Disclosures

• I have no financial disclosure or conflicts of interest with the presented material in this presentation
Objectives

• Understand the diagnostic evaluation

• Know the differences in approaches treating the same disease

• Realize the implications on prognosis this entails
Carcinogenesis and the Genome

Targeting the Mutation

T315I Mutation

A Threonine

Important for hydrogen bonding

Thr31


Rossari F., et al. Journal of Hematology & Oncology. 2018;11(84)

a Nilotinib

b Dasatinib

c Bosutinib
d Ponatinib
• **Targeted therapy:**
  - Inhibits cell survival advantage
  - Must be downstream from other mutation(s)

• **Acquired mutations may confer resistance!**

Initial Approach to a Case

• Is this disease targetable?
  – How best to assess the molecular/genomics

• Is the treatment approved in this setting?

• Is the patient a candidate for this therapy?
Techniques

• Tissue-based analysis
  – Benefits: allows genome and whole transcriptome analysis
  – Limitations: requires sufficient tissue and may not reflect tumor heterogeneity
Techniques

• Liquid-based analysis
  – Benefits: quick and may bypass tumor heterogeneity
  – Limitations: unable to evaluate molecular features, limited transcriptomic analysis
The NILE Study

• 55 y/o male patient newly diagnosed by FNA with metastatic lung adenocarcinoma
  
  – Many targetable therapies available
  – Most approved frontline
  – Patient is a healthy non-smoker
Non-Small Cell Lung Cancer

• Tumor-Specific
  – EGFR
  – ALK
  – ROS1
  – MET
  – RET
  – HER2
  – KRAS

• Tumor-Agnostic
  – NTRK
  – BRAF V600E
  – High TMB

• Prevalence
  – Adenocarcinoma: ~30%
  – Squamous: ~5%
Case 1

- Scant tissue is sent for molecular analysis only. PD-L1 staining is 0% by 22C3 IHC

- Liquid biopsy reveals an $EGFR$ L858R mutation
Initial EGFR-Targeting


Erlotinib (n=86)
Chemotherapy (n=87)
HR 0.37 (95% CI 0.25–0.54); log-rank p<0.0001
<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Erlotinib group (n=84)</th>
<th>Standard chemotherapy group (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>82 (98%)</td>
<td>81 (99%)</td>
</tr>
<tr>
<td>Treatment-related adverse event (all grades)</td>
<td>78 (93%)</td>
<td>78 (95%)</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event</td>
<td>38 (45%)</td>
<td>55 (67%)</td>
</tr>
<tr>
<td>Dose reduction due to adverse event</td>
<td>18 (21%)</td>
<td>23 (28%)</td>
</tr>
<tr>
<td>Dose reduction due to drug-related adverse event</td>
<td>18 (21%)</td>
<td>21 (26%)</td>
</tr>
<tr>
<td>Discontinuation due to an adverse event</td>
<td>11 (13%)</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>Discontinuation due to drug-related adverse event</td>
<td>5 (6%)</td>
<td>16 (20%)</td>
</tr>
<tr>
<td>Any severe adverse event</td>
<td>27 (32%)</td>
<td>25 (30%)</td>
</tr>
<tr>
<td>Treatment-related severe adverse event</td>
<td>5 (6%)</td>
<td>16 (20%)</td>
</tr>
<tr>
<td>Treatment-related death*</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Resistance to *EGFR*-Targeting

- **EGFR T790M**
  - Common mechanism with earlier generation drugs

- **Osimertinib**
  - 3rd generation TKI that can target T790M
  - Should we use upfront?
Progression-free Survival in Full Analysis Set

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. of Patients</th>
<th>Median Progression-free Survival (95% CI)</th>
<th>Hazard ratio for disease progression or death, P&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>279</td>
<td>18.9 (15.2–21.4)</td>
<td>0.46 (95% CI, 0.37–0.57)</td>
</tr>
<tr>
<td>Standard EGFR-TKI</td>
<td>277</td>
<td>10.2 (9.6–11.1)</td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th>Medication</th>
<th>0-270 mo</th>
<th>271-297 mo</th>
<th>298-324 mo</th>
<th>325-351 mo</th>
<th>352-378 mo</th>
<th>379-405 mo</th>
<th>406-432 mo</th>
<th>433-460 mo</th>
<th>461+ mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>279</td>
<td>262</td>
<td>233</td>
<td>210</td>
<td>178</td>
<td>139</td>
<td>71</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Standard EGFR-TKI</td>
<td>277</td>
<td>239</td>
<td>197</td>
<td>152</td>
<td>107</td>
<td>78</td>
<td>37</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>
Progression-free Survival in Patients with CNS Metastases

<table>
<thead>
<tr>
<th></th>
<th>Median Progression-free Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>15.2 (12.1–21.4)</td>
</tr>
<tr>
<td>Standard EGFR-TKI</td>
<td>9.6 (7.0–12.4)</td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.30–0.74)

P < 0.001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib</th>
<th>Standard EGFR-TKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td>3 months</td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td>6 months</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>9 months</td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td>12 months</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>15 months</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>18 months</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>21 months</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>24 months</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>27 months</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End Point</th>
<th>Osimertinib (N=279)</th>
<th>Standard EGFR-TKI (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of response — no. (%) ‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>7 (3)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Partial</td>
<td>216 (77)</td>
<td>206 (74)</td>
</tr>
<tr>
<td>Stable disease for ≥6 wk</td>
<td>47 (17)</td>
<td>46 (17)</td>
</tr>
<tr>
<td>Progression</td>
<td>3 (1)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>6 (2)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Objective response rate — % of patients (95% CI)</td>
<td>80 (75–85)</td>
<td>76 (70–81)</td>
</tr>
<tr>
<td>Disease-control rate — % of patients (95% CI)</td>
<td>97 (94–99)</td>
<td>92 (89–95)</td>
</tr>
<tr>
<td>Time to response §</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of weeks — median (95% CI)</td>
<td>6.1 (6.0–6.1)</td>
<td>6.1 (NC–NC)</td>
</tr>
<tr>
<td>≤6 wk after first dose — no./total no. (%)</td>
<td>154/223 (69)</td>
<td>148/210 (70)</td>
</tr>
</tbody>
</table>
Case 1 (revisited)

• 55 y/o male patient with metastatic lung adenocarcinoma progresses on EGFR-targeted therapy

• What next?  
  – Biopsy!
Case 1 (revisited)

- HER2 mutation identified as resistance mechanism

- What next?
  - Trastuzumab deruxtecan (T-DXd)
Trastuzumab Deruxtecan

DESTINY-Lung01

Case 2

• 55 y/o male patient newly diagnosed resected stage IIB lung adenocarcinoma

  – Targetable therapies available
  – Approved in post-chemo adjuvant setting
  – Patient is a healthy *non-smoker*
Localized NSCLC: EGFR

Patients with Stage II to IIIA Disease

Median Disease-free Survival (95% CI)
- Osimertinib: m0 (NR: 38.8–NC)
- Placebo: 19.6 (16.6–24.5)

Hazard ratio for disease recurrence or death, 0.17 (99.06% CI, 0.11–0.26) P<0.001

No. at Risk
- Osimertinib: 233, 219, 189, 137, 97, 52, 18, 2, 0
- Placebo: 237, 190, 127, 82, 51, 27, 9, 1, 0
Localized NSCLC: EGFR

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Osimertinib (N = 337)</th>
<th></th>
<th></th>
<th>Placebo (N = 343)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Any Grade</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>156 (46)</td>
<td>116 (34)</td>
<td>32 (9)</td>
<td>8 (2)</td>
<td>68 (20)</td>
<td>54 (16)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>85 (25)</td>
<td>31 (9)</td>
<td>50 (15)</td>
<td>3 (1)</td>
<td>5 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>79 (23)</td>
<td>75 (22)</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
<td>22 (6)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>65 (19)</td>
<td>49 (15)</td>
<td>16 (5)</td>
<td>0</td>
<td>30 (9)</td>
<td>28 (8)</td>
</tr>
<tr>
<td>Cough</td>
<td>62 (18)</td>
<td>43 (13)</td>
<td>19 (6)</td>
<td>0</td>
<td>57 (17)</td>
<td>42 (12)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>59 (18)</td>
<td>35 (10)</td>
<td>18 (5)</td>
<td>6 (2)</td>
<td>14 (4)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>47 (14)</td>
<td>30 (9)</td>
<td>17 (5)</td>
<td>0</td>
<td>35 (10)</td>
<td>25 (7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>45 (13)</td>
<td>24 (7)</td>
<td>19 (6)</td>
<td>2 (1)</td>
<td>35 (10)</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>44 (12)</td>
<td>29 (9)</td>
<td>13 (4)</td>
<td>2 (1)</td>
<td>13 (4)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>39 (12)</td>
<td>32 (9)</td>
<td>7 (2)</td>
<td>0</td>
<td>8 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Dermatitis aciform</td>
<td>37 (11)</td>
<td>29 (9)</td>
<td>8 (2)</td>
<td>0</td>
<td>16 (5)</td>
<td>12 (3)</td>
</tr>
</tbody>
</table>

*Number of patients (percent)*
55 y/o male patient with resected EGFR-mutated stage IIIB lung adenocarcinoma on adjuvant osimertinib progresses. Next step?

Biopsy!
Case 2 (revisited)

- **EGFR** Exon 20 insertion mutation identified as resistance mechanism

- What next?
  - Until 2021, no further target available
  - Now we have amivantamab and mobocertinib
Case 3

• 51 y/o female presents with *BRCA1*-mutated triple negative localized breast cancer
  – Received standard neoadjuvant therapy and lumpectomy
  – Pathology shows partial response
  – *Is there a role for further therapy?*
Risk of Breast Cancer

Lifetime Risk of Breast Cancer According to Age

BRCA1/2 Mutations

- Germline pathogenic variants result in:
  - Loss of function
  - Impaired DNA homologous recombination (HR)
  - Increased genomic instability and oncogenesis
Normal cell

- BRCA1/2
- PARP inhibitors
- HR repair
- SSB repair

HR backup → Cell survival

BRCA-incompetent cancer cell

- Epigenetic silencing of BRCA1/2 expression
- PARP inhibitors
- SSB repair → Defect of HR
- HR repair

Cell death
Adjuvant Olaparib: IDFS

First 900 patients entered with median follow up of 3.5 years

Stratified hazard ratio 0.61 (99.5% CI, 0.39–0.95)*
Difference: 3-year IDFS rate 8.6% (95% CI, 3.3–13.9%)+

Lingering Questions

- Does adjuvant chemotherapy still contribute in TNBC without a path CR?
- Should we incorporate *neoadjuvant* PARP-I?
Case 4

- 51 y/o female with localized BRCA1-mutated triple negative breast cancer develops metastases after standard therapy. Next step?
  - Biopsy!
Case 4

• HER2 IHC returns 2+ (equivocal)
• HER2 ISH returns amplified

• This changes everything
  • THP (CLEOPATRA Trial\textsuperscript{1})
  • T-DXd (DESTINY-Breast 03 Trial\textsuperscript{2})

T-DXd vs T-DM1: PFS


<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab deruxtecan</th>
<th>Trastuzumab emtansine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months (95% CI)</td>
<td>28.8 (22.4-37.9)</td>
<td>6.8 (5.6-8.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.33 (0.26-0.43)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Number at risk

Trastuzumab deruxtecan
261 256 250 244 240 225 216 207 205 191 176 173 167 154 146 140 134 131 130 125 123 117 113 107 99 96 90 82 73 64 55 41 32 28 23 20 18 13 7 5 4 2 1 0

Trastuzumab emtansine
263 253 201 164 156 134 111 99 96 81 69 67 63 58 54 51 49 47 44 41 39 37 36 32 28 27 22 19 15 14 8 7 4 2 2 1 1 1 1 0

Legend:
- Censor
- Trastuzumab deruxtecan (n = 261)
- Trastuzumab emtansine (n = 263)
T-DXd vs T-DM1: OS

Median, months (95% CI)
Trastuzumab deruxtecan Trastuzumab emtansine
HR (95% CI) NR (40.5-NE) NR (34.0-NE)
p value 0.64 (0.47-0.87) 0.0037

Number at risk
Trastuzumab deruxtecan
261 256 255 254 251 249 244 243 241 238 236 236 231 224 218 213 211 206 201 200 196 193 187 182 173 156 142 124 109 91 73 64 51 44 38 30 22 18 11 9 7 6 1 1 1 0
Trastuzumab emtansine
263 257 252 248 243 242 237 233 222 227 224 217 211 203 199 197 191 186 183 179 172 169 167 164 164 158 140 129 117 106 90 70 59 45 41 38 27 20 15 8 7 4 3 3 1 1 0

T-DXd vs T-DM1: OR

Case 5

• 61 y/o male presents with newly diagnosed acute myeloid leukemia

• How do we formulate a prognosis-defined treatment strategy?
<table>
<thead>
<tr>
<th>Risk category†</th>
<th>Genetic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>• t(8;21)(q22;q22.1)/RUNX1::RUNX1T1†,‡</td>
</tr>
<tr>
<td></td>
<td>• inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11†,‡</td>
</tr>
<tr>
<td></td>
<td>• Mutated NPM1†,§ without FLT3-ITD</td>
</tr>
<tr>
<td></td>
<td>• bZIP in-frame mutated CECPA</td>
</tr>
<tr>
<td>Intermediate</td>
<td>• Mutated NPM1†,§ with FLT3-ITD</td>
</tr>
<tr>
<td></td>
<td>• Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions)</td>
</tr>
<tr>
<td></td>
<td>• t(9;11)(p21.3;q23.3)/MLLT3::KMT2A†,¶</td>
</tr>
<tr>
<td></td>
<td>• Cyogenetic and/or molecular abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td>Adverse</td>
<td>• t(6;9)(p23.3;q34.1)/DEK::NUP214</td>
</tr>
<tr>
<td></td>
<td>• t(v;11q23.3)/KMT2A-rearranged#</td>
</tr>
<tr>
<td></td>
<td>• t(9;22)(q34.1;q11.2)/BCR::ABL1</td>
</tr>
<tr>
<td></td>
<td>• t(8;16)(p11.2;p13.3)/KAT6A::CREBBP</td>
</tr>
<tr>
<td></td>
<td>• inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1)</td>
</tr>
<tr>
<td></td>
<td>• t(3q26.2;v)/MECOM(EVI1)-rearranged</td>
</tr>
<tr>
<td></td>
<td>• −5 or del(5q); −7; −17/abn(17p)</td>
</tr>
<tr>
<td></td>
<td>• Complex karyotype,** monosomal karyotype††</td>
</tr>
<tr>
<td></td>
<td>• Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2‡,‡</td>
</tr>
<tr>
<td></td>
<td>• Mutated TP53³</td>
</tr>
</tbody>
</table>


- **Genetics:**
  - Guides treatment
  - Allows MRD assessment

- **Consolidative BMT**
  - Adverse disease
  - Non-adverse w/ persistent MRD
Case 6

• 76 y/o male with AML progresses after frontline palliative therapy
  – Wishes for treatment
  – Genetics reveal an *IDH1* mutation

• Can we target this?
Figure 1. Wild-type IDH function in homeostasis and activity of mutant IDH in disease. 2HG, D-2-hydroxyglutarate; αKG, α-ketoglutarate; IDH, isocitrate dehydrogenase; IDHm, mutant IDH.
Ivosidenib in IDH1

A Platelets and Neutrophils

No. of Patients

| Platelets | 125 | 11 | 101 | 88 | 79 | 67 | 52 | 45 | 42 | 33 | 30 | 21 | 20 |
| Neutrophils | 118 | 9  | 97  | 86 | 78 | 66 | 52 | 45 | 42 | 32 | 30 | 22 | 20 |

Ivosidenib in IDH1

B Hemoglobin and Bone Marrow Blasts

No. of Patients

<table>
<thead>
<tr>
<th>Hemoglobin 125</th>
<th>Hemoglobin 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow blasts 124</td>
<td>Bone marrow blasts 11</td>
</tr>
</tbody>
</table>

Ivosidenib in *IDH1*

C Transfusion Independence

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>CRh</th>
<th>Response other than CR or CRh</th>
<th>No response</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet (N=69)</td>
<td>100</td>
<td>71</td>
<td>58</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>Red Cell (N=68)</td>
<td>85</td>
<td>75</td>
<td>50</td>
<td>15</td>
<td>40</td>
</tr>
</tbody>
</table>

## Targeted Agents in AML

<table>
<thead>
<tr>
<th>Drug</th>
<th>Midostaurin</th>
<th>Gilteritinib</th>
<th>Ivosidenib</th>
<th>Enasidenib</th>
<th>GO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td><strong>FLT3</strong></td>
<td><strong>FLT3</strong></td>
<td><strong>IDH1</strong></td>
<td><strong>IDH2</strong></td>
<td><strong>inv(16) or t(8;21)</strong></td>
</tr>
<tr>
<td>Induction</td>
<td><img src="lightning-bolt.png" alt="Lightning bolt" /></td>
<td><img src="x.png" alt="X" /></td>
<td><img src="x.png" alt="X" /></td>
<td><img src="x.png" alt="X" /></td>
<td><img src="lightning-bolt.png" alt="Lightning bolt" /></td>
</tr>
<tr>
<td>Palliative</td>
<td><img src="x.png" alt="X" /></td>
<td><img src="lightning-bolt.png" alt="Lightning bolt" /></td>
<td><img src="lightning-bolt.png" alt="Lightning bolt" /></td>
<td><img src="lightning-bolt.png" alt="Lightning bolt" /></td>
<td><img src="x.png" alt="X" /></td>
</tr>
</tbody>
</table>

Figure: GO, gemtuzumab ozogamicin
A 52 y/o male presents with progressive peripheral polyneuropathy
– Evaluation reveals fat pad TTR amyloid deposition
– Confirmed autosomal dominant TTR amyloidosis

How can we treat this?
• Small interfering RNA
  – Uses cellular mechanisms to degrade target mRNA

• Approved in TTR amyloidosis
Inotersen: QOL

B Norfolk QOL-DN Score

Least-Squares Mean Change from Baseline in Norfolk QOL-DN Score

Weeks

Placebo

Inotersen

6.1
P=0.03

11.7
P<0.001

The Cost?

• Most very tolerable, some unique toxicities
  – Erdafitinib: ↑Phos, retinopathy

• Financial toxicities
  – Cost of 1 year Osimertinib = $235,567

• QOL
  – Increased burden/duration of therapy
Role of genomic guided therapy expanding at rapid rate across all of heme/onc

Established agents being pushed up
- In order of use in advanced disease
- Incorporated into the curative setting
Questions

Thank you