比例ハザード性の仮定が成立しないタイプの生存時間データの取り扱い

―事例と論点―

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ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

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ABSTRACT

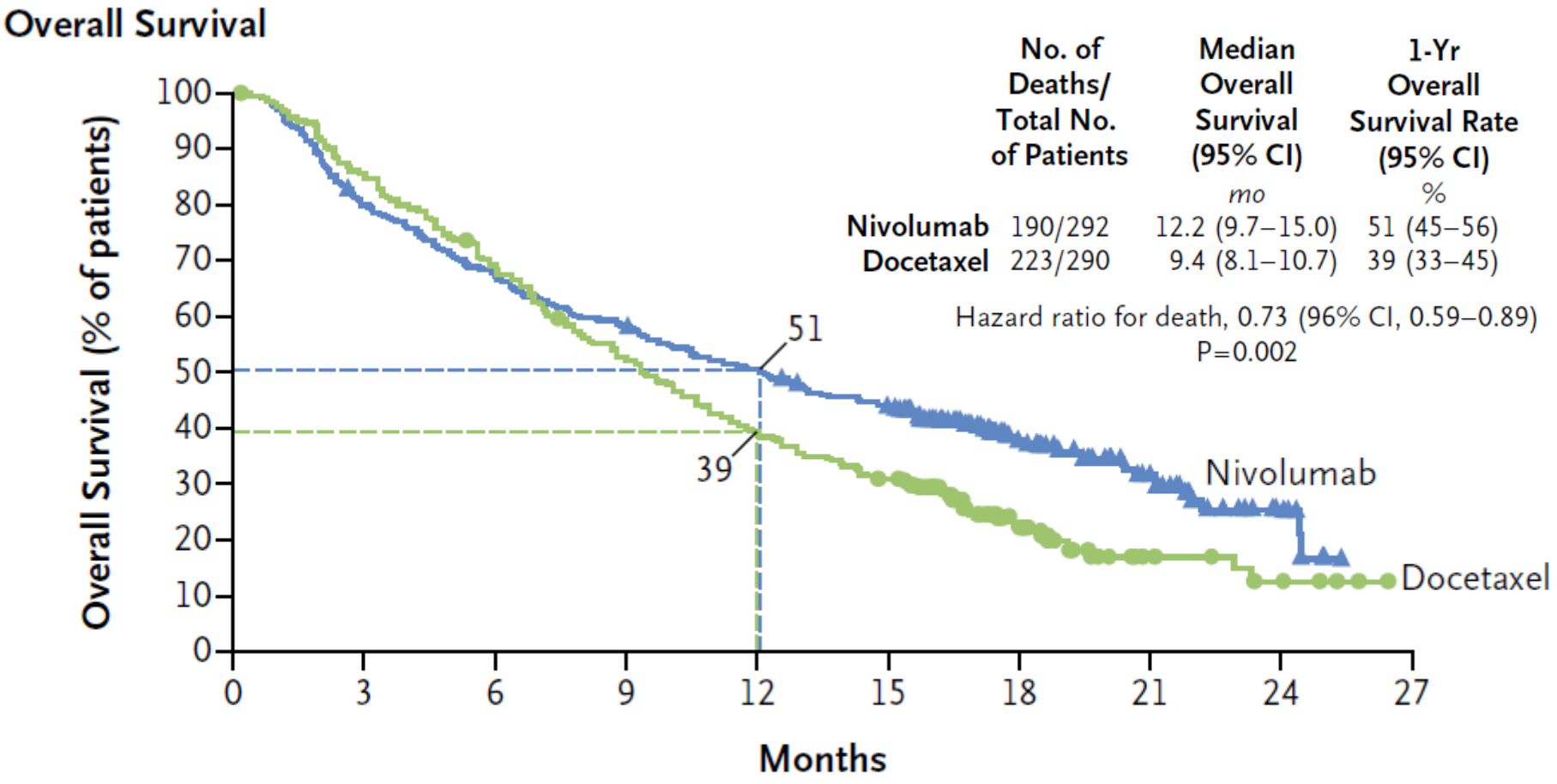
BACKGROUND

Nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody, disrupts PD-1–mediated signaling and may restore antitumor immunity.

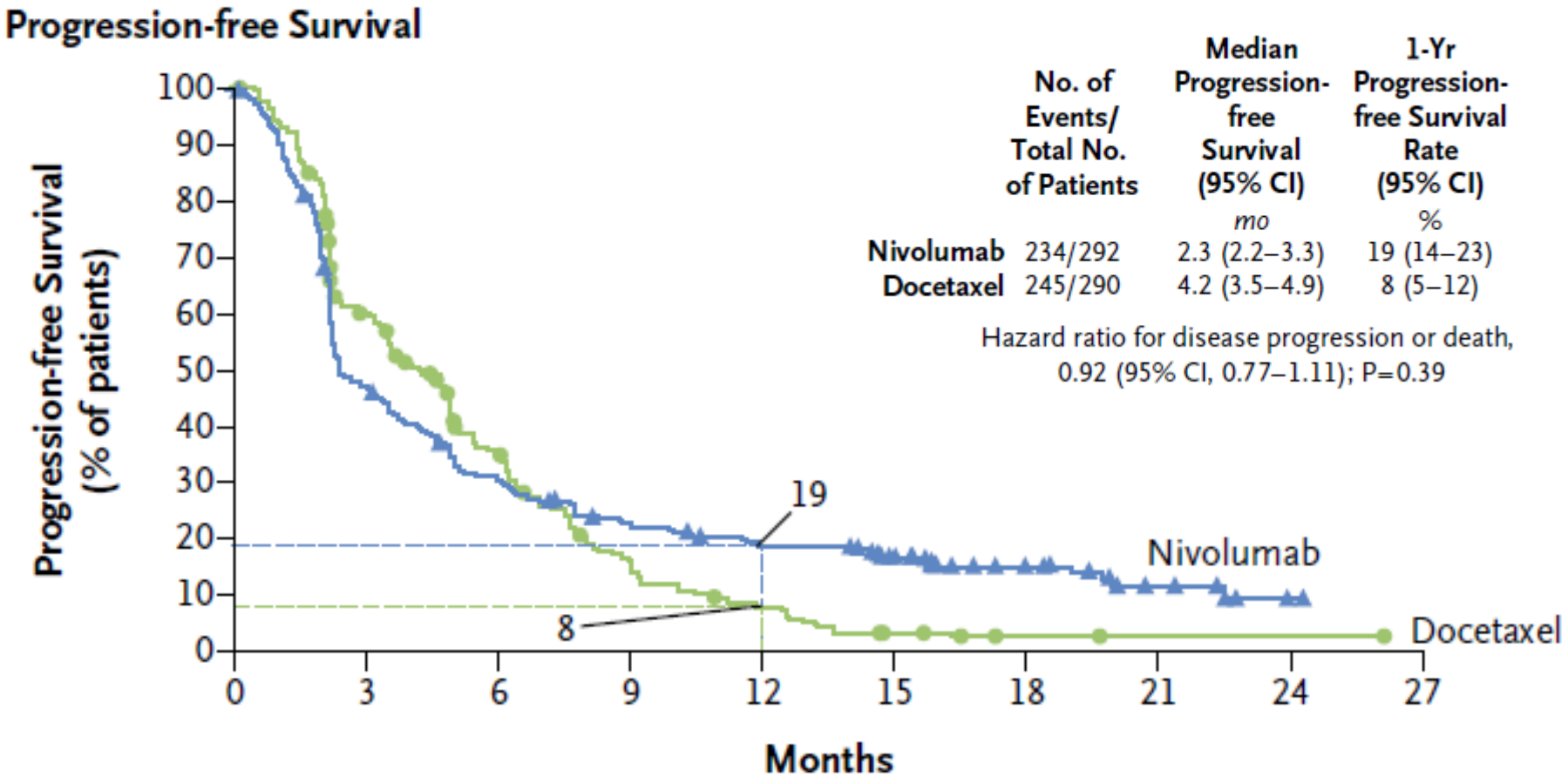
METHODS

In this randomized, open-label, international phase 3 study, we assigned patients with nonsquamous non–small-cell lung cancer (NSCLC) that had progressed during or after platinum-based doublet chemotherapy to receive nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks or docetaxel at a dose of 75 mg per square meter of body-surface area every 3 weeks. The primary end point was overall survival.

全生存期間


Overall Survival
No. of Deaths/ Total No. of Patients
Median Overall Survival (95% CI)
1-Yr Overall Survival Rate (95% CI)
mo
%
Nivolumab 190/292 12.2 (9.7–15.0) 51 (45–56)
Docetaxel 223/290 9.4 (8.1–10.7) 39 (33–45)
Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002
Overall Survival (% of patients)
100
90
80
70
60
50
40
30
20
10
0
51
39
Nivolumab
Docetaxel
0 3 6 9 12 15 18 21 24 27
Months
No. at Risk
Nivolumab 292 232 194 169 146 123 62 32 9 0
Docetaxel 290 244 194 150 111 88 34 10 5 0

無増悪生存期間


Progression-free Survival
Progression-free Survival (% of patients)
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
18
21
24
27
Months
19
8
Nivolumab
Docetaxel
No. of Events/ Total No. of Patients
Median Progression-free Survival (95% CI)
1-Yr Progression-free Survival Rate (95% CI)
mo
%
Nivolumab 234/292 2.3 (2.2–3.3) 19 (14–23)
Docetaxel 245/290 4.2 (3.5–4.9) 8 (5–12)
Hazard ratio for disease progression or death, 0.92 (95% CI, 0.77–1.11); P=0.39
No. at Risk
Nivolumab 292 128 82 58 46 35 17 7 2 0
Docetaxel 290 156 87 38 18 6 2 1 1 0

Nivolumab in Nonsquamous Non–Small-Cell Lung Cancer

TO THE EDITOR: In the article on the CheckMate 057 trial, Borghaei et al. (Oct. 22 issue)[1] provide data on overall and progression-free survival among patients with advanced nonsquamous non–small-cell lung cancer who were receiving either nivolumab or docetaxel. In this trial, docetaxel initially appeared to have better outcomes than nivolumab, but the trends were reversed after 9 months (Fig. 1 of the article, available at NEJM.org). In such instances in which hazard functions for two treatment groups cross during the study follow-up, it is not clear how to interpret the observed hazard ratios of 0.73 for death and 0.92 for disease progression or death for nivolumab as compared with docetaxel. An alternative is to use the restricted mean survival time to quantify the treatment benefit.[2,3] For overall survival, an estimated restricted mean survival time up to 24 months for nivolumab is the area under the Kaplan–Meier curve up to 24 months, which is 13 months. In other words, future patients receiving nivolumab for 2 years would survive for an average of 13 months. The difference in the restricted mean survival time between the two groups would be 1.7 months (95% confidence interval [CI], 0.4 to 3.1) in favor of nivolumab.[2-4] For progression-free survival, the difference in the restricted mean survival time is 1.3 months (95% CI, 0.2 to 2.3), again in favor of nivolumab. This quantification of treatment benefit has a much clearer clinical interpretation than its hazard-ratio counterpart, especially in cases in which hazard functions for two groups cross.

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Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

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ABSTRACT

BACKGROUND

Previous, uncontrolled studies have suggested that first-line treatment with gefitinib would be efficacious in selected patients with non–small-cell lung cancer.

METHODS

In this phase 3, open-label study, we randomly assigned previously untreated patients in East Asia who had advanced pulmonary adenocarcinoma and who were nonsmokers or former light smokers to receive gefitinib (250 mg per day) (609 patients) or carboplatin (at a dose calculated to produce an area under the curve of 5 or 6 mg per milliliter per minute) plus paclitaxel (200 mg per square meter of body-surface area) (608 patients). The primary end point was progression-free survival.

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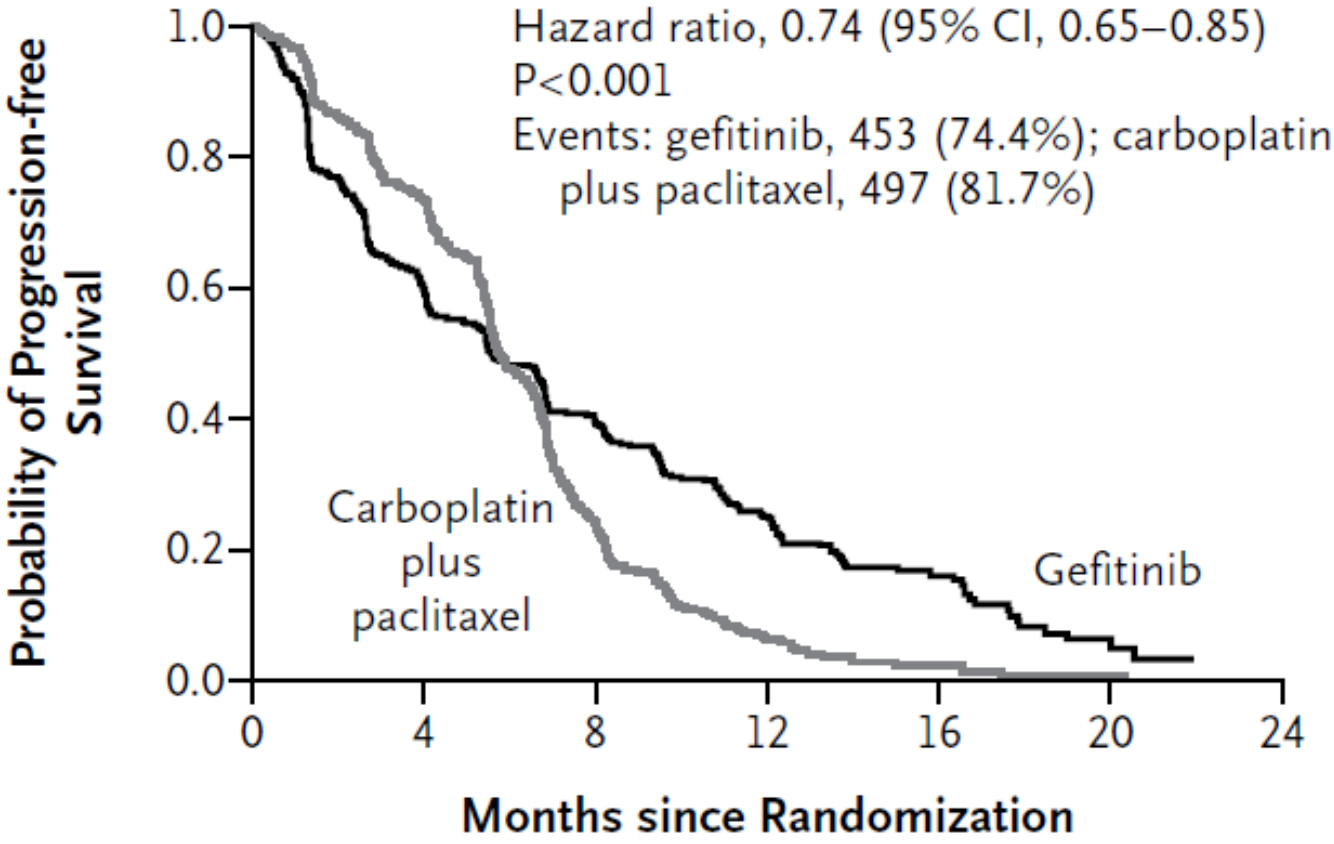
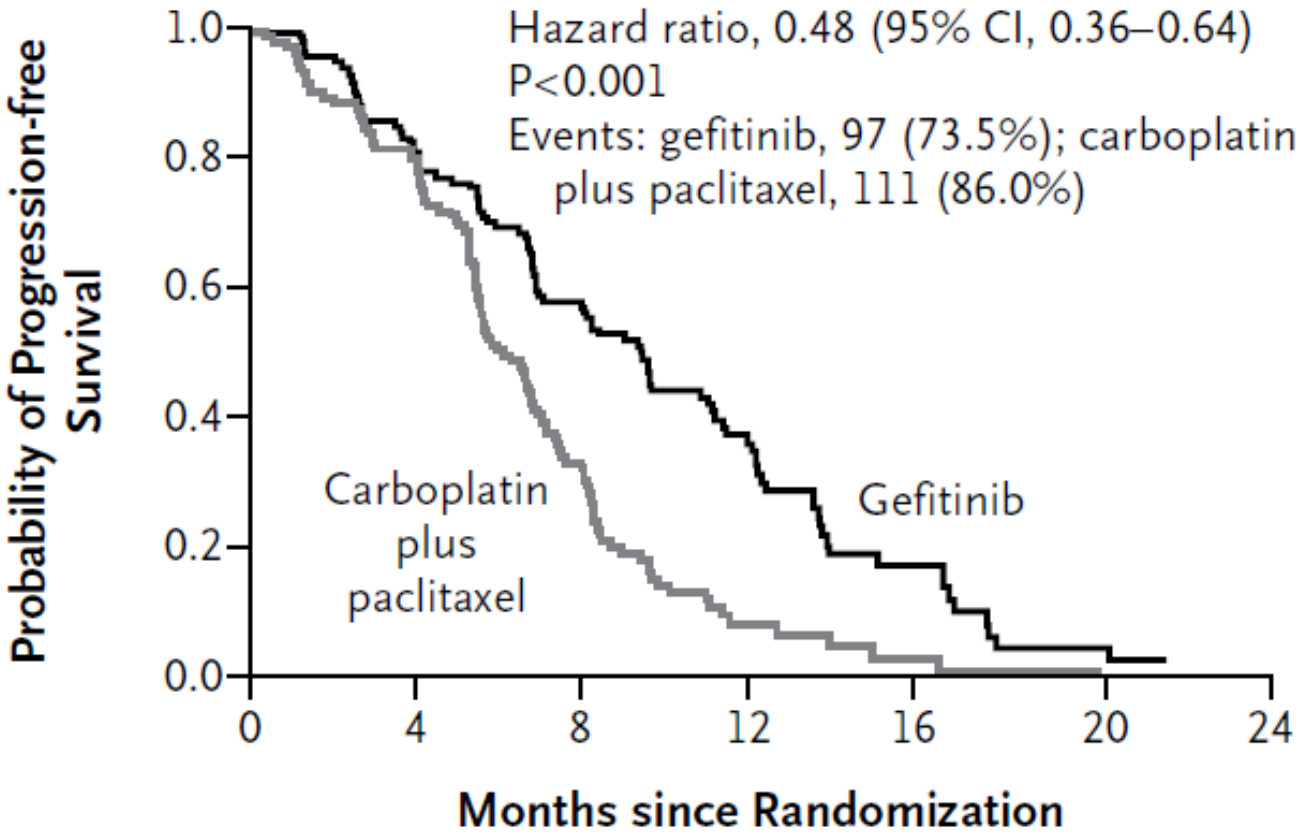
無増悪生存期間(全集団)



No. at Risk

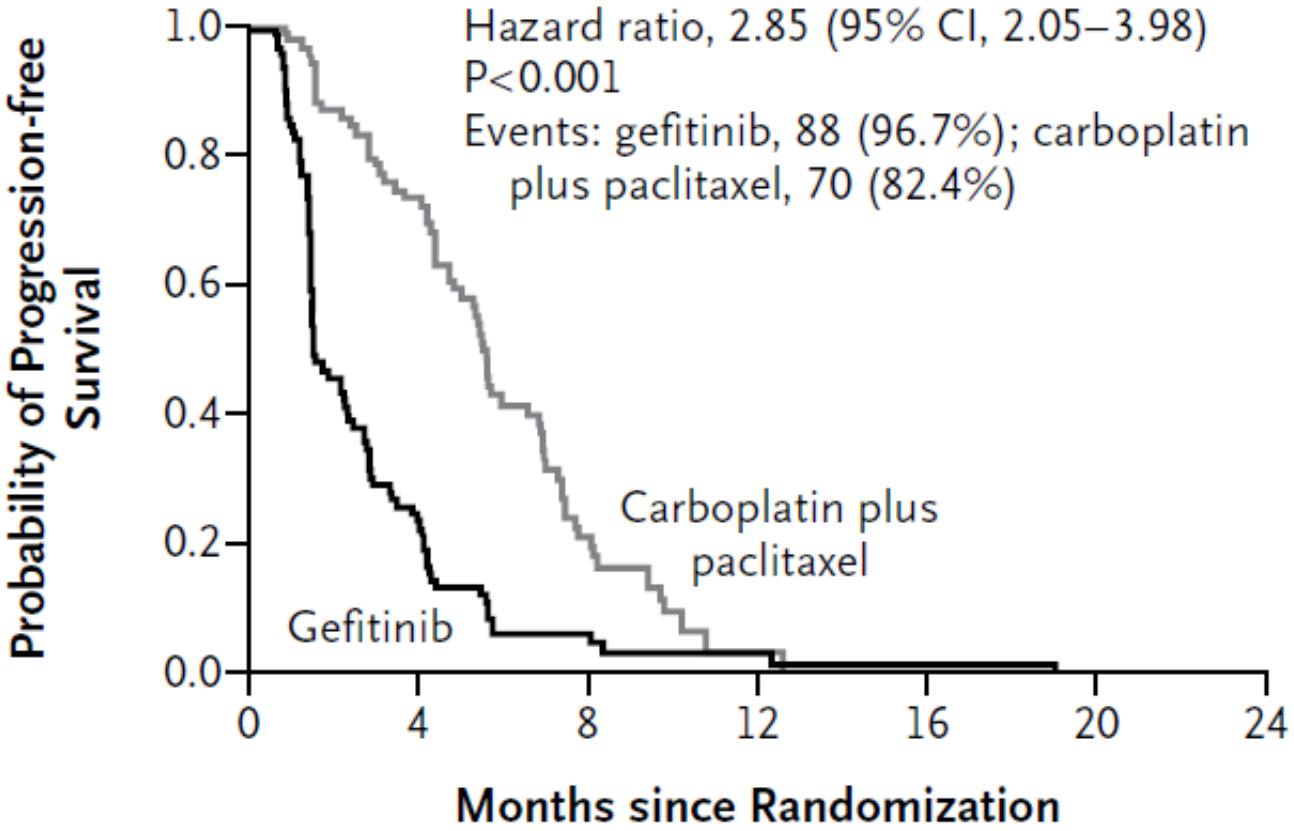
Gefitinib	609	363	212	76	24	5	0
Carboplatin plus paclitaxel	608	412	118	22	3	1	0

無増悪生存期間（EGFR変異陽性）



No. at Risk							
Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0

無増悪生存期間（EGFR変異陰性）



No. at Risk							
Gefitinib	91	21	4	2	1	0	0
Carboplatin plus paclitaxel	85	58	14	1	0	0	0

論点
生存時間データの主たる解析（検定）①

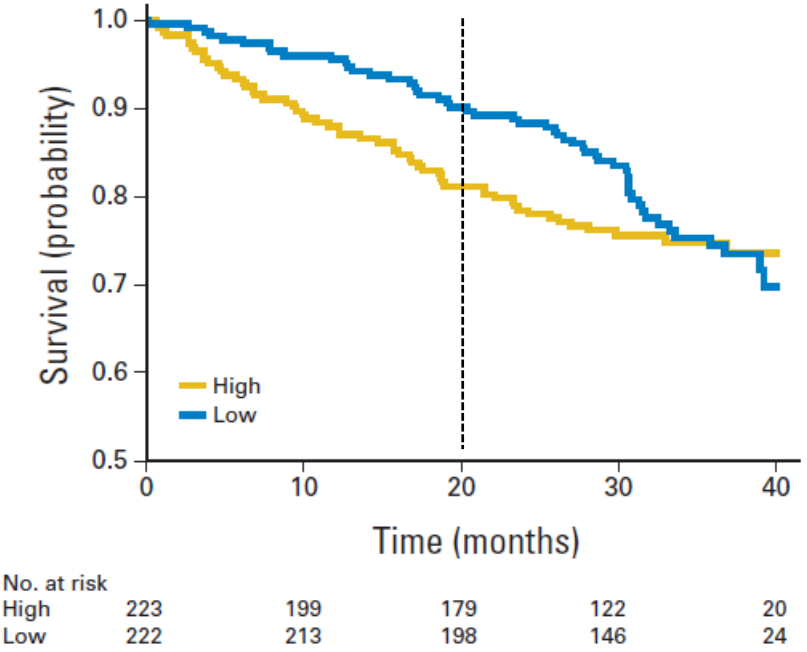
- 比例ハザード性が成立しなかった場合，ログランク検定やCox回帰以外の検定手法を用いた経験はありますか？
  - 検定手法の内容
  - 比例ハザード性が成立しなかった理由
  - 何か困難が生じた点（症例数設計，中間解析など）
  - その他，疑問点などがあれば

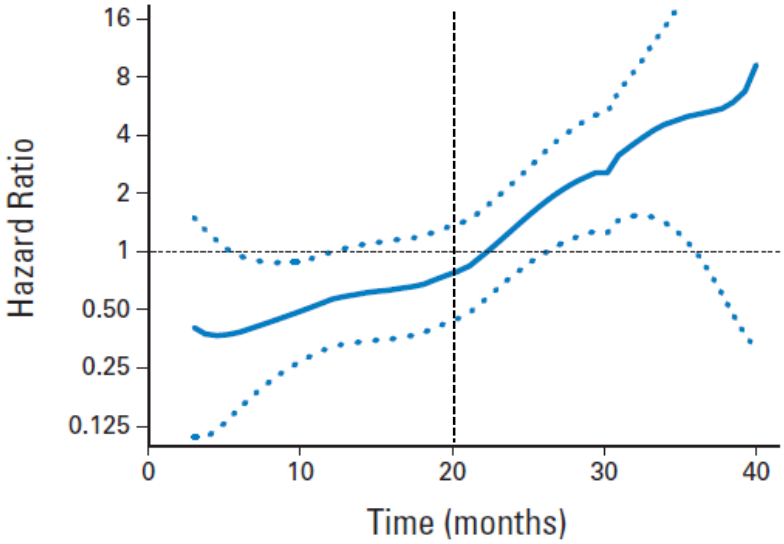
論点
生存時間データの主たる解析（検定）②

- 比例ハザード性が成立しない場合
  - ログランク検定やコックス回帰を用いるべきか？
  - ログランク検定やコックス回帰以外の検定手法を用いることは適切か？

論点
比例ハザード性と追跡期間

- 適切な追跡期間の設定方法は？





Uno H, JCO, 2014

論点
生存時間データの主たる解析（推定）①

- 比例ハザード性が成立しなかった場合，治療効果の推定にハザード比以外の要約指標を用いた経験はありますか？
  - 指標の例
    - 中央値（パーセント点）
    - ある時点の生存率
    - RMST（RMTL）
    - …

論点
生存時間データの主たる解析（推定）②

- 比例ハザード性が成立しない場合
  - 治療効果の推定にハザード比を用いるべきか？
  - 用いるべきではない場合，適切な要約指標は？

論点
RMSTを指標とした解析の利用可能性①

- 有効性の主たる解析（検定）として用いることは可能か？
  不可能な場合，方法論上の課題は？
  - 検討事項の例
    - 検定方式
    - 推定
    - 評価項目（差，比など）
    - 症例数設計
    - 調整解析
    - 境界範囲τの設定
    - 中間解析
    - …

論点
RMSTを指標とした解析の利用可能性②

- 本解析をどのような状況・目的で実施するのが良いか？