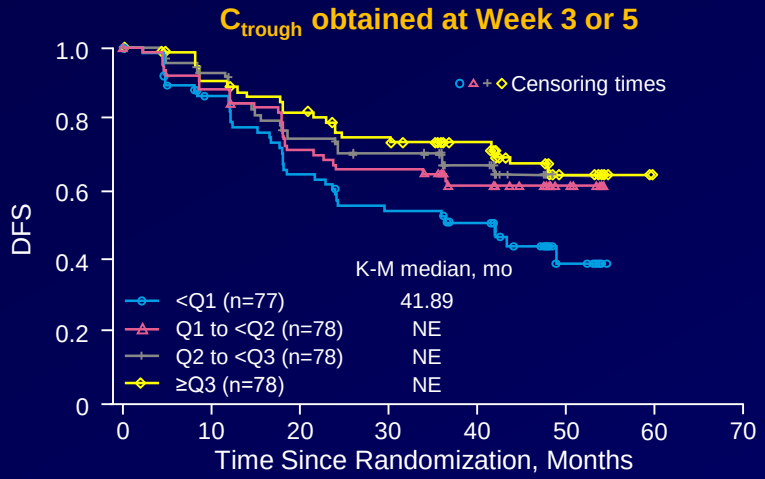
- **Sensitivity analysis of the primary estimand: Imputation method evaluating the impact of potential informative censoring**

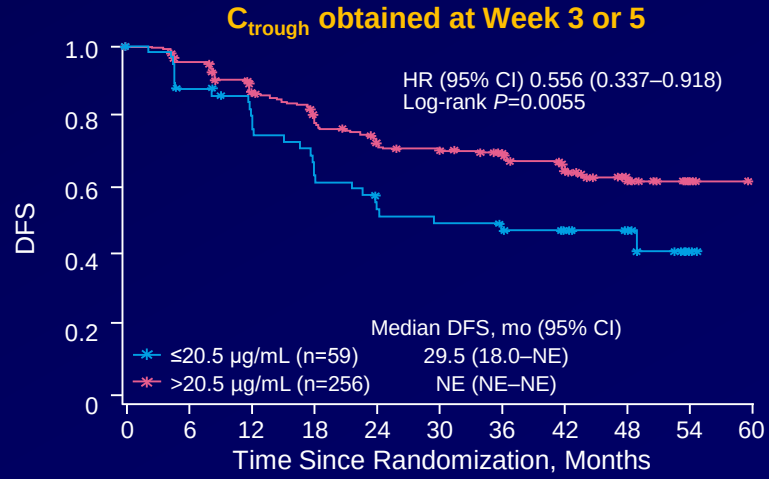


1. FDA. Pfizer presentations for the September 19, 2017 meeting of the Oncologic Drugs Advisory Committee. Available at: https://www.fda.gov/media/107590/download. Accessed 6 June 2019.
CI=confidence interval; HR=hazard ratio

Additional analyses to consider: PROTECT[1], pazopanib concentrations for 600 mg starting dose

- **Main question: What is the difference in DFS between patients by exposure after 3–5 weeks of treatment?**
- **Not all analyses, such as exploratory analyses, need full estimand description in the protocol/SAP, but the research question and handling of intercurrent events should still be considered**
  - **Should intercurrent events be handled the same way as the primary analysis?**
  - **How should early discontinuations due to AE, PD, or death be handled?**





1. Sternberg CN, et al. ASCO 2017.

AE=adverse event; CI=confidence interval; C_{trough}=maximum trough concentration; DFS=disease-free survival; HR=hazard ratio; K-M=Kaplan–Meier; NE=not estimable; PD=progressive disease; Q=quarter; SAP=statistical analysis plan

Conclusions

- Estimand framework seeks increased transparency on the treatment effect of interest
  - eg, “does the drug improve DFS if no patient had received new therapy” vs “does the drug improve DFS and delay the start of new therapy”?
- Stating the endpoint alone does not provide sufficient clarity on the clinical question addressed
- Estimand facilitates discussions during clinical trial design to ensure alignment among the key stakeholders (including HA) on the key questions of interest, the definition of treatment effect, the analysis, and the interpretation
- Critical take-away of the estimand framework is to ensure data capture, with intercurrent events in mind, to facilitate supplemental estimands as well as sensitivity analyses to support the robustness of the primary result
  - Continue to collect data until relapse/progression regardless of intercurrent events

DFS=disease-free survival; HA=xxxxxxxxxxxxxxxxxxxx

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