Part 1 – Background.

The study uses three different drugs in sequence, first, Pembrolizumab (large molecule) which is a human monoclonal antibody that acts a checkpoint inhibitor, blocking the programmed cell death 1 receptor on the T-cell, increasing T-cell cytotoxicity against cancer cells. The second drug is a BRAF (V600) kinase inhibitor, Vemurafenib (small molecule) which blocks certain proteins made by the mutated BRAF gene, preventing cancer cell growth. The third drug is a Selumetinib again prevents cancer cell growth by blocking proteins called MEK1 &MEK2, it is a type of kinase inhibitor.

Interesting study which involved pooled analysis of 3 clinical trials KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006. The study was used to investigate the Outcomes in Advanced Melanoma. Specifically the association of BRAF V600E/K Mutation Status and Prior BRAF / MEK inhibition post Pembrolizumab administration.

The study used three clinical endpoints;

Objective Response Rate (ORR) – percentage of patients whose cancer shrinks or disappears after treatment

Progression Free Survival (PFS) – The length of time during and after treatment of the cancer that a patient lives with disease, but it does not get worse.

Part 2

Overall Survival (OS) – The length of time from either the date of diagnosis or the start of treatment where the patients diagnosed with disease are still alive.

The ORR endpoint gives the percentage of patients that are relatively disease free, i.e. gone into complete remission (CR), PFS endpoint indicates the length of time disease is stable, which may encompass CR or partial remission (PR). OS endpoint give the length of time the patients with the disease survive. In terms of quality of life the ORR endpoint is probably the most credible.

Looking at the study population overall the pooled data gives n=1558 which is a reasonably large sample size and should yield good results and show differences between groups. The ratio of men to women is 60:40 which should make the study generalizable. The mean age is 60, older adults, the age range is quite wide 68% of patients in the study between 46 and 74 years. This will probably distort the results a 46 year old will respond differently to the drugs used in the study compared to a 74 year old.

Part 3

The percentage of patients overall for the three study endpoints ORR 38.3%, 4yr-PFS 22.0% and 4yr-OS 36.9% are similar to those attained in the subgroups BRAF wild type (WT) and BRAF V600E/K-mutant melanoma. This indicates that both subgroups contribute equally to the overall result. The subgroups are of different sizes BRAF-WT(n=1124), BRAF V600/K-mutant melanoma (n=434). This may present a problem when comparing the survival rates in the different groups, indeed the KM-curve for PFS of patients in the BRAF-WT vs BRAF V600/K-mutant melanoma shows the curves very close together. The difference between the survival rates for the two groups may not be significant because of the unequal sample sizes of each of the groups. (Mantel & Haenszel). The author has not given Log-rank tests for the KM-Curves which is quite telling! The Log-rank test is a weighted test and unequal sample sizes produced biased results. The same problem is present in the KM-curve for the treatment groups although the sample sizes are more equal.

Part 4

Moving on to the subgroup analysis the three clinical endpoints are more favourable in the BRAFi naïve patient group with or without MEKi therapy post-Pembrolizamab therapy. The patients previously exposed to BRAFi performed poorly because their disease was more advanced. This is ‘borne-out’ by the univariate and multivariate logistic regression analysis.

The author cites the limitations of the trial, is that it is a retrospective analysis that relies on pooling of data from three different studies, the inclusion criteria particularly for the BRAF V600E/K-mutant melanoma where not the same. The author cites that proper conclusions about sequencing of drug treatment, i.e. Pembrolizamab, then BRAFi +/- MEKi cannot be made because of the retrospective nature of the study and the small sample size of the sub-groups, the BRAF V600 E/K-mutant subgroup of 434 patients was split into even smaller groups, n=271 and n=163 and then compared.

The use of pembrolizmab is supported regardless of BRAF V600E/K mutant status or use of BRAFi +/- MEKi therapy, further study of subgroups is necessary. Altogether a good study, but the skewed sample sizes of the major groups and sub groups may have affected the results of this study.