Advanced Therapy Treatment Centres

Midlands-Wales Advanced Therapy Treatment Centre

Technoleg Iechyd Cymru
Health Technology Wales

Cost Comparison of Tumour Collection Strategies for TIL Therapy

Creator: Health Technology Wales

Author: Matthew Prettyjohns

Document version number: V1

Date written: 06/07/2020

INDUSTRIAL STRATEGY

UK Research and Innovation

Coordinated by CATAPULT Cell and Gene Therapy

Cost Comparison of Tumour Collection Strategies for TIL Therapy

Technoleg Iechyd Cymru
Health Technology Wales

ATTC Advanced Therapy Treatment Centres

Midlands-Wales Advanced Therapy Treatment Centre

Background and objective

Immetacyte has developed a patient-specific immunotherapy using UTIL-01, the trial product designation for tumour infiltrating lymphocytes (TIL), that can be used in the management of recurrent ovarian cancer and malignant melanoma. The treatment process uses T-cells isolated from the patient's tumour to target and attack it.

The treatment is used in patients with recurrent cancer after other treatment approaches have failed. The TIL samples may be collected at the point at which treatment is required or may be collected routinely in patients undergoing surgery for the primary cancer tumour or as part of standard surgical procedures for tumour removal or debulking. Collecting routinely may offer advantages by reducing the collection cost as well as delivering the UTIL-01 therapy in a more timely fashion and reducing the number of surgical procedures a patient would need to undergo. However, it is not known whether the overall cost would be reduced in comparison to collecting when required as it is dependent upon the proportion of patients that progress to the stage where UTIL-01 treatment is required.

At this point in time, Immetacyte is particularly interested in the relative costs of each strategy in the context of ovarian cancer. Specifically, there is interest in whether routinely collecting tumour tissue samples as part of standard debulking surgery, in patients likely to progress (stage III or IV disease), has the potential to reduce treatment costs compared to collecting tumour samples just prior to treatment. UTIL-01 treatment is offered to this patient group if they have platinum resistant disease, defined as a recurrence within six months of previous treatment with platinum-based chemotherapy.

An economic analysis was developed to estimate the costs of routine collection and storage of tumour samples in comparison to collection when UTIL-01 treatment is required and determine the least costly strategy overall.

Methods

Strategies considered in the analysis

Two strategies were considered in the analysis:

1. TIL collection at the point that UTIL-01 treatment is required (when patient has progressed to platinum resistant disease)
2. Routine TIL collection alongside surgery for the primary cancer tumour or as part of standard surgical procedures for tumour removal or debulking

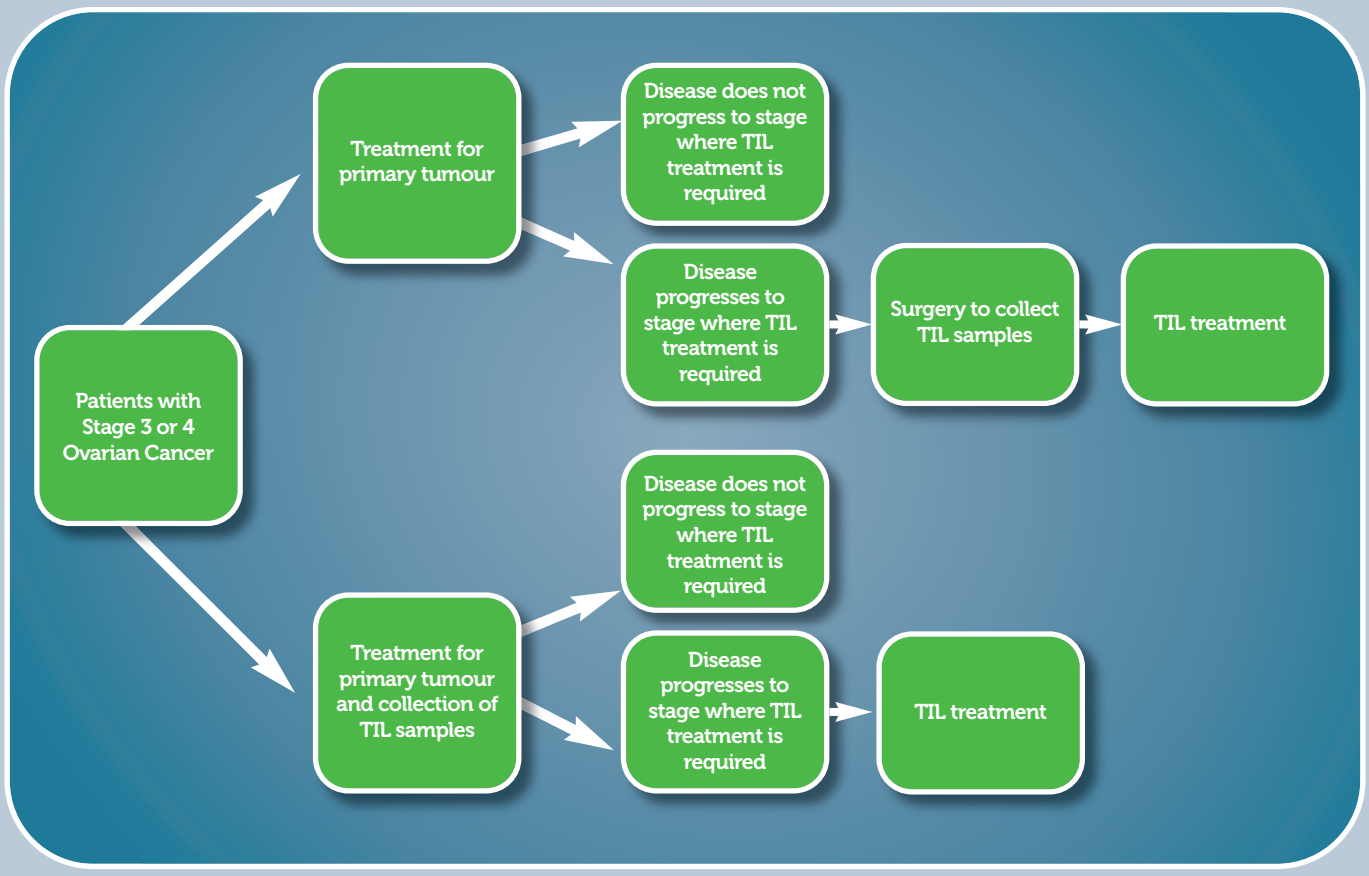
In the first strategy, patients undergo treatment for the primary tumour and may subsequently require UTIL-01 treatment if disease progresses to platinum resistant cancer. If this is the case then a separate surgery would be required to collect the TIL samples before treatment can be administered.

In the second strategy, TIL samples are collected alongside the treatment for the primary tumour. Patients may subsequently require UTIL-01 treatment if disease progresses to platinum resistant cancer. If this is the case then UTIL-01 treatment can be administered using the samples that were collected at the outset.

INDUSTRIAL STRATEGY
UK Research and Innovation
Coordinated by CATAPULT Cell and Gene Therapy

Figure 1 depicts the two TIL collection strategies that will be compared in the analysis.

Figure 1: Modelled TIL collection strategies

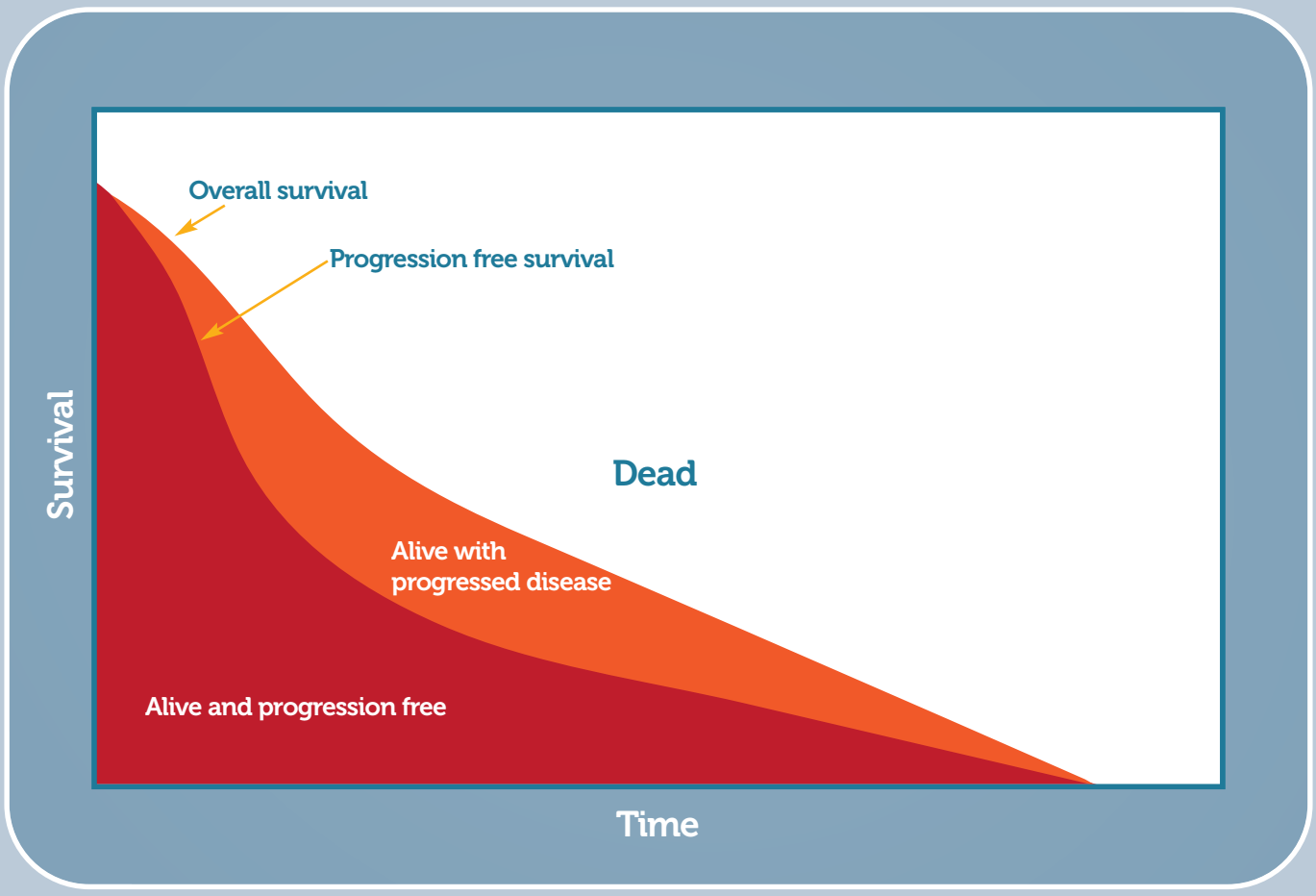


Disease progression model

No direct evidence was identified on the proportion of patients that initially have stage III or IV cancer that progress to platinum resistant cancer. Therefore, a disease progression model was developed to estimate the proportion of patients diagnosed with stage III or IV ovarian cancer that progress to platinum resistant disease.

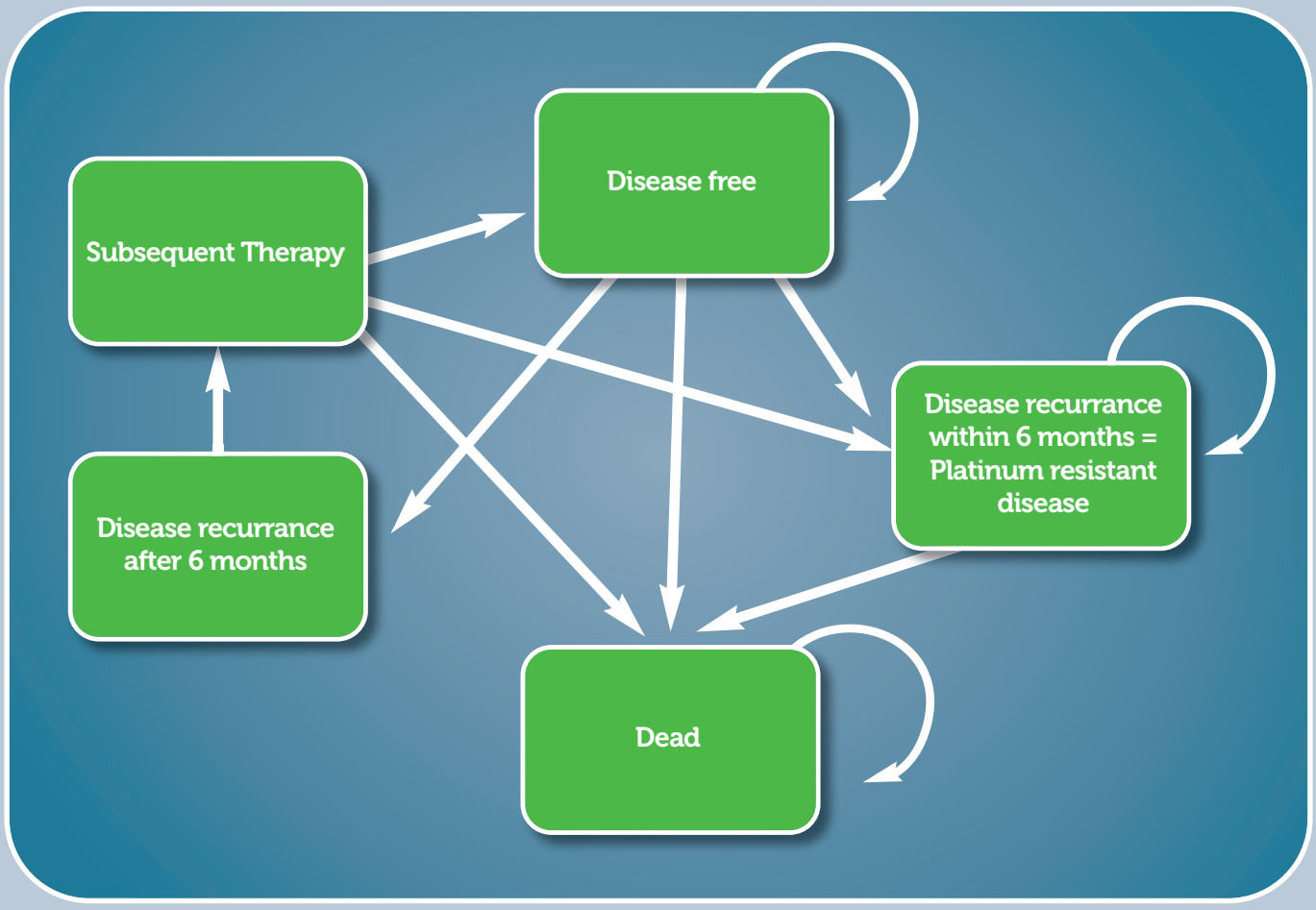
The analysis was constructed based upon overall survival and progression free survival estimates (see clinical data section below for details). These estimates were employed in a similar manner to a partitioned survival analysis whereby patients can be categorized into three distinct groups; alive and progression free, alive with progressed disease and dead (see Figure 2). However, the analysis involved a variation on the typical partitioned survival analysis as it required that the 'alive with progressed disease' state was itself partitioned into those with and without platinum resistant disease (i.e. recurrence within six months of previous treatment).

Figure 2: Example of a partitioned survival analysis



In order to determine those patients that would be deemed to have platinum resistant disease, it was necessary to track the time between previous treatment and progression for individual patients. The analysis was therefore implemented as a Markov state transition model with tunnel states to capture time since previous treatment. A model cycle length of six months was employed, in order to capture those patients that have progressed within six months of previous treatment. Figure 3 depicts the structure of the model. There are four health states; "disease free", "disease recurrence within six months", "disease recurrence after six months" and "dead". The "recurrence after six months" health state is implemented as a tunnel state meaning that patients cannot remain in this state but instead move through it after receiving subsequent therapy and thereafter may again be disease free, have another recurrence or die.

Figure 3: Potential structure of Markov model



At cycle zero, all patients start in the "disease free" health state following completion of treatment for stage III-IV ovarian cancer. At each cycle, patients may remain in the "disease free" health state or may instead transition to "disease recurrence within 6 months", "disease recurrence after 6 months" or "dead". Patients that transition to "disease recurrence within six months" are recorded as having platinum resistant disease. In subsequent cycles, patients may remain in this state or transition to the "dead" health state. Note that such patients are likely to receive further treatment lines but these were not recorded as it is not of interest for this particular analysis. Patients with a recurrence after six months are assumed to receive a subsequent therapy line and in the next cycle will transition to disease free, recurrence or death. If the recurrence after the subsequent therapy line is within six months, then this would be recorded as platinum resistant disease. Patients that transition to the dead state remain in this state (sometimes termed an 'absorbing state').

The model considered a 10 year time horizon, which would cover the expected lifetime of the majority of patients. Shorter time horizons were considered in sensitivity analysis.

Clinical data

This model was based on overall survival and progression free survival data from the ICON7 trial, which investigated the use of standard therapy (carboplatin and paclitaxel) with and without bevacizumab in women with newly diagnosed ovarian cancer. The trial included women with either high-risk early-stage disease (stage I–IIa, grade 3 or clear cell histology) or more advanced disease (stage IIb–IV). Note that this population is broader than the population of interest for this analysis (stage III-IV). However, the majority of patients in the ICON7 trial were in the stage III-IV group; 82% compared to 18% with stage II disease. Therefore, the estimates are likely to provide a good approximation of progression in patients with stage III-IV disease. Alternative estimates of disease progression are explored in alternative scenarios in the sensitivity analysis.

Data on overall survival from the ICON7 trial showed that 54% and 53% of patients were alive at five years following treatment with standard therapy and standard therapy with bevacizumab, respectively. Data on progression free survival from the ICON7 trial showed that 31% and 27% of patients were progression free at five years following treatment with standard therapy and standard therapy with bevacizumab, respectively.

Data from the standard therapy arm of the trial was used for the base case estimates of overall survival and progression free survival. This arm was selected as it is likely to reflect standard care for most patients and is in line with recommendations from the National Institute for Health and Care Excellence (NICE) as bevacizumab was not recommended for first-line treatment of advanced ovarian cancer in NICE TA284. However, alternative data was explored in sensitivity analyses, including using data from the bevacizumab arm of the trial. Further alternative scenarios include using data from the high-risk subgroup form the ICON7 trial and using data from another study in which Olaparib maintenance therapy is used following completion of platinum-based chemotherapy (SOLO1 trial).

Table 1 details the overall survival and progression free survival data used to inform the base case analysis as well as alternative estimates that are used in sensitivity analyses.

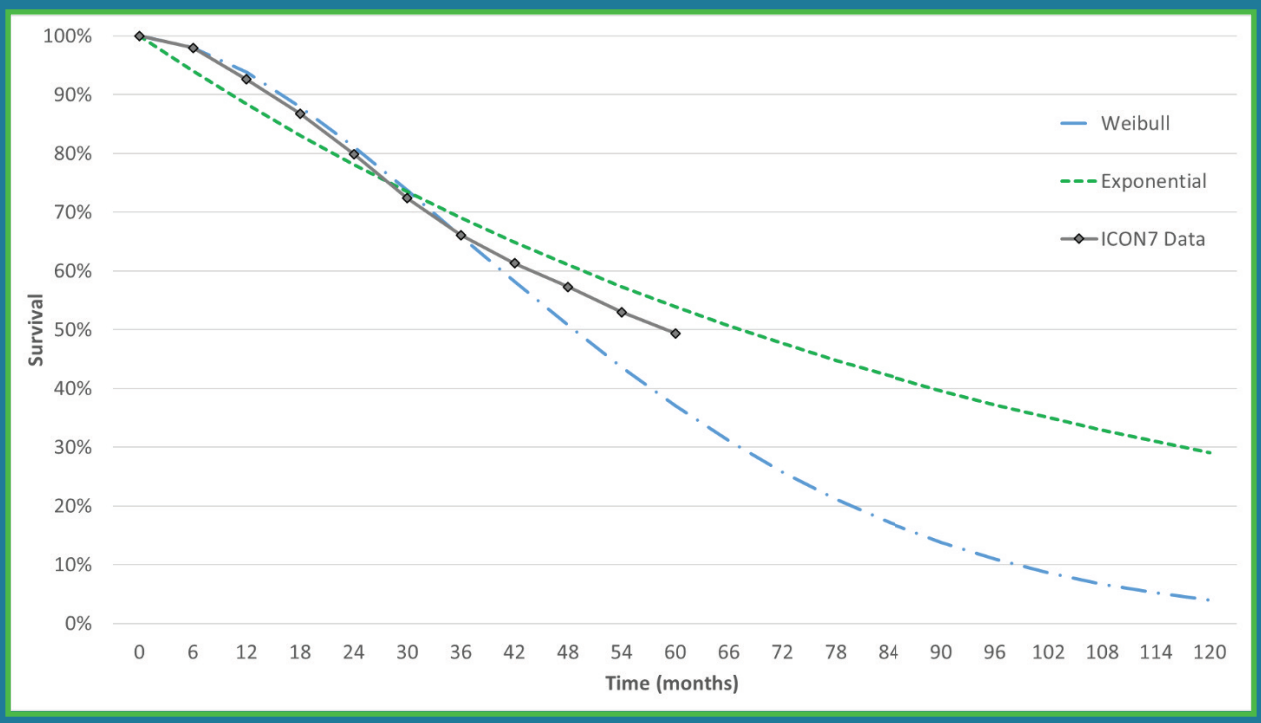
Strategy	Deaths (%)	Overall survival	Progressed (%)	Progression free survival
ICON 7 trial – outcomes at five years				
All patients				
Standard therapy (n=764)	352 (46%)	54%	526 (69%*)	31%
Bevacizumab (n=764)	362 (47%)	53%	554 (73%)	27%
High risk patients				
Standard therapy (n=254)	174 (69%)	31%	228 (90%)	10%
Bevacizumab (n=248)	158 (64%)	36%	223 (90%)	10%
SOLO1 trial – outcomes at three years				
Placebo (n=131)	26 (20%)†	80%	96 (73%)	27%
Olaparib (n=260)	42 (16%)†	84%	102 (39%)	61%
*ICON7 reports 74% progressed but this does not match the reported number of patients progressed. †Number of deaths was not reported in SOLO1 trial. Numbers have been estimated based on total patientsand reported overall survival				

The economic analysis requires going beyond the time period covered in the ICON7. It was therefore necessary to extrapolate the data to our desired time horizon of 10 years. Two alternative methods were employed to generate the extrapolated estimates; one involved fitting a Weibull distribution to the trial data while the other involved fitting an exponential function based on baseline data and reported outcomes at five years (as shown in table on the previous page).

Fitting the Weibull distribution required data on overall survival and progression free survival at multiple time points from the ICON7 trial. This data was estimated from the Kaplan-Meier plots of overall survival and progression free survival presented in Oza et al. 2015. Digitizing software (DigitizeIt) was used to read-off data points along the survival curves. The survival curve data was then used to inform the estimation of a Weibull distribution using methodology developed by Hoyle and Henley 2011. The methodology involves using an Excel-based tool to generate data based on survival curve data that can then be inputted into the statistical software R alongside the relevant code for the Weibull function.

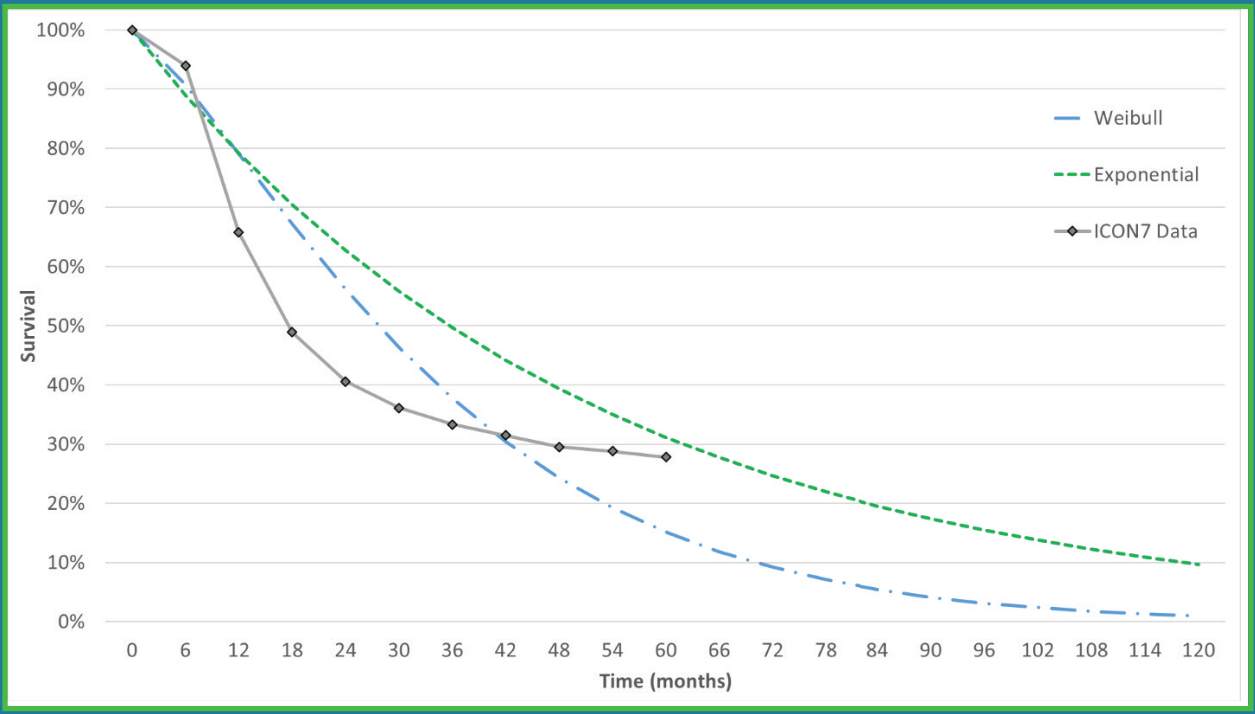
Figure 4 and Figure 5 shows a comparison of modelled overall survival and progression free survival using the Weibull and exponential method alongside the ICON7 data. It can be seen that estimated values for progression free survival and overall survival when using the Weibull distribution are initially higher than values generated with the exponential. However, the curves then cross and the longer-term estimates using the Weibull distribution are much lower than those generated with the exponential function. Since the long-term prognosis of ovarian cancer is poor, it was considered that the Weibull estimates are likely to give the best approximation of long-term survival. Therefore, the Weibull estimates were used in the base case, while the exponential values were applied in sensitivity analysis.

Figure 4: Modelled overall survival for standard therapy arm of ICON7 trial[1]



[1]Note that ordinarily one would expect the exponential curve at 60 months to be equal to the final data endpoint from the ICON7 trial. This is not the case here because the exponential curve is based upon overall survival of 54% at five years as reported in Oza et al. 2015, whereas the ICON7 data shown in Figure 4 is based on values read from the Kaplan-Meier curves from Oza et al. 2015 and there is a slight discrepancy between the two.

Figure 5: Modelled progression free survival for standard therapy arm of ICON7 trial[2]



[2]Note that ordinarily one would expect the exponential curve at 60 months to be equal to the final data endpoint from the ICON7 trial. This is not the case here because the exponential curve is based upon progression free survival of 31% at five years as reported in Oza et al. 2015, whereas the ICON7 data shown in Figure 5 is based on values read from the Kaplan-Meier curves from Oza et al. 2015 and there is a slight discrepancy between the two.

The estimated overall survival and progression free survival estimates over the ten year time horizon were used to estimate the proportion of patients alive with and without recurrence at each six monthly cycle.

Mortality was divided into disease specific and other cause mortality by using general mortality estimates from national life tables for England and Wales from the Office of National Statistics (ONS; 2016-18). The life tables provide estimates of the probability of mortality within the next year for a given age and gender. A starting age of 57 years old was used in the analysis reflecting the average age of participants in the ICON7 trial. Disease specific mortality was then estimated as the difference between overall mortality from ICON7 and the expected rate of mortality for the general population from the ONS life table.

Estimating disease specific mortality allows for disease specific deaths within six months of the last treatment can be incorporated in the estimated number of people with platinum resistant disease. The rationale for doing this is that recurrent disease is likely to have been observed in such patients prior to death. Therefore, in a scenario where UTIL-01 is a treatment option, it is possible that they may have been able to receive UTIL-01 before the occurrence death. However, it is recognized that this approach is somewhat speculative as it is likely that some patients would die without an observed recurrence of disease and the proportion of recurrences that would be observed prior to death is not known. Therefore, a sensitivity analysis was conducted in which disease specific deaths were excluded from the estimated number of platinum resistant recurrences.

Costs

Costs were estimated from the perspective of the National Health Service (NHS) and personal social services (PSS) perspective. Costs were estimated based upon 2020 prices. Future costs were discounted at a rate of 3.5% per annum, as recommended in the NICE reference case.

The cost of surgery for the primary ovarian cancer tumour was not included in the analysis because this would be equivalent in both strategies. It was assumed that there would be no cost associated with the procedure to collect TIL samples when it is undertaken alongside surgical treatment of the primary tumour. This makes the assumption that there would be no cost over and above the cost of the surgical treatment itself. In reality, there may be some marginally increased costs due to the extra time required to collect the sample but any increase is likely to be negligible.

The cost of the TIL sample collection when undertaken as a separate procedure was estimated to be £1,688 based on data from St Mary's hospital, Manchester. In addition, Immetacyte estimate that there would be a cost of £2,211 for them to collect, transport and freeze the TIL samples as well as a storage cost of £8 over a six month period. While it is Immetacyte that would incur such costs, it is assumed that they would be used as the basis for any costs charged to the NHS and it was therefore considered appropriate for them to be included in this analysis from the NHS and PSS perspective.

Once collected, the TIL samples will be checked to ensure that they are of sufficient quality for the UTIL-01 treatment to be developed. Immetacyte estimate that around 10% of samples will be of insufficient quality for the UTIL-01 treatment to be developed. In the analysis, it was assumed that, in such cases, a separate collection procedure would be required to obtain a new TIL sample. The proportion of samples that may be of insufficient quality is not known with certainty and so was varied in sensitivity analyses.

The time period over which collected TIL samples remain stable is also not known. In the base case, it was assumed that the TIL samples would be stable for three years. This is based upon an estimate from Immetacyte. TIL sample stability has implications for the strategy of routine TIL collection alongside surgery. It was assumed that if a patient develops platinum resistant disease beyond the period over which the collected samples are expected to remain stable, then a new sample would be required with a separate collection procedure. Variations in TIL stability time were explored in sensitivity analysis.

Subsequent treatment, management, investigation and follow-up costs for ovarian cancer were not considered in the analysis (including the cost of administering UTIL-01 treatment itself). This is because the focus of the analysis is on cost differences between the approaches and these costs are likely to be equivalent in each arm. It is conceivable that there might be differences in management costs between the strategies if upfront collection of TIL samples leads to more timely delivery of UTIL-01 treatment, which in turn improves disease control. However, such a difference is likely to be modest and is as yet unproven.

Results

Base case results

The base case results of the analysis are shown for a hypothetical cohort of 1,000 patients and on a per patient basis in Table 2 and Table 3, respectively. It can be seen that a strategy of routine TIL collection alongside surgery is substantially more costly overall than a strategy of deferred collection. The overall cost of TIL collection procedures was less costly with a strategy of routine TIL collection alongside surgery but all other costs were higher. Most notably, the costs associated with Immetacyte collecting, transporting and freezing the TIL samples was much higher with a strategy of routine TIL collection alongside surgery compared to deferred collection. This is result of collecting, transporting and freezing samples for all patients, including those that may never progress to platinum resistant disease.

Table 2: Base case results for hypothetical cohort of 1,000 patients

Strategy	TIL collection procedure cost	Immetacyte costs for collection, transportation and freezing	TIL storage cost	Total cost
Collection at surgery	£199,992	£2,211,460	£64,117	£2,475,569
Deferred collection	£318,088	£378,844	£236	£697,167
Difference	**£118,096**	**-£1,832,616**	**-£63,882**	**-£1,778,401**

Table 3: Base case results on a per patient basis

Strategy	TIL collection procedure cost	Immetacyte costs for collection, transportation and freezing	TIL storage cost	Total cost
Collection at surgery	£200	£2,211	£64	£2,476
Deferred collection	£318	£379	£0	£697
Difference	**£118**	**-£1,833**	**-£64**	**-£1,778**

Sensitivity analysis

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new results are recorded. This is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the deterministic sensitivity analyses are presented in Table 3 for a hypothetical cohort of 1,000 patients.

Sensitivity analyses demonstrate that the outcome of the analysis is relatively insensitive to changes in most input parameters. In all modelled scenarios, deferred collection was found to be less costly than a strategy of routine collection alongside surgery.

Perhaps unsurprisingly, changes to estimates of disease progression were found to be particularly influential in determining the magnitude of the cost savings with the deferred collection approach. Of particular note are scenarios where the rate of progression was assumed to be higher (such as the high risk subgroup from ICON7). In such scenarios, the higher rate of progression increases collection costs in the deferred collection arm, thereby reducing the cost savings associated with the approach.

Also of interest is the scenario based on SOLO1, in which it is assumed that patients receive maintenance therapy with olaparib following completion of platinum-based chemotherapy. Advice from a clinical expert suggests that the use of olaparib may become part of standard clinical practice for patients with ovarian cancer. If this transpires then the rate of disease progression in patients with stage III or IV disease may be lower (based on the results from the SOLO1 trial). As such, the deferred collection strategy becomes may become even less costly as fewer patients progress to platinum resistant disease (or, at least, progress less quickly).

Table 4: Sensitivity analysis results (based on hypothetical cohort of 1,000 patients

Modelled scenario	Total cost		
	Collection at surgery	Deferred collection	Difference
Base case	£2,475,569	£697,167	-£1,778,401
Alternative disease progression estimates using Weibull extrapolation			
ICON7 - Bevacizumab	£2,517,262	£791,513	-£1,725,749
ICON7 - Standard therapy in high risk subgroup	£2,595,025	£1,321,513	-£1,273,512
ICON7 - Bevacizumab in high risk subgroup	£2,723,278	£1,610,090	-£1,113,188
Alternative disease progression estimates using exponential extrapolation			
ICON7 – Standard therapy	£2,489,111	£605,685	-£1,883,427
ICON7 - Bevacizumab	£2,494,662	£691,615	-£1,803,047
ICON7 - Standard therapy in high risk subgroup	£2,483,011	£1,177,693	-£1,305,318
ICON7 - Bevacizumab in high risk subgroup	£2,505,628	£1,257,480	-£1,248,148
SOLO1 - Placebo	£2,671,894	£1,594,110	-£1,077,784
SOLO1 - Olaparib	£2,523,188	£472,013	-£2,051,175
Disease specific deaths within 6 months of last therapy excluded from platinum resistant disease estimate	£2,475,569	£426,907	-£2,048,661
No disease specific deaths	£2,993,527	£1,689,697	-£1,303,830
TIL stability time			
1 year	£2,507,332	£697,167	-£1,810,165
2 years	£2,495,098	£697,167	-£1,797,931
5 years	£2,453,407	£697,167	-£1,756,240
Laboratory failures at collection			
0%	£2,303,933	£668,250	-£1,635,683
5%	£2,389,751	£682,709	-£1,707,042
15%	£2,561,386	£711,626	-£1,849,760
25%	£2,733,022	£740,543	-£1,992,479
Time horizon			
1 year	£2,402,800	£359,331	-£2,043,468
3 years	£2,431,836	£526,289	-£1,905,547
5 years	£2,461,168	£633,526	-£1,827,642
7 years	£2,471,836	£680,167	-£1,791,668
No discounting	£2,486,613	£749,611	-£1,737,002

Conclusion

The results of the analysis suggest that a strategy of deferring TIL sample collection until the point that UTIL-01 treatment is required is likely to be less costly overall than a strategy of routine TIL collection alongside surgery for the primary cancer tumour. The result was found to be robust to changes in sensitivity analysis with the conclusion of the analysis remaining unchanged in all modelled scenarios.

While the analysis shows the deferred collection strategy to be less costly, it is worth noting that there may be patient benefits associated with a strategy of routine collection alongside surgery if it leads to more timely initiation of treatment. From an economic perspective, there may be value in routine collection if it could be shown that routine collection leads to earlier initiation of treatment and this in-turn led to improvements in quality of life and survival to the extent that additional costs for routine collection would be a cost worth paying.

References

Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol 2015;16(8): 928-936.

NICE Technology appraisal guidance [TA284]. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (2013). Available from: https://www.nice.org.uk/guidance/ta284

Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance Olaparib in patients with newly diagnosed advanced ovarian Cancer. N Engl J Med. 2018;379(26):2495–505.

NICE. Process and methods [PMG9]. Guide to the methods of technology appraisal (2013). Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case

Office for National Statistics (ONS). National life tables for England and Wales (2016-18). Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables

INDUSTRIAL STRATEGY

UK Research and Innovation

Coordinated by CATAPULT Cell and Gene Therapy