Gilead wants to thank Fimea for the assessment “Tecartus manttelisolulymfooman hoidossa” (published 1.4.2021 in Fimea website). With the following comments Gilead hopes to clarify around the key uncertainties raised in the assessment report.

Regarding the number of patients treated with Tecartus

Gilead has estimated that the number of patients treated with Tecartus would be 2-4 patients per year. According to Fimea, this estimate can be considered accurate if Tecartus treatment is used only in a patient population matching the inclusion and exclusion criteria of the ZUMA-2 study. According to feedback that Gilead has received from Finnish experts, ZUMA-2 criteria would be the most important criteria when selecting patients for Tecartus treatment. In addition, Gilead's first CAR-T product, Yescarta, has recently been introduced in Finland and our understanding is that the criteria for patient selection are in line with those of the ZUMA-1 study. Therefore, we anticipate that a similar practice will be followed for Tecartus.

Regarding the average age of a Tecartus patient

Gilead would like to further clarify the comment related to the mean age of a Tecartus patient. The mean age for MCL diagnosis in Finland is 68 years (1). The mean age of patients at the time of diagnosis is unlikely to correspond to the age of patients eligible to be treated with Tecartus. In the cost-effectiveness analysis base-case, the mean age of patients was estimated to be 63.7 years, according to the ZUMA-2 study. Scenario analysis was run for a patient population with mean age of 70 years. As Tecartus treatment will be used in Finland for a very small proportion of patients with MCL, it is challenging to determine the mean age for the pool of patients that eventually will be treated with Tecartus in later lines. One of the most important criteria for starting CAR-T treatment is the patient's condition. Eligibility for Tecartus treatment is linked to the patient’s condition and performance status and these eligible patients are usually younger. Therefore, the patients that will be selected for Tecartus treatment are patients who have been diagnosed earlier in time and they are therefore closer to the ZUMA-2 patient population in terms of age and performance score.

Regarding the Phase II single-arm study

According to the assessment report, one of the main uncertainties relates to the fact that the ZUMA-2 study was a single-arm study without a control group. While the lack of comparative evidence coming from Tecartus’ clinical trial can pose a challenge related to determining the efficacy of the product vs. current standard of care in Finland, in the same time, there are ethical and methodological challenges linked to performing randomised-controlled trials (Phase III) in this setting with a population with a high unmet need (2).

Taking into account the significant improvements in r/r MCL patients’ response to treatment (over 90%) and OS (83% at 12 months) that Tecartus has demonstrated, it would be considered unethical to withhold patients from this therapy by running an extensive development program for it and/or by

randomising patients in a Phase III clinical trial (2), to the control group, which would be palliative care, with poor survival prognosis (median OS of approximately 6–10 months reported in observational studies for currently available treatments (3-7)). Moreover, it is challenging to enrol enough patients for a randomized Phase III study for an orphan indication, such as r/r MCL (2), and, in addition, a randomized study would need to allow for a cross over design in the control group due to the very short OS in this setting (3-7), leading to large difficulties to dissect any difference in OS between the arms.

Therefore, Gilead has taken extra steps in order to add comparative evidence for the efficacy of Tecartus vs. standard of care for r/r MCL patients, by running an observational study in Europe where real-world survival evidence was collected for standard of care treatments used for a similar population to ZUMA-2. In addition, we performed an indirect treatment comparison based on efficacy data for standard of care identified from the literature (through a systematic literature review study). With this approach Gilead is bridging the gap of the uncertainty that the lack of comparative evidence data can create.

Regarding the survival extrapolation and modelling of survival for Tecartus

The economic evaluation of Tecartus was performed using a three-state partition survival model, which is in line with what has been previously used for treatments resulting in long-term survival/curative intent (8, 9), and it is what is recommended from the Center for Reviews and Dissemination/Center for Health Economics at University of York through their appraisal; they revealed that this type of model is suitable and highly relevant for the cost-effectiveness analysis of CAR-T products like Tecartus with ”curative intent”, i.e. long-term survival after treatment (10).

In order to estimate Tecartus’ overall survival (OS) and progression-free survival (PFS) in the economic evaluation, a mixture cure methodology was used, which was the methodology with the best statistical fit and also the one that fitted optimal to the data from ZUMA-2, reflecting the observed flat tail (plateau) in the OS and PFS (11). This methodology is also shown to be, through a comparative study of several methodologies used in economic evaluation in immuno-oncology, the best survival extrapolation method for the type of therapies that result in long-term survival (12). Gilead/ tested other methodologies for the extrapolation of OS and PFS for Tecartus but their statistical fit and representation of the observed data from ZUMA-2 has not been equally good or better than the mixture cure model methodology. Hence, in the economic evaluation presented to Fimea, the best, and most conservative approach of the estimation of OS and PFS has been used in the base-case analysis; the incremental cost-effectiveness ratio of this analysis was estimated to be €75,649 per quality-adjusted life-years gained.

Using the mixture cure methodology for the extrapolation of OS and PFS, a “cure-fraction” is defined in the economic evaluation for Tecartus, i.e. the proportion of patients expected to have a long-term survival. With regards to the concern that has been expressed in the report, i.e. that this proportion of patients (68%) is overestimated in the economic evaluation, and it should not be defined according to the overall survival data from ZUMA-2 (11), but instead using the percentage of patients from the trial

that respond and remain in response to the therapy over time (47% according to the assessment report), we would like to clarify that two different groups of patients are compared here (i.e. those that respond to therapy and are in remission vs. those that survive over time regardless of their initial response status to therapy). And most importantly, we would like to point out that we have already considered both patients with overall survival regardless of their response to therapy, and those that remain progression-free over time, in the base-case analysis of our economic evaluation.

The 68% of patients that are long-term survivors, as also estimated from the ZUMA-2 study (24-month OS was 68% for the n=68 patients of the analysis; the 28 patients who had an even longer follow-up in the ZUMA-2 study also had 68% OS at 24 months and even at 30 months), is only a consequence of the long-term remission that Tecartus patients achieved. The fraction that is the most important in the analysis is the one connected with progression-free survival (PFS), i.e. the pre-progression fraction, as it is called in the health economic model (47.7%). This pre-progression fraction is congruent with the progression-free duration observed in ZUMA-2 (in fact, it is even a little lower since the observed PFS in ZUMA-2 is 53% at 24 months for the n=68 patients; for those 28 patients in ZUMA-2 with a longer follow-up, PFS was 54% at 24 months and 49% at 33 months). And it represents the patients that remain in remission (in other words, as defined in the report, the ones that respond to therapy over time). And this percentage of patients is of course in accordance with Fimea's calculations as they suggest in their report (47%).

If we would change the "cure-fraction" in the presented economic evaluation to the one suggested in FIMEA's report (to 47%), clinically implausible results would have been obtained (see Figure 1 and 2 in the appendix), because patients treated with Tecartus would be ether progression-free or dead, indicating that Tecartus treated patients would have a very high likelihood of death once they progress (close to 1), which is not clinically plausible and which is not in line with what has been observed in ZUMA-2 (even when patients progress they are still contributing with several survival months, given that OS > PFS at all time points; they never become equal or close to being equal) (11).

Another way to demonstrate this problem is to look at the ratio of time spent in post progression over time. In the base case analysis, that Gilead has submitted to Fimea, the model predicts similar repartitions for both arms:

Tecartus-> 0.385

Standard of Care-> 0.435

Under FIMEA's assumption that the "cure-fraction" would be close to 47%, the ratios would be:

Tecartus ->**0.019**

Standard of Care ->0.435

Such a result would eventually indicate a higher long-term remission for the standard of care population than with Tecartus, which is of course not in line with what it is observed regarding the remission and survival of r/r MCL patients treated with SoC today (3-7).

According to assessment report, uncertainty about the long-term survival and the number of patients could be the starting points for managed introduction. Gilead is willing to participate in negotiations in order to provide this innovative therapy to treating physicians and MCL patients in Finland.

Appendix

Figure 1: Base-case (according to Gilead) Markov traces, with cure-fraction for OS as predicted by MCM-exponential ~68%; PFS cure fraction 47.7%

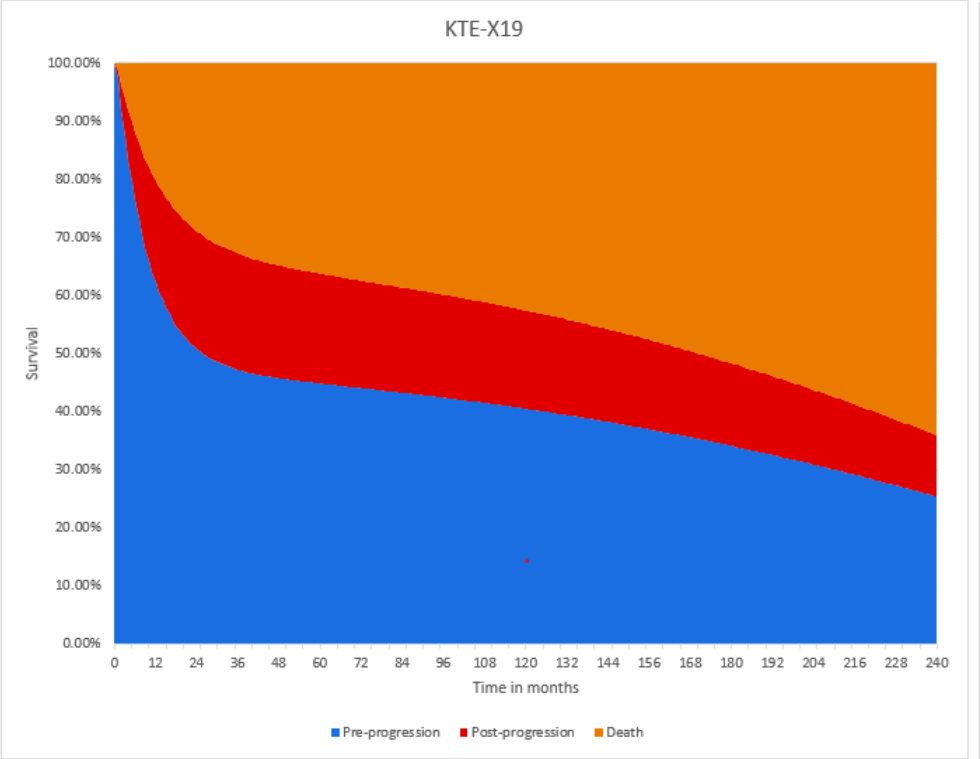
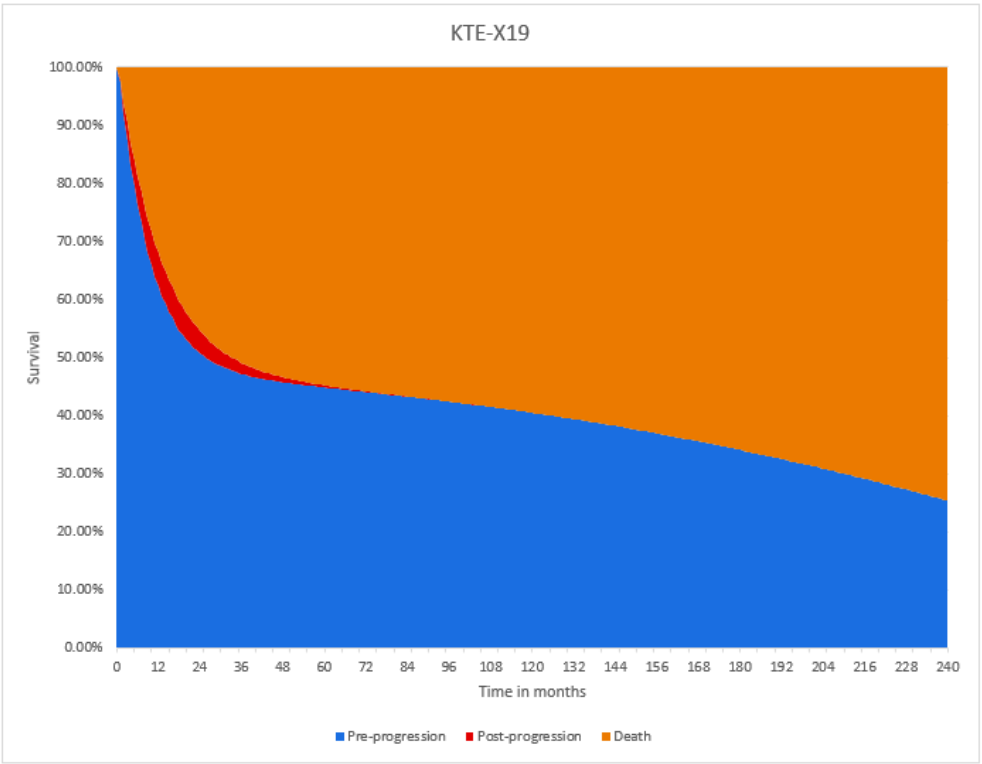


Figure 2: Markov Trace Scenario forcing' a "cure-fraction" of 47%



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