Horizon Scanning in Oncology

Trastuzumab (Herceptin®) in addition to standard chemotherapy as first-line therapy for advanced gastric cancer
Horizon Scanning in Oncology

Trastuzumab (Herceptin®) in addition to standard chemotherapy as first-line therapy for advanced gastric cancer

Vienna, May 2010
DISCLAIMER

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

CONTACT INFORMATION

Publisher:
Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:
Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at "http://eprints.hta.lbg.ac.at":

DSD: Horizon Scanning in Oncology Nr. 012
ISSN online 2076-5940
http://eprints.hta.lbg.ac.at/view/types/dsd.html
© 2010 LBI-HTA – All rights reserved
1 Drug description

Generic/Brand name:
Trastuzumab/ Herceptin®

Developer/Company:
Roche

Description:
Trastuzumab (Herceptin®) is a humanised monoclonal antibody that binds to the human epidermal growth factor 2 (HER2) protein expressed on the cell surface, inhibiting cell proliferation. Immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) are typically used to assess HER2 levels. Approximately 22% of advanced gastric cancers overexpress HER2 (IHC3+ and/or FISH+), a similar percentage as seen in breast cancer. A higher HER2-positivity rate is seen in cancer of the gastroesophageal junction than in stomach cancer. While several studies have shown HER2 overexpression to be associated with poorer prognosis and survival, some have failed to find a direct association between HER2 positivity and prognosis [1].

The dosing schedule for metastatic gastric cancer is an intravenous (iv) infusion with an initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight every three weeks, until disease progression or unacceptable toxicity.

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for trastuzumab therapy. HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures.

Because the use of trastuzumab is associated with cardiotoxicity, all candidates for treatment with trastuzumab should undergo baseline cardiac assessment including history and physical examination, electrocardiogram, echocardiogram, or Multi Gated Acquisition (MUGA)-scan or magnetic resonance imaging. Cardiac function should be further monitored during treatment [1].

2 Indication

Trastuzumab (Herceptin®) is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction in combination with capecitabine or 5-fluorouracil and cisplatin who have not received prior anti-cancer treatment for their metastatic disease [1].

mechanism of action: inhibiting cell proliferation by binding to HER2

tumours have to be screened for HER2 overexpression

directed for HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction in combination with fluorouracil and cisplatin

indicated for HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction in combination with fluorouracil and cisplatin
3 Current regulatory status

The European Medicines Agency (EMA) granted market authorization for trastuzumab (Herceptin®) in August 2000 for treatment of metastatic breast cancer. Current indications comprise the treatment of patients with

- HER2 positive metastatic breast cancer as monotherapy if therapy with anthracycline and taxanes has failed or is contraindicated, in combination with paclitaxel in patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable, in combination with docetaxel in patients who have not received chemotherapy for their metastatic disease and in combination with an aromatase inhibitor in postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab,
- HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable),
- HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction in combination with capecitabine or 5-fluorouracil and cisplatin who have not received prior anti-cancer treatment for their metastatic disease. Herceptin should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory FISH+ result, or IHC3+, as determined by an accurate and validated assay (since January 2010) [1, 2].

The United States Food and Drug Administration (FDA) has granted market authorization for trastuzumab (Herceptin®) in 1998. In the U.S., trastuzumab (Herceptin®) is currently approved for the treatment of early and metastatic breast cancer [3].

4 Burden of disease

Despite a sharp worldwide decline in incidence and mortality during the second half of the 20th century, gastric cancer remains one of the most common malignancies in the world with an estimated one million new cases and more than 800,000 deaths worldwide in 2007. Gastric cancer is the second leading cause of cancer-related death in men and fourth among women [4].

Incidence of gastric cancer varies widely across geographic regions. The highest rates are found in Eastern Asia (Japan, Korea and China), Eastern Europe and certain countries in Central and South America. The incidence in women is about 50% lower than in men and generally follows a similar geographic pattern. Incidence of gastric cancer increases with age, with a peak between 50-70 years. 5-year survival rate for stomach cancer overall does not exceed 25% [1, 4].
Like worldwide, the incidence of malignant stomach tumours has decreased markedly in the last two decades in Austria, both in absolute numbers and as a percentage of new malignancies. Whereas 2,500 new cases of malignant tumours were reported in 1987 (8.4% of all new neoplasms), in 2007 scarcely 1,300 neoplasms of the stomach were registered, representing a mere 3.7% of all new malignancies. As elsewhere, the incidence of gastric cancer in men in Austria is roughly two times higher than of Austrian women. Also, the mortality rate has declined rapidly, from 2,045 deaths in 1987 to 934 in 2007. The mortality rate, per 100,000 people, has remained roughly twice as high for men as for women throughout this period. At the time of diagnosis, about 1 % of diseases are carcinoma in situ, 20 % are localized, 23 % locally advanced and 17 % metastasized (unknown 26 %, death certificate only 13 %)[5].

About 90 % of stomach tumours are adenocarcinomas, which can be subdivided into two histologic subtypes (Lauren classification): well differentiated or intestinal type and undifferentiated or diffuse type. In addition, they may be classified according to their site in proximal (cardia) or distal stomach (non-cardia) cancers. Infection with Helicobacter pylori, atrophic gastritis, intestinal metaplasia and dysplasia have been identified as important steps in the pathogenesis of gastric cancer. A falling incidence of H. pylori infection and non-cardia gastric cancer in developed countries is in contrast with increasing incidence rates of cardial and gastroesophageal junction tumours. A proportion of these cases seems to be associated with Barrett’s epithelium (intestinal metaplasia of the distal oesophagus), developing from chronic oesophageal reflux disease. Although it is difficult to determine whether these cancers are gastroesophageal junction tumours or distal oesophageal malignancies, in clinical trials for advanced disease they are usually treated in the same manner. There is no data on the incidence of gastroesophageal junction tumours available [4, 5, 6].

Apart from Helicobacter pylori infection, other risk factors for gastric cancer are smoking, lower socioeconomic status, and dietary factors such as salty food as well as obesity [1].

Stomach cancer is often asymptomatic or causes only nonspecific symptoms in its early stages. As it progresses, symptoms may include weight loss, abdominal pain, early satiety, nausea and vomiting, bleeding and anaemia [1].

Tumours are staged according to the extent of invasion and spread with the TNM-Classification. Invasive gastric cancer (stages T2 – T4) is fatal without surgery. In advanced stages of gastric cancer, mean survival with best supportive care is less than 6 months from diagnosis [6, 7].

5 Current treatment

The aim of treatment in advanced gastric cancer is to prevent progression, extend survival and relieve symptoms with minimal adverse effects.

Surgery is typically carried out in the earlier stages of gastric cancer, but may also be carried out in advanced stages to relieve pain and discomfort of the disease. In addition, chemotherapy and/or radiotherapy is offered, depending on the stage of the disease and patient characteristics. The results of
6 Evidence

The evidence identified for this report comprises one phase III study [1, 9] and two phase II studies [10, 11], all of them published only as abstracts. Additionally, one previous horizon scanning report on trastuzumab (Herceptin®) for advanced gastric cancer was identified, which was published in 2007 and is based on preliminary study results [12].

The phase III study, which compared standard chemotherapy (5-FU or capecitabine plus cisplatin) with and without trastuzumab, showed improved overall survival of patients with advanced HER2 positive gastric cancer treated with add-on trastuzumab. The toxicities in the two arms were comparable, except that a higher number of trastuzumab-treated patients had a significant decrease in left ventricular ejection fraction (LVEF; ≥ 10 % from baseline to an absolute LVEF < 50 %: 11/237 patients, 4.6 % vs. 2/167 patients, 1.1 %). However, only one patient in the trastuzumab group developed grade 3 to 4 cardiac failure versus two in the control group.

The two phase II studies described in abstracts included only a very small number of patients with HER2 positive tumours (n = 3 and n = 21) [10, 11]. In addition, published data on these studies is too sparse to take their results into account for evaluating the use of trastuzumab.
## 6.1 Efficacy and safety - Phase III studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>NCT01041404, ToGA trial (BO18255) EMA assessment report, abstract published [1, 9]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Hoffmann-La Roche</td>
</tr>
<tr>
<td>Country</td>
<td>141 study locations in 24 countries in Asia, Europe, Latin America</td>
</tr>
<tr>
<td>Design</td>
<td>Parallel, randomized, open label, multicentre</td>
</tr>
<tr>
<td>Participants characteristics</td>
<td>I: 294 pts., C: 290 pts., sex: 444 male, 140 female, median age and range in years I: 59.4 (23 – 83) C: 58.5 (21 – 82)</td>
</tr>
<tr>
<td>Treatments</td>
<td>I: Trastuzumab intravenous 6 mg/kg (loading dose 8 mg/kg) every 3 weeks in addition to chemotherapy (see below). Treatment with trastuzumab continued until disease progression or unmanageable toxicity. C: Combination of 6 cycles of a fluoropyrimidine (capecitabine 1000 mg/m² per os twice daily for 14 days every 3 weeks, or fluorouracil 800 mg/m²/day intravenous infusion over 5 days every 3 weeks) and cisplatin (80 mg/m² as a two hour intravenous infusion every 3 weeks)</td>
</tr>
<tr>
<td>In-/exclusion criteria</td>
<td>Inclusion: pts. ≥ 18 years of age with inoperable locally advanced, recurrent, and/or metastatic HER2 positive adenocarcinoma of the stomach or gastroesophageal junction, ECOG PS 0, 1 or 2, LVEF ≥ 50 %. Exclusion: pts. with previous chemotherapy for advanced/metastatic disease, lack of physical integrity of the upper gastrointestinal tract, or malabsorption syndrome</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Until death or study completion (January 2009)</td>
</tr>
</tbody>
</table>
| Outcomes  | **Primary:** Overall survival (OS)  
**Secondary:**  
- Progression free survival (PFS), time to progression (TTP), overall response rate (ORR; complete response (CR) + partial response (PR)), clinical benefit rate (CBR; CR + PR + stable disease), duration of response (DR)  
- Safety profile, quality of life (QoL), pain intensity, analgesic consumption, weight gain/loss  
- Pharmacokinetics |
| Key results | **Primary:** OS: HR³ 0.74, 95 % CI² 0.60 - 0.91 (median OS: I 13.8 vs. C 11.1 months, p = 0.0046)  
**Secondary:**  
- PFS: HR 0.71, 95 % CI 0.59 – 0.85 (median PFS: I 6.7 vs. C 5.5 months, p = 0.0002)  
- TTP: HR 0.70, 95 % CI 0.58 – 0.85 (median TTP: I 7.1 vs. C 5.6 months, p = 0.0003)  
- ORR: Odds ratio 1.70, 95 % CI 1.22 – 2.38 (Responders I 47.3 % vs. C 34.5 %, p = 0.0017)  
- DR: HR 0.54, 95 % CI 0.40 – 0.73 (median time to event: I 6.9 vs. C 4.8 months, p < 0.0001)  
- CBR: Odds ratio 1.66 95 % CI 1.14 – 2.41 (I 78.9 % vs. C 69.3 %, p = 0.0081)  
- QoL: improvements in both arms over time, gastrointestinal symptom scores slightly better in C  
- Pain scores and analgesics use: similar in I and C  
- Pharmacokinetics: lower trastuzumab levels in gastric cancer pts. compared to metastatic breast cancer pts. |
| Adverse effects | Any adverse event (AE): I 202/294, 99 % vs. C 284/290, 98 %  
Significant LVEF decreases: I 4.6 % vs. C 1.1 %, no difference in symptomatic congestive heart failure  
Grade 3/4 AE: I 201/294, 99 % vs. C 198/290, 68 %  
Treatment related deaths/deaths as a result of an adverse event: I 10/17, 59 % vs. C 3/14, 21 %  
Study withdrawals as a result of an AE: I 32 pts., 11 % vs. C 43 pts., 15 % |
| Commentary | The second interim efficacy analysis was performed after 349 events (patient deaths), corresponding to 75.9 % of the planned 460 events had been reported. The IDMC⁶ recommended that the study be terminated. |

¹ I = Intervention  
² pts. = Patients  
³ C = Control  
⁴ HR = Hazard ratio  
⁵ CI = Confidence interval  
⁶ IDMC = Independent data monitoring centre  
⁷ ECOG = Eastern Cooperative Oncology Group Performance Status
The ToGA (Trastuzumab for HER2 positive metastatic gastric cancer) trial assessed trastuzumab in combination with a fluoropyrimidine and cisplatin (FP+H) versus chemotherapy alone (FP) as first line therapy in patients with HER2 positive advanced gastric cancer. The choice of fluoropyrimidine was decided by the investigator on an individual patient basis.

Within the screening programme for the ToGA trial 3,667 evaluable patient samples were assessed and 810 were defined as HER2-positive (IHC3+ and/or FISH+; HER2-positivity rate of 22.1%).

Patients previously untreated for HER2 positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction not amenable to curative therapy (some have had adjuvant chemotherapy for gastric cancer before) were included. They were stratified prior to randomization for a number of parameters, including prognostic factors that could affect outcome: Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs. 2), chemotherapy regimen (5-FU plus cisplatin vs. capecitabine plus cisplatin), locally advanced vs. metastatic disease, stomach vs. gastro-oesophageal junction, and measurable vs. non-measurable evaluable disease.

Following the HER2 testing, patients were classified in different HER2 subgroups. Overall, the proportion of patients with low HER2 overexpression (IHC0/FISH+, IHC1+/FISH+) was small (22 %) as compared to patients with high HER2 (IHC2+/FISH+, IHC3+) overexpression (76 %).

During the course of the trial, the independent data monitoring centre (IDMC) advised the sample size to be increased from 248 events to 460 events. In addition, following the 1st interim analysis after 50 % of the 460 events, IDMC recommended an additional interim analysis, which was performed when 349 (75.9 %) of the events had been reported in the study across the two treatment arms. The results were reviewed by the IDMC, who recommended that the study should be terminated.

Treatment with trastuzumab in combination with FP chemotherapy resulted in a significant improvement in overall survival compared to treatment with FP alone at approximately 1.5 years of follow up (median of follow up 17.1 months in the FP arm and 18.6 months in the FP+H). At this point, there were 182 deaths in the FP arm and 167 deaths in the FP+H arm (62.8 % vs. 56.8 %), an absolute risk reduction of 6 % (Number needed to treat (NNT) 17). The majority of the deaths were due to events related to the underlying cancer. In addition to fewer deaths, the median overall survival time in the FP+H arm was extended to 13.8 months compared to 11.1 months in the FP arm. This corresponds to a statistically significant reduction in the risk of death by 26% for patients treated with trastuzumab plus FP (hazard ratio (HR) 0.74; 95% CI 0.60-0.91, p = 0.0046).

Consistent effects were observed in the secondary endpoints. Significant benefit from the addition of trastuzumab to FP therapy was seen for progression-free survival, overall response rate, time to progression, duration of response and clinical benefit rate (see table for details).

Post-hoc subgroup analyses indicated that positive treatment effects are limited to targeting tumours with higher levels of HER2 protein. The median overall survival for the high HER2 expressing group (IHC2+/FISH+, IHC3+) was 16 months versus 11.8 months for the low HER2 expressing group (HR 0.65; 95 % CI 0.51-0.83). In contrast, in patients with low HER2-expressing tumours (IHC0/FISH+ and IHC1+/FISH+), limited treatment
benefit was observed (median survival times of 8.7 and 10 months in the FP and FP+H arms, respectively, HR 1.07; 95% CI 0.70-1.62).

Subgroup analyses as well created doubt regarding the benefit of add-on trastuzumab treatment in other patient subgroups, for instance those with locally advanced disease, non-measurable disease and poor performance status (ECOG 2). Therefore, these patients were excluded from the indication.

The most common adverse events in both treatment arms were nausea, vomiting, neutropenia and anorexia. Apart from the above mentioned decrease of LVEF, adverse events which occurred with a higher frequency in the FP+H arm than in the FP arm (≥ 5% difference) included diarrhea, stomatitis, anemia and thrombocytopenia.

The frequency of infections was higher in patients treated with fluoropyrimidine, cisplatin and trastuzumab, compared with those treated with fluoropyrimidine and cisplatin (32% versus 20%) and two patients in the trastuzumab containing arm died because of pneumonia, versus none in the fluoropyrimidine and cisplatin arm.

Overall, the incidence of Grade ≥ 3 adverse events was similar in the two treatment groups (68% in each arm). Neutropenia, commonly associated with fluoropyrimidine plus platinum therapy, was the most common Grade ≥ 3 event in both treatment arms (29% in FP, 35% in FP+H). An increased incidence of Grade 3 or 4 diarrhea was reported in the FP + H arm (9 % vs. 4 %). Seventeen patients (6%) experienced at least one typical infusion-related AE of CTC Grade ≥ 3 on the day of or the day after a trastuzumab infusion.

Taken together, safety data from the ToGA trial suggest that there are no additional significant safety issues with trastuzumab used in the treatment of advanced gastric cancer over and above those seen when it is used to treat breast cancer. Therefore, risks of cardiac dysfunction and pulmonary, gastrointestinal and infusion-related adverse reactions persist [1].

### 6.2 Efficacy and safety - further studies

Two phase II trials were available only as abstracts [10, 11]. One describes a partial response to trastuzumab monotherapy sustained for > 24 weeks for one out of three treated patients [11], whereas the other reported response in six out of 21 treated patients treated with trastuzumab in combination with cisplatin [10].

trastuzumab was associated with decrease in LVEF and gastrointestinal toxicity

no other phase II/III trials published in full
7 Estimated costs

One vial Herceptin® containing 150 mg costs € 715 [13]. Hence, a loading dose of trastuzumab 8 mg/kg costs approximately € 2,860.-, and € 2,145.- for each subsequent 6 mg/kg dose¹ [13]. The median treatment duration in patients treated with trastuzumab in the ToGA study was 4.9 months (equating to approximately 6 x 3 week cycles). Trastuzumab over this time period would cost approximately € 13,585.- per patient. This is in addition to current chemotherapy costs. Other costs include the preliminary assessment of HER2 levels in all patients (on average, approximately 6 patients have to be screened to find one with high overexpression of HER2), regular measurement of LVEF by echocardiogram before and during treatment (approximately every three months) and treatment of patients developing trastuzumab-related cardiotoxicity.

High HER2 expressing tumours (IHC2+/FISH+ or IHC3+) were found in 16 % of patients of the ToGA study. About 17 % of the 1300 newly diagnosed gastric cancers in Austria are metastasized [5]. According to its indication for metastasized gastric cancer, trastuzumab might be offered to an estimated 35 patients per year. Thus, the costs for the drug itself will raise the treatment costs for gastric cancer by approximately € 475,000 per year.

8 Ongoing research

There are no other ongoing or completed phase II/III trials for trastuzumab in advanced gastric cancer registered [14].

However, trastuzumab is tested in a variety of other HER2 positive neoplasms such as breast cancer, pancreatic cancer, endometrial cancer, bladder cancer, lung cancer, prostate cancer, sarcoma and B-acute lymphoblastic leukemia, in most of these neoplasms in combination with other cytotoxic drugs.

In advanced gastric cancer, other monoclonal antibodies such as cetuximab, bevacizumab and panitumumab are currently investigated in phase III clinical trials [14].

¹ calculated for a 70 kg person and per package
The EMA extended the indication for the use of trastuzumab for the treatment of patients who were previously untreated for HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction in combination with capecitabine or 5-FU and cisplatin in January 2010 based on the results of one randomised, open-label phase III study which demonstrated increased overall survival [1]. At a median follow up of approximately 1.5 years, treatment with trastuzumab in combination with FP chemotherapy resulted in a significant improvement in overall survival compared to treatment with FP alone (median overall survival 11.1 vs. 13.8 months, HR 0.74, 95% CI 0.60-0.91, p = 0.0046) [1].

The toxicity of both treatment arms in the ToGA trial was comparable. However, treatment duration with trastuzumab was short and a longer exposition might lead to a higher cardiotoxicity [15].

Quality of life was assessed using standardized quality of life questionnaires for cancer patients (EORTC QLQ-C30, gastric module STO22). The actual scores and change from baseline indicated improved quality of life in both treatment arms over time, especially at the end of chemotherapy, but no added value for trastuzumab. On the contrary, gastrointestinal symptom scores were slightly worse in patients receiving trastuzumab which correlates with the slightly increased frequency of gastrointestinal adverse events in these patients. Pains scores and use of analgesics were similar in both arms [1].

However, the favourable efficacy results of the study should be interpreted with some caution, since it has been shown that efficacy results of randomized controlled trials (RCTs) stopped early for benefit are prone to exaggeration. The observed treatment effect may therefore be a chance finding [16, 17].

The indication of trastuzumab for patient subgroups in advanced gastric cancer was based on the results of post-hoc subgroup analyses which suggested that positive treatment effects are limited to targeting tumours with higher levels of HER2 protein, whereas no apparent benefit was seen in patients with poor performance status at baseline, non-measurable and locally advanced disease. Accordingly, these patients were excluded from the indication. Analysed subgroups were small (e. g., locally advanced disease n = 20 patients). Post-hoc subgroup observations, in general, should be treated with scepticism [18]. Hence, these results need to be confirmed in further trials.

In addition, patients with a lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome, and patients with acute intestinal bleeding were not allowed to enter the study. Therefore the target patient population may not be representative for those patients which will be treated with trastuzumab after market authorization [1].

Since the optimal duration of trastuzumab therapy is not known further trials assessing metastasized gastric cancer should investigate when treatment with trastuzumab can be stopped and whether patients can benefit from a prolonged administration of chemotherapeutic agents. In addition, the role of newer agents such as taxanes for the treatment of advanced gastric cancer has to be defined.
Analysis of pharmacokinetics of trastuzumab in gastric cancer gave remarkable differences to pharmacokinetics in breast cancer, e.g., lower trough concentrations. Further clarification on the involved mechanisms is needed.

It is likely that trastuzumab will be used more frequently in the near future. Off label use will probably be practised in patient subgroups currently excluded from the indication, such as locally advanced disease. Also, other HER2 positive neoplasms might be treated with trastuzumab.

Despite the limitations of the available data, tumours of patients with metastasized gastric cancer who are potential candidates for trastuzumab should be screened for overexpression of HER2. It is reasonable to offer trastuzumab in addition to standard chemotherapy if the tumour expresses high levels of HER2 protein (IHC2+/FISH+ and IHC3+/regardless of the FISH status), after explaining to the patient the possible risks and benefit of the treatment.

The use of trastuzumab will raise the costs for the treatment of gastric cancer. The expensive drug is to be continued until the disease progresses and will most likely be used off-label. Furthermore, there are indirect costs such as screening tumours for HER2 overexpression and cardiac monitoring of patients.
References


