METASTATIC MELANOMA TREATMENT

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US FDA APPROVAL OF MELANOMA THERAPIES

Michielin O., J Immunother Cancer 2020;8:e000948. Reproduced under the terms of the Creative Commons Attribution Non Commercial (CC BY-NC 4.0). Available at: http://creativecommons.org/licenses/by-nc/4.0/; accessed March 2021.
FIRST-LINE THERAPY: OVERALL SURVIVAL

Mean survival curves created by weighted averaging of digitised Kaplan-Meier survival curves of metastatic melanoma patients treated in selected clinical trials.

LONG-TERM OS IN CLINICAL TRIALS WITH IMMUNO-Oncology Agents AND TARGETED THERAPIES

In patients with advanced melanoma

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Diagnosis of cutaneous melanoma pT2bN0M0

B-RAF mutation detected (V600E)

Metastatic melanoma to liver (multiple lesions)

Start Vemurafenib in COLUMBUS study

First tumour assessment

Start Ipilimumab

Start Nivolumab

ECOG = 1

ECOG = 2

LDH level (204-480) 760 390 860 1030 2130

CLINICAL CASE
39-year-old Male

Images courtesy of Prof PA Ascierto
CLINICAL CASE
39-year-old-Male

December 2015
- Stop Nivolumab
  - For fast PD
  - ECOG = 2

January 2016
- Dabrafenib + Trametinib
  - Re-challenge

March 2016
- CT Scan

November 2019
- Still on treatment mFU (30 mos)

January 2020
- Brain progression disease

March 2020
- Death for progression disease

LDH level (204-480)
- 2130

Image courtesy of Prof PA Ascierto
TARGET THERAPY
THE ROLE OF BRAF V600 MUTATION IN MELANOMA
ANTI-BRAF + ANTI-MEK COMBINATION
Decreases the risk of death of 30 to 37% vs. anti-BRAF monotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoBrim</td>
<td>Cobimetinib 60 mg QD* + vemurafenib 960 mg BID (n=247)</td>
<td>PFS</td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td>Vermurafenib 960 mg BID + placebo (n=248)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combi-D</td>
<td>Dabrafenib 150 mg BID + trametinib 2 mg QD (n=211)</td>
<td>PFS</td>
<td>OS, ORR, DOR, Safety, PK</td>
</tr>
<tr>
<td></td>
<td>Dabrafenib 150 mg BID + placebo (n=212)</td>
<td></td>
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</tr>
<tr>
<td>Combi-V</td>
<td>Dabrafenib 150 mg BID + trametinib 2 mg QD (n=352)</td>
<td>OS</td>
<td>PFS, ORR, DOR, Safety</td>
</tr>
<tr>
<td></td>
<td>Vermurafenib 960 mg BID (n=352)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COLUMBUS</td>
<td>COMBO450 (N=192)</td>
<td>PFS</td>
<td>OS</td>
</tr>
<tr>
<td>Part 1</td>
<td>Encorafenib 450 mg QD + binimetinib 45 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vermurafenib 960 mg BID (n=191)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Encorafenib 300 mg QD (n=194)</td>
<td></td>
<td></td>
</tr>
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</table>

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials
ORR FROM PHASE 3 PIVOTAL TRIALS WITH BRAF/MEK INHIBITORS


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Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials
PFS CURVES FROM PHASE 3 PIVOTAL TRIALS WITH BRAF/MEK INHIBITORS

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials


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OS CURVES FROM PHASE 3 PIVOTAL TRIALS WITH BRAF/MEK INHIBITORS

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials

ENCORAFENIB/BINIMETINIB COMBO RESULT LOOKS SIMILAR TO THE RESULTS FROM THE OTHER BRAF/MEK INHIBITORS COMBOS
PFS CURVES FROM PHASE 3 PIVOTAL TRIALS WITH BRAF INHIBITORS MONOTHERAPY

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials

OS CURVES FROM PHASE 3 PIVOTAL TRIALS WITH BRAF INHIBITORS MONOTHERAPY

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials

<table>
<thead>
<tr>
<th>Event, %</th>
<th>COMBO450 encorafenib/binimetinib</th>
<th>Combi-v dabrafenib/trametinib</th>
<th>CoBRIM vemurafenib/cobimetinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median duration of exposure: 51 weeks</td>
<td>Median duration of exposure: 12.2 months</td>
<td>Median duration of exposure: 9 months</td>
</tr>
<tr>
<td>Adverse events</td>
<td>98</td>
<td>99</td>
<td>99</td>
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<tr>
<td>Grade 3/4 adverse events</td>
<td>64</td>
<td>58</td>
<td>74,6</td>
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<tr>
<td>Adverse events leading to discontinuation</td>
<td>15</td>
<td>16</td>
<td>20.6</td>
</tr>
</tbody>
</table>

## AESI OF BRAF/MEK INHIBITORS FROM PHASE 3 PIVOTAL TRIALS

<table>
<thead>
<tr>
<th>Event</th>
<th>All Grades</th>
<th>Grade ≥3</th>
<th>All Grades</th>
<th>Grade ≥3</th>
<th>All Grades</th>
<th>Grade ≥3</th>
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<tbody>
<tr>
<td>COMBO450</td>
<td></td>
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<tr>
<td>encorafenib/</td>
<td>15</td>
<td>4</td>
<td>57</td>
<td>5</td>
<td>29</td>
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<tr>
<td>binimetinib</td>
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<tr>
<td>[a]</td>
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<tr>
<td>Combi-V</td>
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</tr>
<tr>
<td>dabrafenib/</td>
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<tr>
<td>trametinib</td>
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<td>[b]</td>
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<td>CoBrim</td>
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<tr>
<td>vemurafenib/</td>
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<tr>
<td>cobimetinib</td>
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<tr>
<td>[c]</td>
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</tr>
<tr>
<td>Pyrexia</td>
<td>4</td>
<td>&lt;1</td>
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<td>Photosensitivity</td>
<td>4</td>
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<td>34</td>
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<tr>
<td>LFT increase</td>
<td>6</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
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<td>11</td>
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<tr>
<td>SCC</td>
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<td>-</td>
<td>2</td>
<td>-</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Ocular</td>
<td>16</td>
<td>3</td>
<td>27</td>
<td>3</td>
<td></td>
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</tr>
<tr>
<td>Cardio-toxicity</td>
<td>8</td>
<td>2</td>
<td>17</td>
<td>3</td>
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</tr>
</tbody>
</table>

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials

IMMUNOTHERAPY
KEYNOTE 006: 5-YEAR OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL

CHECKMATE 067: 5-YEAR OVERALL SURVIVAL

Improved OS with NIVO+IPI and NIVO vs. IPI over 5 years

PROGRESSION-FREE SURVIVAL

- Improved PFS with NIVO+IPI and NIVO vs IPI over 5 years

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI (n = 314)</th>
<th>NIVO (n = 316)</th>
<th>IPI (n = 315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>11.5 (8.7–19.3)</td>
<td>6.9 (5.1–10.2)</td>
<td>2.9 (2.8–3.2)</td>
</tr>
<tr>
<td>HR (95% CI) vs IPI</td>
<td>0.42 (0.35–0.51)</td>
<td>0.53 (0.44–0.64)</td>
<td>–</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO*</td>
<td>0.79 (0.64–0.96)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

SAFETY SUMMARY

No new safety signals were observed with the additional follow-up
No additional deaths due to study drug toxicity were reported since the prior analysis

Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n=1 each; both occurred >100 days after last treatment), neutropenia for NIVO (n=1), and colonic perforation for IPI (n=1); Post-hoc analysis. TRAE, treatment-related adverse event.


![Table of patients reporting events](image)

Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE

- Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)
PATIENT CHARACTERISTICS AFFECTING IMMUNE SURVEILLANCE

Active immune surveillance

Long-term benefit patients
- ≤3 brain metastases (size <2 cm)
- Low tumour burden (<3 organ involved?)
- Normal LDH

Inactive immune surveillance

No long-term benefit patients
- Multiple (>3) brain metastases
- High tumour burden (>3 organ involved?)
- High LDH

LDH, lactate dehydrogenase

IS THERE A PATIENT SUBGROUP WHERE COMBINATION THERAPY MAY HAVE GREATER CLINICAL BENEFIT?

- Patient history (e.g., autoimmune disease)
- Patient's wishes and lifestyle factors
- Performance status
- tumour burden
- Disease tempo
- Mutational status
- Brain metastases
- Organ system function, especially cardiac function
- LDH level
IS THERE A PATIENT SUBGROUP WHERE COMBINATION THERAPY MAY HAVE GREATER CLINICAL BENEFIT?

- Patient history (e.g., autoimmune disease)
- Performance status
- Tumour burden
- Patient's wishes and lifestyle factors
- Organ system function, especially cardiac function
- Mutational status
- Brain metastases
- Disease tempo
- LDH level
KEYNOTE 006: OVERALL SURVIVAL ACCORDING TO LDH LEVEL

Median (95% CI), mo

- Pembro ≤1×ULN: NR (NR-NR)
- Pembro >1–≤2×ULN: 19.5 (14.7-NR)
- Pembro >2×ULN: 5.3 (4.0-9.5)
- Ipi ≤1×ULN: NR (20.8-NR)
- Ipi >1–≤2×ULN: 8.0 (5.8-10.9)
- Ipi >2×ULN: 3.9 (1.8-6.9)

Data cutoff date: Dec 3, 2015.

CHECKMATE 066: 5-YEAR OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL

DABRAFENIB PLUS TRAMETINIB: PFS ACCORDING TO LDH

DABRAFENIB PLUS TRAMETINIB: OS ACCORDING TO LDH

PFS OUTCOMES WITH COBIMETINIB PLUS VEMURAFENIB

Better in patients with normal vs. elevated LDH at baseline

<table>
<thead>
<tr>
<th>LDH Normal (N=131)</th>
<th>Normal LDH n = 131</th>
<th>Elevated LDH n = 112</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, median months (95% CI)</td>
<td>15.0 (12.9 – 22.0)</td>
<td>8.6 (7.3 – 10.0)</td>
</tr>
</tbody>
</table>

OS OUTCOMES WITH COBIMETINIB PLUS VEMURAFENIB

Better in patients with normal vs. elevated LDH at baseline

CKM 067: PFS AND OS BY LDH LEVEL
Improved with NIVO+IPI and NIVO vs. IPI regardless of LDH

LDH, lactate dehydrogenase; ULN, upper limit of normal.

Descriptive analysis.

IS THERE A PATIENT SUBGROUP WHERE COMBINATION THERAPY MAY HAVE GREATER CLINICAL BENEFIT?

Patient history (e.g., autoimmune disease)
Patient's wishes and lifestyle factors
Performance status
Disease tempo
Brain metastases
LDH level
Mutational status
Organ system function, especially cardiac function

tumour burden
DABRAFENIB PLUS TRAMETINIB: PFS IN PATIENTS WITH NORMAL LDH AND <3 ORGAN SITES

Descriptive analysis.

ESMO CONSENSUS CONFERENCE
RECOMMENDATIONS
On the management of metastatic melanoma: Under the auspices of the ESMO Guidelines Committee

Recommendation 2.2
In metastatic melanoma, there is no clear definition for tumour burden. As such, there is no consensus regarding how this should be used to select treatment
Level of evidence: IV
Strength of recommendation: E
Level of consensus: 93% (26) yes, 4% (1) no, 4% (1) abstain (28 voters)
IS THERE A PATIENT SUBGROUP WHERE COMBINATION THERAPY MAY HAVE GREATER CLINICAL BENEFIT?

Patient history (e.g., autoimmune disease)

Organ system function, especially cardiac function

Patient's wishes and lifestyle factors

Mutational status

Performance status

Brain metastases

tumour burden

LDH level

Disease tempo
BRAIN METASTASES:

- Single
- Few (≤3)
- Multiple

Symptomatic or Asymptomatic

Better to say: who requires steroid or not

Without visceral involvement  With visceral involvement
CHECKMATE 204 PFS AND OS (ASYMPTOMATIC PATIENTS)

Progression-Free Survival – Asymptomatic Patients

Overall Survival – Asymptomatic Patients

Demographic and Patient Characteristics – Asymptomatic Patients

Few (≤3)
Cohort B:
- Symptomatic patients
- ECOG PS 0–2
- ≤4 mg dexamethasone or equivalent/day allowed

Demographic and patient characteristics – Symptomatic patients

One patient did not have extracranial disease
Recommendation 14.1

For patients with multiple asymptomatic BMs, combination treatment with ipilimumab and nivolumab is recommended due to its more durable disease control compared with targeted therapy

Level of evidence: V
Strength of recommendation: B
Level of consensus: 100% (32) yes (32 voters)
WHAT ABOUT THE RIGHT SEQUENCE... ?
FIRST REPORT OF EFFICACY AND SAFETY FROM THE PHASE II STUDY SECOMBIT
(SEquential COMBo Immuno and Targeted therapy study)


1-Department of Melanoma, Cancer Immunotherapy and Development Therapeutics. I.N.T. IRCCS Fondazione “G. Pascale” Napoli; 2-Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; 3- Unit of Oncology of Melanoma, European Institute of Oncology, 20141 - Milan/IT; 4-Department of Soft Tissue/Bone Sarcoma, Maria Skłodowska Curie National Research Institute of Oncology, 02-781 - Warsaw/PL; 5-Immunotherapy and Cell Therapy Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; 6-Department of Medical Oncology, Hospital Clinic Barcelona, 08036 - Barcelona/ES; 7-Department of Medical Oncology 1; 7-IRCCS Regina Elena National Cancer Institute, Rome, Italy; 8-Department of Oncology, Fondazione IRCCS Casa Sollievo della Sofferenza, Foggia, Italy; 9-Medical Oncology Department, National Cancer Research Centre "Giovanni Paolo II", Bari, Italy; 10-Unit of Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 11-Department of Medical Sciences, Dermatologic Clinic, University of Turin, Turin, Italy; 12-IRCCS Ospedale Policlinico San Martino, Skin Cancer Unit, Genova, Italy; 13-Institut de Recherche Saint Louis (IRSL), Université de Paris, F-75010 Paris, France; 14-Department of Oncology-Pathology, Karolinska Institutet and Karolinska University Hospital Solna, Stockholm, Sweden; 15-Department of Immunology and Immunotherapy, Clínica Universidad de Navarra, Pamplona, Spain; 16-Unit of Cancer Genetics, CNR, Sassari, Italy; 17-Regina Elena National Cancer Institute, IRCCS - Biostatistical Unit, Rome, Italy; 18-Department of Dermatology, University and University Hospital Zurich, Zurich, Switzerland; 19-Melanoma Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy.

*contributed equally to this study
SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT): STUDY DESIGN

Primary endpoint:
- OS

Secondary endpoints:
- PFS
- Total PFS
- Time to second progression
- % patients alive at 2–3 years
- Best ORR
- DOR

**ARM A**
- Combo T
  - Encorafenib 450 mg
  - Binimetinib 45 mg
- PD
- ipi/nivo until PD

**ARM B**
- Combo I
  - Ipilimumab 3 mg/kg
  - Nivolumab 1 mg/kg
- PD
- enco/bini until PD

**ARM C**
- Sandwich
  - Encorafenib 450 mg
  - Binimetinib 45 mg for 8 weeks
- ipi/nivo until PD
- enco/bini until PD

**Stratification Factors:**
- IIIb/c – M1a – M1b
- M1c with normal LDH (≤2ULN)
- M1c with elevated LDH (>2 ULN)

DOR, duration of response; ECOG-PS, Eastern Cooperative Oncology Group performance status; LGX, encorafenib (BRAFi); MEK162, binimetinib (MEKi); ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease.

Clinicaltrials.gov: NCT02631447.
## BASELINE CHARACTERISTICS OF ITT POPULATIONS

<table>
<thead>
<tr>
<th></th>
<th>Arm A (n. 69)</th>
<th>Arm B (n. 71)</th>
<th>Arm C (n. 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>55.0 (19-77)</td>
<td>55.0 (18-81)</td>
<td>51.0 (28-80)</td>
</tr>
<tr>
<td>Sex - Male no (%)</td>
<td>42 (60.9%)</td>
<td>34 (47.9%)</td>
<td>42 (60.9%)</td>
</tr>
<tr>
<td>ECOG-PS 0 no. (%)</td>
<td>57 (82.6%)</td>
<td>62 (87.3%)</td>
<td>62 (89.9%)</td>
</tr>
<tr>
<td>Lactate Dehydrogenase (LDH) levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=1.00 x ULN</td>
<td>41 (59.4%)</td>
<td>37 (52.1%)</td>
<td>44 (63.8%)</td>
</tr>
<tr>
<td>&gt;1.00 x ULN</td>
<td>28 (40.6%)</td>
<td>34 (47.9%)</td>
<td>25 (36.2%)</td>
</tr>
<tr>
<td>&gt;2.00 x ULN</td>
<td>7 (10.1%)</td>
<td>9 (12.7%)</td>
<td>7 (10.1%)</td>
</tr>
<tr>
<td>Stage n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0-M1a- M1b</td>
<td>29 (42%)</td>
<td>28 (39.4%)</td>
<td>29 (42%)</td>
</tr>
<tr>
<td>M1c</td>
<td>40 (58.0%)</td>
<td>42 (59.1%)</td>
<td>39 (56.5%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>0</td>
<td>1 (1.5%)</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>History of brain metastases n. (%)</td>
<td>0</td>
<td>1 (1.4%)</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Number of lesion sites, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>43 (62.3%)</td>
<td>41 (57.7%)</td>
<td>43 (62.3%)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>25 (36.2%)</td>
<td>29 (40.9%)</td>
<td>25 (36.2%)</td>
</tr>
<tr>
<td>NE</td>
<td>1 (1.5%)</td>
<td>1 (1.4%)</td>
<td>1 (1.5%)</td>
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</table>
SECOMBIT: PROGRESSION-FREE SURVIVAL

<table>
<thead>
<tr>
<th></th>
<th>Arm A (n. 69)</th>
<th>Arm B (n. 71)</th>
<th>Arm C (n. 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BORR. %*(95% CI)</td>
<td>82.6 (73.7-91.6)</td>
<td>45.1 (33.5-53.6)</td>
<td>78.3 (68.5-88.0)</td>
</tr>
<tr>
<td>DCR. % (95% CI)</td>
<td>89.8 (82.7-97.0)</td>
<td>55.0 (43.3-66.5)</td>
<td>92.8 (86.6-98.9)</td>
</tr>
<tr>
<td>Best overall response N (%)</td>
<td>Complete response</td>
<td>Partial response</td>
<td>Stable disease</td>
</tr>
<tr>
<td></td>
<td>15 (21.7)</td>
<td>42 (60.9)</td>
<td>5 (7.2)</td>
</tr>
<tr>
<td></td>
<td>11 (15.5)</td>
<td>21 (29.6)</td>
<td>7 (9.9)</td>
</tr>
<tr>
<td></td>
<td>20 (29.0)</td>
<td>34 (49.3)</td>
<td>10 (14.5)</td>
</tr>
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</table>

**SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT): BORR**

SECOMBIT: DOR

<table>
<thead>
<tr>
<th></th>
<th>ARM A</th>
<th>ARM B</th>
<th>ARM C</th>
</tr>
</thead>
<tbody>
<tr>
<td>mDoR, months (95% CI)</td>
<td>17.8 (10.5-25.1)</td>
<td>NR</td>
<td>9.8 (0.8-18.8)</td>
</tr>
<tr>
<td>12-months DR rate (%) (95% CI)</td>
<td>56.5 (43.4-69.6)</td>
<td>69.9 (52.2-87.5)</td>
<td>48.5 (34.2-62.8)</td>
</tr>
<tr>
<td>24-months DR rate (%) (95% CI)</td>
<td>34.2 (18.7-49.7)</td>
<td>69.9 (52.2-87.5)</td>
<td>33.7 (14.7-52.7)</td>
</tr>
</tbody>
</table>

**ARM A**: Enco/Bini  
**ARM B**: Ipi/Nivo  
**ARM C**: Enco/Bini (8 weeks) → Ipi/Nivo

NR = not reached; DR = durable responses


<table>
<thead>
<tr>
<th>Patients reporting event</th>
<th>ARM A (n = 69)</th>
<th>ARM B (n = 71)</th>
<th>ARM C (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
</tr>
<tr>
<td>Any Adverse Event, n, (%)</td>
<td>63 (91)</td>
<td>34 (49)</td>
<td>68 (96)</td>
</tr>
<tr>
<td>Treatment-related AE, n, (%)</td>
<td>53 (77)</td>
<td>19 (28)</td>
<td>59 (83)</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation, n, (%)</td>
<td>7 (10)</td>
<td>8 (11)</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

- No new safety signals were observed as compared with the data from clinical trials with IPI+NIVO and ENCO+BINI
- No treatment-related deaths
SECOMBIT: TOTAL PROGRESSION-FREE SURVIVAL

Preliminary report

<table>
<thead>
<tr>
<th>Arm</th>
<th>N of events (%)</th>
<th>1y tot PFS (95% CI)</th>
<th>2y tot PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>29 (42.0)</td>
<td>76 (66-86)</td>
<td>48 (33-63)</td>
</tr>
<tr>
<td>Arm B</td>
<td>28 (39.4)</td>
<td>65 (53-77)</td>
<td>58 (45-71)</td>
</tr>
<tr>
<td>Arm C</td>
<td>25 (35.2)</td>
<td>73 (62-84)</td>
<td>62 (50-74)</td>
</tr>
</tbody>
</table>

**ARM A:** Enco/Bini → Ipi/Nivo
**ARM B:** Ipi/Nivo → Enco/Bini
**ARM C:** Enco/Bini (8 weeks) → Ipi/Nivo PD → Enco/Bini

Total Progression-free Survival = time from randomisation until the date of the second progression.

ONGOING CLINICAL STUDIES

NCT02224781: Phase 3 Study of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab vs Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib

Randomised Phase 3 trial of dabrafenib + trametinib followed by ipilimumab + nivolumab at progression vs ipilimumab + nivolumab followed by dabrafenib + trametinib at progression in patients with advanced BRAF V600 mutant melanoma.

Primary endpoint:
- OS rate, defined as the proportion of patients alive after 2 years of follow-up time

Secondary endpoints:
- PFS (RECIST version 1.1)
- Response rate (REDOSt version 1.1)

Objective:
- Does the initial treatment with the dabrafenib-trametinib combination (and subsequent ipilimumab-nivolumab) or ipilimumab-nivolumab combination (and subsequent dabrafenib-trametinib combination) improve the 2-year OS significantly in patients with unresectable stage III or stage IV BRAF V600 mutant melanoma?

ImmunoCobiVem: Phase 2 Sequencing Study of Cobimetinib + Vemurafenib Followed by Atezolizumab (Anti–PD-L1) in Patients With BRAF V600 Mutant Melanoma

Phase 2, open-label, randomised, controlled trial evaluating the efficacy and safety of a sequencing schedule of cobimetinib + vemurafenib followed by immunotherapy with an anti–PD-L1 antibody in patients with unresectable or metastatic BRAF V600 mutant melanoma.

Primary endpoint:
- Time to PFS2

Secondary endpoints:
- Safety, tolerability
- 12-, 24-month OS rate
- 12-, 24-month disease control rate
- PFS1, PFS2

---

ECOG-PS: Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival; Q4W, every 4 weeks; Q2W, every 2 weeks; REDOSt, Response Evaluation Criteria in Solid Tumors.
ONGOING CLINICAL STUDIES (CONT’D)

EORTC EBIN: Study design

Objective: to assess whether PFS can be improved with a sequential approach, using a 12-week induction of encorafenib + binimetinib, followed by combination nivolumab + ipilimumab, compared with nivolumab + ipilimumab alone, in patients with BRAFV600 mutation-positive unresectable or metastatic melanoma

Multicentre, two-arm, open-label, randomised comparative Phase 2 study

Key eligibility criteria
- Aged ≥ 18 years
- Treatment-naive patients
- Presence of BRAFV600E or V600K mutation in tumour tissue prior to enrolment
- ECOG PS 0–1

Primary endpoint
- PFS

Secondary endpoints
- OS
- CR
- ORR
- PFS2*
- Safety

*PFS2 is defined as the time from randomisation to second objective disease progression, or death from any cause, whichever first

DESPITE THE DURABLE RESPONSES OBSERVED, MANY PATIENTS DO NOT BENEFIT FROM THE TREATMENT

30% 10-year survival rates are still poor in 50% of melanoma patients

No biomarkers can predict long-term benefit

Ascierto PA. Presented at ESMO Annual Congress 2019. By permission of Prof PA Ascierto.
How can we make the tumour more responsive? (overcoming primary resistance)

How can we reduce the risk of relapse? (overcoming acquired resistance)
THE TUMOUR MICROENVIRONMENT IS A KEY DRIVER OF RESPONSE OR RESISTANCE TO TREATMENT

APC = antigen-presenting cell; IDO = indoleamine 2,3 dioxygenase; LN = lymph node; MHC = major histocompatibility complex; TAP = transporter associated with antigen processing; TCR = T-cell receptor; TDO = tryptophan 2,3-dioxygenase; TGF = tumour growth factor; VEGF = vascular endothelial growth factor.

POTENTIAL COMBINATION STRATEGIES FOR THE TREATMENT OF CANCER

- Immunotherapy plus loco-regional treatment
- Immunotherapy plus targeted therapy
- Immunotherapy plus chemotherapy
- Immunotherapy plus immunotherapy
POTENTIAL COMBINATION STRATEGIES FOR THE TREATMENT OF CANCER

- Immunotherapy plus loco-regional treatment
- Immunotherapy plus targeted therapy
- Immunotherapy plus chemotherapy
- Immunotherapy plus immunotherapy
BRAF/MEK INHIBITORS AS IMMUNOMODULATING AGENTS


BRAFi/MEKi induce profound changes in:
- Antigen display ↑
- Expression of MHC ↑
- IFNAR ↑ and CD73 ↓

Tumour microenvironment after BRAFi and MEKi:
- ↓ Adenosine
- ↓ Treg and myeloid-derived suppressor cells
- ↑ Activity of CD4-CD8+ lymphocytes

ADE, adenosine; IFNAR, interferon-α/β receptor; MHC, major histocompatibility complex; TAA, tumour-associated antigen; Treg, regulatory T cell

ADE, adenosine; IFNAR, interferon-α/β receptor; MHC, major histocompatibility complex; TAA, tumour-associated antigen; Treg, regulatory T cell

TARGETED THERAPY WITH IMMUNOTHERAPY
A rational combination for advanced BRAFV600 mutant melanoma

Dummer R, et al.. Reproduced with permission from JAMA Oncol 2020;6(12) :1957–66. Copyright©2020 American Medical Association. All rights reserved.
DIFFERENT TRIPLE COMBINATION BRAF/MEK + ANTI-PD-1/PD-L1

Dabrafenib + trametinib + durvalumab

Dabrafenib + trametinib + pembrolizumab

Vemurafenib + cobimetinib + atezolizumab

Dabrafenib + trametinib + spatalizumab

Dabrafenib + trametinib + nivolumab

BID, twice daily; CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease. a Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change for non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget lesions. b Patients with PR and 100% change in SOD have (a) 100% change for all target lesions and (b) non-CR/non-PD response for nontarget lesions.

WHAT DO WE KNOW ABOUT THE TRIPLET TT+IO FROM RANDOMISED STUDIES… ?
**KEYNOTE-022 Part 3 Study Design**
(NCT02130466)

**NEGATIVE!**

- Histo logically cold or metastatic stage mutant melanoma
- No prior therapy
- Measurable disease
- ECOG PS 0/1

**Posizol? Q3W + Dabrafenib 150 mg BD + Tremetinib 2 mg OD for up to 2 y**

**NEGATIVE!**

**Stratification factors**
- ECOG PS (0 vs 1)
- LDH level (≤1.1 × ULN vs ≥1.1 × ULN)

**N = 60**
- Primary end point: PFS
- Secondary end points: ORR, DOR, and OS
- Date cutoff: Jun 28, 2019

**Evaluation of Atezolizumab, Cobimetinib, and Vemurafenib in Previously Untreated Patients With BRAFV600 Mutation–Positive Advanced Melanoma:**

**POSITIVE!**

Grant A. McArthur, M.I  
Caroline Robert, M.D., Ph.D.  
Thomas ANT.  
Piotr Rutkowski, M.D., Ph.D.  
Lev Dabrowko, M.D.  
Anton Makarich, M.D.  
Yibing Yan, M.D.  
Kuan-Chi Huang, Ph.D.  
Anne Uzel, M.D.  
Vinnau McNally, Ph.D.  
Ralf Gutzmer, M.D.  
Paolo Ascierto, M.D.
Based on Kaplan-Meier estimate of PFS, per investigator assessment.

Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH > 1.1 × ULN vs ≤1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

One-sided p-value based on stratified log-rank test.


**KEYNOTE-022 OVERALL SURVIVAL**

![Graph showing overall survival with percentages 79% and 73%]

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median(^a) (95% CI), mo</th>
<th>HR(^b) (95% CI)(^b)</th>
<th>p-value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + D + T</td>
<td>19</td>
<td>NR (19.6-NR)</td>
<td>0.76 (0.41-1.39)</td>
</tr>
<tr>
<td>Placebo + D + T</td>
<td>24</td>
<td>23.4 (17.8-NR)</td>
<td>0.76 (0.41-1.39)</td>
</tr>
</tbody>
</table>

\(^a\)Based on Kaplan-Meier estimate of overall survival.

\(^b\)Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

\(^c\)P values are provided for descriptive purposes only, no multiplicity adjustment is made. One-sided P value based on stratified log-rank test.


**KEYNOTE-022: ONCOLOGIC THERAPIES AFTER DISCONTINUING STUDY TREATMENT**

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Pembro + D + T N = 60</th>
<th>Placebo + D + T N = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 New systemic therapy</td>
<td>21 (35.0)</td>
<td>34 (56.7)</td>
</tr>
<tr>
<td>BRAF/MEK inhibitor&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 (23.3)</td>
<td>7 (11.7)</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>8 (13.3)</td>
<td>8 (13.3)</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>8 (13.3)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Trametinib</td>
<td>7 (11.7)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>8 (13.3)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Chemotherapy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (1.7)</td>
<td>2 (3.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Pembro + D + T N = 60</th>
<th>Placebo + D + T N = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy</td>
<td>9 (15.0)</td>
<td>29 (48.3)</td>
</tr>
<tr>
<td>Pembro</td>
<td>7 (11.7)</td>
<td>21 (35.0)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>0 (0)</td>
<td>10 (16.7)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>2 (3.3)</td>
<td>8 (13.3)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes BRAF inhibitors or MEK inhibitors.

<sup>b</sup>Carboplatin, paclitaxel, and 1 unspecified chemotherapy.

OVERALL SURVIVAL

KN022 first report
Ascierto et al ESMO 2018
mFU = 9.6 months

KN022 second report
Ferrucci et al SMR 2019
mFU = 29.6 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>Median(^a) (95% CI), mo</th>
<th>HR(^b) (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + D + T</td>
<td>26 (43.3)</td>
<td>NR (23.9-NR)</td>
<td>0.64 (0.38-1.06)</td>
</tr>
<tr>
<td>Placebo + D + T</td>
<td>36 (60.0)</td>
<td>26.3 (18.2-NR)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Based on Kaplan-Meier estimate of overall survival.

\(^b\)Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN; owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

Data cutoff: Jun 26, 2019.
COMBI-I STUDY DESIGN (PART 3)

N = 532

Key eligibility criteria
• BRAF V600 mutation-positive unresectable or metastatic melanoma
• Previously untreated
• No active brain metastases
• ECOG PS ≤ 2

Randomization stratification
• ECOG PS
• LDH level

Primary endpoint: Investigator-assessed PFS using RECIST 1.1
Secondary endpoints: OS, ORR, DOR, DCR, safety, PRO, PK

Spartalizumab 400 mg Q4W + dabrafenib 150 mg BID + trametinib 2 mg QD

Placebo Q4W + dabrafenib 150 mg BID + trametinib 2 mg QD

BID, twice daily; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q4W, every 4 weeks; QD, once daily;
RECIST, Response Evaluation Criteria in Solid Tumours.
Nathan P, et al. ESMO 2020
The primary endpoint was investigator-assessed progression-free survival using RECIST 1.1

- The study design assumed a 5-month delay in the treatment effect of Sparta-DabTram
- A target number of 352 events was set to ensure 80% power. Note: The prespecified final analysis could occur at 24 months after the last patient was randomised if this occurred before the target number was reached
- A prespecified interim analysis was conducted after 276 events were observed, at which time the data monitoring committee recommended not to unblind the study
- This primary analysis is based on a minimum follow-up of 24 months, with 312 events (statistical threshold, \( P=0.02497 \) [1-sided])

Overall survival was a key secondary endpoint

- Overall survival could be statistically tested only after the primary endpoint was determined to be statistically significant

All efficacy analyses were performed using the full analysis set, which comprised all patients randomised to receive study treatment; safety analyses included all patients who received ≥1 dose of at least 1 drug in each treatment regimen

Nathan P, et al. ESMO 2020
INVESTIGATOR-ASSESSED PROGRESSION-FREE SURVIVAL

Event, n (%) | Median (95% CI), mo | HR (95% CI)
--- | --- | ---
Sparta-DabTram | 147 (55.1) | 16.2 (12.7-23.9) | 0.820 (0.655-1.027)
Placebo-DabTram | 165 (62.3) | 12.0 (10.2-15.4) | Not significant

HR, hazard ratio.
PFS FROM KEYNOTE-022, IMSPRIRE 150 AND COMBI-I (TRIPLET ARMS)

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials.

Ascierto P. ESMO Educational Session 2020. By permission of Prof P Ascierto.
PFS FROM KEYNOTE-022, IMSPIRE 150 AND COMBI-I (CONTROL ARMS)

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials

Ascierto P. ESMO Educational Session 2020. By permission of Prof P Ascierto.

OS FROM KEYNOTE-022, IMSPRIRE 150 AND COMBI-I (TRIPLET ARMS)

2-yr OS
68%
63%
60.4%

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials

Ascierto P. ESMO Educational Session 2020. By permission of Prof P Ascierto.
OS FROM KEYNOTE-022, IMSPRIRE 150 AND COMBI-I (CONTROL ARMS)

2-yr OS
62%
52%
53.1%

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials

Ascierto P. ESMO Educational Session 2020. By permission of Prof P Ascierto.
Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials.
## TRIPLET COMBOS SAFETY PROFILE

<table>
<thead>
<tr>
<th>Keynote-022 (n=60)</th>
<th>IMspire 150 (n=230)</th>
<th>Combi-I (n=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients reporting event</strong></td>
<td><strong>Any grade</strong></td>
<td><strong>Grade 3/4</strong></td>
</tr>
<tr>
<td>Any Adverse Event, n, (%)</td>
<td>60 (100)</td>
<td>42 (70)</td>
</tr>
<tr>
<td>Treatment-related AE, n, (%)</td>
<td>57 (95)</td>
<td>35 (58.3)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (3)</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td>Treatment-related deaths, n, (%)</td>
<td>1 (2)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation of ≥ 1 study drug, n, (%)</td>
<td>28 (46.7)</td>
<td>NR</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation of all 3 study drugs, n, (%)</td>
<td>18 (30)</td>
<td>29 (13)</td>
</tr>
</tbody>
</table>

NR = not reported

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials

Ascierto P. ESMO Educational Session 2020. By permission of Prof P Ascierto.
DO WE REALLY NEED A TRIPLET COMBO…?
OS FROM KEYNOTE-022, IMSPRIRE 150 AND COMBI-I (TRIPLET ARMS) AND ...

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials

Ascierto PA. ESMO Educational Session 2020. By permission of Prof P Ascierto.
Larkin et al. NEJM 2019; Ferrucci et al. SMR 2019; McArthur et al. AACR 2020; Nathan et al. ESMO 2020
IS THERE A PATIENT'S SUBGROUP WHERE COMBINATION MIGHT BE MORE USEFUL...?
CHECKMATE 204: PFS AND OS IN BM SYMPTOMATIC PATIENTS

Progression-free survival – Symptomatic patients

Overall survival – Symptomatic patients

ANY ROLE IN CASE OF PD AFTER/DURING ADJUVANT…?
TRiDeNT STUDY: PATIENT DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Measure</th>
<th>All Patients (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>19 (73)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>7 (27)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (58)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (42)</td>
</tr>
<tr>
<td><strong>ECOG status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (65)</td>
</tr>
<tr>
<td>1</td>
<td>9 (35)</td>
</tr>
<tr>
<td><strong>LDH, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 1 x ULN</td>
<td>15 (58)</td>
</tr>
<tr>
<td>&gt; 1 – ≤ 2 x ULN</td>
<td>6 (23)</td>
</tr>
<tr>
<td>&gt; 2 x ULN</td>
<td>5 (19)</td>
</tr>
<tr>
<td><strong>Sites of disease, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 3</td>
<td>9 (35)</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>17 (65)</td>
</tr>
<tr>
<td><strong>Follow-up time in months (all patients)</strong></td>
<td>13.1 (0.3 – 30.6)</td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td></td>
</tr>
</tbody>
</table>

TRIDeNT STUDY: OUTCOMES BY BRAIN METS STATUS

88% (7/8) ORR in pts w/ brain mets (2 CR)
93% (13/14) ORR in pts w/out brain mets (1 CR)
67% (4/6) evaluable pts experienced an intracranial response, including 2 CRs

Median PFS:
- w/ brain mets 8.6 mos
- w/out brain mets 8.4 mos

TRIDENT STUDY: OUTCOMES BY PD1 TREATMENT STATUS

100% ORR in PD1 naive patients (2 CR)
83% ORR in PD1 refractory patients (1 CR)


<table>
<thead>
<tr>
<th>Prior PD1 treatment</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence after adjuvant tx</td>
<td>4</td>
</tr>
<tr>
<td>Primary resistance</td>
<td>10</td>
</tr>
<tr>
<td>PD1 + Ipi</td>
<td>2</td>
</tr>
<tr>
<td>PD1 + other</td>
<td>6</td>
</tr>
<tr>
<td>PD1 single agent</td>
<td>2</td>
</tr>
<tr>
<td>Secondary resistance</td>
<td>2</td>
</tr>
</tbody>
</table>
OS FROM KEYNOTE-022, IMSPIRE 150 AND COMBI-I (TRIPLET ARMS)

Citation of data without the intention of direct or indirect comparison in the absence of head-to-head clinical trials

Ascierto P. ESMO Educational Session 2020; by permission of Prof P Ascierto.
IMMUNE EFFECTS OF VEGF

Bevacizumab plus Ipilimumab in Patients with Metastatic Melanoma

Clinical Trial

LENVATINIB PLUS PEMBROLIZUMAB IN PATIENTS WITH ADVANCED MELANOMA

Previously exposed to anti-PD-1/anti-PD-L1 agents: Phase 1 LEAP-004 study

Patients
- Unresectable stage III or IV melanoma
  - All comers with regard to PD-L1 and BRAF status
  - Confirmed progression with ≥2 doses of anti-PD-1/anti-PD-L1 monotherapy or combination therapy
  - ECOG PS 0 or 1

Pembrolizumab 200 mg IV Q3W + Levatinib 20 mg PO QD Up to 35 cycles

Levatinib 20 mg PO QD

Treatment to continue until Disease progression or unacceptable toxicity

Posttreatment follow-up to assess
- Safety
- Disease
- Survival status

LEAP-004: BICR-CONFIRMED RESPONSE BY PD ON PRIOR ANTI-CTLA-4 + ANTI-PD-(L)1

<table>
<thead>
<tr>
<th></th>
<th>Total Population N = 103</th>
<th>PD on Prior Anti–CTLA-4 + Anti–PD-(L)1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes n = 29</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>21.4% (13.9-30.5)</td>
<td>31.0% (15.3-50.8)</td>
</tr>
<tr>
<td>DCR, % (95% CI)</td>
<td>65.0% (55.0-74.2)</td>
<td>62.1% (42.3-79.3)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>2 (1.9%)</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>PR</td>
<td>20 (19.4%)</td>
<td>8 (27.6%)</td>
</tr>
<tr>
<td>SD</td>
<td>45 (43.7%)</td>
<td>9 (31.0%)</td>
</tr>
<tr>
<td>PD</td>
<td>31 (30.1%)</td>
<td>10 (34.5%)</td>
</tr>
<tr>
<td>Not assesseda</td>
<td>5 (4.9%)</td>
<td>1 (3.4%)</td>
</tr>
</tbody>
</table>

*Patients who had no post-baseline imaging assessments. Data cut-off date: June 10, 2020.
Arance A, LEAP-004 ESMO 2020; abstract LBA44.
POTENTIAL COMBINATION STRATEGIES FOR THE TREATMENT OF CANCER

- Immunotherapy plus loco-regional treatment
- Immunotherapy plus targeted therapy
- Immunotherapy plus chemotherapy
- Immunotherapy plus immunotherapy
TUMOUR-DIRECTED IMMUNO-ONCOLOGY

**T-VEC + IPILIMUMAB**

**All lesions**


**Non injected visceral lesions**


**4-year PFS**

**4-year OS**
TOLL-LIKE RECEPTOR 9 (TLR9) INHIBITION

Intratumoural mechanism of action of tilsotolimod

Extracted from Babiker HM, et al. Presented at AACR 2019; abstract 4062. By permission of Dr Shah Rahimian
**FINAL RESULTS FROM ILLUMINATE-204**

A Phase I/II trial of intratumoural tilsotolimod in combination with ipilimumab in PD-1 inhibitor refractory advanced melanoma

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>In 49 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, months (95% CI)</td>
<td>21.0 (9.8-NR)</td>
</tr>
<tr>
<td>mPFS, months (95% CI)</td>
<td>5.1 (3.65-7)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>22.4 (11.8-36.6)</td>
</tr>
<tr>
<td>DCR, % (95% CI)</td>
<td>71.4 (56.7-83.4)</td>
</tr>
<tr>
<td>mDOR, months (95% CI)</td>
<td>11.4 (3.3-NR)</td>
</tr>
</tbody>
</table>

- Tumour reduction was observed in both injected and noninjected tumours

DCR = disease control rate; IPI = ipilimumab; irAEs = immune-related adverse events; mDOR = median duration of response; mOS = median overall survival; NR = not reached; ORR = objective response rate; PD-1 = programmed cell death protein 1; RECIST = Response Evaluation Criteria in Solid Tumours; TEAE = treatment-emergent adverse event. Haymaker C, et al. ESMO 2020; by permission of Prof C. Haymaker. Clinical trial information: https://clinicaltrials.gov/ct2/show/NCT02644967.
A RANDOMISED PHASE 3 COMPARISON OF IMO-2125
With ipilimumab vs. ipilimumab alone in subjects with anti-PD-1 refractory melanoma

Ascierto PA, et al. ESMO 2018. By permission of Prof PA Ascierto.
OTHER TLRS AGONIST ON DEVELOPMENT: SD101 AND CMP-001

Best Percent Change from Baseline in All Target Lesions

ORR (2 mg/kg) = 70%

ORR (8 mg/kg) = 70%

Percent Change from Baseline over Time in All Target Lesions for Patients Who Received ≤ 2 mg vs. 8 mg SD-101 Per Lesion (3)

OTHER TLRS AGONIST ON DEVELOPMENT:
SD101 AND CMP-001

KEYNOTE 695 INTERIM DATA

Durable responses and immune activation with intratumoural electroporation of pIL-12 plus pembrolizumab in actively progressing anti-PD-1 refractory advanced melanoma

Best overall response

Treated and untreated lesions from 16 responding patients

Percent change in tumour size over time
NEW EMERGING PATHWAYS FOR FUTURE COMBINATION WITH ANTI-PD-1/PD-L1 COMPOUNDS

IDO1 inhibitor (e.g., epacadostat [Ph 3], etc.)

Anti-LAG-3 (e.g., relatlimab [Ph 1/2])

HDAC inhibitor (e.g., entinostat [Ph 2])

IDO1 inhibitor (e.g., epacadostat [Ph 3], etc.)

Anti-GITR (e.g., BMS-986156 (Ph 1/2))

GITR, glucocorticoid-induced TNFR-related protein; HDAC, histone deacetylases; IDO1, indoleamine 2,3-dioxygenase 1; LAG-3, lymphocyte-activation gene 3.

Presented by Paolo A. Ascierto at ASCO 2018; Ascierto PA, McArthur JA. J Transl Med 2017;15:173. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (available at: http://creativecommons.org/licenses/by/4.0/; accessed April 2021).
INITIAL EFFICACY OF ANTI-LYMPHOCYTE ACTIVATION GENE-3 (ANTI-LAG-3; BMS-986016)

In combination with nivolumab in patients with melanoma previously treated with anti-PD-1/PD-L1 therapy

Ascierto PA, et al. ESMO 2017. By permission of Prof PA Ascierto.
CA224-047
Randomised, double-blind Phase 2/3 study of relatlimab combined with nivolumab vs. nivolumab in participants with previously untreated metastatic or unresectable melanoma


Phase 2 primary endpoint: PFS assessed by a BICR
Phase 2 secondary endpoint: ORR, DOR, DCR, PFS rates, and 1- and 2-year OS rates according LAG-3 and PD-L1 status, safety and tolerability

Stratify by:
- LAG-3 status
- PD-L1 status
- BRAF status
- AJCC M-stage

Unresectable or metastatic melanoma
- Previously untreated
- Tissue available for LAG-3, PD-L1, TMB assessment

ARM A
relatlimab + nivolumab
160/480 mg IV Q4W

ARM B
nivolumab
480 mg IV Q4W

Phase 3 primary endpoint: PFS
Phase 3 secondary endpoint: ORR, OS

Additional N = 300 pts

N = 400 pts

Positive
NEW EMERGING PATHWAYS FOR FUTURE COMBINATION WITH ANTI-PD-1/PD-L1 COMPOUNDS

HDAC inhibitors

(eg., entinostat, etc.)

McArthur JA. J Transl Med 2017;15:173. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (available at: http://creativecommons.org/licenses/by/4.0/; accessed April 2021).
RATIONALE FOR ENTINOSTAT IN COMBINATION WITH ANTI-PD-(L)1 THERAPY

- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT leads to downregulation of immunosuppressive cell types in the tumour microenvironment
- Synergy with anti-PD-1 inhibition in preclinical models

1 In vivo and in vitro studies were performed using Lewis Lung Carcinoma (LLC) cells. **p<0.001; *p<0.05.

Ab, antibody; Arg1, arginase 1; COX2, cytochrome oxidase subunit 2; iNOS, inducible nitric oxide synthase; MDSC, myeloid-derived suppressor cells.

ENCORE-601: OPEN-LABEL STUDY EVALUATING ENT + PEMBRO

In patients with recurrent or metastatic melanoma and prior progression on or after anti-PD-1 therapy

Inclusion criteria
- Recurrent or metastatic melanoma, measurable by RECIST 1.1
- Prior progression on or after anti-PD-(L)1 treatment
- Prior BRAF treatment if indicated
- ECOG Performance Status < 2
- Willingness to participate in baseline and on-treatment biopsy and blood samples

Phase 1b: Dose & safety confirmation

Phase 2:
ENT 5 mg PO QW + PEMBRO 200 mg IV Q3W

Primary Endpoint
- ORR (irRECIST)

Secondary Endpoints
- CBR, PFS, OS, safety & tolerability

Mismatch Repair-Proficient CRC Anti-PD-1/PD-L1-naive

Malignancy
- NSCLC Progressing on Anti-PD-1/PD-L1
- NSCLC Anti-PD-1/PD-L1–naive
- Melanoma Progressing On/After Anti-PD-1

Mismatch Repair-Deficient NSCLC Anti-PD-1/PD-L1-naive

Mismatch Repair-Dysfunctional NSCLC Anti-PD-1/PD-L1-naive

Mismatch Repair-Afflicted NSCLC Anti-PD-1/PD-L1-naive

Mismatch Repair-Deficient CRC Anti-PD-1/PD-L1-naive

Mismatch Repair-Dysfunctional CRC Anti-PD-1/PD-L1-naive

Mismatch Repair-Afflicted CRC Anti-PD-1/PD-L1-naive

Mismatch Repair-Proficient CRC Anti-PD-1/PD-L1-naive

53 patients enrolled, last patient enrolled April 2018

CBR, clinical benefit rate; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; ENT, entinostat; irRECIST, immune-related Response Evaluation Criteria in Solid Tumours; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PO, orally; QW, once a week; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours.

10 confirmed responses of 53 treated [19% ORR (95% CI: 9, 32)]
  - 1 CR, 9 PRs
Median duration of response: 13 months (range 3–20)
  - 4 responders ongoing
An additional 9 patients have had SD for >6 months
  - 36% CBR (95% CI: 23, 50)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; irRECIST, immune-related Response Evaluation Criteria in Solid Tumours; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
STUDY DESIGN AND OBJECTIVES SENSITISE STUDY (NCT03278665)

3 dose escalation cohorts (up to 10 patients/cohort)
- QD and BID dosing explored

Dose optimisation* cohort with 6 patients
Phase II expansion planned with defined optimal biological dose and schedule
Study conducted at 7 sites in Europe; including National Tumour Institute Fondazione G. Pascale in Naples

Phase Ib: dose escalation and dose optimization
Domatinostat (p.o.) + Pembrolizumab (D1, q3w; i.v.)

Dose escalation cohort 1 (n=10)
100 mg QD D1-14, q3w

Dose escalation cohort 2a (n=6)
200 mg QD D1-14, q3w

Dose escalation cohort 3 (n=7)
200 mg BID D1-14, q3w

Dose optimization cohort 2b*
200 mg QD D1-21, q3w

Phase II: expansion
Domatinostat (p.o.); optimized dose and schedule + Pembrolizumab (D1, q3w; i.v.)

*currently recruiting; not discussed today
BID: twice daily; QD: once daily; q3w: every 3 weeks
Heavily pre-treated patient population with >50% 3+ lines of prior therapies
- Last treatment with anti-PD1/anti-CTLA4 + anti-PD1, last dose within 6 months

All patients primary refractory to prior checkpoint inhibitor therapy
Treatment currently ongoing for 3 patients in cohort 3
Bempegaldesleukin (BEMPEG; NKTR-214): is a CD122-preferential IL-2 pathway agonist shown to increase tumour-infiltrating lymphocytes (TILs), T cell clonality and PD-1 expression\(^1,2\)

BEMPEG plus checkpoint inhibitor (CPI) nivolumab (NIVO) has been shown to convert baseline tumours from PD-L1(-) to PD-L1(+)\(^3-6\)

Low levels of baseline TILs\(^7-9\) and T cell-inflammation\(^10\) is predictive of a poor response to CPIs
STAGE IV 1L MELANOMA: BEST OVERALL RESPONSE BY INDEPENDENT RADIOLOGY

Data cut-off: 01 Sept 2020. Response evaluable population includes eligible patients with measurable disease (per RECIST 1.1) at baseline and have ≥1 post-baseline tumour assessment. All objective responses are confirmed. #Best overall response is progressive disease due to non-target lesion progression or presence of new lesion; *Best overall response is SD; +Best overall response is PR. CR for target lesion, non-target lesion still present.

CR, complete response; LDH, lactate dehydrogenase
RESPONSES WITH BEMPEG PLUS NIVO WERE DURABLE AND DEEPENED OVER TIME

Stage IV 1L melanoma: ORR 53% with CR 34%

Datacutoff: 1 Sept 2020. aPatient achieved PR in Mar 2018; EoT in Jul 2018; achieved CR in Oct 2018. bPatient achieved PR in Mar 2018; EoT in May 2018 due to patient decision (QoL issues); achieved CR in May 2018; disease relapse in Sept 2018 due to new lesion (brain).

OVERALL STUDY DESIGN CA045-001

PIVOT IO 001: Phase 3

**Screening**

Population:
- Treatment naïve (1L setting)
- Unresectable stage III or stage IV

**Treatment**

Arm A
NKTR-214 and Nivolumab

Arm B
Nivolumab

Treat until RECIST 1.1 progression or unacceptable toxicity

**Follow-up**

Follow-up for safety, RECIST 1.1 progression, and survival

Endpoints Primary:
- ORR by BICR
- PFS by BICR
- OS

ClinicalTrials.gov. NCT03635983.
FUTURE PERSPECTIVES
MGD019: BISPECIFIC MOLECULE ENGINEERED FOR CO-BLOCKADE OF PD-1 AND CTLA-4

PD-1 and CTLA-4 are checkpoint molecules with complementary mechanisms of action. Dual blockade has yielded enhanced efficacy with approved agents, albeit with increased toxicity.

MGD019, an investigational DART molecule:
- Maintains uncompromised PD-1 blockade vs benchmark mAbs
- Blocks both PD-1 and CTLA-4 pathways with potentially enhanced CTLA-4 blockade on dual-expressing cells prevalent in TME

DART bispecific platform:
- Diabody based structure
- Flexible design supports various configurations (e.g. bivalent or tetravalent)

10-100 fold enhanced activity by MGD019 relative to PD-1/CTLA-4 mAb combination

Sharma MR, et al. ESMO 2020; abstract 1020O. By permission of Prof Manish R. Sharma
CTLA-4-NF DEPLETES IMMUNOSUPPRESSIVE TREGS AND INCREASES T-CELL ACTIVATION

Anti-CTLA-4-NF monoclonal antibody

Non-fucosylated antagonists of CTLA-4 demonstrate increased effector T-cell activation due to reduced immunosuppressive Tregs

- Non-fucosylated antibodies bind with high affinity to FcγR, leading to potent depletion of Tregs by immune-mediated ADCC

BMS’ CTLA-4-NF antagonistic antibody alone or in combination with an anti–PD-1 has the potential for antitumour activity

By suppressing immune responses

And promoting tumour cells proliferation, angiogenesis and metastasis

A NEW EMERGING PATHWAY FOR I-O: ADENOSINE PROMOTES TUMOUR GROWTH

ADENOSINE: A KEY SUPPRESSOR OF IMMUNE CELLS IN THE TUMOUR MICROENVIRONMENT

Adapted from Stagg J, Smyth MJ. Oncogene 2010;29:5346–58.

Image: Halozyme Inc. Available at: https://www.halozyme.com/default.aspx?SectionId=aaf28594-4bb3-438d-917b-d720e26fe088&LanguageId=1; accessed April 2021; by permission from Halozyme Inc.
CD73 high (red line) is >38.8 pmol/min/mg protein and CD73 low is <38.8 pmol/min/mg protein (blue line)
PROGNOSTIC VALUE OF SOLUBLE CD73
In subgroups of patients with metastatic melanoma
CO-INHIBITION OF CD73 AND A2AR ADENOSINE SIGNALLING IMPROVES ANTI-TUMOUR IMMUNE RESPONSES

Reprinted from Cancer Cell, 30(3) Young A, et al. Co-inhibition of CD73 and A2AR Adenosine Signaling Improves Anti-tumour Immune Responses, 391–403. Copyright 2016, with permission from Elsevier.
NEW EMERGING PATHWAYS FOR FUTURE COMBINATION WITH ANTI-PD-1/PD-L1 COMPOUNDS

HDAC inhibitors

IDO1 inhibitors

Anti-LAG-3s

GITR, glucocorticoid-induced TNFR-related protein; HDAC, histone deacetylases; IDO1, indoleamine 2,3-dioxygenase 1; LAG-3, lymphocyte-activation gene 3

Ascierto PA, McArthur JA. J Transl Med 2017;15:173. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (available at: http://creativecommons.org/licenses/by/4.0/; accessed April 2021).
RELATLIMAB TOWARDS TRIPLE COMBINATIONS: CA224-048

A Phase 1/2 study of relatlimab administered in combination with both nivolumab and BMS-986205 (IDO1 Inhibitor) or in combination with both nivolumab and ipilimumab in advanced malignant tumours

Screening (28 Days)  Treatment  Clinical Safety Follow-up  Survival Follow-up Response Follow-up

- Selected solid tumour types except primary CNS tumours
- Subjects naïve to IO therapy
- IO pretreated including but not limited to anti-PD-1/anti-PD-L1/CTLA-4 therapy allowed
- ECOG 0-1
- Melanoma, NSCLC, RCC, SCCHN, GC/GEJ, will be enrolled in Parts 1A and 1B

230 solid tumour patients, Parallel assignment

Relatlimab + Nivolumab + IDO-1i

Relatlimab + Nivolumab + Ipilimumab

Safety Follow-up: ALL Participants
Clinic Visits: Day 30, 60, 100 after EOT

Survival Follow-up: ALL Participants
Contact: Every 3 months after EOT

Primary endpoint: Safety, ORR, DCR, mDOR
Secondary endpoint: PFS

ClinicalTrials.gov. NCT 03459222
EVALUATION OF THE HDACI +ANTI-PD1+ANTI-LAG3 TRIPLE COMBINATION

TRIPLE CHECKPOINT BLOCKADE TARGETING PD-1, TIM-3, AND LAG-3

Improves T cell reinvigoration and antitumour efficacy over single and double combinations

IL-6 AND CRP AS POSSIBLE BIOMARKERS

CheckMate 064: Association of Baseline and On-Treatment IL-6 Levels With OS Across Treatment Arms

High baseline and on-treatment IL-6 levels were associated with shorter OS

CheckMate 067: Association of Baseline IL-6 Levels With OS Across Treatment Arms

High IL-6 levels were associated with shorter OS

CheckMate 064: Association of Baseline and On-Treatment IL-6 Levels With BOR

Lower baseline and on-treatment IL-6 levels were observed in patients with CR/PR vs SD/PD/NE

CheckMate 064: Association of Baseline and On-Treatment CRP Levels With BOR

Lower baseline and on-treatment CRP levels were observed in patients with CR/PR vs SD/PD/NE

PHASE 2 TRIAL OF IPI + NIVO + TOCILIZUMAB IN MELANOMA

Simon design, two-stage study of “flipped dose” IPI + NIVO with IL-6R blocking antibody tocilizumab in first-line stage IV melanoma; 18 patients in stage I, 49 patients in stage II = 67 total patients

IPI at 1 mg/kg and NIVO at 3 mg/kg X 4 doses then NIVO at 240 mg every 2 weeks X 12 weeks, then NIVO at 480 mg every 4 weeks up to 2 years; TOCI at 4 mg/kg every 6 weeks X 5 total up to week 24

Primary endpoints: reduction in grades 3-4 irAEs to 25% or less, and/or increase ORR to 60% from 45% (seen in the Checkmate 511 trial)

Secondary endpoints are PFS, duration of response, and correlative endpoints; so far 14 patients treated since February 2020; finish first stage by end of 2020, and finish second stage by end of 2021/early 2022

ClinicalTrials.gov: NCT03999749. Courtesy of Prof Jeff Weber
LONG-TERM FOLLOW UP OF LIFILEUCEL (LN-144)

Cryopreserved autologous tumour infiltrating lymphocyte therapy in patients with advanced melanoma progressed on multiple prior therapies

- ORR by investigator was 36.4% (2 CR, 22 PR)
- DCR was 80.3%
- Mean time to response was 1.9 months (range: 1.3-5.6)
- mDOR was not reached at 17.0 months of median study follow up
CLINICAL TRIALS FOR MELANOMA USING CHIMERIC ANTIGEN RECEPTORS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ClinicalTrials.gov</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>CD20</td>
<td>NCT03893019</td>
<td>Recruiting</td>
</tr>
<tr>
<td>IL13Ralpha2</td>
<td>NCT04119024</td>
<td>Recruiting</td>
</tr>
<tr>
<td>GPA-TriMAR-T</td>
<td>NCT03649529</td>
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<tr>
<td>Anti-VEGFR2</td>
<td>NCT01218867</td>
<td>Completed</td>
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<td>Anti-GD2</td>
<td>NCT02107963</td>
<td>Completed</td>
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<tr>
<td>Multi-target Gene-modified CAR-T/TCR-T</td>
<td>NCT03638206</td>
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<tr>
<td>B7H3</td>
<td>NCT04483778</td>
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<tr>
<td>Anti-hCD70</td>
<td>NCT02830724</td>
<td>Suspended</td>
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</table>

Image adapted from: Zhao Z, et al. Acta Pharmaceutic Sinic B 2018;8(4):539–51. reproduced under the terms of the Attribution-NonCommercial-NoDerivatives 4.0 International license (CC BY-NC-ND 4.0; available at: https://creativecommons.org/licenses/by-nc-nd/4.0; accessed April 2021).
The best is yet to come.
Thank you!

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