Update on the management of locally advanced and metastatic thyroid cancer

Grand Rounds
November 12, 2021

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Learning Objectives

- Overview clinicopathological and genomic characteristics of advanced thyroid cancer
- Describe current therapies
- Define future treatment strategies
Disclosures

- Eli Lilly
Thyroid cancer: Cell type and Histology

- **Follicular cells** (90-95%)
  - Anaplastic
  - Papillary
  - Follicular
  - Hürthle cell

- **Parafollicular cells** (3-5%)
  - Medullary thyroid carcinoma (MTC)
Differentiated Thyroid Cancer

DTCs are classified histologically as:
- 75% papillary thyroid cancer
- 15-20% follicular thyroid cancers
- <10% oncocytic thyroid cancer (Hürthle cell cancers)

Poorly Differentiated Thyroid Cancer

PDTC clinical characteristics:
- presents with locally invasive disease
- 10% of DM at presentation
- high risk of relapse, higher risk of mortality
- some are refractory to TSH suppression
- some are refractory to RAIR therapy
Anaplastic Thyroid Cancer

- ATC remains one of the most aggressive and fatal solid tumors
- ATC usually present with a rapidly growing and invasive neck mass, regional cervical lymph node involvement
- 50% have DM at presentation
- ATC are usually inoperable at presentation
- Historically been treated palliatively or referred to hospice
- All ATC are stage IV:
  - Stage IV A confined to the thyroid
  - Stage IV B confined to the neck but extending beyond the thyroid gland
  - Stage IV C spread distantly
Medullary Thyroid Cancer

- <5% of all thyroid cancers, C-Cell origin
- DM 8% at presentation
- DM to the liver, lungs, and bone
- Calcitonin doubling time <6 mo poor prognosis
Thyroid Cancer Prognosis

Estimated New Cases in 2021: 44,280
% of All New Cancer Cases: 2.3%

Estimated Deaths in 2021: 2,200
% of All Cancer Deaths: 0.4%

5-Year Relative Survival: 98.3%
2011-2017

Advanced Thyroid Cancer Survival

10-year OS:

- Metastatic DTC ~50%
- RAIR metastatic DTC 38%
- PDTC <50%
- ATC >99% (median OS 0.79 years)
- MTC 21%
Signaling pathways involved in thyroid carcinogenesis

MAPK Pathway

PI3K Pathway

Khatami 2018
Thyroid Cancer Genome Atlas
Genomic Evolution of Thyroid Cancer

NORMAL FOLLICULAR CELLS

LOW RISK

BRAF, RET fusions

RET fusions

ALK fusions

RAS

PAX8/PPARγ fusions

PTC

Pediatric PTC

PTC

FTC

HIGH RISK DIFFERENTIATED

TERT

TP53, RBM10

CDKN2A, CDKN2B

PIK3CA

APOBEC activity

Aggressive PTC

Aggressive FTC

HCTC

ANAPLASTIC

TP53

PIK3CA, AKT1

ARID2

CDKN2A, CDKN2B

APOBEC activity

Type 1 ATC

Type 2 ATC

Type 3 ATC

Pozdeyev et al, Cancer Res 2018
Thyroid Cancer Spectrum

- **Papillary**
  - Well-differentiated

- **Follicular**
  - Poorly differentiated

- **Anaplastic**
  - Undifferentiated

**Mutation burden**

**NIS expression**

**RAI avidity**

**PET-avidity**
Molecular and Genetic Testing in Thyroid Cancer
Indications for molecular testing: ATA

- **DTC 2015:**
  - Mutation profiling of metastatic has not yet definitively proven to be of value for estimating patient prognosis or for predicting response to treatments such as anti-angiogenic kinase inhibitors, although the presence of certain mutations such as BRAFV600E or PAX8/PPARγ are required for some clinical trials. *Thus, routine mutation profiling cannot be recommended at this time outside of research settings.*

- **ATC 2021:**
  - Molecular profiling should be performed at the time of ATC diagnosis to inform decisions related to the use of targeted therapies.

Haugen et al, Thyroid. 2016, Bible et al, Thyroid. 2021
Indications for molecular testing: NCCN 2021

PTC, FTC, HCC:
• Genomic testing is indicated to identify actionable mutations for advanced, progressive, or threatening disease (including ALK, NTRK, and RET gene fusions, DNA mismatch repair, microsatellite instability and tumor mutational burden)

MTC
• All MTC recommended to be screened for germline RET proto-oncogene mutations
• Genomic testing including TMB or RET somatic genotyping for locally advanced and metastatic

ATC:
• Molecular testing for actionable mutations is indicated
Treatment of Advanced Thyroid Cancer
# Treatment choices for thyroid cancer patients in the past

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DTC</th>
<th>MTC</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thyroidectomy</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>RAI</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TSH suppression</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EBRT</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Conventional chemo</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Local therapies</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>
RAI therapy

- Since 1940's used for treatment of DTC with DM
- Two-thirds of metastatic patients became refractory to RAI

**Definition of RAI-refractory (any of the following)**

- No iodine uptake at known sites of disease
- Confirmed disease progression within 6-12 no after RAI tx with confirmed RAI uptake
- Total cumulative dose of RAI of $\geq 600$ mCi
- FDG avidity on PET scan
Current thyroid cancer treatment

- Extent of surgery
- Selective use of RAI
- Neoadjuvant therapies
- Targeted therapy
- Redifferentiation therapies
- Immunotherapy
Advanced Thyroid Cancer FDA-approved therapies

- Doxorubicin
- Cabozantinib (MTC)
- Vandetanib
- Sorafenib
- Lenvatinib
- Dabrafenib
- Trametinib
- Larotrectinib
- Entrectinib
- Selpecantinib
- Pralsetinib
- Cabozantinib (DTC)
Molecular Basis of Thyroid Cancer

Cabanillas et al Endocr Rev. 2019
## Systemic Targeted Therapy for MTC

<table>
<thead>
<tr>
<th></th>
<th>Vandetanib (Caprelsa)</th>
<th>Cabozantenib (Cometriq)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 3 trial (N patients)</strong></td>
<td>ZETA (n=331)</td>
<td>EXAM (n=330)</td>
</tr>
<tr>
<td><strong>Randomization and design</strong></td>
<td>2:1, Crossover allowed</td>
<td>2:1, No crossover</td>
</tr>
<tr>
<td><strong>Prior treatment</strong></td>
<td>Allowed (50%)</td>
<td></td>
</tr>
<tr>
<td><strong>Documented progression</strong></td>
<td>Not required</td>
<td></td>
</tr>
<tr>
<td><strong>Progression free survival, mo</strong></td>
<td>30.5 vs 19.3 months</td>
<td>11.2 vs 4.0 months</td>
</tr>
<tr>
<td><strong>Response rate (%)</strong></td>
<td>45%</td>
<td>29%</td>
</tr>
<tr>
<td>Complete</td>
<td>45%</td>
<td>28%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Median duration of response</strong></td>
<td>NR</td>
<td>14.6 months</td>
</tr>
<tr>
<td><strong>Black Box Warning</strong></td>
<td>QT prolongation REMS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(69% QTcF&gt;450 ms, 7% &gt;500 ms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 sudden death, 1 death from cardiopulmonary arrest)</td>
<td></td>
</tr>
</tbody>
</table>
## Systemic Therapy for RAIR DTC

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib <em>(Nexavar)</em></th>
<th>Lenvatinib <em>(Lenvima)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 3 trial (N patients)</strong></td>
<td>DECISION (n=417)</td>
<td>SELECT (n=392)</td>
</tr>
<tr>
<td><strong>Randomization and design</strong></td>
<td>1:1, crossover allowed</td>
<td>2:1, crossover allowed</td>
</tr>
<tr>
<td><strong>Prior treatment</strong></td>
<td>No</td>
<td>Yes (25%)</td>
</tr>
<tr>
<td><strong>Documented progression</strong></td>
<td>14 mo</td>
<td>13 mo</td>
</tr>
<tr>
<td><strong>Progression free survival</strong></td>
<td>11 vs 6 mo (5 mo)</td>
<td>18 vs 4 mo (14 mo)</td>
</tr>
<tr>
<td><strong>Response rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial (≥30% reduction)</td>
<td>12%</td>
<td>65%</td>
</tr>
<tr>
<td>Complete</td>
<td>0</td>
<td>2%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>42%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Median duration of response</strong></td>
<td>10 mo</td>
<td>17 mo</td>
</tr>
<tr>
<td><strong>Time to response</strong></td>
<td>2 mo</td>
<td></td>
</tr>
</tbody>
</table>

*OS advantage in older patients (>65 years of age)*

NTRK inhibitors in NTRK-fusion DTC and ATC

- Larotrectinib is a highly selective inhibitor of tropomyosin receptor kinase (TRK) A (TRKA), TRKB, and TRKC.
- 55 patients with NTRK fusions
- 9% of pts had thyroid cancer (subtypes were not reported)
- ORR 80%
  - 13% CR
  - 62% PR
  - 13% SD

- Well tolerated, with few Grade 3 SE and no Grade 4 SE.
- SE: transaminitis, fatigue, vomiting, dizziness, and nausea.

**Selpercatinib (Retevmo) in RET-Altered Thyroid Cancers LIBRETT0-001**

<table>
<thead>
<tr>
<th></th>
<th>MTC (RET-mutant)</th>
<th>RET fusion–positive thyroid cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Previously treated</td>
<td>Treatment naïve</td>
</tr>
<tr>
<td></td>
<td>N=55</td>
<td>N=88</td>
</tr>
<tr>
<td>ORR</td>
<td>69% (95% CI, 55 to 81)</td>
<td>73% (95% CI, 62 to 82)</td>
</tr>
<tr>
<td>1-year PFS</td>
<td>82% (95% CI, 69 to 90)</td>
<td>92% (95% CI, 82 to 97)</td>
</tr>
</tbody>
</table>

**Previously treated**

- **N=55**
- **ORR**: 69% (95% CI, 55 to 81)
- **1-year PFS**: 82% (95% CI, 69 to 90)

**Treatment naïve**

- **N=88**
- **ORR**: 73% (95% CI, 62 to 82)
- **1-year PFS**: 92% (95% CI, 82 to 97)

**RET fusion–positive thyroid cancer**

- **N=19**
- **ORR**: 79% (95% CI, 54 to 94)
- **1-year PFS**: 64% (95% CI, 37 to 82)
Efficacy of Selpercatinib in RET-mutant MTC

A RET-Mutant MTC Previously Treated with Vandetanib, Cabozantinib, or Both

B RET-Mutant MTC Not Previously Treated with Vandetanib or Cabozantinib
Efficacy of Selpercatinib in RET-fusion positive thyroid cancer

C  Previously Treated RET Fusion–Positive Thyroid Cancer

- Papillary thyroid cancer
- Poorly differentiated thyroid cancer
- Anaplastic thyroid cancer
- Hürthle-cell thyroid cancer

Maximum Change in Tumor Size (%)
Selpercatinib safety profile

Side effects (grade 3 or 4 adverse events):
- 21% hypertension
- 11% increased alanine aminotransferase level
- 9% increased aspartate aminotransferase level
- 8% hyponatremia
- 6% diarrhea
Pralsetinib (Gavreto) for patients with advanced or metastatic RET-altered thyroid cancer

ARROW phase 1/2 study a multi-cohort, open-label clinical trial

Treatment-related adverse events:
Grade 3 and above:
- 17% hypertension
- 13% neutropenia
- 12% lymphopenia
- 10% anemia

Subbiah et al, Lancet Diabetes Endocrinol. 2021
Cabozantinib for RAIR DTC (COSMIC 311)

- Randomized, double-blind, placebo-controlled, phase 3 trial
- 187 pts with RAIR DTC, previously treated
- ORR 15%, SD 69%, disease control rate 84%
- PFS not reached in cabo group at median of 6.2 mo vs 1.9 mo for placebo
- 75% had grade 3 and 4 SE
Tolerability of systemic therapy in thyroid cancer


ATC: Dabrafenib and Trametinib

Phase II, open-label trial
N=16 BRAF mutated ATC
All received radiation ± surgery
• ORR 69%
• PFS 79%
• PFS 80%

Side effects:
38% fatigue
37% pyrexia
35% nausea
 ATA guidelines 2021: Treatment of ATC

- Clinical Trials are strongly recommended if available
- Best Supportive Care/Hospice option can be elected at any point

**IVC**

- Aggressive Care Desired?
- Yes: BRAFV600E mut present?
  - Yes: Targeted therapy (e.g., fusions, ALK: crizotinib, ceritinib, alecitinib; RET: pralitinib, selpercatinib; NTRK: larotrectinib, entrectinib)
  - No: Checkpoint inhibitor e.g. pembrolizumab, etc.¹
  - No: High PD-L1 expression and/or >10 mutations/Mb TMB
    - Yes: Favorable tumor response?  
      - Yes: Consider consolidative therapy as feasible**
      - No: Palliative Cytotoxic Chemotherapy and/or Radiation
    - No: Palliative Cytotoxic Chemotherapy and/or Radiation

- No: Palliative Cytotoxic Chemotherapy and/or Radiation

**Best Supportive Care/Hospice**

- Palliative Cytotoxic Chemotherapy and/or Radiation

¹ Checkpoint inhibitor: e.g., pembrolizumab, etc.

**Targeted therapy**

1. For ALK: crizotinib, ceritinib, alecitinib
2. For RET: pralitinib, selpercatinib
3. For NTRK: larotrectinib, entrectinib

**Favorable tumor response**

**Consider consolidative therapy as feasible**

Bible et al, Thyroid. 2021
## ATC systemic therapies

<table>
<thead>
<tr>
<th>Lenvatinib</th>
<th>Sorafenib</th>
<th>Pembro + Dabrafenib Trametinib</th>
<th>Lenvatinib+ Pembro</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective studies</strong></td>
<td></td>
<td>[Clinical Trail (MDA)]</td>
<td></td>
</tr>
<tr>
<td>N=34 (International)</td>
<td>N=10 (Japan)</td>
<td>N=10</td>
<td></td>
</tr>
<tr>
<td>ORR 2.9%</td>
<td>ORR 0</td>
<td>ORR 0</td>
<td></td>
</tr>
<tr>
<td>PFS 2.6 mo</td>
<td>PFS 2.8 mo, OS 5 mo</td>
<td>PFS 2.8 mo, OS 5 mo</td>
<td></td>
</tr>
<tr>
<td>OS 3.2 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=14 (Japan)</td>
<td>N=20 (Cleveland)</td>
<td>N=20</td>
<td></td>
</tr>
<tr>
<td>RR=24%</td>
<td>ORR 10%</td>
<td>ORR 10%</td>
<td></td>
</tr>
<tr>
<td>PFS 7.4 mo</td>
<td>OS 3.9 mo</td>
<td>OS 3.9 mo</td>
<td></td>
</tr>
<tr>
<td>OS 10.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Retrospective studies** | | |
| N=5 (MDA) | N=12 (Japan) | N=6 (Germany) |
| PR 60%, OS 5.5 mo | OR 66% (16% SD 16 PD | Precbrom after D+T |
| N=5 (MDA) | N=12 (Japan) | N=6 (Germany) |
| PR=30% | OR 42% | OR 66% (16% SD 16 PD |
| PFS=2.6 mo, OS=3.9 mo | PFS 2.9 mo | PFS 16.5 mo |
| | OS 6.9 mo | OS 18.5 mo |

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Wirth J Clin Oncol. 2021  
Tahara et al, Front Oncol. 2017  
Iyer et al Thyroid 2018  
Koyama et al Eur Thyroid J 2018  
Iyer et al J Immunother Cancer. 2018  
Dierks, Thyroid 2021  
Ito et al Thyroid 2017  
Savvides et al Thyroid 2013
Redifferentiation Therapy for Thyroid Cancer
Redifferentiation Therapy for DTC

- Patients with advanced DTC often have RAI refractory disease due to decreased NIS expression.

- Redifferentiation therapy refers to treatment designed to increase or restore RAI uptake in tumors, enabling treatment with RAI.

- Inhibition of the MAPK pathway by MEK or BRAF inhibitors partially restored expression of these genes and RAI uptake in the animal model.
Redifferentiation therapy: Selumetinib for advanced thyroid cancer

20 pts with RAIR DTC
12 increased uptake on diagnostic WBS
8 received therapy
5/8 PR (4 RAS, 1 BRAF)

Iodine-124 PET-CT Scans obtained before and after Selumetinib
## Trials and clinical case reports with redifferentiating strategy with MAPK inhibitor

<table>
<thead>
<tr>
<th>Study</th>
<th>TKI/Duration of treatment</th>
<th>Evaluable patients (n)</th>
<th>Restoration of RAI uptake (n)</th>
<th>Treatment (n)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho et al. 2013</td>
<td>Selumetinib/4 weeks</td>
<td>20</td>
<td>12</td>
<td>8: 5/5 NRAS; 1/9 BRAF; 1/3 RET/PTC; 1/3 WT</td>
<td>At 6 months: 5 PR, 3 SD</td>
</tr>
<tr>
<td>Rothenberg et al. 2015</td>
<td>Dabrafenib/6 weeks</td>
<td>10 BRAF V600E</td>
<td>6</td>
<td>6</td>
<td>At 3 months: 2 PR, 4 SD</td>
</tr>
<tr>
<td>Dunn et al. 2019</td>
<td>Vemurafenib/4 weeks</td>
<td>10 BRAF V600E</td>
<td>6</td>
<td>4</td>
<td>At 6 months: 2 PR, 2 SD</td>
</tr>
<tr>
<td>Jaber et al. 2018</td>
<td>Dabrafenib or vemurafenib +/- trametinib/1–76.4 months</td>
<td>13 with RAI uptake on long-term TKI</td>
<td>13</td>
<td>9: 3/3 RAS, 5/9 BRAF, 1/1 WT.</td>
<td>At 8.3 months: 3 PR, 6 SD</td>
</tr>
<tr>
<td>Iravani et al. 2019</td>
<td>Dabrafenib +/-trametinib or vemurafenib + cobimetinib/4 weeks</td>
<td>6</td>
<td>4</td>
<td>4: 1/3 NRAS, 3/3 BRAF</td>
<td>At 3 months: 3 PR, 1SD</td>
</tr>
<tr>
<td>Huillard et al. 2017</td>
<td>Vemurafenib/8 months and then dabrafenib/3 months</td>
<td>1 BRAF V600E</td>
<td>1</td>
<td>1</td>
<td>1 PR after each treatment</td>
</tr>
<tr>
<td>Leboulleux et al. 2019</td>
<td>Dabrafenib + trametinib/8 weeks</td>
<td>1 BRAF K601E</td>
<td>1</td>
<td>0</td>
<td>Thyrotoxicosis</td>
</tr>
</tbody>
</table>
Case report of a 64 yo man with a 34-year history of PTC

- RAIR (12 treatments 1405 mCi)
- *EML4-NTRK3*
- Diagnostic RAI scintigraphy performed during lenvatinib treatment showed no substantial RAI uptake in the lungs
- RAI scintigraphy performed 3 weeks after the initiation of larotrectinib treatment showed restoration of RAI uptake
NTRK and RET fusion-directed therapy in pediatric thyroid cancer yields a tumor response and radioiodine uptake

2 pediatric pts (TPR-NTRK1 or CCDC6-RET)
Treated with larotrectinib and selpercatinib
Restoration of RAI uptake

7 yo girl with CCDC6-RET fusion oncogene received 131I therapy combined with selpercatinib, resulting in a tumor response
Redifferentiation therapy: Adjuvant Selumetinib for high-risk DTC (ASTRA)

- A randomized, placebo-controlled phase 3 study evaluating the CR rate for selumetinib in the setting of adjuvant treatment with RAI.

Inclusion criteria: pT > 4 cm, pT4 (gross ETE), N1 with ≥ 5 lymph nodes or with at least one lymph node ≥1 cm)

Exclusion criteria: DM

- 400 enrolled, 233 were randomized to receive selumetinib plus RAI (n = 155) or a placebo plus RAI (n = 78).
- At 18 months, the CR rate was not significantly higher in the selumetinib plus RAI group than in the control group (OR, 1.07; 95% CI, 0.61 to 1.87; P =0.8205)
- Selumetinib + RAI did not improve the CR rate in patients with a high risk of primary treatment failure.
Neoadjuvant Therapy for Locally Advanced Thyroid Cancer
Complete Surgical Resection Following Neoadjuvant Dabrafenib Plus Trametinib in BRAFV600E-Mutated Anaplastic Thyroid Carcinoma

Case series:
6 pts with BRAF mutated ATC
6 pts received dabrafenib and trametinib followed by surgical resection and adjuvant chemoradiation
3 pts also received pembrolizumab
Complete surgical resection was achieved in all patients
OS 6 mo 100%, 12 mo 83%
Locoregional disease control 100%
ATA guidelines 2021: Treatment of ATC

- Clinical Trials are strongly recommended if available
- Best Supportive Care/Hospice option can be elected at any point

**IVA**
- Encourage definitive-intention therapy (because of potential for long-term survival for IVA patients)

**IVB**
- **Resectable?**
  - Rapid BRAF assessment (IHC, molecular), parallel
  - Comprehensive genetic testing*

**Surgery**
- Goal: R0/R1 resection
- Avoid debulking
- Avoid laryngectomy

**Definitive intention radiation (IMRT) +/- Chemotherapy**
- (taxane monotherapy or with platin or anthracycline)

**Targeted therapy**
- (e.g. fusions, ALK: crizotinib, ceritinib, alectinib; RET: pralsetinib, selpercatinib; NTRK: larotrectinib, entrectinib)

**Other tumor genetics?**
- e.g. ALK, NTRK, RET fusions

**Surgery (if feasible)**
- Excellent tumor response?

**Best Supportive Care/Hospice**

**BRAFV600E mut present?**
- Y
- N

**Dabrafenib + Trametinib**
- Y
- N

**or**

**or**

**Palliative Chemotherapy and/or Radiation**

*BRAFV600E mutation testing with next generation sequencing (NGS) is highly recommended for patients with symptoms suggestive of advanced disease in ATA guidelines 2021*
Neoadjuvant Selpercatinib for advanced MTC

20 yo man with widely metastatic symptomatic MTC
somatic RET deletion Y900_S904delinsP
6 cycles of Selpercatinib, held for 3 days, R1 resection, resumed at day 9
Neoadjuvant Clinical Trials (USA)

- **ATC**
  - Dabrafenib, Trametinib, Pemprolizumab (BRAF+) (MDA)

- **MTC**
  - Selpercatinib (RET+) (MDA)

- **DTC**
  - Lenvatinib (Mass General)
  - Vemurafenib (MDA)
  - Selpercatinib (RET+) (MDA)
Future Therapeutic Directions

- Redifferentiation therapies
- Neoadjuvant therapies
- Cell therapy for ATC
- Radiopharmaceuticals for MTC: 177Lu-DOTATATE and yttrium-90–DOTATOC
- Combination therapies
Multidisciplinary Approach
THANK YOU