

# Rare cancers: challenges for new treatment developments in the precision medicine era

J-Y Blay



# Disclosures

( presenter orange, institution grey)

| Company        | Scientific advice | Research support | Symposia & oral communications |
|----------------|-------------------|------------------|--------------------------------|
| Abbvie         | X                 | X                |                                |
| Amgen          | X                 | X                | X                              |
| ARIAD          | X                 | X                |                                |
| AstraZeneca    |                   | X                | X                              |
| Bayer          | X                 | X                | X                              |
| BMS            | X                 | X                | X                              |
| DDB            | X                 | X                |                                |
| EISAI          | X                 | X                | X                              |
| Genomic Health |                   | X                | X                              |
| Gilead         |                   | X                | X                              |
| GSK            |                   | X                | X                              |
| Innate-Pharma  | X                 | X                |                                |
| Jansen         |                   | X                | X                              |
| LILLY          |                   | X                | X                              |
| Merck Serono   |                   | X                | X                              |
| MSD            |                   | X                | X                              |
| Nanobiotix     | X                 | X                |                                |
| Novartis       | X                 | X                | X                              |
| Novex          |                   | X                | X                              |
| Onxeo          | X                 |                  |                                |
| Pfizer         |                   | X                | X                              |
| Pharmamar      | X                 | X                |                                |
| PRA            |                   | X                |                                |
| Roche          | X                 | X                | X                              |
| Sanofi Aventis |                   | X                | X                              |
| Swedish Orphan |                   | X                | X                              |
| Takeda         |                   | X                |                                |
| Toray          | X                 | X                |                                |

# Challenges?

Nosologies

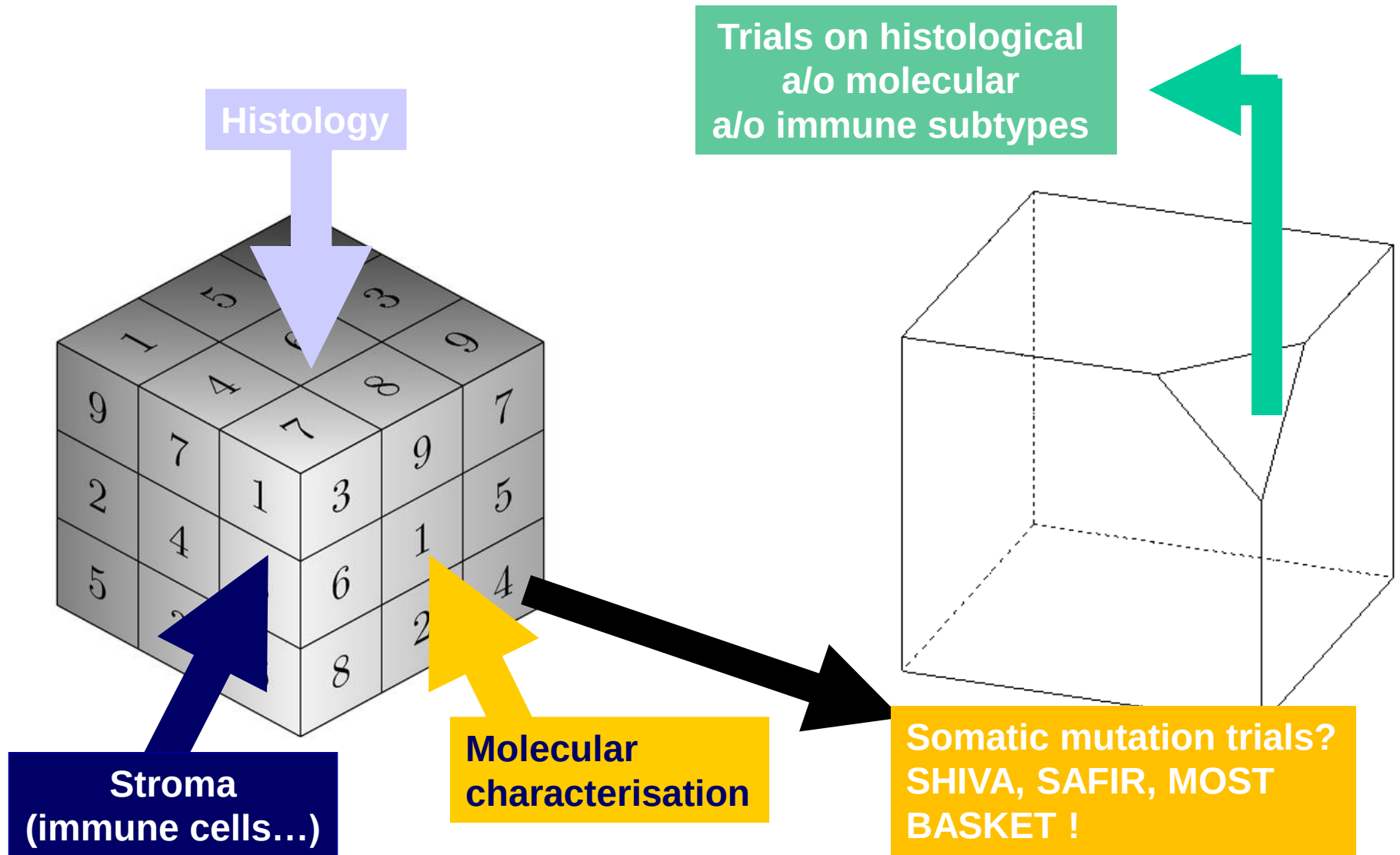
First optimal local treatment

Which molecular test, which molecular subsets

New designs for clinical trials

New strategies, new paradigms

# Nosology & treatment 2024+



# SCREENING FOR GENOMIC ALTERATIONS

## 4 strategies

### SINGLE GENE

- Exemple: *EGFR*, *BRAF*, *ALK*...
- RT-PCR, IHC, FISH

### HOT SPOT PANELS

- NGS : INCa panel (18 genes)
- Selected mutations in selected zones of selected genes

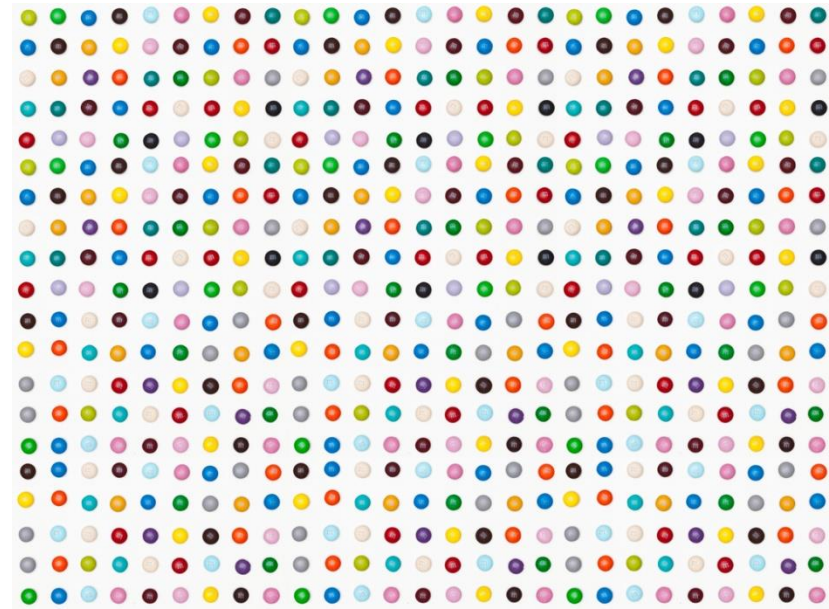
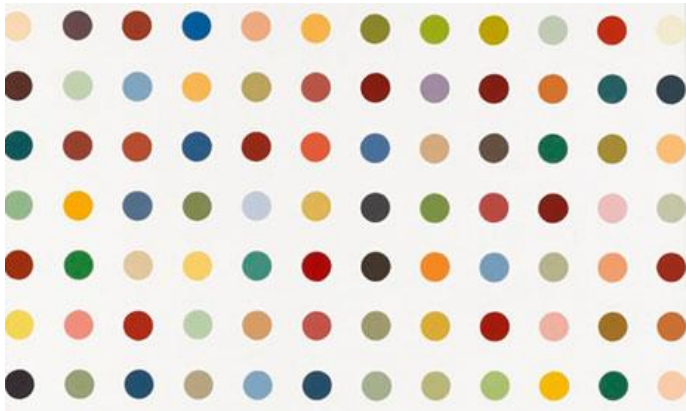
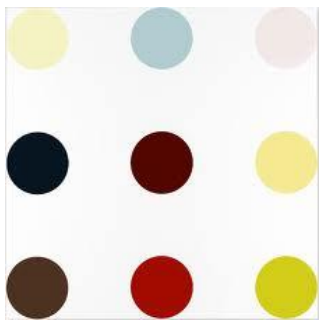
### COMPREHENSIVE GENOMIC PROFILING

- e.g. FoundationOne
- Explores 4 major alterations on the full sequence of genes

### COMPREHENSIVE GENOMIC PROFILING

- WES, WGS, RNAseq
- e.g. National initiatives (FMG2025..)

# Nosological fragmentation



Damien Hirst  
« 1-bromoadamantane »  
« Acivicin »  
« Arginosuccinic acid »

# Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT)



Fabrice Barlesi, Julien Mazieres, Jean-Philippe Merlio, Didier Debieuvre, Jean Mosser, Hervé Lena, L'Houcine Ouafik, Benjamin Besse, Isabelle Rouquette, Virginie Westeel, Fabienne Escande, Isabelle Monnet, Antoinette Lemoine, Rémi Veillon, Hélène Blons, Clarisse Audigier-Valette, Pierre-Paul Bringuier, Régine Lamy, Michèle Beau-Faller, Jean-Louis Pujol, Jean-Christophe Sabourin, Frédérique Penault-Llorca, Marc G Denis, Sylvie Lantuejoul, Franck Morin, Quân Tran, Pascale Missy, Alexandra Langlais, Bernard Milleron, Jacques Cadranet, Jean-Charles Soria, Gérard Zalcman, for the Biomarkers France contributors\*

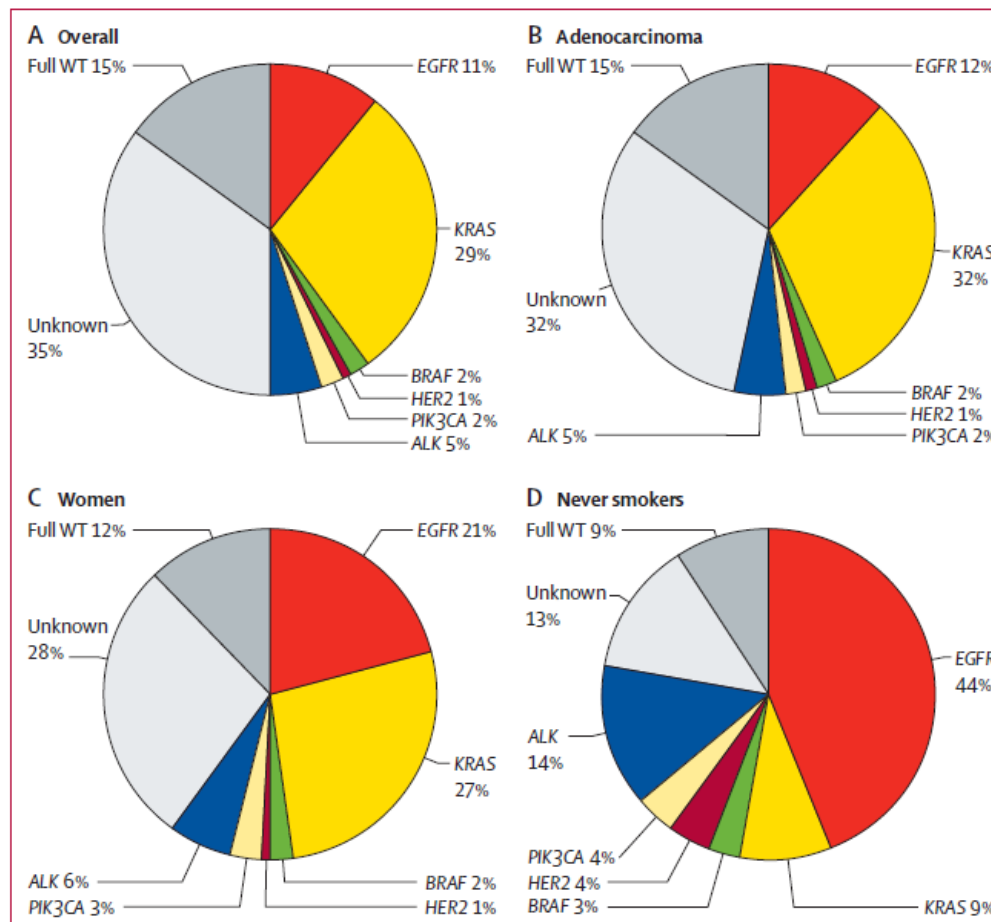
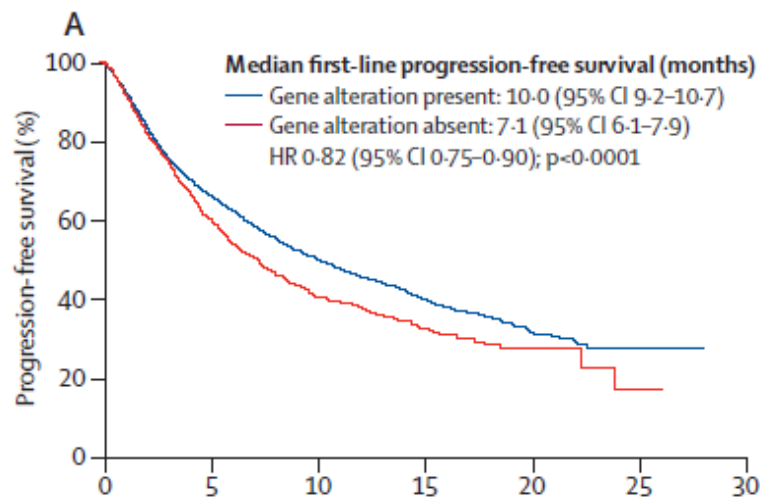


Figure 2: Frequency of genetic alterations

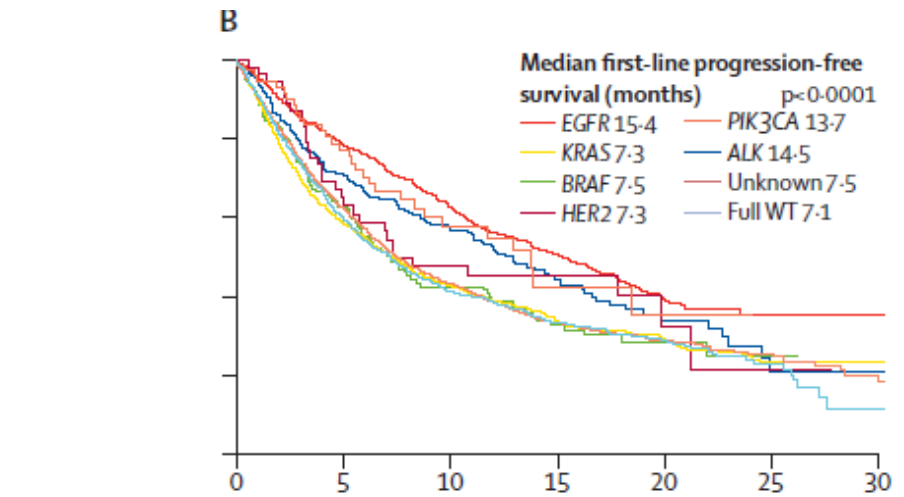
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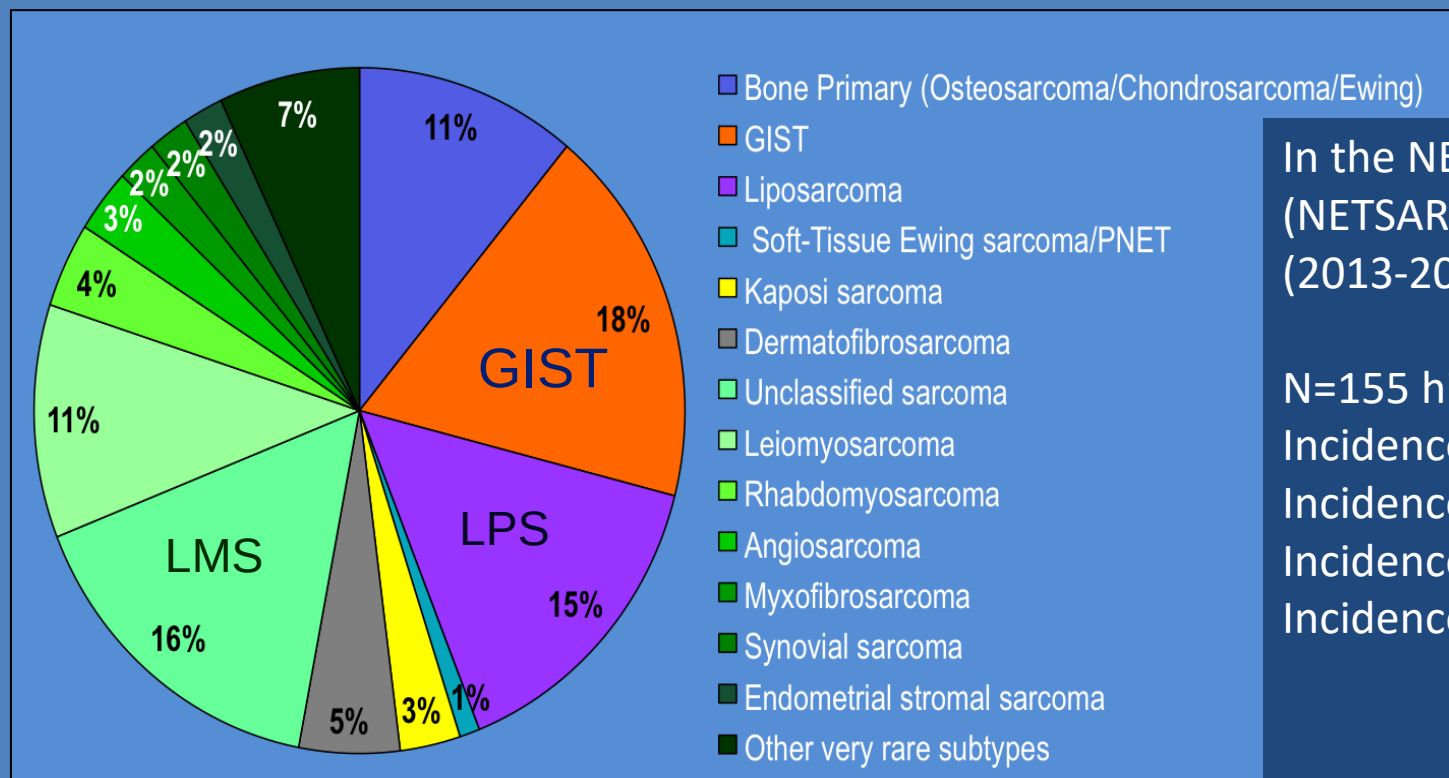


| Number at risk          | 0    | 5    | 10   | 15  | 20  | 25 | 30 |
|-------------------------|------|------|------|-----|-----|----|----|
| Gene alteration present | 3498 | 1873 | 1134 | 453 | 119 | 8  | 0  |
| Gene alteration absent  | 1126 | 504  | 251  | 90  | 17  | 2  | 0  |



| Number at risk | 0    | 5    | 10  | 15  | 20 | 25 | 30 |
|----------------|------|------|-----|-----|----|----|----|
| EGFR           | 1008 | 675  | 485 | 167 | 37 | 2  | 0  |
| KRAS           | 1926 | 870  | 611 | 216 | 46 | 3  | 0  |
| BRAF           | 131  | 70   | 43  | 21  | 4  | 0  | 0  |
| HER2           | 56   | 30   | 21  | 9   | 4  | 0  | 0  |
| PIK3CA         | 70   | 45   | 21  | 8   | 2  | 0  | 0  |
| ALK            | 212  | 133  | 93  | 47  | 13 | 2  | 0  |
| Unknown        | 3082 | 1510 | 789 | 304 | 89 | 11 | 1  |
| Full WT        | 1126 | 504  | 251 | 90  | 17 | 2  | 0  |

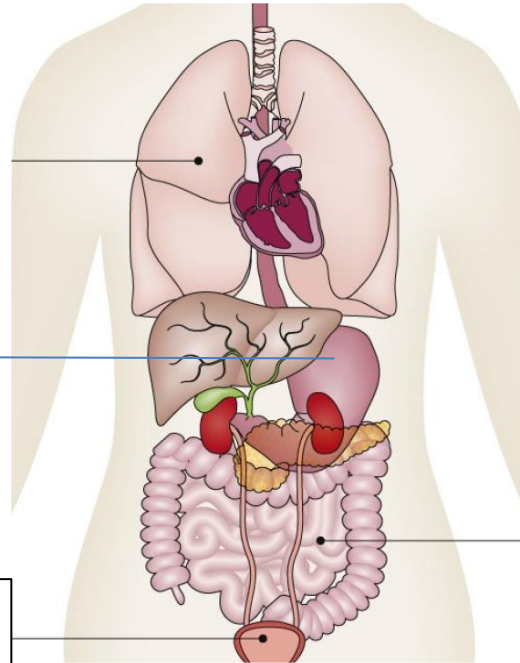
# Sarcomas represent a very heterogeneous set of diseases



In the NETSARC Database  
(NETSARC.org, N=25203  
(2013-2016)

N=155 histotypes  
Incidence  $>10^5$ : n=1 (GIST)  
Incidence  $10^5$ - $10^6$ , n=23  
Incidence  $10^6$ - $10^7$ , n=64  
Incidence  $<10^7$ , n=68

# Distribution of mutations in the gastric, small bowel, and rectal GIST



## Gastric GIST (60-65%)

- KIT exon 11 mutation : 54-60%
- KIT exon 9 mutation: <5%
- PDGFRA exon18: 15-18%
- Other mutations : 10-12%

## Rectal GIST (3-5%)

- KIT exon 11 mutation : 70-80%
- KIT exon 9 mutation :10-15%
- Other mutations : 5-10%

## Small bowel GIST (20-35%)

- KIT exon 11 mutation : 43-50%
- KIT exon 9 mutation : 20-25%
- PDGFRA mutation: 5-7%
- Other mutations : 8-10%

# Challenges?

Nosologies

First optimal local treatment

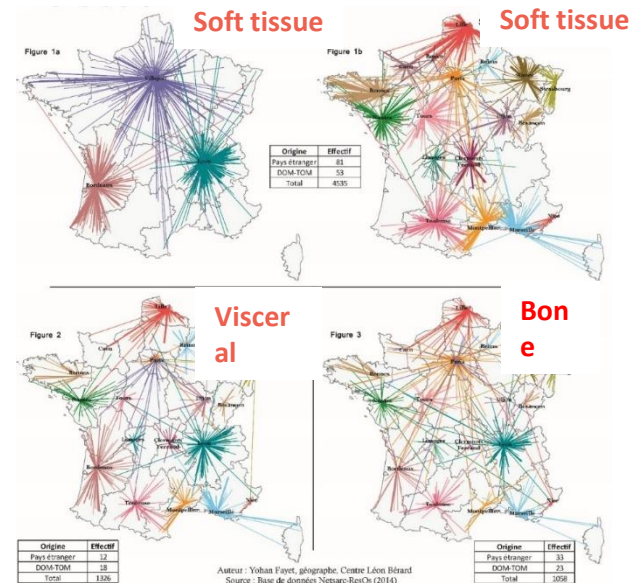
Which molecular test, which molecular subsets

New designs for clinical trials

New strategies, new paradigms

## NetSARC: a network of 26 sarcoma reference centers in France 35784 pts with follow-up presented in MDT since 2010

- 26 centers of reference in **Netsarc**
- Linked with Pathology network (**RREPS**)
- Linked with Bone Network **RESOS** (2014)
- 3 networks to be merged (2019)
- Single website
- Entry in the site by CRAs
- Not a clinical trial, a registry
- **Aims:**
  - Guidelines
  - Guiding best practices/patient pathways
  - Measuring
  - Research



## ORIGINAL ARTICLE

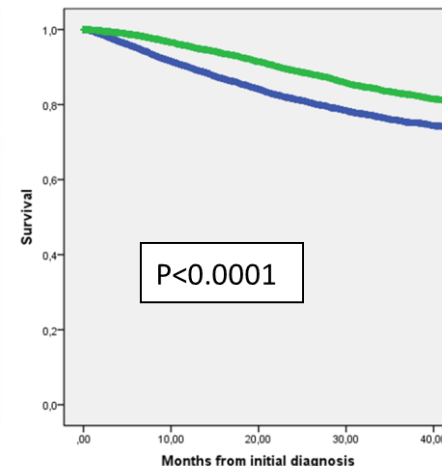
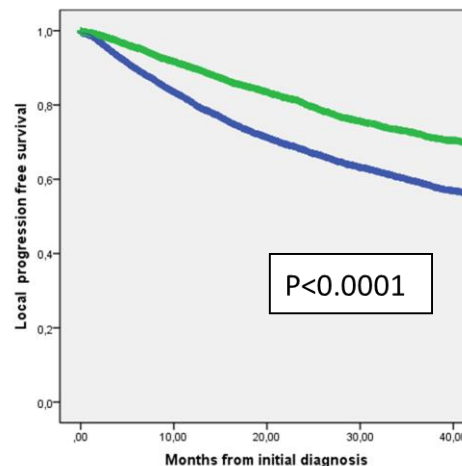
### Improved survival using specialized multidisciplinary board in sarcoma patients

J.-Y. Blay<sup>1,2\*</sup>, P. Soibinet<sup>3</sup>, N. Penel<sup>4</sup>, E. Bompas<sup>5</sup>, F. Duffaud<sup>6</sup>, E. Stoeckle<sup>7</sup>, O. Mir<sup>8</sup>, J. Adam<sup>8</sup>, C. Chevreau<sup>9</sup>, S. Bonvalot<sup>8,10</sup>, M. Rios<sup>11</sup>, P. Kerbrat<sup>12</sup>, D. Cupissol<sup>13</sup>, P. Anract<sup>14</sup>, F. Gouin<sup>15</sup>, J.-E. Kurtz<sup>16</sup>, C. Lebbe<sup>17</sup>, N. Isambert<sup>18</sup>, F. Bertucci<sup>19</sup>, M. Toumonde<sup>20</sup>, A. Thyss<sup>20</sup>, S. Piperno-Neumann<sup>10</sup>, P. Dubray-Longeras<sup>21</sup>, P. Meeus<sup>1,2</sup>, F. Ducimetière<sup>1,2</sup>, A. Giraud<sup>7</sup>, J.-M. Coindre<sup>2</sup>, I. Ray-Coquard<sup>1,2</sup>, A. Italiano<sup>7†</sup> & A. Le Cesne<sup>8†</sup>, on behalf of the NETSARC/RREPS and French Sarcoma Group–Groupe d'Etude des Tumeurs Osseuses (GSF-GETO) networks<sup>‡</sup>

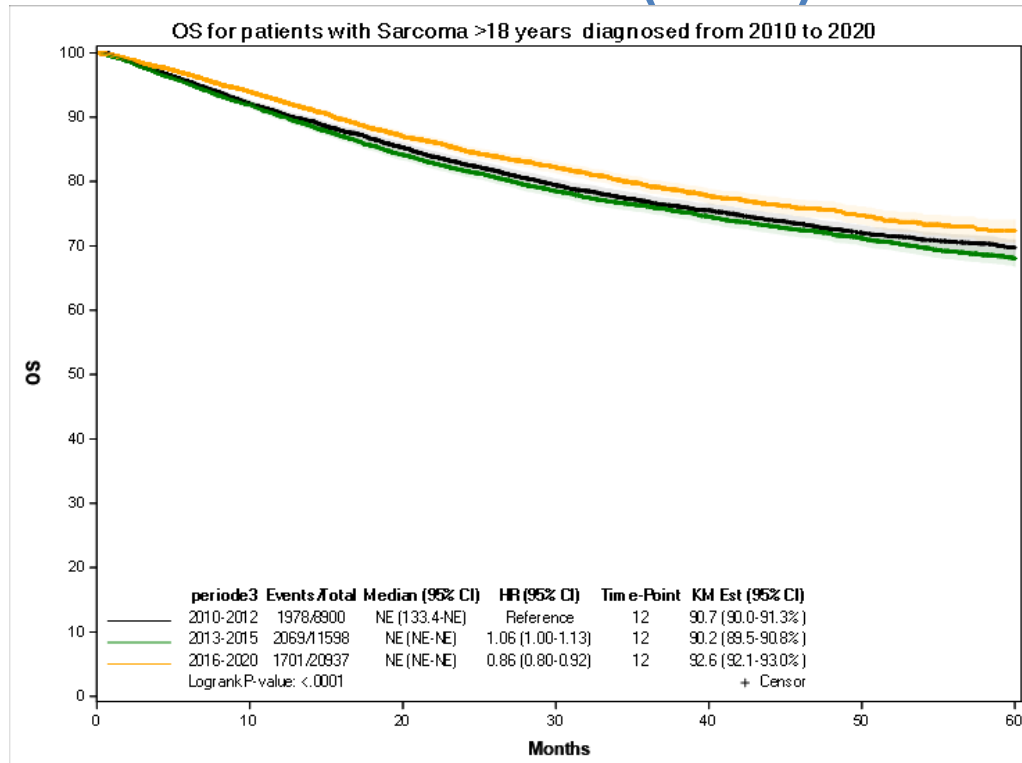
## ORIGINAL ARTICLE

### Surgery in reference centers improves survival of sarcoma patients: a nationwide study

J.-Y. Blay<sup>1,2,3\*</sup>, C. Honoré<sup>4</sup>, E. Stoeckle<sup>5</sup>, P. Meeus<sup>1,2,3</sup>, M. Jafari<sup>6,7</sup>, F. Gouin<sup>1,2,3,8,9</sup>, P. Anract<sup>10</sup>, G. Ferron<sup>11</sup>, A. Rochwerger<sup>12</sup>, M. Ropars<sup>13,14</sup>, S. Carrere<sup>15</sup>, F. Marchal<sup>16</sup>, F. Sirveaux<sup>16</sup>, A. Di Marco<sup>17</sup>, L. R. Le Nail<sup>18</sup>, J. Guirmand<sup>19</sup>, G. Vaz<sup>1,2,3</sup>, J.-C. Machiavello<sup>20</sup>, O. Marco<sup>21</sup>, S. Causeret<sup>22</sup>, P. Gimbergues<sup>23</sup>, F. Fiorenza<sup>24</sup>, L. Chaigneau<sup>25</sup>, F. Guillemin<sup>26</sup>, J.-M. Guilloit<sup>27</sup>, F. Dujardin<sup>28</sup>, J.-P. Spano<sup>29</sup>, J.-C. Ruzic<sup>30</sup>, A. Michot<sup>3</sup>, P. Soibinet<sup>30</sup>, E. Bompas<sup>3</sup>, C. Chevreau<sup>11</sup>, F. Duffaud<sup>12</sup>, M. Rios<sup>13,14</sup>, C. Perrin<sup>13,14</sup>, N. Firmin<sup>15</sup>, F. Bertucci<sup>19</sup>, C. Le Pechoux<sup>4</sup>, F. Le Loarer<sup>4</sup>, O. Collard<sup>1,2,3</sup>, M. Karanian-Philippe<sup>1,2,3</sup>, M. Brahmi<sup>1,2,3</sup>, A. Dufresne<sup>1,2,3</sup>, A. Dupré<sup>1,2,3</sup>, F. Ducimetière<sup>1,2,3</sup>, A. Giraud<sup>10</sup>, D. Pérol<sup>1,2,3</sup>, M. Toulmonde<sup>5</sup>, I. Ray-Coquard<sup>1,2,3</sup>, A. Italiano<sup>5</sup>, A. Le Cesne<sup>8</sup>, N. Penel<sup>6,7</sup> & S. Bonvalot<sup>31</sup>, on behalf of the NETSARC/RREPS/RESOS and French Sarcoma Group–Groupe d'Etude des Tumeurs Osseuses (GSF-GETO) Networks<sup>‡</sup>



# Survival (>17)



HR=0,81

|                                                                    | Event/Total | Median<br>(95% CI) <sup>1</sup> | Hazard Ratio<br>(95% CI) <sup>2</sup> | Survival Estimates<br>(95% CI) <sup>1</sup> | P-value             |
|--------------------------------------------------------------------|-------------|---------------------------------|---------------------------------------|---------------------------------------------|---------------------|
| OS for patients with Sarcoma >18 years diagnosed from 2010 to 2020 |             |                                 |                                       |                                             |                     |
| periode3                                                           |             |                                 |                                       |                                             | <.0001 <sup>3</sup> |
| 2010-2012                                                          | 1978/8900   | NE (133.4-NE)                   | Reference                             | 12 : 90.7 (90.0-91.3%)                      |                     |
| 2013-2015                                                          | 2069/11598  | NE (NE-NE)                      | 1.06 (1.00-1.13)                      | 12 : 90.2 (89.5-90.8%)                      |                     |
| 2016-2020                                                          | 1701/20937  | NE (NE-NE)                      | 0.86 (0.80-0.92)                      | 12 : 92.6 (92.1-93.0%)                      |                     |

<sup>1</sup>Kaplan-Meier method; <sup>2</sup>Cox model; <sup>3</sup>Logrank test;

Nationwide incidence of sarcomas and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network

Gonzague de Pinieux<sup>1‡</sup>, Marie Karanian<sup>2‡</sup>, Francois Le Loarer<sup>3‡</sup>, Sophie Le Guellec<sup>4</sup>,

Ordered incidences of sarcomas and connective tissue tumors in NETSARC & published clinical trials

| Histotypes                               | Total       | Incidence  | Ph III | RPh II | Ph II |
|------------------------------------------|-------------|------------|--------|--------|-------|
|                                          | (2013-2016) | /10e6/year |        |        |       |
|                                          | 25172       | 95,104     |        |        |       |
| Incidence >10/10e6/year                  |             |            |        |        |       |
| Fibroblastic and myofibroblastic tumours | 5274        | 19,977     |        |        |       |
| Gastrointestinal stromal tumors (GIST).  | 3272        | 12,394     |        |        |       |
| Adipocytic tumours                       | 3247        | 12,299     |        |        |       |
| ALL Undifferentiated sarcoma             | 2717        | 10,292     |        |        |       |
| ALL smooth muscle tumours                | 2679        | 10,148     |        |        |       |
| Incidence <10/10e6/year                  |             |            |        |        |       |
| Undifferentiated pleomorphic sarcoma     | 1556        | 5,894      |        |        |       |
| All vascular tumor                       | 1520        | 5,758      |        |        |       |
| Liposarcoma – dedifferentiated           | 1345        | 5,095      |        |        |       |
| Desmoid fibromatosis                     | 1339        | 5,072      |        |        |       |
| Atypical lipomatous tumour/WDLPS         | 1266        | 4,795      |        |        |       |
| Uterine sarcoma                          | 1138        | 4,311      |        |        |       |
| Leiomyosarcoma                           | 1094        | 4,144      |        |        |       |
| Dermatofibrosarcoma Protuberans          | 1040        | 3,939      |        |        |       |
| Leiomyosarcoma - differentiated          | 945         | 3,580      |        |        |       |
| Solitary fibrous tumour (all)            | 925         | 3,504      |        |        |       |
| Undifferentiated sarcoma NOS             | 853         | 3,231      |        |        |       |
| Sarcoma NOS                              | 844         | 3,197      |        |        |       |
| Solitary fibrous tumor                   | 751         | 2,845      |        |        |       |
| Angiosarcoma                             | 728         | 2,758      |        |        |       |
| Kaposi sarcoma                           | 663         | 2,511      |        |        |       |
| Conventional osteosarcoma                | 661         | 2,504      |        |        |       |
| Myxofibrosarcoma                         | 630         | 2,386      |        |        |       |
| Ewing sarcoma                            | 614         | 2,326      |        |        |       |
| ALL Rhabdomyosarcoma                     | 608         | 2,303      |        |        |       |
| Chondrosarcoma NOS                       | 572         | 2,167      |        |        |       |
| Uterine leiomyosarcoma                   | 545         | 2,064      |        |        |       |
| Leiomyosarcoma – poorly differentiated   | 516         | 1,955      |        |        |       |
| ALL Synovial sarcoma                     | 442         | 1,674      |        |        |       |
| Atypical fibroxanthoma                   | 429         | 1,625      |        |        |       |
| Myxoid or round cell liposarcoma         | 409         | 1,549      |        |        |       |
| Liposarcoma - myxoid                     | 355         | 1,345      |        |        |       |
| All GCTB                                 | 330         | 1,250      |        |        |       |
| Giant cell tumour of bone                | 324         | 1,227      |        |        |       |
| Undifferentiated spindle cell sarcoma    | 308         | 1,167      |        |        |       |
| ALL Peripheral nerve sheath tumours      | 286         | 1,083      |        |        |       |

| Histotypes                                                        | Total       | Incidence  | Ph III | RPh II | Ph II |
|-------------------------------------------------------------------|-------------|------------|--------|--------|-------|
|                                                                   | (2013-2016) | /10e6/year |        |        |       |
|                                                                   |             | 95,104     |        |        |       |
| Incidence <1/10e6/year                                            |             |            |        |        |       |
| Synovial sarcoma - monophasic                                     | 244         | 0,924      |        |        |       |
| Endometrial stromal sarcoma, low grade                            | 238         | 0,902      |        |        |       |
| Embryonal RMS                                                     | 179         | 0,678      |        |        |       |
| High risk SFT                                                     | 174         | 0,659      |        |        |       |
| Malignant peripheral nerve sheath tumour                          | 173         | 0,655      |        |        |       |
| Other histological subtypes of bone sarcoma                       | 171         | 0,648      |        |        |       |
| Osteosarcoma NOS                                                  | 168         | 0,636      |        |        |       |
| Conventional chordoma                                             | 164         | 0,621      |        |        |       |
| Adenosarcoma                                                      | 156         | 0,591      |        |        |       |
| All undifferentiated sarcoma of bone                              | 152         | 0,576      |        |        |       |
| Inflammatory myofibroblastic Tumour                               | 145         | 0,549      |        |        |       |
| Pleomorphic RMS                                                   | 144         | 0,545      |        |        |       |
| Undifferentiated uterine sarcoma                                  | 141         | 0,534      |        |        |       |
| Liposarcoma - pleomorphic                                         | 139         | 0,527      |        |        |       |
| Phyllode sarcoma                                                  | 138         | 0,523      |        |        |       |
| Embryonal rhabdomyosarcoma usual type                             | 137         | 0,519      |        |        |       |
| Low grade fibromyxoid sarcoma                                     | 136         | 0,515      |        |        |       |
| Alveolar RMS                                                      | 123         | 0,466      |        |        |       |
| Smooth muscle tumour of undetermined malignancy                   | 122         | 0,462      |        |        |       |
| Epithelioid sarcoma                                               | 120         | 0,455      |        |        |       |
| Central chondrosarcoma, grades 2 and 3                            | 117         | 0,443      |        |        |       |
| So-called fibrohistiocytic tumours                                | 106         | 0,402      |        |        |       |
| Epithelioid hemangioendothelioma                                  | 100         | 0,379      |        |        |       |
| Epithelioid sarcoma                                               | 98          | 0,371      |        |        |       |
| Extraskeletal osteosarcoma                                        | 96          | 0,364      |        |        |       |
| Myoepithelioma, myoepithelial carcinoma, myoepithelioid carcinoma | 96          | 0,364      |        |        |       |
| Dedifferentiated chondrosarcoma                                   | 93          | 0,352      |        |        |       |
| RMS NOS                                                           | 88          | 0,333      |        |        |       |
| Myoepithelioma                                                    | 85          | 0,322      |        |        |       |
| Central atypical cartilaginous tumour / chondrosarcoma            | 76          | 0,288      |        |        |       |
| Clear cell sarcoma of soft tissue                                 | 71          | 0,269      |        |        |       |
| Giant cell tumour of soft tissue                                  | 70          | 0,265      |        |        |       |
| Synovial sarcoma - biphasic                                       | 70          | 0,265      |        |        |       |
| Undifferentiated pleomorphic sarcoma of bone                      | 69          | 0,261      |        |        |       |
| PECOMA - NOS                                                      | 67          | 0,254      |        |        |       |
| Extraskeletal myxoid chondrosarcoma                               | 58          | 0,220      |        |        |       |
| Round cell sarcoma with EWSR1-non-ETS fusion                      | 56          | 0,212      |        |        |       |
| Liposarcoma - round cell                                          | 54          | 0,205      |        |        |       |
| Aneurysmal bone cyst                                              | 53          | 0,201      |        |        |       |
| Desmoplastic small round cell tumour                              | 52          | 0,197      |        |        |       |
| Tumors of intermediate malignancy NOS ALL                         | 52          | 0,197      |        |        |       |
| Chondroblastoma                                                   | 52          | 0,197      |        |        |       |
| Extrarenal rhabdoid tumour                                        | 51          | 0,193      |        |        |       |
| Intimal sarcoma                                                   | 46          | 0,174      |        |        |       |
| Angiomatoid fibrous histiocytoma                                  | 43          | 0,163      |        |        |       |
| Sclerosing epithelioid fibrosarcoma                               | 41          | 0,155      |        |        |       |
| Endometrial stromal sarcoma - high-grade                          | 41          | 0,155      |        |        |       |
| All parosteal osteosarcoma                                        | 40          | 0,152      |        |        |       |
| Leiomyosarcoma of bone                                            | 40          | 0,152      |        |        |       |
| Spindle cell RMS                                                  | 39          | 0,148      |        |        |       |
| Peripheral chondrosarcoma                                         | 39          | 0,148      |        |        |       |
| Synovial sarcoma - poorly Differentiated                          | 37          | 0,140      |        |        |       |
| Malignant rhabdoid tumor                                          | 36          | 0,136      |        |        |       |
| Ossifying fibromyxoid Tumour                                      | 32          | 0,121      |        |        |       |
| Alveolar soft part sarcoma                                        | 31          | 0,117      |        |        |       |
| Mesenchymal chondrosarcoma                                        | 31          | 0,117      |        |        |       |
| Osteoblastoma                                                     | 31          | 0,117      |        |        |       |
| Plexiform fibrohistiocytic tumors                                 | 29          | 0,110      |        |        |       |
| Embryonal rhabdomyosarcoma spindle cell                           | 29          | 0,110      |        |        |       |
| Angiosarcoma of bone                                              | 29          | 0,110      |        |        |       |
| Adult fibrosarcoma                                                | 28          | 0,106      |        |        |       |
| Parosteal osteosarcoma                                            | 27          | 0,102      |        |        |       |

| Histotypes                                      | Total       | Incidence  | Ph III | RPh II | Ph II |
|-------------------------------------------------|-------------|------------|--------|--------|-------|
|                                                 | (2013-2016) | /10e6/year |        |        |       |
| Incidence <0.1/10e6/year                        |             |            |        |        |       |
| Osteoblastoma-like osteosarcoma                 |             |            |        |        |       |
| Chondromyxoid fibroma                           | 26          | 0,098      |        |        |       |
| Undifferentiated spindle cell sarcoma           | 26          | 0,098      |        |        |       |
| Periosteal chondrosarcoma                       | 25          | 0,095      |        |        |       |
| High-grade surface osteosarcoma                 | 25          | 0,095      |        |        |       |
| Myxoinflammatory Fibroblastic Sarcoma           | 23          | 0,087      |        |        |       |
| Embryonal RMS sarcoma - botryoid type           | 23          | 0,087      |        |        |       |
| Undifferentiated epithelioid sarcoma            | 22          | 0,083      |        |        |       |
| Langerhans cell histiocytosis                   | 20          | 0,076      |        |        |       |
| Malignant PECOMA                                | 19          | 0,072      |        |        |       |
| Low grade central osteosarcoma (ALL)            | 19          | 0,072      |        |        |       |
| Adamantinoma                                    | 19          | 0,072      |        |        |       |
| UTROSC                                          | 17          | 0,064      |        |        |       |
| Endometrial stromal nodule                      | 16          | 0,061      |        |        |       |
| Telangiectatic osteosarcoma                     | 16          | 0,061      |        |        |       |
| SMARCA4-deficient thoracic sarcoma              | 15          | 0,057      |        |        |       |
| Clear cell chondrosarcoma                       | 14          | 0,053      |        |        |       |
| Low grade Myxofibroblastic Sarcoma              | 13          | 0,049      |        |        |       |
| Dedifferentiated parosteal osteosarcoma         | 13          | 0,049      |        |        |       |
| Dedifferentiated low grade central osteosarcoma | 12          | 0,045      |        |        |       |
| Giant cell Fibroblastoma                        | 11          | 0,042      |        |        |       |
| Sclerosing RMS                                  | 11          | 0,042      |        |        |       |
| CIC-rearranged sarcoma                          | 11          | 0,042      |        |        |       |
| Infantile fibrosarcoma                          | 10          | 0,038      |        |        |       |
| Pericytic (perivascular) tumours                | 10          | 0,038      |        |        |       |
| Malignant Triton tumour                         | 10          | 0,038      |        |        |       |
| Retiform hemangio-endothelioma                  | 9           | 0,034      |        |        |       |
| Ectomesenchymoma : Malignant mesenchymoma       | 9           | 0,034      |        |        |       |
| Malignant granular cell Tumour                  | 9           | 0,034      |        |        |       |
| Haemosiderotic fibrolipomatous tumour           | 9           | 0,034      |        |        |       |
| Synovial sarcoma of bone                        | 9           | 0,034      |        |        |       |
| RMS of bone                                     | 9           | 0,034      |        |        |       |
| Lipofibromatosis                                | 8           | 0,030      |        |        |       |
| Sarcoma with BCOR genetic alterations           | 7           | 0,027      |        |        |       |
| Low-grade central osteosarcoma                  | 7           | 0,027      |        |        |       |
| Pseudomyogenic hemangioendothelioma             | 6           | 0,023      |        |        |       |
| Intermediate vascular tumours                   | 6           | 0,023      |        |        |       |
| MPNST - epithelioid type                        | 6           | 0,023      |        |        |       |
| Mixed tumour                                    | 6           | 0,023      |        |        |       |
| Desmoplastic fibroma of bone                    | 6           | 0,023      |        |        |       |
| Malignant/dedifferentiated GCTB                 | 6           | 0,023      |        |        |       |
| BCOR Sarcoma of bone                            | 6           | 0,023      |        |        |       |
| Intermediate fibrohistiocytic tumors            | 5           | 0,019      |        |        |       |
| Adult spindle cell RMS                          | 5           | 0,019      |        |        |       |
| Phosphaturic mesenchymal tumour                 | 5           | 0,019      |        |        |       |
| Low grade sinonasal sarcoma                     | 5           | 0,019      |        |        |       |
| Periosteal osteosarcoma                         | 5           | 0,019      |        |        |       |
| Kaposiform hemangioendothelioma                 | 4           | 0,015      |        |        |       |
| Small cell osteosarcoma                         | 4           | 0,015      |        |        |       |
| Myoepithelioma of bone                          | 4           | 0,015      |        |        |       |
| Liposarcoma of bone                             | 4           | 0,015      |        |        |       |
| Composite hemangioendothelioma                  | 3           | 0,011      |        |        |       |
| Malignant perineuroma                           | 3           | 0,011      |        |        |       |
| Adult fibrosarcoma of bone                      | 3           | 0,011      |        |        |       |
| Liposarcoma - mixed type                        | 2           | 0,008      |        |        |       |
| Malignant tenosynovial giant cell tumors        | 2           | 0,008      |        |        |       |
| Metastatic leiomyoma                            | 2           | 0,008      |        |        |       |
| Malignant myoepithelial Tumour                  | 2           | 0,008      |        |        |       |
| Osteoblastoma-like osteosarcoma                 | 2           | 0,008      |        |        |       |
| Dedifferentiated chordoma                       | 2           | 0,008      |        |        |       |
| Lipomatous spindle cell/pleomorphic tumour      | 1           | 0,004      |        |        |       |
| Papillary intralymphatic angioendothelioma      | 1           | 0,004      |        |        |       |
| Melanotic neuroectodermal tumour of infant      | 1           | 0,004      |        |        |       |
| Osteogenic tumor of uncertain prognosis         | 1           | 0,004      |        |        |       |
| Fibro-osseous tumour of bone NOS                | 1           | 0,004      |        |        |       |
| Undifferentiated epithelioid sarcoma            | 1           | 0,004      |        |        |       |

# Much more than what we think?



(James Webb telescope)

# Challenges?

Nosologies

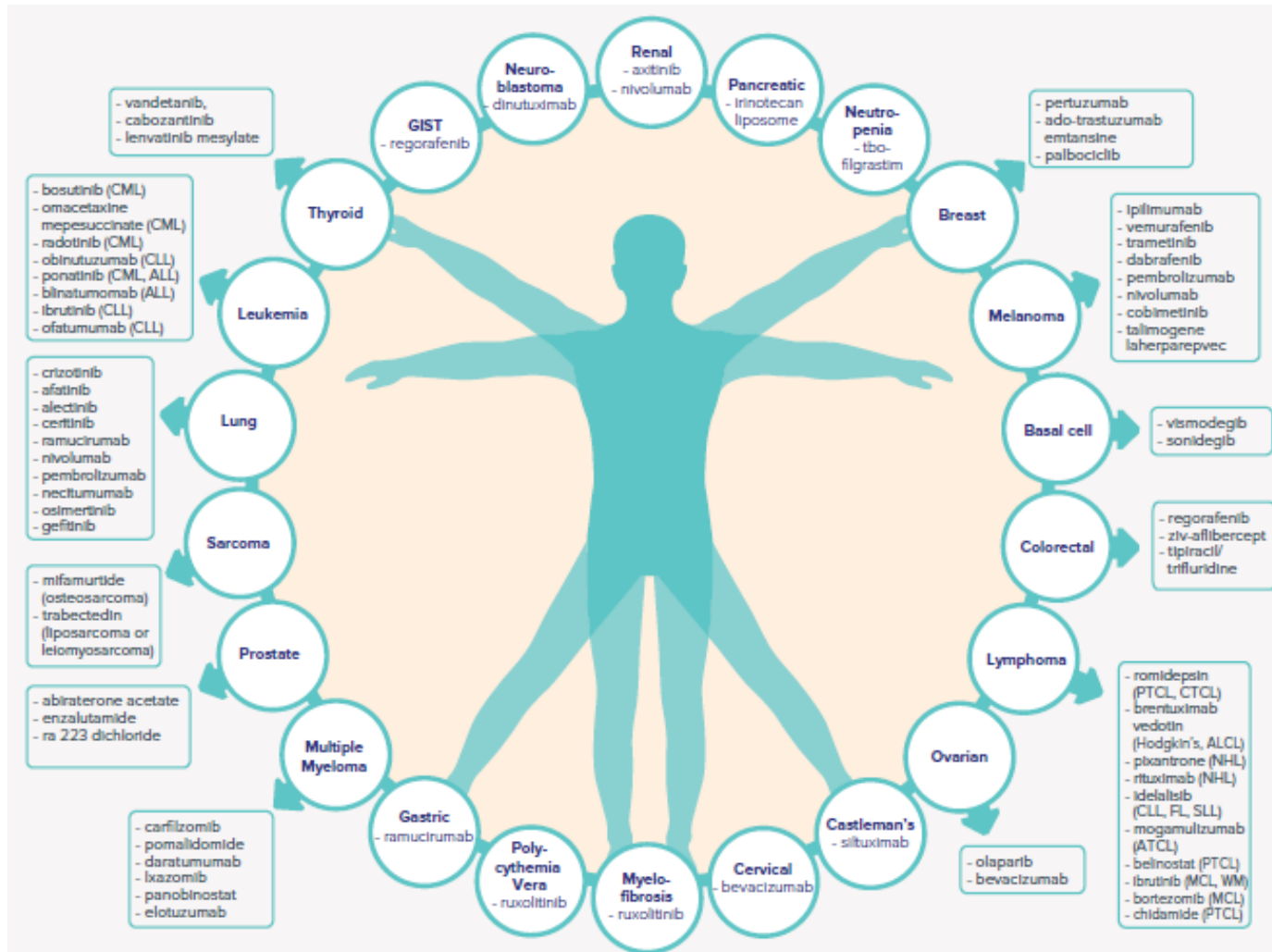
First optimal local treatment

Which molecular test, which molecular subsets

New designs for clinical trials

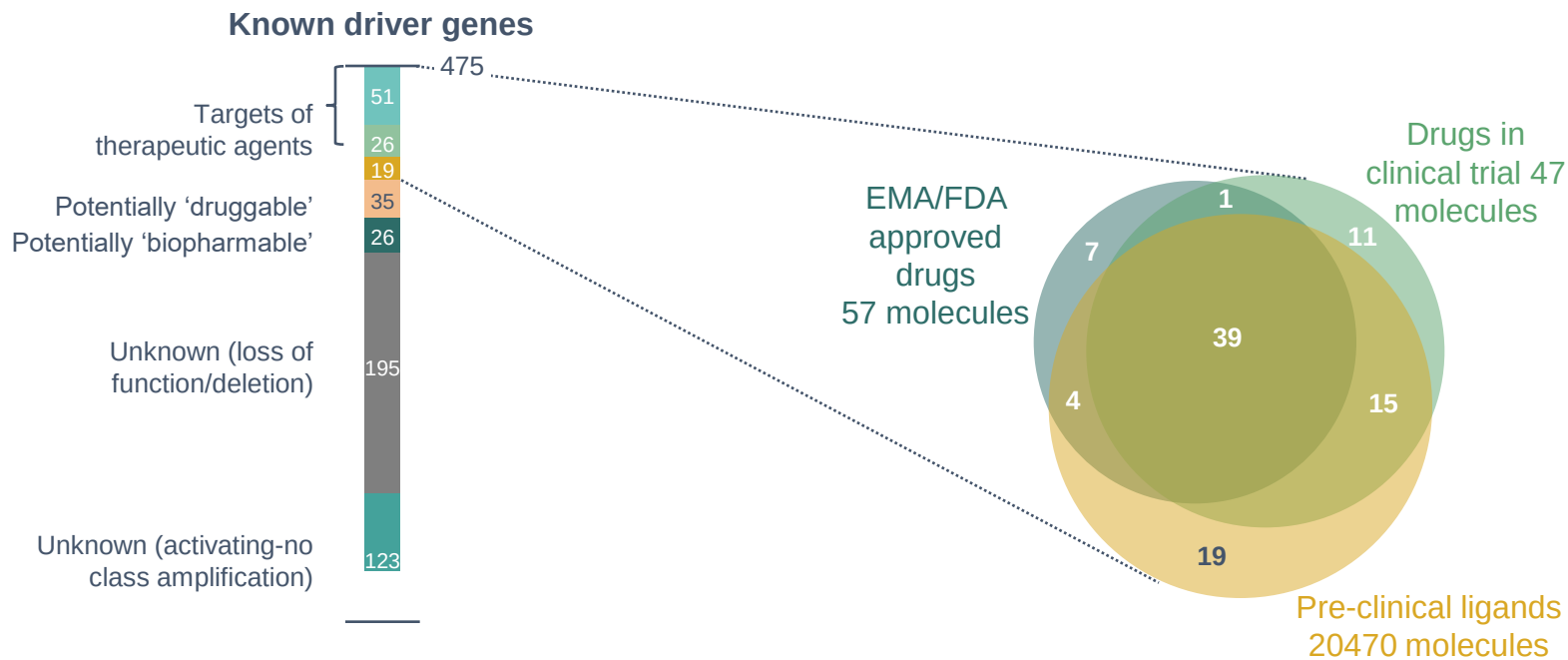
New strategies, new paradigms

# Since 2011, >100 new medications in oncology



Source: IMS Health, MIDAS, Lifecycle, R&D Focus, IMS Institute for Healthcare Informatics

# Access to therapy: only ~20% of known driver genes have an associated therapy

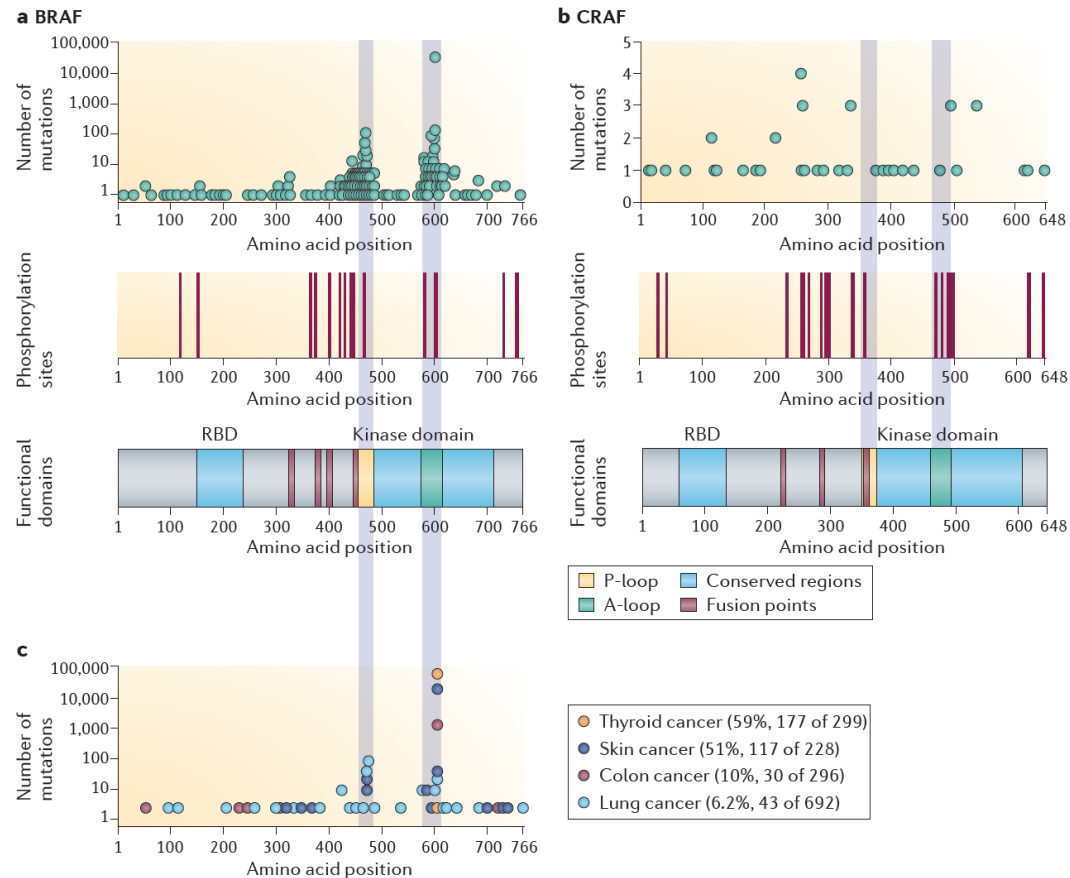


# What is a strong driver?

## Median PFS

|                                       |               |
|---------------------------------------|---------------|
| <b>GIST KIT exon 11 (70%)</b>         | <b>40 mos</b> |
| <b>Thymoma KIT exon 11 (?%)</b>       | <b>?6 mos</b> |
| <b>Melanoma KIT exon 11 (&lt;10%)</b> | <b>4 mos</b>  |

# Mutations de BRAF



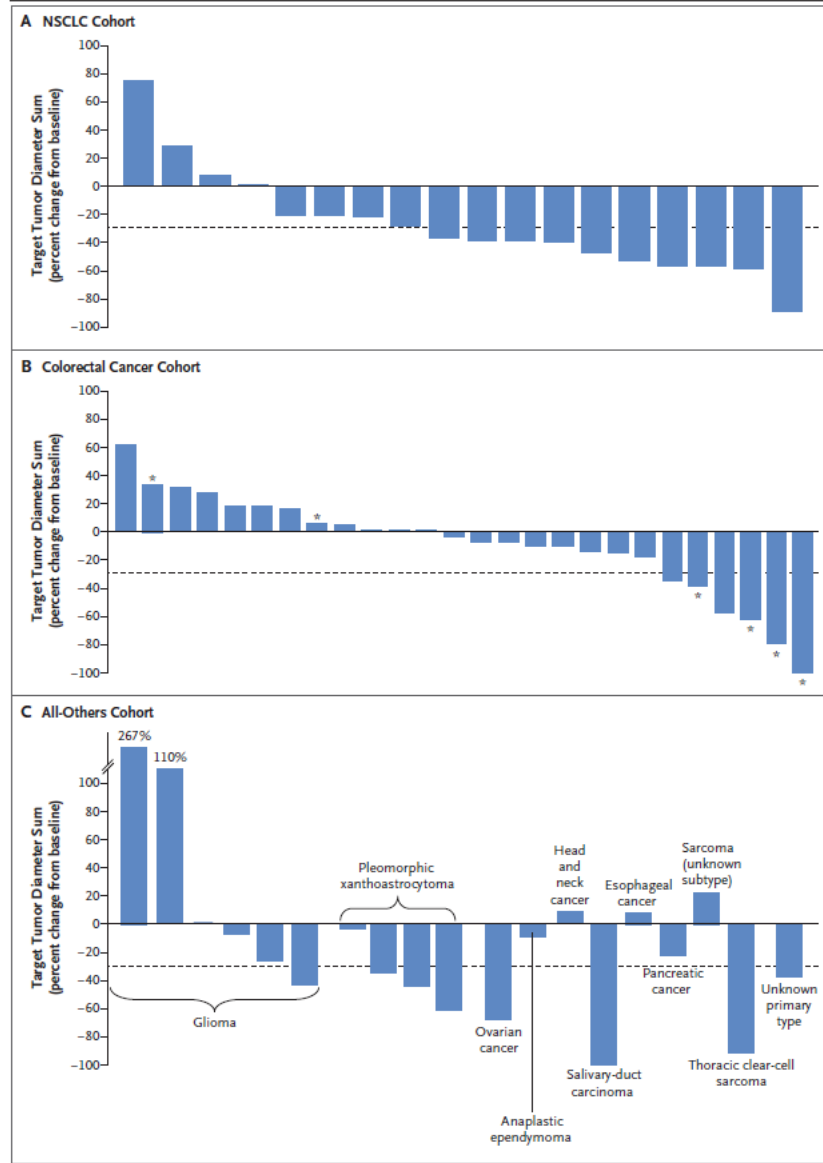
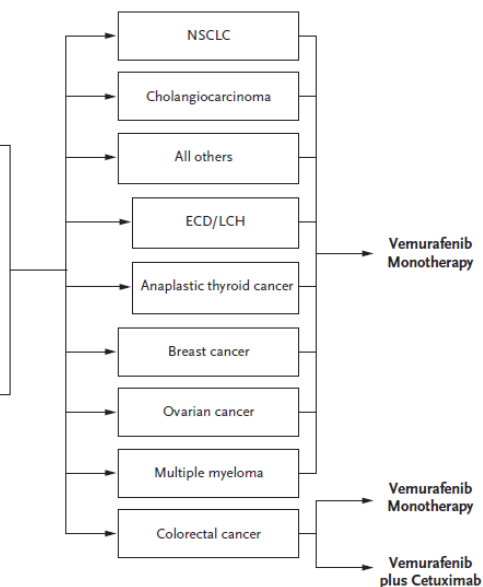
**Figure 1 | BRAF and CRAF mutations in cancer.** BRAF amino acid positions (1–766) (part **a**) and CRAF amino acid positions (1–648) (part **b**) are depicted on the x-axis. In both part **a** and part **b**, the top graphs show the number of mutations that are reported for each position<sup>15</sup>; the middle panels show the position of putative phosphorylation sites that are reported to have a functional consequence on kinase activity, stability or localization; and the bottom panels show BRAF and CRAF functional domains: the RAS-binding domain (RBD) and the kinase domain are highlighted in blue, the phosphate-binding loop (P-loop) is highlighted in yellow, the activation loop (A-loop) is highlighted in green and fusion points are highlighted in magenta. Part **c** shows the spectrum of BRAF mutations compiled from multiple studies<sup>75</sup> in thyroid<sup>19</sup>, skin<sup>141,142</sup>, colon<sup>143,144</sup> and lung<sup>40,145,146</sup> cancers (no equivalent graph is shown for CRAF mutations owing to their low frequency across all cancers). The sample size of the compiled sequencing data and the percentage of BRAF mutations for each indication are also shown.

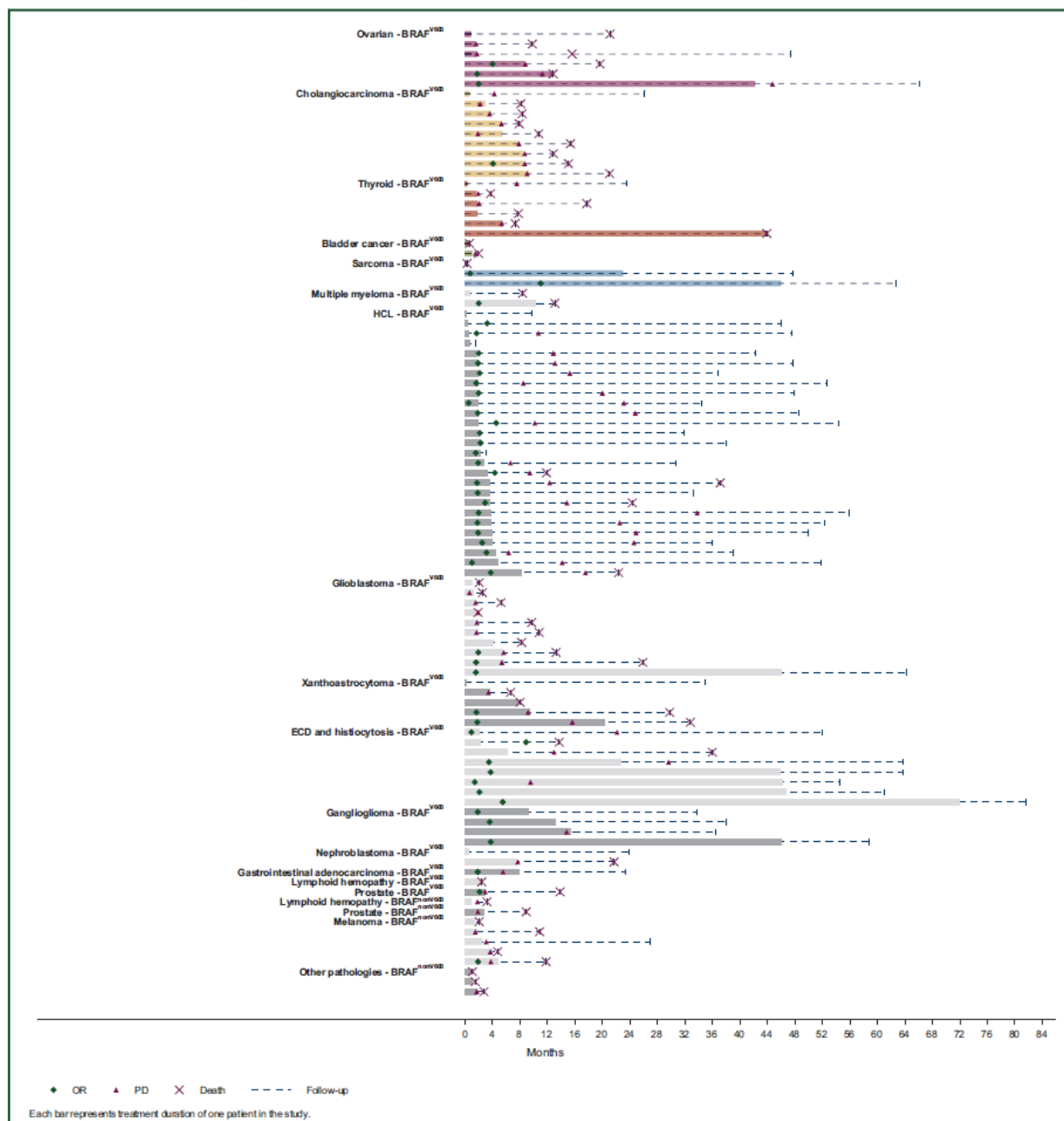
## ORIGINAL ARTICLE

# Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.

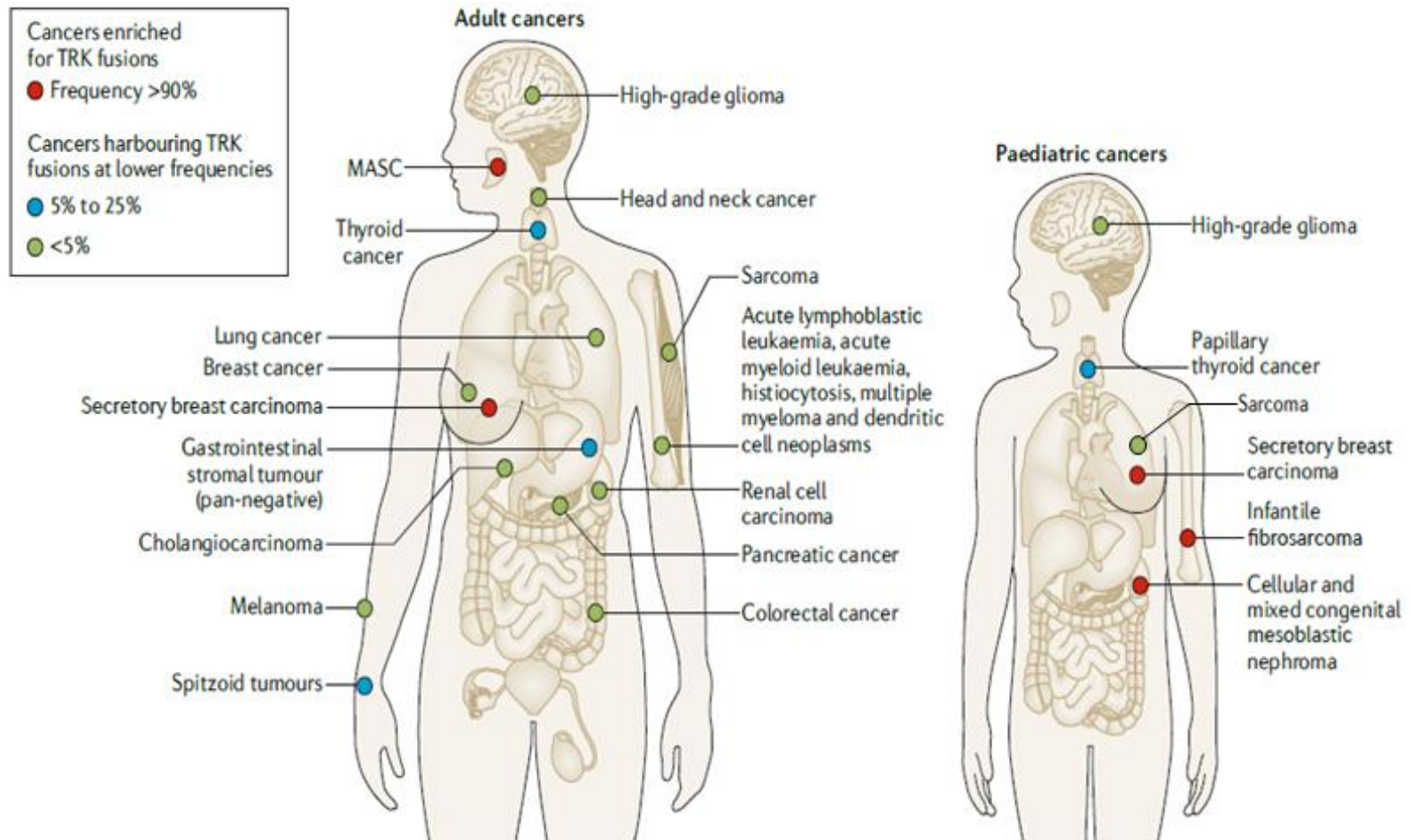
*BRAF* V600-positive (testing per local methods)  
Vemurafenib, 960 mg twice daily orally  
Primary end point  
Response rate at wk 8  
Secondary end points  
Progression-free survival  
Time to progression  
Best overall response  
Time to response  
Duration of response  
Clinical benefit rate  
Overall survival  
Safety





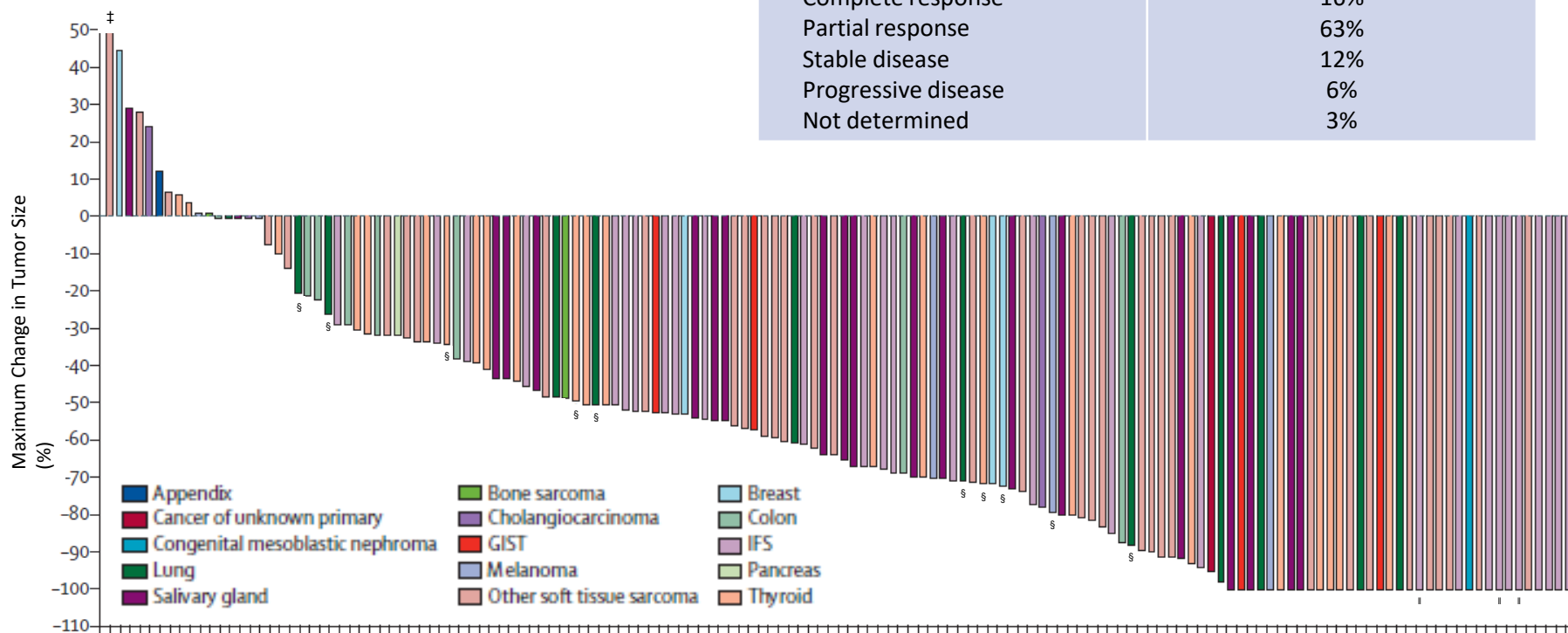
**Figure 2. Vemurafenib treatment duration and activity.** For hairy cell leukaemia (HCL), vemurafenib is prescribed for two cycles (first assessment) and possibly for two additional cycles if a complete response is not achieved at cycle 2. In total, treatment is stopped at day 112 (maximum) whatever the response. OR, objective response; PD, progressive disease.

# NTRK fusions across cancers



# Larotrectinib Overall Response Rates

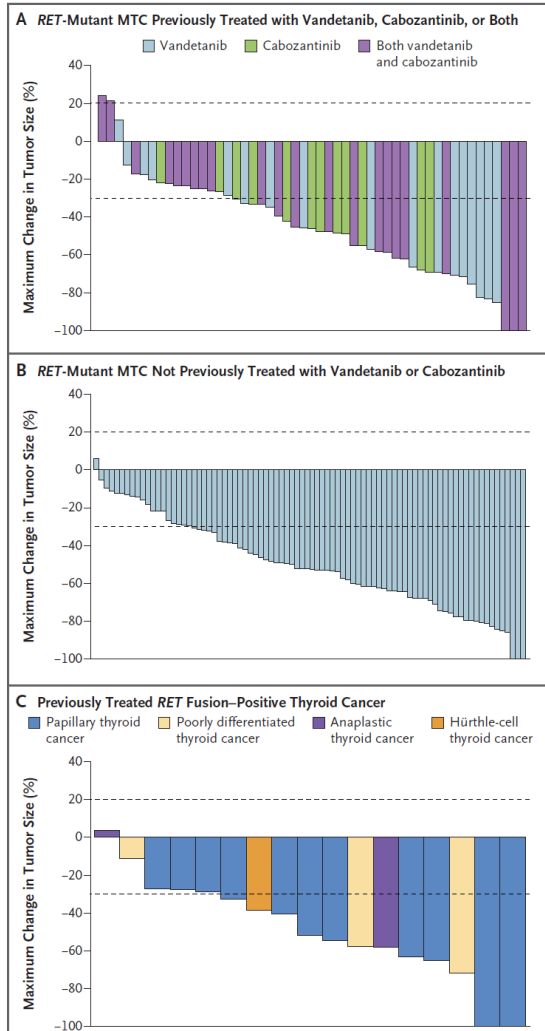
|                                  | Investigator assessment (n=159) |
|----------------------------------|---------------------------------|
| Evaluable patients               | 153*                            |
| Objective response rate (95% CI) | 79% (72-85)                     |
| Best response                    |                                 |
| Complete response <sup>†</sup>   | 16%                             |
| Partial response                 | 63%                             |
| Stable disease                   | 12%                             |
| Progressive disease              | 6%                              |
| Not determined                   | 3%                              |



\*Evaluative patients include 13 patients with unconfirmed partial responses pending confirmation (deemed to be responses), but does not include 6 patients continuing on study and awaiting an initial response assessment. Best response percentages are calculated from the evaluable patient population (n=153). <sup>†</sup>Including 3 patients with pathological complete response; 2 patients had complete responses pending confirmation after an earlier assessment of partial response (ie, classified overall as confirmed responses). <sup>‡</sup>Maximum change in tumour size of 93% tumour growth. <sup>§</sup>Patients with brain metastases. <sup>||</sup>Patients with a pathological complete response. Hong DS et al. *Lancet Oncol.* 2020;S1470-2045(19)30856-3.

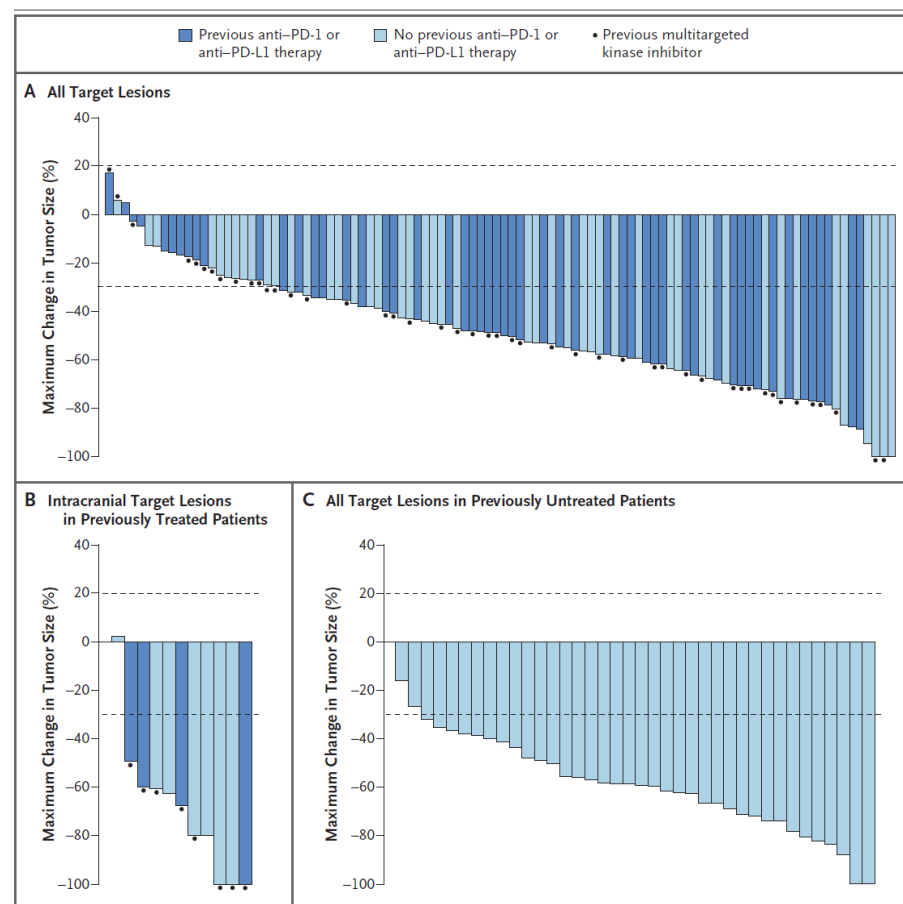
# Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers

L.J. Wirth, E. Sherman, B. Robinson, B. Solomon, H. Kang, J. Lorch, F. Worden, M. Brose, J. Patel, S. Leboulleux, Y. Godbert, F. Barlesi, J.C. Morris, T.K. Owonikoko, D.S.W. Tan, O. Gautschi, J. Weiss, C. de la Fouchardière, M.E. Burkard, J. Laskin, M.H. Taylor, M. Kroiss, J. Medioni, J.W. Goldman, T.M. Bauer, B. Levy, V.W. Zhu, N. Lakhani, V. Moreno, K. Ebata, M. Nguyen, D. Heirich, E.Y. Zhu, X. Huang, L. Yang, J. Kherani, S.M. Rothenberg, A. Drilon,

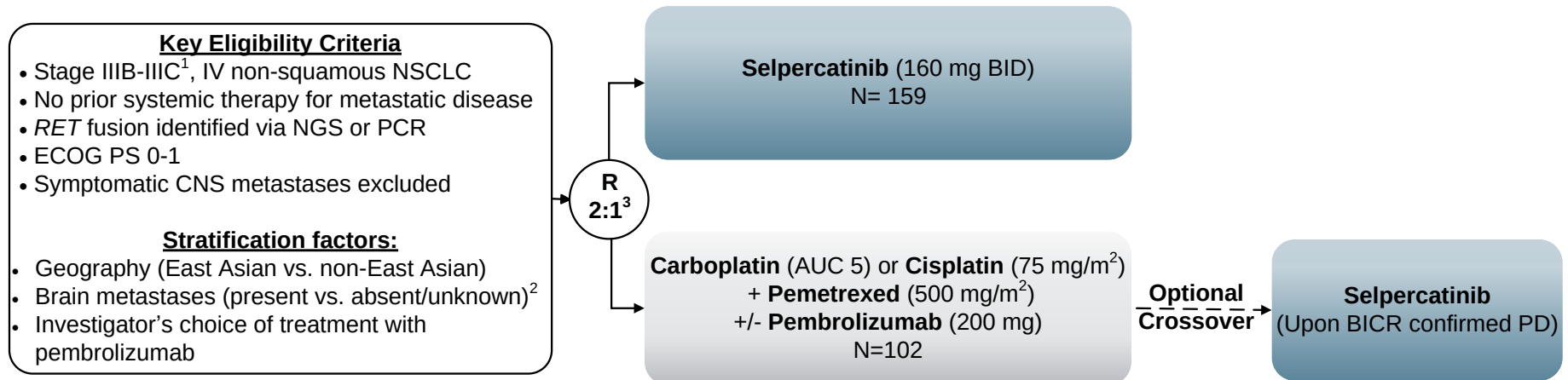


# Efficacy of Selpercatinib in *RET* Fusion-Positive Non-Small-Cell Lung Cancer

A. Drilon, G.R. Oxnard, D.S.W. Tan, H.H.F. Loong, M. Johnson, J. Gainor, C.E. McCoach, O. Gautschi, B. Besse, B.C. Cho, N. Peled, J. Weiss, Y.-J. Kim, Y. Ohe, M. Nishio, K. Park, J. Patel, T. Seto, T. Sakamoto, E. Rosen, M.H. Shah, F. Barlesi, P.A. Cassier, L. Bazhenova, F. De Braud, E. Garraza, V. Velcheti, M. Satouchi, K. Ohashi, N.A. Pennell, K.L. Reckamp, G.K. Dy, J. Wolf, B. Solomon, G. Falchook, K. Ebata, M. Nguyen, B. Nair, E.Y. Zhu, L. Yang, X. Huang, E. Olek, S.M. Rothenberg, K. Goto, and V. Subbiah



# LIBRETTO-431 phase 3 open-label study design



**Gated Primary Endpoints:** PFS by blinded independent central review (BICR) in ITT-Pembrolizumab<sup>4</sup> and ITT population

**Secondary Endpoints:**

- **Efficacy** ([OS, ORR, DOR], CNS [ORR, DOR, time to progression]<sup>5</sup>)
- **Safety**
- **Patient Reported Outcomes** (NSCLC-SAQ [tertiary endpoint EORTC QLQ-C30])

<sup>1</sup> not suitable for radical surgery/radiation therapy

<sup>2</sup> Investigator assessed

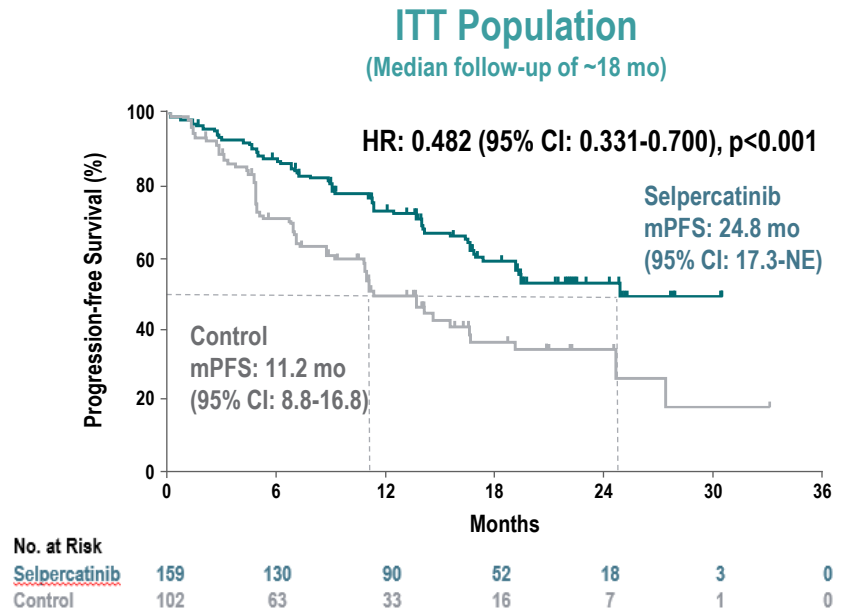
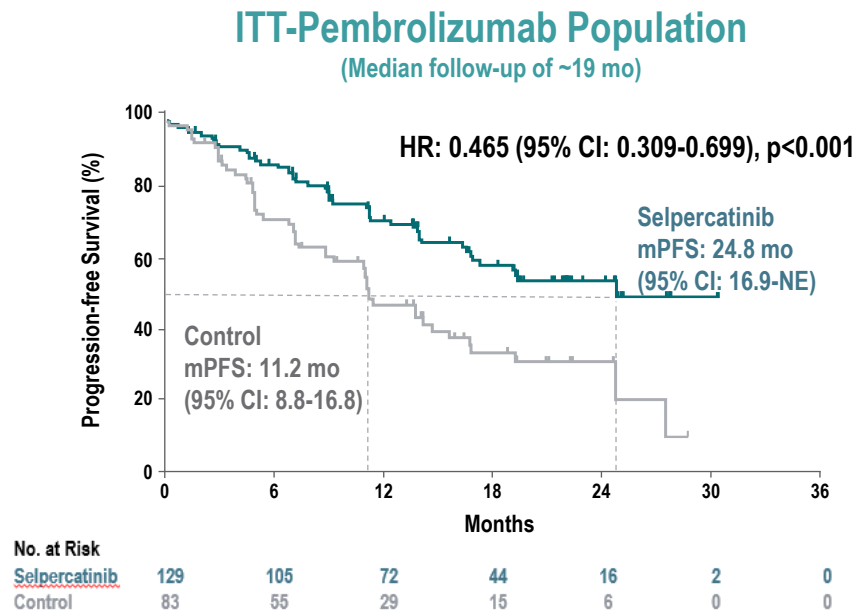
<sup>3</sup> the initial randomization ratio was 1:1, but amended to 2:1

<sup>4</sup> ITT-Pembrolizumab are patients stratified with investigator intent to receive chemotherapy with pembrolizumab and per protocol had to be at least 80% of the ITT population

<sup>5</sup> Baseline and longitudinal intracranial scans were required for all patients following an amendment. Prior to the amendment, longitudinal intracranial scans were required if known CNS metastases at baseline

Herbert H. Loong

# Progression-free survival (PFS) assessed by BICR



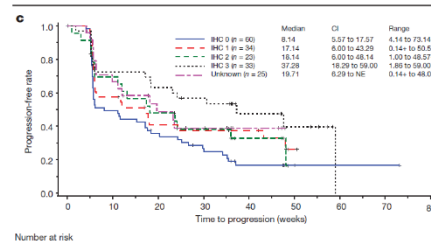
The primary endpoints were met, as selpercatinib resulted in a statistically significant improvement in PFS in both pre-specified populations

Herbert H. Loong

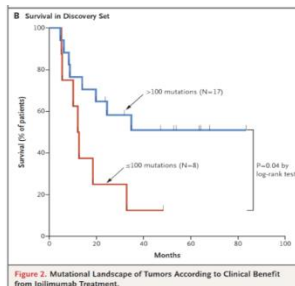
Immunotherapy : early and  
everywhere?

# Predictive immune markers

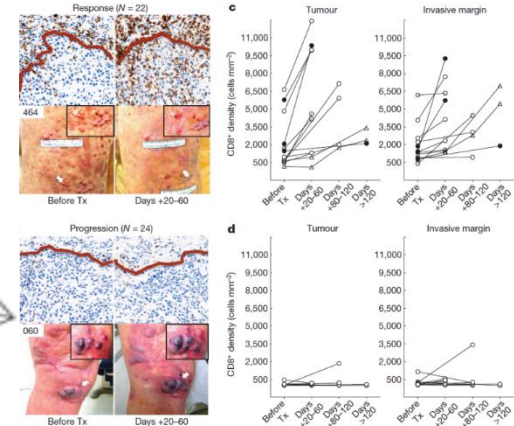
## PDL1 expression



## Mutation load



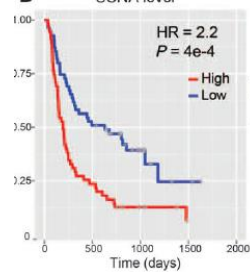
## Immune infiltrates



## Aneuploidy

**Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy**

Teresa Davoli,<sup>1</sup> Hajime Uno,<sup>2</sup> Eric C. Wooten,<sup>1</sup> Stephen J. Elledge<sup>1\*</sup>



Herbst Nature 2014, Tumei Nature 2014, Snyder NEJM 2014, Davoli et al, Science 2017

# The NEW ENGLAND JOURNAL of MEDICINE

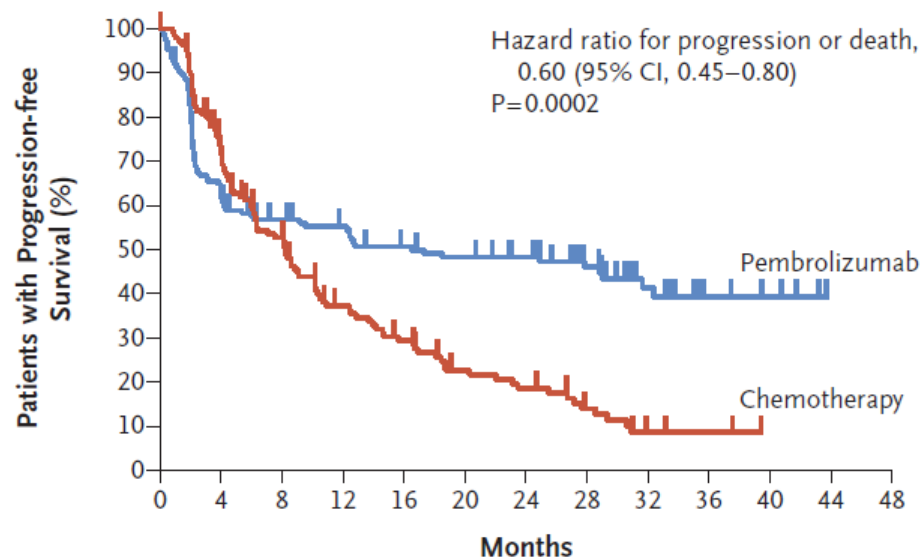
ESTABLISHED IN 1812

DECEMBER 3, 2020

VOL. 383 NO. 23

## Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators\*



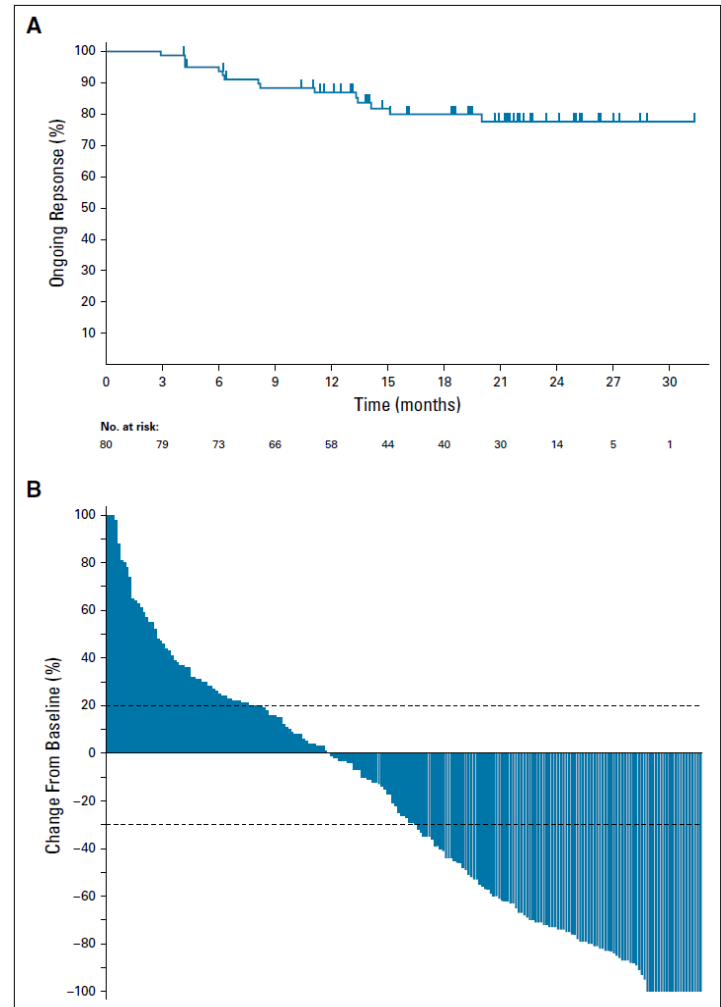
### No. at Risk

|               |     |     |    |    |    |    |    |    |    |   |   |   |   |
|---------------|-----|-----|----|----|----|----|----|----|----|---|---|---|---|
| Pembrolizumab | 153 | 96  | 77 | 72 | 64 | 60 | 55 | 37 | 20 | 7 | 5 | 0 | 0 |
| Chemotherapy  | 154 | 100 | 68 | 43 | 33 | 22 | 18 | 11 | 4  | 3 | 0 | 0 | 0 |

**Figure 1. Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer.**

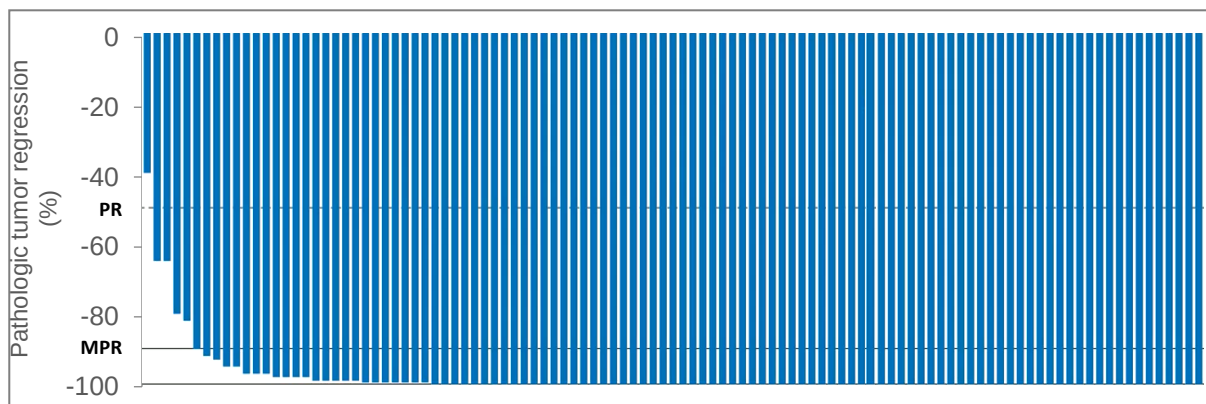
## Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

Aurelien Marabelle, MD, PhD<sup>1</sup>; Dung T. Le, MD<sup>2</sup>; Paolo A. Ascierto, MD<sup>3</sup>; Anna Maria Di Giacomo, MD<sup>4</sup>; Ana De Jesus-Acosta, MD<sup>5</sup>; Jean-Pierre Delord, MD, PhD<sup>6</sup>; Ravit Geva, MD, MSc<sup>6</sup>; Maya Gottfried, MD<sup>7</sup>; Nicolas Penel, MD, PhD<sup>8</sup>; Aaron R. Hansen, MBBS<sup>9</sup>; Sarina A. Piha-Paul, MD<sup>10</sup>; Toshihiko Doi, MD, PhD<sup>11</sup>; Bo Gao, MBBS, PhD<sup>12</sup>; Hyun Cheol Chung, MD, PhD<sup>13</sup>; Jose Lopez-Martin, MD, PhD<sup>14</sup>; Yung-Jue Bang, MD, PhD<sup>15</sup>; Ronnie Shapira Frommer, MD<sup>16</sup>; Manisha Shah, MD<sup>17</sup>; Razi Ghorri, PhD<sup>18</sup>; Andrew K. Joe, MD<sup>19</sup>; Scott K. Pruitt, MD, PhD<sup>18</sup>; and Luis A. Diaz Jr, MD<sup>19</sup>



## Results

# Nivolumab + ipilimumab : neoadjuvant for localized CRC dMMR/MSI NICHE2



- **Major path response = 95% incl 67% pCR**  
→ 58% CC sporadic vs 78% Lynch (p=0.056)
- **Surgery in 100%, 2 with delay > 2 wks(98% ok)**  
→ Tox all grade : 61%, 4% grade 3/4.  
→ Tox grade 3/4 immuno-related : 3% des pts.
- **Median follow up 13.1 mos : no relapse**

| Histological response |             | Patients<br>n= 107 |
|-----------------------|-------------|--------------------|
| Yes                   | (≤ 50%)     | 106 (99%)          |
| Major                 | (≤ 50%)     | 102 (95%)          |
| Complete              | (0%)        | 72 (67%)           |
| Partial               | (10% - 50%) | 4 (4%)             |
| No                    | (≥ 50%)     | 1 (1%)             |

RVT = residual viable tumor



**New standard !**

---

# Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial

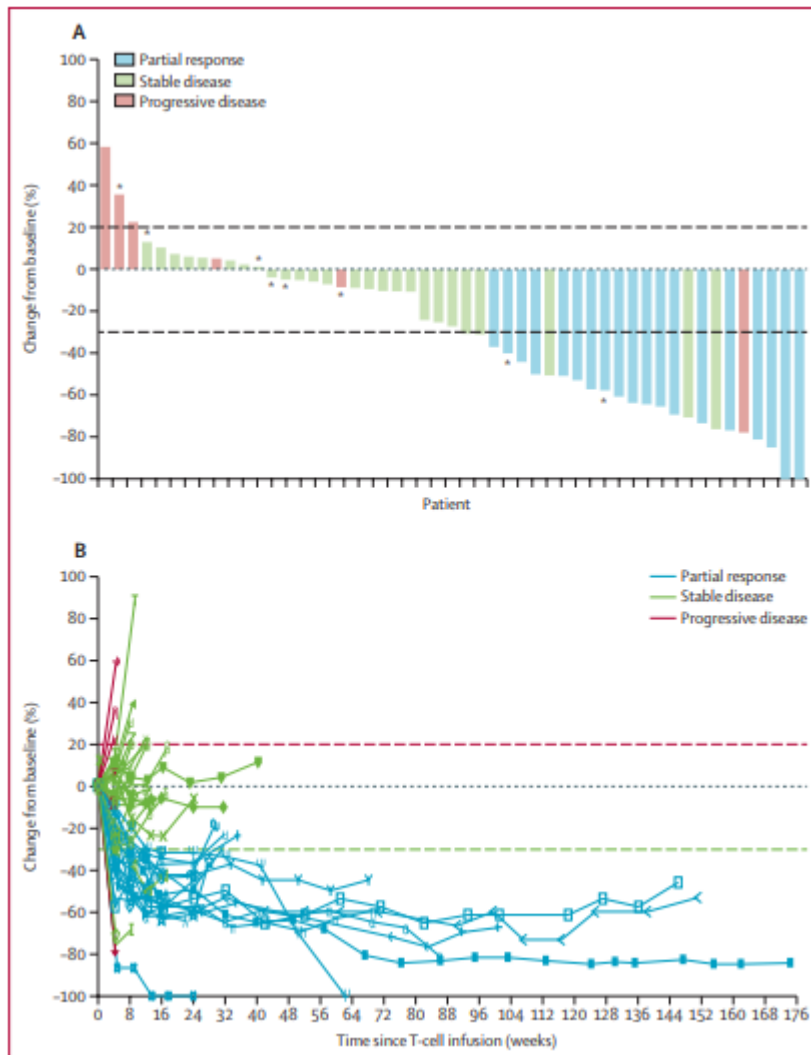


*Sandra P D'Angelo, Dejka M Araujo, Albiruni R Abdul Razak, Mark Agulnik, Steven Attia, Jean-Yves Blay, Irene Carrasco Garcia, John A Charlson, Edwin Choy, George D Demetri, Mihaela Druta, Edouard Forcade, Kristen N Ganjoo, John Glod, Vicki L Keedy, Axel Le Cesne, David A Liebner, Victor Moreno, Seth M Pollack, Scott M Schuetze, Gary K Schwartz, Sandra J Strauss, William D Tap, Fiona Thistlethwaite, Claudia Maria Valverde Morales, Michael J Wagner, Breeelyn A Wilky, Cheryl McAlpine, Laura Hudson, Jean-Marc Navenot, Tianjiao Wang, Jane Bai, Stavros Rafail, Ruoxi Wang, Amy Sun, Lilliam Fernandes, Erin Van Winkle, Erica Elefant, Colin Lunt, Elliot Norry, Dennis Williams, Swethajit Biswas, Brian A Van Tine*

# Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial



Sandra P D'Angelo, Dejka M Araujo, Albiun R Abdul Razak, Mark Agulnik, Steven Attia, Jean-Yves Blay, Irene Carrasco Garcia, John A Charlson, Edwin Choy, George D Demetri, Mihaela Druta, Edouard Forcade, Kristen N Ganjoo, John Glod, Vicki L Keedy, Axel Le Cesne, David A Lieber, Victor Moreno, Seth M Pollack, Scott M Schuetz, Gary K Schwartz, Sandra J Strauss, William D Tap, Fiona Thistlethwaite, Claudia Maria Valverde Morales, Michael J Wagner, Breeley A Wilky, Cheryl McAlpine, Laura Hudson, Jean-Marc Navenot, Tianjiao Wang, Jane Bai, Stavros Rafail, Ruoxi Wang, Amy Sun, Lilliam Fernandes, Erin Van Winkle, Erica Elefant, Colin Lunt, Elliot Norry, Dennis Williams, Swethajit Biswas, Brian A Van Tine



(Figure 2 continues on next page)

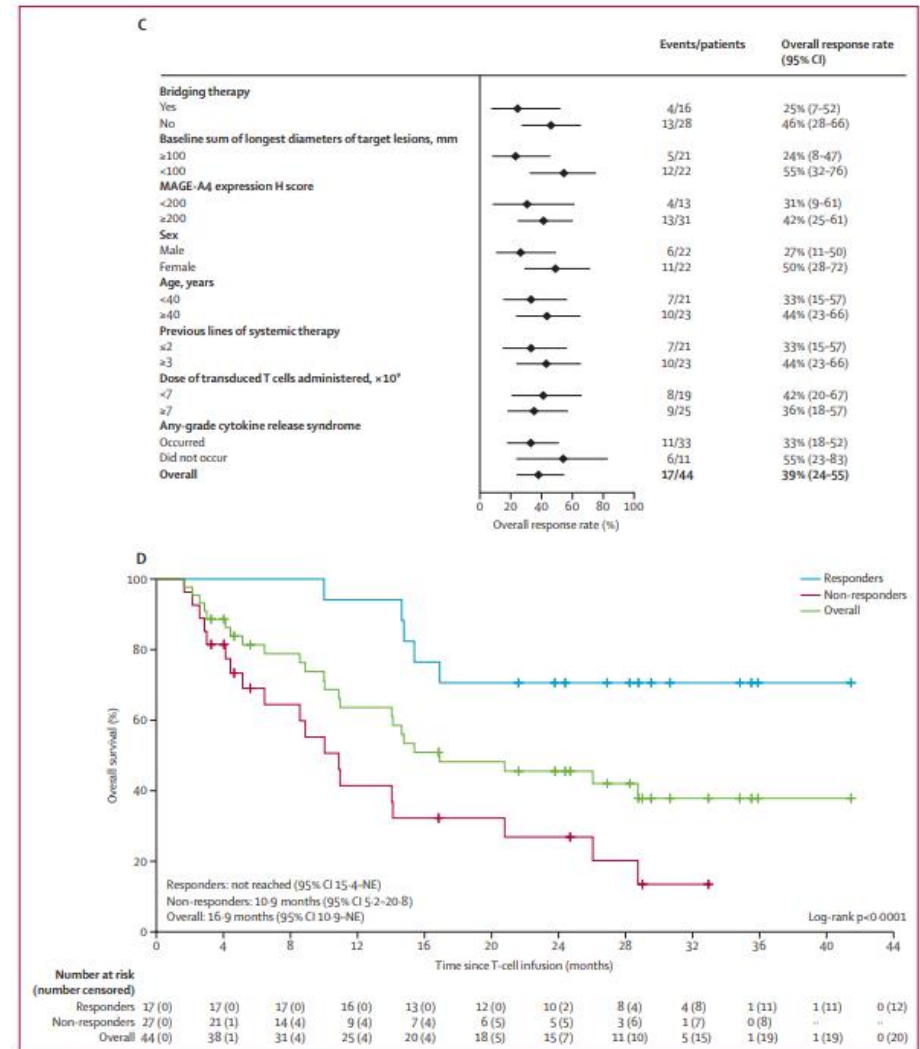


Figure 2: Response and prognostic characteristics of patients in the modified intention-to-treat population

# Challenges?

Nosologies

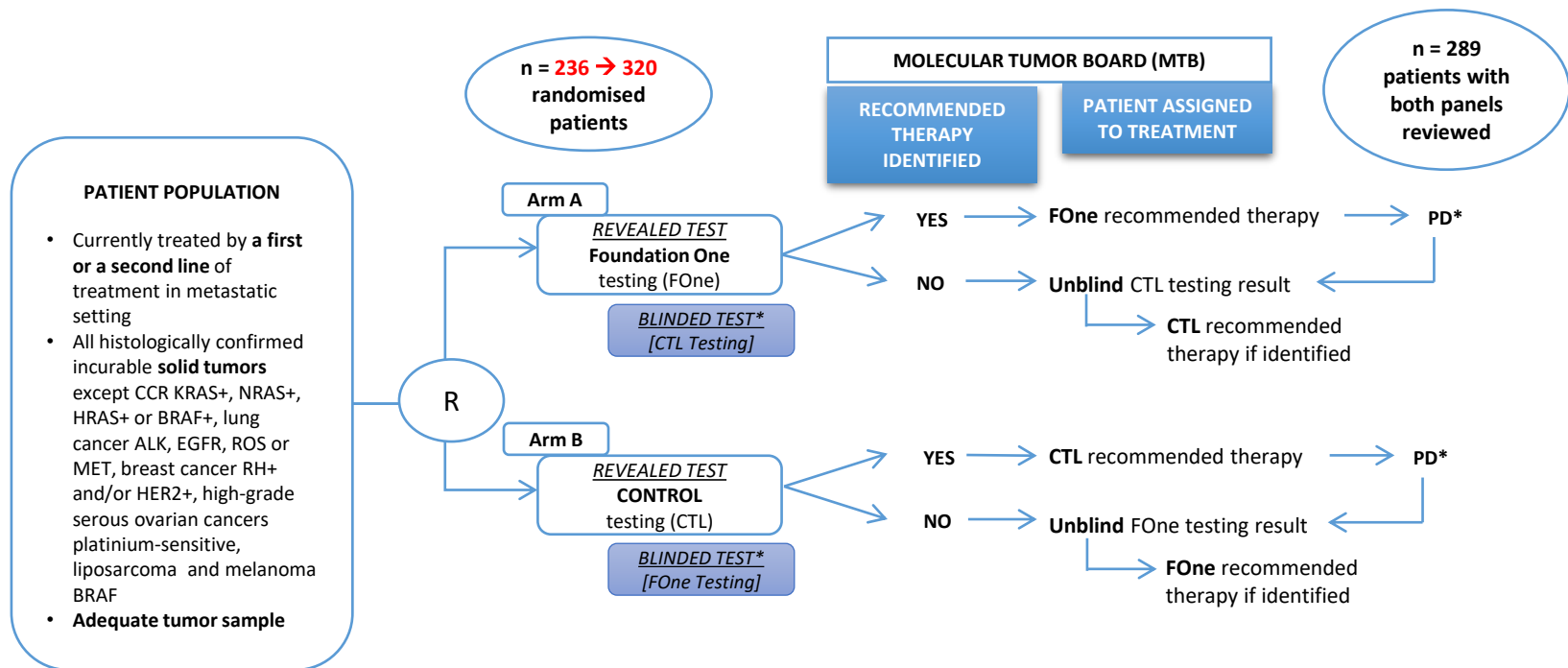
First optimal local treatment

Which molecular test, which molecular subsets

New designs for clinical trials

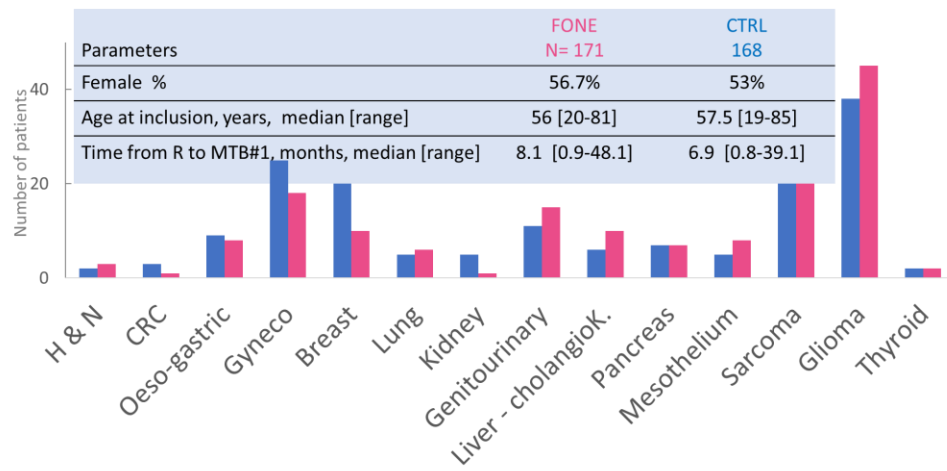
New strategies, new paradigms

## PROFILER 02 - DESIGN



## BASILINE CHARACTERISTICS

From June 2017 to June 2019, 339 pts were randomised (Arm FONE: 171 and Arm CTRL: 168 pts). Main\* tumor types per arm are presented below.



\* Only tumor types with > 1 patient in both study arms are presented.

## PRIMARY ENDPOINT

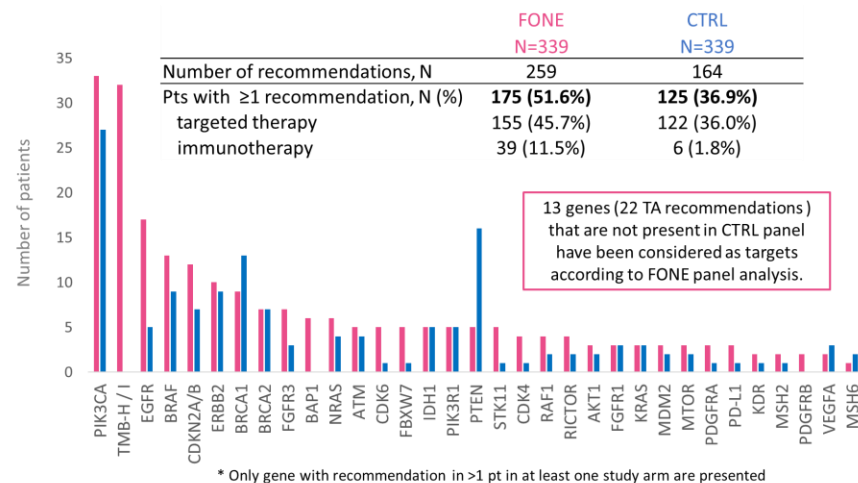
Overall, 108 randomized pts (31.9%) had at least one TA recommendation according to both panels.

**67 pts (19.8%) had at least one TA recommendation according to FONE panel only vs 17 pts (5%) according to CTRL panel only, McNemar:  $p < 0.001$ .**

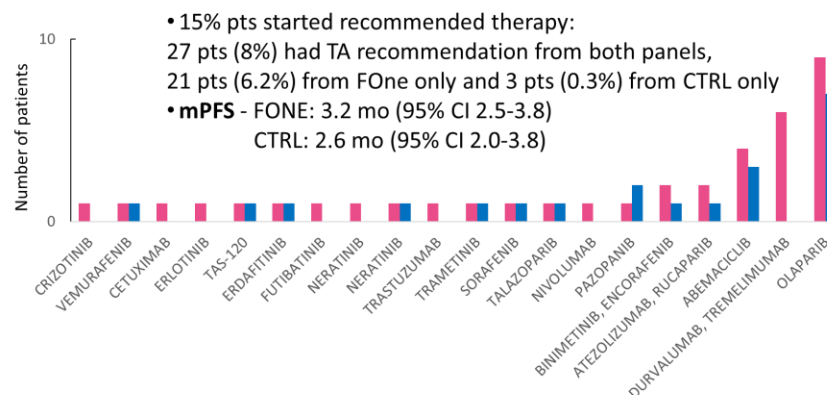
| % of pts with at least one recommended TA |       | CTRL panel  |              |       |
|-------------------------------------------|-------|-------------|--------------|-------|
|                                           |       | +           | -            | Total |
| FONE panel                                | +     | 31.9%       | <b>19.8%</b> | 51.6% |
|                                           | -     | <b>5.0%</b> | 43.4%        | 48.4% |
|                                           | Total | 36.9%       | 63.3%        | 100%  |

Excluding pts with only 1 panel available (N=30) or excluding pts with recommendation of immunotherapy do not modify the primary end point result: FONE panel allows more TA recommendation than CTRL panel.

## MAIN\* RECOMMENDATIONS ACCORDING TO GENE ALTERATIONS



## TA RECOMMENDATION INITIATED



**Foundation Medicine® NGS panel increased the number of recommended targeted agent and the number of treated patients.**

# Added value of whole-exome and RNA sequencing in advanced and refractory cancer patients with no molecular-based treatment recommendation based on a 90-gene panel

Armelle Dufresne<sup>1</sup> | Valéry Attignon<sup>2</sup> | Anthony Ferrari<sup>3</sup> | Laurie Tonon<sup>3</sup> | Sandrine Boyault<sup>2</sup> | Séverine Tabone-Eglinger<sup>4</sup> | Philippe Cassier<sup>1</sup> | Olivier Trédan<sup>1</sup> | Nadège Corradini<sup>5</sup> | Armelle Vinceneux<sup>1</sup> | Aurélie Swalduz<sup>1</sup> | Alain Viari<sup>3</sup> | Sylvie Chabaud<sup>6</sup> | David Pérol<sup>6</sup> | Jean Yves Blay<sup>1,7</sup> | Pierre Saintigny<sup>1,7</sup>

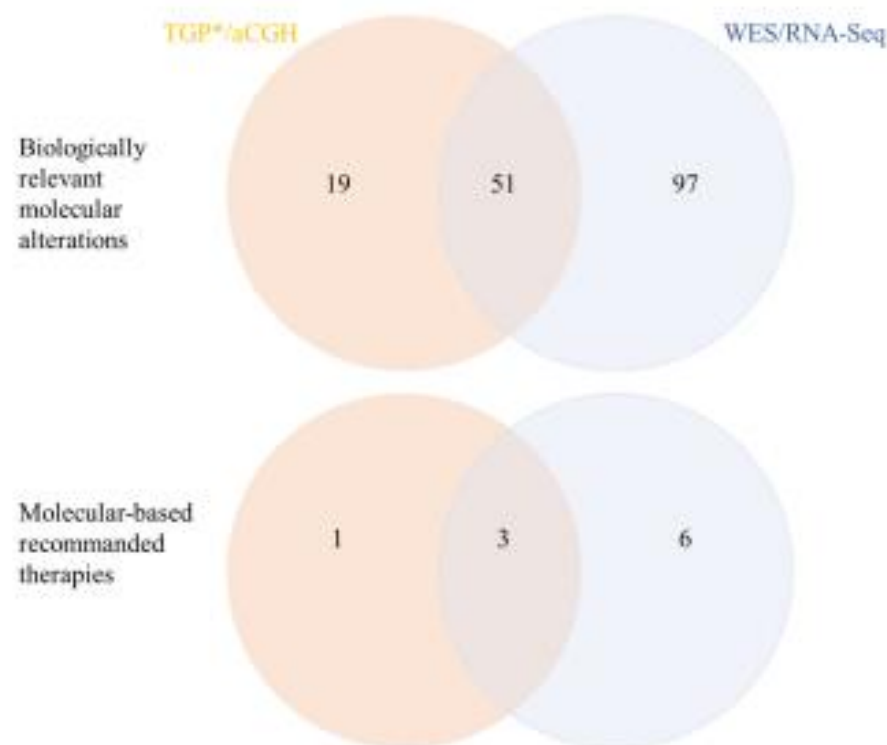
4 of 6

WILEY—Cancer Medicine

**TABLE 2** Frequency of molecular alterations identified with the 90-gene TGP/aCGH or WES/RNA-Seq the classified according to ESCAT.<sup>11</sup>

|          | 90-gene TGP/aCGH | WES/RNA-Seq |
|----------|------------------|-------------|
| TIER I   | 3 (4%)           | 6 (4%)      |
| TIER II  | 13 (19%)         | 17 (12%)    |
| TIER III | 33 (47%)         | 44 (30%)    |
| TIER IV  | 10 (14%)         | 33 (22%)    |
| TIER X   | 11 (16%)         | 48 (32%)    |
| Total    | 70 (100%)        | 148 (100%)  |

Note: Proportion of variants in each Tier of the ESCAT classification identified with TGP/aCGH versus WES/RNA-Seq was compared using a Fisher's exact test ( $p = 0.0154$ ).



# Challenges?

Nosologies

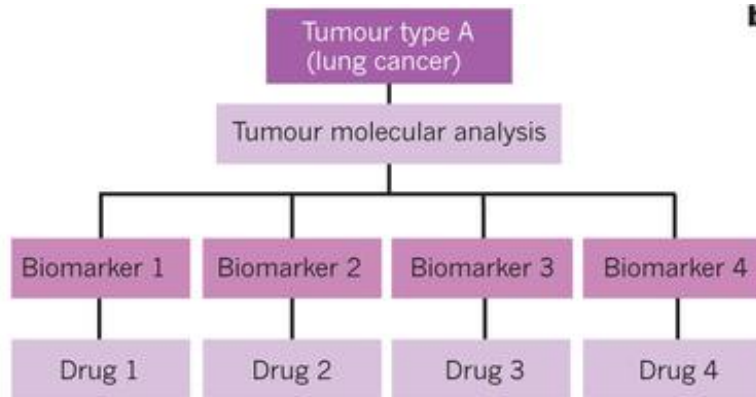
First optimal local treatment

Which molecular test, which molecular subsets

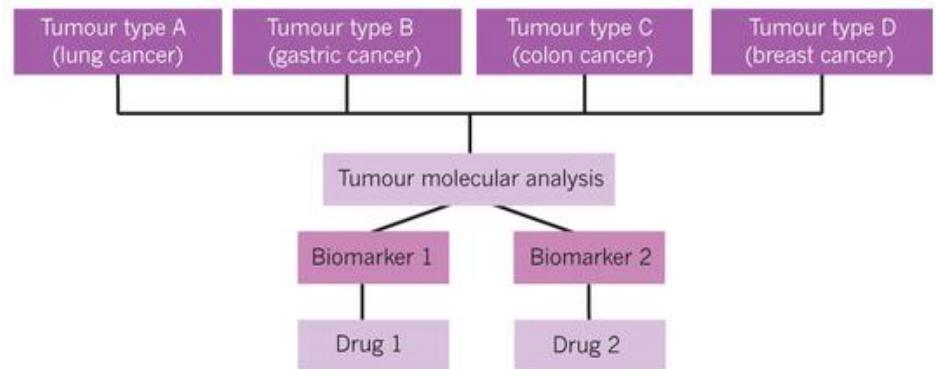
New designs for clinical trials

New strategies, new paradigms

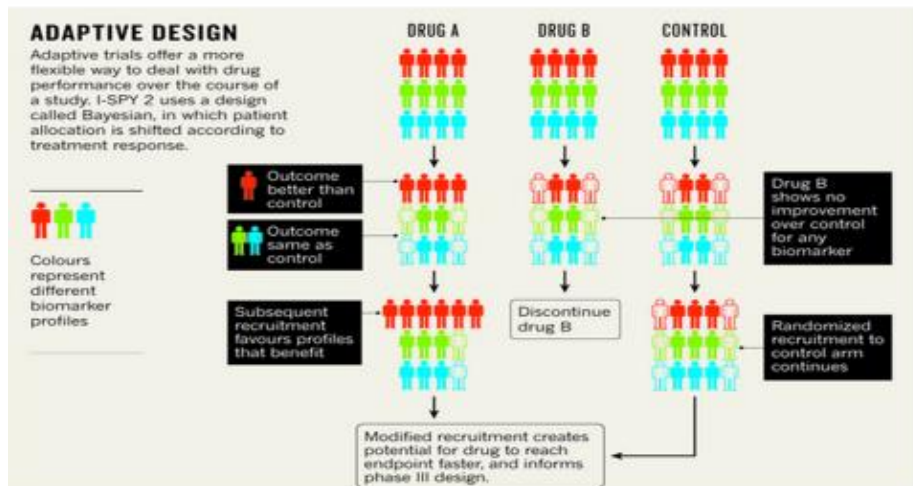
# New methods...



**b**



## Adaptive trial design



## N-of-1 trials

- Recruitment of patients exposed to different experimental agents or placebo in different sequencing, with washout periods in between
- Each involved patient serves as his or her own comparator, through the comparison of the efficacy seen for the different experimental agents that the patient receives

# Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIRO1/UNICANCER)



Fabrice André, Thomas Bachelot, Frederic Commo, Mario Campone, Monica Arnedos, Véronique Dieras, Magali Lacroix-Triki, Ludovic Lacroix, Pascale Cohen, David Gentien, Jose Adélaide, Florence Dalenc, Anthony Goncalves, Christelle Levy, Jean-Marc Ferrero, Jacques Bonnetterre, Claudia Lefeuvre, Marta Jimenez, Thomas Filleron, Hervé Bonnefoi

**Lancet Oncol 2014; 15: 267-74**

## High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial

Christophe Massard<sup>1</sup>, Stefan Michiels<sup>2</sup>, Charles Ferte<sup>1</sup>, Marie-Cécile Le Deley<sup>2</sup>, Ludovic Lacroix<sup>3</sup>, Antoine Hollebecque<sup>4</sup>, Loïc Verlingue<sup>5</sup>, Ecaterina Ileana<sup>6</sup>, Silvia Rosellini<sup>7</sup>, Samy Ammari<sup>8</sup>, Maud Ngo-Camus<sup>1</sup>, Rastislav Bahleda<sup>1</sup>, Anas Gazzah<sup>1</sup>, Andrea Varga<sup>1</sup>, Sophie Postel-Vinay<sup>1</sup>, Yohann Loriot<sup>1</sup>, Caroline Even<sup>7</sup>, Ingrid Breuskin<sup>7</sup>, Nathalie Auger<sup>8</sup>, Bastien Job<sup>9</sup>, Thierry De Baere<sup>10</sup>, Frederic Deschamps<sup>10</sup>, Philippe Vielh<sup>11</sup>, Jean-Yves Scoazec<sup>6</sup>, Vladimir Lazar<sup>12</sup>, Catherine Richon<sup>13</sup>, Vincent Ribrag<sup>14</sup>, Eric Deutsch<sup>15</sup>, Eric Angevin<sup>1</sup>, Gilles Vassal<sup>16</sup>, Alexander Eggermont<sup>17</sup>, Fabrice André<sup>18</sup>, and Jean-Charles Soria<sup>19</sup>

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## Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sébastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators



### ORIGINAL ARTICLE

## Molecular screening program to select molecular-based recommended therapies for metastatic cancer patients: analysis from the ProfILER trial

O. Trédan<sup>1</sup>, Q. Wang<sup>2</sup>, D. Pissaloux<sup>2</sup>, P. Cassier<sup>3</sup>, A. de la Fouchardière<sup>4</sup>, J. Fayette<sup>5</sup>, F. Desseigne<sup>6</sup>, I. Ray-Coquard<sup>7</sup>, C. de la Fouchardière<sup>8</sup>, D. Frappaz<sup>9</sup>, P.-E. Heudel<sup>10</sup>, A. Bonneville-Levard<sup>11</sup>, A. Fléchon<sup>12</sup>, M. Sarabi<sup>13</sup>, P. Guibert<sup>14</sup>, T. Bachelot<sup>15</sup>, M. Péro<sup>16</sup>, B. You<sup>17</sup>, N. Bonnin<sup>18</sup>, O. Collard<sup>19</sup>, C. Leyronnas<sup>20</sup>, V. Attignon<sup>21</sup>, C. Baudet<sup>22</sup>, E. Sohier<sup>23</sup>, J.-P. Villemain<sup>24</sup>, A. Viari<sup>25</sup>, S. Boyault<sup>26</sup>, S. Lantuejoul<sup>27</sup>, S. Paindavoine<sup>28</sup>, I. Treilleux<sup>29</sup>, C. Rodriguez<sup>30</sup>, V. Agrapart<sup>31</sup>, V. Corset<sup>32</sup>, G. Garin<sup>33</sup>, S. Chabaud<sup>34</sup>, D. Péro<sup>35</sup> & J.-Y. Blay<sup>1\*</sup>, for the ProfILER investigators

Annals of Oncology 30, 757–765, 2019  
doi:10.1093/annonc/mdz080  
Published online 13 March 2019

# PRECISION MEDICINE TRIALS

## MOLECULAR SCREENING PROGRAMS

Profiler 01 et Profiler 02

Home-based and FoundationOne panels (≈ 70 molecular portrait / months)

illumina



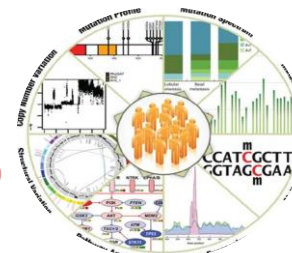
Agilent Technologies

FOUNDATION ONE



## WEEKLY MOLECULAR BOARD

MOLECULAR BASED RECOMMENDED  
THERAPIES



## PRECISION MEDICINE INVESTIGATOR INITIATED TRIALS

### PI3K - mTOR

Buparlisib  
(PIK-ORL),  
Everolimus  
(MOST),  
AZD2014  
(VICTORIA)

### CDK4 / CDK6

Abemaciclib  
(ABORL),  
Ribociclib  
(MEGAMOST)

### RTK

Sorafenib,  
Lapatinib,  
Pazopanib  
(MOST)

### HER2

Pertuzumab+  
Trastuzumab  
(MegaMOST)

### MAPK

Trametinib  
(TRADH)

### MDM2

HDM201  
(TRADH,  
MegaMOST)

### PARP

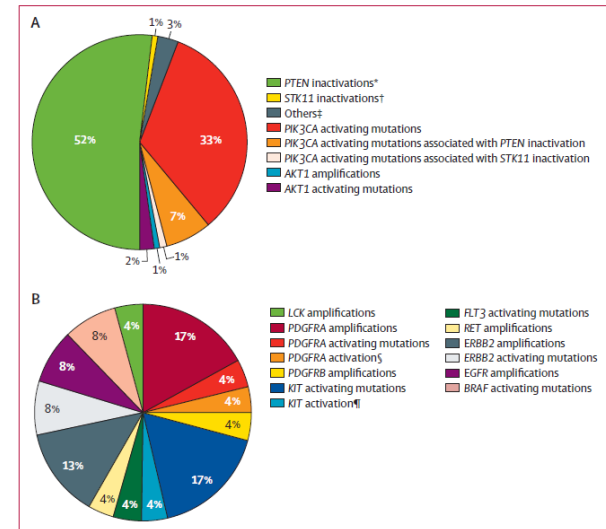
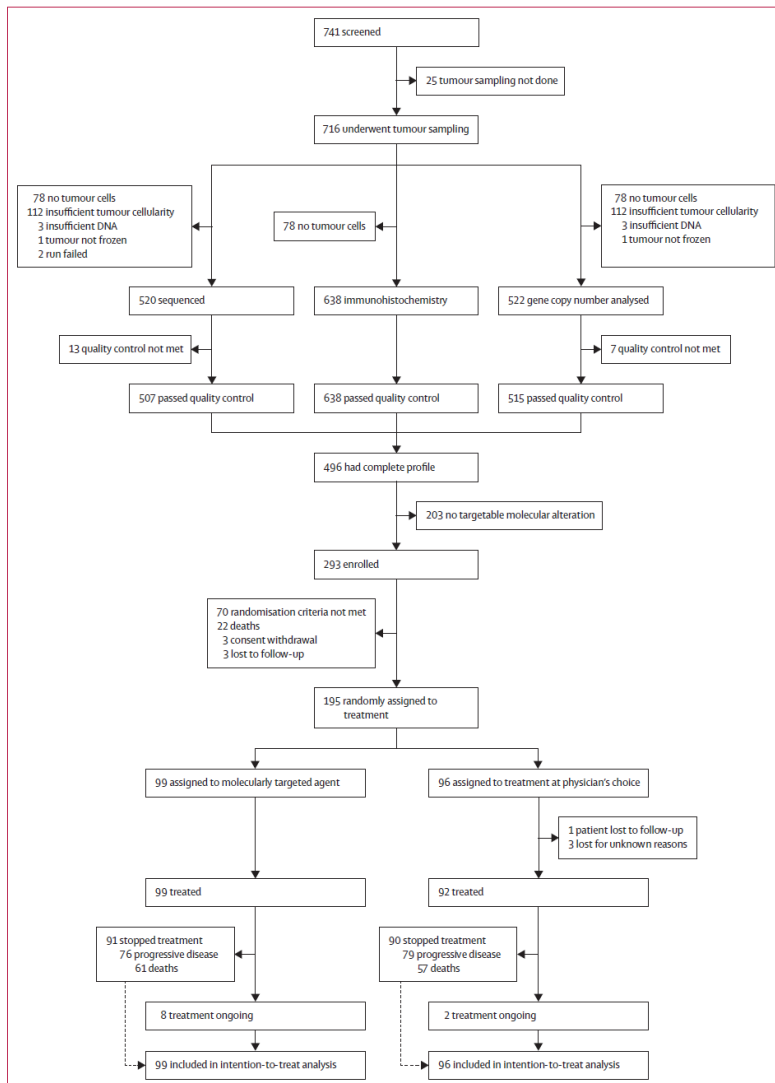
Olaparib  
(MOST-Plus)

Benefit for the patient with  
cancer?

# Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

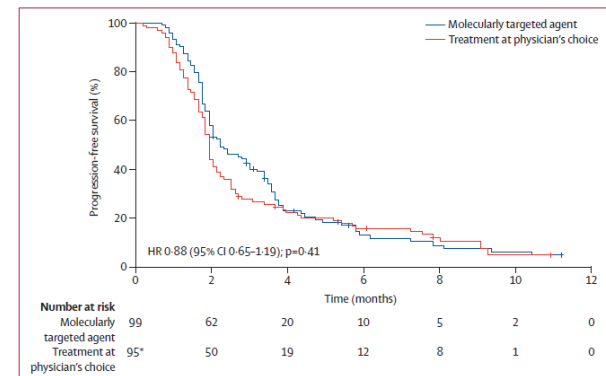
*Lancet Oncol 2015; 16: 1324-34*

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sébastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Serois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators



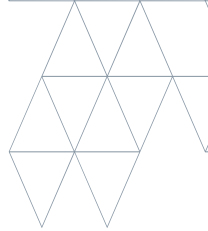
**Figure 2: Distribution of molecular alterations in the PI3K/AKT/mTOR pathway (A) and RAF/MEK pathway (B)**

\*PTEN inactivations included homozygous deletions and heterozygous deletions associated with inactivating mutations or validated by absence of expression of PTEN in immunohistochemistry. †STK11 inactivations included homozygous deletions and heterozygous deletions associated with inactivating mutations of STK11. ‡Focal gains of several PIK3 pathway genes including AKT1, AKT2, AKT3, RPTOR, and RICTOR (three patients). §Intragenic deletion within PDGFRα validated by overexpression of PDGFRα in immunohistochemistry. ¶Intragenic deletion within KIT validated by overexpression of the KIT in immunohistochemistry.



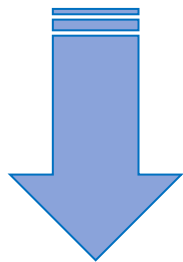
**Figure 3: Progression-free survival**

# Meta analysis of ~85,000 patients in Phase I, II and III trials



Targeted therapy in of itself is not generally effective – a biomarker is needed

Worst outcome



Best outcome

|                           | Pooled Analysis |           |          | Meta-analysis |           |          |
|---------------------------|-----------------|-----------|----------|---------------|-----------|----------|
| ARMS type                 | RR (%)          | PFS (Mos) | OS (Mos) | RR (%)        | PFS (Mos) | OS (Mos) |
| Non-personalized targeted | 4               | 2.6       | 8.7      | 7.5           | 2.5       | 8.3      |
| Cytotoxic                 | 12              | 3.3       | 9.4      | 16.1          | 3.3       | 9.3      |
| Personalized targeted     | 30              | 6.9       | 15.9     | 31.3          | 6.1       | 13.7     |

# Challenges?

Nosologies

First optimal local treatment

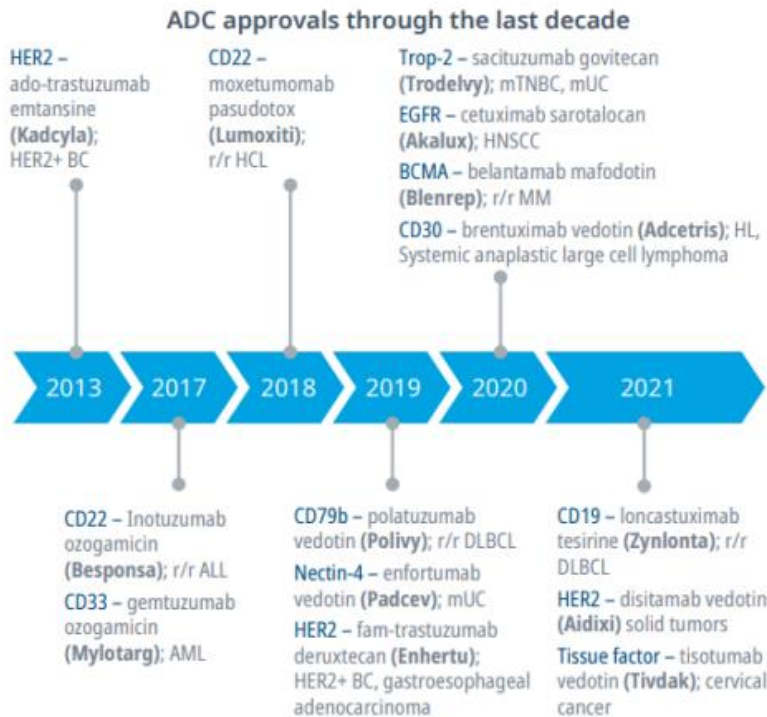
Which molecular test, which molecular subsets

New designs for clinical trials

New strategies, new paradigms

# ADCs

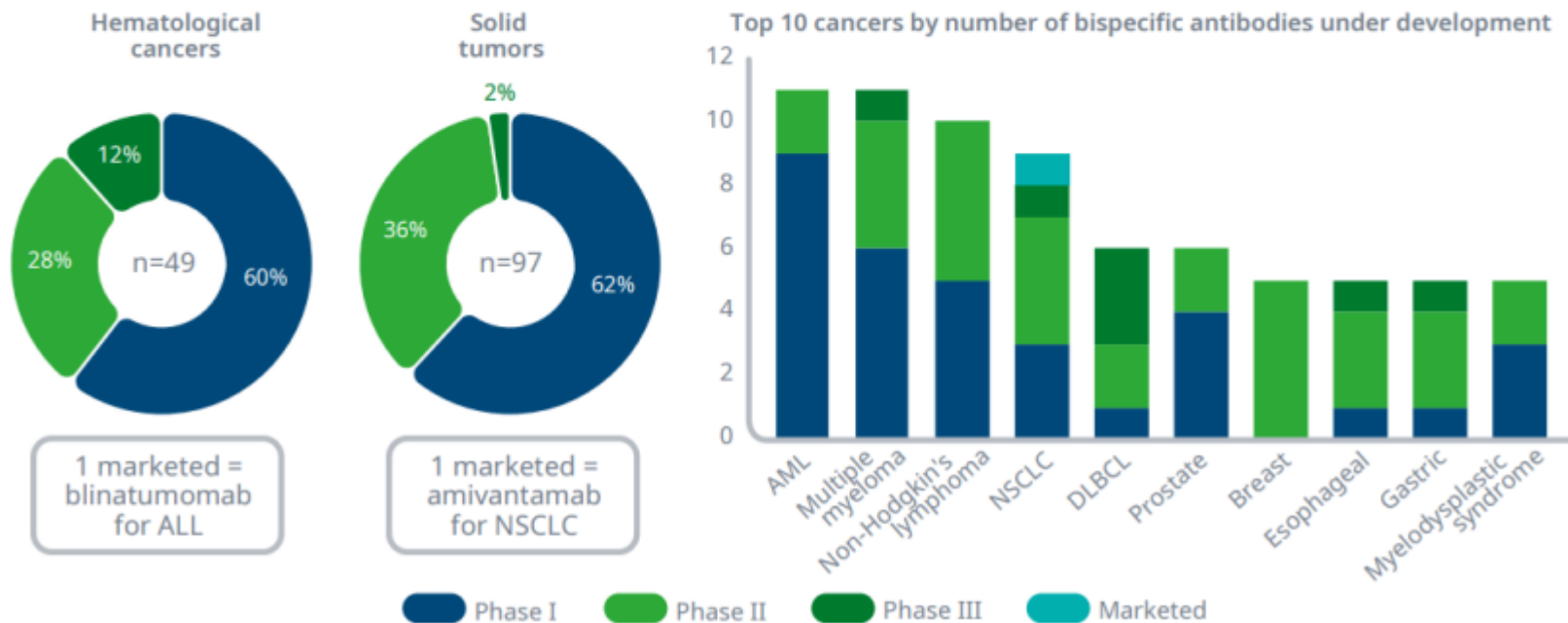
## : Antibody-drug conjugates approved and under development by target



# Bispecific Abs

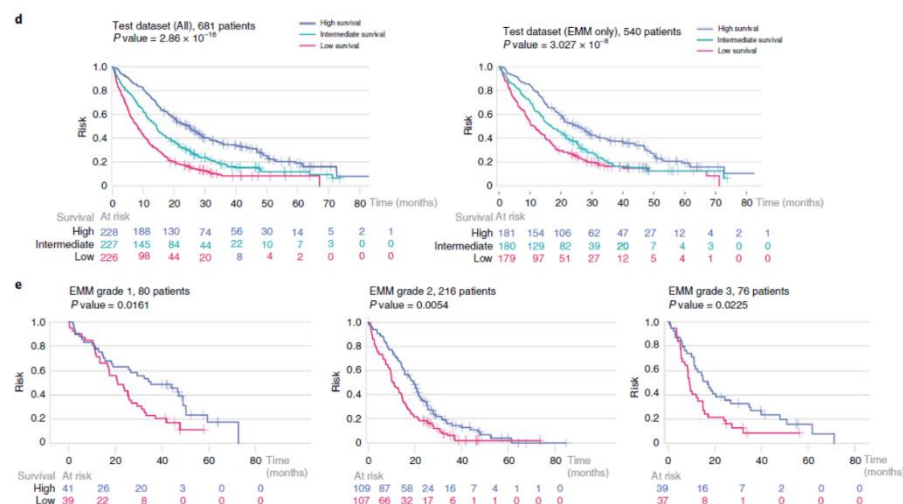
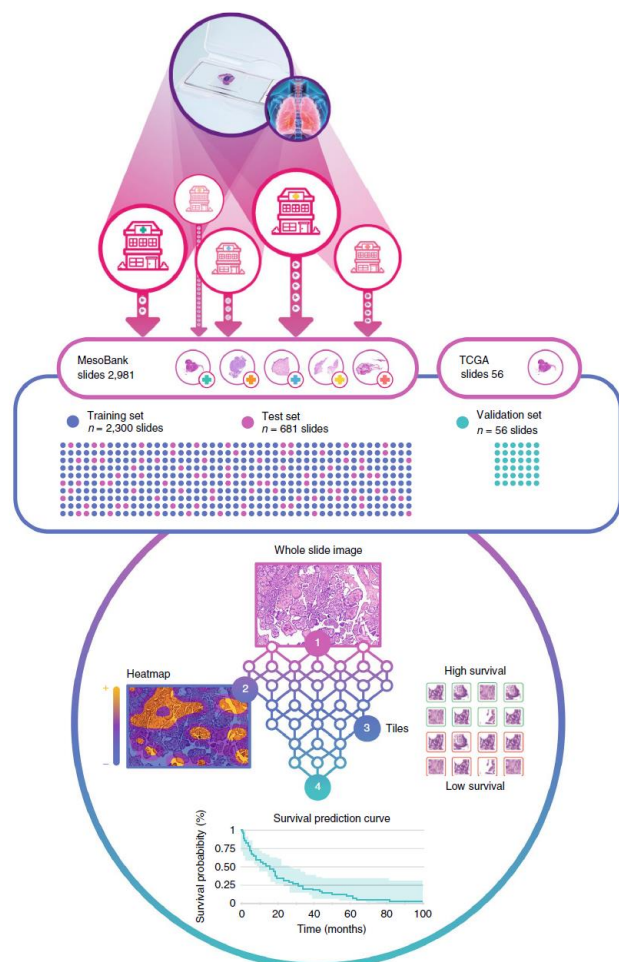
**Two bispecific antibodies are marketed globally for oncology with many in development for rare hematological cancers**

Bispecific antibody pipeline by tumor and phase, 2021



# Deep learning-based classification of mesothelioma improves prediction of patient outcome

Pierre Courtiol<sup>1,8</sup>, Charles Maussion<sup>1,8</sup>, Matahi Moarii<sup>1</sup>, Elodie Pronier<sup>1</sup>, Samuel Pilcer<sup>1</sup>, Meriem Sefta<sup>1</sup>, Pierre Manceron<sup>1</sup>, Sylvain Toldo<sup>1</sup>, Mikhail Zaslavskiy<sup>1</sup>, Nolwenn Le Stang<sup>2</sup>, Nicolas Girard<sup>3,4</sup>, Olivier Elemento<sup>5</sup>, Andrew G. Nicholson<sup>6</sup>, Jean-Yves Blay<sup>7</sup>, Françoise Galateau-Sallé<sup>2,8</sup>, Gilles Wainrib<sup>1,8</sup> and Thomas Clozel<sup>1,8\*</sup>



**Fig. 2 |** Comparison of the performance between MesoNet and other histology-based models to predict MM patient overall survival. **a**, Distribution of the

# Deep learning predicts patients' outcome and mutations from H&E slides in Gastrointestinal stromal tumor (GIST)

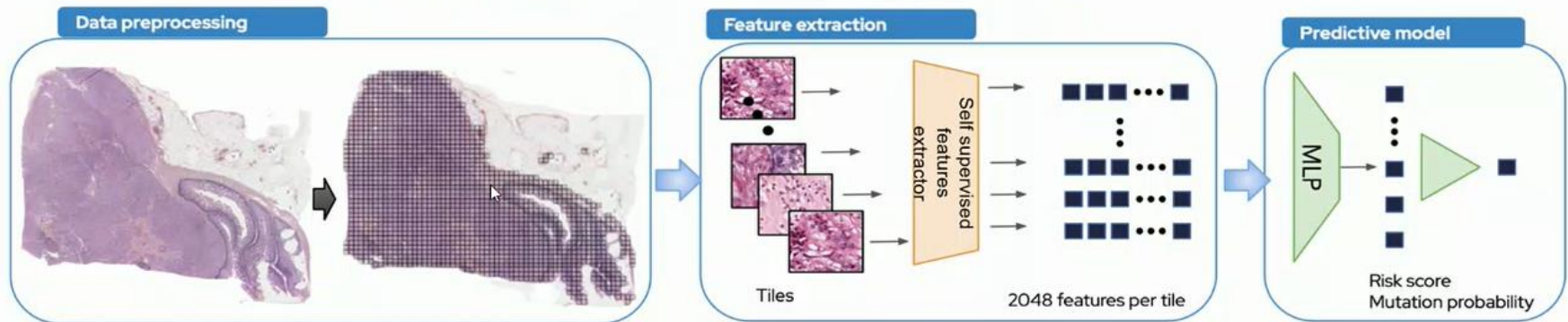
**Raul Perret**, Yu Fu, Marie Karanian, Axel Camara, François Le Loarer, Myriam Jean-Denis, Isabelle Hostein, Audrey Michot, Françoise Ducimetiere, Antoine Giraud, Jean-Baptiste Courreges, Kevin Courtet, Yech'an Laizet, Etienne Bendjebbar, Jean Ogier Du Terrail, Benoit Schmauch, Charles Maussion, Jean-Yves Blay, Antoine Italiano, Jean-Michel Coindre

Paris, 10/09/2022



# Deep learning workflow

3 main steps in deep learning from histology whole slide images.



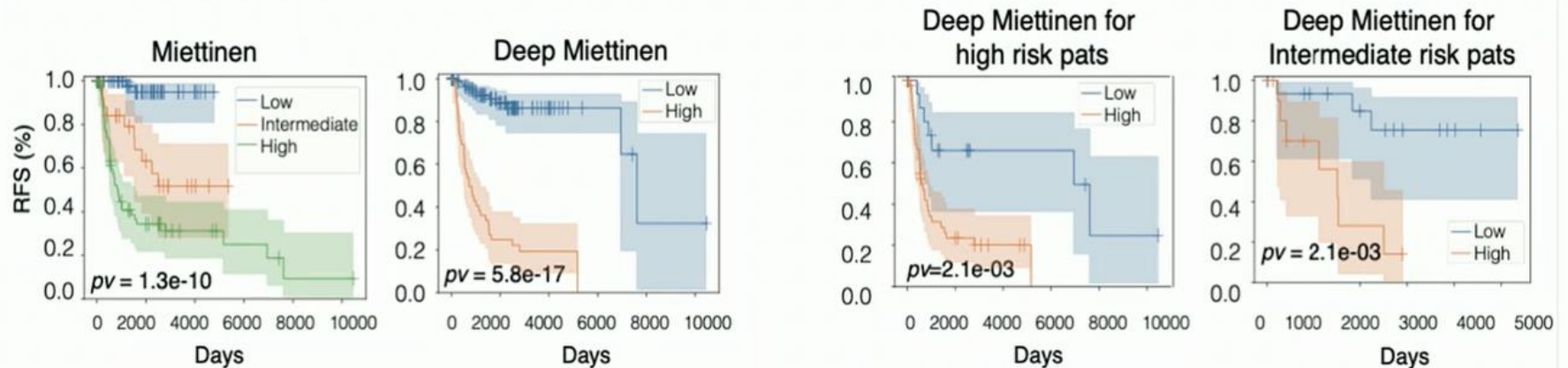
## Main steps:

1. Matter detection following by a tiling process.  
→ To avoid dimensionality issues, small patches of the slide are used during the training instead of the whole slide
2. Use of an in-domain feature extractor pre-trained in a self-supervised manner
3. A Multi Layer Perceptron is used as a predictive model to output the risk score or the mutation probability

# Results - Relapse prediction

## Better risk stratification of patients using Deep Miettinen

Deep Miettinen stratifies patients in high and low risk groups



# Roadblocks?

- Speed of science vs speed of administration
- Costs
- How to help health authorities/HTA
- Unadapted/late regulations: IVDR
- Rigorous and timely scientific evaluation is a priority

Tweet from .Schoffski, Leuven

Major frustration for the experimental oncologist: being deeply involved in strategic guidance on/preclinical and early and late clinical testing of active novel agents which finally never reach patients in small markets due to either corporate or regulatory decisions.



# Conclusions

## *Challenges for drug development in rare cancers in 2024*

- Molecular diagnosis and fragmentation
- More rare entities
- Precision medicine of cancer accelerating
- Rare cancers were often paradigmatic models
  - Yet further fragmentations: ultrarare cancers...
- New methodologies of trials needed
- New paradigms for evaluation urgently needed