ESMO ADVANCED COURSE ON NTRK GENE FUSION

Epidemiology and distribution of NTRK gene fusions in human tumors

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Gustave Roussy, FRANCE
Lyon, 13-14 September 2019
DISCLOSURE OF INTEREST

No disclosure
OUTLINE OF THE PRESENTATION

- General information about distribution of NTRK Gene Fusions
- Incidence of NTRK Gene Fusions:
  - In which tumor type …
  - In which age …
  … can we highlight NTRK gene fusions?
- Relation between NTRK gene fusions and the other oncogenic drivers
- What is the prognosis?
OUTLINE OF THE PRESENTATION

- General information of *NTRK* Gene Fusions

  - Incidence of *NTRK* Gene Fusions:
    - In which tumor type?
    - In which age?
  
  ... can we highlight *NTRK* gene fusions?

- Relation between NTRK gene fusions and the other oncogenic drivers

- What is the prognosis?
The discovery of gene fusions dates back to the 1980s.
TWO QUESTIONS ..... 

- Are *NTRKs* detected in primary tumors or metastases?
- Do they have several fusion partners?
ARE NTRKS DETECTED IN PRIMARY TUMORS OR METASTASES?

Cocco E. et al. NaTure Reviews, december 2018
A. Retrospective study
751 metastatic melanomas were analyzed by next generation sequencing
4 metastatic melanomas presented NTRK fusions; expression confirmed by immunohistochemistry
NTRK1 (n = 3)
NTRK2 (n= 1)
A. 751 metastatic melanomas were analyzed by next generation sequencing
4 metastatic melanomas were identified with NTRK fusions
   NTRK1 (n = 3)
   NTRK2 (n = 1)

B. Analysis of the only two primary tumors of metastases available
→ They were immunoreactive for NTRK.

The melanoma in situ is immunoreactive for NTRK.
**conclusion**: this study shows that tumors and their metastasis can express the same *NTRK* gene fusion but there are a lack of data on this subject.
Among metastatic cancers, gene fusions were reported in 1,597 individuals (15%).

The most famous gene fusions: ALK, RET, ROS

Behind them: NTRK3 and NTRK1
DO THEY HAVE SEVERAL FUSION PARTNERS?

1/ NTRK1,2,3 have both 61 Partners across tumor types in adult and paediatric cancers

2/ NTRK1 has more fusion partners than NTRK2 and NTRK3 which have a limited number of fusion partners

3/ Different types of cancer

General informations of \textit{NTRK} Gene Fusions

Incidence of \textit{NTRK} Gene Fusions:
  - In which tumor type?
  - In which age?

... can we highlight \textit{NTRK} gene fusions?

Is their presence mutually exclusive of the other oncogenic drivers?

What is the prognosis?
IDENTIFICATION OF 3 DIFFERENT GROUPS FOR THE INCIDENCE OF NTRK.

1/ Tumors with HIGH FREQUENCY >75%

2/ Tumors with INTERMEDIATE FREQUENCY : 5%-25%

3/ Tumors with LOWER FREQUENCY < 5%
Tumors with high frequency of $NTRK > 90\%$

Mammary analog secretory carcinoma of the salivary gland (MASC)

Secretory breast cancer
rare subtype of breast cancer (0.02\% of patients)

$NTRK3$ gene fusion

Amatu A, et al. ESMO Open 2016;1:e000023
Cocco E et al. NaTure Reviews, december 2018
**Tumors with high frequency of NTRK > 75%**

**PAEDIATRIC CANCERS**

- **Secretory breast cancer**
  - *NTRK3* fusion

- **Infantile fibrosarcoma**
  - Most common soft tissue sarcoma in children younger than 1 year old (20%)
  - 7% in people younger than 20 years
  - *NTRK3* and *NTRK1* fusions

- **Cellular congenital mesoblastic nephroma**
  - Most kidney tumor in the first month of life
  - *NTRK3* fusions > 75%

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Albert et al. J Clin Oncol 37:513-524; 2018
Cocco E et al. Nature Reviews, december 2018
Which are fusion partners?

<table>
<thead>
<tr>
<th>Adult cancers</th>
<th>NTRK1</th>
<th>NTRK2</th>
<th>NTRK3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma of the salivary gland</td>
<td></td>
<td></td>
<td>ETV6</td>
</tr>
<tr>
<td>Secretory breast cancer</td>
<td></td>
<td></td>
<td>ETV6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paediatric cancers</th>
<th>NTRK1</th>
<th>NTRK2</th>
<th>NTRK3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretory breast cancer</td>
<td></td>
<td></td>
<td>ETV6</td>
</tr>
<tr>
<td>Infantile fibrosarcoma</td>
<td>SQSTM1</td>
<td></td>
<td>EML4</td>
</tr>
<tr>
<td></td>
<td>TPM3</td>
<td></td>
<td>ETV6</td>
</tr>
<tr>
<td></td>
<td>LMNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular and mixed congenital mesoblastic nephroma</td>
<td>TPR</td>
<td></td>
<td>ETV6</td>
</tr>
<tr>
<td></td>
<td>LMNA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TAKE HOME MESSAGE**

1/ If you want to analyse tumors with a high frequency of *NTRK* gene fusions....

<table>
<thead>
<tr>
<th>In adult cancers</th>
<th>In paediatric cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No common tumors</td>
<td>- Two common tumors in infancy:</td>
</tr>
<tr>
<td>- Two rare tumors:</td>
<td>- Infantile fibrosarcoma</td>
</tr>
<tr>
<td>- Salivary gland carcinoma</td>
<td>- Cellular congenital mesoblastic nephroma</td>
</tr>
<tr>
<td>- Secretory breast cancer</td>
<td>- One rare tumor: <strong>secretory breast cancer</strong></td>
</tr>
</tbody>
</table>

2/ Type of *NTRK* gene fusion: 

- **ETV6-NTRK3 > LMNA-NTRK1**
- **NTRK2**
Tumors with intermediate frequency of \textit{NTRK} fusions: 5\%-25\%

\textbf{ADULT CANCERS}

- Papillary thyroid cancer
- Spitzoid tumors (an uncommon melanocytic lesion)
- « Wild-Type » Gastrointestinal stromal tumor (without cKIT /PDFRA /RAS alterations)

\textbf{PAEDIATRIC CANCERS}

- High-grade glioma

\textbf{References}

Albert et al. J Clin Oncol 37:513-524; 2018
Amatu A, et al. ESMO Open 2016;1
Cocco E et al. Nature Reviews, december 2018
## Which are fusion partners?

<table>
<thead>
<tr>
<th>Adult/Paediatric cancers</th>
<th>NTRK1</th>
<th>NTRK2</th>
<th>NTRK3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary thyroid cancer</td>
<td>TPR</td>
<td></td>
<td>ETV6</td>
</tr>
<tr>
<td></td>
<td>IRF2BP2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TPM3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>« Wild-Type » Gastrointestinal stromal tumor</td>
<td></td>
<td></td>
<td>ETV6</td>
</tr>
<tr>
<td>Spitz tumors</td>
<td>TP53</td>
<td></td>
<td>ETV6</td>
</tr>
<tr>
<td></td>
<td>LMNA</td>
<td></td>
<td>MYH9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MYO5A</td>
</tr>
<tr>
<td>Paediatric high-grade gliomas</td>
<td>TPM3</td>
<td>AGBL4</td>
<td>ETV6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VCL</td>
<td>BTB1</td>
</tr>
</tbody>
</table>
## TAKE HOME MESSAGE

1/ If you test NTRK gene fusion ....

<table>
<thead>
<tr>
<th>In adult cancer</th>
<th>In paediatric cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Papillary thyroid cancer</td>
<td>- Papillary thyroid cancer</td>
</tr>
<tr>
<td>- « Wild-Type » Gastrointestinal stromal tumor</td>
<td>- Spitz tumor</td>
</tr>
<tr>
<td>- Spitz tumor</td>
<td>- High-grade glioma</td>
</tr>
</tbody>
</table>

...you will find them in 5-25% of the time

2/ Type of NTRK fusion gene: **ETV6-NTRK3 > NTRK1 > NTRK2** (only in paediatric cancers)
Tumors with lower frequency of NTRK < 5%

ADULT CANCERS

- Head and neck cancer
- High-grade glioma
- Lung cancer
- Breast cancer
- Cholangiocarcinoma
- Melanoma
- Renal cell carcinoma
- Pancreatic cancer
- Colorectal cancer
- Sarcoma
- Acute lymphoblastic leukaemia

Cocco E et al. Nature Reviews, December 2018
<table>
<thead>
<tr>
<th>Tumour</th>
<th>NTRK1</th>
<th>NTRK2</th>
<th>NTRK3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioma/glioblastoma</td>
<td>ARHGEF2, 19, BCAN, 20, 21, CHTOP, 19, NFAS, 20</td>
<td>BCR, 18, AFAP1, 9, SQSTM1, 9</td>
<td>AFAP1, 18, ZNF710, 18, EML4, 18</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td></td>
<td>QK1, 7, NACC2</td>
<td>ETV6, 15</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>CD74, 7, GRPAP1, 23, IRF2BP2, 18, MPRIP, 18, P2RY8, 18, SQSTM1, 24, TPM3, 18</td>
<td>TRIM24, 9</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>TPM3, 9, LMNA, 18</td>
<td></td>
<td>ETV6, 10</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>CGN, 25, GATAD2B, 25, LMNA, 25, MDM4, 25, PEAR1, 25, TPM3, 10, 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute lymphoblastic leukaemia, acute myeloid leukaemia, histiocytosis, multiple myeloma, dendritic cell neoplasms</td>
<td></td>
<td></td>
<td>ETV6, 25</td>
</tr>
<tr>
<td>Uterine sarcoma</td>
<td>LMNA, 27, TPM3, 27, TPR, 27</td>
<td></td>
<td>RBPM, 27</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>LMNA, 10, RABGAP1L, 28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>CTRC, 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>DDR2, 29, G0N4L, 29, TRIM63, 29</td>
<td>TRAF2, 29</td>
<td>ETV6, 8</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>LMNA, 10, TPM3, 10, SCYI, 30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Tumors with lower frequency of $NTRK < 5\%$

- Low-grade gliomas
- Inflammatory myofibroblastic tumor
- Sarcoma

PAEDIATRIC CANCERS

Albert et al. J Clin Oncol 37:513-524; 2018
Cocco E et al. NaTure Reviews, december 2018
<table>
<thead>
<tr>
<th>Tumour</th>
<th>Fusion partner</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganglioglioma</td>
<td>NTRK1</td>
<td>NTRK2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TLE$^{38}$</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>NTRK1</td>
<td>NTRK2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NACC2,$^{37}$ QK1$^{37}$</td>
</tr>
</tbody>
</table>
TAKE HOME MESSAGE

1/ If you want to detect *NTRK* gene fusion ....

<table>
<thead>
<tr>
<th>In common adult cancer</th>
<th>In paediatric cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>like breast cancer, colorectal cancer...</td>
<td>- Low-grade gliomas</td>
</tr>
<tr>
<td></td>
<td>- Sarcoma</td>
</tr>
<tr>
<td></td>
<td>- Inflammatory myofibroblastic tumor</td>
</tr>
</tbody>
</table>

2/ Type of *NTRK* fusion gene

: *NTRK1* > *NTRK3* > *NTRK2*

...you'll have little chance of finding them.
OUTLINE OF THE PRESENTATION

- General information of NTRK Gene Fusions
- Incidence of NTRK Gene Fusions in Cancer
  - In which tumor type?
  - In which age?
- Relation between NTRK gene fusions and the other oncogenic drivers
- What is the prognosis?
RELATION BETWEEN NTRK GENE FUSIONS AND THE OTHER ONCOGENIC DRIVERS

They are mutually exclusive of other genomic alterations (cKIT, PDFRA, BRAF V600 and RAS mutations...)

For example:

Tumors with intermediate frequency of NTRK fusions: 5%-25%

ADULT CANCERS

1. "Wild-Type" Gastrointestinal stromal tumor (without cKIT/PDFRA/RAS alterations)

2. Papillary thyroid cancer

3. Spitzoid tumors (an uncommon melanocytic lesion)

PAEDIATRIC CANCERS

1. High-grade glioma

References:
- Cocco et al. Cancer Research 2019
- Pietrantonio, F et al. JNCI 2017
- Albert et al. J Clin Oncol 37:513-524; 2018
- Amatu A, et al. ESMO Open 2016;1
- Cocco E et al. Nature Reviews, december 2018

Cocco et al. Cancer Research 2019
Pietrantonio, F et al. JNCI 2017
2,314 colorectal carcinomas

*NTRK* gene fusions are mutually exclusive of other genomic alterations

*NTRK* gene fusions are associated to MSI-high tumors
NTRK have been reported as more frequently expressed in MSI-high tumors in colorectal carcinoma patients

Pietrantonio, F et al. JNCI 2017
Relation between \textit{MLH1} hypermethylation status and the presence of gene fusions

Oncogenic fusions are associated to hypermethylation of the \textit{MLH1} promoter and lacked activating mutations in \textit{BRAF} and \textit{KRAS}.

Wang et al. Modern Pathology (2019)
Proposed strategy for screening oncogenic fusions such as ALK, NTRK, and RET rearrangements in CRCs.

OUTLINE OF THE PRESENTATION

- General information of *NTRK* Gene Fusions
- Incidence of *NTRK* Gene Fusions in Cancer
  - In which tumor type?
  - In which age?
- Relation between *NTRK* gene fusions and the other oncogenic drivers
- What is the prognosis?
WHICH PROGNOSIS?

Generally associated with worst prognosis and aggressiveness

1/ Tumors with HIGH FREQUENCY > 75%

2/ Tumors with INTERMEDIATE FREQUENCY: 5%-25%

3/ Tumors with LOWER FREQUENCY < 5%

secretory breast carcinoma

Boon et al. Oral Oncology 82 (2018) 29–33
Secretory carcinoma of the breast is a rare and indolent tumor

The age at presentation varies from 3 to 87 years with a median age of 25 years

Distant metastases from secretory carcinoma are extremely rare with only four cases reported.
8-year-old girl at diagnosis
Bangladesh
Secretory breast carcinoma
After 6 years of unsuccessful treatment
Left chestwall lesion and lung metastasis

Typical histopathology of the secretory breast
Rare case of refractory secretory breast carcinoma

Her treating oncologist presented her case at a virtual multidisciplinary tumor board organized by the Global Cancer Institute

→ the board recommended molecular testing for an \textit{ETV6-NTRK3} fusion

Immunohistochemical staining for pan-Trk expression revealed diffuse, strong positive staining in a nuclear pattern (Abcam, mAb EPR17341, 1:250).

Presence of an \textit{ETV6-NTRK3} fusion
Treatment: larotrectinib (pan-Trk inhibitor)

Successful targeted therapy for this refractory pediatric secretory breast carcinoma
Radiographic response of chest wall lesion and lung metastases
WHICH PROGNOSIS?

1/ Tumors with HIGH FREQUENCY >75%

2/ Tumors with INTERMEDIATE FREQUENCY: 5%-25%

3/ Tumors with LOWER FREQUENCY < 5%

Colorectal cancer

Boon et al. Oral Oncology 82 (2018) 29–33
Relationship between *MLH1* hypermethylation status and the presence of *NTRK*

![Survival outcomes graphic](image)

**Fig. 4** Survival outcomes in patients with Stage III/IV dMMR colorectal cancer. Cancer-specific survival in patients with oncogenic fusions (red line) is compared with those without oncogenic fusions (blue line) using the Kaplan–Meier method. dMMR: DNA mismatch repair deficient.
**NTRK** rearranged tumors had short OS independent from MSI status.

Survival in metastatic colorectal cancer patients carrying ALK, ROS1, and NTRK rearranged tumors.
<table>
<thead>
<tr>
<th>LAST TAKE ON MESSAGES</th>
<th><strong>NTRK1</strong></th>
<th><strong>NTRK2</strong></th>
<th><strong>NTRK3</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUSION PARTNERS</strong></td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>(&gt; 61)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIGH FREQUENCY &gt;75%</strong></td>
<td>Infantile fibrosarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INTERMEDIATE FREQUENCY &gt; 5%-25%</strong></td>
<td>Rare tumors (3 types) ++</td>
<td>Rare tumors (1 type) + only in paediatric cancers</td>
<td>Rare tumors (4 types) +++</td>
</tr>
<tr>
<td>(adult and paediatric cancers)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LOWER FREQUENCY &lt; 5%</strong></td>
<td><strong>ADULT CANCERS:</strong> Several common cancers +++</td>
<td><strong>ADULT CANCERS:</strong> common and rare cancers</td>
<td><strong>ADULT CANCERS:</strong> Common cancers Rare tumors ++</td>
</tr>
<tr>
<td></td>
<td><strong>PAEDIATRIC CANCERS:</strong> only with rare tumors +</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## LAST TAKE ON MESSAGES

<table>
<thead>
<tr>
<th></th>
<th>NTRK1</th>
<th>NTRK2</th>
<th>NTRK3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncogenic driver</td>
<td>Mutually exclusive of other genomic alterations (BRAF, RAS…)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td></td>
<td>Associated with worst prognosis and aggressiveness</td>
<td></td>
</tr>
</tbody>
</table>

Development of TRK inhibitors treatment
THANK YOU FOR YOUR ATTENTION

elise.deluche@gustaveroussy.fr

Contacts ESMO

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