Immune-Stimulants and Immune Modulators

694 POSSIBLE IMMUNE-MODULATION OF CDK4/6 INHIBITORS AND CLINICAL TRIAL DEVELOPMENT IN BETEL-NUTS RELATED HEAD AND NECK SQUAMOUS CELL CARCINOMA IN TAIWAN

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Background Betel nuts in Taiwan might contribute to strong angiogenesis & invasion with resistance to traditional therapies. In our research, betel-nuts exposed HNSCC cell line, TW2.6, had high PDL1, defective p53 mutation, p16 loss, and BCL2 overexpression. PI3K/AKT/mTOR inhibitors, anti-angiogenesis therapies, CDK4/6 inhibitors, DDR interventions, and immunotherapy-containing regimens will be future backbones and reverse treatment refractoriness(AACR-AHNS2017). The genomic signature of TW2.6 has been figured out (AACR2020) mainly with PIK3CA H1047R mutation, high TMB(8.42 muts /Mb)/MSS, p53/MYC/HRAS/DDR2/ PDGFRbeta/ EPHB1/ATM mutations, FAT1 loss, amplification of VEGF-A/TERT/ FGF10/CCND3/SOX9/IL-7R/SDHA/RICTOR/FLCN, CDK12 loss of function, and deletions of STK11/ARID1B/MITF/TNFAIP3. CDK4/6 inhibitor was effective in HPV-negative and pRB-positive HNSCC and had strong immuno-modulation(suppress Treg, increase CTLs, enhance MHC I/II upregulation and antigen presentation). Palbociclib was effective on TW2.6 and could resensitize TW2.6 to docetaxel, afatinib, & radiation & enhance further response to BYL719& foretinib(VEGFR2/c-MET/Axl triple inhibitor). Western blotting showed (1) Slug, Snail, N-cadherin, Twist, Vimentin, Claudin-1, Axl, p-Akt and p70S6K decrease; (2) BMI-1, pRB, and PDL1 drop(ASCO218).

Methods SCC4, SCC9, SCC15, SCC25, FaDu, KB, Cal27, SAS, and TW2.6 for (1)in vitro sensitivity to palbociclib, ribociclib, abemaciclib; (2)synergistic effects with other therapies by MTT assay, colony formation assay, and western blotting. NGS studies were used to study molecular biomarkers of CDK4/6 inhibitors efficacy.

Results Palbociclib had greatest efficacy over SCC15(classical HPV-negative type with EGFR overexpression) followed by SCC25, SAS, TW2.6(HPV-negative EMT type), & CAL27; but little efficacy over KB. In HPV-positive cell lines, palbociclib had (1) promising response on SCC25(classical HPV+ type); (2) little response on FaDu(HPV+ mesenchymal type) & KB (basal type in TCGA). In other HNSCC cell lines with basal types, however, SAS & CAL27 responded well to palbocilclib. Palbociclib response seemed to correlate to CCND1 gain and CDKN2A deletion; but FaDu had not so good palbociclib response with these two changes and TW2.6 had good response even without these two. TW2.6 was most sensitive to palbociclib, moderately sensitive to ribociclib, and mildly sensitive to abemaciclib.

Conclusions TW2.6 is responsive to CDK4/6 inhibitor(palbociclib>ribociclib>abemaciclib). FAT1 loss, CCND1/3 overt amplification, PI3K/AKT/mTOR derangements, and FGFR amplification might confer CDK4/6 inhibitor resistance in our genomic study. Based on immuno-modulatory effects of CDK4/6 inhibitor, we have initiated a study using ribociclib with spartalizumab in R/M HNSCC(RISE-HN: NCT04213404). We might develop a ctDNA-driven(intact PTEN & FAT1, CDKN2A deletion, high CDK4/6 copy numbers, no CCND1/3 overt amplification or FGFR amplification or other PI3K/AKT/mTOR derangements) clinical trial with palbocilcib and avelumab in betel-nuts related R/M HNSCC in Taiwan. Abemaciclib may have better immune-modulation.

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