

**SLIDES FOR PUBLIC**

**Trifluridine–tipiracil for treating metastatic  
gastric or gastro-oesophageal junction cancer  
after 2 or more therapies [ID1507]  
ACM 3 presentation**

Evidence review group  
(ERG): ScHARR

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Company: Servier Laboratories

Date: 5<sup>th</sup> November 2020

# Recap

- ACM 1 – not recommended, ACD released
- ACM 2 – not recommended, FAD drafted but not released

|                                       |   |
|---------------------------------------|---|
| <b>Main issues discussed at ACM 2</b> | <ol style="list-style-type: none"> <li>1. Plausibility of subgroup analyses for people who had 2 previous treatments (i.e. third-line [3L] treatment only) +/- from European region [EU]</li> <li>2. End-of-life criteria (is extension to life criteria met for the 3L subgroup?)</li> </ol>   |
| <b>Outcomes</b>                       | <ol style="list-style-type: none"> <li>1. ICERs were lower in the 3L subgroup but there were imbalances in patient characteristics that could favour survival with trifluridine–tipiracil (TFT) <ul style="list-style-type: none"> <li>– company acknowledged imbalances may be possible but did not make any adjustments to rebalance</li> <li>– so, 3L analyses were not considered suitable for decision-making</li> </ul> </li> <li>2. Mean overall survival (OS) gains for TFT were higher in the 3L subgroups <ul style="list-style-type: none"> <li>– not considered robust because the 3L analyses were not suitable for decision-making</li> </ul> </li> </ol> |
| <b>Company results at ACM 2</b>       | <ul style="list-style-type: none"> <li>• 3L subgroup → <b>£43,052/ QALY</b> gained, OS gain = <b>3.2 months</b></li> <li>• 3L &amp; EU (cttee preferred) → <b>£46,731/ QALY</b> gained, OS gain = <b>3.1 months</b></li> <li>• Committee considered ‘EU, no prior ramucirumab’ subgroup as proxy for 3L → <b>£68,061</b> per QALY gained, OS gain = <b>1.7 months</b> → not recommended</li> </ul>  |

# New analyses to adjust for imbalances

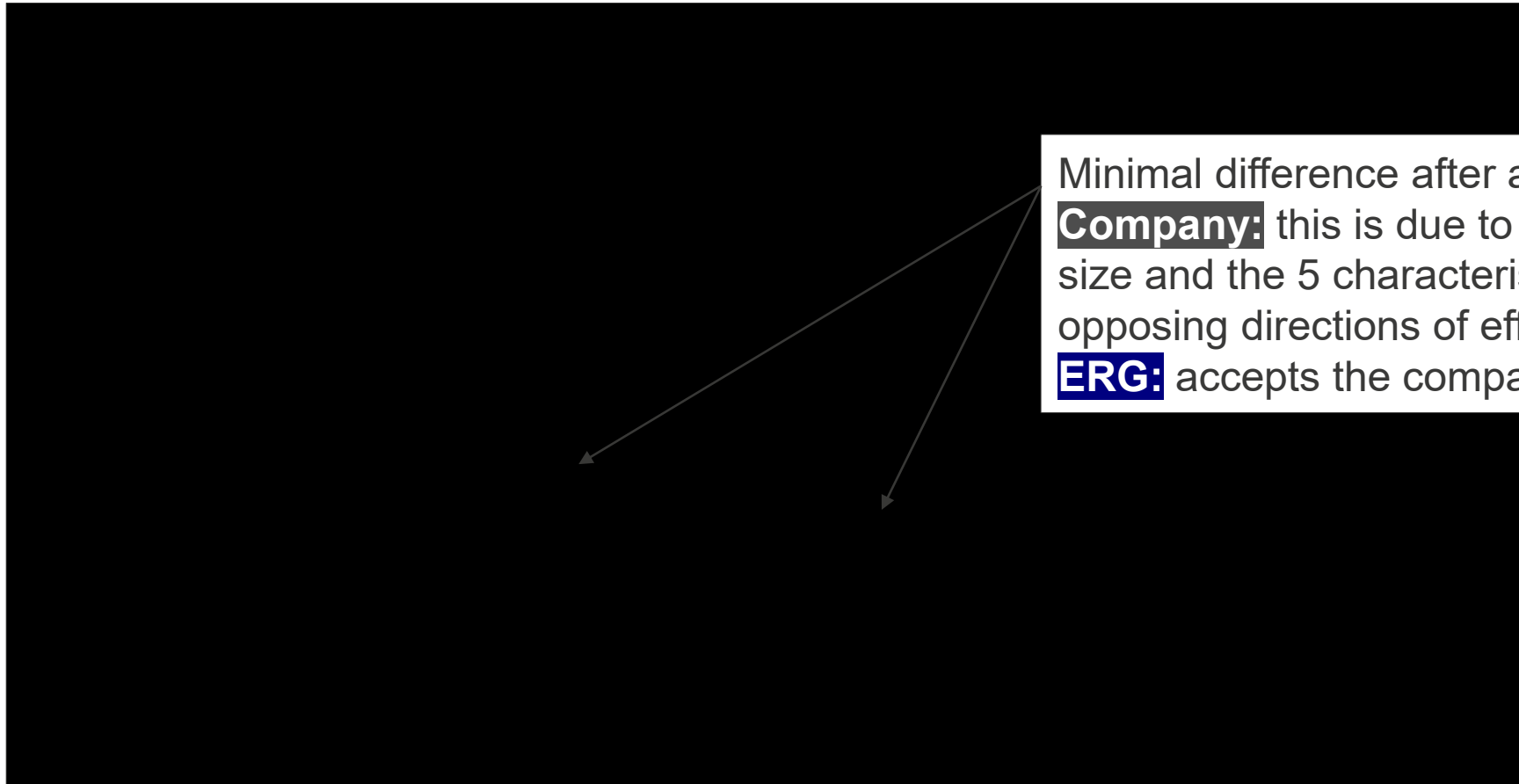
- After discussion with NICE, the company provided propensity-score weighted analyses to adjust for imbalances in the 3L subgroup in:
  - ECOG performance status: 0 versus 1
  - Histology: intestinal versus non-intestinal
  - Peritoneal metastases
  - Prior irinotecan
  - Region: patients living in Japan versus the rest of the world (“region”)
    - also explored ethnicity (Asian versus non-Asian)
- Company used propensity score weights to obtain a balanced 3L dataset
  - each patient assigned a weight for each combination of selected characteristics, more weight given to those with unexpected propensity score

## ERG

- Key assumption of propensity score approach is no unmeasured confounders
- Unclear if the model adjusted for all measured confounders
  - 5 potential confounders were included following discussion with NICE
- Not possible to quantify the extent of the bias or the impact on standard errors
- Would have preferred regression analysis using whole dataset, including prior ramucirumab, relevant prognostic factors, and interaction between treatment arm & number of prior therapies

## NICE

# Adjusted OS data: 3L, all regions



Minimal difference after adjustment.  
**Company:** this is due to small sample size and the 5 characteristics having opposing directions of effect.  
**ERG:** accepts the company's rationale.

Source: figure 3 in company's additional analyses

— Placebo weighted  
 - - - Placebo unweighted  
 — TFT weighted  
 - - - TFT unweighted

Company used **log-normal** model fitted to adjusted dataset (previous cttee preference).

# Adjusted OS data: 3L, Europe only



Minimal difference after adjustment.  
**Company:** this is due to small sample size and the 5 characteristics having opposing directions of effect.  
**ERG:** accepts the company's rationale.

Source: figure 7 in company's additional analyses

— Placebo weighted  
 - - - Placebo unweighted  
 — TFT weighted  
 - - - TFT unweighted

Company used **log-normal** model fitted to adjusted dataset (previous cttee preference).

# ERG comments on new survival data

## ERG

- Assuming propensity score model is correct, ERG is reasonably satisfied with the survival functions used in the base case:
  - Generalised gamma has best statistical fit for independent models, but BSC arm had long tail and curves cross → previously judged implausible by clinicians
  - Log-normal 2<sup>nd</sup> best statistical fit
    - Therefore, reasonable to choose log-normal
  - Log-logistic 3<sup>rd</sup> best statistical fit
- No adjustment according to prior ramucirumab use
  - But this was not requested by NICE
- Prefers EU subgroup rather than whole population analysis, based on previous clinical advice.
  - Committee also preferred EU subgroup (see ACD).

# Adjusted time-to-discontinuation (TTD, 3L EU)

- Negligible difference in TTD following adjustment → company retains cttee-preferred generalised gamma model in base case
- **ERG:** Generalised gamma model is only 4<sup>th</sup> best statistical fit according to BIC, and cannot rule out log-normal (5<sup>th</sup> best, but small differences in BIC statistics).



In order of  
BIC  
statistical fit

% estimates  
on next  
slide

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| 3L EU        | BIC* | 3 months | 6 mos. | 9 mos. | 12 mos. | 15 mos. | 18 mos. |
|--------------|------|----------|--------|--------|---------|---------|---------|
| Observed     |      | ■        | ■      | ■      | ■       | ■       | ■       |
| Exponential  | ■    | ■        | ■      | ■      | ■       | ■       | ■       |
| Weibull      | ■    | ■        | ■      | ■      | ■       | ■       | ■       |
| Gompertz     | ■    | ■        | ■      | ■      | ■       | ■       | ■       |
| Gen. gamma** | ■    | ■        | ■      | ■      | ■       | ■       | ■       |
| Log-normal   | ■    | ■        | ■      | ■      | ■       | ■       | ■       |
| Log-logistic | ■    | ■        | ■      | ■      | ■       | ■       | ■       |

\* Lower BIC indicates better statistical fit; \*\* Company's base-case analysis.



# Cost effectiveness: adjusted 3L

Company also increased PAS after ACM2

| 3L subgroup<br>OS: log-normal<br>New PAS | Arm | Total    |       |       | Incremental |       |       | ICER<br>(£/QALY) | OS gain<br>(mean, months) |
|--|-----|----------|-------|-------|-------------|-------|-------|------------------|---------------------------|
|  |     | Costs    | QALY  | LYs   | Costs       | QALY  | LYs   |                  |                           |
| All regions                              | BSC | ████████ | 0.367 | 0.541 |             |       |       |                  |                           |
|  | TFT | ████████ | 0.531 | 0.782 | ████████    | 0.164 | 0.241 | <b>£45,662</b>   | <b>2.9 (+44%)</b>         |
| Europe only *                            | BSC | ████████ | 0.371 | 0.547 |             |       |       |                  |                           |
|  | TFT | ████████ | 0.527 | 0.774 | ████████    | 0.156 | 0.227 | <b>£49,771</b>   | <b>2.7 (+41%)</b>         |

\* Committee's previous preference

| 3L Europe<br>TTD scenarios | ICER                 |
|----------------------------|----------------------|
| Exponential                | £49,866              |
| Weibull                    | £49,342              |
| Gompertz                   | £49,197              |
| Gen. gamma                 | £49,771              |
| Log-normal                 | £52,902              |
| Log-logistic               | £53,557              |
| OS scenario                | ICER & LYG           |
| Log-logistic               | £45,168<br>+3.0 mos. |

**NICE tech. team**

- Two main sources of uncertainty:
  1. Potential unmeasured confounders in weighted analysis (effect not known)
  2. Choice of parametric model for TTD (gen gamma vs. log-normal)
- End of life criteria: mean OS gain is < 3 months but:
  - Much closer than analysis used for decision-making at ACM2: 1.7 mos. (+26%)
  - Similar to proportional gain accepted in TA476: 2.4 months (+40%)

# Key issues for decision making

