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Article

Clinical Significance of a Prospective Large Genomic Screening for SCLC: The Genetic Classification and a Biomarker-Driven Phase 2 Trial of Gedatolisib.

Umemura S, Udagawa H, Ikeda T, et al. J Thorac Oncol. 2025 Feb;20(2):177-193.

はじめに：肺小細胞癌は肺癌全体の10-15%を占め5年生存率は10%と予後不良である。非小細胞肺癌と異なり新しい治療法の開発があまりなされていない。その理由として小細胞癌が単一の疾患として診断・治療されてきたため、分子病理学的分類に基づく研究が立ち後れていたことが挙げられる。

方法：1035例の小細胞癌をNGSを用いた遺伝子パネル検査で解析した(LC-SCRUM-Asia)。

結果：944例の解析に成功し、遺伝子変化の違いによって4つのサブグループを分類することができた。(Fig.1) 。上から非小細胞癌でよく同定される変異をもった群(NSCLC-subgroup)、腫瘍で一般的に同定される変異を持った群(Hotspot-subgroup)、PI3K関連の変異を持った群(PI3K-subgroup), MYC増幅群(MYC-subgroup)である。ただ約70%はTP53の異常のみあるいは不明なものであった。Fig.2:NSCLC-subroup, Hotspot-subgroup, PI3K-subgroupにおける遺伝子変異の詳細。Fig.3:このサブグループ間においてNSCLC-subgroupとMYC-subgroupは従来のプラチナ製剤を併用した化学療法の効果が乏しかった。Fig.4: 上記とは別にヒストン修飾酵素の遺伝子変異が17.6%に認められ、それらを有する患者ではPD-l/PD-L1阻害薬が有効であった。Fig.5:PI3K阻害薬であるGeratolinibの治験結果。PI3K関連の変異を持つ15例に対し投薬した。数は少ないが、NSCLC-subgroup, MYC-subgroupはこの治験では効果不良であった。

まとめ：肺小細胞癌のmolecular profilingは治療効果を予測するのに有用であり、治療選択に効果的である。

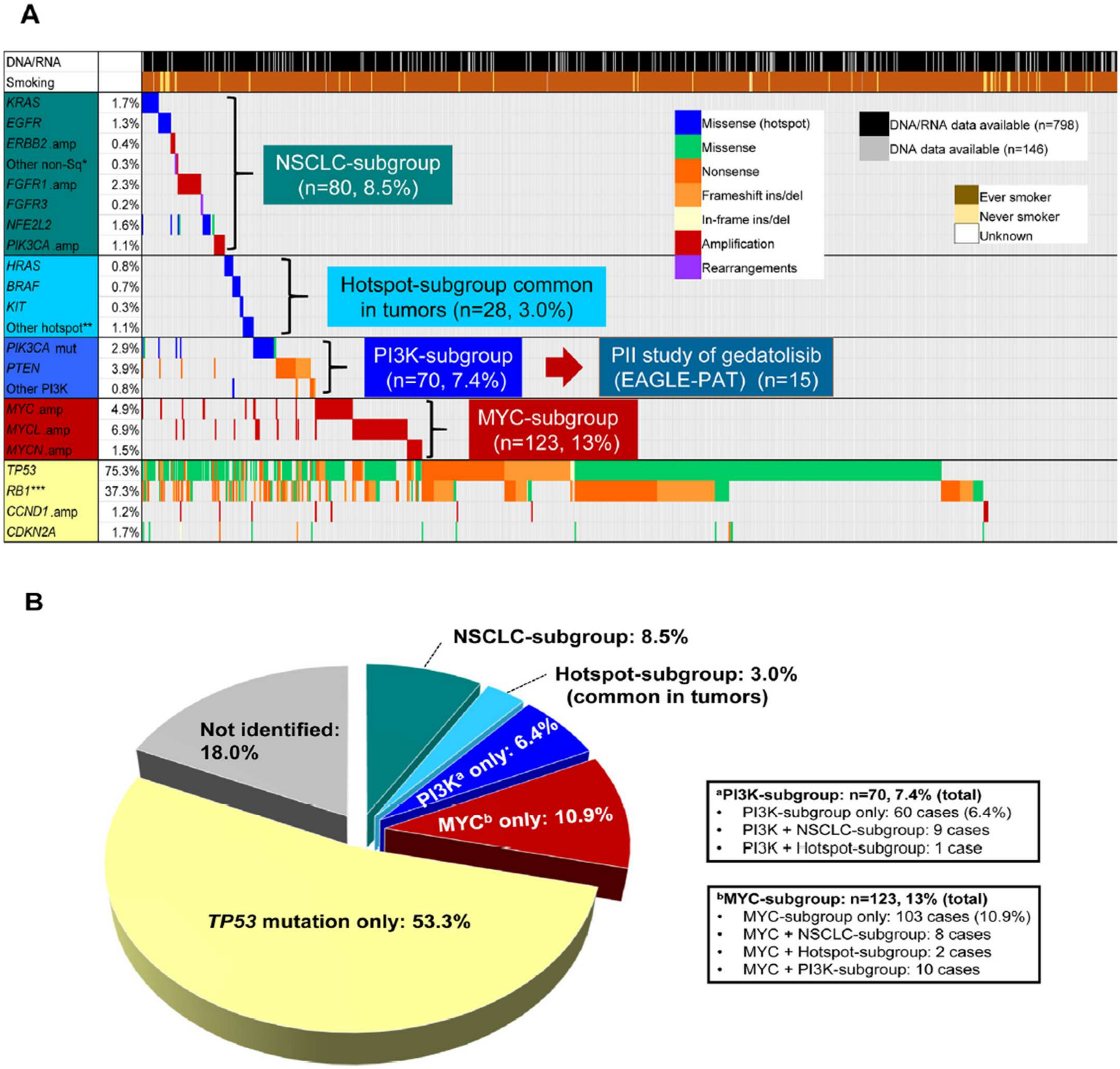

Figure 1. Key genetic alterations in SCLC and the genetic classification model for this cancer. (*A*) An overview of the key genetic alterations in 944 SCLCs and the major associated clinical features. The frequency of each genetic alteration is noted on the left. The genes are displayed as rows, and the samples are displayed as columns, along with the major associated clinical features. (*B*) Pie charts revealing the distribution of biologically relevant genetic alterations in the entire cohort (944 SCLCs). SCLCs were divided into subgroups based on the key genetic alterations: the NSCLC-subgroup (harboring biologically relevant genetic alterations found in NSCLCs); the Hotspot-subgroup (harboring targetable hotspot mutations that are common in tumors); the PI3K-subgroup (harboring P13K/AKT/mTOR pathway gene mutations); and the MYC-subgroup (harboring MYC family amplifications). *ALK/RET fusion or *MET* amplification. **Other hotspot genetic mutations. ***Frequency not including splice site mutations and copy number loss in the exon sequencing. [a]PI3K/AKT/mTOR. [b]MYC family.

上から非小細胞癌でよく同定される変異をもった群(NSCLC-subgroup)、腫瘍で一般的に同定される変異群(Hotspot-subgroup)、PI3K関連の変異を持った群(PI3K-subgroup), MYC増幅群(MYC-subgroup)である。ただ約70%はTP53の異常のみあるいは不明なものであった。

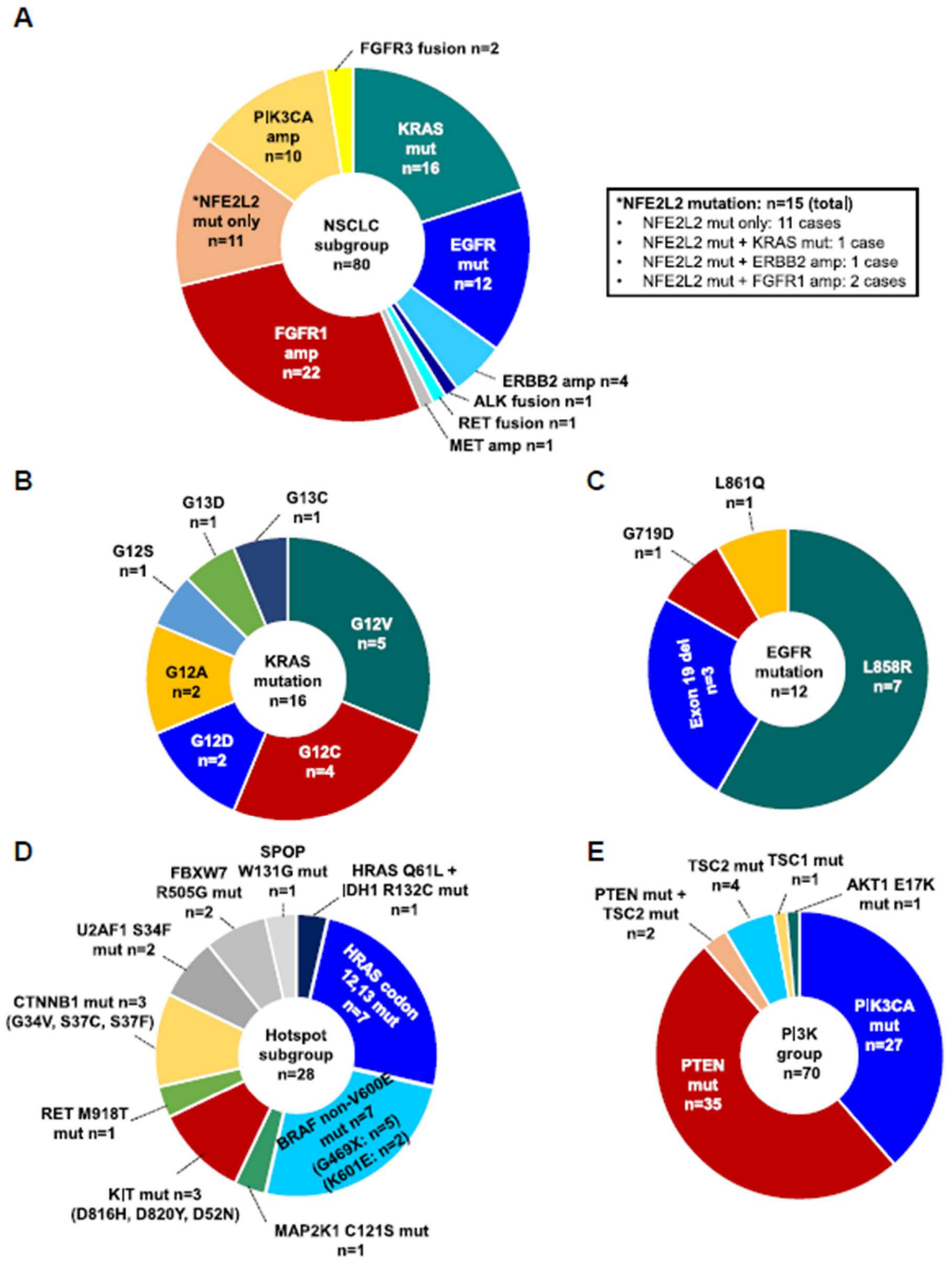

Figure 2. Details of the genetic alterations detected in this study. (*A*) Pie chart revealing the distribution of the NSCLC-subgroup genetic alterations. (*B*) Pie chart revealing the *KRAS* mutation spectrum. (*C*) Pie chart revealing the *EGFR* mutation spectrum. (*D*) Pie chart revealing the distribution of targetable hotspot genetic mutations of biological interest (common in tumors). (*E*) Pie chart revealing the PI3K/AKT/mTOR pathway mutation spectrum.

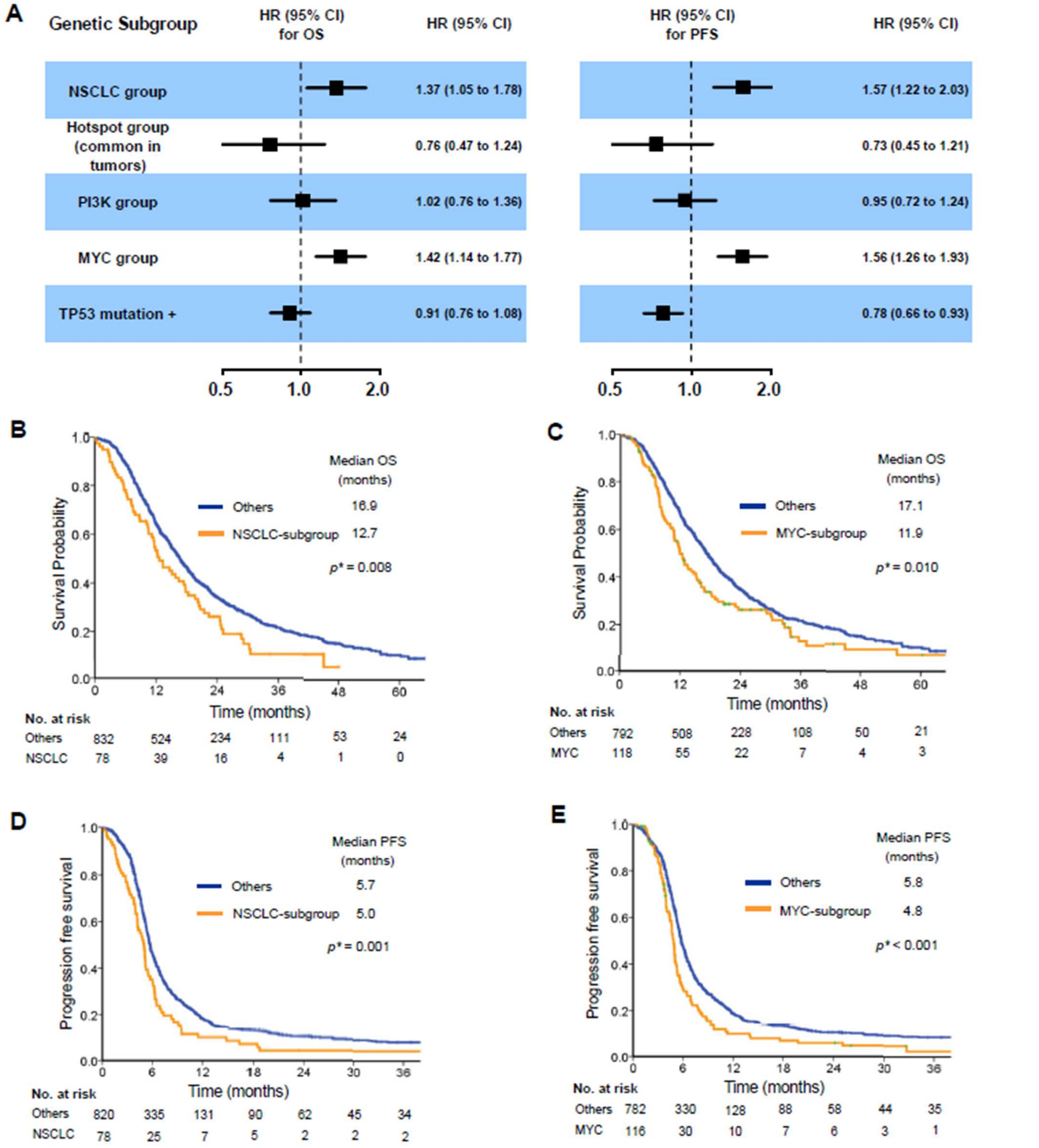

Figure 3. Genetic classification could be useful for predicting the treatment outcomes for platinum-based therapy. (*A*) Hazard ratios for OS (left panel) and PFS (right panel) according to the genetic subgroups. (*B*) Kaplan-Meier curves plotted to determine the OS: NSCLC-subgroup versus others. (*C*) Kaplan-Meier curves plotted to determine the OS: MYC-subgroup versus others. (*D*) Kaplan-Meier curves plotted to determine the PFS: NSCLC-subgroup versus others. (*E*) Kaplan-Meier curves plotted to determine the PFS: MYC-subgroup versus others. **p* values are based on the log-rank test. OS, overa progression-free survival.

このサブグループ間においてNSCLC-subgroupとMYC-subgroupは従来のプラチナ製剤を併用した化学療法の効果が乏しかった。

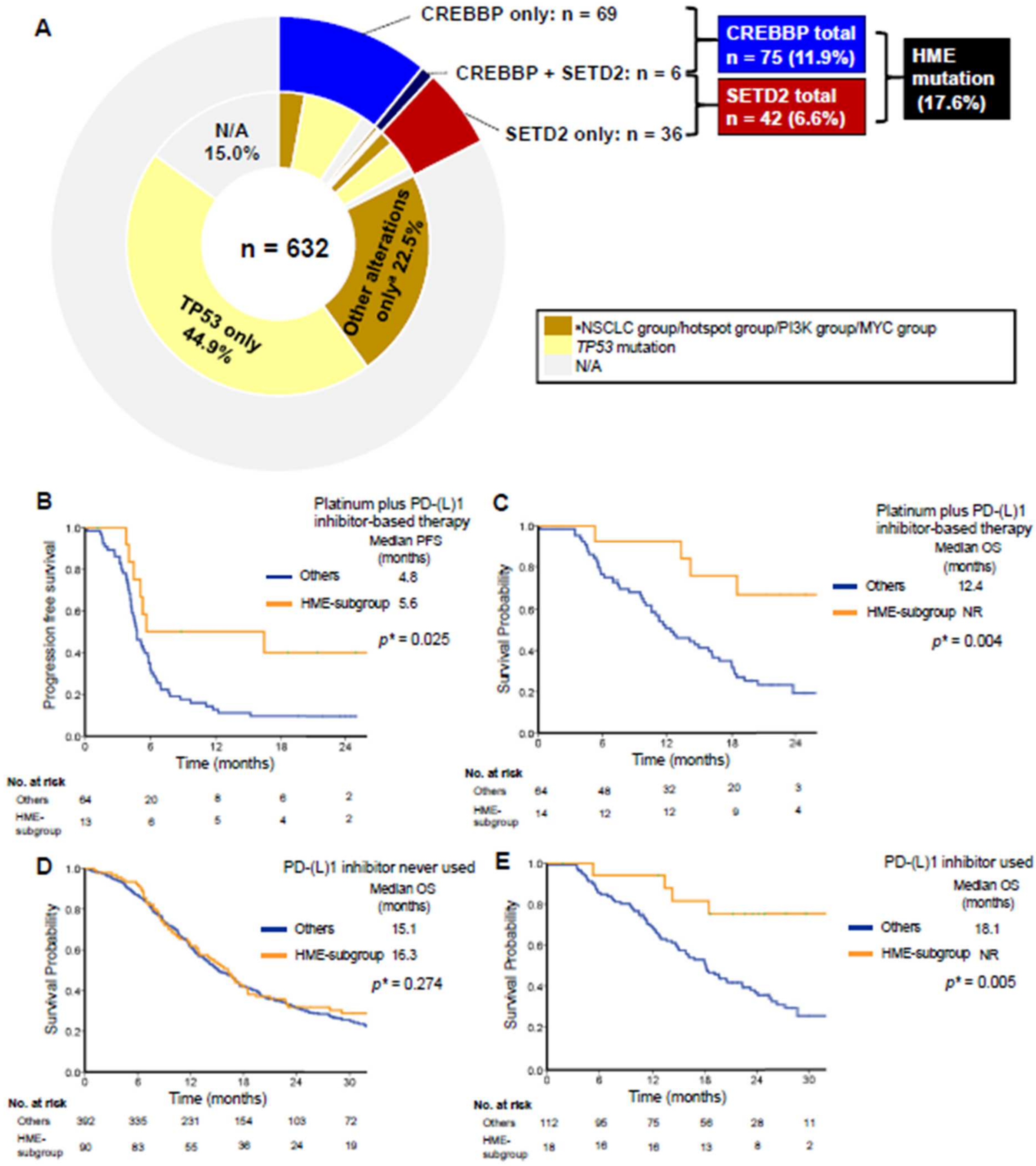

Figure 4. Epigenetic regulator gene mutations and the effect of PD-(L)1 inhibitor on survival. (*A*) Pie chart revealing the frequency of HME mutations detected in the 632 samples analyzed using OCA version 3. (*B*) Kaplan-Meier curves plotted to determine the PFS according to the HME mutation status (HME-subgroup versus others) in 78 cases. (*C*) Kaplan-Meier curves plotted to determine the OS according to the HME mutation status (HME-subgroup versus others) in 78 cases. (*D*) Kaplan-Meier curves plotted to determine the OS in patients who had never received PD-(L)1 inhibitor-based therapy according to the HME mutation status (HME-subgroup versus others). (*E*) Kaplan-Meier curves plotted to determine the OS in patients who had received PD-(L)1 inhibitor-based therapy at any treatment line according to the HME mutation status (HME-subgroup versus others). **p* values are based on the log-rank test. HME, histone-modifying enzyme; OS, overall survival.

上記とは別にヒストン修飾酵素の遺伝子変異が17.6%に認められ、それらを有する患者ではPD-l/PD-L1阻害薬が有効であった。

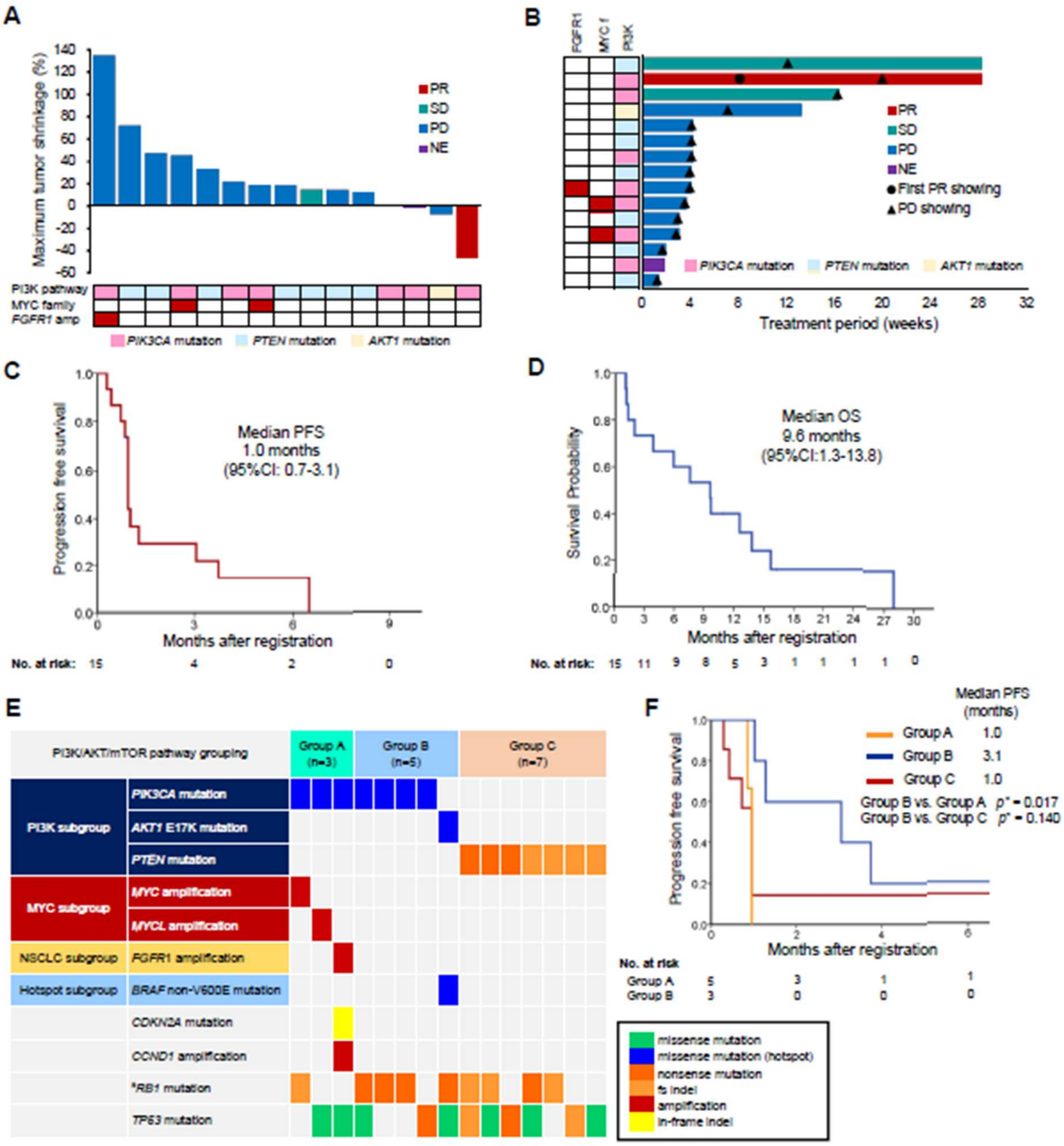

Figure 5. A phase 2 trial of gedatolisib for patients with SCLC with mutations in the PI3K/AKT/mTOR pathway genes. (*A*) Maximum tumor shrinkage and results for available biomarkers. (*B*) Swimmer plot revealing the treatment period and best response. (*C*) Kaplan-Meier curves plotted to determine the PFS. (*D*) Kaplan-Meier curves plotted to determine the OS. (*E*) An overview of the key genetic alterations in tumor samples obtained from the 15 patients treated with gedatolisib. The genes are displayed in rows, and the samples are displayed in columns. (*F*) Kaplan-Meier curves plotted according to the PI3K/AKT/mTOR pathway grouping (group A versus group B versus group C). *p value based on the log-rank test for comparison of the survivals. The genetic profiles of the PI3K-subgroup, *MYC*-subgroup, NSCLC-subgroup, and Hotspot-subgroup are found in the colored boxes. [a]*RB1* mutations not including splice site mutations and copy number loss. OS, overall survival; PFS, progression-free survival.

PI3K阻害薬であるGeratolinibの治験結果。PI3K関連の変異を持つ15例に対し投薬した。数は少ないが、

NSCLC-subgroup, MYC-subgroupはこの治験では効果不良であった。