

MooveCare: a web-mediated follow-up based on weekly self-reported symptoms.

From chaos theory to clinical practices

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A simple model of tumor growth

Interactions between cell populations in a single tumor site

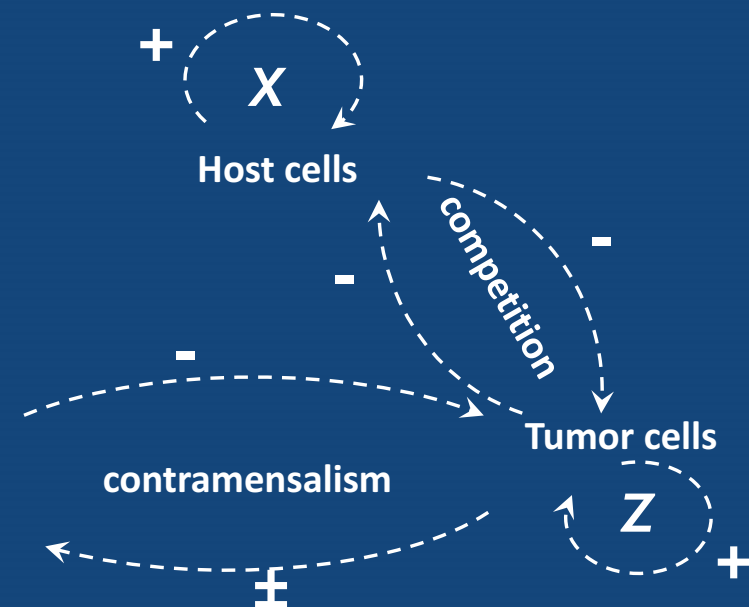
$$\begin{cases} \dot{x} = \rho_1 x(1 - x) - \alpha_{13} xz \\ \dot{y} = \frac{\rho_2 yz}{1 + z} - \alpha_{23} yz - \delta_2 y \\ \dot{z} = z(1 - z) - xz - \alpha_{32} yz \end{cases}$$

Journal of Theoretical Medicine, Vol. 3, pp. 79-100
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A Mathematical Tumor Model with Immune Resistance and Drug Therapy: an Optimal Control Approach

L.G. DE PILLIS^{a,*} and A. RADUNSKAYA^{b,†}



OIKOS 77:2 (1996)

371

Contramensal interactions between species

Simon Hodge and Wallace Arthur, *The Ecology Centre, Univ. of Sunderland, Sunderland, UK SR1 3SD.*

PRESENTED AT: Mathematical Perspectives in the
Biology and Therapeutics of Cancer

PRESENTED BY: Clément Draghi

Do we have a full observability if we measure a single variable?

Original state space

(Rössler system)

$$\begin{cases} \dot{x} = -y - z \\ \dot{y} = x + ay \\ \dot{z} = -b + z(x - c) \end{cases}$$

Coordinate transformation

$$\Phi_y = \begin{cases} X = y \\ Y = \dot{y} = x + ay \\ Z = \ddot{y} = ax + (a^2 - 1)y - z \end{cases}$$

Reconstructed space

$$\begin{cases} \dot{X} = Y \\ \dot{Y} = Z \\ \dot{Z} = F(X, Y, Z) \end{cases}$$

Diffeomorphism if $\text{Det } J_{\Phi} \neq 0$

$$\text{Det } J_{\Phi_y} = \text{Det} \begin{bmatrix} 0 & 1 & 0 \\ 1 & a & 0 \\ a & a^2 - 1 & -1 \end{bmatrix}$$

True when the Rössler system is observed from variable $y(t)$

➤ The system is **fully observable**

Observability from different variables

PHYSICAL REVIEW E 71, 066213 (2005)

Relation between observability and differential embeddings for nonlinear dynamical systems

Christophe Letellier,¹ Luis A. Aguirre,² and Jean Maquet¹

J. Phys. A: Math. Gen. 31 (1998) 7913–7927. Printed in the UK

PII: S0305-4470(98)93312-1

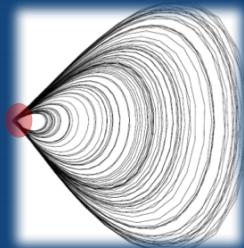
On the non-equivalence of observables in phase-space reconstructions from recorded time series

C Letellier^{†§}, J Maquet[†], L Le Sceller[†], G Gouesbet[†] and L A Aguirre[‡]

PHYSICAL REVIEW E 79, 066210 (2009)

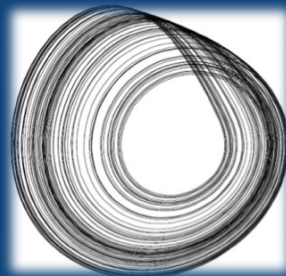
Symbolic observability coefficients for univariate and multivariate analysis

Christophe Letellier¹ and Luis A. Aguirre²

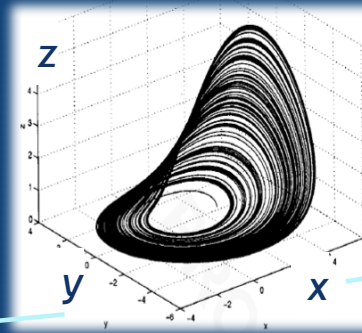


$\eta_z = 0.44$

$\text{Det } J_\Phi = 0 \text{ when } z^2 = 0$

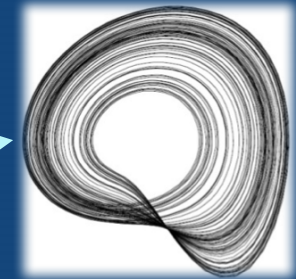


$\eta_y = 1.0$



Original state space

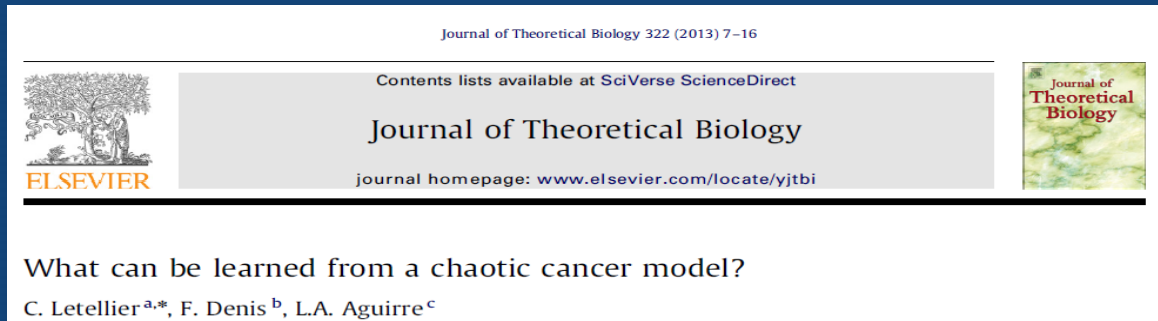
$\eta_x = 0.88$



$\text{Det } J_\Phi = 0 \text{ when } x = a + c$

➤ These conditions define the **singular observability manifold**

Observability coefficients computed for the cancer model



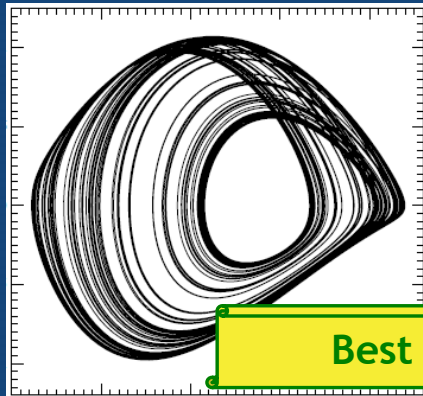
$$\eta_{x^3} = 0.56$$

>

$$\eta_{z^3} = 0.36$$

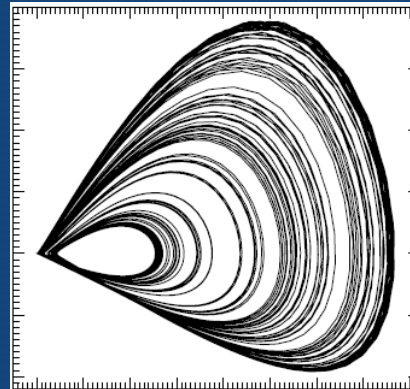
>

$$\eta_{y^3} = 0.30$$

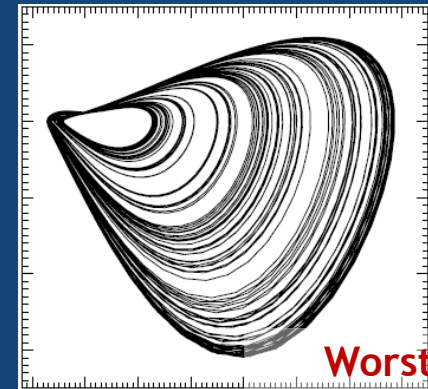


Best

Host cells



Tumor cells



Worst !

Active Immune cells

It should be more efficient to track the tumor environment rather than the tumor itself

Application to Lung cancer

- Lung cancer: more than one million deaths/year worldwide
- Two types of cancer: Non small cells lung cancer (NSCLC) 80% / small cells lung cancer (SCLC)
- 5 Stages (stage 0 = noninvasive tumor)



Stage 1: tumor < 3 cm
no metastasis



Stage 2: tumor < 6 cm
Isolated metastasis in the lung



Stage 3: tumor > 6 cm
Metastases in the lymph nodes



Stage 4: Tumor invades
other organs

Application to Lung cancer

- Treatments: surgery, radiation therapy, tyrosine kinase inhibitor (TKI), immunotherapy...
- Commonly, the follow-up is based on CT scan every 3-6 months depending on the stage
- Relapsing patients often wait many weeks before a visit during which symptoms are detected**
- 75%-90% of lung cancer relapses are symptomatic*

* GL Walsh et al. *Ann Thorac Surg* 1990

** F Denis et al *Support Care Cancer* 2014

*** F Denis et al *JNCI* 2017

**** E Basch *JAMA* 2017

Self-reported symptoms using a weekly questionnaire filled at home

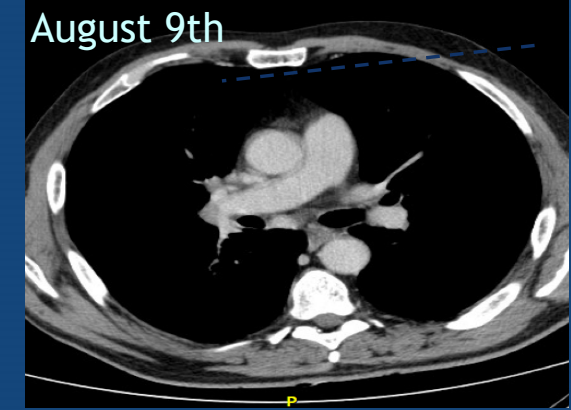
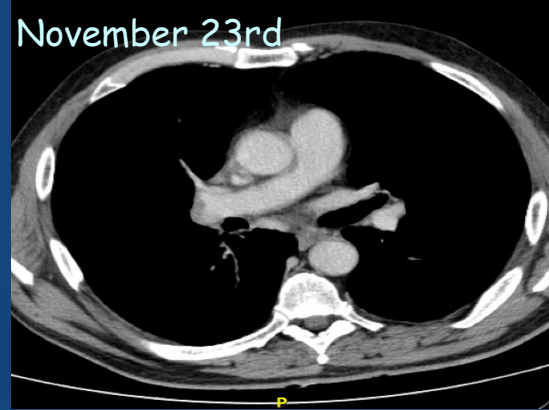
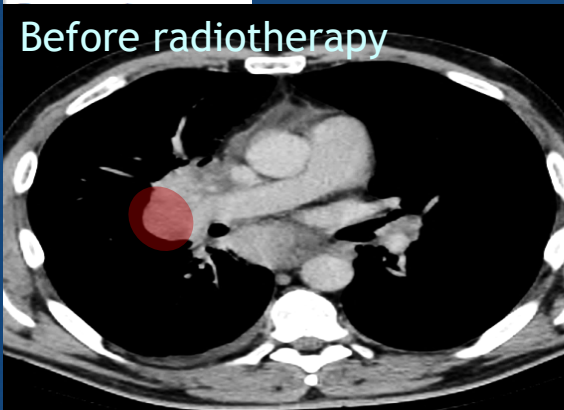
Man, 63 years

Smoker, 90 kg, No physical activity

Treated by Radiotherapy
probability of relapse = 75%

➤ Patient **without relapse**

jj/mm	23/11	30/11	07/12	15/12	21/12	28/12	04/01	11/01	18/01	25/01	02/02	08/02	15/02	22/02	01/03	08/03	15/03	22/03	29/03	05/04	12/04	19/04	26/04	03/05	10/05	17/05	24/05	31/05	07/06	14/06	21/06	28/06	05/07	13/07	19/07	26/07	02/08	09/08	
aa	12	12	12	12	12	12	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Weight	89	89.5	90	91	91	92	92	91.5	91.5	91.5	91.5	91.5	91.5	91.5	92	92	92	93	93.5	93.5	94	95	95	95.5	96	95	95	95.5	95	95	95	96.5	97	97	96	96	97	95	
Weight variation	0	-0.5	-1	-2	-2	-3	-3	-2.5	-2.5	-2.5	-2.5	-2.5	-2.5	-2	-2	-1	-1	-1	-1.5	-2	-2.5	-3.5	-3.5	-4	-4.5	-3.5	-3	-3.5	-3	-2	-1.5	-3	-3	-2	-1	-0.5	-1	0	
Appetite loss	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Weakness	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pain	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Cough	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Breathlessness	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0



Self-reported symptoms using a weekly questionnaire filled at home

Man, 65 years

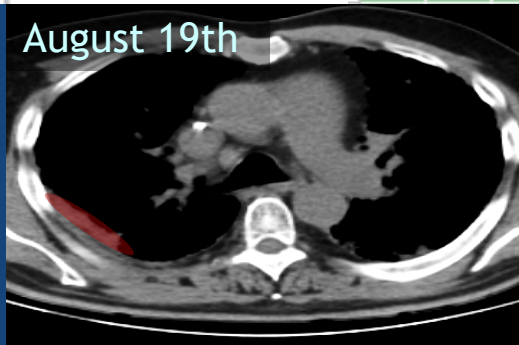
Smoker, 86 kg, No physical activity

Treated by chemotherapy
probability of relapse = 75%

➤ Patient **with relapse**

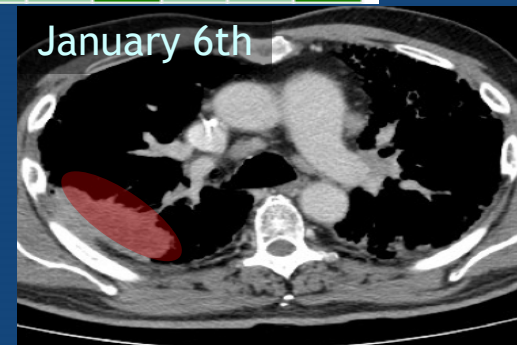
jj/mm	19/08	26/08	02/09	09/09	19/09	23/09	30/09	07/10	14/10	21/10	28/10	04/11	11/11	18/11	25/11	16/12	23/12	30/12	06/01
aa	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	1	3	3	14
Weight	86	86.9	87.2	86.9	87.2	87.4	87.8	87.5	87.9	88.1	88.1	87.7	87.5	88.3	87.5	86	86	86	86
Weight variation	0	-0.9	-1.2	-0.9	-1.2	-1.4	-1.8	-1.5	-1.9	-2.1	-2.1	-1.7	-1.5	-1.4	-0.3	0.7	0.6	0.6	1.8
Appetite loss	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Weakness	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2
Pain	0	1	1	0	0	1	1	0	0	1	0	1	0	0	2	3	3	3	3
Cough	0	0	0	0	0	0	0	1	1	1	1	1	0	1	1	1	1	1	0
Breathlessness	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Depression	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1

August 19th



2 months before routine imaging

January 6th

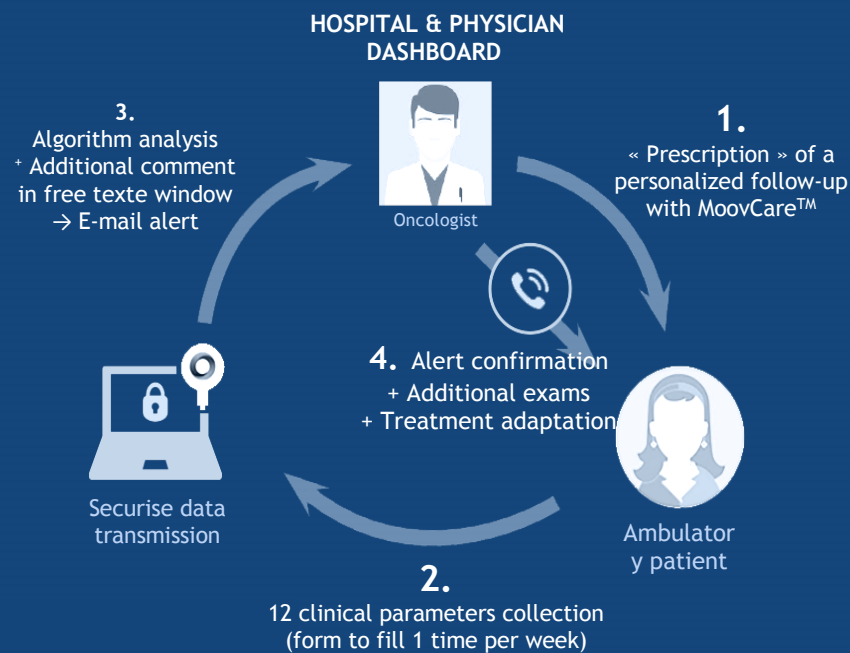


Web-Mediated Follow-Up by Moovcare™

- Patient (or relative) WEEKLY reports 12 symptoms
- Prospectively assessed in 3 trials
- Relapse and dangerous medical conditions suggested
- Notifications sent to nurse/oncologist → phone call
- Early visit +/- imaging

F Denis et al Support Care Cancer 2013
F Denis et al Support Care Cancer 2014
F Denis et al JNCI 2017

Operating principles of MoovCare™



Weight	
85	kg
Appetite	
<input checked="" type="radio"/> No problem	<input type="radio"/> Slight problem
<input type="radio"/> Average problem	<input type="radio"/> Heavy problem
Weakness feeling	
<input checked="" type="radio"/> No problem	<input type="radio"/> Slight problem
<input type="radio"/> Average problem	<input type="radio"/> Heavy problem
Pain	
<input checked="" type="radio"/> No problem	<input type="radio"/> Slight problem
<input type="radio"/> Average problem	<input type="radio"/> Heavy problem
Cough	
<input type="radio"/> No problem	<input type="radio"/> Slight problem
<input type="radio"/> Average problem	<input checked="" type="radio"/> Heavy problem
Breathlessness	
<input type="radio"/> No problem	<input type="radio"/> Slight problem
<input type="radio"/> Average problem	<input checked="" type="radio"/> Heavy problem
Depression	
<input type="radio"/> No problem	<input checked="" type="radio"/> Slight problem
<input type="radio"/> Average problem	<input type="radio"/> Heavy problem

MooveCare versus a routine follow-up (Phase I)

➤ Confusion matrix

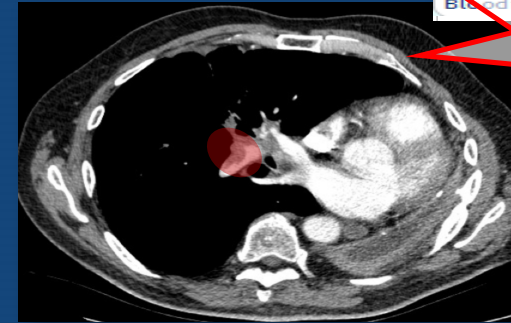
	relapse	Without relapse
MoovCare positive	13	3
MoovCare negative	0	25

Other pathology

[illegible]

jijlmm	24/03	30/03	07/04	13/04	22/04
aa	15	15	15	15	15
POIDS	92	92	92	90	88
DELTA POIDS	0	0	0	0	0
Weight	0	0	0	0	0
Weight variation	0	0	0	2	2
Appetite/loss	0	0	2	2	0
Weakness	0	0	0	0	0
Pain	0	0	0	0	0
Cough	2	0	2	3	0
Breathlessness	0	0	0	0	0
Depression	0	0	0	0	0
Fever	0	0	0	0	0
Facet swelling	0	0	0	0	0
Lump under skin	0	0	0	0	0
Wound/bruising	0	0	0	0	0
Bleed in spots	0	0	0	0	0

Pulmonary embolism



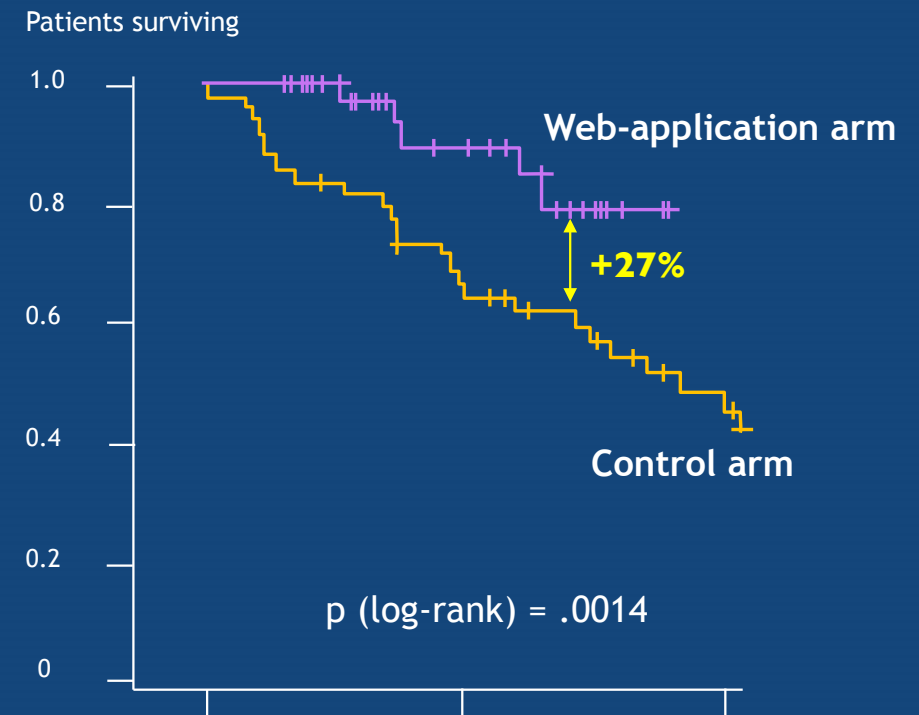
- | | | |
|---------------|------|-----|
| ➤ Sensitivity | 100% | 85% |
| ➤ Specificity | 89% | 96% |

- detection of cancer relapse anticipated by 5 weeks compared to routine imaging ...
- **Moovecare has a reliability equivalent to the one of a routine follow-up!**

Phase II trial

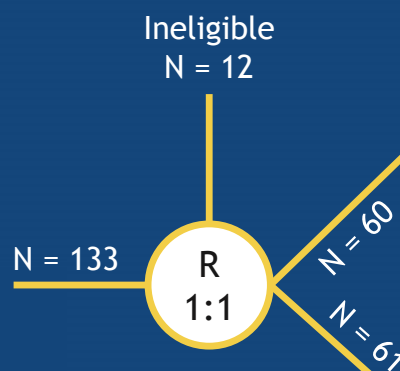
- Non-randomized mono-centric study
- 98 Patients (Stage III/IV Lung cancer)
- **+ 27% one-year survival improvement***

* F Denis, Am JCO 2015



Phase III Multi-Centric Randomized Study

- Non-progressive Stage II (only N+) - IV
- SCLC and NSCLC
- Internet access
- PS 0-2 and symptomatic score < 7
- TKI or maintenance therapy allowed
- Planned visit similar in both arms
- Reduction of scheduled imaging



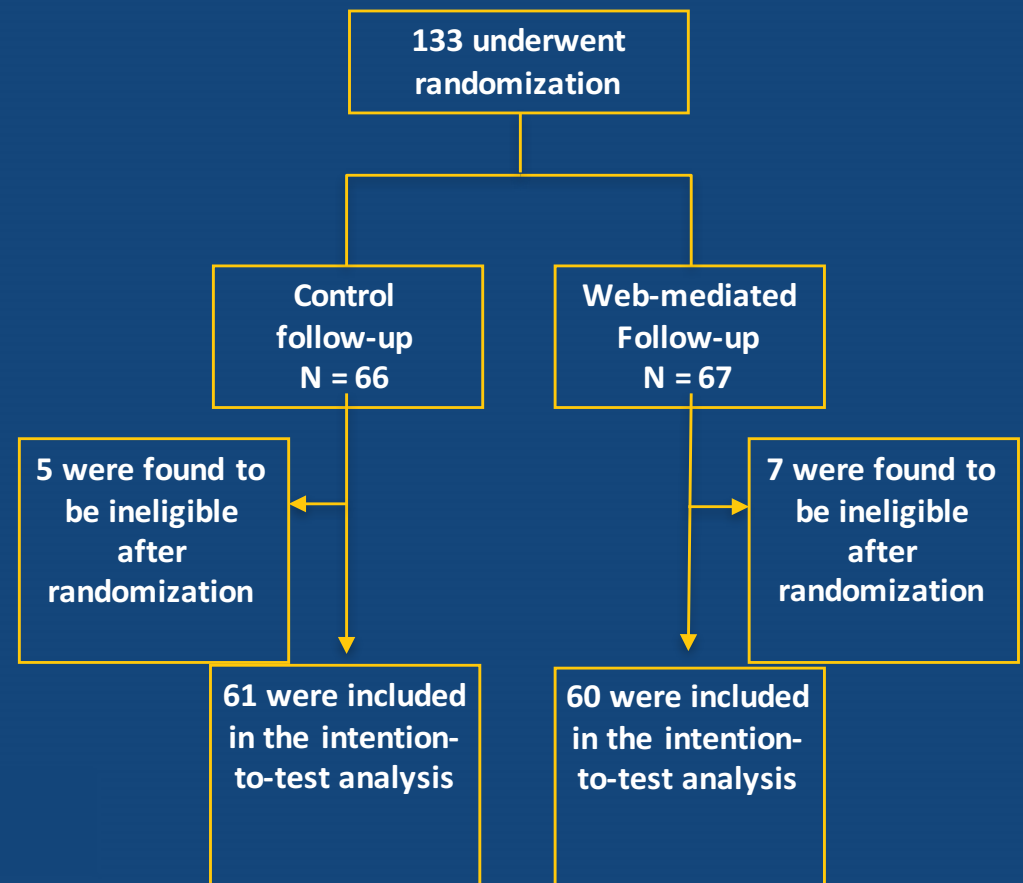
PRIMARY OUTCOME: OVERALL SURVIVAL

	Stage	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	21 mo	24 mo
Webapp arm	II-III A		CT		CT				CT
	IIIB-IV				CT				CT

	Stage	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	21 mo	24 mo
Control arm	II-III A		CT		CT		CT		CT
	IIIB-IV	CT	CT	CT	CT	CT	CT	CT	CT

Consort Diagram

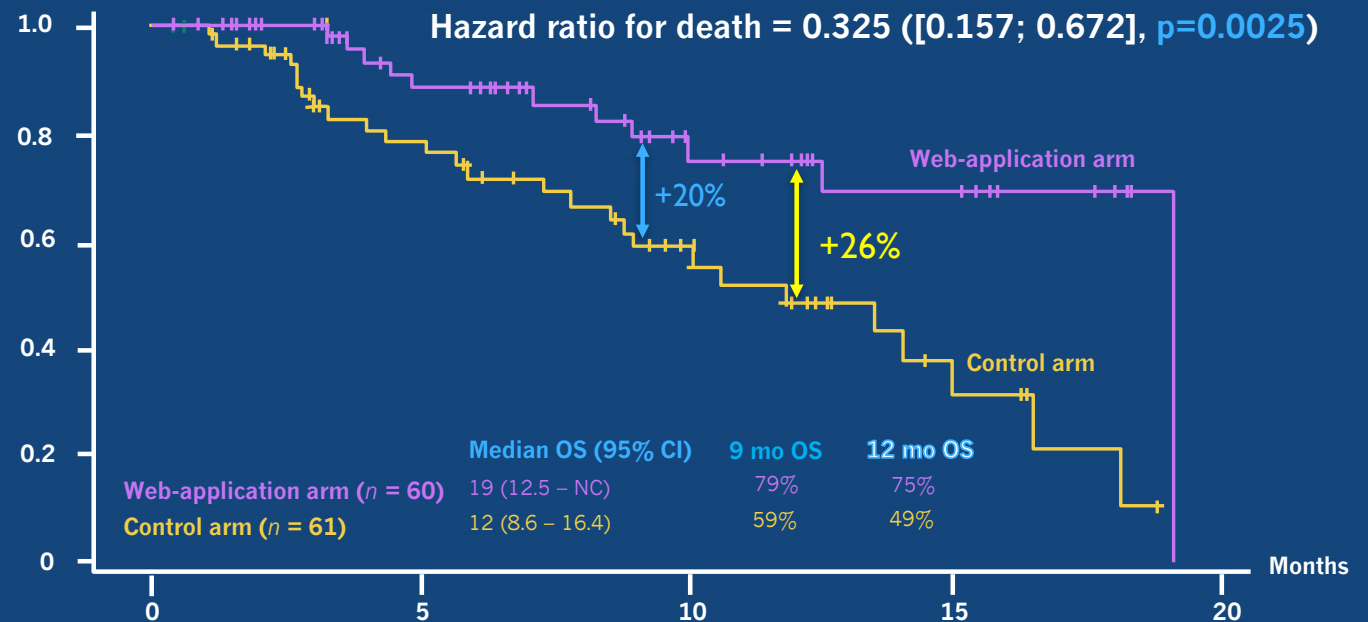
- Ineligibility after randomization (12)
 - No internet access
 - No proven lung cancer
 - Progressive disease at randomization
 - Non-authorized maintenance treatment
- Comparable groups
 - Median age 65 yrs
 - 33% stage III, 63% stage IV
 - 41% maintenance/TKI
 - 17% SCLC



Planned Interim Analysis (1/2016)

Primary endpoint: Overall Survival

- 133 randomized patients
- 9 months follow-up
- **+7 months median OS**
- Inclusions stopped by IDMC
- Switch of eligible patients
- Kept in control arm for ITT analysis



F Denis et al. JNCI 2017

Performance Status at Relapse

PS 0-1

77% of patients (Web-app arm) vs 33% (Control arm): $p < 0.001$

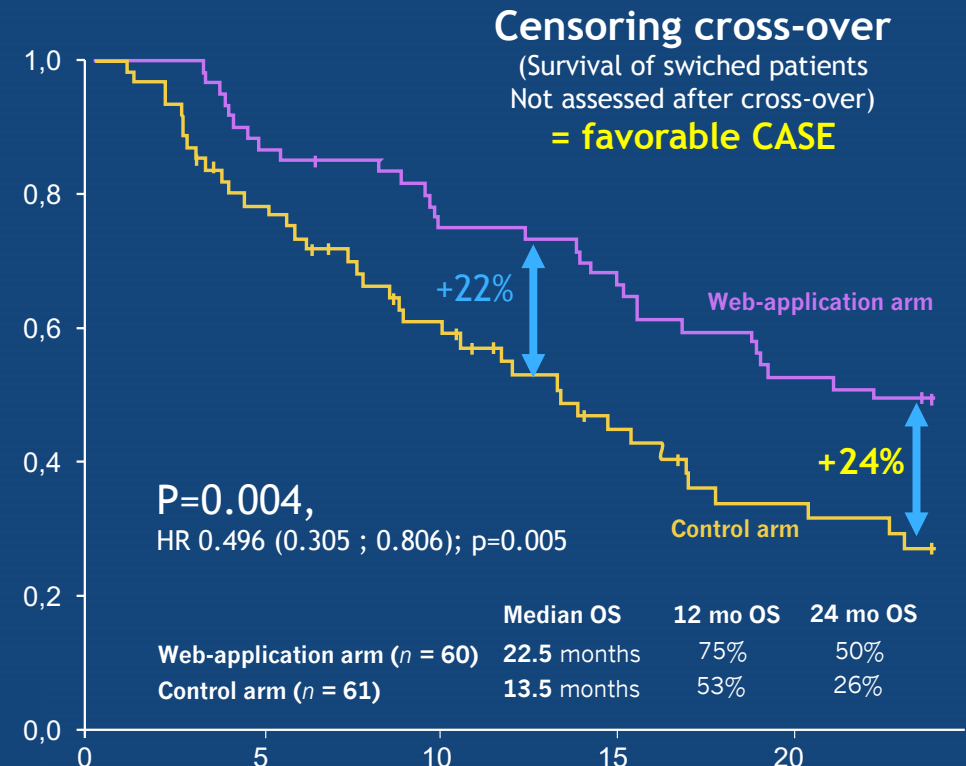
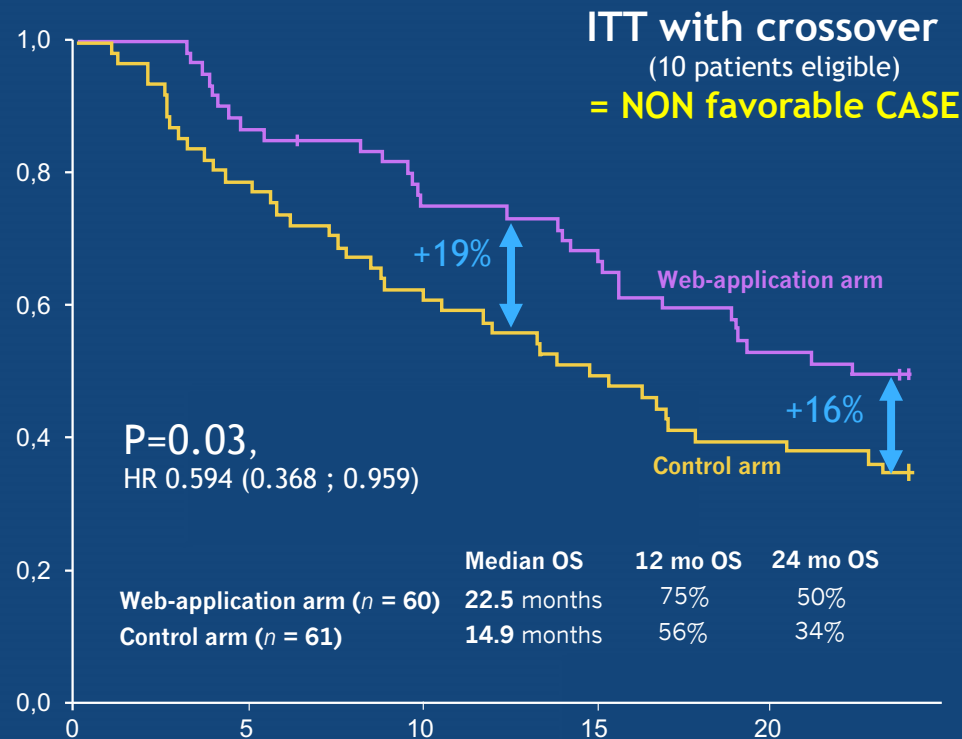


Treatment of Relapse

74% « Optimal » (Web-app arm) vs 33% (Control arm): $p < 0.001$

Earlier and increased supportive care → improved QUALITY OF LIFE

Final OS analysis (2-years follow-up)



Incremental Cost-Effectiveness Ratio (ICER)

	Survival benefit	Assessed cost	ICER
CT-scan for Lung Cancer	4 weeks	265,000 \$	66,250 \$
CT-scan for Lymphoma	2 weeks	800,000 \$	400,000 \$
PET for cervical Cancer	1 weeks	1,000,000 \$	1,000,000 \$
Nivolumab for Lung Cancer	14 weeks	184,000 \$	13,143 \$
Moovcare™	32 weeks	< 30,000 \$	< 940 \$

Van Loon et al, Eur J C 2010

Huntington et al, JCO 2015

Auguste P al, BJOG 2014

Matter-Walstra, JTO 2016

Conclusion

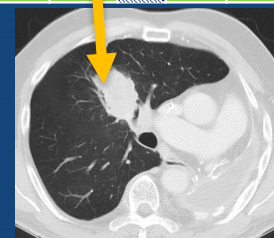
- First study with overall median survival benefit (+7.6 to 9.0-month)
- Moovcare™ assessed prospectively in > 300 patients (and PRO in > 1200 pts)
- First real personalized follow-up in lung cancer... soon available for pilot sites
- Larger multicentric international studies to be initiated in other cancers (>1000 patients)
- Other application coming soon: cancer screening in smokers (Smokecheck™)

Moovecare can also be used for better assessing tumor response to treatment

>1-year immunotherapy duration... and so on

JJ/MM	04/04	10/04	18/04	24/04	09/05	16/05	22/05	29/05	06/06	12/06	27/06	04/07	10/07	24/07		19/02	26/02	05/03	11/03	19/03	02/04
aa	17	17	17	17	17	17	17	17	17	17	17	17	17	17		18	18	18	18	18	18
Weight	93.3	93	93.3	93	93	93	93	92.5	92.3	92.3	91.3	91.3	92.5	92.3		91	91	91	91	90.5	90.5
Weight variation	-0.3	0.3	0	0.5	1	0.5	0.5	1	1.2	1	2	2	0.8	0.7		0	0	0	0	0.5	0.5
Appetite loss	1	2	2	2	2	2	2	1	1	2	2	2	2	2		1	1	1	1	1	1
Weakness	1	2	1	1	2	3	2	1	1	1	1	1	1	1		1	1	1	2	1	1
Pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0
Cough	0	0	0	0	0	0	0	0	0	0	0	0	0	0							
Breathlessness	1	1	2	2	2	2	0	1	1	1	1	1	1	1		0	0	0	0	0	0
Depression	3	0	0	0	0	0	0	0	0	0	0	0	0	0		2	2	2	2	2	2
Fiever	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0
Face swelling	0	0	0	0	0	0	0	0	0	0	0	1	0	0		0	0	0	0	0	0
Lump under skin	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0
Voice changing	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0
Blood in sputum	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0

4/2017
Nivolumab
initiated



6/2018
Nivolumab
ongoing

Acknowledgements

Many thanks to all patients who participated in our study

Co-Investigators (France)

Claire Lethrosne, MD, Nicolas Poure, MD, Olivier Molinier, MD, Yoann Pointreau, MD, Julien Domont, MD, Hugues Bourgeois, MD, Hélène Senellart, MD, Pierre Trémolières, MD, Thibaut Lizée, MD, Jaafar Bennouna, MD, Prof, Thierry Urban, MD, Prof, Claude El Khouri, MD, Alexandre Charron, MD, Anne-Lise Septans, PhD, Magali Balavoine, MSc, Sébastien Landry, MSc, Philippe Solal-Céligny, MD and Christophe Letellier, PhD, Prof

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Weprom, Angers, France

My institution

ILC Jean Bernard, Le Mans, France

Sponsor

SIVAN Innovation Ltd.

US Scientific support

Ethan Basch MD, FASCO, BA (Chapell Hill, NC), Amylou Dueck, PhD (Mayo Clinic), Bridget Koontz, MD (Duke University)

Institutional supports

Société Française de Radiothérapie Oncologique (SFRO),
Syndicat National des Radiothérapeutes Oncologues (SNRO),
Conseil National de l'Ordre de Médecins (CNOM)

Follow-up and Patient-Reported Outcomes...

- 75%-90% of lung cancer relapse are symptomatic*
- Relapsing patient often wait many weeks before visit with symptoms**
- Patients and caregivers are « connected »
- Relapses may be detected 5-weeks earlier at first symptoms**
- Patient-reported outcomes may improve survival*** /****

* GL Walsh et al. *Ann Thorac Surg* 1990

** F Denis et al *Support Care Cancer* 2014

*** F Denis et al *JNCI* 2017

**** E Basch *JAMA* 2017

Predefined subgroups analysis

