Partial Credit Model with random effects for Quality of Life longitudinal analysis

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QUALITY OF LIFE

Subjective
(everyone has their own definition)

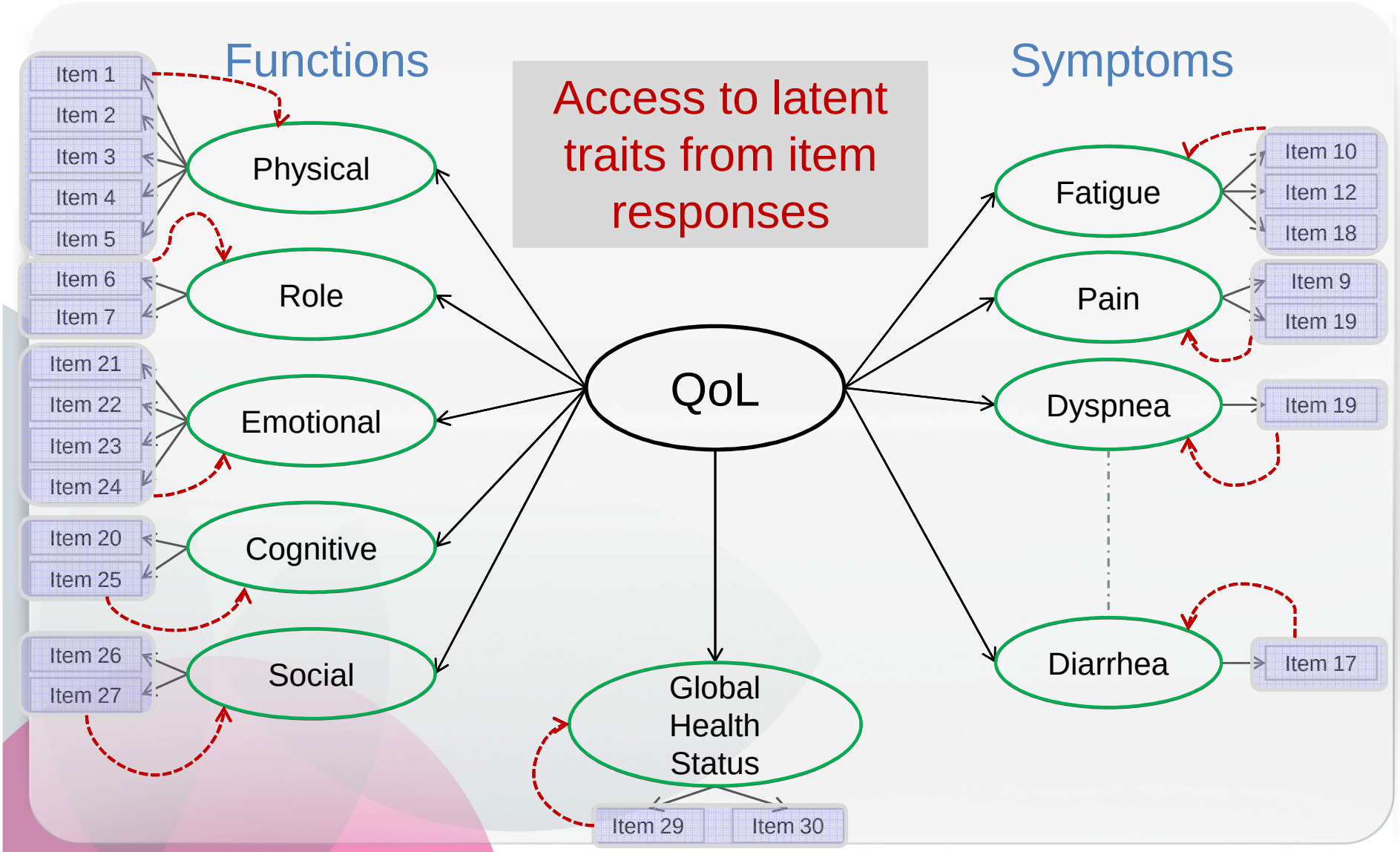
Dynamic
(their definition changes over time)

Multidimensional
(physical, psychological and social domains, as well as the symptoms associated with the disease and treatment)

Not directly measurable → Latent Trait

→ **Use of questionnaires** (eg: EORTC QLQ-C30)
Measures reported by the subjects themselves (PROs)

QUALITY OF LIFE (EORTC QLQ-C30)



DATA

Structure Data (eg: pain symptom)

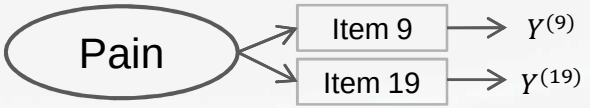
✓ Item responses

- Ordinal Categorical Data

During the past week : (Pain Symptom)	Not at all	A little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4

✓ Scale analysis

- Multiple response (Uni or multi-items)



✓ Repeated measures

- Patients complete questionnaires over time

$\left\{Y_{i0}^{(9)}, Y_{i0}^{(19)}\right\}$ Patient i

$\left\{Y_{i1}^{(9)}, Y_{i1}^{(19)}\right\}$

$\ddots$

$\left\{Y_{it}^{(9)}, Y_{it}^{(19)}\right\}$

→ Longitudinal Aspect

→ Dependence between the data from a same patient

ASSESSMENT OF QOL

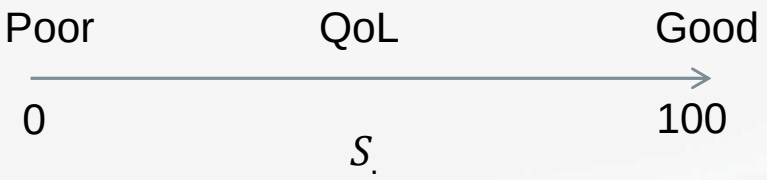
- Assessment QoL
  - ✓ Independent analyses of QoL scales
    - Latent trait: continuous variable
    - Take into account data structure
      - Longitudinal analysis
    - Assess some factors which can influence the response items
      - Treatment, center, age, etc…
- Why use mixed models ?
  - ✓ Fixed effect interest
    - Assess the impact of the explanatory variables
  - ✓ Random effect interest
    - Separate the total variability (random effect + error)
  - ✓ Two theories

CLASSICAL TEST THEORY (CTT)

- EORTC scoring procedure
  - ✓ For each scale, one score
    - Score (S) = Item response mean

$$S_{pain} = \frac{\frac{1}{2}\sum_{i=9,19} Y_i}{3} \times 100$$

$$S_{PF2} = \left[1 - \frac{\frac{1}{5}\sum_{i=1,\ldots,5} Y_i}{3}\right] \times 100$$



- Hypothesis

⇒ CTT supposed $\boldsymbol{S}$ close to real score of QoL T

⇓

$$S_i = T_i + \varepsilon_i$$

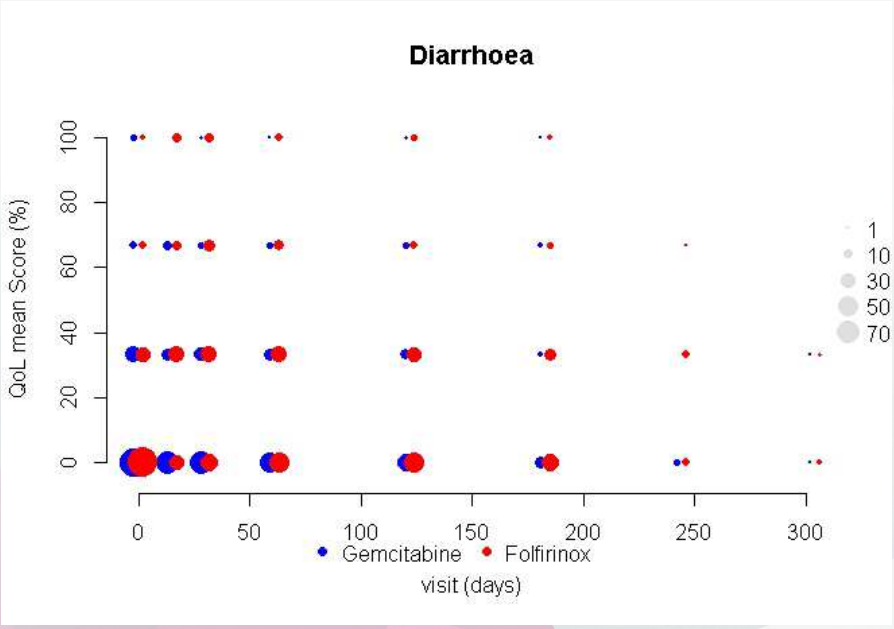
CLASSICAL TEST THEORY (CTT)

- Use of linear mixed model

Fixed part | Random part

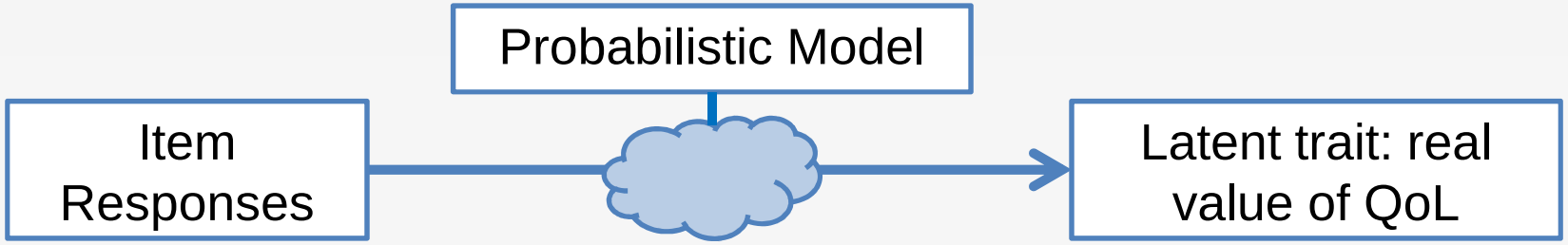
$$S_{it} = cte + \boldsymbol{x}_{it}'\boldsymbol{\beta}^{L} + \boldsymbol{u}_{t}'\boldsymbol{\xi}_{i}^{L} + \varepsilon_{it}$$

Common part to all people ← → Specific part to the individual i



- Drawbacks
  - ✓ Score is not really continuous
  - ✓ Bias:
    - ✓ ordinal data is asymetric
    - ✓ Biased estimates (not take into account the ceiling and floor effects of the ordinal outcome)
    - ✓ Prediction

ITEM RESPONSE THEORY (IRT)



$Y_{pain} = \{Y_9, Y_{19}\}$ where Y_{19}=1,…,4

- IRT models distinguish item parameters and individual parameters
- The latent trait
  - ✓ Represents the individual part of model
  - ✓ Represents the QoL concept
  - ✓ Specific to individual and QoL scale
- Advantage
  - ✓ Idem CTT + raw data
  - ✓ Persons and items on the same continuum
  - ✓ Several levels of interpretation
    - Scales, items, categories
- Drawback: transversal models
  - ✓ Rasch model for dichotomous data
  - ✓ Partial Credit Model (PCM) for polytomous data

PARTIAL CREDIT MODEL (PCM)

- PCM belongs to the Rasch model family
- Modeling of response probability

$$\Pr\left(Y_{ij} = k \middle| \theta_i, \delta\right) = \frac{\exp\left\{k\theta_i - \sum_{c=2}^{k} \delta_{jc}\right\}}{\sum_{h=1}^{m_j} \exp\left\{h\theta_i - \sum_{c=2}^{h} \delta_{jc}\right\}}$$

  - ✓ Where:
    - $k = 1, \ldots, m_j$ (responses categories)
    - Y_{ij} : response variable of patient i at item j
    - δ_{jc} : difficulty parameter of item j associated to categories c and $c - 1$ $(\delta_{j1} = 0)$
  - ✓ θ_i The latent trait or the individual part of model

- Approach for longitudinal analysis
  - ✓ Bacci (2008): latent trait changes over time
  - ✓ Extended the PCM to longitudinal analysis

PCM LONGITUDINAL (LPCM)

- LPCM for longitudinal analysis

$$\Pr\left(Y_{it}^{(j)} = k \middle| \theta_{it}, \delta\right) = \frac{\exp\left\{k\theta_{it} - \sum_{c=2}^{k} \delta_{jc}\right\}}{\sum_{h=1}^{m_j} \exp\left\{h\theta_{it} - \sum_{c=2}^{h} \delta_{jc}\right\}}$$

  - ✓ Where:
    - t index of different visits
    - θ_{it}: latent trait of patient i at visit t
  - ✓ Linear decomposition of latent trait
    - Assess explanatory variable influence over time
    - Take into account variability with random effects (repeated measure or clusters)

Specific part to the individual i

$$\theta_{it} = \boldsymbol{x}'_{it}\boldsymbol{\beta}^{G} + \boldsymbol{u}'_{t}\boldsymbol{\xi}_{i}^{G}$$

Common part to all people

- LPCM is a generalized linear mixed model for ordinal data
  - ✓ Baseline categories logit model
  - ✓ Adjacent categories logit model

PCM LONGITUDINAL (LPCM)

- LPCM as GLMM : link function
  - ✓ Let consider:

$$c = 2, \ldots, m_j$$

$$\pi_{itc}^{(j)} = \Pr\left(Y_{it}^{j} = c | \theta_{it}, \delta_j\right)$$

$$\phi_c = c$$

  - ✓ Baseline categories logit link:
    - Logically for nominal data
    - Kind of *stereotype model* (Anderson, 1984) used for ordinal data

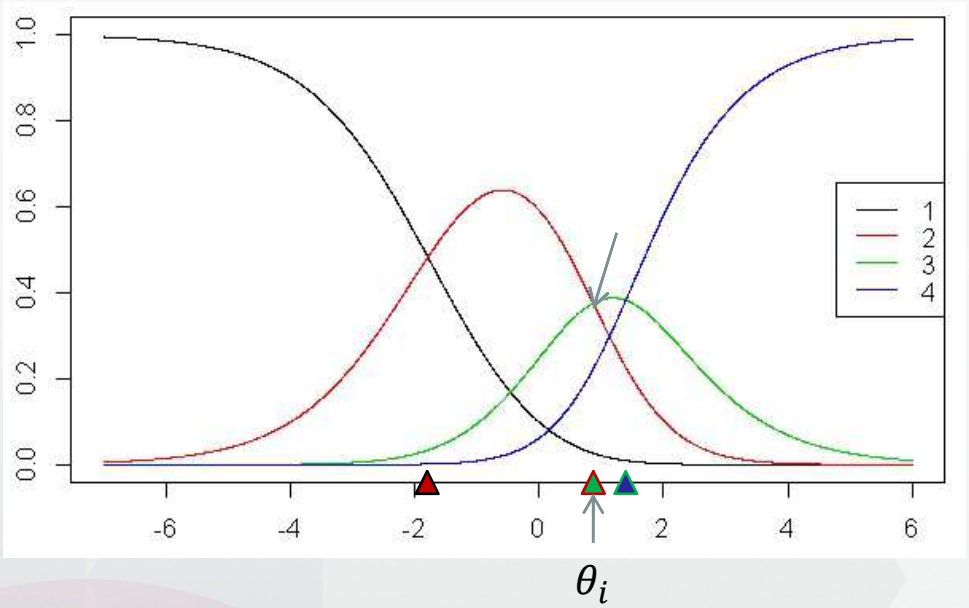
$$\log\left(\frac{\pi_{itc}^{(j)}}{\pi_{it1}^{(j)}}\right) = \phi_c\theta_{it} - \sum_{k=1}^{c}\delta_{jc}$$

  - ✓ Adjacent categories logit link:
    - For ordinal data

$$\log\left(\frac{\pi_{itc}^{(j)}}{\pi_{itc-1}^{(j)}}\right) = \theta_{it} - \delta_{jc}$$

ITEM PARAMETERS (LPCM)

- From IRT view
  - ✓ Incertitude parameters δ_{jc}
    - Latent trait value where the patient had the same chance to respond category c as the category $c-1$



▲ $= \delta_{j2}$

▲ $= \delta_{j3}$

▲ $= \delta_{j4}$

Example : $\theta_i = \delta_{j3}$

$Pr(Y_i = 2) = Pr(Y_i = 3)$

- From GLMM view
  - ✓ Intercept of model for each category

SOFTWARE

- STATA Software
  - ✓ *gllamm* and *gllapred*

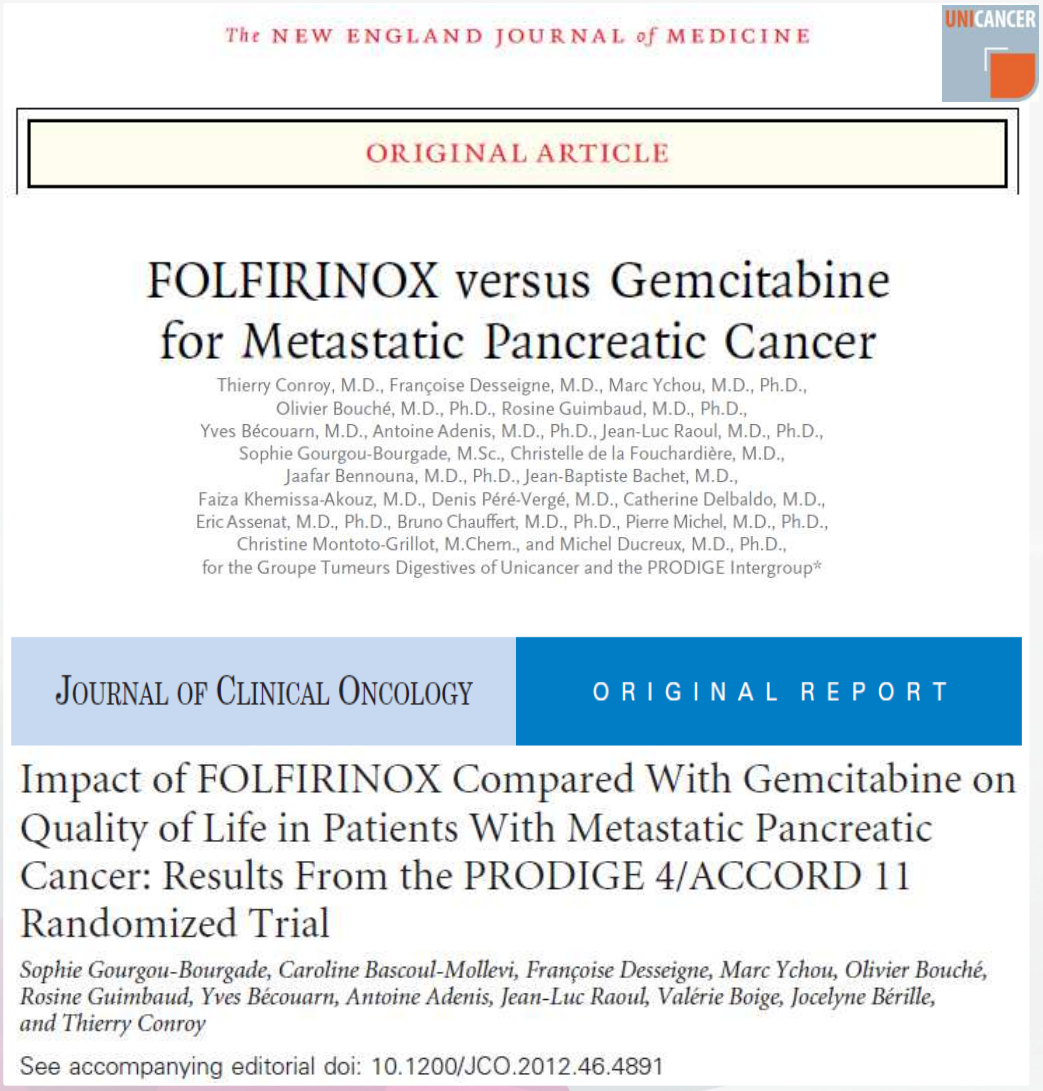
```
eq slope: visitx
eq inter: x
```

- SAS Software
  - ✓ *mixed* procedure for LMI
  - ✓ *nlmixed* procedure for G
    - Writing of the Model

```
/* Longitudinal PCM Model with interaction*/
proc nlmixed data = IRT.lpcm_pa_data_bis tech=NEWRAP ITDETAILS;
parms
d11=-0,d12=0,d13=0,
d21=0,d22=0,d23=0,
time=0,bras=0,interaction=0,s0=0.5,s1=0.5,c01=0;
eta1=d11*it9+d21*it19;
eta2=d12*it9+d22*it19;
eta3=d13*it9+d23*it19;
meantheta=time*visit+bras*arm+interaction*arm*visit;
theta=meantheta+u0+u1*visit;
denom=1+exp(theta-eta1)
      + exp(2*theta-eta1-eta2)
      + exp(3*theta-eta1-eta2-eta3);
if score=0 then z=1/denom;
if score=1 then z=exp(theta-eta1)/denom;
if score=2 then z=exp(2*theta-eta1-eta2)/denom;
if score=3 then z=exp(3*theta-eta1-eta2-eta3)/denom;
ll=log(z);
model score ~ general(ll);
random u0 u1 ~ normal([0,0],[s0,c01,S1])subject=npat;
PREDICT theta OUT=Data_pa;
TITLE 'Model PA with interaction';
run;
```

- R Software
  - ✓ An equivalent ?
    - GLMMmcmc package ?

PRODIGE 4 / ACCORD 11*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

Thierry Conroy, M.D., Françoise Desseigne, M.D., Marc Ychou, M.D., Ph.D., Olivier Bouché, M.D., Ph.D., Rosine Guimbaud, M.D., Ph.D., Yves Bécouarn, M.D., Antoine Adenis, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Sophie Gourgou-Bourgade, M.Sc., Christelle de la Fouchardière, M.D., Jaafar Bennouna, M.D., Ph.D., Jean-Baptiste Bachet, M.D., Faiza Khemissa-Akouz, M.D., Denis Péré-Vergé, M.D., Catherine Delbaldo, M.D., Eric Assenat, M.D., Ph.D., Bruno Chauffert, M.D., Ph.D., Pierre Michel, M.D., Ph.D., Christine Montoto-Grillot, M.Chem., and Michel Ducreux, M.D., Ph.D., for the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup*

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial

Sophie Gourgou-Bourgade, Caroline Bascoul-Mollevi, Françoise Desseigne, Marc Ychou, Olivier Bouché, Rosine Guimbaud, Yves Bécouarn, Antoine Adenis, Jean-Luc Raoul, Valérie Boige, Jocelyne Bérille, and Thierry Conroy

See accompanying editorial doi: 10.1200/JCO.2012.46.4891

- Phase 3 trial in first-line metastatic pancreatic cancer
  - ✓ Gemcitabine *vs* Folfirinox
- Main Article (NEJM, 2011)
  - ✓ Folfirinox superiority in overall survival
- Detailed study of QoL (JCO, 2013)
  - ✓ Longitudinal analysis based on a survival model
    - Time until definitive deterioration of QoL score

* Essai NCT00112658

MIXED MODEL BUILDING

- Model effects
  - ✓ Fixed part
    - Treatment arm
    - Changes over time
  - ✓ Random part
    - Take into account data variability

$$x_i = \begin{cases} 1 \ if \ Folfirinox \ arm \\ 0 \ otherwise \end{cases}$$

ξ_i : Random effects

v_t : Time

- ✓ CTT

$$S_{it} = cte + \xi_{i0}^{L} + \beta_1^L x_i + v_t\left(\xi_{i1}^{L} + \beta_2^L\right) + \beta_3^L x_i v_t + \varepsilon_{it}$$

- ✓ IRT

$$\theta_{it} = \xi_{i0}^{G} + \beta_1^G x_i + v_t\left(\xi_{i1}^{G} + \beta_2^G\right) + \beta_3^G x_i v_t$$

- Interpretation
  - ✓ The same for both approach

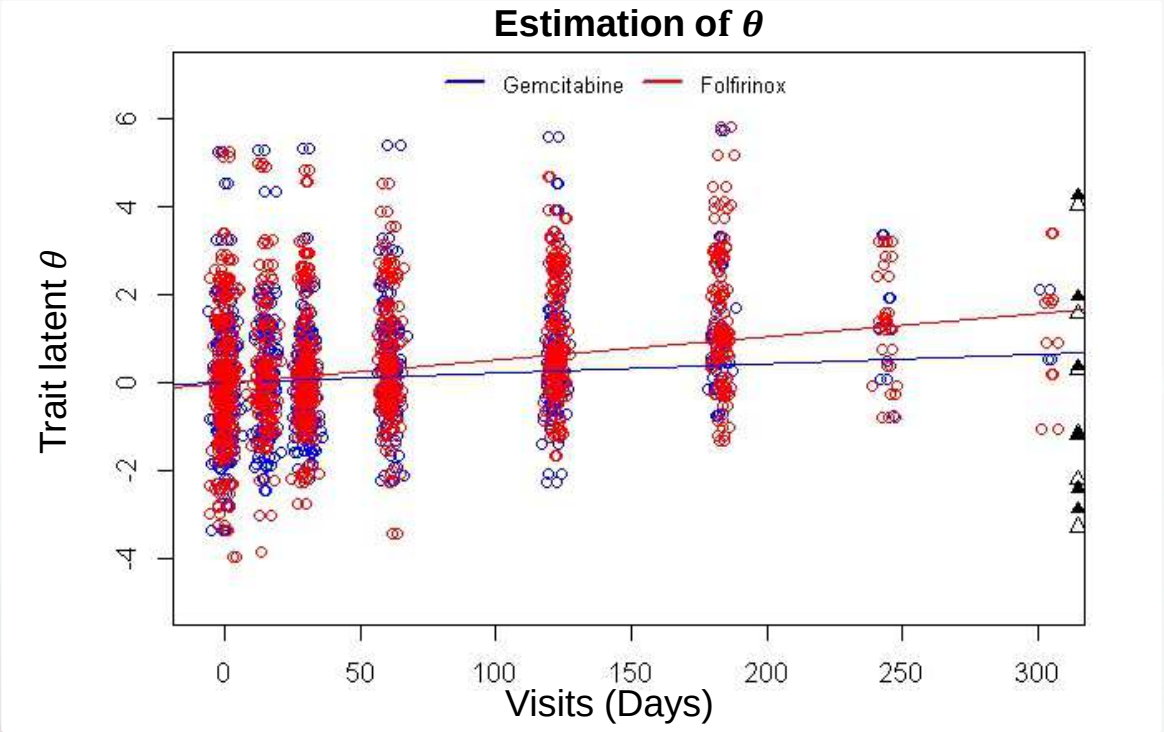
$$\begin{cases} \beta_1 \ treatment \ effect \ at \ baseline \\ \beta_2 \ standard \ group \ slope \\ \beta_2 + \beta_3 \ experimental \ group \ slope \end{cases}$$

FUNCTIONAL SCALES RESULTS

	CTT			IRT		
	Coefficient	*SD*	*P*	*Coefficient*	*SD*	*P*
Global health status / QoL						
β_2	0.03705	0.01214	0.0025	0.002180	0.001499	0.1466
β_3	0.02360	0.01382	0.0884	0.003005	0.001834	0.1022
Physical functioning						
β_2	0.01183	0.01351	0.3821	0.003630	0.001950	0.0635
β_3	-0.00019	0.01607	0.9905	-0.00361	0.002516	0.1523
Role functioning						
β_2	0.03008	0.01980	0.1299	0.000148	0.002116	0.9443
β_3	0.01591	0.02331	0.4952	-0.00413	0.002736	0.1324
Emotional functioning						
β_2	0.06901	0.01489	<.0001	-0.00978	0.001916	<.0001
β_3	-0.00037	0.01758	0.9833	-0.00004	0.002376	0.9852
Cognitive functioning						
β_2	0.000678	0.01277	0.9577	0.000153	0.001489	0.9182
β_3	0.01663	0.01525	0.2758	-0.00306	0.001834	0.0958
Social functioning						
β_2	0.01310	0.01762	0.4577	-0.00051	0.001985	0.7990
β_3	0.01481	0.02102	0.4812	-0.00306	0.002539	0.2284

RESULT ILLUSTRATION WITH IRT APPROACH

- Global Health Status
  - ✓ Trend of QoL perception



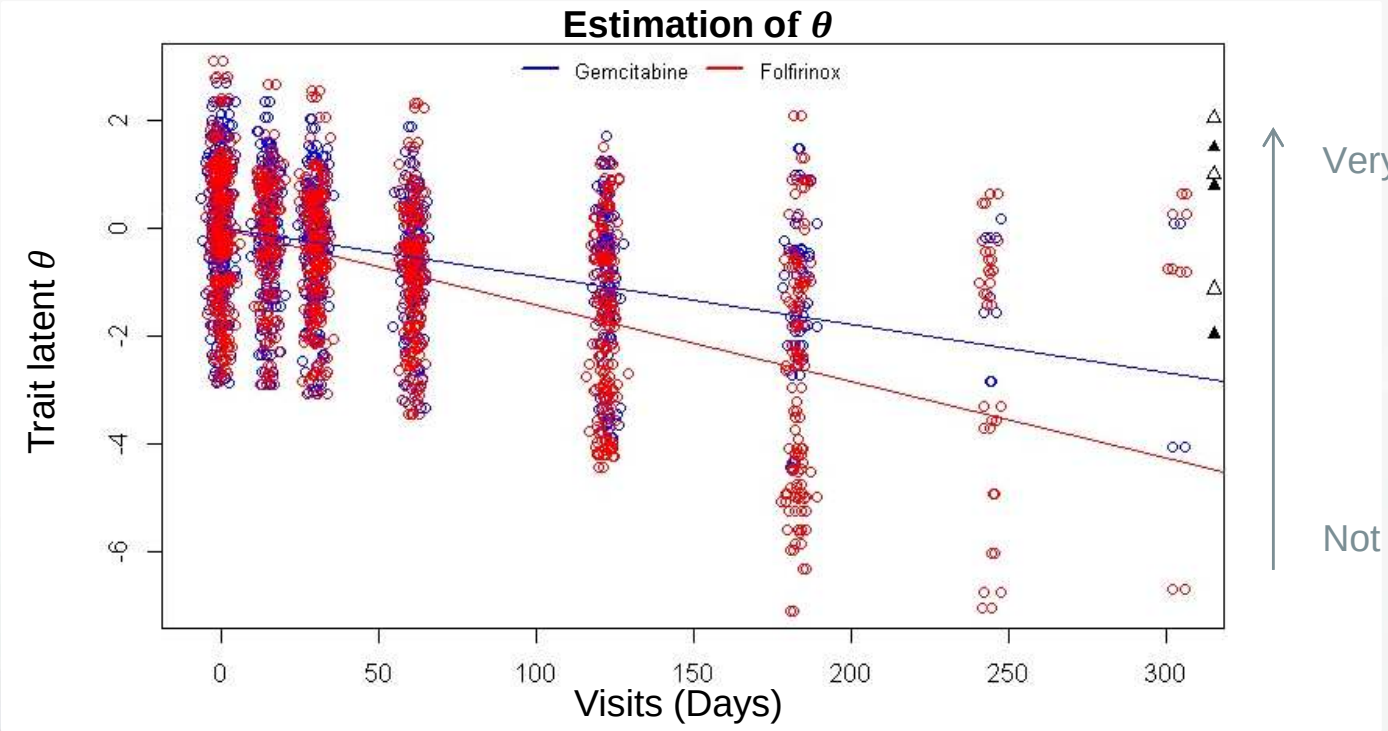
- No difference at baseline
- Their changing perception is the same for both groups
  - ✓ Trend to increase (no significant)

SYMPTOM SCALE RESULTS

	CTT			IRT		
	Coefficient	*SD*	*P*	*Coefficient*	*SD*	*P*
Fatigue						
β_2	-0.05024	0.01826	0.0064	-0.00253	0.002347	0.2828
β_3	0.003829	0.02174	0.8603	-0.00094	0.002996	0.7530
Nausea/vomiting						
β_2	-0.02966	0.01430	0.0390	-0.00146	0.001519	0.3366
β_3	-0.00458	0.01595	0.7740	-0.00196	0.001790	0.2731
Pain						
β_2	-0.08263	0.01808	<.0001	-0.00889	0.002060	<.0001
β_3	-0.03638	0.02013	0.0712	-0.00527	0.002465	0.0333
Dyspnea						
β_2	-0.01295	0.01641	0.4306	-0.00132	0.002224	0.5522
β_3	-0.02354	0.01910	0.2182	-0.00386	0.002686	0.1512
Insomnia						
β_2	-0.1103	0.01929	<.0001	-0.01029	0.002256	<.0001
β_3	0.008089	0.02142	0.7059	0.001058	0.002280	0.6429
Loss of appetite						
β_2	-0.1289	0.02154	<.0001	-0.007984	0.0017115	<.0001
β_3	-0.01491	0.02413	0.5369	-0.0010665	0.001873	0.5695
Constipation						
β_2	-0.1124	0.01899	<.0001	-0.00839	0.001901	<.0001
β_3	0.01075	0.02045	0.5994	-0.00006	0.002025	0.9770
Diarrhea						
β_1	9.0733	2.5793	0.0005	0.5167	0.1749	0.0034
β_2	0.01435	0.01853	0.4393	.000077	0.001771	0.9652
β_3	-0.02726	0.02278	0.2318	-0.000341	0.001833	0.8525
Financial difficulties						
β_2	-0.00454	0.01252	0.7169	-0.011488	0.0074434	0.1237
β_3	0.02610	0.01553	0.0933	0.009319	0.0055039	0.0914

RESULT ILLUSTRATION WITH IRT APPROACH

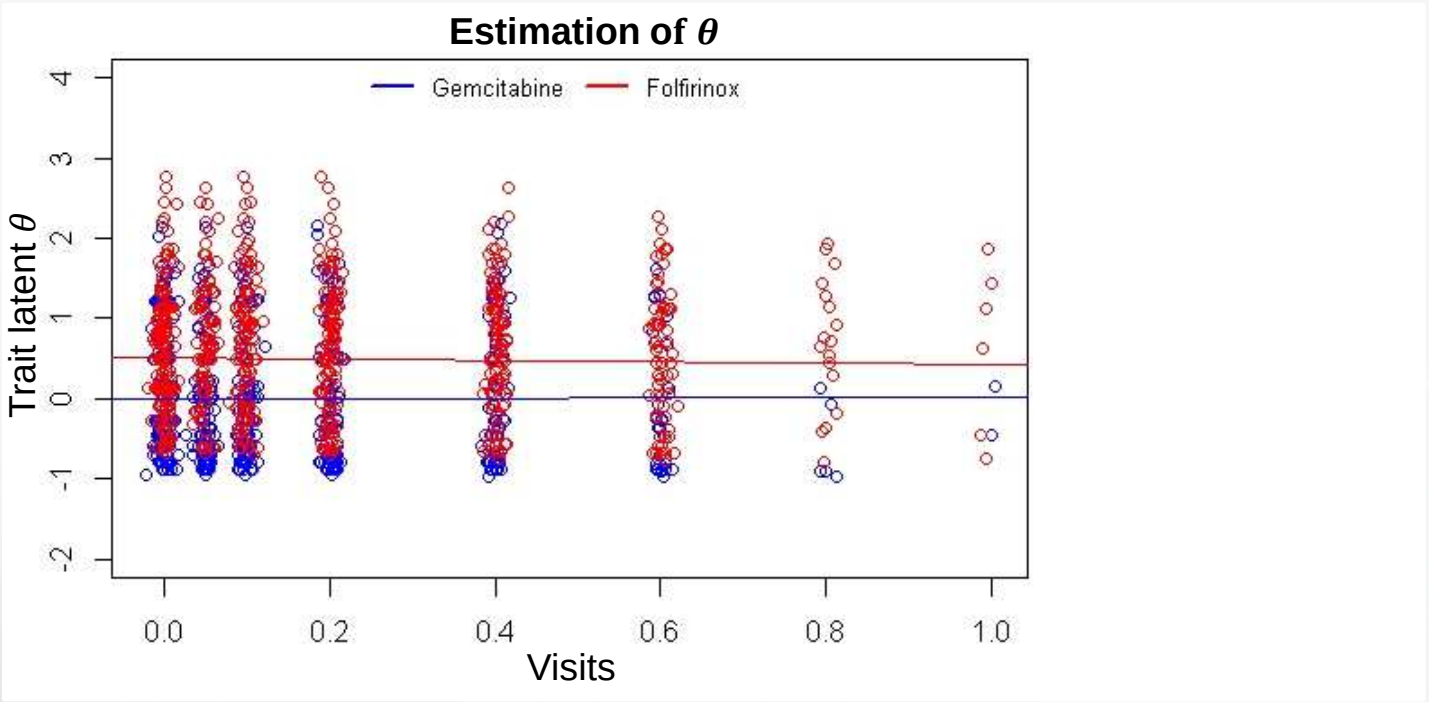
- Pain symptom
  - ✓ Trend of QoL perception



- No different effect at baseline
- Pain perception diminishes significantly over time for both groups
  - ✓ Experimental group slope is significantly more important than the other group

RESULT ILLUSTRATION WITH IRT APPROACH

- Diarrhea Symptom
  - ✓ Trend of QoL perception



- Different effect following treatment arm
  - ✓ The diarrhea symptom perception is higher in experimental arm
  - ✓ The latent trait didn't vary over time

DETAILED STUDY OF QOL

- Use survival model
  - ✓ Treatment effect

Table 2. Univariate Cox Analysis According to 10-Point and 20-Point MCID to Calculation of TUDD for QLQ-C30 Domain Scores

Domain	10-Point Deterioration					20-Point Deterioration				
	No. of Events					No. of Events				
	FOLFIRINOX (n = 163)	Gemcitabine (n = 157)	HR	95% CI	*P*	FOLFIRINOX (n = 163)	Gemcitabine (n = 157)	HR	95% CI	*P*
Global health status	32	42	2.3	1.4 to 3.7	< .001	13	32	4.7	2.3 to 9.5	< .001
Physical functioning	47	59	1.9	1.3 to 2.8	.001	27	37	2.2	1.3 to 3.6	.001
Role functioning	44	59	2.2	1.5 to 3.4	< .001	27	43	2.7	1.6 to 4.4	< .001
Emotional functioning	18	26	2.9	1.6 to 5.6	< .001	14	14	2.1	1.0 to 4.5	.057
Cognitive functioning	30	49	3.0	1.9 to 4.8	< .001	11	16	2.6	1.2 to 5.6	.015
Social functioning	42	54	2.1	1.4 to 3.1	< .001	23	40	2.7	1.6 to 4.7	< .001
Fatigue	52	62	1.9	1.3 to 2.7	.001	36	49	2.4	1.5 to 3.8	< .001
Nausea/vomiting	40	53	2.1	1.4 to 3.2	< .001	19	30	2.8	1.5 to 5.0	< .001
Pain	27	36	2.7	1.6 to 4.6	< .001	12	22	3.7	1.7 to 7.7	< .001
Dyspnea	32	38	2.3	1.4 to 3.8	< .001	32	38	2.3	1.4 to 3.8	< .001
Insomnia	20	15	1.4	0.7 to 2.9	.300	20	15	1.4	0.7 to 2.9	.300
Loss of appetite	24	28	1.9	1.1 to 3.4	.022	24	28	1.9	1.1 to 3.4	.022
Constipation	18	21	2.0	1.0 to 3.8	.033	18	21	2.0	1.0 to 3.8	.033
Diarrhea	37	32	1.5	0.9 to 2.5	.086	37	32	1.5	0.9 to 2.5	.086
Financial difficulties	22	8	0.6	0.2 to 1.4	.214	22	8	0.6	0.2 to 1.4	.214

NOTE. For global health status and functional scales, a high score indicates a better function. For symptoms and financial difficulties, a high score indicates more symptoms or more difficulties.

Abbreviations: FOLFIRINOX, oxaliplatin/irinotecan/fluorouracil/leucovorin; HR, hazard ratio; MCID, minimal clinically important difference; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; TUDD, time until definitive deterioration.

CONCLUSIONS

ACCORD 11

- ✓ Same impact of both treatments on the QoL
  - Exception: pain symptom
  - Difference at baseline: Diarrhea symptom
- ✓ The QoL perception varies over time for several scales
  - Treatment effect
  - Disease effect
  - Response Shift
- ✓ Model mixed results are similar
- ✓ Difference between mixed models and survival models
  - Not same interpretation
  - Complementary methods

CONCLUSIONS

- Methodology view (IRT)

  - ✓ Advantages
    - Adapt to data (repeated measures, multiple response, ordinal data)
    - Assess different factors (explanatory variables)
    - Interpretation for several level (scale, item and categories)

  - ✓ Drawbacks
    - Model implementation
    - Little used in oncology

PERSPECTIVES

- Model Behavior relative to random effects
  - ✓ Simulation with SAS
    - Model choice through BIC, AIC
    - Problem in the results
    - LPCM detects a random effect when there is none
  - ✓ Alternative approach: Schall Linearization (1991)
    - Estimate a GLMM
    - Consider a pseudo linear model
- Study other model
  - ✓ Cumulative model (GLMM)
    - Adapt the graded Response Model to data (IRT)
- Take into account missing data (EM)

De Boeck, P. & Wilson, M (2003). *Explanatory Item Response Models, A generalized linear and nonlinear Approach*. Springer.

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Anderson, J. A. (1984). *Regression and Ordered Categorical Variables.* Journal of the Royal Statistical Society. Vol. 46, No. 1(1984), pp. 1-30