全生存期間に対する後治療の影響について

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本セッションの目標

- 後治療の影響を受けないようにするために計画立案時に考慮すべき点や，後治療の影響を補正した解析結果の利用可能性や適用上の課題について議論する

抗がん剤試験における評価項目

- FDAガイダンスからの抜粋
  - For regular approval, it is critical that the applicant show **direct evidence of clinical benefit** or **improvement in an established surrogate for clinical benefit**. In oncology, survival improvement is considered an appropriate measure of clinical benefit…
  - …**Survival is considered the most reliable cancer endpoint**, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint…

    US FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, 2007.
- 無増悪生存期間に基づく承認事例は増えているものの，全生存期間を評価することは重要

米国におけるアバスチンの乳がんに対する適応削除

- PFS（主要評価項目）で差が認められたものの，OSで差が認められなかった

	Treatment regimen (s)	HR for PFS	Difference in Median PFS	HR for OS	Difference in Median OS
E2100	Paclitaxel +/- bevacizumab 15 mg/kg	0.48	+ 5.5 mos	0.87	+ 1.7 mos
AVADO	Docetaxel+/- bevacizumab 7.5 mg/kg	0.70	+ 0.8 mos	1.103	- 1.1 mos
AVADO	Docetaxel+/- bevacizumab 15 mg/kg	0.62	+ 0.9 mos	1.003	-1.7 mos
RIBBON	Taxane/Anth +/- bevacizumab 15 mg/kg	0.64	+ 1.2 mos	1.1 *1.24 (taxane)*	N/A
RIBBON	Capecitabine +/- bevacizumab 15 mg/kg	0.69	+ 2.9 mos	0.88	+ 2.9 mos

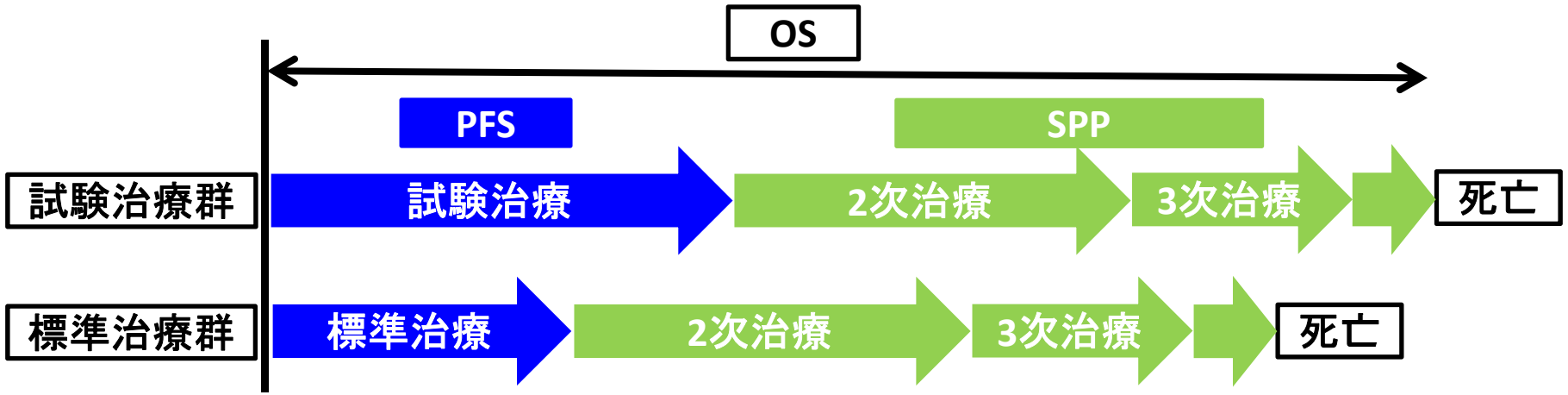
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM219978.pdf

- クロスオーバーや後治療の影響を指摘　Cortes, JCO, 2012

全生存期間に対する後治療の影響

- FDAガイダンスからの抜粋
  - Difficulties in performing and analyzing survival studies include long follow-up periods in large trials and **subsequent cancer therapy potentially confounding survival analysis.**

US FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, 2007.



- SPP（survival post-progression）が長いほど，OSにおける試験治療群の標準治療群に対する効果（ハザード比）は薄まる

Broglio, J Natl Cancer Inst, 2009

クロスオーバーの問題

- プラセボ対照2群比較試験（クロスオーバー許容）
  - 治療A vs プラセボ
  - 増悪後，治療A→治療A，プラセボ→治療A
- 実薬対照2群比較試験（クロスオーバー許容）
  - 治療A vs 治療B
  - 増悪後，治療A→治療B，治療B→治療A
- 実薬対照2群比較試験（クロスオーバー禁止）
  - 治療A vs 治療B
  - 例1）増悪後，治療A→治療C，治療B→治療C
  - 例2）増悪後，治療A→治療D，治療B→治療E

後治療の影響を考慮した解析

- 後治療ごとのサブグループ解析
- 時間依存性共変量を含めたCox回帰分析
- 後治療開始時点で打ち切り
- Per-protocol解析
- RPSFT法やIPCW法
- …

Cancer Therapy: Clinical

Clinical Cancer Research

Complete Longitudinal Analyses of the Randomized, Placebo-Controlled, Phase III Trial of Sunitinib in Patients with Gastrointestinal Stromal Tumor following Imatinib Failure

George D. Demetri[1], Christopher R. Garrett[2], Patrick Schöffski[3], Manisha H. Shah[4], Jaap Verweij[5], Serge Leyvraz[6], Herbert I. Hurwitz[7], Antonio Lopez Pousa[8], Axel Le Cesne[9], David Goldstein[10], Luis Paz-Ares[11], Jean-Yves Blay[12], Grant A. McArthur[13], Qiang (Casey) Xu[14], Xin Huang[15], Charles S. Harmon[15], Vanessa Tassell[15], Darrel P. Cohen[15], and Paolo G. Casali[16]

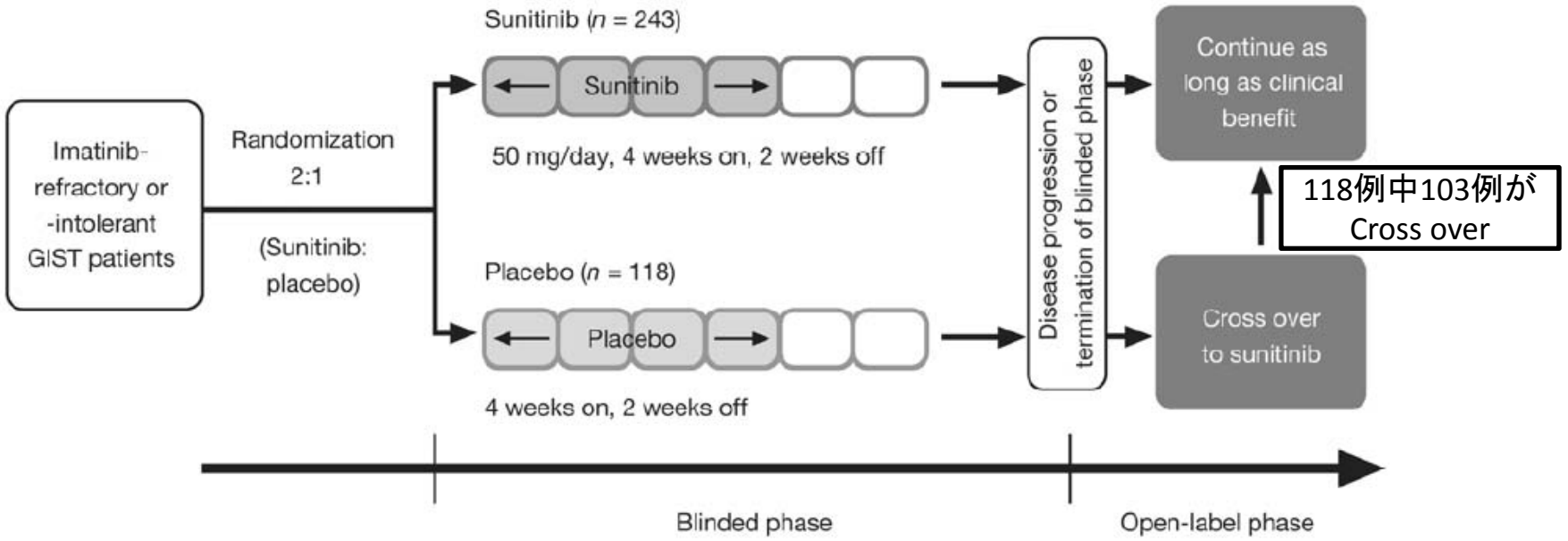
Abstract

Purpose: To analyze final long-term survival and clinical outcomes from the randomized phase III study of sunitinib in gastrointestinal stromal tumor patients after imatinib failure; to assess correlative angiogenesis biomarkers with patient outcomes.

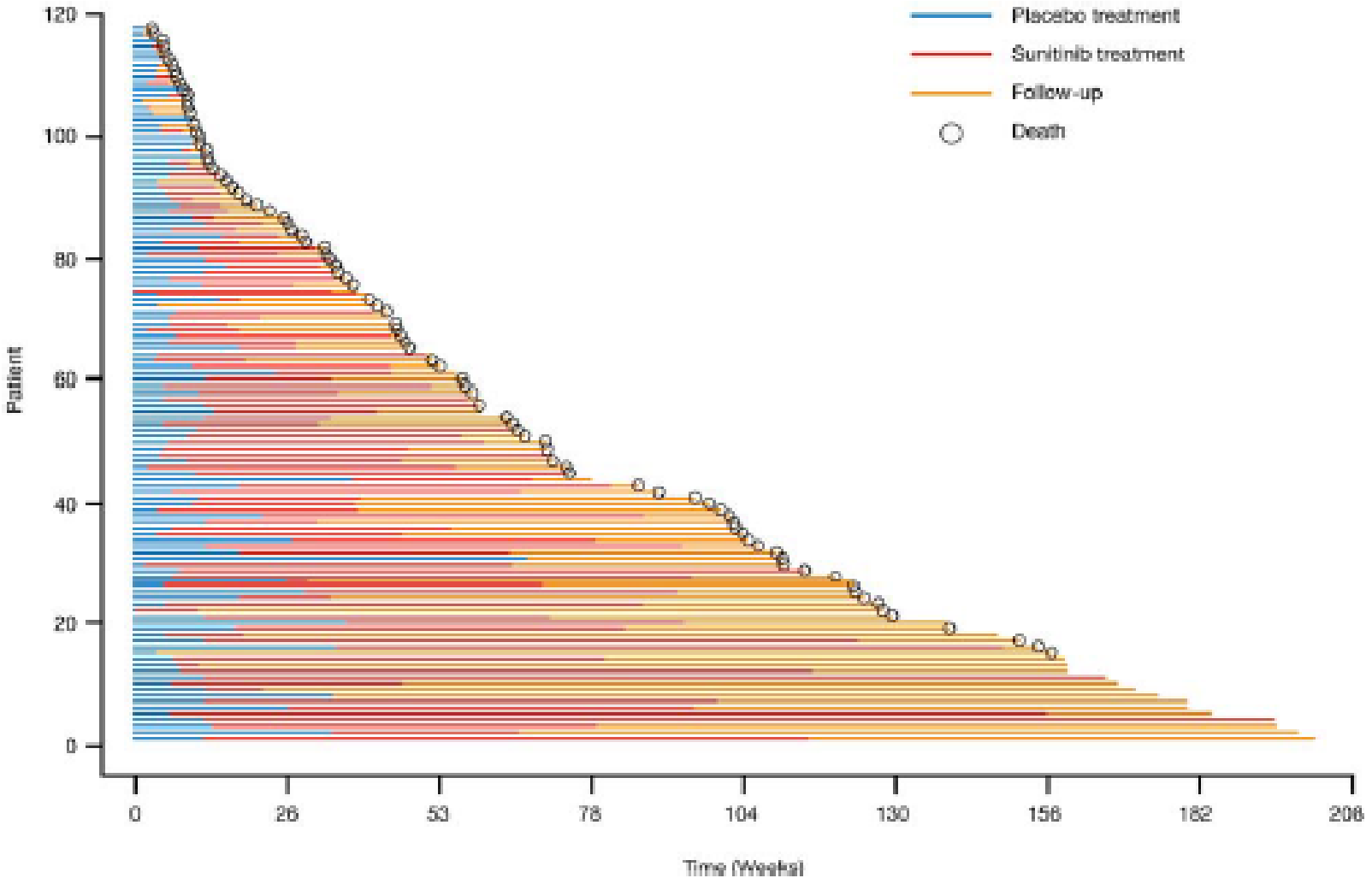
Experimental Design: Blinded sunitinib or placebo was given daily on a 4-week-on/2-week-off treatment schedule. Placebo-assigned patients could cross over to sunitinib at disease progression/study unblinding. Overall survival (OS) was analyzed using conventional statistical methods and the rank-preserving structural failure time (RPSFT) method to explore cross-over impact. Circulating levels of angiogenesis biomarkers were analyzed.

試験デザイン

- 無作為化2重盲検プラセボ対照2群比較臨床試験
- 主要評価項目：TTP，副次評価項目：OS，PFS，ORR
- 解析手法：ログランク検定，コックス回帰

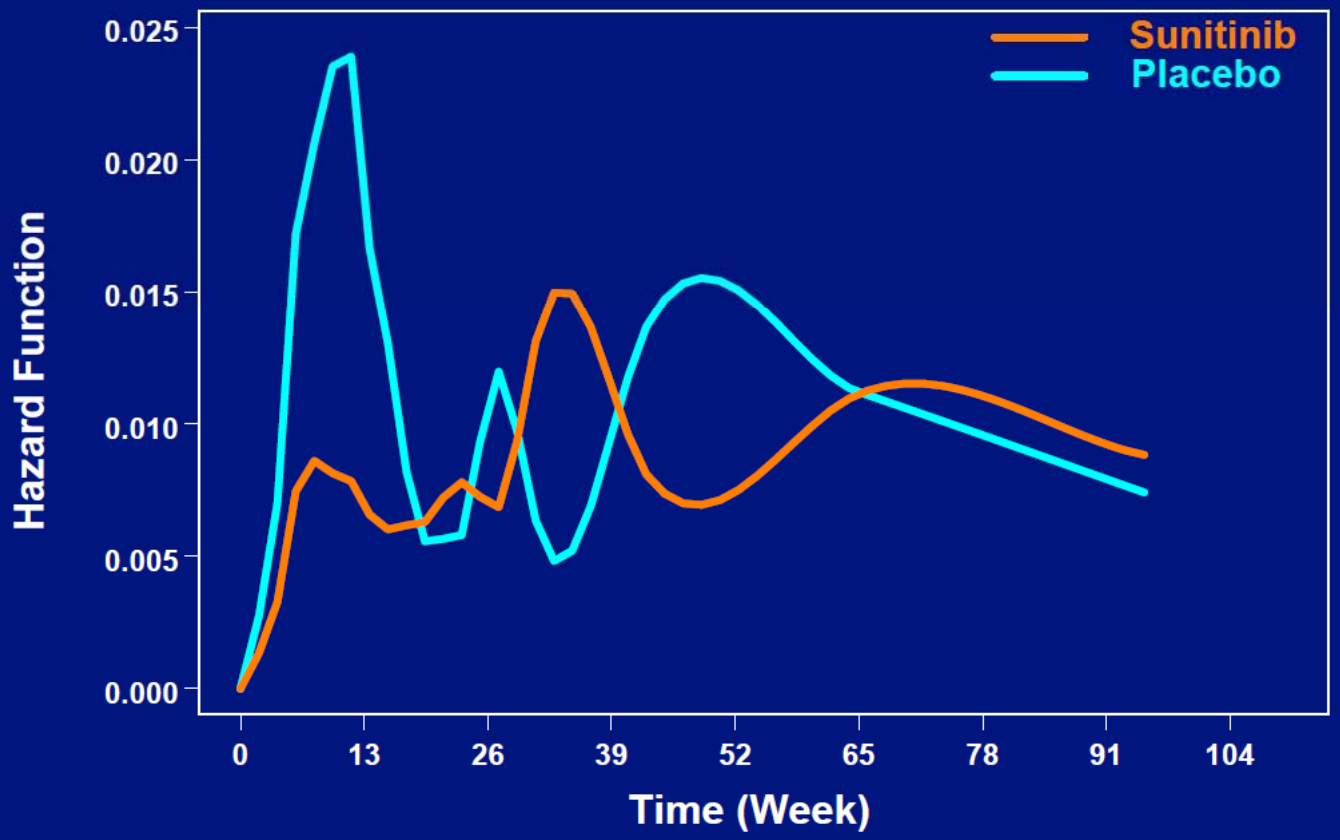


プラセボ群の治療歴



Supplementary Fig. S3. Treatment histories of individual patients randomized to placebo.

Estimated Hazard Functions by Treatment



Hazard function is the *instantaneous* failure rate at any point in time

https://www.network-hubs.org.uk/files/6314/3671/6073/Xin_RPSFTlondon2012.pdf

RPSFT（rank preserving structural failure time）法

- クロスオーバーがなかった場合の因果治療効果の推定
- ランダム化に基づく方法

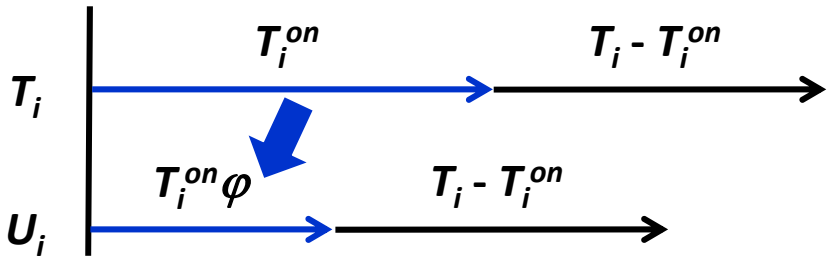
Notation

T_i　患者iの全生存期間

T_i^{on}　患者iのSunitinib治療を受けた期間

U_i　患者iのSunitinib治療を受けなかった場合の潜在全生存期間

φ　因果効果

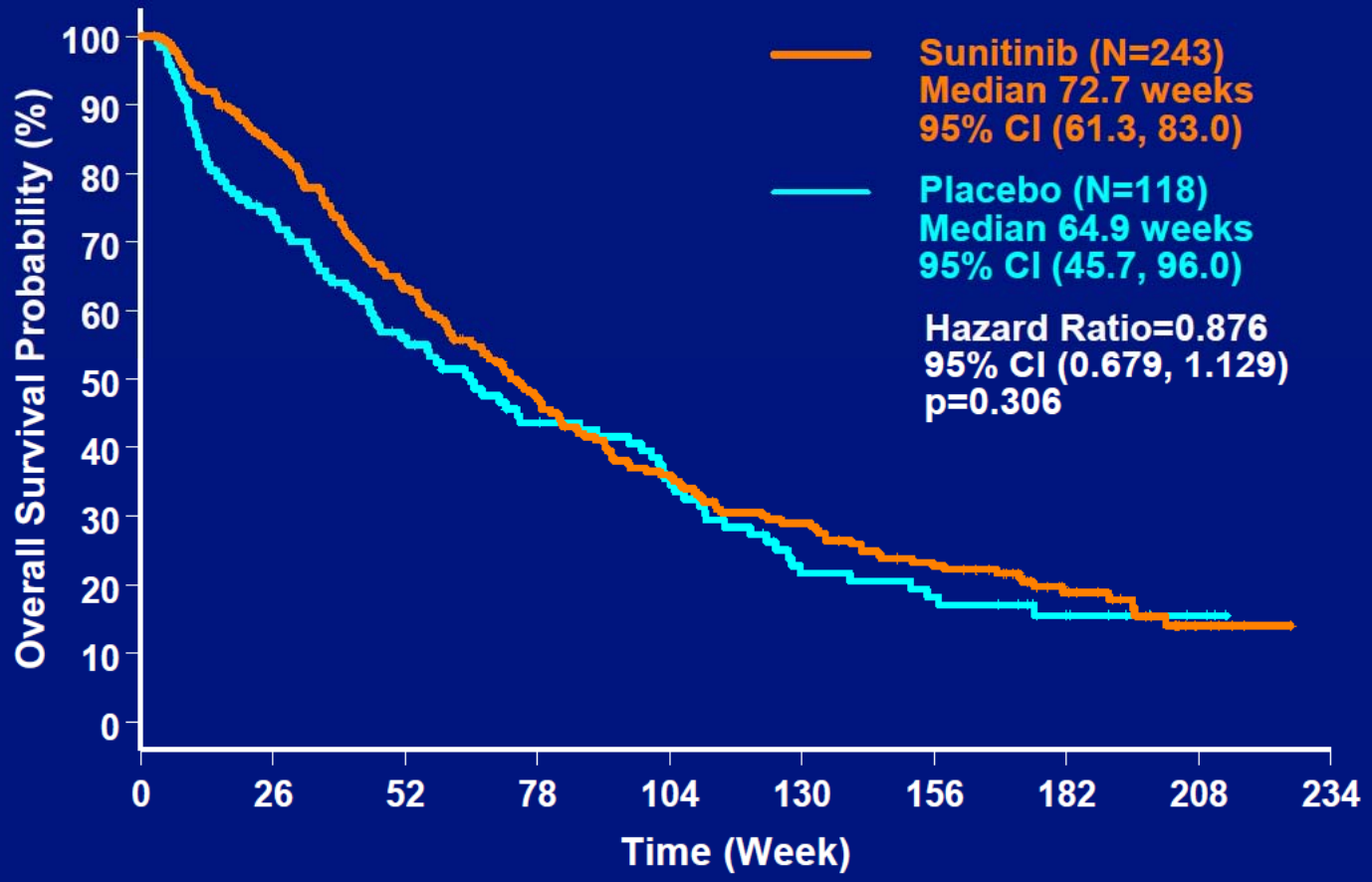


$$U_i = T_i - T_i^{on}(1 - \varphi)$$

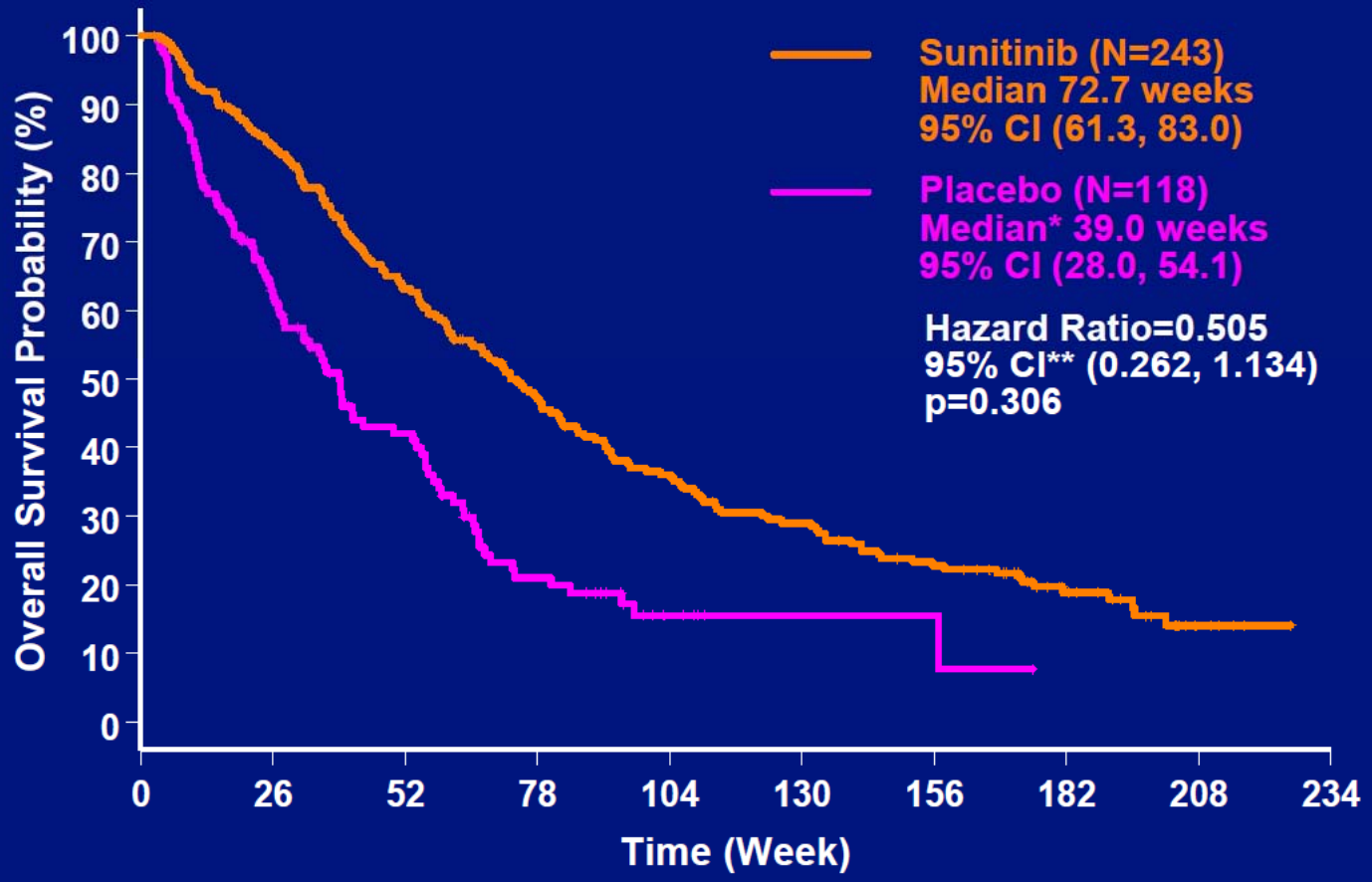
– U_i が割付け群間で同じ分布に従うことを利用

- common treatment effectの仮定
  – どの時点でSunitinib治療を開始してもその効果は同じ

Overall Survival (Final, 2008)



Overall Survival (Final, 2008)
Crossover Adjusted by RPSFT



*Estimated by RPSFT model **Empirical 95% CI obtained using bootstrap samples.

Lenvatinib
STATISTICAL REVIEW(S)からの抜粋

Table 3.11 Applicant's Overall Survival Analysis (using RPSFT Model)

	Lenvatinib n=261	Placebo n=131
Number of Event (%)	71(27.2)	47 (35.9)
Number of Censored (%)	190 (72.8)	84 (64.1)
Median OS in Months (95% CI)	NA (22.0, NA)	NA (14.3, NA)
Hazard ratio** (95%CI)	0.62 (0.40, 1.00)	
p-value	0.0510	

*[Source: Clinical Study Report Table 23] *NA=Not Available due to only small number of events occurred. ** a hazard ratio of less than 1 indicates that the treatment with lenvatinib is associated with lower risk of death compared to placebo treatment.*

- As shown in Table 3.11, the result of OS analysis using RPSFT model seems to show a trend that lenvatinib decreases the risk of death compared to placebo. However, there is limitation when applying RPSFT model, **one has to verify that one of the key assumptions of RPSFT model "common treatment effect" is satisfied**. It means that the treatment effect for the patient is the same regardless of when the patient started taking the study drug. To verify this key assumption, ...

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206947Orig1s000StatR.pdf#search=%27Lenvatinib+statistical+review%27

Sunitinib
NICE Technology appraisal guidanceからの抜粋

- The ERG considered the updated analyses and clarification provided by the manufacturer. It agreed that **the RPSFT method appeared appropriate**. The ERG confirmed that the RPSFT method applied a multiplicative factor to the time spent after crossover rather than to the whole of overall survival. The ERG highlighted that the hazard ratio for overall survival produced using the RPSFT method (0.505) was similar to the hazard ratio for overall survival produced at the interim ITT analyses before crossover had occurred (0.49). It stated that this strengthened the confidence it had in the results derived using the RPSFT method. Additionally, the ERG agreed with the manufacturer that **censoring the participants at crossover in this instance was an unreliable method for controlling for crossover**…

https://www.nice.org.uk/guidance/ta179

論点
デザインによる後治療の考慮

- 後治療の影響を除くため，計画立案時あるいは試験途中に考慮した事項はありますか？

論点
解析による後治療の考慮

- 後治療の影響を補正した解析を実施した経験はありますか？
  - 状況（がん腫，ラインなど）
  - 解析内容
  - その解析の位置付け
  - 何か困難が生じた点があれば

論点
RPSFT法の利用可能性①

- どのような状況で利用するのが良いか？
  - RPSFT法の適用が適切と考えられる状況
  - 収集すべき情報（計画時に考慮すべき事項）
  - 適用上の課題

論点
RPSFT法の利用可能性②

- どのような目的で利用するのが良いか？
  - 後治療の影響を補正する目的
  - 後治療の影響を補正した解析結果の解釈と，その解析結果の位置付け

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