Catumaxomab for intraperitoneal treatment of malignant ascites in epithelial cellular adhesion molecule-positive carcinomas when further systemic anticancer treatment is unsuitable

Technology appraisal committee D [10 June 2026]

For projector – confidential information redacted

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Catumaxomab for intraperitoneal treatment of malignant ascites in EpCAM-positive carcinomas when further anticancer treatment is unsuitable

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on malignant ascites

Few malignant ascites cases per year, mainly from ovarian and pancreatic cancer

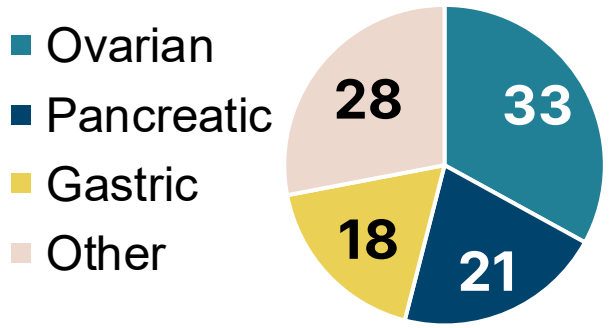
Causes of malignant ascites

- Complication of cancer and can be a manifestation of cancer progressing
- Build-up of fluid (tumour cells) in abdomen (peritoneal cavity), causing severe swelling. Caused by:
  1. Increased fluid enters abdomen because cancer-related substances cause blood vessels to leak
  2. Tumour cells spread along peritoneum which blocks normal fluid drainage from abdomen

Epidemiology

- Annual malignant ascites cases in England that are EpCAM positive: 519
  - ➢ Likely most malignant ascites are EpCAM positive (85%)
- Anticipated 73% ovarian and most gastrointestinal cancers are EpCAM positive

Primary tumour site %



Other: breast, oesophageal, colorectal, lung

Diagnosis

- Diagnosis through physical examination, imaging and laboratory tests
- Drainage typically 1-1.5L of fluid, but thresholds vary and no guidelines exists

Symptoms and prognosis

- Symptoms of malignant ascites are consistent irrespective of primary cancer type
  - People may have pain, bloating, breathlessness, restricted mobility, fatigue and loss of independence.
- England pan-tumour study: median survival 5.7 months

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Abbreviations; EPCAM, epithelial cellular adhesion molecules; L, litre

Patient perspectives

Malignant ascites has detrimental impact on quality of life due to pain, discomfort, inability to walk, breathlessness and reduced appetite

Submissions from The Cholangiocarcinoma Charity (AMMF), Breast Cancer Now, Ovarian Cancer Action and 2 patient experts

- Living with malignant ascites can be very distressing for patients and loved ones and is associated with a very poor prognosis
- High unmet need:
  - ❖ Earlier detection of malignant ascites and better communication and support about treatment options is needed for patients and carers
  - ❖ Delays in initiating treatment need to be reduced
  - ❖ Current treatment does not treat underlying cause of ascites
  - ❖ Draining fluid can be painful, time consuming and needed frequently
  - ❖ Diuretics can be prescribed which helps, although still symptomatic
- Paracentesis only provides short symptom relief and is invasive which carries risk such as pain, discomfort and infection

"Had a 6 hour drain, they got about 5 litres. I was still massive but could eat a little more. It was excruciating, I couldn't even sit up enough to take paracetamol, which is all that was offered. I couldn't even move my toe without extreme pain; I just lay as still as I could"

"2 treatments in 1 month; both had to beg for. Discharged with drain in and no aftercare advice, help or pain meds" - caregiver

Clinical perspectives

Catumaxomab would improve quality of life by reducing catheter use

Submissions from The Royal College of Pathologists and a clinical expert

Unmet need:

- Current management includes:
  - ❖ Permanent drain (IPC) managed by patient. These are invasive, uncomfortable and can become infected
  - ❖ Repeated short drainage (LVP). Requiring frequent day or overnight admissions to hospital

Catumaxomab would need to be given:

- ❖ In a healthcare setting with radiology and either a systemic therapy suite, a daycare facility or day assessment.
- ❖ By staff experienced in catheters and managing acute antibody reactions.

Testing for EpCAM:

- ❖ Different antibodies test for EpCAM. Some carcinomas are positive with 1 antibody and not the other. Do not routinely evaluate staining intensity
- ❖ Issue: unclear definition of EpCAM positivity - any detectable staining for any EpCAM antibody (most carcinomas) or a set staining level with specific antibody

Catumaxomab would cause significant reduction for repeated drainage. Removing requirement for repeated puncture or a permanent catheter is likely to improve quality of life.

Current management of malignant ascites varies between hospitals depending on resource and expertise with long term peritoneal catheters

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Abbreviations: EpCAM, epithelial cellular adhesion molecules; IPC, indwelling peritoneal catheter; LVP, large volume paracentesis

Equality and health inequality considerations

Differences in setting of paracentesis

Issue raised at the scoping stage:

- Inequality in access to current standards of care for people who have recurrent malignant ascites.
  - Some with recurrent malignant ascites receive paracentesis as a hospital inpatient but some NHS providers offer paracentesis as a day clinic procedure.
  - People with recurrent malignant ascites are nearing end of life and should have minimal medical appointments.

Other equality points raised:

- Late-stage cancer more common in people from socioeconomic deprived areas and people who are among black, Asian and other ethnic minority groups
- Clinical evidence being considered is from mostly female population

Scoping equality impact assessment:

- The committee will consider the equalities issues presented.
- Treatment availability based on geographical location is outside remit of a NICE technology appraisal

Are there any equalities or health inequalities the committee should consider?

Catumaxomab (Korjuny, Pharmanovia)

Marketing authorisation	• Anticipated marketing authorisation wording: catumaxomab in the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas, who are not eligible for further systemic anti-cancer therapy. • MHRA marketing authorisation was expected [redacted]
Mechanism of action	• Catumaxomab targets EpCAM, which is found on many epithelial cancers, and CD3 antigen, which is expressed on mature T-cells. • Catumaxomab brings T-cells in closer proximity to cancer cells, and activates T-cell mediated killing and T-cell activation leading to the destruction of tumour cells in the peritoneal cavity • Third functional region on catumaxomab activates dendritic cells, natural killer cells and macrophages
Administration	• Catumaxomab is an intraperitoneal infusion in conjunction with drainage • Single treatment course: 4 infusions (10µg, 20µg, 50µg, 150µg) over 10 days. Interval between infusions can be prolonged at discretion of clinician but should not exceed 21 days
Price	• Catumaxomab list price: £2,070.36 pack of 3 x 10µg and £13,802.40 pack of 4 x 50µg • Catumaxomab has a confidential patient access scheme

Abbreviations: EpCAM, epithelial cellular adhesion molecules; MHRA, medicines and healthcare products regulatory agency; µ, micro;

Issues raised for consideration

Key issues

	Key issue	ICER impact
1	Treatment pathway	Small
2	Indwelling peritoneal catheter usage	Small
3	Population in AC-01 and AC-03	Unknown
4	Unclear PuFS benefit of catumaxomab	Moderate
5	Unclear OS benefit of catumaxomab	Large
6	Model structure and health state utility values	Large
7	Subsequent puncture rate	Large

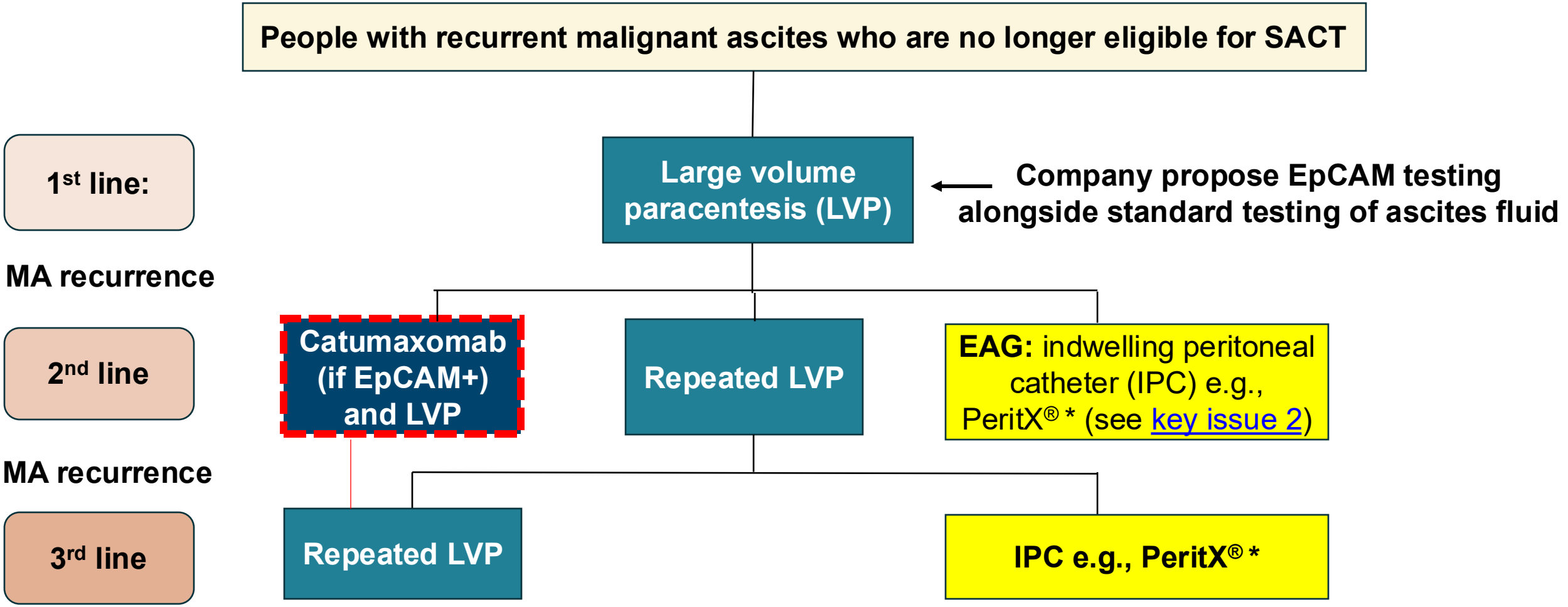
Secondary issue

	Other issues	ICER impact
8	Adverse events of catumaxomab	Small

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PuFS, puncture free survival;

Malignant ascites treatment pathway

Company propose EpCAM test at 1st line, catumaxomab as 2nd line treatment



Abbreviation: EpCAM, epithelial cellular adhesion molecules; IPC, indwelling peritoneal catheter; MA, malignant ascites; LVP, large volume paracentesis; SACT, systemic anti-cancer therapy

*NICE HealthTech Guidance 282 recommends PeritX® system as an option for drainage of treatment-resistant, recurrent malignant peritoneal ascites

Small impact

Key issues: Treatment pathway (1/3)

Company assume first recurrence of malignant ascites occurs after SACT

Background

- Company: assume LVP is 1st line treatment after SACT
- EAG: some people could have IPC by time they become no longer eligible for SACT

Company

Treatment pathway

- Malignant ascites recurrence after SACT: company define LVP as first line treatment, counts this as first LVP

EAG comments

Treatment pathway

- People remain on SACT as long as possible
- Malignant ascites occurs at any point in cancer
- People no longer eligible for SACT with recurrent malignant ascites may already have IPC

1) Is the treatment pathway accurate? 2) Could a person have an IPC before they reach end of SACT? 3) Could catumaxomab be the first treatment after SACT?

Abbreviations: EAG, external assessment group; IPC, indwelling peritoneal catheter; LVP, large volume paracentesis; SACT, systemic anti-cancer treatment

Small impact

Key issues: Treatment pathway (2/3)

Company state EpCAM testing is established, NHS England state is not a routine test

EpCAM testing

Company:

- EpCAM testing routine in NHS, cost = £49.81
- Propose EpCAM tested at first recurrence of malignant ascites after SACT
- Catumaxomab SmPC: EpCAM expression assessed by validated method and does not mandate antibody
  - Likely NHS method: microscopy-based enumeration with a defined eligibility threshold applied.
    - Defined threshold in SmPC for catumaxomab = ≥400 EpCAM-positive cells per 10^6 total cells
    - Operational: 100 EpCAM-positive cells identified on cytospin slide containing 250,000 total analysed cells determined manually, under microscopy.

EAG comments

- EpCAM test: £49.81 uncertain – do not factor in re-testing or not everyone tested goes on to treatment

NHS England comments

- EpCAM testing is not routine
  - Cost: £100 for immunohistochemistry test plus 30-minute consultant time (mid pay scale)

1) Is the placement of EpCAM testing accurate in the pathway? 2) Is EpCAM testing routine? 3) How would EpCAM testing be done in NHS? 4) Is EpCAM costed appropriately i.e not factoring in re-testing etc?

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Abbreviations: EAG, external assessment group; EpCAM, epithelial cellular adhesion molecules; SACT, systemic anti-cancer treatment; SmPC, summary of product characteristics

Key issues: Treatment pathway (3/3)

Small impact setting Catumaxomab

Large impact setting LVP

Catumaxomab studied over 20 years ago

Administration of treatment

Company:

- Catumaxomab infused via IPC and prior to each subsequent infusion, fluid in peritoneal cavity drained
- Setting for first infusion catumaxomab: 20% day-case, 80% inpatient
- LVP setting: 20% day-case, 80% inpatient

EAG comments

- Catumaxomab setting: 100% inpatient + 1 day hospital stay. Expert: 100% would have inpatient setting due to AE. Catumaxomab studied over 20 years ago.
- LVP setting: uncertain, aligned with company. Expert: LVP day case, proportion unclear

NHS England comments

- Catumaxomab setting first infusion: 100% inpatient, 24-hour monitoring
- LVP setting: ambulatory outpatient setting

1) What is likely setting of initial catumaxomab administration? 2) Which setting would LVP be administered? 3) Would catumaxomab be administered in the NHS in the same way as it was done in the trial?

Abbreviations: AE, adverse events; EAG, external assessment group; IPC, indwelling peritoneal catheter; LVP, large volume paracentesis;

Small impact

Key issues: Indwelling peritoneal catheter usage

Company: IPC for specific population so not a comparator or subsequent treatment

Background

- Company: do not include IPC as comparator or a subsequent treatment (scenario: 10% IPC usage subsequent treatment)
- EAG: IPC is likely to be a comparator

Company

- IPC not SoC - works best in cases where ascitic fluid build up is rapid and out-of-hospital management is appropriate. No available data to compare IPC directly or indirectly to catumaxomab in this population
- Jehn (2015): European RWE study 71% had initial treatment malignant ascites by paracentesis
- Seah (2022): malignant ascites paracentesis - 73% LVP, 21% IPC (5 countries incl. England)

EAG comments

- EAG clinical experts: at least 40% of people with frequent recurrent or rapidly forming malignant ascites would receive IPC
- Assume around 10% of people IPC is a comparator and subsequent treatment

At which point in the pathway is an IPC used? What proportion of people would have an IPC at each stage?

Abbreviations: EAG, external assessment group; IPC, indwelling peritoneal catheter; RWE, real-world evidence; SOC, standard of care; LVP, large volume paracentesis;

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Key clinical trials

Clinical trial designs and outcomes

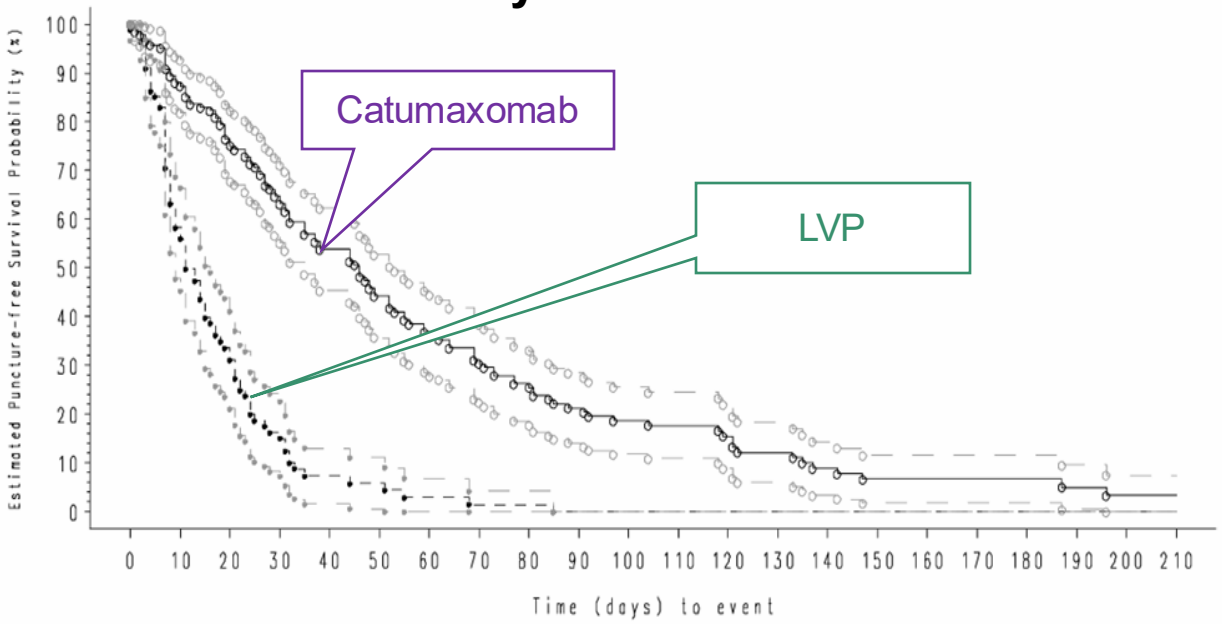
	AC-01 (NCT00836654)	AC-03 / CASIMAS (NCT008223809)
Design	Open-label, RCT, Phase 2/3	Open-label, RCT, phase 3b
Population	Adults aged 18 and over with malignant ascites requiring therapeutic paracentesis and KI ≥60	
	Life expectancy: >8 weeks EpCAM positive tumours	Life expectancy: >12 weeks Retrospective EpCAM (83.3% EpCAM positive)
Intervention	Catumaxomab with LVP (n=170)	Catumaxomab with prednisolone and LVP (n=111)
Comparators	LVP (n=88) – allow cross over after 2nd LVP	Catumaxomab with LVP on day 0 (n=108)
Duration	2-years (September 2004 to August 2006)	28 months (December 2008 to April 2011)
Primary outcomes	PuFS	PuFS for non-inferiority Composite safety score
Key secondary outcomes	OS, ascites signs and symptoms, Tumour cell load, quality of life	OS, TTPu, ascites signs and symptoms, quality of life
Stratification	Cancer type (ovarian/non-ovarian), country	None
Locations	13 European countries, including UK sites	10 European countries, no UK sites
Used in model?	Yes	Yes

Abbreviations: EpCAM, epithelial cellular adhesion molecules; KI, Karnofsky index; LVP, large volume paracentesis; n, number; OS, overall survival; PuFS, puncture-free survival; RCT, randomised controlled trial; TTPu, time to therapeutic puncture/time to next puncture

AC-01: ITT results

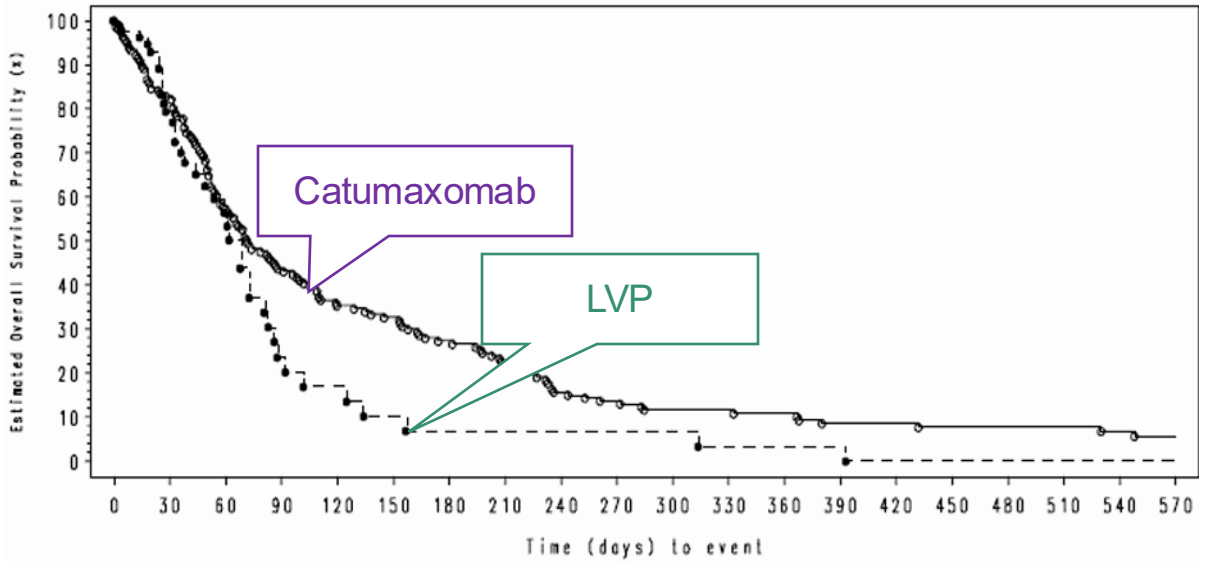
Catumaxomab significantly reduces risk of puncture, no evidence to suggest a significant extension in length of life

PuFS KM curve - May 2007



PuFS ITT	Catumaxomab n=170	LVP n=88
Median PuFS (days) (95% CI)	46 (35 to 53)	11 (9 to 16)
HR (95% CI; p-value)	0.25 (0.19 to 0.35), p < 0.0001	

OS KM curve - May 2007: censors those who cross-over



OS ITT	Catumaxomab n=170	LVP n=88
May 2007 – censoring for cross over		
Median OS (days)	72 (62 to 98)	68 (49 to 81)
HR (95% CI; p-value)	0.72 (0.50 to 1.05, p=0.085)	
September 2009 – censoring for cross over		
Median OS (days)	72	68
HR (95% CI; p-value)	0.72 (0.50 to 1.04 p=0.078)	

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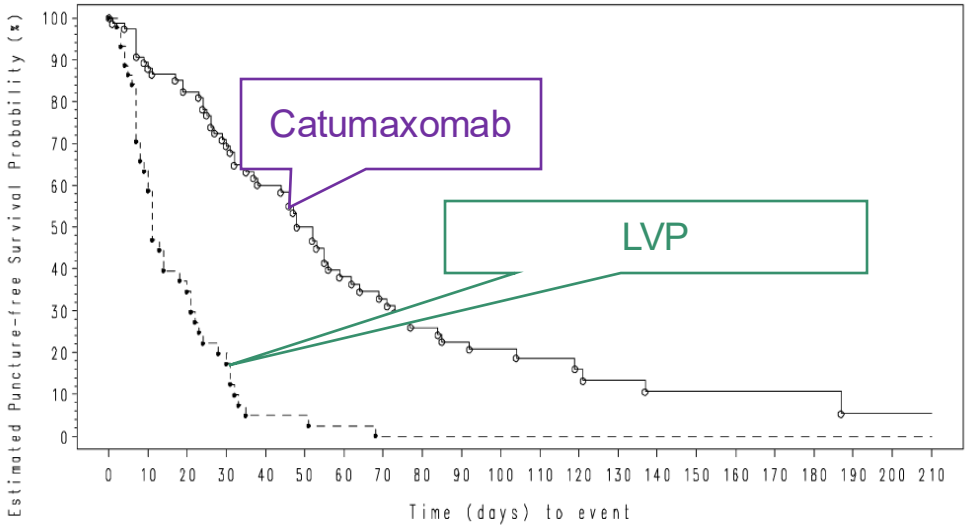
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; KM, Kaplan-Meier; LVP, large volume paracentesis; n, number; OS, overall survival; PuFS, puncture-free survival

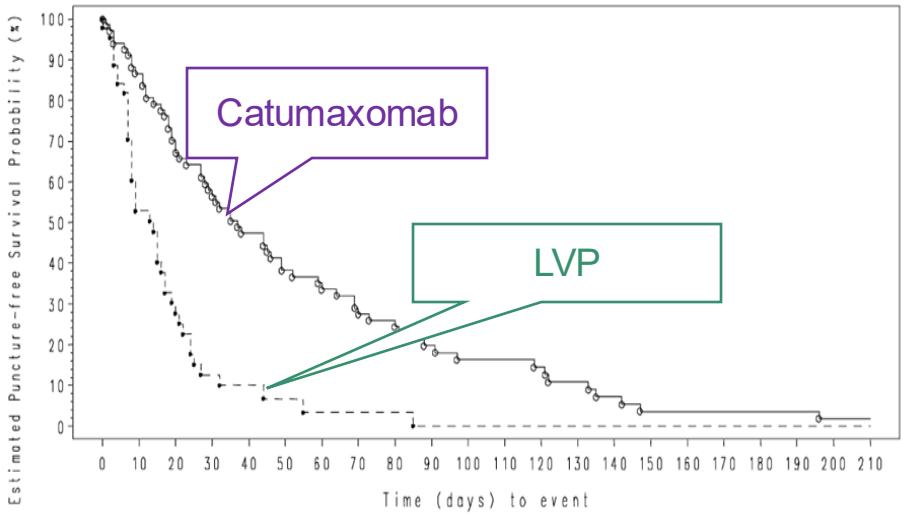
AC-01 subgroup results: PuFS

PuFS is longer in people with ovarian cancer compared to non-ovarian cancer

May 2007 - Ovarian subgroup KM curve



May 2007 - Non-ovarian subgroup KM curve



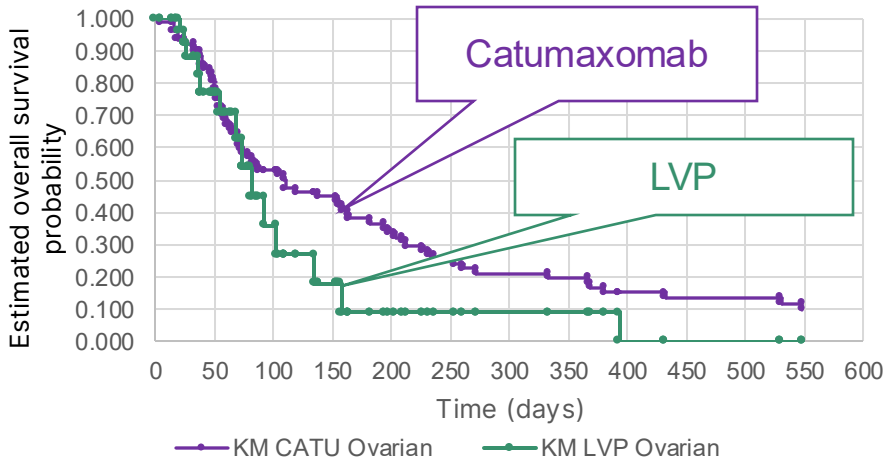
Ovarian cancer	**Catumaxomab n=85**	**LVP n=44**
Median PuFS (days) (95% CI)	52 (38 to 62)	11 (9 to 20)
HR (95% CI; p-value)	0.205 (0.129 to 0.327), p<0.0001	
Non-ovarian cancer	**Catumaxomab n=85**	**LVP n=44**
Median PuFS (days) (95% CI)	37 (27 to 49)	14 (8 to 17)
HR (95% CI; p-value)	0.309 (0.199 to 0.482), p<0.0001	

Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; LVP, large volume paracentesis; n, number; PuFS, puncture-free survival

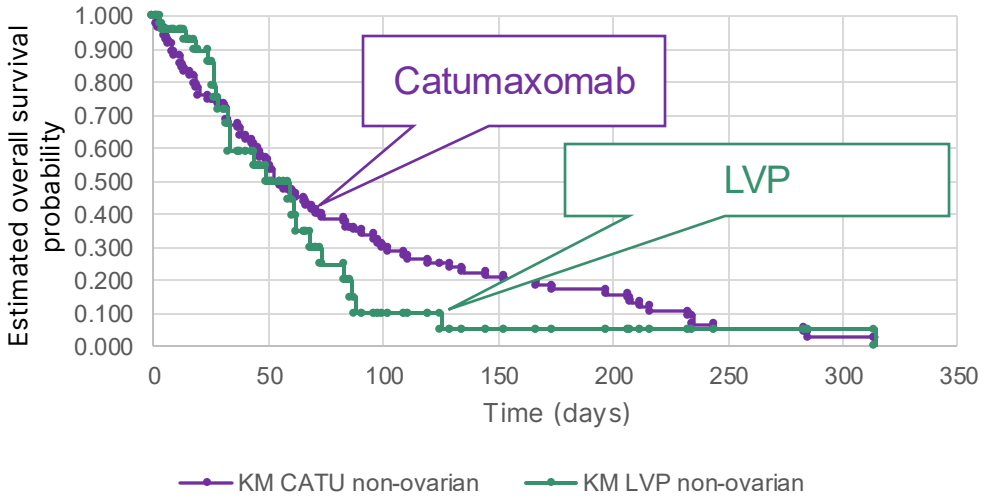
AC-01 sub-group results: OS

Company: AC-01 was not powered to detect differences by primary cancer type

May 2007 - Ovarian subgroup KM curve



May 2007 – Non-ovarian subgroup KM curve



AC-01 May 2007 OS by subgroup

Ovarian cancer	Catumaxomab n=85	LVP n=44
Median OS (days) (95% CI)	110 (70 to 164)	81 (68 to 134
HR (95% CI; p-value)	0.650 (0.357 to 1.183) p=0.1543	
Non-ovarian cancer	**Catumaxomab n=85**	**LVP n=44**
Median OS (days) (95% CI)	52 (44 to 74)	49 (33 to 68)
HR (95% CI; p-value)	0.825 (0.514 to 1.324) p=0.4226	

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Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; LVP, large volume paracentesis; n, number; OS, overall survival;

Key issues: Population in AC-01 and AC-03 (1/2)

Background

- AC-01: over 20 years old and mainly recruited people with ovarian or gastric cancer
- EAG: concerns around 1) changes since trial, 2) ovarian cancer overrepresented (50%), 3) subsequent SACT

Characteristics of trial population:

Company

- If AC-01 conducted today, plausible the observed treatment effect of catumaxomab would be greater.
- Treatment of underlying cancer evolved → trial baseline characteristics may differ from current practice
  - E.g., treatment history, extended survival (new therapies), age, life-expectancy, and PS
    - ❖ New ovarian cancer treatment (e.g bevacizumab) → improved PS = greater catumaxomab benefit
    - ❖ RWE: catumaxomab OS significantly longer in people with better PS (KI 80-100 vs KI <80)
- Clinical experts: AC-01 population, care-setting, and outcomes remain representative of current NHS

EAG

- Trial done 20 years ago in very different clinical context from current practice = influence on outcomes unclear
- Clinical experts: participants younger, fitter, with different treatment history, survival expectations and PS
  - Substantial advances in cancer treatments - many more effective and better-tolerated options resulting in more possible lines of therapy e.g., 10+ lines of ovarian cancer treatments = longer survival
- RWE: higher median age, lower proportion female, more ethnic diverse compared to AC-01

Abbreviations: EAG, external assessment group; KI, Karnofsky index; RWE, real-world evidence; PS, performance status; OS, overall survival; SACT, systemic anti-cancer therapy

Unknown ICER impact

Key issues: Population of AC-01 and AC-03 (2/2)

Proportion of primary tumour type in AC-01

Company:

- >50% of participants in AC-01 had ovarian cancer
- Observational study found 36.7% people with newly diagnosed malignant ascites had ovarian cancer.
  - ❖ AC-01: 30-day relative survival 1.42x greater among ovarian compared to non-ovarian cancer cases
  - ❖ Adjusting 36.7% by 1.42 = ovarian cancer accounts for >50% population treated for malignant ascites

EAG:

- AC-01 overrepresents ovarian cancer - experts state more heterogenous tumour population causes malignant ascites (pancreatic, lung, breast) which are underrepresented in AC-01
  - ❖ AC-01: better outcomes in ovarian so treatment effect could be overestimated for catumaxomab

Subsequent anti-cancer treatment allowed in trial

Company:

- Subsequent SACT not anticipated as trial enrolled people considered refractory/resistant to chemotherapy
- Catumaxomab creates potential for further treatment rounds in people thought to have no remaining treatment options → considered highly clinically valuable

EAG:

- Catumaxomab arm had ~[redacted] times more subsequent treatments than LVP ([redacted] vs [redacted])
  - ○ Concern: survival and puncture-related benefits may be overestimated for intended positioning

Are the characteristics of AC-01 generalisable to NHS? What is the impact of different tumour types? Is the SACT use generalisable to the NHS population?

Abbreviations: SACT, systemic anti-cancer therapy; LVP, large volume paracentesis

Large ICER impact

Key issues: Unclear PuFS benefit of catumaxomab

AC-01 results potentially biased due to open-label trial and censoring at 7 months

Background

- Company: AC-01 catumaxomab demonstrated a statistically significant PuFS compared to control
- EAG: catumaxomab may have large PuFS benefit, is potentially subject to bias and overestimation: 1) open label trial 2) PuFS analysis censored people event-free at 7 months 3) AC-01 PuFS definition differed

Company

- Catumaxomab significantly slowed ascites build up vs LVP (slower symptom onset, reduced burden)
- Bias from open-label design minimised by protocol restrictions on cross-over, objective/blinded assessment of puncture need, central randomisation, and conservative survival analysis methods

EAG comments:

1. Catumaxomab arm [redacted]% higher volume drained in ovarian group, measured by CT, at PuFS than LVP arm
   - Open-label: control arm could request LVPs to switch to catumaxomab sooner (criteria: after 2 LVPs)
2. Censoring biases against catumaxomab, more remain puncture free but not captured (n=[redacted] cat, n=[redacted] LVP).
   - Unable to adjust for bias, but chose optimistic extrapolation to account for possibility of event-free people beyond primary PuFS analysis
3. PuFS defined differently in each arm of AC-01 (LVP arm = day 0, catumaxomab = day 11) = small impact

Is the company analysis appropriate for decision making?

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Abbreviations: cat, catumaxomab; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; LVP, large volume paracentesis; n, number; PuFS, puncture-free survival;

Key issues: Unclear OS benefit of catumaxomab

Large ICER impact

Background

- Company: AC-01 shows OS benefit for catumaxomab compared to LVP
- EAG: OS benefit small and uncertain: 1) crossover censoring, 2) pooled AC-01/AC-03 and used 2007 data cut

Company

1. OS efficacy endpoint potentially impacted by cross-over from the control to catumaxomab arm (51%)
   - People who require 2 punctures have poorer prognosis and in need of further treatment
2. Pooling gives greater sample size along with longer follow-up when using data from AC-03
   - Reweighted AC-01 to match AC-03, pooled data, then applied inter-trial HR to AC-01 survival estimates

EAG:

1. LVP non-switchers were less healthy than switchers (AC-01 criteria) = LVP OS may be underestimated
   - Minimal catumaxomab OS benefit in first 90 days, so some may not have benefitted from switching
   - OS using full follow-up data, including post crossover information unavailable = censoring effect unclear
     - Apply inverse HR (1/0.795) from non-censored analysis to adjust LVP survival
2. Method to pool unclear and lack justification - breaks randomisation and biases in favour of catumaxomab
   - Cannot adjust for key dataset differences (e.g. prognosis eligibility ≥12 vs ≥8 weeks)
   - Company experts: AC-01 population similar to people likely to receive catumaxomab in England.
   - Prefer to use only AC-01 data from 2009 data cut – preserves randomisation, relevance and follow up

Should AC-01 and AC-03 data be pooled? What is the most appropriate method to account for OS censoring? Is it biological plausible that catumaxomab can improve survival in this population?

Abbreviations: CI, confidence interval; EAG, external assessment group; HR, hazard ratio; LVP, large volume paracentesis; OS, overall survival

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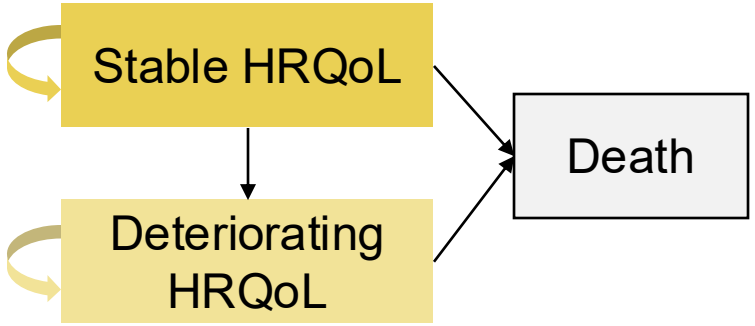
Large impact

Key issues: Model structure and health state utilities (1/4)

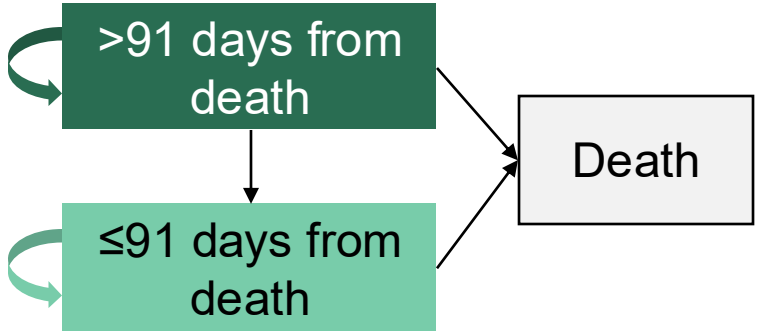
Background

- Company: 3 state partitioned survival model (by TFDQ) and models health states. Did not model disutility
- EAG: model time to event utilities. Applied disutility for punctures and cytokine release syndrome

Company Model Structure



EAG Model Structure



Comparison of company and EAG model

Model assumption	Company	EAG
Health state occupancy	• Informed by TFDQ • Informs proportion remaining in stable and deteriorating HRQoL model states	Model time to death utilities • Stable >91 days from death • Deteriorating: ≤91 days from death
Health state utility values	• Stable HSUV >200 days from death • Deteriorating HSUV: TTD	Use TTD utility values duration model
Disutility	No disutility	Disutility for grade 3+ AEs and punctures

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Abbreviations: AE, adverse event; EAG, external assessment group; HSUV, health state utility value; HRQoL, health related quality of life; TFDQ, time to first deterioration of quality of life; TTD, time to death

Large impact

Key issues: Model structure and health state utilities (2/4)

Background

- **EAG**: model structure and HSUV are misaligned with the data = likely overestimates catumaxomab QoL
  1. Model structure: QoL in model not linked to puncture events (PuFS) – main catumaxomab benefit
  2. Stable HSUV: Apply utilities from people >200 days from death, regardless of how long they live for
     - Apply higher treatment specific utilities for catumaxomab - higher QoL for catumaxomab assumed
  3. Disutility: Company apply no disutility in the model for AEs or punctures

Company:

Model structure: TFDQ preferred to PuFS: more direct impact on HRQoL and resource use

- AC-01 did not capture QoL data after PuFS – dividing OS by PuFS would confine trial data to 'pre-PUFS' state

Stable HSUVs:

- ≥200 day threshold based on TFDQ KM plateau = assume observations after this from people with stable HRQoL
- Wimberger et al (2012): statistically significant catumaxomab treatment effect in prolongation of stable HRQoL.
- Clinical expert: significant delay in global QoL deterioration observed in AC 01 reflects clinician experience.

Disutility:

- Clinical experts and EMA report: CRS events reduced/better managed since AC-01 - no meaningful QALY impact
- Longer term events captured in AC-01 HRQoL data plus time of first puncture visit

Abbreviations: CRS, cytokine release syndrome; EMA, European medicines agency; HRQoL, health related quality of life; HSUV, health state utility value; KM, Kaplan-Meier; LVP, large volume paracentesis; OS, overall survival; PuFS, puncture-free survival; TFDQ, time to first deterioration of quality of life; QALY, quality adjusted life year; QoL, quality of life

Large impact

Key issues: Model structure and health state utilities (3/4)

EAG: concerns benefits catumaxomab overestimated in "stable HRQoL" health state

EAG:

Model structure:

- Prefer to remove TFDQ outcome: does not capture absolute HRQoL and censors death and PuFS outcomes
- Prefer to model state occupancy using time to death structure (>91 days = stable vs ≤91 days = deteriorating)
  - >91-day TTD utility value similar to company "stable" HSUV for LVP arm (0.628)
  - Uses all available relevant AC-01 data across both arms, based on larger dataset (65 observations vs catumaxomab (n=17) and LVP (n=8))

Utilities:

- No meaningful evidence to support utility difference between arms in stable health state (>91 days from death)
  - Evidence is limited, from a small number of people and is not adjusted for PuFS.
  - 200-day cut-off poorly justified - based on TFDQ plateau at 200 days from randomisation but applied to TTD
- Prefer to use TTD utility values for full model time horizon, with the same utility values applied for both arms
  - Utilities values align with data collection period so applied to same group of people were calculated from

Disutility:

- Applied disutility for initial and subsequent punctures, grade 3+ AE (32.5%), QoL of 0 for 1 day based on assumption people kept in overnight and experience high burden.
- TA ID6325 disutility of 0.76 applied for severe CRS, using 0.76 disutility would result in negative utility value

Which model structure and utilities are most appropriate to use? Should disutility be applied in the model ?

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Abbreviations: AE, adverse event; CRS, cytokine release syndrome; EAG, external assessment group; HRQoL, health related quality of life; HSUV, health state utility value; LVP, large volume paracentesis; n, number; PuFS, puncture-free survival; TFDQ, time to first deterioration of quality of life; quality-adjusted life year; TTD, time to death

Key issues: Model structure and health state utilities (4/4)

Company and EAG utility values

Health state	Treatment arm	Company base case		EAG base case	
Company: Stable state EAG: >91 days from death	Catumaxomab + LVP	0.730 (n=17)		0.628	
	LVP	0.621 (n=8)		0.628	
Company: Deteriorating state EAG: ≤91 days from death	Both arms	TFD 91+ days	0.628	TFD 30-91 days	0.469
		TFD 30-91 days	0.469		
		TFD 7-30 days	0.398	TFD 7-30 days	0.398
		TFD 0-7 days	0.149	TFD 0-7 days	0.149

EAG base case models disutility

Event	Utility	Duration (days)
Puncture event	0	1
First catumaxomab administration	0	1
CRS	0	4.3

Are any of these utility values appropriate? If so, company or EAG values?

NICE Abbreviations: CRS, cytokine release syndrome; EAG, external assessment group; HRQoL, health related quality of life; LVP, large volume paracentesis; n, number; TFD, time from death;

Key issue: Subsequent puncture rate (1/2)

Large impact

Company: assume sustained benefit of catumaxomab after first PuFS puncture

Background

- **Company:** assume fixed treatment-specific time between subsequent punctures (TBSP) = sustained catumaxomab benefit
- **EAG**: AC-01 does not suggest clear sustained benefit of catumaxomab in terms of subsequent punctures
  - TBSP estimated as "time to 1st post-study puncture" - incorrectly defined by company

Company:

- Correct TBSP definitions used and align with CSR:
  - Catumaxomab and non-cross over controls: Time from 1st on-study puncture to 1st puncture post-study
  - Controls who cross-over: Time from 1st cross-over puncture to 1st puncture post-cross-over
- Assume initial TBSP data applied to all subsequent punctures, later TBSP data unreliable due to small sample

EAG comments

- Fixed, indefinite, treatment-specific TBSP rate is inconsistent with data = overestimates catumaxomab benefit
  - ➢ AC-01: catumaxomab TBSP declined post-study for subgroups, LVP TBSP longer at final follow up
  - ➢ EAG clinical expert: unlikely catumaxomab benefits would be sustained indefinitely
- LVP arm excludes those who crossed over to catumaxomab = small sample size – difficult to compare groups
- Unclear why company does not use all available subsequent puncture data, beyond 1st post-study puncture
- Base case: no ongoing catumaxomab benefit (equal rate in both arms) and use all available TBSP data

NICE

Abbreviations: CATU, catumaxomab; CSR, clinical study report; LVP, large volume paracentesis; PuFS, puncture-free survival; TBSP, Time between subsequent punctures

Key issue: Subsequent puncture rate (2/2)

Modelled time between subsequent punctures (days)

Population	Company		EAG (base case)***	EAG (scenario)***
	LVP, (n)**	CATU, (n)	Includes crossover	Exclude crossover
ITT*	21.55 (7)	39.80 (28)	33.7	N/A
Ovarian	26.8 (4)	44.7 (20)	37.3	39.3
Non-ovarian	16.3 (3)	34.9 (8)	23.6	26.9

*Weighted average times of the two subpopulations (ovarian and non-ovarian)
** Excludes those who crossed over to catumaxomab
*** Values calculated using weighted average duration from T3 and T4 data.

AC-01 post study time to subsequent puncture events

Mean days (N)	Catumaxomab	Control who crossed over	Control who did not crossover
Ovarian			
T3	44.7 (20)	36.1 (13)	26.8 (4)
T4	29.5 (15)	30.9 (10)	68.3 (3)
Non-ovarian			
T3	34.9 (8)	8.8 (4)	16.3 (4)
T4	18.0 (4)	25.0 (2)	28.5 (2)

T3: time from start of post study period to first puncture in post-study period.
T4: time from first puncture in post-study period to second puncture in post-study period.

Should a benefit of catumaxomab be modelled beyond the first puncture? Which data should inform subsequent puncture rate?

Abbreviations: CATU, catumaxomab; ITT, intention to treat; N, number; N/A, not available; T, time; LVP, large volume paracentesis

Key issues: Modelling OS

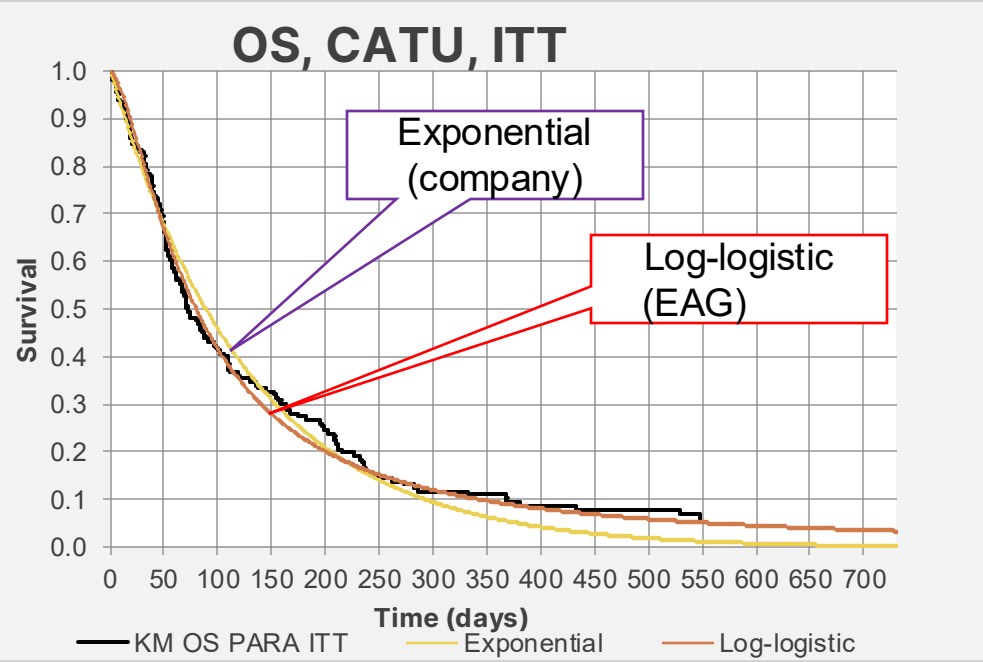
Abbreviations: CATU, catumaxomab; EAG, external assessment group; HR, hazard ratio; ITT, intention- to-treat; KM, Kaplan-Meier; OS, overall survival; LVP, large volume paracentesis; SOC, standard of care

Large ICER impact

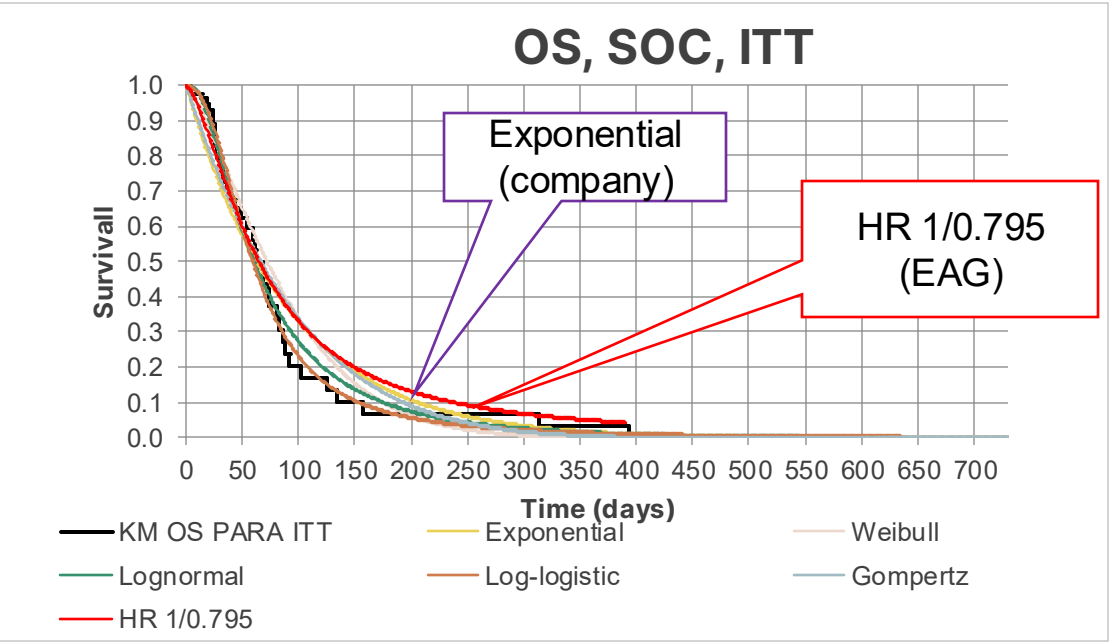
Company: apply 0.926 HR to CATU

EAG: apply 1/0.795 HR to CATU for LVP extrapolation

Catumaxomab long term OS estimates



LVP long term OS estimates



Time (months)	CATU ITT		LVP ITT	
	Exponential (company)	Log-logistic (EAG)	Exponential (company)	Apply 1/0.795 HR to extrapolation of catumaxomab (EAG)
1	79%	81%	72%	77%
2	63%	60%	51%	53%
3	49%	45%	37%	37%
6	24%	23%	14%	16%
12	6%	9%	2%	5%

What is the most plausible distribution to extrapolate OS for catumaxomab and LVP?

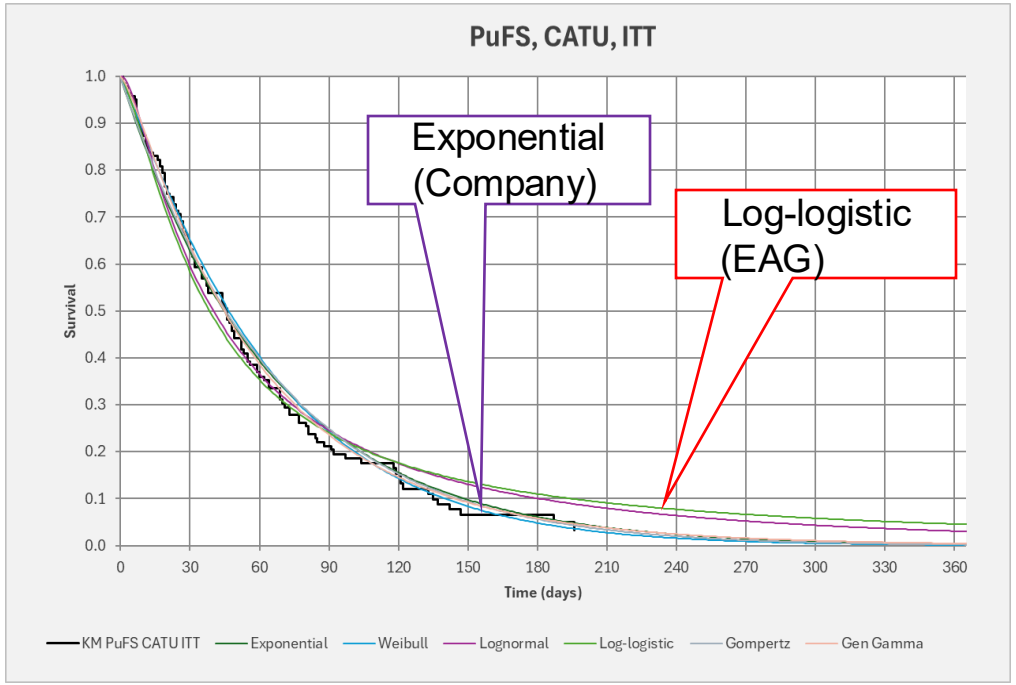
Key issues: Modelling PuFS

Model PuFS predictions

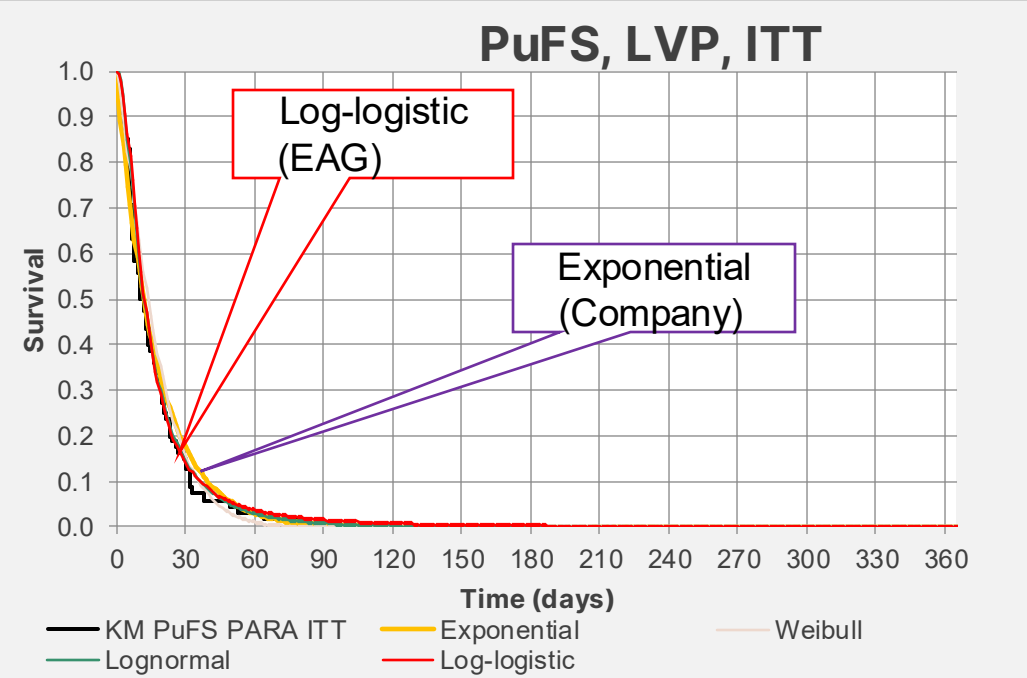
Large ICER impact

Long term PuFS estimates for catumaxomab

Company: HR of 0.994 applied to CATU curves



Long term PuFS estimates for LVP



Time (months)	CATU ITT		LVP ITT	
	Exponential (company)	Log-logistic (EAG)	Exponential (company)	Log-logistic (EAG)
1	63%	58%	18%	14%
2	39%	35%	3%	4%
3	25%	24%	1%	1%
6	6%	11%	0%	0%
12	0%	5%	0%	0%

What is the most plausible distribution to extrapolate PuFS for catumaxomab and LVP?

Abbreviations: CATU, catumaxomab; EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; ITT, intention-to-treat; LVP, large volume paracentesis; PuFS, puncture free survival

Secondary issue: Modelled adverse events

Small impact

Company does not breakdown AE proportions based on severity

Background

- **Company:** costed for CRS AEs based on 1) CRS symptoms reported in trial 2) expert opinion on proportion expected to develop any grade CRS during treatment
- **EAG:** reasons behind hospitalisation not clearly reported

EAG comments

- Company does not breakdown AE proportions by severity
  - High-grade CRS need hospitalisation = significant costs
- EAG: One-off grade 3+ CRS cost applied (incidence 8.9% AC-01) → cost 4.3 days hospitalisation and tocilizumab infusion

Other issues:

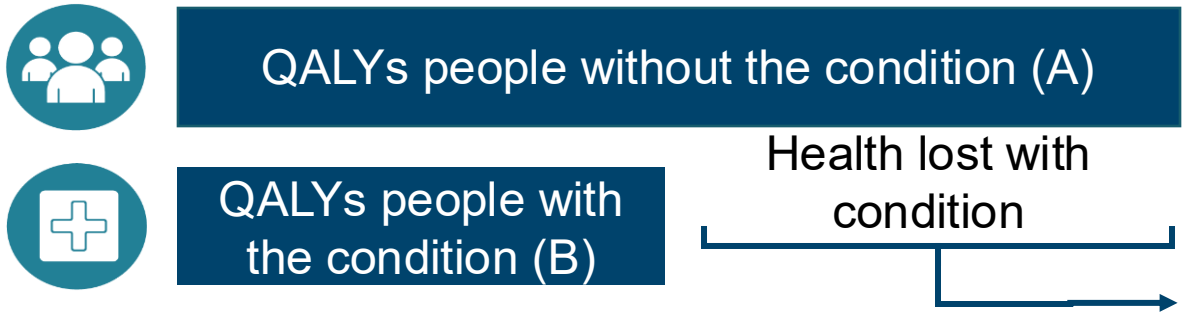
- More deaths and neoplasm progression reported in catumaxomab but cross-over makes interpretation difficult
- Reason for hospitalisation not reported clearly so difficult to link to AE, treatment admin or other

What is the most appropriate method to model AEs?

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; EAG, external assessment group; ICU, intensive care unit;

QALY weightings for severity

Severity: future health lost by people living with the condition with SOC in NHS, severity modifier reflects burden of disease



QALY weight	Absolute shortfall (A-B)	Proportional shortfall (A - B) / A
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Summary of company and EAG QALY calculations	Company	EAG
Baseline age	58.6 years	61.5 years
Female (%)	79.5%	78.5%
QALYs of people without condition	13.94	12.98
QALYs with the condition on current treatment	0.14	0.13
Absolute QALY shortfall (severity weight)	13.94 (1.2)	12.85 (1.2)
Proportional QALY shortfall (severity weight)	0.99 (1.7)	0.99 (1.7)
Severity weight	**1.7**	**1.7**

Is it appropriate to apply a QALY weighting for severity?

Abbreviations: SOC, standard of care; QALY, quality-adjusted life year

Summary of company and EAG model (1/2)

	Company base case	EAG base case	Issue/slide
IPC use	Comparator: not modelled Subsequent treatment: not modelled	Comparator: LVP arm (10%) Subsequent treatment: both arms (10%)	See key issue 2
Baseline age	AC-01 58.6 years	RWE: 61.5 years	See key issue 3
Cancer weighting	Ovarian: 50%, Non-ovarian: 50%	Ovarian: 40%, Non-ovarian: 60%	See key issue 3
Data	Pooled AC-01 (May 2007) and AC-03	AC-01 only – May 2007	See key issue 5
OS (ITT)	Both arms: independent exponential models Apply HR 0.926 to catumaxomab extrapolation curves	Catumaxomab: log-logistic. LVP: HR 1/0.795 applied to catumaxomab extrapolation.	See: • Key issue 5 • OS models
PuFS (ITT)	Both arms: independent exponential models HR 0.994 extrapolation of catumaxomab	Both arms: independent log-logistic models	See PuFS models
Model structure	Use TFDQ to model health states	Remove TFQD, model time-to-event using OS	See key issue 6
Utilities	Different HSUV for “stable HRQoL”	Apply same HSUV for “>91 days from death”	See key issue 6
AE and disutilities	Did not model disutility for CRS or punctures. CRS event rate from expert	Model disutility for CRS and punctures. Use CRS event rate from AC-01	See key issue 6
Puncture rate	Sustained benefit catumaxomab	No benefit beyond first puncture	See key issue 7

Abbreviations: CRS, cytokine release syndrome; EAG, external assessment group; HR, hazard ratio; HSUV, health state utility value; HRQoL, health related quality of life; ITT, intention-to-treat; IPC, indwelling peritoneal catheter; LVP, large volume paracentesis; OS, overall survival; PuFS, puncture-free survival;

Summary of company and EAG model (2/2)

	Company base case	EAG base case	Issue/slide
EpCAM test	£49.81	Aligned with company, but value uncertain	See key issue 1
Setting catumaxomab 1st infusion	20% day case, 80% inpatient	100% inpatient	See key issue 1
LVP setting	20% day case, 80% inpatient	Align with company but exact value unknown	See key issue 1
Adverse event costs	AE events costed based on: 1) CRS symptoms reported in trial 2) Clinical expert predictions on proportion expected to develop any grade CRS during treatment	Apply costs based on proportion that experienced grade 3+ CRS in AC-01	See secondary issue

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; EAG, external assessment group; EpCAM, epithelial cellular adhesion molecules; LVP, large volume paracentesis

Catumaxomab for intraperitoneal treatment of malignant ascites in EpCAM-positive carcinomas when further anticancer treatment is unsuitable

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Uncaptured benefits

Company

Caregiver QALYs:

- Catumaxomab would provide benefit to caregivers e.g., extension of life, delay to next LVP, fewer lifetime LVPs, and delay to the first deterioration in patient HRQoL (carer scenario provided).
  - ❖ Carer scenario does not provide carer QALY gain for catumaxomab compared to LVP:
    - HRQoL improvement after death of person with malignant ascites

Treatment effect size from AC-01 could be underestimated:

- CRS likely managed better now than in AC-01, so potentially improving compliance and outcomes
- Clinical experts: some eligible catumaxomab patients may have higher performance status due to more targeted anti-cancer therapies.
  - ❖ Evidence shows treatment effect larger in those with higher performance status.

EAG comments

Caregiver QALYs:

- Not strongly supported – catumaxomabs requires 4 initial infusions, involving travel and long hospital visits

Treatment effect size AC-01:

- CRS underrepresented in model. EAG cannot verify that higher performance status = greater QALY benefit

Abbreviations: EAG, external assessment group; HRQoL, health-related quality of life; LVP, large volume paracentesis; QALY, quality adjusted life year

Cost-effectiveness results

ICERs including the PAS for catumaxomab and list prices for other drugs are presented in part 1

Confidential tocilizumab price has small impact on ICERs, presented in part 2

Both the EAG and Company's base case ICERs are above the range that NICE usually considers an acceptable use of NHS resources.

Base case results: ITT population

Company base case: Deterministic and probabilistic results

Technology	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs (x1)	Inc QALYs (x1.7)	ICER (£/QALY) (x1)	ICER (£/QALY) (x1.7)
Deterministic							
Catumaxomab	[redacted]	[redacted]					
Paracentesis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£66,563	£39,154
Probabilistic							
Catumaxomab	[redacted]	[redacted]					
Paracentesis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,019	£47,673

EAG base case: Deterministic and probabilistic results

Technology	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs (x1)	Inc QALYs (x1.7)	ICER (£/QALY) (x1)	ICER (£/QALY) (x1.7)
Deterministic							
Catumaxomab	[redacted]	[redacted]					
Paracentesis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£150,871	£88,748
Probabilistic							
Catumaxomab	[redacted]	[redacted]					
Paracentesis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£141,697	£83,032

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Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality adjusted life year

Subgroup results: ovarian and non-ovarian

Company deterministic subgroup results

Technology	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs (x1)	Inc QALYs (x1.7)	ICER (£/QALY) (x1)	ICER (£/QALY) (x1.7)
Ovarian							
Catumaxomab	[redacted]	[redacted]					
Paracentesis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,860	£34,035
Non-ovarian							
Catumaxomab	[redacted]	[redacted]					
Paracentesis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£59,823	£35,190

EAG deterministic subgroup results

Technology	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs (x1)	Inc QALYs (x1.7)	ICER (£/QALY) (x1)	ICER (£/QALY) (x1.7)
Ovarian							
Catumaxomab	[redacted]	[redacted]					
Paracentesis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£121,273	£71,337
Non-ovarian							
Catumaxomab	[redacted]	[redacted]					
Paracentesis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£390,142	£229,495

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Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality adjusted life year

EAG scenario results: ITT population

	Scenario applied to EAG's base case	Inc costs (£)	Inc QALYs (x1)	Inc QALYs (x1.7)	ICER £/QALY (x1)	ICER £/QALY (x1.7)
	Base case	[redacted]	[redacted]	[redacted]	**£150,871**	**£88,748**
1	LVP OS equal to catumaxomab OS; (discard LVP data)	[redacted]	[redacted]	[redacted]	Catumaxomab is dominated	Catumaxomab is dominated
2	Use ITT HR = 1/0.795 for ovarian and non-ovarian LVP OS	[redacted]	[redacted]	[redacted]	Same as base case	Same as base case
3	ITT = log-logistic for ITT LVP OS	[redacted]	[redacted]	[redacted]	£117,680	£69,223
4	LVP setting: 100% day case	[redacted]	[redacted]	[redacted]	£187,406	£110,239
5	Subsequent IPC uptake: 30%	[redacted]	[redacted]	[redacted]	£148,253	£87,207
6	Assume a disutility for all LVPs (utility = 0 for 1 day)	[redacted]	[redacted]	[redacted]	£152,623	£89,778
7	EpCAM testing removed	[redacted]	[redacted]	[redacted]	£150,182	£88,342
8	Higher EpCAM cost: £400	[redacted]	[redacted]	[redacted]	£155,716	£91,597

Abbreviations: EpCAM, epithelial cellular adhesion molecule; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPC, indwelling peritoneal catheter; ITT, intention-to-treat; LVP, large volume paracentesis; OS, overall survival; QALY, quality-adjusted life year

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- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Issues raised for consideration

Key issues

	Key issue	ICER impact
1	Treatment pathway	Small
2	Indwelling peritoneal catheter usage	Small
3	Population in AC-01 and AC-03	Unknown
4	Unclear PuFS benefit of catumaxomab	Large
5	Unclear OS benefit of catumaxomab	Large
6	Model structure and health state utility values	Large
7	Subsequent puncture rate	Large

Secondary issue

	Other issues	ICER impact
8	Adverse events of catumaxomab	Small

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PuFS, puncture free survival;