Cost of Diagnostics vs. Overall Patient Management

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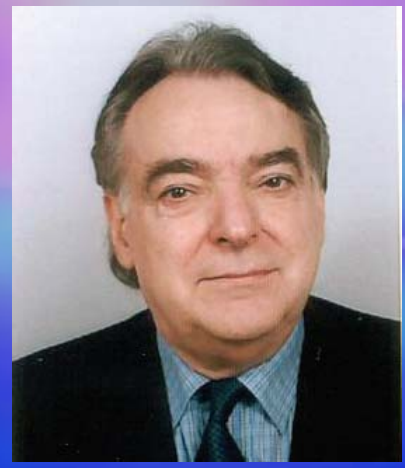
and the HER.ME.S Group
http://www.rees-france.com



FORMULA for Change

Bayer HealthCare
Diagnostics Division

The French National Herceptin® Trial (HER.ME.S)

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Funding: Ministry of Health

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Clinical Objectives

- To optimize trastuzumab treatment initiated in Metastatic Breast Cancer (MBC) patients by targeting drug therapy on an individual basis according to the overexpession of Human Epidermal growth factor Receptor-2 protein (HER2/neu)
- To establish whether or not serum levels of circulating Extra cellular Domain HER-2 (HER-2 ECD) would better predict the course of disease in MBC patients than gene or protein testing in primary tumour tissue
- To develop a framework for evaluating the potential cost- effectiveness of the pharmacogenomic strategies

Concerns of the Legal Authorities

- To facilitate patients' access to new monoclonal antibody therapy (MAb) by providing hospitals with a specific subsidy for implementing trastuzumab
- To design sustainable methods of financing for costly care
- A pharmacoeconomic study has been required to justify the funding and to evaluate potential financial needs

METHODS

FORMULA for Change

Bayer HealthCare
Diagnostics Division

Screening Methods

- HER-2 tumor status was determined using Immunohistochemistry (IHC) method (3+) and FISH (+, >2 genes copies per nucleus) to confirm weak positive IHC results (2+)
- HER-2 Extracellular Domain status (HER-2 ECD or serum HER-2/neu) was determined using a centralised ELISA method for serum HER-2/neu (Oncogene Science-Bayer HealthCare Diagnostics - ELISA kit)

Inclusion Criteria

- Patients in first or second line MBC untreated with trastuzumab (Herceptin®) with HER-2 overexpressing tumors
- Patients pre-treated by anthracyclines, received trastuzumab in combination with paclitaxel
- Patients who had received at least an anthracycline and a taxane chemotherapies , were administred trastuzumab in monotherapy

Exclusion Criteria

- Eligible for anthracyclines treatment
- Left ventricular ejection fraction < 50 %
- Polynuclear neutrophiles count <1,5 109/L
- Serum bilirubin value <1,25 lower normal limit
- Alcalin phosphatase >2,5 upper normal limit

Treatment Regimens

Week	1	2	3	4	5	6	7	8
trastuzumab + paclitaxel weekly								
	4 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg
	80 mg/m²	80 mg/m²	80 mg/m²	80 mg/m²	80 mg/m²	80 mg/m²		
trastuzumab + paclitaxel every 3 weeks								
	4 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg
	175 mg/m²			175 mg/m²			175 mg/m²	
trastuzumab weekly								
	4 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg	2 mg/kg
trastuzumab every 3 weeks								
	8 mg/kg			6 mg/kg			6 mg/kg	

Design of the Study

Pre-inclusion

1st or 2nd line Evaluable Metastatic Breast Cancer

HER-2 status

HER-2 screening (ImmunoHistoChemistry ± Fluorescence *In Situ* Hybridization (+, > 2 genes copies per nucleus)) + levels of circulating HER-2 Extracellular Domain

Herceptin treated patients

1st line therapy:
trastuzumab + paclitaxel
2nd line therapy:
trastuzumab monotherapy

+ ECD HER-2 study

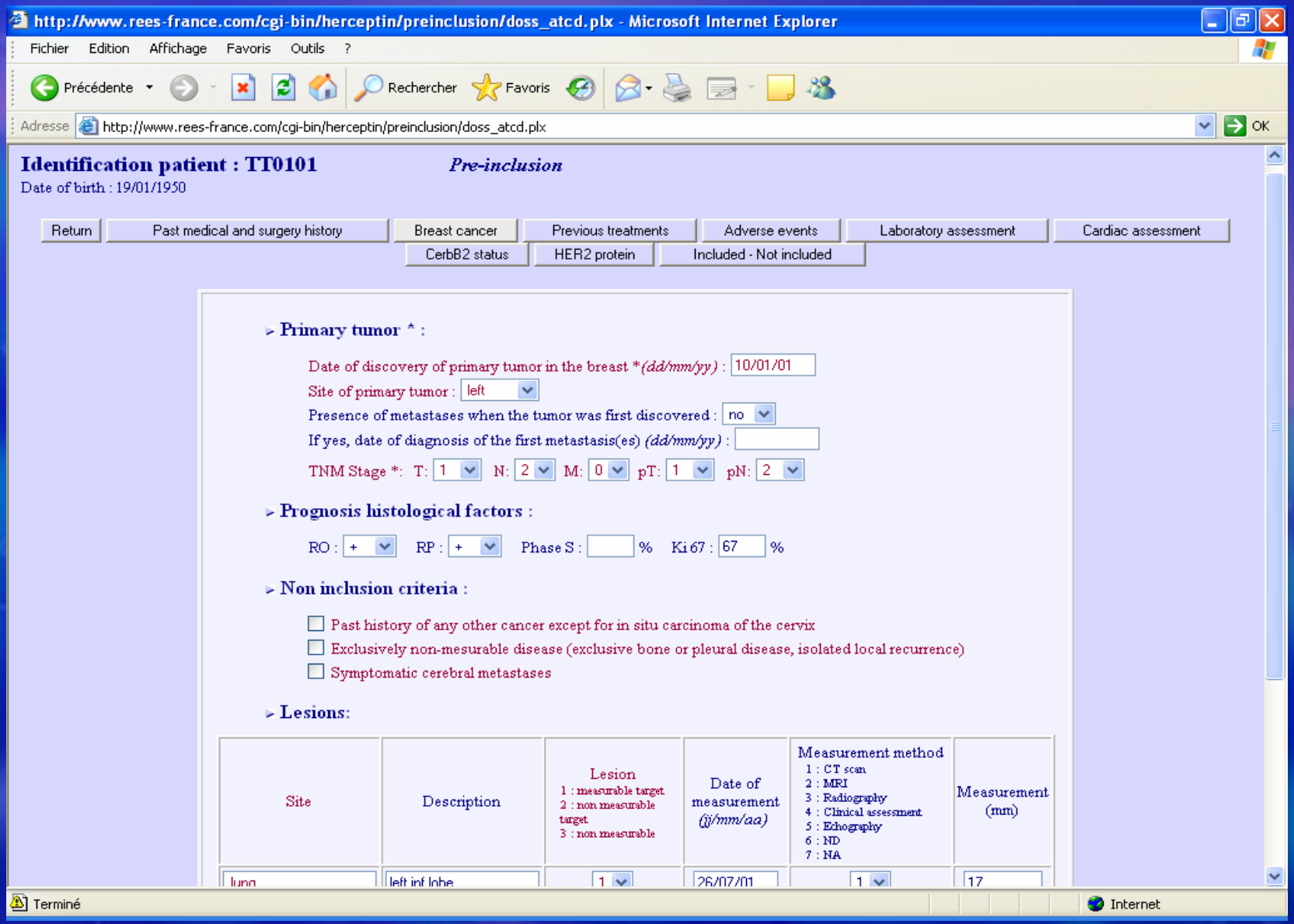
Free chemotherapy

Group control

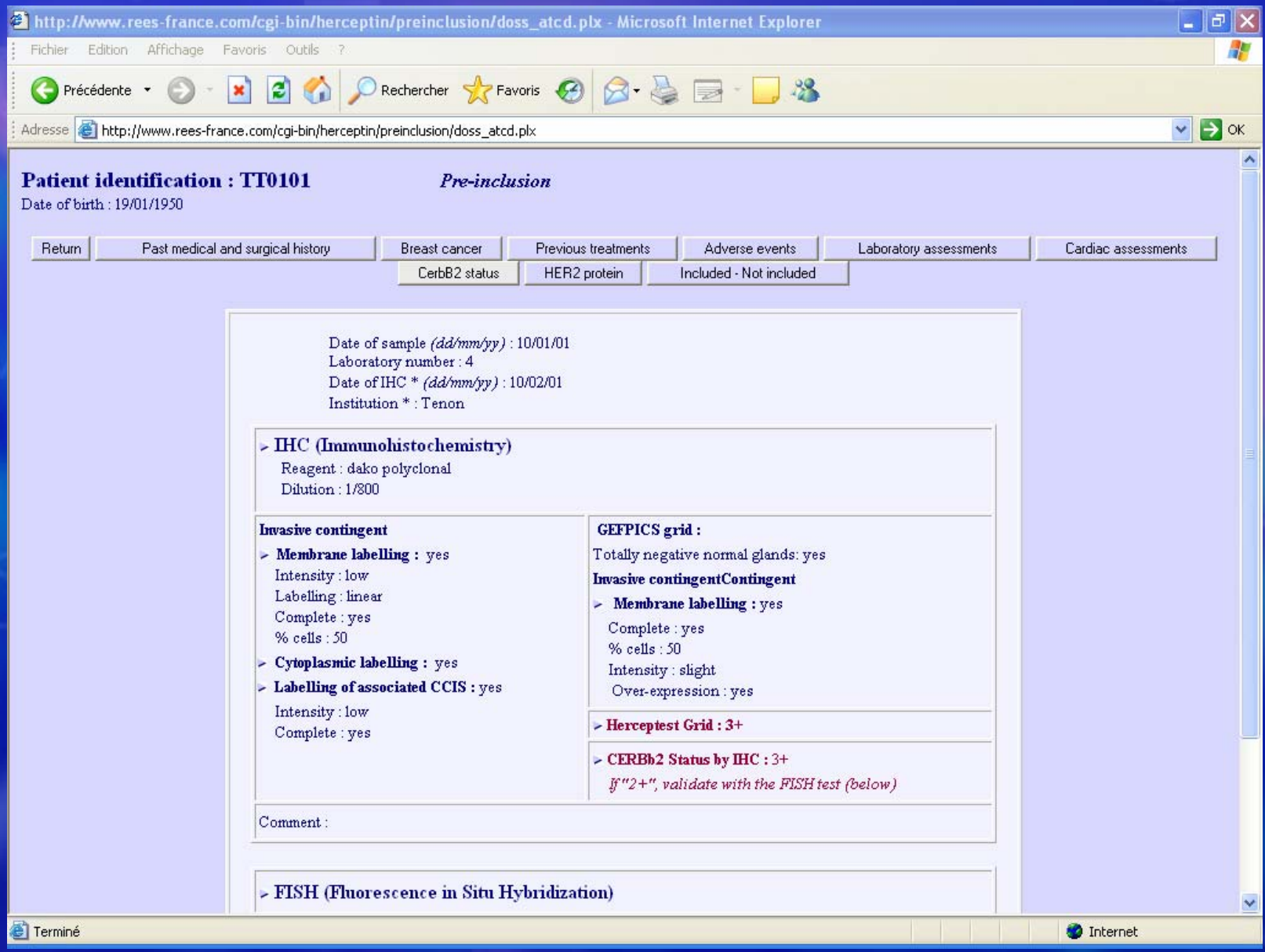
Web- based Electronic Medical Records (Rees France®)

- Multiples trial sites
- E-CRF specifically defined and customized
- Real time view of trial progress on demand
- Electronic audit
- Invalid data entry checks
- Multiple security layers

Pre-Inclusion Dossier



HER-2 Status


http://www.rees-france.com/cgi-bin/herceptin/preinclusion/doss_atcd.plx - Microsoft Internet Explorer
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Précédente
Rechercher
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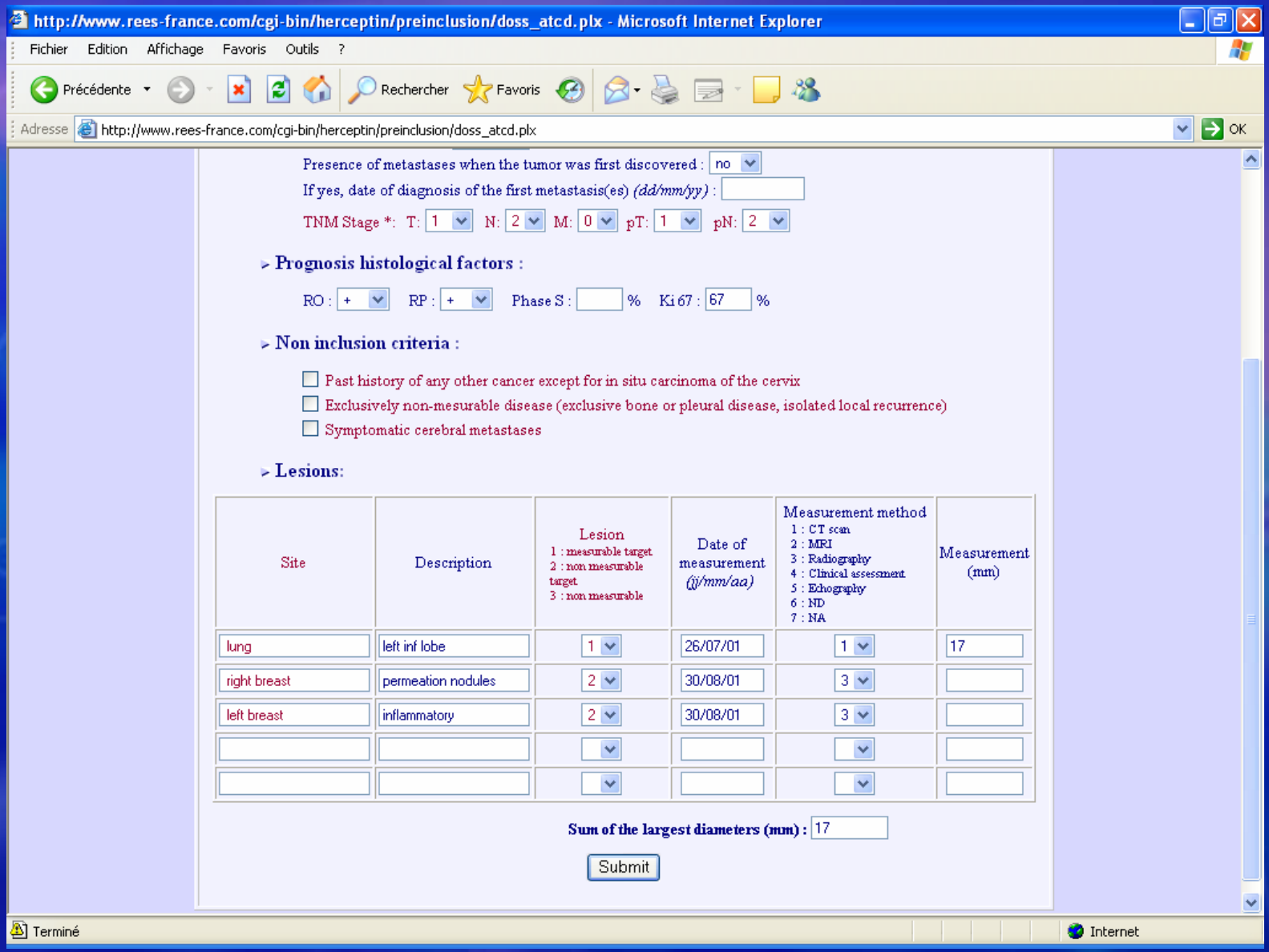
Adresse
http://www.rees-france.com/cgi-bin/herceptin/preinclusion/doss_atcd.plx
OK
Patient identification : TT0101
Pre-inclusion
Date of birth : 19/01/1950
Return
Past medical and surgical history
Breast cancer
Previous treatments
Adverse events
Laboratory assessments
Cardiac assessments
CerbB2 status
HER2 protein
Included - Not included
Date of sample (dd/mm/yy) : 10/01/01
Laboratory number : 4
Date of IHC * (dd/mm/yy) : 10/02/01
Institution * : Tenon
IHC (Immunohistochemistry)
Reagent : dako polyclonal
Dilution : 1/800
Invasive contingent
Membrane labelling : yes
Intensity : low
Labelling : linear
Complete : yes
% cells : 50
Cytoplasmic labelling : yes
Labelling of associated CCIS : yes
Intensity : low
Complete : yes
GEFPICS grid :
Totally negative normal glands: yes
Invasive contingentContingent
Membrane labelling : yes
Complete : yes
% cells : 50
Intensity : slight
Over-expression : yes
Herceptest Grid : 3+
CERBb2 Status by IHC : 3+
If "2+", validate with the FISH test (below)
Comment :
FISH (Fluorescence in Situ Hybridization)
Terminé
Internet

Tumor Staging Assessment



Medico-Economic Analysis is a Subsidiary Discipline Following on from Medical Management

- It takes “fingerprints” of the clinical process
- It creates a mould of them
- And the Euro costs flow from the mould

Clinical Data are Individual and Random Events

CLINICAL CONDITION →	MEDICAL PRACTICES →	RESULTS
➢ Performance status ➢ Co-morbidities ➢ Metastatic sites ➢ Body surface area index ➢ Body weight	➢ Laboratory tests ➢ Tumor volume assessment ➢ Cardiac assessment ➢ MAb and cytotoxic therapies ➢ Concomitant treatments ➢ Hospitalization	➢ Overall survival ➢ TTP ➢ Adverse events ➢ QLQ-C30
↓	↓	↓
Staging the disease	**Medical care utilization**	**Therapeutic benefit**

Tariffs are Exogenous and Deterministic Parameters

They are available on the shelves of the administrative libraries and external to the Case Report Form

Standard Unit Tariffs

- IHC (B200) : 60 €
- FISH (kit Ventana) : 153 €
- Trastuzumab (maintenance 2mg /kg; 66.2 kg) : 648 €
- Paclitaxel weekly (80 mg/m^2;1.68 m^2) : 825 €
- Paclitaxel every 3 weeks : 1 443 €
- Hospitalization (< 24 h) : 575 €
- Hospitalization (> 24 h) : 1 806 €

Choosing Hospital as the Viewpoint

DRGs 17 M06V, 24 Z02Z were used for valuing hospital costs after adjustements for variable expenses directly linked to the new protocoles

- Inclusion assessment cost: radiology, biology, cardiology
- Follow up assessment cost: radiology, biology, cardiology
- Acquisition cost of MAb & cytotoxic agents
- Concomitant treatments cost

Source Documents for Cost Allocation

- Procedures cost were valued using weights from the National Physicians Fees Schedule codes and unit cost prices from one cancer centre (Nantes) which was applied to all participating centres
- Antibody and cytotoxic therapies, concomitant treatments were valued at negotiated drug prices 2001, 2002, 2003, validated on line by pharmacists
- Administration cost was based on the DRG national costs scale 2001 and 2002 net of the cost of common procedures and chemotherapies

Estimating Cost of Treatment from Charges: A Patient Case

	Total cost (€)	Mean cost per week (€)
DRG's prospective tariffs (36 days +1full hospitalization)	**22 506**	**489**
DRG's prospective tariff net of the *routine cost* of chemotherapies, laboratory tests and imaging	**14 745**	320
Real cost of Complex therapies (37 administrations)	**41 243**	**896**
- trastuzumab + paclitaxel every 3 weeks (16)	17 321	376
- trastuzumab weekly (15)	9 389	204
- trastuzumab every 3 weeks (6)	11 262	244
Tumor staging assessments	932	20
Laboratory assessments	722	16
Cardiac assessments	1 598	35
Adjusted total DRG's real cost	**55 968**	**1 216**

Treatment duration : 46 weeks

RESULTS

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Diagnostics Division

HER.ME.S Trial Recruitment

- **120** patients from 12 centres were pre-included between September 2001 and November 2003
- **88** patients were included over the same period and followed until February 2005 (73%)
- **76** patients had discontinued the study (67% experienced progressive disease, 18% for Cardiac Toxicities)
- **12** patients are continuing treatment with trastuzumab
- **30** out of 88 included patients died (25%)

Pre-included Population Characteristics (N = 120)

- Age: 53.70 years ± 10.5
- PS: 81=0 (68%), 32=1(26%), 7=2 (6%)
- Median time from primary diagnosis: 4.3 years
- 78% of women had an overexpression of the growth factor receptor HER-2
- 22% had cardiac related diseases (hypertension, ectopic heart beats)

HER-2 Status (N = 120)

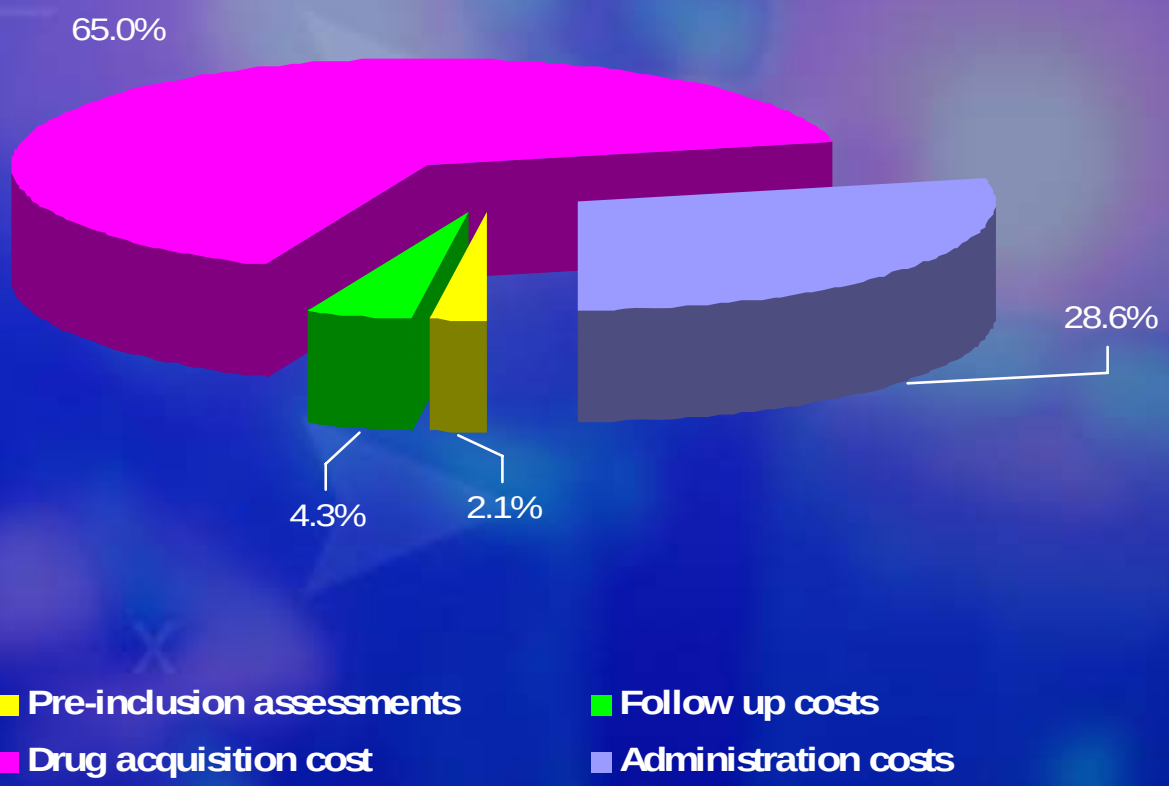
	Not Included	**Included**
Overexpression 3+ *(centralised IHC technique)*	5	67
Overexpression 2+ *(centralised IHC+FISH technique)*	1	8
Overexpression 3+ or 2 + *(on site assessment IHC+FISH)*	7	9
No overexpression	19	4
Pre-included patients	32	88

Included and Treated Population Characteristics (N = 88)

- Mean Age :54 years ±10.2
- Body surface index :1.68 m^2 ± 0.17
- Average weight :66.2 kg ± 14.42
- Mean number of courses :25 [2-108]
- 27/88 were treated with the same regimen during the study : 65% Trast+P3w, 30% Trast+P1w, 5% Trast only
- 61/88 switched at least once to the trastuzumab monotherapy regimen : 75% Trast+P1w and 25% Trast+P3w > Trast seul

Overall Patient Management Cost: 4 494 513 €

(N = 120 pre-included and 88 included patients)

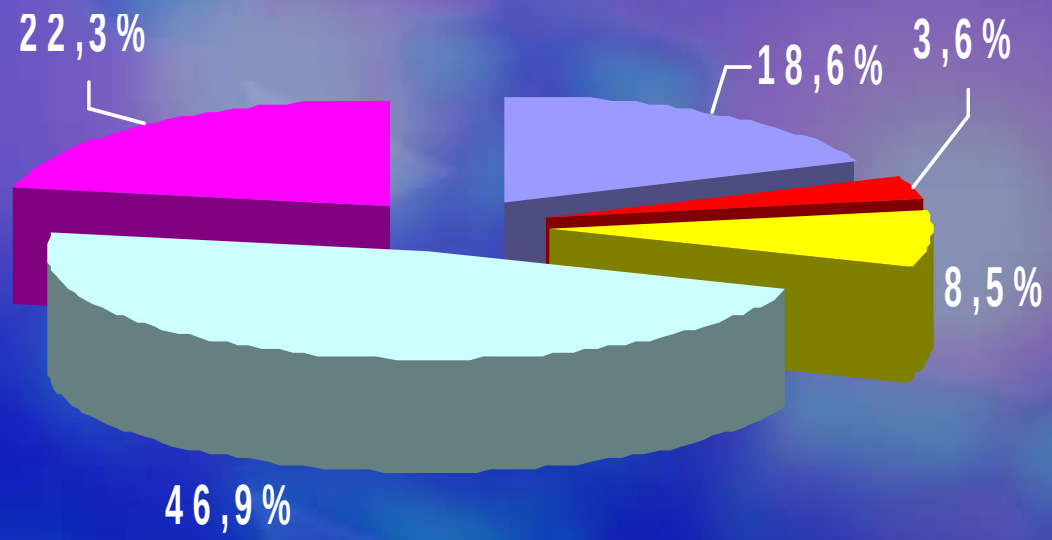


Breakdown of the Overall Patient Management Cost

(N = 120 pre-included et 88 included patients)

- Pre-Inclusion Assessments : 96 427 €
- Drug acquisition cost : 2 922 876 €
- Follow up costs : 191 517 €
- Administration costs : 1 283 692 €
- Total Cost : 4 494 513 €

Average Pre-Inclusion Screening Cost per Patient: 873 € (N = 120)

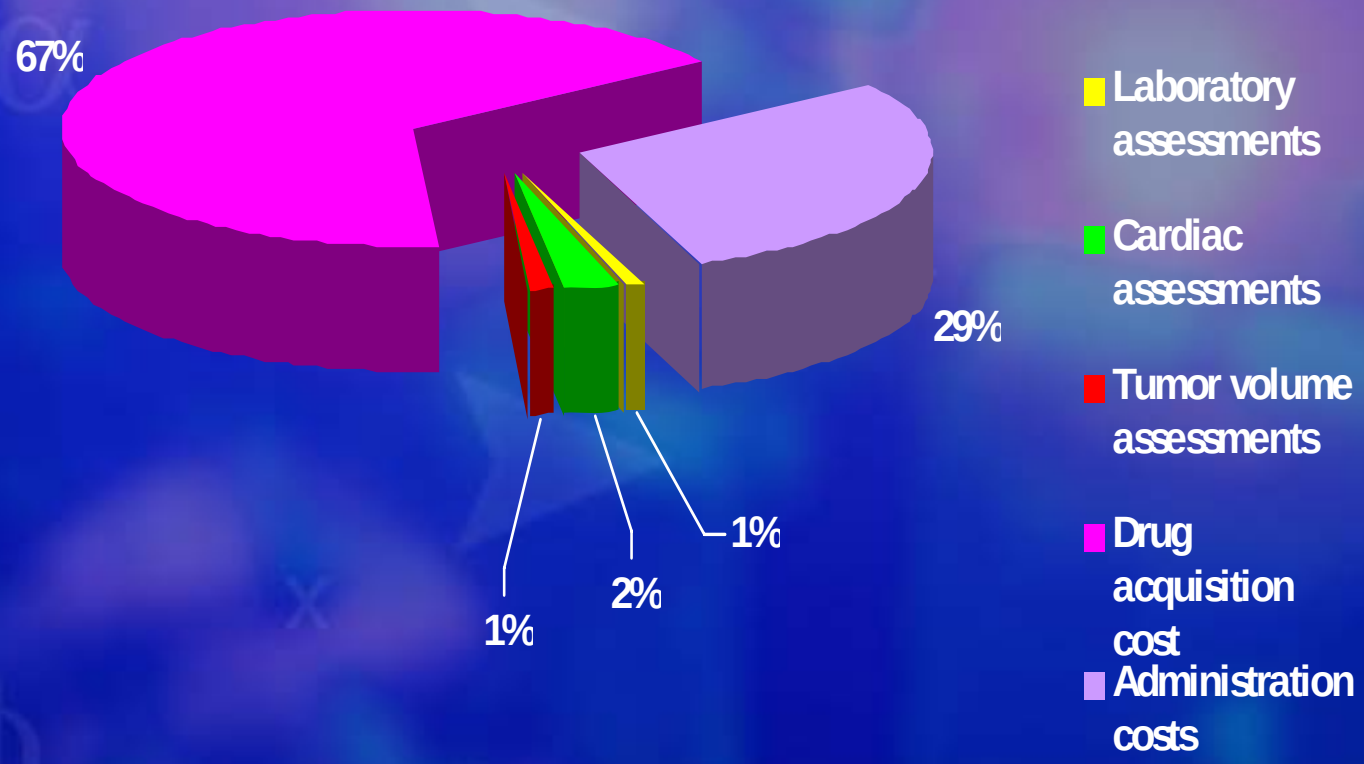


Breakdown of Average Pre-Inclusion Screening Cost per Patient (N = 120)

- Tumor staging assessment : 197 € [34 – 470]
- Laboratory assessment : 194 € [65 – 227]
- Cardiac assessment : 410 € [349 – 456]
- HER-2 Testing : 72 € [60 – 213]
- Total pre-inclusion cost : 873 € [515 – 1 349]

Average Treatment Cost per Patient Over 36 Weeks: 49 978 €

(N = 88)



Breakdown of Average Treatment Cost per Patient Over 36 Weeks (N = 88)

- Drug acquisition cost : 33 215 € [2 592 – 98 460]
- Follow up cost : 2 176 € [48 – 9 448]
- Administration cost : 14 587 € [1 082 – 58 428]
- Adjusted total DRG's cost : 49 978 € [3 797 – 156 382]

Mean Duration of treatment : 36 weeks [1.15 – 132]
Average number of administrations 25 [2 – 108]

Treatment Cost per Week and per Patient (N = 88)

- Drug acquisition cost : 1 105,8 € [336,20 – 2 297,6]
- Follow up cost : 70,1 € [1,35 – 434,7]
- Administration costs : 488,3 € [181 – 1 010]
- Adjusted total DRG cost : 1 664,2 € [518,5 – 3 742,2]

- Mean duration of treatment: 36 weeks

Efficacy Outcomes for Time to Events Measures (N = 76)

- Time to Treatment failure : 29 weeks [24 – 35]
- Time to Progression : 34 weeks [25 – 49]
- Median survival : 49 weeks [43 – 79]

Conclusion

- Identification of molecular alterations leads to the development of targeted therapeutics which are more effective than currently available agents
- Inappropriate use of trastuzumab in women who would not benefit (FP) is equally as bad as denying trastuzumab to women who need it (FN)
- HER-2 assays are less expensive than cytotoxic and/or MAb treatments : 72 € [60 – 213] once for all vs 1700 € [518,5 – 3 742,2] per patient and per week for the average treatment cost. From an economic perpective, HER-2 assays in primary tumor tissue are cost-effective