NEW DRUGS & TRIALS ON THE HORIZON

The AURORA initiative for advanced breast cancer

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ULB Institut Jules Bordet réseau iris structuur Instituut

BIG Breast International Group

Disclosures

- Board member: PharmaMar
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- Research grants to my Institute: most companies
- Speakers bureau/stock ownership: none

Evaluation of targeted therapies in advanced B.C.

Plan of the talk

- Current knowledge of the landscape of genomic alterations in B.C. and the « clonal evolution » of the disease

- The « AURORA » program : a first initiative aimed at scaling-up the number of metastatic breast cancer patients screened across Europe

- « Omics-based » trial designs: challenges and possible solutions

I.
Current knowledge of the landscape of genomic alterations in B.C. and the « clonal evolution » of the disease

2012 Nature Year of NGS in BC

LETTER

doi:10.1038/nature11154

Sequence analysis of mutations and translocations across breast cancer subtypes

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ARTICLE

doi:10.1038/nature11143

Whole-genome analysis informs breast cancer response to aromatase inhibition

Matthew J. Ellis[1,2,3]*, Li Ding[4,5]*, Dong Shen[4,5]*, Jingqin Luo[3,6], Vera J. Suman[7], John W. Wallis[4,5], Brian A. Van Tine[1], Jeremy Hoog[1], Reece J. Goiffon[8,9,10], Theodore C. Goldstein[11], Sam Ng[11], Li Lin[1], Robert Crowder[1], Jacqueline Snider[1], Karla Ballman[7], Jason Weber[1,8,12], Ken Chen[13], Daniel C. Koboldt[4,5], Cyriac Kandoth[4,5], William S. Schierding[4,5], Joshua F. McMichael[4,5], Christopher A. Miller[4,5], Charles Lu[4,5], Christopher C. Harris[4,5], Michael D. McLellan[4,5], Michael C. Wendl[4,5], Katherine DeSchryver[1], D. Craig Allred[3,14], Laura Esserman[15], Gary Unzeitig[16], Julie Margenthaler[2], G. V. Babiera[13], P. Kelly Marcom[17], J. M. Guenther[18], Marilyn Leitch[19], Kelly Hunt[13], John Olson[17], Yu Tao[6], Christopher A. Maher[1,4], Lucinda L. Fulton[4,5], Robert S. Fulton[4,5], Michelle Harrison[4,5], Ben Oberkfell[4,5], Feiyu Du[4,5], Ryan Demeter[4,5], Tammi L. Vickery[4,5], Adnan Elhammali[8,9,10], Helen Piwnica-Worms[8,12,20,21], Sandra McDonald[2,22], Mark Watson[6,14,22], David J. Dooling[4,5], David Ota[23], Li-Wei Chang[3,14], Ron Bose[2,3], Timothy J. Ley[1,2,4], David Piwnica-Worms[8,9,10,12,24], Joshua M. Stuart[11], Richard K. Wilson[2,4,5] & Elaine R. Mardis[2,4,5]

LETTER

doi:10.1038/nature10933

The clonal and mutational evolution spectrum of primary triple-negative breast cancers

Sohrab P. Shah[1,2], Andrew Roth[1,2]*, Rodrigo Goya[3]*, Arusha Oloumi[1,2]*, Gavin Ha[1,2]*, Yongjun Zhao[3]*, Gulisa Turashvili[1,2]*, Jiarui Ding[1,2]*, Kane Tse[3]*, Gholamreza Haffari[1,2]*, Ali Bashashati[1,2]*, Leah M. Prentice[1,2], Jaswinder Khattra[1,2], Angela Burleigh[1,2], Damian Yap[1,2], Virginie Bernard[4], Andrew McPherson[1,2], Karey Shumansky[1,2], Anamaria Crisan[1,2], Ryan Giuliany[1,2], Alireza Heravi-Moussavi[1,2], Jamie Rosner[1,2], Daniel Lai[1,2], Inanc Birol[3], Richard Varhol[3], Angela Tam[3], Noreen Dhalla[3], Thomas Zeng[3], Kevin Ma[3], Simon K. Chan[3], Malachi Griffith[3], Annie Moradian[3], S.-W. Grace Cheng[3], Gregg B. Morin[3,5], Peter Watson[1,6], Karen Gelmon[6], Stephen Chia[6], Suet-Feung Chin[7,8], Christina Curtis[7,8,9], Oscar M. Rueda[7,8], Paul D. Pharoah[7], Sambasivarao Damaraju[10], John Mackey[10], Kelly Hoon[11], Timothy Harkins[11], Vasisht Tadigotla[11], Mahvash Sigaroudinia[12], Philippe Gascard[12], Thea Tlsty[12], Joseph F. Costello[13], Irmtraud M. Meyer[5,14,15], Connie J. Eaves[16], Wyeth W. Wasserman[4,5], Steven Jones[3,5,17], David Huntsman[1,2,18], Martin Hirst[3,15,19], Carlos Caldas[7,8,20,21], Marco A. Marra[3,5] & Samuel Aparicio[1,2]

LETTER

doi:10.1038/nature11017

The landscape of cancer genes and mutational processes in breast cancer

Philip J. Stephens[1]*, Patrick S. Tarpey[1]*, Helen Davies[1], Peter Van Loo[1,2], Chris Greenman[1,3,4], David C. Wedge[1], Serena Nik-Zainal[1], Sancha Martin[1], Ignacio Varela[1], Graham R. Bignell[1], Lucy R. Yates[1,5,6], Elli Papaemmanuil[1], David Beare[1], Adam Butler[1], Angela Cheverton[1], John Gamble[1], Jonathan Hinton[1], Mingming Jia[1], Alagu Jayakumar[1], David Jones[1], Calli Latimer[1], King Wai Lau[1], Stuart McLaren[1], David J. McBride[1], Andrew Menzies[1], Laura Mudie[1], Keiran Raine[1], Roland Rad[1], Michael Spencer Chapman[1], Jon Teague[1], Douglas Easton[7,8], Anita Langerød[9], OSBREAC†, Ming Ta Michael Lee[10], Chen-Yang Shen[10], Benita Tan Kiat Tee[11], Bernice Wong Huimin[12], Annegien Broeks[13], Ana Cristina Vargas[14], Gulisa Turashvili[15,16], John Martens[17], Aquila Fatima[18], Penelope Miron[18], Suet-Feung Chin[19], Gilles Thomas[20], Sandrine Boyault[20], Odette Mariani[21], Sunil R. Lakhani[14,22,23], Marc van de Vijver[24], Laura van 't Veer[13], John Foekens[17], Christine Desmedt[25], Christos Sotiriou[25], Andrew Tutt[5], Carlos Caldas[19,26], Jorge S. Reis-Filho[27], Samuel A. J. R. Aparicio[15,16], Anne Vincent Salomon[21,28], Anne-Lise Børresen-Dale[9,29], Andrea L. Richardson[18,30], Peter J. Campbell[1,31,32], P. Andrew Futreal[1] & Michael R. Stratton[1]

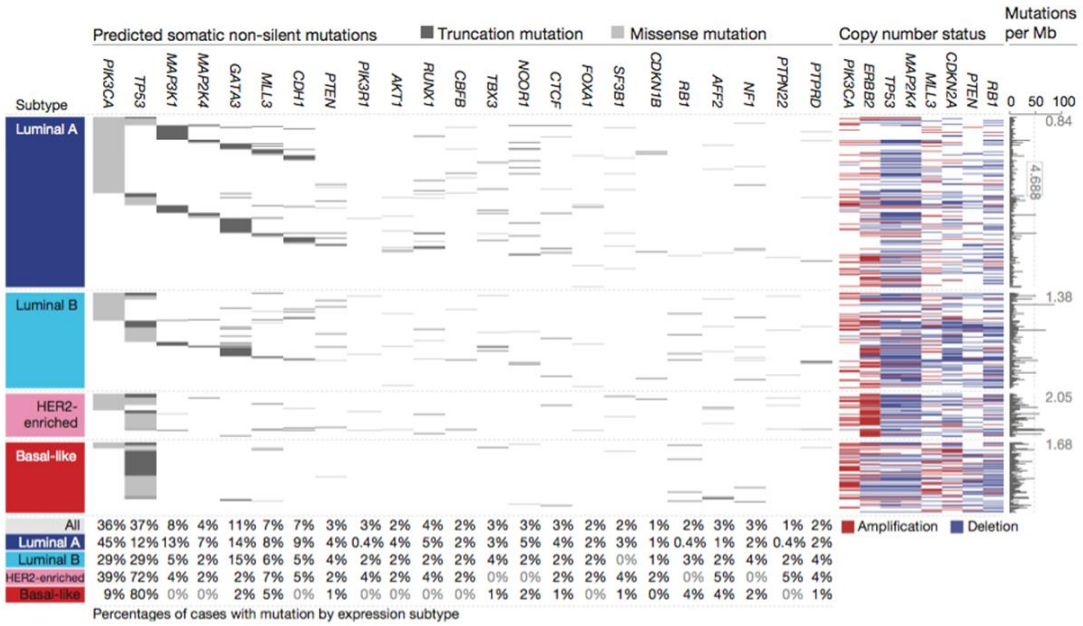
ARTICLE

doi:10.1038/nature11412

Comprehensive molecular portraits of human breast tumours

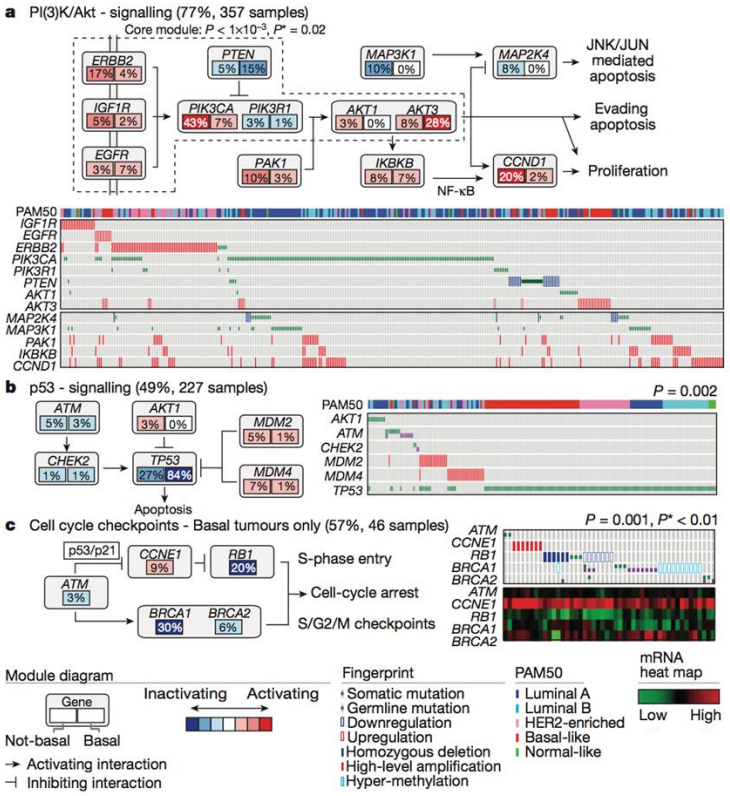
The Cancer Genome Atlas Network*

The landscape of genomic alterations in breast cancer

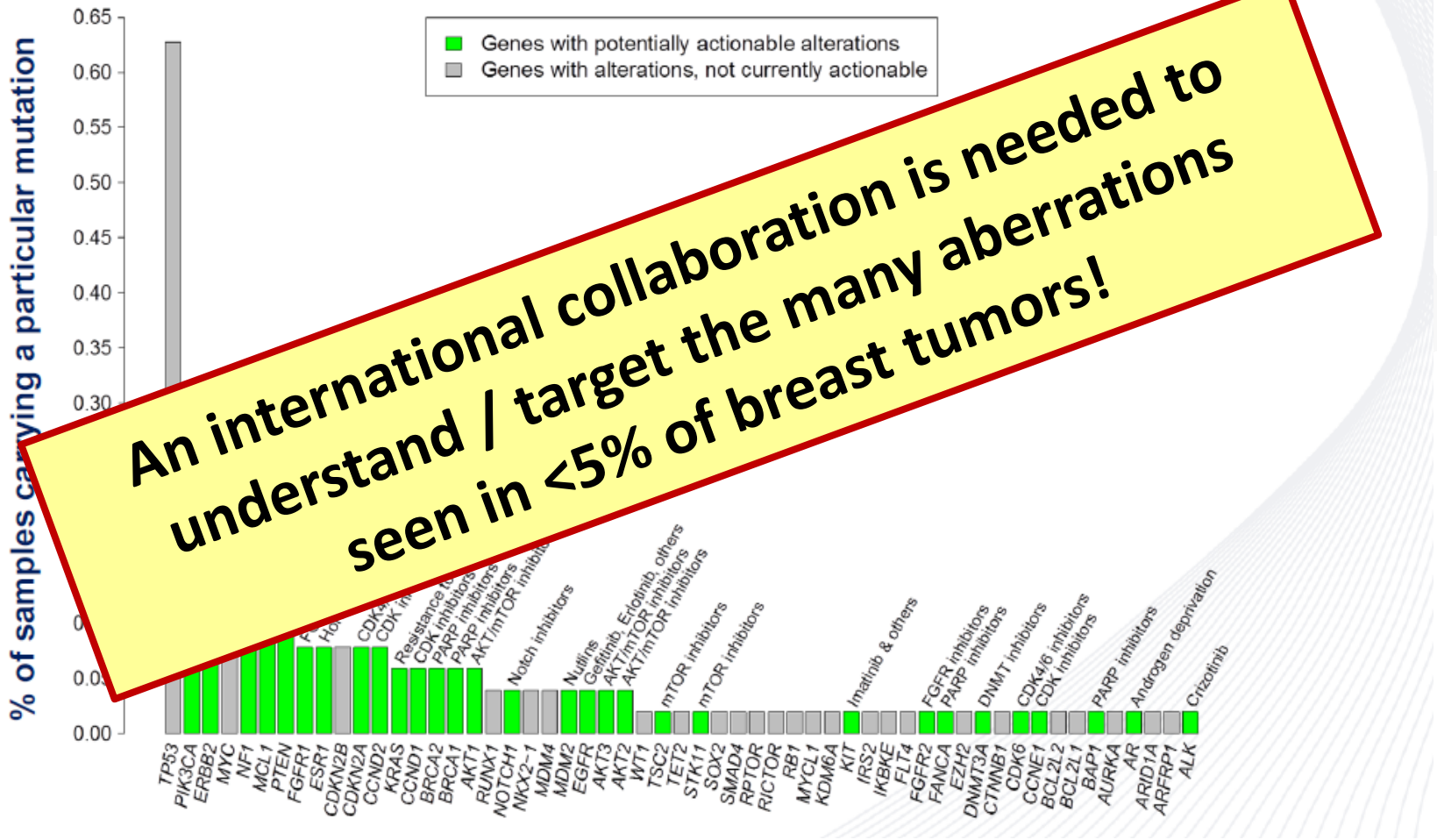


Subtype-specific patterns of mutations

Alterations may be grouped into functional pathways



Currently druggable abnormalities are individually rare but collectively effect up to 50% of breast cancers



An international collaboration is needed to understand / target the many aberrations seen in <5% of breast tumors!

BIG against breast cancer

II.

The « AURORA » program: a first initiative aimed at scaling-up the number of metastatic breast cancer patients screened across Europe.

Supported by BCRF , Fondation Luxembourgeoise contre le Cancer, the Belgian National Lottery , BIG against breast cancer and other donors

Why focus on metastatic breast cancer?

1. **The disease remains incurable … despite 3 decades of research efforts**

2. **The median survival of these women remains poor** (about 30 months)

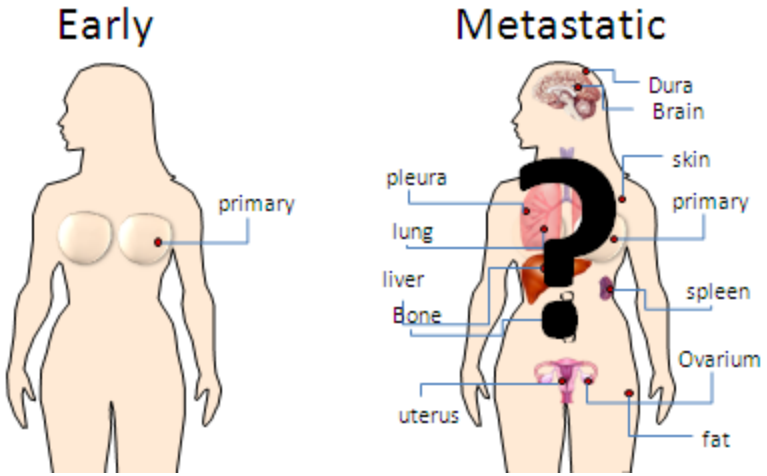
3. **Unprecedented opportunity to make more rapid progress**
   new revolutionary tools are now available
   to analyze the genetic make-up of the cancer cells
   that have « spread » and identify their Achilles' heel

ONCOLOGISTS TREATING ADVANCED BREAST CANCER TODAY…!

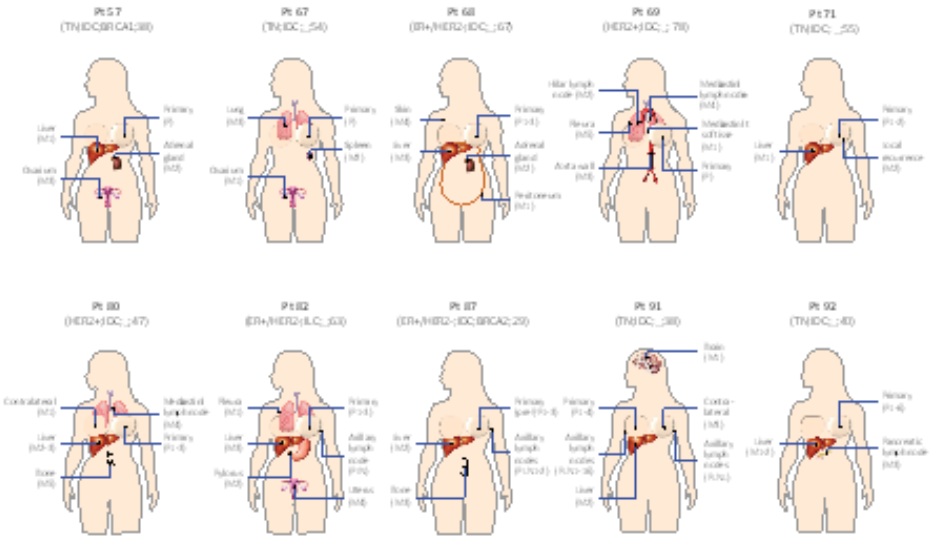
The Economist, July 7th, 2007

The landscape of genomic alterations in breast cancer

Almost nothing is known for metastatic BC disease…!



Breast cancer autopsy sequencing program
A collaboration between Belgium & Hungary
N= 10 pts; Samples = 95



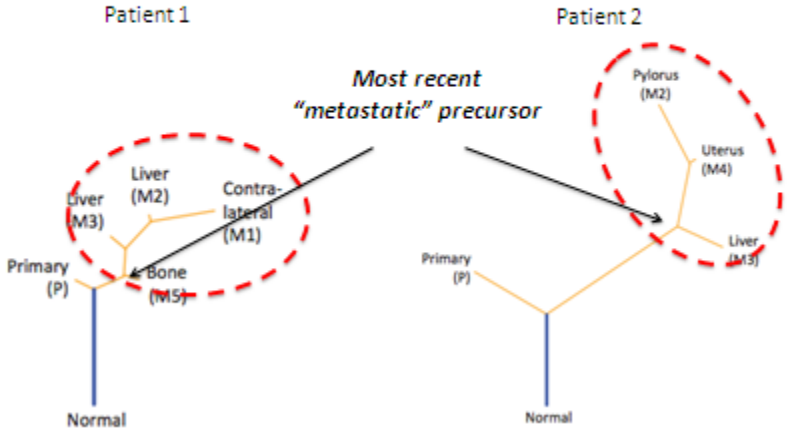
C Desmedt et al – AACR San Diego, 2014

Breast cancer autopsy sequencing program
A collaboration between Belgium & Hungary

Take-home messages

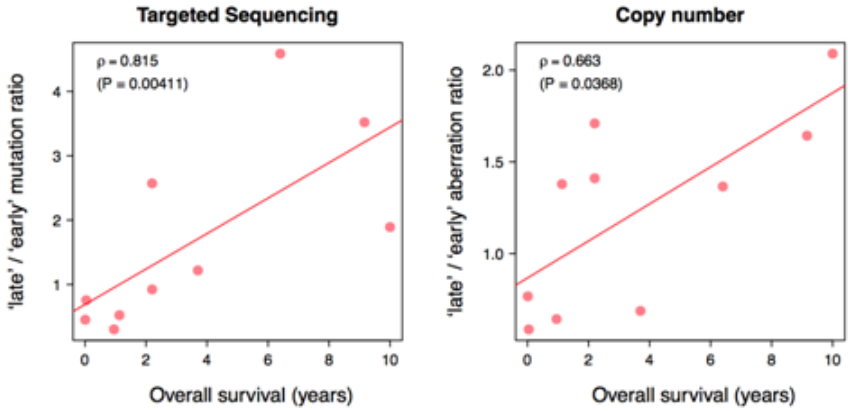
1) ***Late relapses*** show additional genomic aberrations compared to the primary tumor → need to ***re-biopsy*** metastatic lesions

Metastases arose from a ***single seeding event***, with one or more distant sites further ***re-seeding*** additional organs



Breast cancer autopsy sequencing program (Belgium & Hungary)

The ***genetic diversity*** is proportional to the ***time*** elapsed between the diagnosis of the primary tumor and the emergence of metastases



C Desmedt et al – AACR San Diego, 2014

2) Most distant metastases seem to arise *from a first single seeding event* → ***« common metastatic precursor »*** which may or may not be present in the primary tumor

C. Desmedt et al. – AACR San Diego, 2014

AURORA
Metastatic Breast Cancer - molecular aberrations

Newly diagnosed or 1st Line MBC Patients

N=1,300

Screening Failure n=300

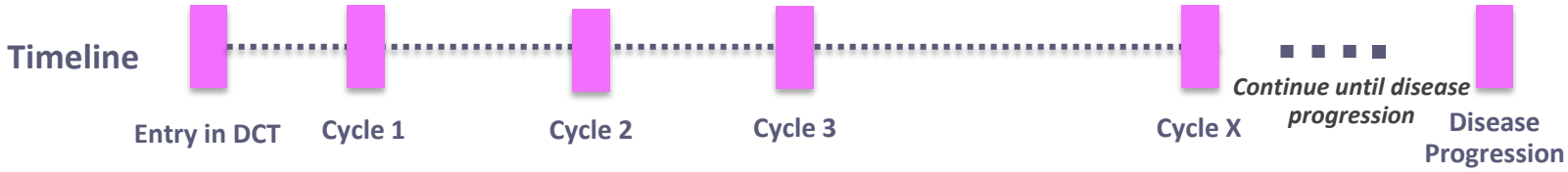
'Actionable' Mutation(s) (n~300)

Downstream Targeted Clinical Trials as first or second line

'Non-Actionable' Mutations (n~700)

Standard of Care

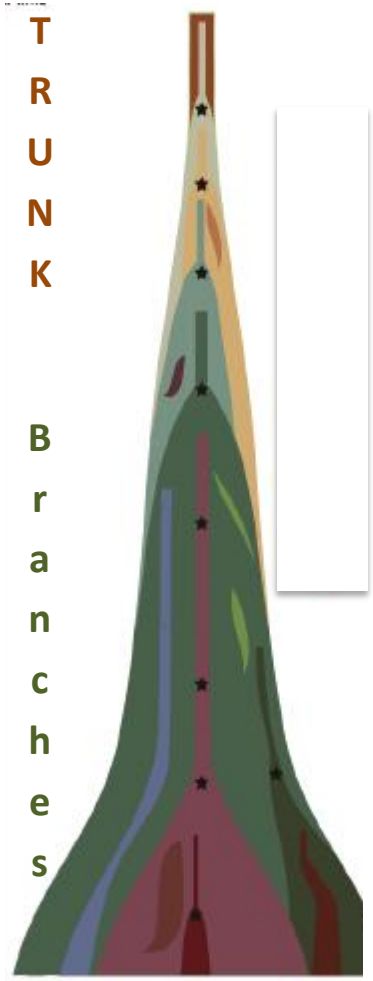
Clinical Outliers (Exceptional Responders and Rapid Progressors) to be subjected to WES



Metastatic Lesion	Biopsy – TGS (real time) and RNAseq (on batches)
Primary Tumour	Archival – TGS (real time) and RNAseq (on batches)
Blood	TGS (real time)
Plasma/Serum	Collection every 6 months – up to 10 years
Clinical Outcome Information	Collection every 6 months – up to 10 years

Academia needs to take the “driving seat” in next gene sequencing approaches to advanced disease !

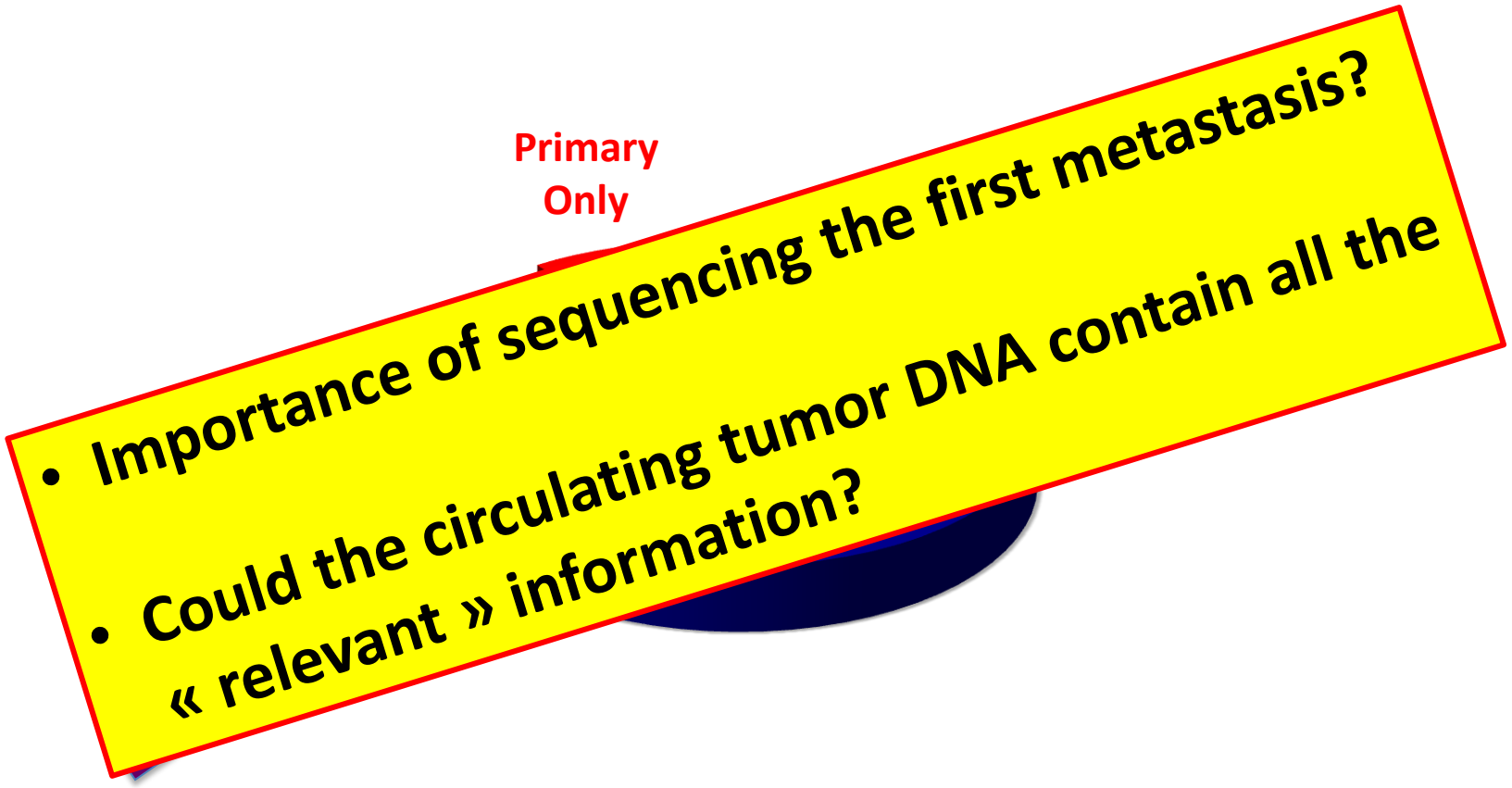
Burning questions to be addressed :



Nik-Zainal Cell 2012

- ***What are the dynamics of the tumor subclonal architecture over-time (primary → metastases) ?***
- ***What is the relative importance of “driver” mutations in the “trunk” and in the “branches” ?***
- ***How is the genome landscape of the tumor impacted by our current drugs ?***
- ***Which “clones” are going to play a major role in the lethal evolution of the disease ?***
- ***Can truncal and branches “driver” mutations be captured by tumor DNA in plasma ?***

Futility of Targeting a Subclonal Driver at One Site of Disease?



Targeting a subclonal driver event in one metastasis would have no effect on the others

Courtesy Ch. Swanton

AURORA: improving our understanding of the efficacy of traditional therapies

Recruit 1,300 patients
suffering from metastatic breast cancer

Targeted gene sequencing (<400 genes)
of metastatic and primary tumor

Patients with mutations that are targeted by experimental medications (collaborations with Pharma)
300 - 400 patients

Patients with NON actionable mutations receive standard treatments with variable levels of efficacy
600 patients

++	=	- -
30	*540*	*30*
More complex genetic sequencing	Targeted genetic sequencing	More complex genetic sequencing

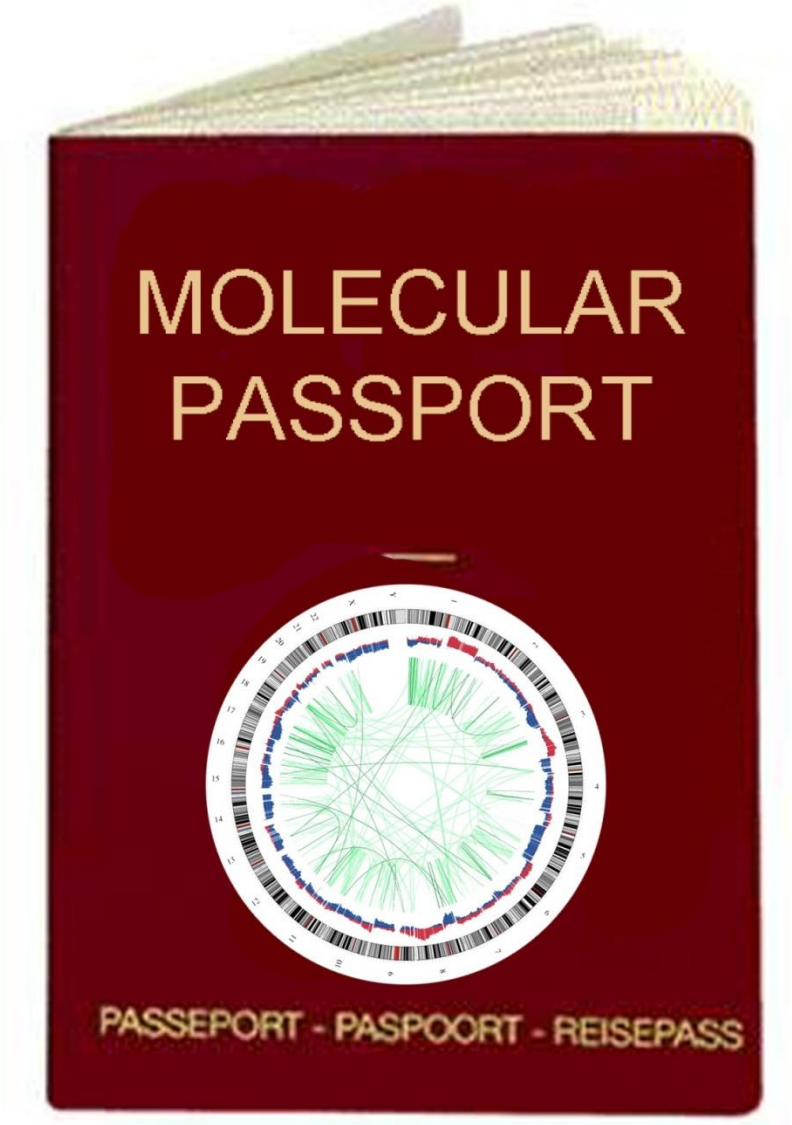
AURORA Program: Multiple Benefits Expected

1	Downstream clinical trials supported by the AURORA-generated molecular data	Efficient clinical development of targeted agents in MBC
2	Coupling of molecular and clinical outcome data for primary tumor	Potential predictive and prognostic biomarkers for early stage disease
3	Coupling of molecular and clinical outcome data for metastatic disease	Potential predictive and prognostic biomarkers for metastatic disease
4	Extensive biorepository of multiple biological samples	Opportunity for numerous subsequent TR studies
5	Reporting of genomic results to treating physicians on real-time	Great educational impact to familiarize them with genomics-based oncology
6	Targeted Gene Sequencing of primary tumor and metastatic lesion	Elucidation of intra-tumor heterogeneity on major cancer related genes

AURORA

Metastatic Breast Cancer - molecular aberrations

AURORA: empowering patients!

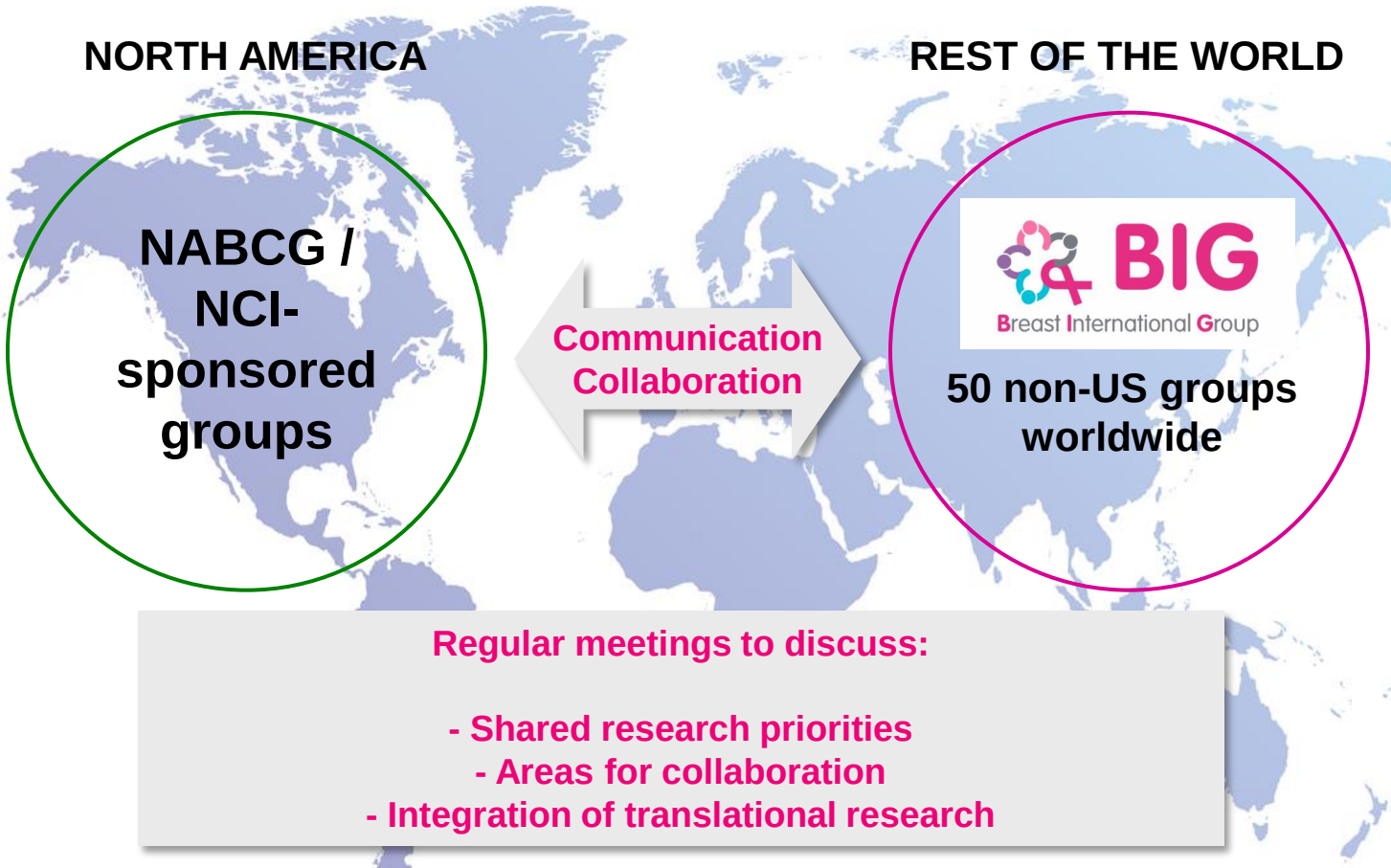


III.

« Omics-based » trial designs: challenges and possible solutions

Worlwide collaboration in breast cancer research

Together, BIG and NABCG strive to improve the care and cure rates of patients with breast cancer through international collaboration.



Regular meetings to discuss:

- **Shared research priorities**
- **Areas for collaboration**
- **Integration of translational research**

The increased collaboration further reduces duplication of efforts.

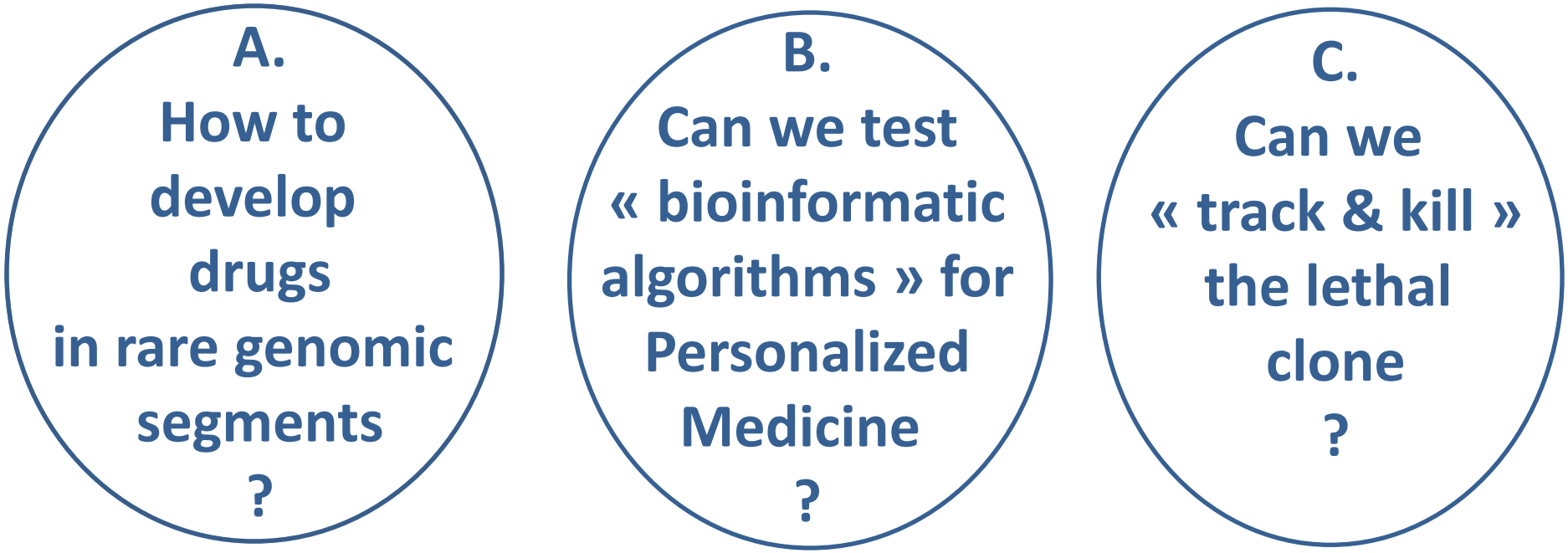
More efficient fight against the disease

The « OMICS » trials TASK FORCE

Members of the Omics Working group : M. Arnedos, W. Barry, P. Bedard, J. Bogaerts, S. Chandarlapaty, J. Guinney, M. Ignatiadis, I. Krop, S. Loi, S. Michiels, J. Rae, J. Sparano, C. Swanton, N. Turner, A. Wolff

The BIG-NABCG Task Force

« OMICS-BASED » trial designs for metastatic B.C.



« OMICS-BASED » trial designs for metastatic B.C.

Targeted drugs developed in rare genomic segments

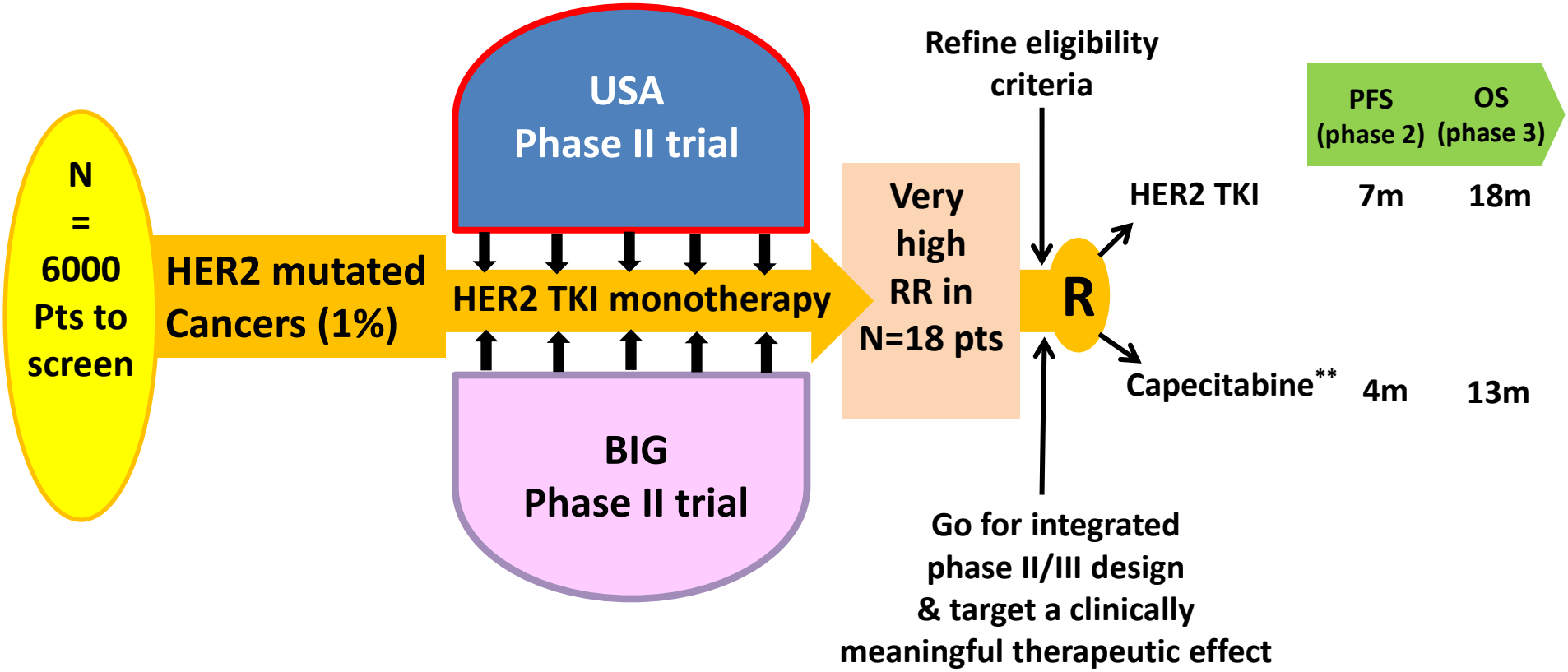
- Multiple-biomarker signal-finding design
- Multiple-biomarker randomized design

Downstream clinical trials in the AURORA Program

Weaknesses of the "Multiple biomarker signal finding" design

Target of interest	Drug under testing	Clinical trial « design »	No. of patients to be screened and eligibility	What comes next?
FGFR or 11q amplification 9% to 15% incidence (mostly luminal Ca)	FGFR inh	Phase II trial in 3 cohorts (BM+ or BM-) ↓ ORR H_0 5% H_1 20% Power 90% α = 5% N≥2 resp/21 → add 20 pts	N≈800 • ≥ 1 and < 3 lines of ET • ≤ 2 lines of CTX for MBC	Random vs... Everolimus?
HER2 mutations 1 to 2% incidence in HER2- B.C. (ER+ or ER-)	HER2 TKi	Phase II trial in BM+ ↓ Clinical Benefit Rate H_0 10% H_1 30% Power 85% α = 5% N = 11 →≥2 responses N = 35 →≥7 responses	N=6500 • ≥ 1 line of ET if ER+ • ≥ 1 line of CTX if ER-	Random vs... Capecitabine?

Developing targeted drugs in « small » genomic segments: can we do better ?



* Prior A and T mandatory; prior first line CTX for MBC mandatory

** Expected median PFS ≈ 3.7m, expected OS ≈ 13 m *(1)*

(1) Blum JL et al, Br Cancer Res Treat 2012

Integrated phase II/III design

- **Phase II, primary endpoint PFS**

  Expected Median PFS control arm : **4 months**

  Median PFS experimental arm considered sufficiently active to continue to phase III: **7 months**

  HR=0.57

  Requires 84 events

  Accrual: 40 patients/year, accrual period= 2.8 years

  Total Sample size: 112 patients

  Follow-up period: 0 years (no accrual stop)

  Total study duration 2.8 years

- **Phase III, primary endpoint OS**

  Expected Median OS control arm: **13 months**

  Median OS experimental arm that is considered clinically meaningful: **18 months**

  HR=0.72

  Requires 297 events

  Accrual: 40 patients/year, accrual period=8.5 years (additional accrual = 5.7 years)

  Total Sample size: 340 patients (112 + 228 patients)

  Follow-up period: 1.1 years

  Total study duration 9.6 years (2.8 + 6.8 years)

Statistics in modern oncology drug development : 3 key messages

- **Try to access tumor tissue from completed phase III trials to study the outcome of genomic segments under « standard » therapy**

- **Resist the temptation to go for « uncontrolled » clinical trials**

  1) Minimal prognostic bias in comparison to historical controls can have a major impact on producing misleading results (e.g. high doses chemo for MBC).

  2) A « response endpoint » can be influenced merely by patient selection

  3) « PFS » is preferred as some new drugs inhibit tumor growth without shrinking tumors... but it can also vary markedly through patient selection. Hence, in a non-randomized trial there is a risk of incorrectly specifying the null PFS rate.

- **Strongly consider integrated phase II/III designs rather than « stand alone » phase II and III trials**

S. Hunsberger, R. Simon, Clin Cancer Res 2009; 15:19

Pros and Cons of Various Trial Design Strategies

	Trial design	PROS	CONS
	Phase II → STOP - - - → Phase III with fresh start	Only 10% chance of accruing full phase III with ineffective new therapy	Lengthiest design (ph… …st »)
INTEGRATED MODEL	Phase II - - - → Phase III	Phase II pts benefit from in-depth eval… …it is more reliable	…orks, …time »
INTEGRATED MODEL	Phase II - - - → Phase III No accrual suspension	Only 10% chance of accruing full phase III with ineffective new therapy	If new treatment does not work, more pts will be accrued « in vain »
	Straight forward phase III with « futility » monitoring	Quickest design	Appr. 50% chance of accruing full phase III with ineffective new therapy

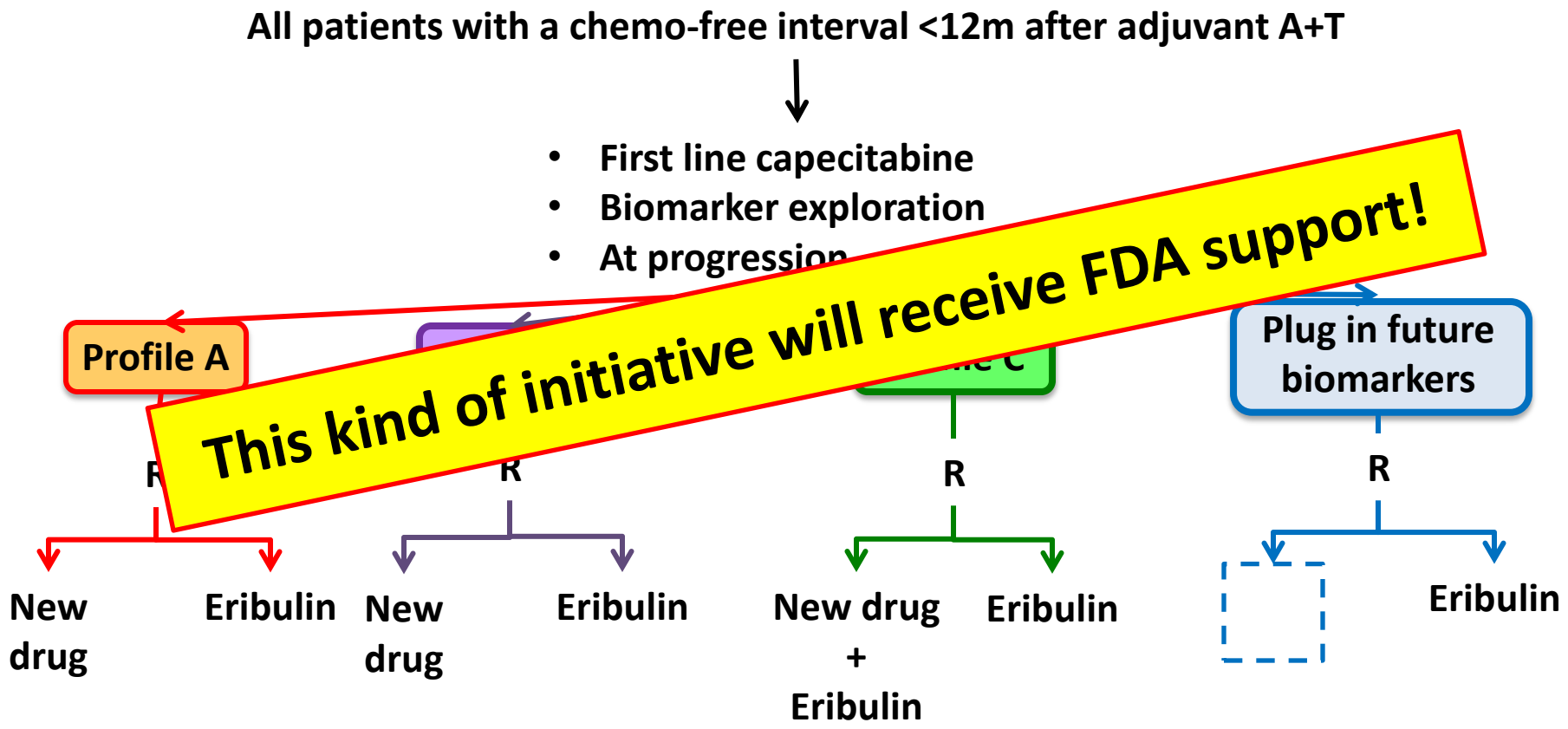
Integrated phase II/III trials to be encouraged in the « omics » era!
Power to be set at 90% for both portions of the trial
(overall power ≈ 81%)

Adapted from E. Korn et al. (NCI), JCO 30, 2012

Advanced triple-negative BC « resistant » to standard chemo

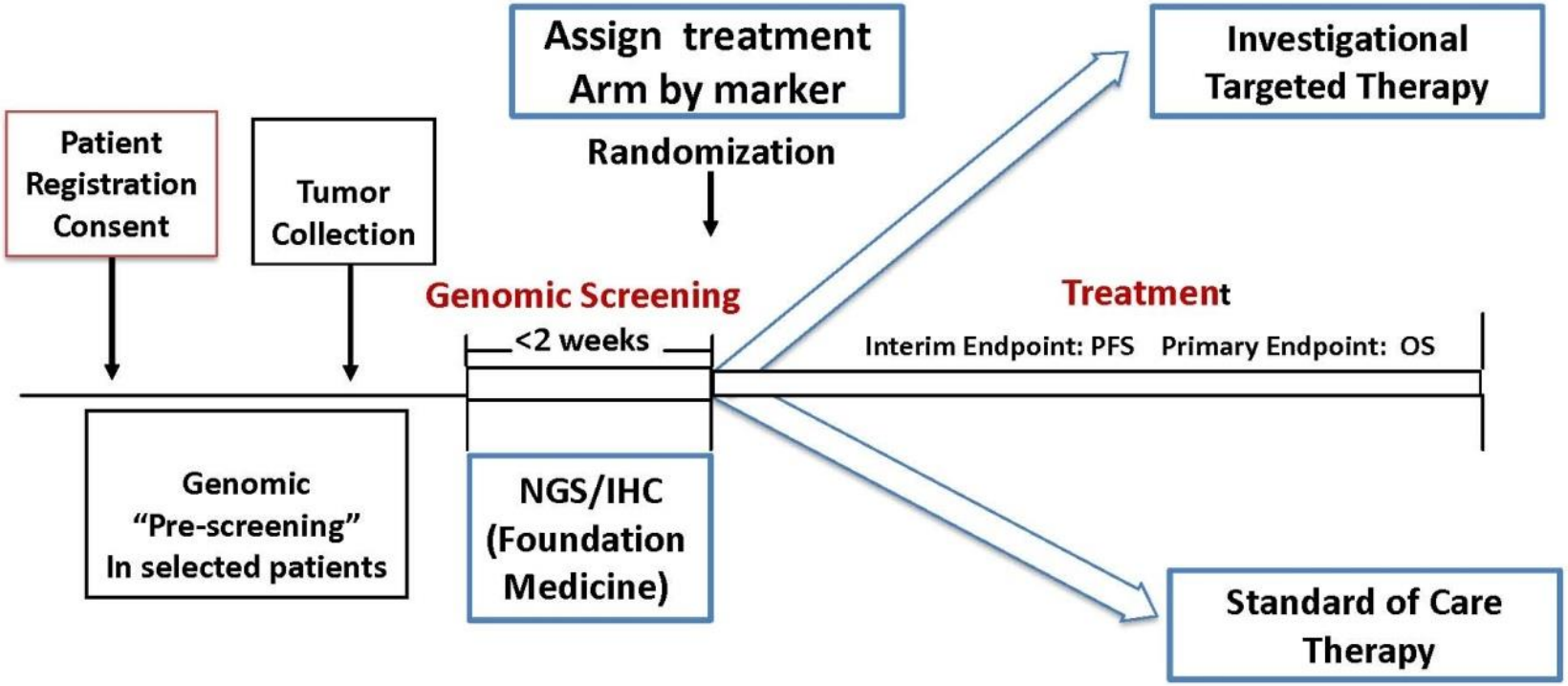
Multiple-biomarker randomized design

« Master Protocol »



- Controls for prognostic effects; cannot assess off-target effects
- In case of overlapping biomarkers... need to prioritize
- Choose meaningful OS effect (HR ≤ 0.7 and absolute gain ≥ 3m)

U.S. Master protocol for refractory squamous cell lung cancer
A private-public partnership



- **Organizers: Friends Of Cancer Research, NCI, FDA, Foundation of the NIH**
- **Participants: Entire North American Lung Intergroup (N=500 sites) (SWOG, Alliance, ECOG-Acrin, NRG, NCI-Canada)**
- **Screening: 500-1,000 patients/year (Foundation Medicine)**
- **With 4-6 arms open simultaneously, « hit » rate ≈70% in matching a patient with a drug/biomarker arm.**

The Cancer Letter, Vol 39 n°43, 2013

NEW DRUGS & TRIALS ON THE HORIZON

The AURORA initiative for advanced breast cancer

TAKE-HOME MESSAGES:

- **There is still much to learn about the « clonal evolution » of B.C. and the molecular heterogeneity of advanced disease**
- **Initiatives to « scale up »molecular screening need to be encouraged and to incorporate a « circulating plasma DNA » component...**
- **There is increasing awareness of the greater efficiency of the integrated phase 2-3 design for biomarker-stratified trials; fewer, more widely accessible « umbrella » trials are needed!**
- **Large collaborative networks are key for an accelerated path towards « personalized medicine »**

What could this program achieve?

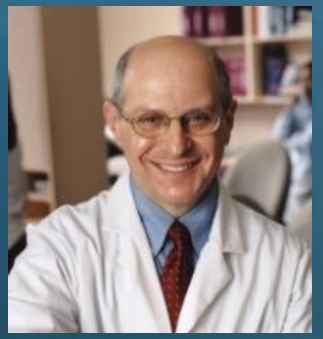
AURORA

New hopes for women with a lethal disease that deserves a large collaborative effort!

Let us build bridges…

Acknowledgements

N. Davidson



L. Norton

Thank You

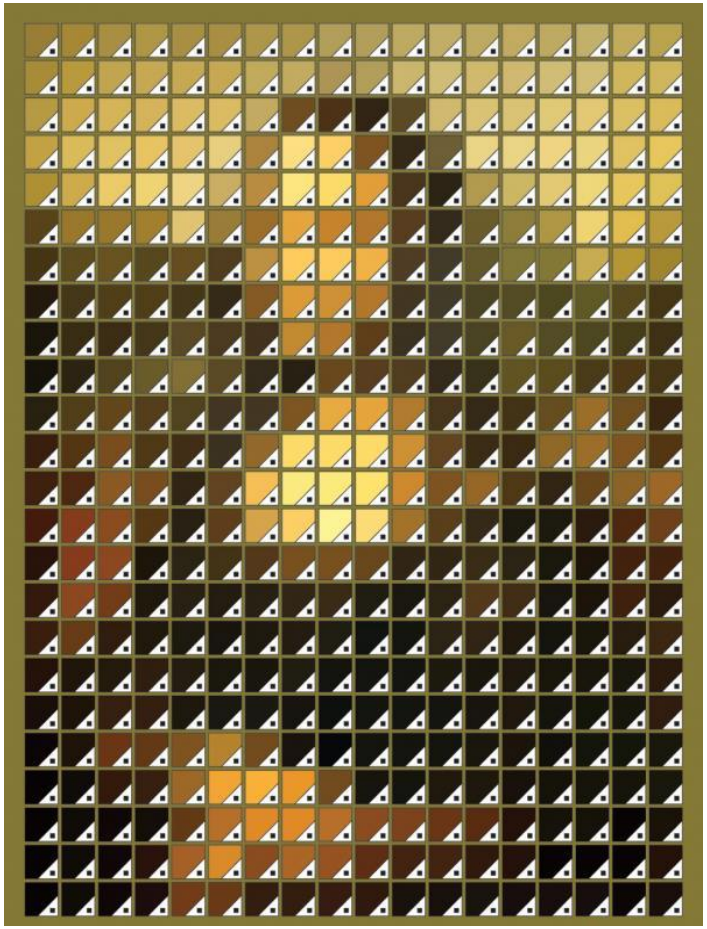
- Breast Cancer Research Foundation (USA)
- Fondation Luxembourgeoise contre le Cancer
- La Lotterie Nationale
- Les donateurs de “BIG against Breast Cancer”

BIG against breast cancer

BACK-UP

Getting to know the « face » of the enemy

TODAY



TOMORROW

BIG against breast cancer