National Institute for Health and Care Excellence

IP1716 Pressurised intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis

IPAC date: 12/09/19

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Manufacturer Capnomed	**1**	Dear all, Capnomed kindly asks the committee to review their draft recommendation and change it to “Special Arragements” . We think it would be consistent to give PIPAC the same guidance as CRS+HIPEC (IPG331) as in our opinion, PIPAC has superior safety and efficacy profiles with significant lower morbidity and mortality. Moreover, in this stage of palliative treatment of Peritoneal Carcinomatosis, the QoL profile of PIPAC patients is stable or improved, which is of the utmost importance for patients at this stage of their disease. In attachment, please find publications, published after the June hearing and that have thus far not be taken into account by the committee. We hope PIPAC will more easily benefit to NHS patients under the strict conditions of a “ Special Arrangements” recommendation. PM: hereunder the NICE guidance for CRS+HIPEC 1.1 Current evidence on the efficacy of cytoreduction surgery (CRS) followed by hyperthermic intraoperative peritoneal chemotherapy (HIPEC) for peritoneal carcinomatosis shows some improvement in survival for selected patients with colorectal metastases, but evidence is limited for other types	Thank you for your comments. The committee noted your comments and reviewed the additional evidence you provided but decided not to change the guidance.

			of cancer. The evidence on safety shows significant risks of morbidity and mortality which need to be balanced against the perceived benefit for each patient. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake CRS followed by HIPEC for peritoneal carcinomatosis should take the following actions. •Inform the clinical governance leads in their Trusts. •Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy in relation to the potential morbidity and mortality and the prolonged recovery period, and provide them with clear written information. In addition, the use of NICE's information for patients('Understanding NICE guidance') is recommended. •Audit and review clinical outcomes of all patients having CRS followed by HIPEC for peritoneal carcinomatosis (see section 3.1). 1.3 Patient selection and treatment should be carried out in the context of a multidisciplinary team, including oncologists and surgeons with experience in this operation. 1.4 NICE encourages further research into this procedure which should take the form of randomised controlled trials (RCTs) with clear descriptions of patient selection criteria and the types of cancer being treated. The chemotherapy regimens used should be well defined. Outcome measures should include survival and quality of life. Please find attached these recently published papers**\\nice.nhs.uk\Data\CHTE\IP\1700 - 1799\1716 Pressurised Intraperitoneal Aerosolised Chemotherapy (PIPAC) and Electrostatic Pressurised Intraperitonal Chemotherapy (ePIPAC)\Consultation\Hugh Wielemans** (Alyami ASCO 2018, Khomiakhov ASCO 2017, Dumont 2019 PIPOX trial ASCO 2019, Graversen et al 2018, Struller et al	Additional publications listed have been reviewed by the committee. Normally Conference abstracts are not considered adequate to support decisions on efficacy and not presented to the committee unless they contain any important new safety events. Therefore, the conference abstracts ((Alyami ASCO 2018, Khomiakhov ASCO 2017, Dumont 2019 PIPOX trial ASCO 2019) are not considered in the overview of evidence.

			2019, Tempfer et al phase 1 2015, Tempfer et al phase 2 2018, LANCET oncology PIPAC, Dumont et al 2018, Alyami 2019 and Willaert 2019)  Lancet Oncology PIPAC.pdf This is not science, but reflects the view of a patient in the UK **https://www.dailypost.co.uk/news/north-wales-news/woman-given-just-months-live-16459801**	Four prospective studies listed (Graversen 2018, Struller 2019, Tempfer 2015, Tempfer 2018) were included in the systematic reviews added to table 2 in the overview. One study (Dumont 2018) is only a rationale and study design paper and does not contain clinical data, therefore it was not considered by the team. Two studies (Alyami 2019 and Willaert 2019) picked up in our update searches have been discussed by the committee and added to table 2 in the overview. Thank you for bringing to the committee's attention the views of a patient in the UK. Committee noted views in their deliberations.
2	Consultee 1 Manufacturer Capnomed	1	Capnomed GmbH kindly asks the Committee to review the recommendation and to change it from "Research Only" to "Special Arrangements" The committee bases their recommendations on the following 3 criteria (as found on **https://www.nice.org.uk/process/pmg28/chapter/draft-recommendations**) 1. the procedure is still considered to be experimental in nature: PIPAC is NOT a "highly experimental method" as stated on p.18 "Existing assessments of this procedure"	Thank you for your comments. The committee noted your comments but decided not to change the guidance. The statement that 'PIPAC is a highly experimental method' (on page 18 in the overview) is the statement by European groups on the use of PIPAC and has been referenced (Dueckelmann 2018). This section aims to highlight and bring to the attention of the committee any key findings and

			Statement by European groups (the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) from Germany, Austria, and Switzerland and the Nord- Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO) on the use of PIPAC (2018). 2.the level of uncertainty about the efficacy or safety evidence is such that it is considered to be in the best interest of patients to recommend controlled investigation of the procedure under the scrutiny and protection of research ethics committees: Intraperitoneal therapy with cisplatin is used for 30+ years in ovarian cancer. Several RCTs have been published, showing a survival advantage (see article Markman et alAnnals of Oncology 23: 2605–2612, 2012 doi:10.1093/annonc/mds203 Published online 21 August 2012). There is a recommendation of the US NCI for IP chemotherapy in OC. The drugs used (platin, anthracyclin) are approved in OC. The dose used is 10 times lower than during HIPEC or during systemic chemotherapy. More than 5000 PIPAC applications have been performed worldwide. A recent authoritative review (Alyami et al Lancet Oncol 2019) concludes that "From our findings, PIPAC has been shown to be feasible and safe. Data on objective response and quality of life were encouraging. Therefore, PIPAC can be considered as a treatment option for refractory, isolated peritoneal metastasis of various origins. However, its use in further indications needs to be validated by prospective studies." 3. resolution of substantial uncertainties about its efficacy or safety would be fundamental to its routine use. Same as above	conclusions from other organisations and groups. The committee makes it recommendations about the procedure on the basis of the evidence and commentary relating to its efficacy and safety and not just based on the conclusions of 'existing assessments of this procedure'. As per response to comment 1, the additional publication listed (Alyami et al 2019) was also picked up in our update searches and has been added to table 2 in the overview.
3	Consultee 1 Manufacturer Capnomed	**1, Overview**	Capnomed GmbH kindly asks the Committee to review the recommendation and to change it from "Research Only" to "Special Arrangements"	Thank you for your comments. The committee noted your comments but decided not to change the guidance.

		page 18	1. PIPAC is NOT a "highly experimental method" as stated on p.18 "Existing assessments of this procedure" Statement by European groups (the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) from Germany, Austria, and Switzerland and the Nord- Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO) on the use of PIPAC (2018). Capnomed estimates that PIPAC threatens revenues of the pharmaceutical industry between 700 mln £ and 1.2 bln £ /annum in all indications of peritoneal metastasis. Ovarian cancer represents around 40% of this amount. In the Paper of Dinkelmann et al, no author declares a conflict of interest. This is not correct. See lower. This article is an opinion paper from the key opinion leaders of the pharmaceutical industry in German-speaking gynecological oncology. Due to undisclosed conflict of interest of several authors, it should not be considered by NICE: Moreover, the article does not meet the quality standard of a systematic review (PRISMA guidelines) and is highly biased. Several statements are not exact (for example the citation of Grass et al in the abstract). Interestingly, the authors see a potential for PIPAC in gastrointestinal but not in gnycological peritoneal netastasis, An adequate counterpoint has been written by C. Tempfer on invitation of the Editor-in-Chief of Arch Gynecol Obstet (see attach). Archives of Gynecology and Obstetrics **https://doi.org/10.1007/s00404-018-4784-7** Intraperitoneal therapy with cisplatin is used for 30+ years in ovarian cancer. Several RCTs have been published, showing a survival advantage (see article Markman et alAnnals of Oncology 23: 2605–2612, 2012 doi:10.1093/annonc/mds203 Published online 21 August 2012). There is a recommendation of the US NCI for IP chemotherapy in OC. The drugs used (platin, anthracyclin) are approved in OC. The dose used is 10 times lower than during HIPEC or during	The statement that 'PIPAC is a highly experimental method'(on page 18 in the overview) is the statement by European groups on the use of PIPAC and has been referenced (Dueckelmann 2018). This section aims to highlight and bring to the attention of the committee any key findings and conclusions from other organisations and groups. The committee makes its final recommendations about the procedure on the basis of the evidence and commentary relating to its efficacy and safety and not just based on the conclusions of 'existing assessments of this procedure'. NICE interventional procedures guidance addresses only efficacy and safety, not the cost effectiveness of procedures. Additional publications listed by the consultee were considered by the committee: Tempfer 2018 is already in table 2 in the overview. As per response to comment 1, Alyami 2019 was picked up in our update searches and has been added to table 2 in the overview.

			systemic chemotherapy. More than 5000 PIPAC applications have been performed worldwide. A recent authoritative review (Alyami et al Lancet Oncol 2019) concludes that "From our findings, PIPAC has been shown to be feasible and safe. Data on objective response and quality of life were encouraging. Therefore, PIPAC can be considered as a treatment option for refractory, isolated peritoneal metastasis of various origins. However, its use in further indications needs to be validated by prospective studies." PIPAC is is no way a "highly experimental" therapy, as long as approved drugs and lower dosage is used. **Conflict of interests :**Prof. Sehouli Honorar from Roche **https://correctiv.org/recherchen/euros-fuer-aerzte/datenbank/empfaenger/jalid-sehouli-berlin/** J. Sehouli: Member of Advisory Board: Roche, AstraZeneca. **https://academic.oup.com/annonc/article/27/suppl_6/867P/2799603** consulted on Feb 1st, 2019 Prof. P. Wimberger Member of Advisory Board: Roche, Novartis, Amgen, MSD, AstraZeneca, Teva, PharmaMar, Fresenius Biotech; Corporate-sponsored research: Roche, Novartis, Amgen, Fresenius Biotech, MSD. **https://academic.oup.com/annonc/article/27/suppl_6/867P/2799603** consulted on Feb 1st, 2019 Prof. A. Reinthaller YO39523 IMagyn050 - Multizentrische, randomisierte Phase-III-Vergleichsstudie von Atezolizumab versus Placebo in Kombination mit Paclitaxel, Carboplatin und Bevacizumab bei Patientinnen mit neu diagnostizierten Ovarial-, Tuben- oder primären Peritonealkarzinomen im Stadium III oder IV. Sponsor: F.Hoffmann-La Roche Ltd. **http://www.ccc.ac.at/aktuelle-studien/?cat=7&search=eierstock%20geb%C3%A4hrmut**	

			ter%20geb%C3%A4rmutter%20uterus%20vulva%20zervix%20ovari%20_retrospektiv%20_lebensqualit%C3%A4t consulted on Feb 1st, 2019 Prof. M. Müller, Bern http://www.frauenheilkunde.insel.ch/uploads/media/DefProgrammBTZ13_12_2018.pdf consulted on Feb 1st, 2019 **http://www.sgmo.ch/wp-content/uploads/ProgrammBTZ_20171412.pdf** Prof. M. Marth, Innsbruck **https://frauenheilkunde-innsbruck.tirol-kliniken.at/page.cfm?vpath=index/forschung/klin-studien** consulted on Feb 1st, 2019 AGO 46 INOVATYON Phase III international, randomized study of trabectedin plus pegylated liposomal doxorubicin (PLD) versus carboplatin plus PLD in patients with ovarian cancer progressing within 6-12 months of last platinum Prof. Marth AGO 47 PAOLA-1 Randomisierte doppelblinde Phase-III-Studie mit Olaparib vs. Placebo bei Patientinnen mit fortgeschrittenem (FIGO IIIb-IV) hochgradig serösem oder endometrioidem Ovarial-, Tuben- oder Peritonealkarzinom, vorbehandelt mit der Standard-First-Line-Therapie mit Platin-Taxol und Bevacizumab in der Chemotherapie sowie in der Erhaltungstherapie Prof. Marth AGO 50 JAVELIN Eine multizentrische, randomisierte Open-Label-Studie der Phase III mit Avelumab (MSB0010718C) als Monotherapie oder in Kombination mit pegyliertem liposomalem Doxorubicin im Vergleich zu pegyliertem liposomalem Doxorubicin als Monotherapie bei Patientinnen mit Platin-resistentem/refraktärem Ovarialkarzinom Prof. Marth PD Harter, Essen **https://gyn-onko-update.com/referenten/** consulted on Feb 1st, 2019.	

			Vortragstätigkeit: AstraZeneca, Roche, Tesaro.Beratertätigkeit: AstraZeneca, Roche, Tesaro, Lilly, Clovis, Pharmamar, Stryker **https://www.ago-online.de/fileadmin/downloads/pdf/2017/BoE-StD_15.11.17.pdf** consulted on Feb 1st, 2019. Prof. D. Fink, Zürich **http://www.swissago.ch/downloads/14_1124_Programm_GYN-UPDate_2015.pdf** Seite 14 Consulted on Feb 1st, 2019	
4	Consultee 1 Manufacturer Capnomed	**3.1 The evidence**	Following studies have to be included in the safety/efficacy assessment and form the primary body of evidence (controlled prospective studies): 1. A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis Clemens B. Tempfer a, Urs Giger-Pabst b, Veronika Seebacher c, Miriam Petersen d, Askin Dogan a, Günther A. Rezniczek a,∗ a DepartmentofObstetricsandGynecology,MarienHospitalHerne,Ruhr-UniversitätBochum,Bochum,Germany b DepartmentofSurgery,MarienHospitalHerne,Ruhr-UniversitätBochum,Bochum,Germany c DepartmentofGynecologyandGynecologicOncology,MedicalUniversityofVienna,Vienna,Austria d LaborMVZEberhardundPartner,Dortmund,Germany **https://doi.org/10.1016/j.ygyno.2018.05.001** 2.Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study Clemens B. Tempfer a,∗, Guido Winnekendonk b, Wiebke Solass c, Reinhard Horvat d, Urs Giger-Pabst c, Juergen Zieren c, Guenther A. Rezniczek a, Marc-André Reymond c	Thank you for your comments. Additional publications listed by the consultee were considered by the committee: Four prospective studies (Graversen 2018, Struller 2019, Tempfer 2015, Tempfer 2018) were included in systematic reviews added to table 2 in the overview. Alyami 2019 picked up in our update searches has been added to table 2 in the overview. IPAC decision making is informed by rapid reviews of the literature and sometimes uses evidence syntheses which incorporate primary studies not otherwise looked at.

			A DepartmentofObstetricsandGynecology,RuhrUniversityBochum,Bochum,Germany b DepartmentofRadiology,RuhrUniversityBochum,Bochum,Germany c DepartmentofSurgery,RuhrUniversityBochum,Bochum,Germany d DepartmentofPathology,MedicalUniversityofVienna,Vienna,Austria **http://dx.doi.org/10.1016/j.ygyno.2015.02.009** 3.Prospective, single-center implementation and response evaluation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastasis Martin Graversen , Sönke Detlefsen , Jon Kroll Bjerregaard, Claus Wilki Fristrup, Per Pfeiffer and Michael Bau Mortensen **https://journals.sagepub.com/home/tam** 4.Pressurized intraperitoneal aerosol chemotherapy with low-dose cisplatin and doxorubicin (PIPAC C/D) in patients with gastric cancer and peritoneal metastasis: a phase II study Florian Struller, Philipp Horvath, Wiebke Solass, Frank-Jürgen Weinreich, Dirk Strumberg, Marios K. Kokkalis, Imma Fischer, Christoph Meisner, Alfred Königsrainer and Marc A. Reymond Ther Adv Med Oncol 2019, Vol. 11: 1–12 hDttOpsI::://d1o0i.o.r1g1/170.711/77/1758835919846402 **https://doi.org/10.1177/1758835919846402** 5.Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications Author links open overlay panelMohammadAlyamiMDab†MartinHübnerMDc†FabianGrassMDcdNaoualBakrinPhDaeLaurentVilleneuvePhDfNathalie	

			LaplaceMDaeProfGuillaumePassotPhDaeProfOlivierGlehenPhDaeVahanKepenekianMDae Show more https://doi.org/10.1016/S1470-2045(19)30318-3	
5	Consultee 1 Manufacturer Capnomed	**3.3**	Safety/Occupational Health 1. Peritoneal Sclerosis: Only occurs with the use of Oxaliplatine. It has never been described occurring with the use of Cisplatin+Doxorubicin 2.Inadvertent leakage of chemotherapy agents: Already in 2011, a safety report of an independent company specialized in occupational health safety in the chemical industry (DEKRA industrial) concluded that protection measures are adequate to ensure safety of the health workers according to TRGS 402. This assessment has been confirmed in the meantime by numerous safety audits by independent bodies in several institutions in 4 countries. All air measurement performed in the meantime in Germany, France, Denmark and Belgium showed no traces of platin in the environmental air, with a detection level down to the picomole range (Ametsbichler) References: original reportg of DEKRA in 2011. Following peer-reviewed publications 1: Delhorme JB, Klipfel A, D'Antonio F, Greget MC, Diemunsch P, Rohr S, Romain B, Brigand C. Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC) in an operating room without laminar airflow. J Visc Surg. 2019 Jul 8. pii: S1878-7886(19)30089-X. doi: 10.1016/j.jviscsurg.2019.06.010. [Epub ahead of print] PubMed PMID: 31296454. 2: Ametsbichler P, Böhlandt A, Nowak D, Schierl R. Occupational exposure to cisplatin/oxaliplatin during Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)? Eur J Surg Oncol. 2018 Nov;44(11):1793-1799. doi:10.1016/j.ejso.2018.05.020. Epub 2018 May 22. PubMed PMID: 29871821.	Thank you for your comments. 2 key safety events listed in section 3.3 were considered important by the specialist advisers and the committee. These are also events that could potentially occur. Study 5 in table 2 in the overview reports severe peritoneal sclerosis after repeated pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in 2 cases. Additional publications on occupational safety, exposure and room contamination listed by the consultee were considered by the committee: Three studies (Solass 2013, Ametsbichler 2018) are added to the appendix in the overview. Three studies (Graversen 2016, Wilaert 2017, Ndaw 2018, Delhorme 2019) found in our update searches have been added to the appendix. Committee considered the comment about environmental risk of chemotherapy agents and amended the wording in 3.6.

			3: Ndaw S, Hanser O, Kenepekian V, Vidal M, Melczer M, Remy A, Robert A, Bakrin N. Occupational exposure to platinum drugs during intraperitoneal chemotherapy. Biomonitoring and surface contamination. Toxicol Lett. 2018 Dec 1;298:171-176. doi: 10.1016/j.toxlet.2018.05.031. Epub 2018 May 28. PubMed PMID: 29852276. 4: Willaert W, Sessink P, Ceelen W. Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC). Pleura Peritoneum. 2017 Sep 1;2(3):121-128. doi: 10.1515/pp-2017-0018. Epub 2017 Aug 12. PubMed PMID: 30911641; PubMed Central PMCID: PMC6328076. 5: Graversen M, Pedersen PB, Mortensen MB. Environmental safety during the administration of Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). Pleura Peritoneum. 2016 Dec 1;1(4):203-208. doi: 10.1515/pp-2016-0019. Epub 2016 Nov 25. PubMed PMID: 30911624; PubMed Central PMCID: PMC6386395. 6: Solass W, Giger-Pabst U, Zieren J, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): occupational health and safety aspects. Ann Surg Oncol. 2013 Oct;20(11):3504-11. doi: 10.1245/s10434-013-3039-x. Epub 2013 Jun 14. PubMed PMID: 23765417; PubMed Central PMCID: PMC3764316. Simulations have shown that, even in the case of a complete release of the aerosol, inhalation (worst case scenario with 30 minutes inhalation - the procedure is remote-controlled !) would be between 1:100'000 and 1:1'000'000 of a systemic chemotherapy dose (see Reymond L et al attached) NICE writes that " There is a potential risk that chemotherapy could be dispersed into the environment, which could be a hazard to operating theatre staff...."	

			Whereas toxic aerosols are manipulated during PIPAC, no data support the hypothesis that PIPAC carries significant occupational health safety risks, when the measures recommended are applied. In fact, available data show the opposite. This statement should be corrected accordingly.	
6	Consultee 1 Manufacturer Capnomed	**3.4 The evidence**	Patient contacts: We sent contact details of 3 patients who gave their consent for being contacted by NICE and who's email address was forwarded: [redacted]. We checked with them and regret to say that none of them were contacted by NICE.	Thank you for your comments. As these 3 patients are from Germany and not treated in the NHS or a private practice the UK, NICE IP team did not contact them for any patient commentary.
7	Consultee 1 Manufacturer Capnomed	**3.1**	We refer here to the published paper in The Lancet Oncology (July 2019) suggesting PIPAC can be considered as a treatment option for refractory, isolated peritoneal metastasis of various origins. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications Author links open overlay panelMohammadAlyamiMDab†MartinHübnerMDc†FabianGrassMDcdNaoualBakrinPhDaeLaurentVilleneuvePhDfNathalieLaplaceMDaeProfGuillaumePassotPhDaeProfOlivierGlehenPhDaeVahanKepenekianMDae Show more **https://doi.org/10.1016/S1470-2045(19)30318-3** They concluded: Therefore, PIPAC can be considered as a treatment option for refractory, isolated peritoneal metastasis of various origins.	Thank you for your comments. As per response to comment 1, Alyami 2019 picked up in our update searches has been added to table 2 in the overview.
8	Consultee 1 Manufacturer Capnomed	**3.1**	**Pr. [redacted] also noted that the committee wrote in the draft recommendation** :" *Studies were mainly small retrospective observational studies with short - term follow up in patients with end stage peritoneal carcinomatosis of various origins.".*As a summary: there are four published prospective, controlled studies published evaluating safety	Thank you for your comments. Additional publications listed (4 small prospective studies [Graversen 2018, Struller 2019, Tempfer 2015, Tempfer 2018]) were included in systematic reviews added to table 2 in the overview.

and efficacy of PIPAC. (We already sent the references to these studies through the NICE website together with our earlier comments last week)

Registry ID	Indication	N patients included	Procedure-related mortality (CTCAE 5)	CTCAE 4	CTCAE 3	Response RECIST	Histological response#	QoL
NCT02475772 Phase-1	Ovarian cancer	15	0	0	1	N/A	64% (PP)	N/A
NCT02475772 Phase-2	Ovarian cancer	53	0	0	8	62% (ITT)	82% (PP)	improved
NCT01854255 Phase-2	Gastric cancer	25	0	0	3	40% (ITT)	100% (PP)	stable

Alyami 2019 picked up in our update searches has been added to table 2 in the overview.

IPAC decision making is informed by rapid reviews of the literature and sometimes uses evidence syntheses which incorporate primary studies not otherwise looked at.

			NCT02320448 Phase-2	Multiple histologies	35*	0	1	4	N/A	67% (PP)	stable
			Total/ pooled data		**128**	**0%**	**0.8 %**	**12.5 %**	**40-62% (ITT)**	**64-100% (PP)**	**Stable or improve**

According to published EBM, EMA and NICE standards, these results from controlled studies are forming the primary body of evidence, all further evidence should be considered anecdotal and presented as such.

A total of 128 patients means prospective trials on approx. 350-400 patients treated with +-3 cycles of PIPAC.

Concerning the length of follow-up:

It has to be noted that the patients included in the above studies are pretreated patients with peritoneal metastasis.

			In contrast to other settings in oncology, there is no long-term survivor in such clinical situation. For example, in gastric cancer, median survival in the 2nd-line situation is 2.4 months with best supportive care[1]. In ovarian cancer in the 3rd line situation, expected median survival is 8.9 months[2].	
9	Consultee 2 Clinician on behalf of BSG	**General**	A recent review published by Lancet Oncol July this year has detailed the rationale, evidence and potential indications for PIPAC (**Alyami et al, Lancet Oncol 2019**). There are 16 retrospectve and 4 propsective studies included in the review. Table 2 gives the efficacy of PIPAC for different conditions. The potential indications for use of PIPAC and HIPEC (**Table 3**) are enumerated in the review. The following figures and slides are from the Peritoneal Malignancy Institute, Basingstoke for the **NHS England 2018/19 Review**. In CPM (colorectal peritoneal metastases) there are a proportion of patients who are not suitable for cytoreduction surgery and HIPEC who could potentially be treated with PIPAC. Demtroder et al (Colorectal Ds 2016) looked at PIPAC in CPM and estimated median survival at 15.7 months, the study number was however small (n=17), and other trials are ongoing. In Peritoneal Mesothelioma there whilst there is a proportion of patients' who may benefit from CRS and HIPEC, there are many who are unfortunately not found at MDT to be suitable for surgery and in these patients PIPAC may serve as an alternative treatment. (Giger-Pabst U et al, BMC Cancer 2018) The National Mesothelioma Audit Report (2018) Pages 18 & 19] also comments on the role of CRS and HIPEC in peritoneal mesothelioma which is a service Basingstoke Peritoneal Malignancy Institute continues to provide. As	Thank you for your comments. Additional publications listed were considered by the committee: As per response to comment 1, Alyami 2019 picked up in our update searches has been added to table 2 in the overview. Demtroder 2016, Giger-Pabst U 2018 have been included in systematic reviews added to table 2 in the overview. The committee also considered comments regarding the NHS England review and noted further uses for HIPEC and PIPAC.

			evident from the slides below from the **NHS England 2018/19 Review**, there may be a selected group of patients not amenable to surgery who could be considered for PIPAC at the National Mesothlioma MDT. In appendix cancers there is a proportion of patients where the tumour is an adenocarcinoma where CRS and HIPEC (cytoreduction surgery and hyperthermic intraperitoneal therapy) may not be beneficial. These patients could potentially be treated with PIPAC.	

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."