Clinical Perspective

Pancreatic cancer: is combination treatment better?

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Practice Points

- Gemcitabine was the first standard treatment to be developed for pancreatic cancer based on the results of Phase III studies, and is applied to unresectable disease and adjuvant treatment after surgery.
- No combination treatment between gemcitabine and molecular-targeted agents has demonstrated superior survival benefit over gemcitabine alone, except for gemcitabine plus erlotinib. The survival benefit of this latter regimen was also very small and the observed incidence of interstitial pneumonitis, infections, diarrhea and rash were increased in the gemcitabine plus erlotinib arm over gemcitabine alone.
- Recently, the FOLFIRINOX regimen (oxaliplatin, irinotecan, 5-fluorouracil and leucovorin) and gemcitabine plus nab-paclitaxel have shown superior survival benefits over gemcitabine alone in patients with metastatic pancreatic cancer. In the future, both treatments are expected to be a priority to be established as first-line treatments for patients with a good performance status.

SUMMARY: Since gemcitabine was first established as a standard treatment for unresectable pancreatic cancer in the 1990s, various chemotherapeutic regimens for pancreatic cancer have been investigated in Phase III studies. However, few chemotherapeutic regimens have demonstrated superior survival benefits over gemcitabine; as such, gemcitabine has been recommended as the first-choice treatment agent for a long time. Recently, the FOLFIRINOX regimen (oxaliplatin, irinotecan, 5-fluorouracil and leucovorin) and gemcitabine plus nab-paclitaxel were shown to yield a statistically significantly superior survival over gemcitabine alone in patients with metastatic pancreatic cancer. These combination treatments are now recommended as the first-line chemotherapies for pancreatic cancer in patients with a good performance status. What factors might affect the choice between these two treatments in individual patients with pancreatic cancer should also be clarified.

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According to GLOBOCAN 2008 of the WHO, the estimated incidence of pancreatic cancer was 278,684 per year and an estimated 266,669 patients died of this disease in 2008 [101]. This finding of an equivalent number of patients detected with the disease and dying of the disease in the same year indicates the dismal prognosis of the disease. Indeed, the 5-year survival rate of patients diagnosed as having pancreatic cancer remains 5–10%. The incidence of pancreatic cancer has continued to increase since then, and the disease has become a significant global health problem. Since it is difficult to diagnose pancreatic cancer at an early stage, 70–80% patients have unresectable disease at diagnosis, including locally advanced or distant metastatic disease.

Single-agent efficacy

Ever since gemcitabine was demonstrated to provide a survival benefit as compared with 5-fluorouracil in a Phase III study carried out more than 10 years ago, the drug has been widely used as the standard chemotherapy for patients with unresectable pancreatic cancer [1].

New promising compounds have been developed, and the efficacy of single-agent therapy with marimastat, BAY 12-9566 (an inhibitor of matrix metalloproteinases) and exatecan compared with gemcitabine monotherapy has been investigated; however, every one of these compounds was found to be inferior to gemcitabine in terms of both the response rate and survival in Phase III trials **(Table 1)** [2–5]. Thus, it would seem difficult to conduct clinical trials using single agents for pancreatic cancer. In Japan, clinical trials of S-1 have been conducted since the early 2000s in patients with metastatic pancreatic cancer. A Phase II study of S-1 has shown a good response rate of 37.5% and prolonged survival of 9.2 months [6]. Based on these results, it was expected that S-1 might be effective for patients with unresectable pancreatic cancer, and a large Phase III study (GEST study) of S-1 in comparison with gemcitabine plus S-1 (GS therapy) was conducted in Japan and Taiwan. The results revealed noninferiority of S-1 to gemcitabine in terms of the overall survival (OS) **(Table 1)** [5]. To date, however, no agent other than S-1 has yielded a survival benefit equal to gemcitabine in patients with unresectable pancreatic cancer.

Combination treatments

A number of combination regimens of cytotoxic agents including oxaliplatin and fluoropyrimidines with gemcitabine have been investigated **(Table 2)** [5,7–10]. In a meta-analysis of randomized trials, gemcitabine plus a platinum agent or fluoropyrimidine was found to provide a survival benefit as compared with gemcitabine alone in pancreatic cancer patients with good performance status [11]. Of these combination treatments, gemcitabine (fixed-dose rate infusion) administered in combination with oxaliplatin (GEMOX) demonstrated promising activity, and the median OS was 9.0 months in the GEMOX arm versus 7.1 months in the gemcitabine-alone arm [7]. However, in a large Phase III trial carried out to compare gemcitabine, fixed-dose rate gemcitabine and GEMOX, GEMOX failed to prolong the survival as compared with gemcitabine alone [8]. On the other hand, the combination of gemcitabine and capecitabine also demonstrated promising activity in two different regimens, however, neither regimen showed statistically significantly improved survival as compared with gemcitabine alone [9,10].

A Phase II study of GS therapy yielded promising results in patients with metastatic pancreatic cancer; the response rate was 44% and the median OS was 10.1 months [12]. The GEST study was also conducted to assess the survival benefit of GS therapy in patients with unresectable pancreatic cancer. As a result, GS therapy also failed to provide improved survival as compared with gemcitabine alone [5]. The GEST study concluded that the lack of a significant difference in the OS between gemcitabine and GS therapy suggests that gemcitabine and S-1 could be used sequentially rather than concurrently. In this study, 50.5% patients received S-1 alone or S-1-based regimens in the gemcitabine group, and 57.9% patients received gemcitabine alone or gemcitabine-based regimens in the S-1 group as second-line chemotherapy. Sequential treatment with gemcitabine and S-1 seemed to have equivalent efficacy to that of GS therapy.

Some growth factors including EGF receptor and VEGF receptor, and also various signal transduction pathways have been identified that play important roles in the progression, proliferation and metastasis of various cancers, including pancreatic cancer. Therefore,

Table 1. Phase III studies comparing gemcitabine monotherapy and monotherapy with newly developed agents.

Author (year)	Agent	n	Response rate (%)	Median OS (months)	Hazard ratio (95% CI)	p-value	Ref.
Bramhall *et al.* (2001)	Gemcitabine	103	25.7	5.6	–	–	[2]
	Marimastat 5 mg b.i.d.	104	2.8	3.7	0.82 (0.62–1.09)	0.82	
	Marimastat 10 mg b.i.d.	105	2.8	3.5	0.76 (0.57–1.01)	0.045	
	Marimastat 25 mg b.i.d.	102	2.8	4.2	0.96 (0.71–1.28)	0.78	
Moore *et al.* (2003)	Gemcitabine	139	5.2	6.6	–	<0.001	[3]
	BAY12-9566	138	0.9	3.7			
Cheverton *et al.* (2004)	Gemcitabine	170	7.6	6.6	–	Not assessed	[4]
	Exatecan	169	0.5	5			
Ueno *et al.* (2013)	Gemcitabine	277	13.3	8.8	0.96 (0.78–1.18[†])	<0.001 for noninferiority	[5]
	S-1	280	21.0	9.7			

[†]97.5% CI.
b.i.d.: Twice daily; OS: Overall survival.

the use of molecular-targeted agents in combination with gemcitabine has been investigated in patients with unresectable pancreatic cancer. However, to date, no combination treatment, except gemcitabine plus erlotinib, has been shown to improve the survival in these patients. In regard to the combination of gemcitabine plus erlotinib, a Phase III study revealed a statistically significant improvement of the survival in patients treated with this regimen as compared with gemcitabine alone, however, the survival benefit was very small, with a difference in the median OS of only about 10 days **(Table 3)** [13–20]. Furthermore, adverse events, including interstitial pneumonitis, were frequently observed in the patients treated with gemcitabine plus erlotinib [14,19]. Nonetheless, gemcitabine plus erlotinib has come to be recognized as one of the standard first-line treatments, while other combination regimens of gemcitabine with biologic agents for the treatment of pancreatic cancer have so far been disappointing.

Thus, while promising results of combination treatments have been obtained in Phase II studies, Phase III studies have failed to demonstrate positive outcomes or survival benefits of any of the regimens used. There could be some possible reasons for this discrepancy. The first is related to the need for appropriate selection of subjects for Phase III studies. Unresectable pancreatic cancer is defined as a locally advanced and metastatic disease. Subgroup analyses of various Phase III studies have demonstrated differences in the efficacy of new treatments between locally advanced and metastatic diseases [5,14]. Performance status also affects the efficacy and safety [11,16]. Therefore, newly investigated treatments have recently tended to be examined only in patients with metastatic pancreatic cancer and those with a good performance status. Furthermore,

Table 2. Phase III studies comparing combined gemcitabine plus oral fluoropyrimidine or oxaliplatin therapy with gemcitabine monotherapy.

Author (year)	Regimen	n	Response rate (%)	Median OS (months)	Hazard ratio (95% CI)	p-value	Ref.
Louvet *et al.* (2005)	Gemcitabine	156	16.7	7.1	1.20 (0.95–1.54)	0.13	[7]
	Gemcitabine/oxaliplatin	157	28.7	9.0			
Poplin *et al.* (2009)	Gemcitabine	275	6	4.9	–	–	[8]
	FDR-gemcitabine	277	10	6.2	0.83 (0.69–1.00)	0.04	
	Gemcitabine/oxaliplatin	272	9	5.7	0.88 (0.73–1.05)	0.22	
Herrmann *et al.* (2007)	Gemcitabine	285	7.9	7.3	–	0.234	[9]
	Gemcitabine/capecitabine	284	10.1	8.4			
Cunningham *et al.* (2009)	Gemcitabine	266	12.4	6.2	0.86 (0.72–1.02)	0.086	[10]
	Gemcitabine/capecitabine	267	16.1	7.1			
Ueno *et al.* (2013)	Gemcitabine	277	13.3	8.8	0.88 (0.71–1.08[‡])	0.15	[5]
	Gemcitabine/S-1	275	23.7	10.1			

[‡]97.5% CI.
FDR: Fixed-dose rate; OS: Overall survival.

Table 3. Phase III studies comparing combined therapy using gemcitabine plus molecular-targeted agents with gemcitabine alone.

Author (year)	Regimen	n	Response rate (%)	Median OS (months)	Hazard ratio (95% CI)	p-value	Ref.
Van Cutsem *et al.* (2004)	Gemcitabine	347	8	6.0	1.03 (0.86–1.23)	0.75	[13]
	Gemcitabine/tipifarnib	341	6	6.3			
Moore *et al.* (2007)	Gemcitabine	284	6.9	5.9	0.82 (0.69–0.99)	0.038	[14]
	Gemcitabine/erlotinib	285	8.2	6.2			
Philip *et al.* (2010)	Gemcitabine	369	14	5.9	1.06 (0.91–1.23)	0.19	[15]
	Gemcitabine/cetuximab	366	12	6.4			
Kindler *et al.* (2010)	Gemcitabine	300	11.3	6.0	1.044 (0.88–1.24)	0.95	[16]
	Gemcitabine/bevacizumab	302	13.1	5.7			
Van Cutsem *et al.* (2009)	Gemcitabine/erlotinib	301	8.6	6.0	0.89 (0.74–1.07)	0.21	[17]
	Gemcitabine/erlotinib/ bevacizumab	306	13.5	7.1			
Kindler *et al.* (2011)	Gemcitabine	316	4	8.3	1.014 (0.786–1.309)	0.5436	[18]
	Gemcitabine/axitinib	314	12	8.5			
Rougier *et al.* (2013)	Gemcitabine	275	–	7.8	1.165 (0.921–1.473)	0.2034	[23]
	Gemcitabine/aflibercept	271	–	6.5			

OS: Overall survival.

appropriate stratification based on the prognostic factors identified in preceding Phase II studies should be set in Phase III studies. Another reason is the lack of predictive markers while developing treatments for pancreatic cancer. If predictive markers for the efficacy of new treatments can be identified from a Phase II study, it would be easier to ensure appropriate subject selection and statistical assumptions in the subsequent Phase III study.

Future perspective

Recently, new regimens have been tested only in patients with metastases, and the combination regimens of oxaliplatin, irinotecan, 5-fluorouracil and leucovorin (FOLFIRINOX) and gemcitabine plus nab-paclitaxel (Gem+nab-PTX) have demonstrated superior OS as compared with gemcitabine alone [21,22]. The FOLFIRINOX regimen has exhibited the most promising activity against pancreatic cancer; the hazard ratio for death of FOLFIRINOX relative to gemcitabine was 0.57 (95% CI: 0.45– 0.73; $p < 0.001$) and the median OS was 11.1 months **(Table 4)** [21,22]. Based on these results, this treatment is currently the most highly recommended for the treatment of patients with metastatic pancreatic cancer and good performance status. Thus, the answer to the question of whether combination treatment is better is yes, and these combination treatments can expect to prolong the survival in those patients compared with gemcitabine alone.

However, serious adverse effects in FOLFIRINOX have been reported to occur at a higher frequency compared with in gemcitabine alone, and the indications for this regimen are limited to patients with good performance status and relatively younger patients. In serious adverse events of FOLFIRINOX, approximately 45% of patients experienced grade 3/4 neutropenia, including febrile neutropenia in 5.4%, and because cholangitis due to obstruction of the bile duct would worsen during treatment, patent biliary stent should be maintained. In the Phase III trial of the FOLFIRINOX, only 38% of patients with carcinoma of the pancreatic head and 14.3% of patients with biliary stents were included [21]; pancreatic head cancer is

Table 4. Recent Phase III studies comparing gemcitabine combination treatments with gemcitabine monotherapy.

Author (year)	Regimen	n	Response rate (%)	Median OS (months)	Hazard ratio (95% CI)	p-value	Ref.
Conroy *et al.* (2011)	Gemcitabine	171	9.4	6.8	0.57 (0.45–0.73)	<0.0001	[20]
	FOLFIRINOX	171	31.6	11.1			
Von Hoff *et al.* (2013)	Gemcitabine	430	7	6.7	0.72 (0.617–0.835)	0.000015	[21]
	Gemcitabine/nab-paclitaxel	431	23	8.5			

FOLFIRINOX: Oxaliplatin, irinotecan, 5-fluorouracil and leucovorin; OS: Overall survival.

Table 5. Common grade 3 or 4 adverse events associated with FOLFIRINOX and gemcitabine plus nab-paclitaxel therapies.

Adverse event	FOLFIRINOX† (%)	Gemcitabine plus nab-paclitaxel‡ (%)
Neutropenia	45.7	38
Febrile neutropenia	5.4	3
Thrombocytopenia	9.1	13
Anemia	7.8	13
Fatigue	23.6	17
Vomiting	14.5	–
Diarrhea	12.7	6
Sensory neuropathy	9.0	17
Elevated serum level of alanine aminotransferase	7.3	–
Thromboembolism	6.6	–

†Data taken from [20].
‡Data taken from [21].
FOLFIRINOX: Oxaliplatin, irinotecan, 5-fluorouracil and leucovorin.

more frequent and biliary stents are applied to more patients in practice. The inclusion criteria regarding liver function included bilirubin ≤1.5-times the upper limit of the normal range in a Phase III study of FOLFIRINOX. Therefore, it is necessary to pay attention to the tumor location, with or without biliary stents and bilirubin level when FOLFIRINOX is applied.

Gem+nab-PTX therapy has also been shown to yield promising activity in a Phase I/II study, with a response rate of 48% and a median OS of 12.2 months [23], comparable with the corresponding figures reported for the FOLFIRINOX regimen. In a Phase III study, Gem+nab-PTX produced a statistically significant improvement of the survival, however, the median OS was 8.5 months and the hazard ratio was 0.72. In regard to the safety, grade 3/4 toxicities, especially neutropenia, febrile neutropenia, fatigue, vomiting and diarrhea, tended to occur more frequently in patients treated with the FOLFIRINOX regimen as compared with that in patients treated with Gem+nab-PTX (Table 5). Granulocyte colony stimulating factor administration was necessitated in 42.5% of patients receiving FOLFIRINOX therapy and 26% of patients receiving Gem+nab-PTX. Thus, Gem+nab-PTX may be recognized as a less toxic regimen as compared with FOLFIRINOX.

These two treatments should be placed on high priority for being applied to the treatment of pancreatic cancer in addition to gemcitabine alone. However, the two regimens were only indicated for patients with metastases in the Phase III studies. The benefits of these treatments in patients with locally advanced or resectable pancreatic cancer have never been tested, and the survival benefits of these treatments for patients with localized disease should be investigated. What factors might affect the choice between these two treatments in individual patients with pancreatic cancer should also be clarified.

The Phase II study of Gem+nab-PTX suggested that secreted protein acidic and rich in cysteine (SPARC) in the stroma would be a predictive biomarker of this treatment, because the survival in patients in the high-SPARC group was significantly improved compared with patients in the low-SPARC group. If the SPARC would be confirmed as a predictive biomarker of Gem+nab-PTX treatment in a Phase III study, it would be of value to select a treatment from the two regimens according to the level of the SPARC. Furthermore, in the future, molecular-targeted agents should be developed based on predictive biology in pancreatic cancer. It is important to establish personalized treatments in pancreatic cancer.

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References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Burris HA 3rd, Moore MJ, Andersen J *et al.* Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J. Clin. Oncol.* 15(6), 2403–2413 (1997).

▪ **Gemcitabine demonstrated the survival benefit and improvement of quality of life in patients with unresectable pancreatic cancer at first in a Phase III study comparing gemcitabine with fluorouracil.**

2 Bramhall SR, Rosemurgy A, Brown PD, Bowry C, Buckels JA. Marimastat Pancreatic Cancer Study Group. Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. *J. Clin. Oncol.* 19(15), 3447–3455 (2001).

3 Moore MJ, Hamm J, Dancey J *et al.* Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a Phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J. Clin. Oncol.* 21(17), 3296–3302 (2003).

4 Cheverton P, Friess H, Andras C *et al.* Phase III results of exatecan (DX-8951f) versus gemcitabine (Gem) in chemotherapy-naive patients with advanced pancreatic cancer (APC). *J. Clin. Oncol.* 22(Suppl. 14), Abstract 4005 (2004).

5 Ueno H, Ioka T, Ikeda M *et al.* Randomized Phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J. Clin. Oncol.* 31(13), 1640–1648 (2013).

▪ **Noninferiority of S-1 to gemcitabine was proven, but superiority of gemcitabine plus S-1 was not confirmed in a Phase III study among gemcitabine, S-1 and gemcitabine plus S-1.**

6 Okusaka T, Funakoshi A, Furuse J *et al.* A late Phase II study of S-1 for metastatic pancreatic cancer. *Cancer Chemother. Pharmacol.* 61(4), 615–621 (2008).

7 Louvet C, Labianca R, Hammel P *et al.* Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD Phase III trial. *J. Clin. Oncol.* 23(15), 3509–3516 (2005).

8 Poplin E, Feng Y, Berlin J *et al.* Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J. Clin. Oncol.* 27(23), 3778–3785 (2009).

9 Herrmann R, Bodoky G, Ruhstaller T *et al.* Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, Phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J. Clin. Oncol.* 25(16), 2212–2217 (2007).

10 Cunningham D, Chau I, Stocken DD *et al.* Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J. Clin. Oncol.* 27(33), 5513–5518 (2009).

11 Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 8, 82 (2008).

12 Ueno H, Okusaka T, Furuse J *et al.* Multicenter Phase II study of gemcitabine and S-1 combination therapy (GS therapy) in patients with metastatic pancreatic cancer. *Jpn J. Clin. Oncol.* 41(8), 953–958 (2011).

13 Van Cutsem E, van de Velde H, Karasek P *et al.* Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J. Clin. Oncol.* 22(8), 1430–1438 (2004).

14 Moore MJ, Goldstein D, Hamm J *et al.* Erlotinib plus gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer. A Phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J. Clin. Oncol.* 25(15), 1960–1966 (2007).

▪ **Combination erlotinib with gemcitabine significantly prolonged the survival in patients with unresectable pancreatic cancer, compared with gemcitabine alone in a Phase III study.**

15 Philip PA, Benedetti J, Corless CL *et al.* Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J. Clin. Oncol.* 28(22), 3605–3610 (2010).

16 Kindler HL, Niedzwiecki D, Hollis D *et al.* Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: Phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J. Clin. Oncol.* 28(22), 3617–3622 (2010).

17 Van Cutsem E, Vervenne WL, Bennouna J *et al.* Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J. Clin. Oncol.* 27(13), 2231–2237 (2009).

18 Kindler HL, Ioka T, Richel DJ *et al.* Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised Phase 3 study. *Lancet Oncol.* 12(3), 256–262 (2011).

19 Okusaka T, Furuse J, Funakoshi A *et al.* Phase II study of erlotinib plus gemcitabine in Japanese patients with unresectable pancreatic cancer. *Cancer Sci.* 102(2), 425–431 (2011).

▪▪ **A regimen of oxaliplatin, irinotecan, 5-fluorouracil and leucovorin demonstrated to be superior to gemcitabine in overall survival in patients with metastatic pancreatic cancer in a Phase III study.**

20 Conroy T, Desseigne F, Ychou M *et al.* FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N. Engl. J. Med.* 364(19), 1817–1825 (2011).

▪▪ **Combination nab-paclitaxel with gemcitabine statistically significantly prolonged the survival in patients with metastatic pancreatic cancer, compared with gemcitabine alone in a Phase III study.**

21 Von Hoff DD, Ervin TJ, Arena FP *et al.* Randomized Phase III study of weekly nab-PTX plus GEM vs. GEM alone in patients with metastatic adenocarcinoma of pancreas (MPACT). *J. Clin. Oncol.* 31(Suppl. 4), LBA148 (2013).

22 Von Hoff DD, Ramanathan RK, Borad MJ *et al.* Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a Phase I/II trial. *J. Clin. Oncol.* 29(34), 4548–4554 (2011).

23 Rougier P, Riess H, Manges R *et al.* Randomised, placebo-controlled, double-blind, parallel-group Phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. *Eur. J. Cancer* 49(12), 2633–2642 (2013).

▪ Website

101 WHO, GLOBOCAN 2008. http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=900