Ivosidenib for treating IDH1 R132-positive cholangiocarcinoma after at least 1 therapy [ID6164]

For public contains no ACIC information

Technology appraisal committee C

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Company: Servier

Ivosidenib for treating IDH1 R132 positive cholangiocarcinoma after at least 1 therapy

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

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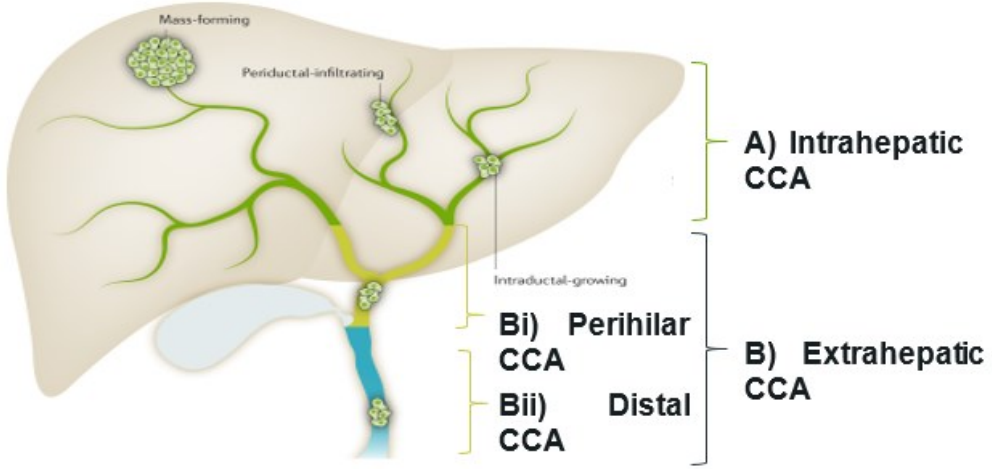
Cholangiocarcinoma*

- Usually presents at an advanced stage; often misdiagnosed as cancer of unknown primary
- NHS Digital cancer registration statistics recorded 2,618 cases for England in 2020
- Estimated 5-year survival <10%

- The main types of CAA subtype include:
  - Intrahepatic tumours (iCCA)
  - Extrahepatic tumours (eCCA)
  - Perihilar (pCCA)
  - Distal (dCCA)



- IDH proteins play a role in several types of tumours; three isoforms: IDH1, IDH2, and IDH3
- **IDH1 mutations: approx. 250 – 300 cases per year**

*See appendix – slide 34

Abbreviations: CCA, cholangiocarcinoma; eCCA, extrahepatic cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; IDH, isocitrate dehydrogenase

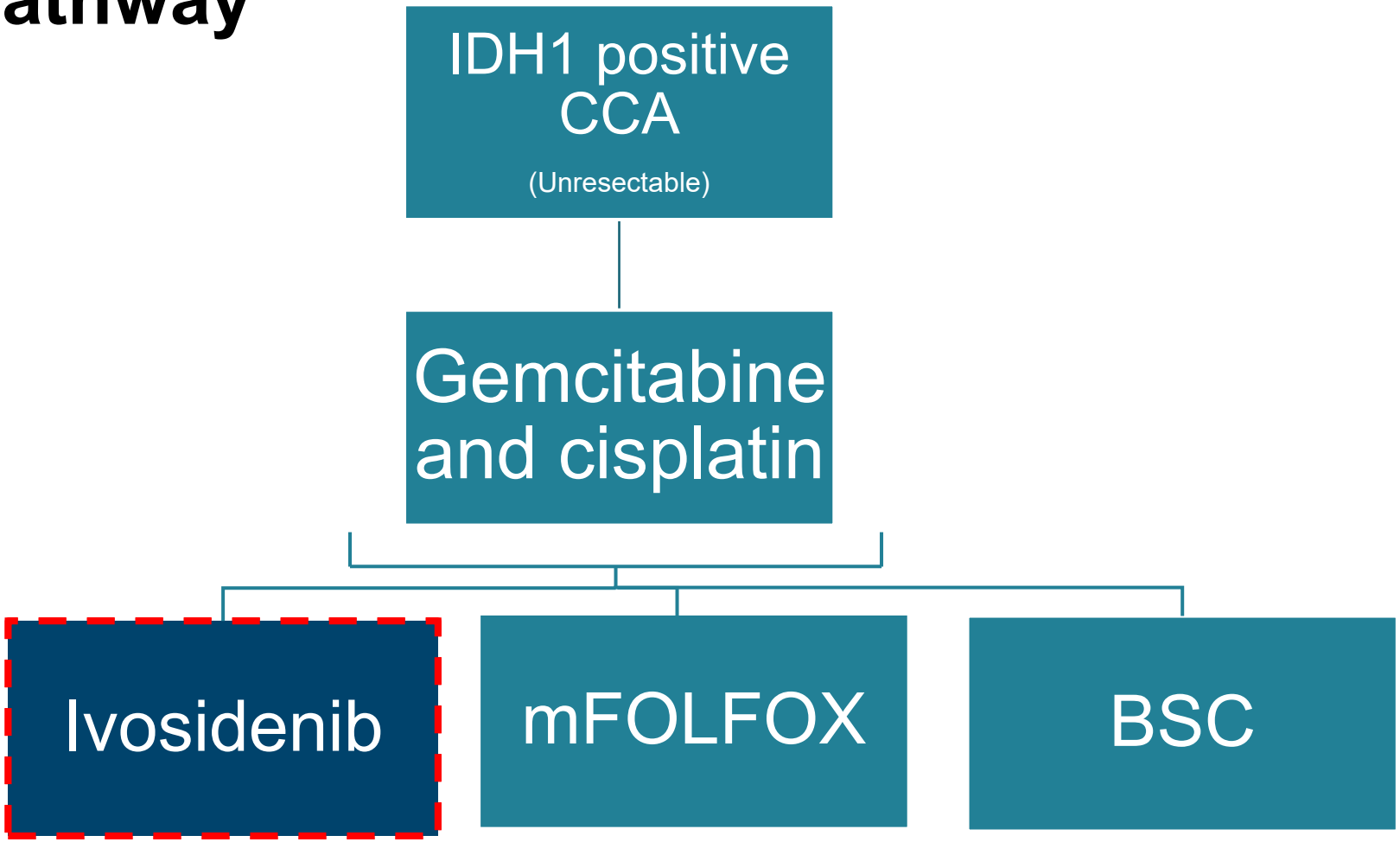
Patient and clinical perspectives*

- Diagnosis and the prognosis can be truly shocking to patients
- Chemotherapy is often at the expense of their QoL, and that of their families
- Resection is the only potentially curative treatment
    - inoperable patients have limited options
    - 50% don't proceed with treatment
- Incidence is increasing with younger adults being diagnosed
- Chemotherapy for inoperable CCA is Gemcitabine and cisplatin (1st line), followed by modified folinic acid + fluorouracil + oxaliplatin [mFOLFOX] (2nd line)
- Ivosidenib might maintain or improve quality of life compared to current care

*See appendix – slides 35 and 36

Abbreviations: CCA, cholangiocarcinoma; QoL, quality of life; SoC, standard of care

Treatment pathway



Abbreviations: BSC, best supportive care; CCA, cholangiocarcinoma; IDH, isocitrate dehydrogenase; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin

Ivosidenib (Tibsovo, Servier)

Technology details

Marketing authorisation	• Tibsovo as a monotherapy for the treatment of adult patient with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated at least one prior line of systemic therapy
Mechanism of action	• Inhibitor of mutated IDH1 enzyme • Mutated IDH1 converts alpha- ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumour growth in both haematologic and non-haematologic malignancies. The mechanism of action of ivosidenib beyond its ability to suppress 2-HG and impair cellular differentiation is not fully understood across indications.
Administration	• 500mg once daily (2x 250mg tablets) to be taken orally. Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient
Price	• List price of ivosidenib is £12,500 (60 x 250 mg tablets – one month supply) • Annual list price cost – £152,083.33 per year • There is a proposed simple patient access scheme (PAS) discount for ivosidenib

Abbreviations: IDH, isocitrate dehydrogenase

Key issues

Key issues	Resolved?	ICER impact
1. a. Concerns about indirect treatment comparison	No	**Unknown**
b. Extrapolation of overall survival for ivosidenib	No	**Large**
2. Continued ivosidenib treatment beyond progression?	No	Moderate
3. a. Modelling of time on treatment for mFOLFOX	No	Moderate
Other issues		
3. b. mFOLFOX acquisition and administration costs	Yes	Small
4. Subsequent treatment costs	No	Small
5. Wastage for ivosidenib?	Yes	Moderate
6. Monthly clinical examination and blood test	Yes	Small
7. Weighted average HRG costs to adverse events	Yes	Small
8. IDH testing for the ivosidenib arm	No	Small
9. Health state utilities based on both progression and treatment status	No	Small

Abbreviations: HRG, healthcare resource groups; IDH, isocitrate dehydrogenase; mFOLFOX, mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin

Ivosidenib for treating IDH1 R132 positive cholangiocarcinoma after at least 1 therapy

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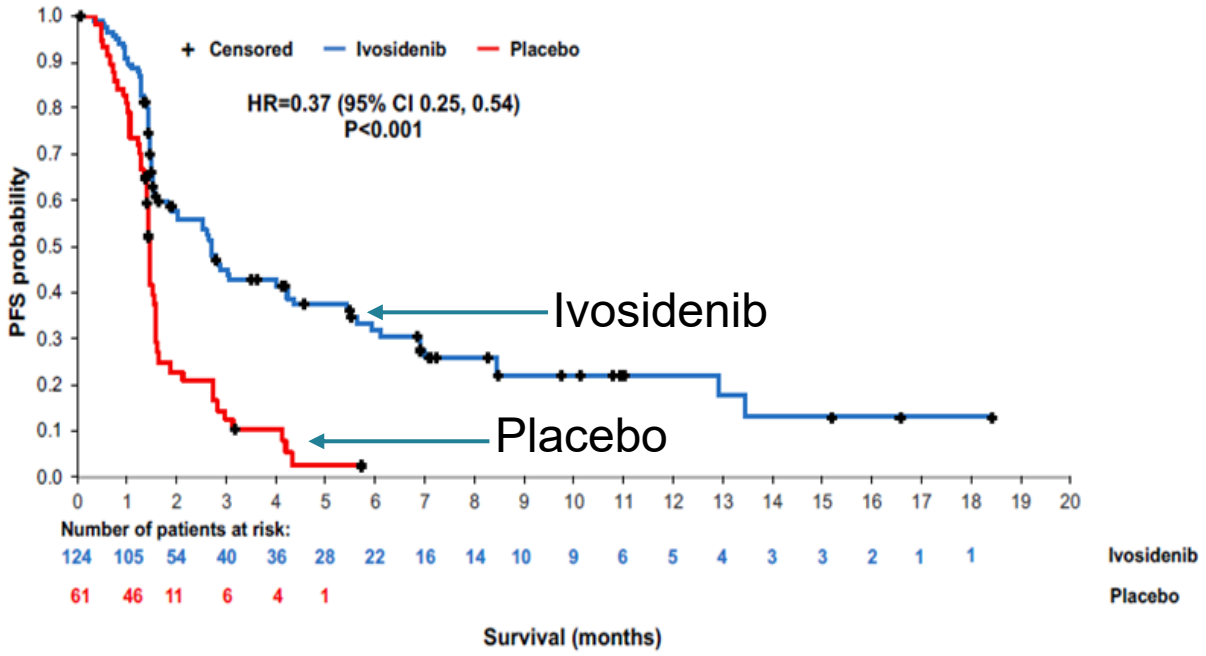
Key clinical trial results – ClarIDHy*

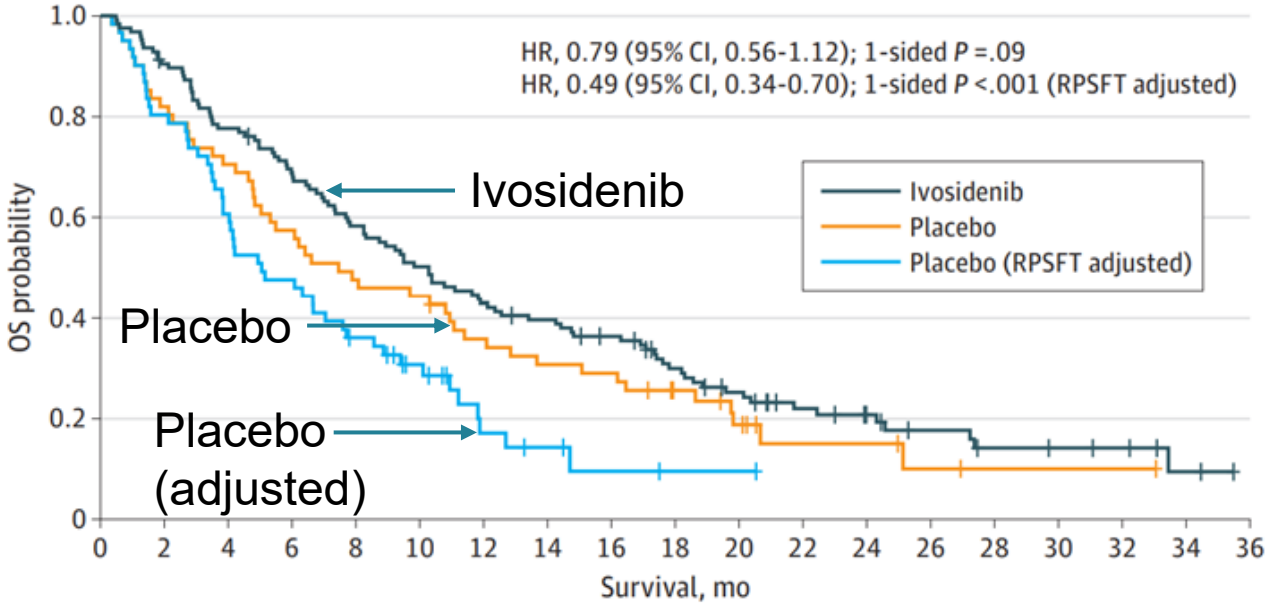
Ivosidenib (n=124) improves PFS and adjusted OS compared to placebo (n=61)

Ivosidenib vs. placebo – PFS (January 2019 DCO)



HR (95% CI; p-value)	0.37 (0.25 to 0.54), p < 0.001

Ivosidenib vs. placebo – OS (May 2020 DCO)



HR (95% CI; p-value), unadjusted	0.79 (0.56 to 1.12), p = 0.093
HR (95% CI; p-value), RPSFT adjusted	0.49 (0.34, 0.70), p < 0.0001

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Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival; PFS, progression free survival; RPSFT, Rank preserving structural failure time model

*See appendix – slide 37

Key clinical trial results – ClarIDHy

Ivosidenib improves PFS and adjusted OS compared to placebo

Outcome (DCO – 31 January 2019)	Ivosidenib (n=124)	Placebo (n=61)
Median PFS	2.7 months	1.4 months
PFS (6 months)	32%	NE
PFS (12 months)	22%	NE
HR (95% CI; p-value)	0.37 (0.25 to 0.54), p < 0.001	
Outcome (DCO – 31 May 2020)	**Ivosidenib (n=126)**	**Placebo (n=61)**
Median OS, unadjusted	10.3 months	7.5 months
OS (6 months), unadjusted	69%	57%
OS (12 months), unadjusted	43%	36%
HR (95% CI; p-value), unadjusted	0.79 (0.56 to 1.12), p = 0.093	
Median OS, months, adjusted for crossover using RPSFT method	10.3 months	5.1 months
HR (95% CI; p-value), adjusted for crossover using RPSFT method	0.49 (0.34, 0.70), p < 0.0001	

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Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression free survival; RPSFT, Rank preserving structural failure time model

Indirect treatment comparison methodology and results*

Subgroup of ClarIDHy used to inform company indirect treatment comparison

- To compare ivosidenib with FOLOX a Bucher ITC was conducted using the ABC-06 trial (phase 3, randomised, open-label trial of FOLFOX plus ASC vs FOLFOX)
- Only possible for OS – PFS not reported for the ASC (control) arm of ABC-06
- A **subgroup** of the ClarIDHy population, that only had **one prior line** of therapy was used for the Bucher ITC to match the ABC-06 trial which only recruited those with one prior line of therapy:
  - ClarIDHy ITT population had received at least one but no more than two prior lines of therapy

Results of the ITC for OS (ivosidenib subgroup vs FOLFOX)

Method	Ivosidenib subgroup vs FOLFOX HR (95% CI)
Unadjusted	[redacted]
RPSFT* adjusted [used in model]	[redacted]
*patients could cross over to ivosidenib in ClarIDHy so company adjusted for cross-over using RPSFT method	

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*See appendix slide 38

Abbreviations: ASC, active symptom control; CI, confidence interval; FOLFOX, folinic acid + fluorouracil + oxaliplatin; HR, hazard ratio; IPCW, inverse-probability-of-censoring weighting; ITC, indirect treatment comparison; ITT, intention to treat; OS, overall survival; PFS, progression free survival; RPSFT, Rank preserving structural failure time model

Ivosidenib for treating IDH1 R132 positive cholangiocarcinoma after at least 1 therapy

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Key issues

Key issues	Resolved?	ICER impact
1. a. Concerns about indirect treatment comparison	No	**Unknown**
b. Extrapolation of overall survival for ivosidenib	No	**Large**
2. Continued ivosidenib treatment beyond progression?	No	Moderate
3. a. Modelling of time on treatment for mFOLFOX	No	Moderate
Other issues		
3. b. mFOLFOX acquisition and administration costs	Yes	Small
4. Subsequent treatment costs*	No	Small
5. Wastage for ivosidenib?	Yes	Moderate
6. Monthly clinical examination and blood test	Yes	Small
7. Weighted average HRG costs to adverse events	Yes	Small
8. IDH testing for the ivosidenib arm	No	Small
9. Health state utilities based on both progression and treatment status	No	Small

*See appendix – slide 42

Abbreviations: HRG, healthcare resource groups; IDH, isocitrate dehydrogenase; mFOLFOX, mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin

1. a. Key issue: Reporting of indirect treatment comparison

Background

- A subgroup of ClarIDHy, that only had one prior line of therapy, was used to inform the indirect comparison with FOLFOX which gave the OS hazard ratios for the model
- [redacted]

Company

- During the clarification stage, provided information on the data and methods informing the indirect comparison, and how the hazard ratio applied in the cost-effectiveness analysis was derived

EAG comments

- This remains an area of uncertainty which has a large influence on the ICER. Concerns with reporting are:
  - Lack of justification and clarity over selection of the ClarIDHy trial subgroup used in the ITC
  - Lack of clarity over the data cut used for the ITC
  - Lack of transparency in reporting of the analysis used to obtain the crossover adjusted survival HR for ivosidenib feeding into the ITC
- Without further details EAG cannot comment on robustness of the HR derived from the ITC
- Ran a scenario where ITT data from ClarIDHy trial was used to derive the HR. HR = 0.71 (95%CI: 0.43-1.16) which had a large increase on the ICER

Is the company's ITC appropriate?

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Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid + fluorouracil + oxaliplatin; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival

1. b. Key issue: Uncertainty in extrapolation of ivosidenib OS (1/3)*

Summary of company extrapolations of OS

[redacted]

Company

In the cost-effectiveness analysis, all survival outcomes were adjusted for background mortality post-hoc within the cost-effectiveness model (by ensuring the hazard of death for the OS curve is equal to or greater than the hazard of death for the age- and sex-matched general population)

Treatment	OS curve
Ivosidenib	Log-normal
BSC	Weibull
mFOLFOX	HR of [redacted] from Bucher ITC applied to ivosidenib reference curve

*See appendix – slide 41

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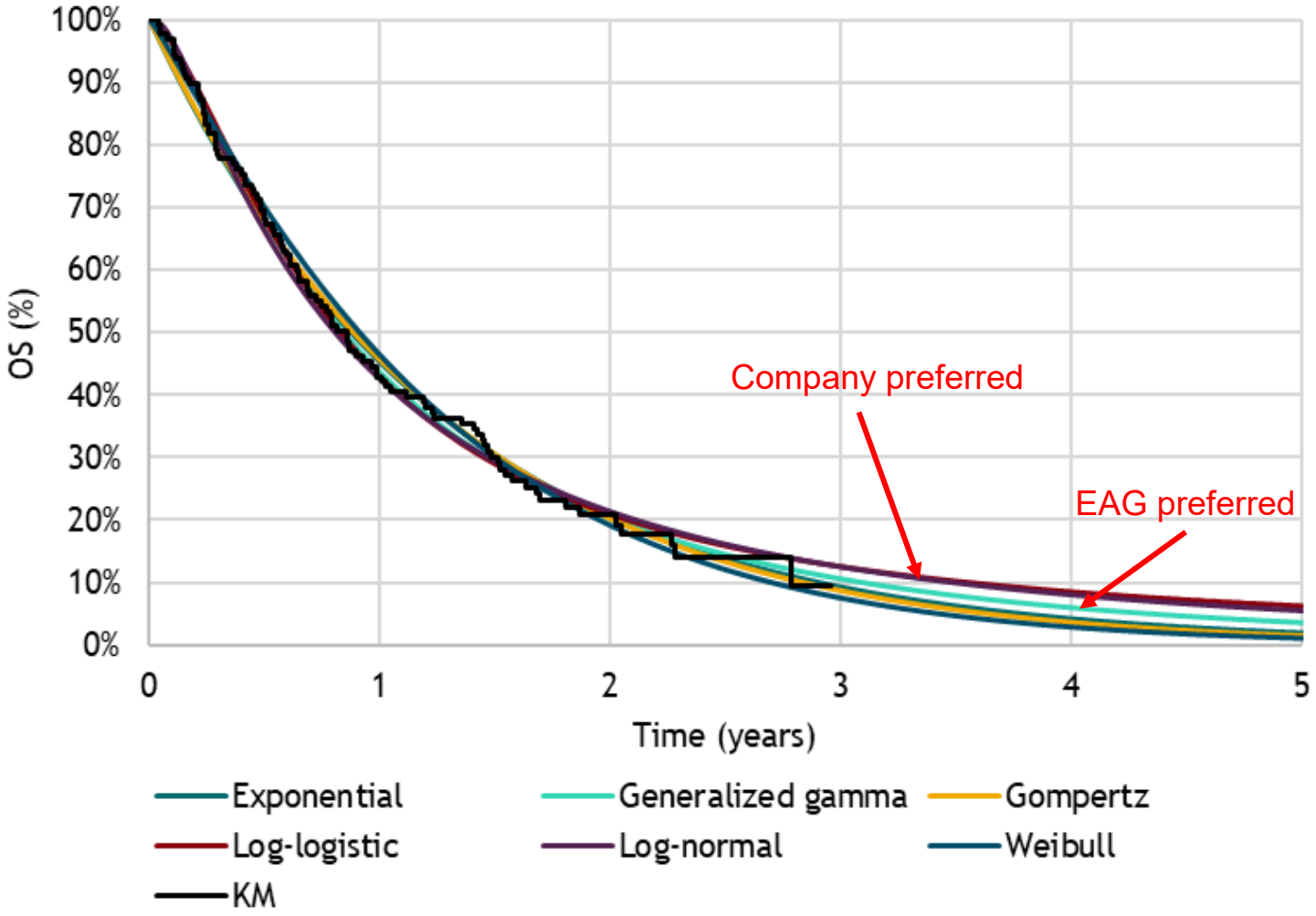
Abbreviations: BSC, best supportive care; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; OS, overall survival

1. b. Key issue: Uncertainty in extrapolation of ivosidenib OS (2/3)

Background

- Six standard parametric curves fitted: company base case log normal, scenarios log-logistic, exponential
- Company clinical experts did not agree on which was the most appropriate to extrapolate ivosidenib OS



EAG comments

- Narrow range for goodness of fit stats
- Choice of curve has large effect on ICERs
- Log normal second most optimistic, exponential (scenario) pessimistic
- Log-normal, log-logistic: possibly slightly worse visual fit to tail of the KM data.
- Generalised gamma: possibly better fit, EAG preferred (middle ground)
- Uncertainty cannot be fully resolved: EAG provide alternative base-case using log-normal (rather than generalised gamma)

Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival

1. b. Key issue: Uncertainty in extrapolation of ivosidenib OS (3/3)

Model	Median OS	AIC	BIC	OS landmarks (years)				
	Months			1	2	5	10	20
KM	10.28	-	-	42.8%	20.7%	-	-	-
Exponential	10.35	248.10	250.93	45.3%	20.5%	1.9%	0.0%	0.0%
Generalised gamma	9.89	247.13	255.64	43.7%	20.3%	3.6%	0.5%	0.0%
Gompertz	10.58	250.05	255.72	45.7%	20.3%	1.5%	0.0%	0.0%
Log-logistic	9.89	246.59	252.27	43.0%	20.9%	6.2%	2.3%	0.8%
Log-normal	9.66	246.19	251.86	42.6%	21.5%	5.6%	1.4%	0.3%
Weibull	10.81	248.69	254.37	46.5%	19.2%	1.1%	0.0%	0.0%

EAG preferred → Generalised gamma

Company preferred → Log-normal

Company

- Maintains that log-normal curve is the most suitable for informing OS in the ivosidenib arm
- Log-normal curve provides both a good visual fit to the observed data, and has the lowest AIC, second lowest BIC, and lowest combined AIC/BIC of all the of the 6 included parametric survival models

What is the committee preference for extrapolating ivosidenib OS?

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; OS, overall survival

2. Key issue: Ivosidenib treatment beyond progression (1/2)

Company

- Capped ToT at progression
- Summary of product characteristics for ivosidenib states treatment should be continued until disease progression or until treatment is no longer tolerated by the patient
- Not possible to adjust the survival estimate for the proportion of patients who received treatment beyond progression within the ClarIDHy study, and would be inappropriate to exclude patients from analysis (without breaking randomisation)

EAG comments

- In ClarIDHy trial, treatment with ivosidenib beyond progression was permitted where investigator deemed that there was clinical benefit – treatment beyond progression may have had a positive effect on OS
- One company expert and the EAG's clinical expert noted that when it is difficult to determine whether a person's disease has progressed or not from diagnostic scans, treatment may continue past progression

Other considerations

- A clinical expert stated that treatment with ivosidenib beyond progression was unlikely
- If the patient were sufficiently fit, they would be offered FOLFOX; if unfit, best supportive care.

Abbreviations: KM, Kaplan-Meier; PFS, progression free survival; OS, overall survival; ToT, time on treatment

2. Key issue: Ivosidenib treatment beyond progression (2/2)

Summary of PFS and ToT extrapolations

[redacted]

EAG comments (continued)

- Observed ivosidenib KM data for PFS and ToT look to be closely related but the ToT data are more mature
- The company's chosen extrapolation for PFS falls below both the observed PFS and ToT data
- Even if treatment is to be stopped upon progression, the poorly fitting PFS curve may artificially reduce extrapolated ToT compared to what would be expected in practice
- Preferred to keep the log-normal PFS curve for ivosidenib but generalised gamma for ivosidenib ToT
- Provided a scenario using generalised gamma for PFS– small reduction in ICER

What is the committee's preference for modelling treatment beyond progression?

Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression free survival; ToT, time on treatment

3. a. Key issue: Modelling of time on treatment for mFOLFOX

Background

- Company use PFS to estimate ToT for mFOLFOX up to 12 cycles rather than estimating a ToT curve

EAG comments

- Suggest ToT for mFOLFOX should be modelled using exponential distribution informed by the median number of treatment cycles observed for patients in the ABC-06
- EAG checked the impact in the model of applying the constant rate of discontinuation based on the median number of mFOLFOX cycles observed in the ABC-06 trial, which resulted in [redacted] of the cohort completing 12 cycles of mFOLFOX, comparable to 16% reported to have completed all 12 cycles in the ABC-06 trial

Company

- Fitting an exponential curve to the median number of treatment cycles to estimate the mFOLFOX ToT curve may underestimate the true cost of administering mFOLFOX in practice
- It is reasonable to assume that patients are more likely to complete a course of treatment with a fixed maximum duration compared with treatment administered in a longer-term setting
- In the absence of a reported mFOLFOX ToT curve, assuming ToT is equivalent to PFS is the most suitable approach for informing the cost-effectiveness model

What is the most appropriate way of modelling ToT for mFOLFOX?

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Abbreviations: CE; cost-effectiveness; EAG, External Assessment Group; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PICC, peripherally inserted central catheter; ToT, time on treatment

Company and EAG base case assumption discrepancies

Assumption	Company revised base case	EAG revised base case
Population to use in ITC	Subgroup of ClarIDHy that only had one prior line of therapy	Same subgroup of ClarIDHy but uncertain of appropriateness
Extrapolation of ivosidenib OS	Log-normal	Generalised gamma [log-normal in scenario]
Ivosidenib treatment beyond progression	Treatment should not be modelled beyond progression	Modelled as per the selected ToT curve, whether beyond progression or not
Modelling mFOLFOX costs	Assume mFOLFOX ToT is equivalent to PFS	Model ToT for mFOLFOX using exponential distribution that aligns with the median number of treatment cycles
Subsequent treatment costs	Subsequent treatment costs excluded	Subsequent treatment costs included following progression on ivosidenib
Inclusion of IDH testing for the ivosidenib arm	IDH1 testing costs should not be included in the model	IDH1 testing costs should be included in the model
Application of health state utility	Health state utility should be incorporated only by treatment status	Prefers utility values linked to progression status and treatment status

Company and EAG aligned on including treatment wastage, not including clinical examination or blood testing costs and the costing approach to adverse events

Abbreviations: BSC, best supportive care; IDH, isocitrate dehydrogenase; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PFS, progression free survival; ToT, time on treatment

Summary of company and EAG base cases

Exact results are reported in part 2

Company base case

- Ivosidenib is more costly and generated more QALYs* than BSC and mFOLFOX.
- ICER for Ivosidenib vs BSC is above £30,000 per QALY gained
- ICER for Ivosidenib vs mFOLFOX is below £30,000 per QALY gained (mFOLFOX extendedly dominated in fully incremental analysis)
- Probabilistic results very similar to deterministic results

EAG base case

- Ivosidenib is more costly and generates more QALYs* than BSC and mFOLFOX.
- ICERs for both Ivosidenib and mFOLFOX vs BSC are considerably higher than £30,000 per QALY gained in deterministic analysis
- ICER for Ivosidenib vs mFOLFOX is considerably higher than £30,000 per QALY gained

***A x1.7 severity modifier was applied to QALYs across all company and EAG analyses**

Abbreviations: CCA, cholangiocarcinoma; QoL, quality of life; SoC, standard of care

Company deterministic scenario analysis vs BSC

All ICERs >£30,000. Allowing treatment beyond progression had greatest impact on ICER

No.	Scenario (applied to company base case)	Incremental costs (£) versus BSC	Incremental QALYs versus BSC*	ICER (£/QALY) versus BSC*
1	**Company base case**	See part 2	See part 2	Over £30,000
2	Log-logistic OS extrapolation (ivosidenib)	↑ Increase	↑ Increase	Over £30,000
3	Generalised gamma OS extrapolation (ivosidenib)	↓ Decrease	↓ Decrease	Over £30,000
4	Exponential OS extrapolation (ivosidenib)	↓ Decrease	↓ Decrease	Over £30,000
5	Utility source: ClarIDHy (progression status)	↔ Equal	↓ Decrease	Over £30,000
6	Utility source: ClarIDHy (progression and treatment status)	↔ Equal	↓ Decrease	Over £30,000
7	Utility source: NICE TA474**	↔ Equal	↔ Equal	Over £30,000
8	Ivosidenib ToT: Exponential	↓ Decrease	↓ Decrease	Over £30,000
9	Allow treatment beyond progression	↑ Increase	↑ Increase	Over £30,000

*x1.7 severity modifier applied. **NICE TA474 Sorafenib for treating advanced hepatocellular carcinoma

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; ToT, time on treatment

Company deterministic scenario analysis vs mFOLFOX

ICERs between £20,000-£30,000 or >£30,000. Using an exponential OS curve had greatest ICER impact

No.	Scenario (applied to company base case)	Incremental costs (£) versus mFOLFOX	Incremental QALYs versus mFOLFOX*	ICER (£/QALY) versus mFOLFOX*
1	**Company base case**	See part 2	See part 2	£20,000 - £30,000
2	Log-logistic OS extrapolation (ivosidenib)	↑ Increase	↑ Increase	£20,000 - £30,000
3	Generalised gamma OS extrapolation (ivosidenib)	↓ Decrease	↓ Decrease	Over £30,000
4	Exponential OS extrapolation (ivosidenib)	↓ Decrease	↓ Decrease	Over £30,000
5	Utility source: ClarIDHy (progression status)	↔ Equal	↓ Decrease	£20,000 - £30,000
6	Utility source: ClarIDHy (progression and treatment status)	↔ Equal	↓ Decrease	£20,000 - £30,000
7	Utility source: NICE TA474**	↔ Equal	↑ Increase	£20,000 - £30,000
8	Ivosidenib ToT: Exponential	↓ Decrease	↔ Equal	£20,000 - £30,000
9	Allow treatment beyond progression	↑ Increase	↑ Increase	Over £30,000

*x1.7 severity modifier applied. **NICE TA474 Sorafenib for treating advanced hepatocellular carcinoma

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY, quality-adjusted life year OS, overall survival; QALY, quality-adjusted life year; ToT, time on treatment

EAG deterministic scenario analysis vs BSC

All ICERs >£30,000. Using a log-normal OS curve had greatest impact on ICER

No.	Scenario (applied to EAG base case)	Incremental costs (£) versus BSC	Incremental QALYs versus BSC*	ICER (£/QALY) versus BSC*
1	**EAG base case**	See part 2	See part 2	Over £30,000
2	Exponential OS extrapolation (ivosidenib)	↓ Decrease	↓ Decrease	Over £30,000
3	Log-normal OS extrapolation (ivosidenib)	↑ Increase	↑ Increase	Over £30,000
4	Utility source: ClarIDHy (progression status)	↔ Equal	↓ Decrease	Over £30,000
5	Utility source: ClarIDHy (treatment status)	↔ Equal	↑ Increase	Over £30,000
6	Utility source: NICE TA208**	↔ Equal	↓ Decrease	Over £30,000
7	Ivosidenib ToT: Cap at PFS	↓ Decrease	↓ Decrease	Over £30,000
8	Ivosidenib wastage: No wastage	↓ Decrease	↔ Equal	Over £30,000
9	Subsequent treatment: Excluded	↓ Decrease	↔ Equal	Over £30,000
10	HR from ITC (using the ITT data from ClarIDHy); HR= 0.71 – Not applicable to comparison with BSC			
11	Generalised gamma PFS extrapolation (ivosidenib)	↓ Decrease	↑ Increase	Over £30,000

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*x1.7 severity modifier applied. ** Trastuzumab for the treatment of HER2-positive metastatic gastric cancer

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; ToT, time on treatment

EAG deterministic scenario analysis

All ICERs >£30,000. Using a HR of 0.71 had greatest impact on ICER

No.	Scenario (applied to EAG base case)	Incremental costs (£) versus mFOLFOX	Incremental QALYs versus mFOLFOX*	ICER (£/QALY) versus mFOLFOX*
1	**EAG base case**	See part 2	See part 2	Over £30,000
2	Exponential OS extrapolation (ivosidenib)	↓ Decrease	↓ Decrease	Over £30,000
3	Log-normal OS extrapolation (ivosidenib)	↑ Increase	↑ Increase	Over £30,000
4	Utility source: ClarIDHy (progression status)	↔ Equal	↓ Decrease	Over £30,000
5	Utility source: ClarIDHy (treatment status)	↔ Equal	↑ Increase	Over £30,000
6	Utility source: NICE TA208**	↔ Equal	↓ Decrease	Over £30,000
7	Ivosidenib ToT: Cap at PFS	↓ Decrease	↔ Equal	Over £30,000
8	Ivosidenib wastage: No wastage	↓ Decrease	↔ Equal	Over £30,000
9	Subsequent treatment: Excluded	↓ Decrease	↔ Equal	Over £30,000
10	HR from ITC (using the ITT data from ClarIDHy); HR= 0.71	↓ Decrease	↓ Big decrease	Over £30,000
11	Generalised gamma PFS extrapolation (ivosidenib)	↓ Decrease	↑ Increase	Over £30,000

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*x1.7 severity modifier applied. ** Trastuzumab for the treatment of HER2-positive metastatic gastric cancer

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; ToT, time on treatment

Ivosidenib for treating IDH1 R132 positive cholangiocarcinoma after at least 1 therapy

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- ✓ **Other considerations**
- ❑ Summary

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Other considerations

- **No equality issues were raised by the company, EAG or stakeholders during the appraisal process**
- **Managed access (inc. CDF) probably not appropriate**
- **Severity weighting: company and EAG agree 1.7 weighting appropriate***

*See appendix – slides 43 and 44

Ivosidenib for treating IDH1 R132 positive cholangiocarcinoma after at least 1 therapy

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

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Key issues

Key issues	Resolved?	ICER impact
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2. Continued ivosidenib treatment beyond progression?	No	Moderate
3. a. Modelling of time on treatment for mFOLFOX	No	Moderate
Other issues		
3. b. mFOLFOX acquisition and administration costs	Yes	Small
4. Subsequent treatment costs	No	Small
5. Wastage for ivosidenib?	Yes	Moderate
6. Monthly clinical examination and blood test	Yes	Small
7. Weighted average HRG costs to adverse events	Yes	Small
8. IDH testing for the ivosidenib arm	No	Small
9. Health state utilities based on both progression and treatment status	No	Small

Abbreviations: HRG, healthcare resource groups; IDH, isocitrate dehydrogenase; mFOLFOX, mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin

Committee decision making slide

What are the committee's preferred assumptions?

Assumption	Question for committee
Population to use in ITC	Is the company's ITC appropriate?
Extrapolation of ivosidenib OS	What is the committee preference for extrapolating ivosidenib OS?
Ivosidenib treatment beyond progression	What is the committee's preference for modelling treatment beyond progression?
Modelling mFOLFOX costs	What is the most appropriate way of modelling ToT for mFOLFOX?
Whether and how to include subsequent treatment costs	What is the most appropriate approach to modelling subsequent treatment costs
Severity modifier	Does the committee agree it is appropriate to apply a QALY weighting for severity?
ICER threshold	What is the committee's preferred ICER threshold
Preferred ICER	What is the committee's preferred ICER?

Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; OS, overall survival; QALY,

Ivosidenib for treating IDH1 R132-positive cholangiocarcinoma after at least 1 therapy [ID6164]

For committee contains **ACIC** information

Technology appraisal committee C

Chair: Stephen O'Brien

Lead team: Britta Stordal, Mike Chambers, Ugochi Nwulu

External assessment group: University of Aberdeen

Technical team: Giacomo De Guisa, Madiha Adam, Victoria Kelly, Jasdeep Hayre

Company: Servier

Ivosidenib for treating IDH1 R132 positive cholangiocarcinoma after at least 1 therapy [ID6164]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Background on cholangiocarcinomas

Causes

- Cholangiocarcinoma (CCA) is uncontrolled division of cells in the biliary tract but excluding the gall bladder
- A range of genetic alterations can promote CCA including in the IDH1, IDH2, IDH3 and FGFR2 genes

Epidemiology

- Around 30,000 CCA diagnoses between 2001–2017: 51.6% were female and median age of diagnosis was 75 years

Symptoms and prognosis

- CAA often presents with non-specific symptoms at a later stage of the disease
- Poor survival outcomes have been reported among patients with CCA (estimated 5-year survival of <10%)

Link to slide 3

 Abbreviations: CCA, cholangiocarcinoma; IDH, isocitrate dehydrogenase

Patient perspectives

Submission from AMMF (The cholangiocarcinoma charity)

Living with cholangiocarcinoma

- Diagnosis and the prognosis can be truly shocking to patients
- Undergoing this chemotherapy is often at the expense of their QoL, and that of their families

Current treatment options

- Currently a resection is the only potentially curative treatment there is for CCA, so inoperable patients are left with very limited options
- Standard first line treatment for those with inoperable CCA is the chemotherapy combination, gemcitabine and cisplatin

Unmet need

- Incidence and mortality increasing, with younger adults being diagnosed
- Few eligible for resection and SoC chemotherapy offers modest (if any) benefit

"After my diagnosis I felt so alone and afraid, I had no one to turn to for help."

"They told me surgery was my only chance of survival, but it might already be too late."

Abbreviations: CCA, cholangiocarcinoma; QoL, quality of life; SoC, standard of care

Link to slide 4

Clinical perspectives

Submissions from Cholangiocarcinoma UK and RCP-ACP-RCR

Current treatment options

- Advanced cholangiocarcinoma is treated with combination gem-cis chemotherapy (1st line), followed by FOLFOX (2nd line)

Unmet need / current treatment

- Overall survival is poor and there is a lack of effective therapies for patient who are refractory to first line systemic therapy
- Uptake of treatment significant regional variation and generally poor uptake of treatment with approximately 50% of patients not receiving treatment at all

Quality of life

- Professional stakeholders believed that ivosidenib would either maintain or improve quality of life compared to current care

"Improvement in survival for this population has been modest"

20% of cholangiocarcinoma patients are estimated to have [the IDH1] mutation

Abbreviations: FOLFOX, modified folinic acid + fluorouracil + oxaliplatin; IDH, isocitrate dehydrogenase

Link to slide 4

Key clinical trial - ClarIDHy

Company pivotal trial for ivosidenib

	ClarIDHy
Design	Multicentre, randomized, double-blind, placebo-controlled phase 3
Population	Patients aged at least 18 years with a confirmed diagnosis of unresectable or metastatic CCA with mIDH1 gene who had received 1 or 2 previous lines of therapy
Intervention	Ivosidenib n=126 (n=124 at time of primary analysis for PFS)
Comparator(s)	Placebo n=61
Treatment crossover?	Yes (patients in the placebo arm who experienced disease progression)
Primary outcome	PFS
Key secondary outcomes	OS, ORR, DOR, TTR, PFS (determined by investigator), safety / tolerability, HRQoL
Locations	France, Italy, South Korea, Spain, UK, US
Used in model?	Yes

Link to slide 9

Abbreviations: ASC, active symptom control; BSC, best supportive care; BTC, biliary tract cancer; CCA, cholangiocarcinoma; DOR, duration of response; HRQoL, health related quality of life; IDH, isocitrate dehydrogenase; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression free survival; TTR, time to recurrence

Cross over adjustment using RPSFT method

43 out of 61 participants in placebo arm of ClarIDHy crossed over to ivosidenib upon progression - company used RPSFT method to adjust for cross-over.

Overall survival effect sizes (ivosidenib vs placebo)

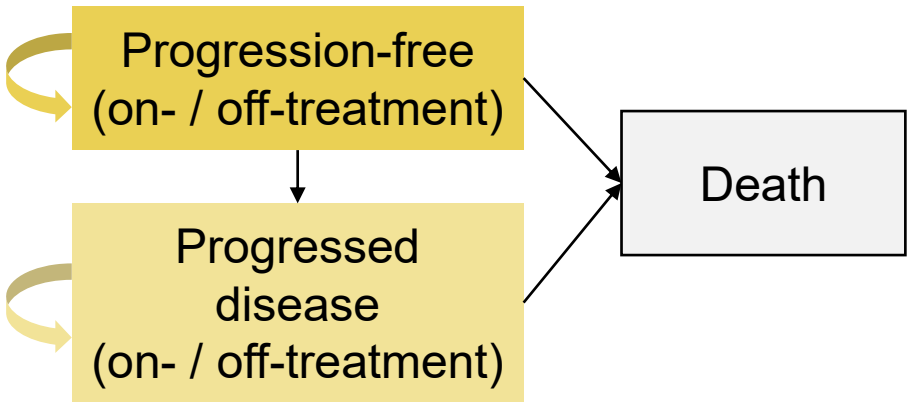
Method	Ivosidenib vs placebo HR (95% CI)
Unadjusted - ITT	0.79 (0.56,1.12)
RPSFT adjusted - ITT	0.49 (0.34,0.70)
unadjusted - subgroup	0.87 (0.54,1.40)
RPSFT adjusted - subgroup	0.40 (0.23,0.68)

See link to slide 11

Abbreviations: : CI, confidence interval; HR, hazard ratio; IPCW, inverse-probability-of-censoring weighting; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; RPSFT, Rank preserving structural failure time model

Company's model overview

Model structure



Assumptions with greatest ICER effect:

- The parametric survival curve selection for overall survival on ivosidenib
- The overall survival hazard ratio for ivosidenib versus mFOLFOX
- The decision to cap ivosidenib ToT with PFS
- Using PFS as a proxy for ToT with mFOLFOX
- Whether to account for the potential wastage costs of ivosidenib
- Whether and how subsequent treatment costs should be included in the different arms of the model.

Technology affects costs by:	Technology affects QALYs by:
Having higher acquisition costs compared to the other modelled treatments.	Increasing overall survival compared to other available treatments.
Having lower administration costs relative to mFOLFOX.	Prolonging time on active treatment and/or delaying progression of disease.
Accumulating greater health care resource use over a period of extended survival.	Having a different adverse event profile compared to other treatments.
Having a different adverse event profile compared to other treatments.	

Abbreviations: ICER, incremental cost-effectiveness ratio; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PFS, progression free survival; QALY, quality-adjusted life year; ToT, time on treatment

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	Taken from ClarIDHy
Intervention efficacy	PFS - ClarIDHy ivosidenib arm Jan 2019 data cut OS – ClaIDHy ivosidenib arm May 2020 data cut
Comparator efficacy	BSC PFS – ClarIDHy placebo arm Jan 2019 data cut BSC OS – ClarIDHy placebo arm May 2020 data cut (RPSFT adjusted) mFOLFOX PFS – mFOLFOX arm of ABC-06 (naïve comparison) mFOLFOX OS – Hazard ratio from ITC of mFOLFOX and ivosidenib
Utilities	Utility values – ClarIDHy trial EQ-5D data converted to EQ-5D-3L score Adverse event-related disutility – prior NICE appraisal in CCA (TA722)
Adverse events	Ivosidenib – ClarIDHy trial (June 2021 data cut); mFOLFOX – ABC-06
Costs	Acquisition, administration health states adverse event and miscellaneous costs sourced from CS, eMIT database, NHS reference cost
Resource use	NHS National Cost Collection (2020/21) and the BNF (for morphine sulphate)
Discontinuation	Ivosidenib - time on treatment (ClarIDHy June 2021 data cut) mFOLFOX – ABC-06 mFOLFOX arm

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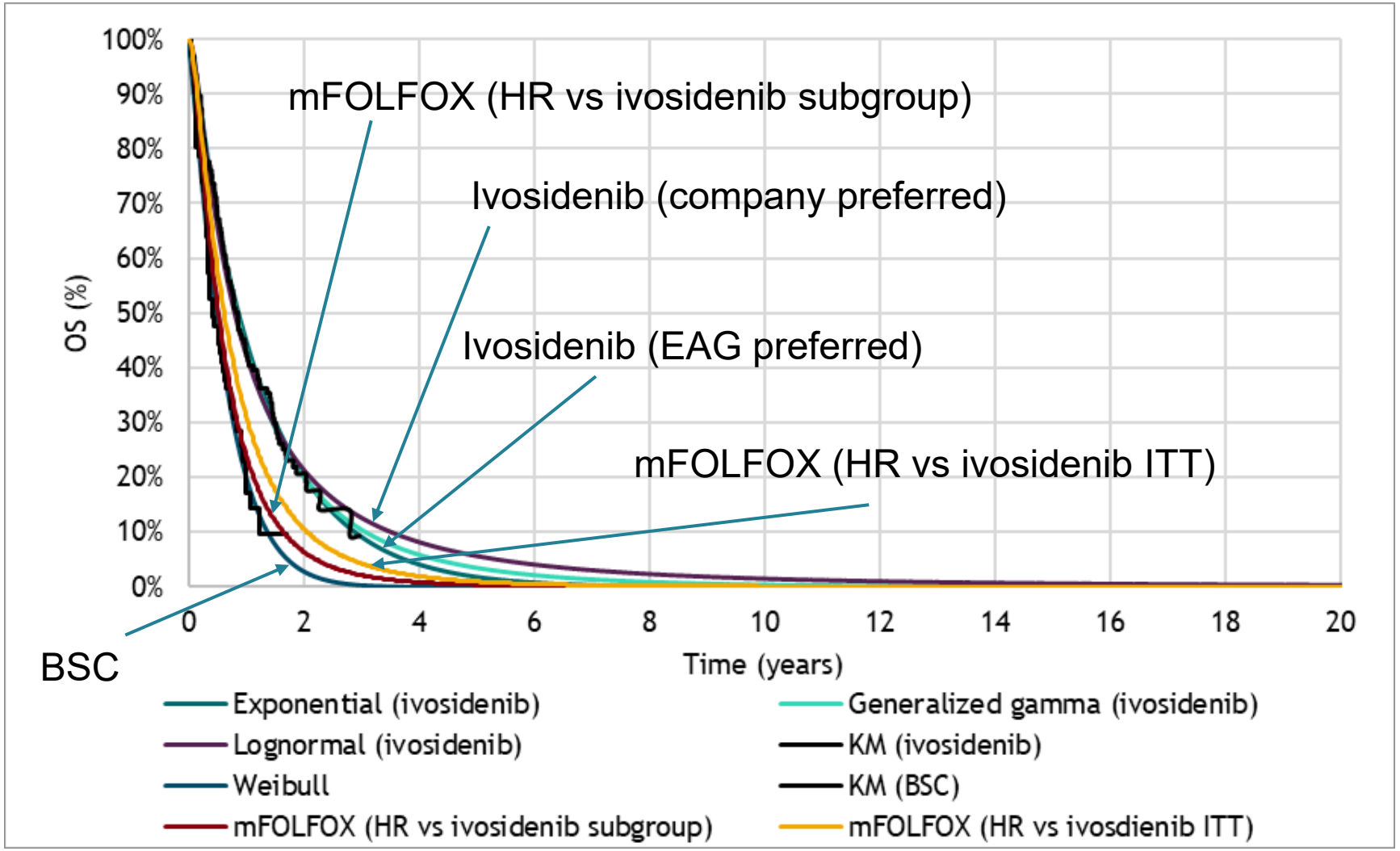
Abbreviations: BNF, British National Formulary; BSC, best supportive care; CCA, cholangiocarcinoma; CS, company submission; eMIT, electronic market information tool; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression free survival; RPSFT, Rank preserving structural failure time model

OS extrapolation for ivosidenib, BSC and mFOLFOX

Referent to EAG preferred generalised gamma curve for ivosidenib



EAG

- Figure shows selected OS curves for ivosidenib, the agreed Weibull curve for BSC, and the derived OS curve for mFOLFOX
- The company prefer the log-normal curve for ivosidenib OS, and apply the HR for mFOLFOX to this instead of EAG preferred generalised gamma
- Smaller difference in OS between mFOLFOX and ivosidenib when HR derived from ClarIDHy ITT population is used – although this infers greater mFOLFOX benefit than that observed in ABC-06 trial

Abbreviations: BSC, best supportive care; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention to treat; KM, Kaplan-Meier; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; OS, overall survival

Link to slide 15

4. Key issue: Inclusion of subsequent treatment costs

Background

- A proportion of patients in the ClarIDHy trial subsequently went on to receive further treatment (most frequently chemotherapy) following progression on ivosidenib
- Company excluded subsequent treatment costs in base case analysis, but included them in scenarios
- In scenarios, the company included subsequent mFOLFOX treatment costs across all treatment arms and calculated them by multiplying treatment cycle cost by a median number of treatment cycles

Company

- Exclusion of subsequent treatment costs is the most suitable approach and is consistent with NICE TA722
- Many of the subsequent treatments received in the ClarIDHy trial were investigational therapies
- Due to the poor prognosis of patients with previously treated advanced/metastatic CCA, it may be more reasonable to assume that most patients would go on to receive BSC in a community palliative setting

EAG comments

- It is more appropriate to account for the cost of subsequent therapy in the ivosidenib arm of the model, as this is consistent with the efficacy data informing the model and expected clinical practice
- Subsequent treatment costs should only be modelled following progression on ivosidenib, not BSC
- EAG modelling for subsequent treatment involves recycling the expected discounted cost of mFOLFOX and applying in ivosidenib arm to the observed proportion of patients who received further treatment

Other considerations: Two clinical experts thought subsequent treatment would be offered if patient is fit

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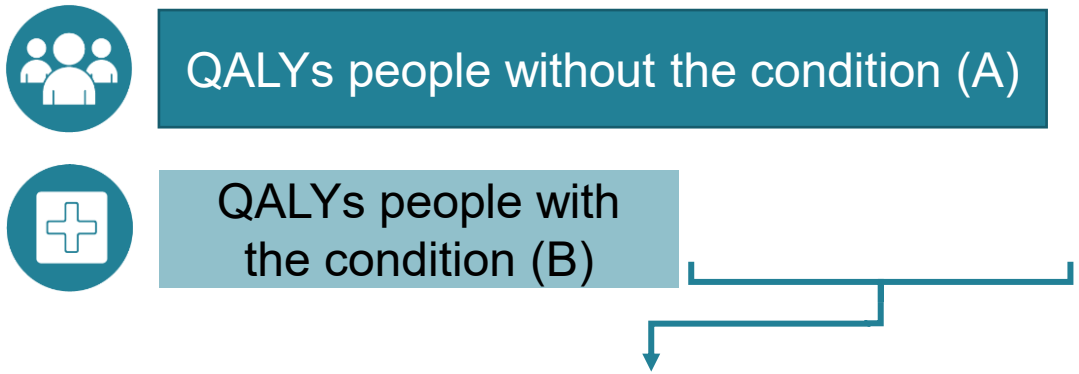
What is the most appropriate approach to modelling subsequent treatment costs?

Link to slide 13

Abbreviations: 3L, third-line; BSC, best supportive care; CCA, cholangiocarcinoma; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin

QALY weightings for severity (1/2)

New severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
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

Link to slide 28

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Abbreviations: QALY, quality-adjusted life year

QALY weightings for severity (2/2)

Background

- Company concluded IDH1 R132 positive cholangiocarcinoma after at least 1 therapy qualify for a 1.7 severity modifier
- Calculated using the R-Shiny tool by Schneider et al. (2021):
  - Trial baseline characteristics: 63.24% female, [redacted] year starting age (ClarIDHy)
  - Utilities for people with the condition: PFS/PD (on treatment) = [redacted]; PFS/PD (off treatment) = [redacted], (ClarIDHy)
- A severity modifier of 1.7 was also suggested across all EAG analyses.
- Results are presented both with QALY weighting using a decision modifier of 1.7

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	**Absolute QALY shortfall (has to be >12)**	**Proportional QALY shortfall (has to be >0.85)**
Company original base case (BSC)	[redacted]	[redacted]	[redacted]	0.9649
Company original base case (mFOLFOX)	[redacted]	[redacted]	[redacted]	0.9589

Does the committee agree it is appropriate to apply a QALY weighting for severity?

Link to slide 27

Abbreviations: IDH, isocitrate dehydrogenase; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year

NICE National Institute for Health and Care Excellence