Access to newly licensed medicines

Professor Charlie Gourley (individual)

I am writing to make you aware of a situation that will compromise our ability to access the best cancer medicines for Scottish cancer patients. This is the inability of the Scottish Medicines Consortium (SMC) to assess unlicensed doses of new licensed drugs and has been highlighted by attempts to access bevacizumab for our ovarian cancer patients. Bevacizumab is the first drug in the last 15 years to improve the survival of ovarian cancer patients. We are clearly keen to access this agent for our patients. As a group, the oncologists who treat ovarian cancer in Aberdeen, Dundee, Edinburgh and Glasgow wrote to Angela Timoney (chair of the SMC) and Nicola Sturgeon on 5th April 2012 to emphasise the importance of assessing the data from a very large study of bevacizumab that used a dose of 7.5mg/kg (half of the dose that was ultimately chosen for license by Roche). I will not reiterate the content of that letter (which I have also attached Annexe A) but in short because of the way that this study was conducted (in Europe rather than the other main study which was conducted in the USA) it has more reliable survival data, making it much easier to make an accurate assessment of cost-effectiveness (the crucial criterion for acceptance by SMC). In addition because it uses half the dose of the US study (with comparable efficacy), the cost of using this dose is half, again helping to make a more favourable case for cost-effectiveness.

However, we have been informed by SMC that they cannot assess unlicensed doses of medicines. Therefore the SMC assessment has to use twice the dose that Scottish consultants would like to use and consider only data which does not accurately assess the improved survival attributable to bevacizumab.

In all likelihood this is going to mean that Scottish ovarian cancer patients will be denied the opportunity to access this agent which improves survival by 8 months in the worst risk patients. They are not being denied the opportunity because the dose that we would like to use is necessarily too expensive but because a mechanism does not exist in Scotland to consider data using this lower preferred dose.

It is important to be clear that there because the dose in question is half the licensed dose, there are no extra safety concerns. Decisions regarding which dose to license are taken by drug companies for a variety of different reasons and although it is tempting to suggest that they ought to license this lower dose at present our overriding concern is that the dose of bevacizumab that we would like to use has not been given a proper cost-effectiveness assessment.

Although this situation has arisen for bevacizumab in ovarian cancer it is likely that other examples will arise going forward because unlike old fashioned chemotherapy agents many of the new cancer agents do not rely on delivering the maximum tolerated dose.

I am very grateful to you for giving this matter your consideration.

ANM018

Annexe A

Dr Charlie Gourley

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Ms Angela Timoney
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5th April 2012

Dear Ms Timoney

Scottish Medicines Consortium: Assessment of Bevacizumab in combination with paclitaxel and carboplatin as first-line treatment of ovarian cancer

We write to you as a group of ovarian cancer experts and patient representatives about concerns that we have regarding the limitations of the forthcoming SMC adjudication of the cost-effectiveness of the use of Bevacizumab in the treatment of ovarian cancer. The key limitation is that SMC appears to only be allowed to consider licensed doses of a drug, and not an alternative dose of the same drug which has similar efficacy but potentially more favourable cost-effectiveness. This limitation may prevent Scottish women having access to the most significant development in ovarian cancer treatment in the last 15 years.

The brief background is that two large international, academically led randomised phase III studies (GOG 218 and ICON7) have been undertaken in order to assess the efficacy of Bevacizumab in this setting. Both trials recruited more than 1500 patients and the results were published back to back in the New England Journal of Medicine on 29th December 2011 (a table comparing these studies is included as an appendix to this letter). For various reasons, the dose of Bevacizumab chosen for these two studies differed. The GOG 218 study which was conducted predominantly in the United States

used a dose of 15mg/kg for a maximum of 15 months whilst the ICON7 study conducted in the United Kingdom (including the main Scottish Centres), Continental Europe, Canada, Australia and New Zealand used a dose of 7.5mg/kg for a maximum of 12 months.

On the 22nd of December 2011 the EMA granted a license for Bevacizumab based upon the GOG 218 dosing schedule. The company that markets Bevacizumab made the decision to submit this higher dose to the licensing authorities, largely because the only data available from ICON7 at this time was an interim analysis of progression-free survival.

Unfortunately, it would seem that because SMC is unable to consider data outside of the licensed dose, the ICON7 data cannot be considered. This presents a problem when demonstrating cost-effectiveness primarily because the GOG 218 study (which was predominantly conducted in the USA where ovarian cancer patients could receive Bevacizumab off license) permitted patients to be unblinded on progression and receive Bevacizumab if they had not already done so. As such, the overall survival data are not a sound dataset to consider the extent of overall survival benefit for the use of Bevacizumab, since patients were able to receive it in both arms of the trial.

In contrast, for patients in the ICON7 study, Bevacizumab was largely unavailable at the time of progression in the countries where it was conducted, so that there was minimal cross-over. This means that the overall survival data provide a more robust data set for the comparison of outcome for patients receiving or not receiving Bevacizumab, and thus would in our view be a more appropriate dataset for the SMC to consider when addressing the potential cost-effectiveness of the use of Bevacizumab in ovarian cancer. In a pre-planned subgroup analysis of patients for whom there is the biggest unmet medical need, namely those with poor risk disease (suboptimally debulked stage III as well as stage IV ovarian cancer) ICON7 demonstrated an improvement in median overall survival of almost 8 months which, in clinical terms, would be a very significant improvement.

We understand that it is the remit of the licensing authorities (in this case the EMA) to determine whether a treatment is safe and effective and that it is the work of the SMC to determine whether the treatment is cost-effective. As the clinicians treating ovarian cancer in Scotland we would strongly urge the SMC to consider the ICON7 data when they assess Bevacizumab for the following reasons:

1) Measurement of the potential gain in overall survival for the use of Bevacizumab using the GOG 218 data will be inaccurate as a result of the extensive cross-over in this study as described above, whereas a considerable survival benefit has been demonstrated in poor risk patients in the ICON7 study for whom there was minimal cross-over. We would argue therefore that the use of the ICON7 dataset is much more appropriate to address the question of Bevacizumab cost-effectiveness.

2) The Bevacizumab dose used in ICON7 (7.5mg/kg) is a dose that we are comfortable with (having participated in the study) and is the dose that we would wish to prescribe for our patients in Scotland, and is potentially associated with less toxicity, based on data from a phase III breast cancer study which used both doses. **As this is half the licensed dose there will be no added concerns about safety that have not already been considered by the licensing authorities for the licensed dose and clearly the cost to the NHS would be considerably less**.
3) The ICON7 study was conceived in the UK and run from an accredited UK clinical trials centre specialising in gynaecological cancer trials. 25% of the patients were recruited from the UK with the remainder recruited from health economies not dissimilar to the UK so the results are highly informative with respect to clinical and cost-effectiveness for patients presenting with ovarian cancer in the UK.
4) ICON7 has been conducted to FDA standards with full source data verification.
5) ICON7 was designed with prospective quality of life and health economics as an integral part of the trial so robust data will be obtained as to the cost-effectiveness ratio for this intervention in the trial overall and for the subset of patients who appear to benefit the most.

Most importantly, the ICON7 and GOG 218 studies are the first for 15 years to demonstrate a significant improvement in outcome following the first line treatment of ovarian cancer. The benefits seen in progression-free and overall survival demonstrated for the significant proportion of women at the highest risk of recurrence due to the inability to remove the tumours are extremely valuable for them and their families as they come to terms with self management and living with this awful disease. While these data have largely been accepted in Continental Europe where clinicians can access bevacizumab, as well as in England where bevacizumab can be accessed through the Cancer Drugs Fund (it is already on the approved list for this fund in some Strategic Health Authorities) the only way that Scottish patients will be able to access this treatment will be through SMC approval. It would not be possible to access bevacizumab through the IPTR process for the vast majority of patients as exceptionality has to be demonstrated and it is a wide cohort of patients that stand to benefit from this therapy. As such, we would strongly urge you to consider the ICON7 data as part of the process of assessing the cost-effectiveness of bevacizumab in combination with carboplatin and paclitaxel as first-line treatment for ovarian cancer.

Yours Sincerely,

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c.c. Nicola Sturgeon, Cabinet Secretary for Health.

Appendix: Summary of the key data from GOG218 and ICON7

	GOG218		**ICON7**		**Notes**
Design	Double blind placebo controlled. Unblinded at time of progression.		Open label		
Number randomised	1873		1528		
Chemotherapy	Carboplatin AUC6 + Paclitaxel 175 mgs/m2 q 3 wks for 6 cycles		Carboplatin AUC5/6 + Paclitaxel 175 mgs/m2 q 3 wks for 6 cycles		
Bevacizumab Dose	15mgs/kq q 3 wks		7.5mgs/kg q 3 wks		
Initiation of bevacizumab/placebo)	From course 2		From course 1 or 2		
Duration of bevacizumab/placebo)	Up to 15 months		Up to 12 months		
Arms	1) Carboplatin/Paclitaxel alone 2) Carboplatin/Paclitaxel with bevacizumab infusion during chemotherapy 3) Carboplatin/Paclitaxel with bevacizumab infusion during chemotherapy and as maintenance	625 625 623	1) Carboplatin/Paclitaxel alone 2) Carboplatin/Paclitaxel with bevacizumab infusion during chemotherapy and as maintenance	764 764	
Patient population	Stage III (optimal, visual/palpable) Stage III (suboptimal) Stage IV	639 752 482	Stage I or IIA (grade 3 or clear cell histology) Stages IIB–IIIB Stage III (optimal) Stage III (sub optimal) Stage III (inoperable) Stage IV Stage IV (operable)	142 315 751 283 11 182 19	
Endpoint analyses	Progression: RECIST & CA-125 OS analysis (formal testing at time of PFS) IRC		Progression: RECIST Defined final OS analysis (end 2012) No IRC		
Time of PFS analysis	Total no. of PFS events in control arm		Total no. of PFS events in both arms and 1 year after last patient randomized		
Patients on therapy at time of PFS analysis	14% arm I, 17% arm II, 24% arm III		2 patients in bevacizumab arm		
No. of events/no. of patients	783/1248 (arm I and III)		759/1528		
Analysis methods	One-sided log-rank test Non-proportional hazards not yet		Two-sided log-rank test Non-proportional hazards explored		

	GOG218		**ICON7**		**Notes**
	presented				
Primary analysis of PFS	Median FUp 17.4 mos. No benefit seen in Arm 2. Arm 1 vs Arm 3 Median PFS 10.3 vs 14.1 mos; HR 0.717; p<0.0001		Median FUp 19 mos. Median PFS 17.3 vs 19.0 mos; HR 0.81; p=0.0041		Non proportional hazards in ICON7 and curves cross over after 23 mos, but few pts at risk in the tail of the curve
OS at time of PFS analysis	444 events in 1873 pts (immature). Arm 2, HR 1.036; p=0.361 Arm 3; HR 0.915; p=0.252		241 of 715 required events. HR 0.81; p=0.98		
GOG 218 Sensitivity analysis censoring for asymptomatic Ca125 progression	Arm 1 vs Arm 3 Median PFS 12.0 vs 18.0 mos; HR 0.645; p<0.0001				594 events (189 events censored (26%))
ICON7 analysis of PFS in the high risk subgroup at the time of primary analysis			Median PFS 10.5 vs 15.9 mos; HR 0.68; p<0.001		465 debulked patients with either stage 3 & >1cm residuum or stage 4 disease
ICON7 Updated analysis of survival (and PFS) performed at the request of FDA			Median FUp 28 mos. (934 PFS & 378 (53% of required) OS events **PFS**: 17.4 mos vs 19.8 mos; HR 0.87; p=0.039 **OS**: HR 0.85; p=0.11		PFS curves no longer cross over
ICON7 pre specified OS analysis of 'high risk subgroup'			Median OS: 28.8.mos vs 36.6 mos; HR 0.64; p=0.002. Curves for low risk subgroup show no effect for bevacizumab; p value for interaction test = 0.011 ie statistically different effect in the 2 subgroups		465 debulked patients with either stage 3 & >1cm residuum or stage 4 disease

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