REGULATORY ONCOLOGY DRUG APPROVALS BASED ON THE NEW CLINICAL RESEARCH LANDSCAPE

Prepared by:
Urania Dafni
Zoi Tsourti
Panagiota Zygoura
Alex A. Adjei
Dirk Arnold
Ahmad Awada
Christian Dittrich
Denis Lacombe
Paul Morten Mau-Sørensen
KEY POINTS

- Explosion of available promising drugs (targeted, agents, antibody drug conjugates, immunotherapies)
- Regulatory pathways for faster approval
- The Immune checkpoint inhibitor paradigm
- The role of accelerated approval: speed, post-market safety and clinical benefit evidence
- Suggestions for improvement
- Novel Designs
SHIFT IN CLASSIFICATION OF CANCER, 2000…

→ parallel shift in how new cancer drugs are developed

Cancer Treatment

Chemotherapy
↓
TARGETED therapies
↓
IMMUNOTHERAPY

Novel clinical trial designs are needed for the molecular age
BEFORE: Large, randomised trials as standard approach to investigate new drugs with \textit{cytotoxic} effects,
NOW: novel \textit{cytostatic} therapies to:

- interrupt cancer cell growth and division along one or more of a set of cellular “pathways” (targeted therapies), or
- unleash the patient’s own immune system against the tumour (\textit{immunotherapies})

→ development of \textbf{smaller, more focused} trials, \textbf{both within and across disease types}

Renfro LA and Mandrekar SJ, J Biopharm Stat 2017
FDA TAKES NEW STEPS

To broaden patient participation in cancer clinical trials

For far too long, certain patients have been unnecessarily excluded from the chance to be a part of a clinical trial (i.e. paediatric patients, patients with HIV, hepatitis B or C, brain metastases, organ dysfunction, and prior or concurrent malignancies)

– Scott Gottlieb MD, FDA Commissioner

Broadening eligibility criteria → Clinical Trials more representative of the patient population:

* Maximise the generalisability of the trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to receive the drug

https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm633202.htm
Traditional Approvals

Expedited Approvals

- Priority Review (FDA to take action on an application within 6 months) – 1992
- Accelerated Approval (for drugs that treat serious conditions and fill an unmet need – provisional approval based on a surrogate endpoint) – 1992
- Fast Track (for drugs that treat serious conditions and fill an unmet need) – 1997
- Breakthrough Therapy (for drugs that demonstrate substantial improvement over available therapy) – 2012

THE EXPLOSION OF CANCER THERAPEUTIC OPTIONS

FDA cancer drug approvals by year

Year

Approvals by year


35
30
25
20
15
10
5
(44) FDA APPROVALS FOR IMMUNE CHECKPOINT BLOCKERS

Updated March 2019: Modified from Topalian SL, ESMO 2017 and Peters S, 2017
Among 44 approvals:
16 (32%) OS
28 (68%) Surrogate

-Accelerated:
24 (55%)

*: multi-cohort

# FDA OVERALL EXPEDITED APPROVALS

How many? How fast?

<table>
<thead>
<tr>
<th>Agency</th>
<th>Period</th>
<th>Total approved</th>
<th>Expedited programs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any</td>
</tr>
<tr>
<td>FDA</td>
<td>2001-2010</td>
<td>222</td>
<td>28 (13%)</td>
</tr>
<tr>
<td></td>
<td>2012-2016</td>
<td>174</td>
<td>105 (60%)</td>
</tr>
</tbody>
</table>

Median time (years) to FDA approval:

- 7.1 (any expedited program) vs. 8 (non-expedited) (p=0.04)
- 4.8 (breakthrough) vs. 8 (non-breakthrough) (p<0.001)

## FDA OVERALL EXPEDITED APPROVALS

How many? How fast?

<table>
<thead>
<tr>
<th>Agency</th>
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<th>Total approved</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any</td>
<td>Accelerated</td>
<td>Priority review</td>
</tr>
<tr>
<td>FDA</td>
<td>2001-2010</td>
<td>222</td>
<td>28 (13%)</td>
<td>77 (35%)</td>
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</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>123 postmarket safety events in 71/222 (32.0%)</td>
<td></td>
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<tr>
<td></td>
<td>2001-2015</td>
<td>11.7 yrs median FU</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Accelerated: more frequent events (multivariable analysis)</td>
<td></td>
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</tr>
</tbody>
</table>

“The high frequency of postmarket safety events highlights the need for continuous monitoring of the safety of novel therapeutics throughout their life cycle”

FDA ACCELERATED APPROVALS

A 25-year experience

Time period: December 11, 1992 – May 31, 2017

FDA granted accelerated approval (AA) to 64 malignant haematology and oncology products for 93 new indications. Of these, 53 were for new molecular entities (NME). Single-arm trial designs provided the data for 67 (72%) of the initial AA indications.
# FDA ACCELERATED APPROVALS

A 25-year experience

<table>
<thead>
<tr>
<th>Agency</th>
<th>Period</th>
<th>Accelerated approvals (AAs)</th>
<th>Regular approvals (initially AA)</th>
<th>Initial regular approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>1992-2017</td>
<td>93</td>
<td>51 (55%)</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37 (40%) pending</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5 (5%) withdrawn</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint – n (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>81 (87%)</td>
<td>13 (26%)</td>
<td>43 (25%)</td>
</tr>
<tr>
<td>Progression-Free Survival/Time To Progression</td>
<td>8 (9%)</td>
<td>20 (39%)</td>
<td>59 (34%)</td>
</tr>
<tr>
<td>Disease-Free Survival/Recurrence-Free Survival</td>
<td>4 (4%)</td>
<td>3 (6%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>-</td>
<td>15 (29%)</td>
<td>60 (35%)</td>
</tr>
</tbody>
</table>

# FDA ACCELERATED APPROVALS

A 25-year experience

<table>
<thead>
<tr>
<th>Agency</th>
<th>Period</th>
<th>Accelerated approvals (AAs) - N=93</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fulfilled postmarket req./verified benefit</td>
</tr>
<tr>
<td>FDA</td>
<td>1992-2017</td>
<td>51 (55%)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from AA to benefit OR cut-off date (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (Min-Max)</td>
</tr>
</tbody>
</table>

*Median time from AA to verified benefit= 3.1 vs. 5.5 years, for indications with ongoing trials vs. those without ongoing trials (9 indications).

**Not yet verified benefit: >5y: 8 indications (22%), <3y: 26 (70%), <2y: 20 (54%)

Note: 5 (5%) have been withdrawn from the market

CANCER DRUG APPROVALS BASED ON SURROGATES

FDA 2008-2012 (med f-up 4.4 y)

- Evidence on OS
  - 67% (36 of 54) based on surrogates
  - 14% verified OS improvement

EMA 2009-2013 (med f-up 5.4 y):

- Among 68 approvals for cancer indications
  - 44 no evidence of OS benefit at the time of market approval,
  - Postmarket:
    - Evidence for OS gain: 3/44 (7%)

FDA 2009-2013 (min f-up 4 y):

- 19 accelerated approvals in cancer
  - Fulfilled postmarket req: 42%

Kim C, Prasad V. JAMA Intern Med 2015;175(12):1992–4

PIVOTAL TRIAL ENDPOINTS AND OUTCOMES

Of US FDA-designated breakthrough versus no breakthrough cancer drugs, 2012-2017

<table>
<thead>
<tr>
<th>End Point or Outcome</th>
<th>Breakthrough-Designated Drugs (n = 25)</th>
<th>Nonbreakthrough Drugs (n = 33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary trial end point, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate</td>
<td>16 (64)</td>
<td>12 (36)</td>
<td>.03</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>8 (32)</td>
<td>11 (33)</td>
<td></td>
</tr>
<tr>
<td>Invasive disease-free survival</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>1 (4)</td>
<td>9 (27)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>38 (24-54)</td>
<td>43 (34-47)</td>
<td>.73</td>
</tr>
<tr>
<td>Pooled estimate (IQR)</td>
<td>37 (26-49)</td>
<td>39 (30-50)</td>
<td>.74</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain, months, median (IQR)</td>
<td>8.6 (4.5-11.9)</td>
<td>4.0 (3.0-6.0)</td>
<td>.11</td>
</tr>
<tr>
<td>Pooled hazard ratio (IQR)</td>
<td>0.43 (0.27-0.69)</td>
<td>0.51 (0.40-0.63)</td>
<td>.28</td>
</tr>
<tr>
<td>Clinically meaningful improvement, No. (%)</td>
<td>5 (83)</td>
<td>9 (75)</td>
<td>.99</td>
</tr>
<tr>
<td>Novelty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel mechanism of action, No. (%)</td>
<td>9 (36)</td>
<td>13 (39)</td>
<td>1.00</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events, No. patients (%)</td>
<td>2,586 of 6,857 (38)</td>
<td>4,347 of 11,933 (36)</td>
<td>.93</td>
</tr>
<tr>
<td>Deaths not caused by progression, No. patients (%)</td>
<td>347 of 6,265 (6)</td>
<td>517 of 12,188 (4)</td>
<td>.99</td>
</tr>
</tbody>
</table>
SUGGESTIONS FOR IMPROVEMENTS to the accelerated pathway for cancer drug approvals

Confirmatory post marketing studies for accelerated drug approvals should include both OS and QoL outcomes because these are the 2 facets of clinical benefit currently being used by the FDA.

Preapproved QoL measures should be published for specific drug classes.

**Anticipated or clinically significant changes in OS and in QoL measures should be defined a priori** to facilitate the identification of drugs whose “postmarketing clinical study fails to verify clinical benefit.”

These are design parameters that should be set from the start of the accelerated path trial

FDA’s various expedited pathways are:

- Less stringent: only 1 pivotal trial, fewer patients, shorter follow-up, **surrogate endpoints**¹

Requirement: Postmarket studies that evaluate OS or QoL

Problems:

- Crossover, Post-hoc analyses (inherently subject to confounding),
- Published results: OS or QoL verification reported only in 7% to 42% (EMA or FDA) after considerable time on market

Importantly, many of the surrogate outcomes are poorly correlated with survival, or the strength of the correlation is untested

**Master Protocols:** Over-arching clinical trial protocols comprised of parallel marker-based sub-trials, arms, or cohorts

**Basket Trials:** parallel marker-based cohorts ("baskets") enrol patients from many tumour types

**Umbrella Trials:** parallel marker-based cohorts are drawn from one tumour type ("umbrella")

**Platform Trials:** paired marker-treatment cohorts continually enter and exit the trial under the same protocol (perpetual manner). May be basket, umbrella, or neither.

Adapted from Renfro LA and Mandrekar SJ, J Biopharm Stat 2017
Goal of precision medicine is conducting

“trials designed to learn”

This aim addressed by master protocols

A. basket trials, platform trials, and phase II portions of phase II/III umbrella trials

→ “trials designed to confirm”

B. potential expansions by phase III portions of phase II/III umbrella trials

Regulatory bodies now approve trials based on novel protocols (e.g. Phase I trials based on single-arm designs, not randomised). Other novelties in the clinical trial design setting:

- Advantage of using new designs developed and tested on targeted therapies (basket, umbrella, multiple endpoints/cohorts, platforms, adaptive)
- Inclusion of immunotherapy arm in these trials when no target exists
- Change in the paradigm of Phase I
  - → expansion cohorts – efficacy evaluation
- Adaptation (co-primary endpoints; interim) possible due to substantial improvements targeted AND OBSERVED (use of lower alpha limits)
- No verdict yet on definite predictive biomarker (PD-L1, TMB)
- Favoured primary endpoints:
  - ORR (RECIST 1.1) & OS, milestone survival
Among 44 approvals:
Randomised: 26 (59%)
Single-arm: 18 (41%)

“DRAMATIC EFFECT”  
(ICH E10; 2001)

- Use of the external control design is restricted to situations in which the effect of treatment is **dramatic** and the usual course of the disease highly predictable;
- Start with externally controlled trial and switch to RCT (or stop) if effect not dramatic;

What is the threshold for “dramatic”?  
Based on what parameter? ORR

# EMA-APPROVED DRUGS – SINGLE ARM STUDIES

- Studies (pub. 2006-2016) which led to EMA-approved drugs graded by MCBS (N=93):
  - 10 single-arm trials (11%)
    - 4 immunotherapy 40%
    - 6 targeted 60%

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD9291 (Osimertinib)*</td>
<td>Lung</td>
</tr>
<tr>
<td>Ceritinib*</td>
<td>Lung</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Lung</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Lung</td>
</tr>
<tr>
<td>Olaparib</td>
<td>Ovarian</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Brain</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Hodgkin’s Lymphoma</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Urothelial</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Head and Neck</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Colorectal</td>
</tr>
</tbody>
</table>

CAR T-CELL IMMUNOTHERAPY
APPROVED BY THE FDA

On August 30, 2017, the FDA granted regular approval to tisagenlecleucel for patients with relapsed or refractory paediatric precursor B-cell ALL

The first chimeric antigen receptor (CAR) T-cell immunotherapy approved by the FDA

Approval was based on a single-arm trial of 63 patients, among them:

- confirmed overall remission rate was 82.5% (95% CI 70.9, 91.0)
  - 63% with complete remission
  - 19% with complete remission with incomplete haematological recovery
- Median remission duration was not reached (range: 1.2 to 14.1+ months)
On May 23, 2017, the FDA granted accelerated approval to pembrolizumab for unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours

First approval of a cancer treatment based on a common biomarker without regard to the tumour’s original location

- Basis: 149 patients with MSI-H or dMMR cancers across five uncontrolled, multi-cohort, single-arm clinical trials
- Major efficacy outcome: ORR – Response duration

Further study is ongoing to confirm clinical benefits

https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm560040.htm
FDA’S ACCELERATED APPROVAL TO PEMBROLIZUMAB
For first tissue/site agnostic indication

The pivotal data for the approval included patients from the:

- KEYNOTE-016 (n=58)
- KEYNOTE-164 (n=61)
- KEYNOTE-012 (n=6)
- KEYNOTE-028 (n=5)
- KEYNOTE-158 (n=19)

Not even basket-trial!

Clinical data that supported the approval of pembrolizumab

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>N</th>
<th>Objective response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>CRC</td>
<td>99</td>
<td>56 (36%) (28%, 45%)</td>
</tr>
<tr>
<td>Non-CRC</td>
<td>59</td>
<td>37 (45%) (33%, 59%)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>14</td>
<td>14 (36%) (13%, 55%)</td>
</tr>
<tr>
<td>Biliary cancer</td>
<td>11</td>
<td>3 (27%) (6%, 81%)</td>
</tr>
<tr>
<td>Gastric or GE junction cancer</td>
<td>9</td>
<td>5 (56%) (21%, 86%)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>6</td>
<td>5 (63%) (36%, 100%)</td>
</tr>
<tr>
<td>Small intestinal cancer</td>
<td>8</td>
<td>3 (36%) (9%, 76%)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>PR, PR</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>PR, SD</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>1</td>
<td>PR</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
<td>PD</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Retropertitoneal adenocarcinoma</td>
<td>1</td>
<td>PR</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>1</td>
<td>CR</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>1</td>
<td>PD</td>
</tr>
</tbody>
</table>

Presented By Steven Lemery at 2017 ASCO Annual Meeting. Courtesy of Dr Steven Lemery.
EMA APPROVAL

- Standard Marketing Authorisation (MA) based on comprehensive data
- Non-standard Marketing Authorisation
  - Conditional Marketing Authorisation (CMA)
    - Before comprehensive data are available
  - Marketing Authorisation under exceptional circumstances
    - Comprehensive data not expected
CONDITIONAL MARKETING AUTHORISATION (CMA)

- MA before comprehensive data are available
- Requirements
  - Comprehensive data expected post-approval (e.g. confirmative phase III trial) within defined timeframes
  - Fulfil unmet medical need
  - Benefit to public health
  - Annual renewals based on fulfilment of specific obligations
- 10-year experience with CMA (2006-16)
  - 17 anticancer drugs were granted CMA
  - No CMAs were revoked or suspended
  - CMAs were converted to conventional MA with 4 years
MARKETING AUTHORISATION (MA) UNDER EXCEPTIONAL CIRCUMSTANCES

- Comprehensive data are not expected due to
  - Rare indications
  - Current state of scientific knowledge
  - Ethical issues

- Annual re-assessment of benefit/risk ratios according to specific obligations
  - Post-marketing safety studies
  - Cohort studies
  - Registries
The FDA and finally also the EMA have shown a willingness to approve anticancer drugs based on a single randomised trial achieving statistical significance, even if the magnitude of benefit is marginal or only quantified using a surrogate outcome.

Neratinib for patients with HER2-positive breast cancer based on a 2.3% improvement in invasive disease-free survival (DFS), a surrogate end point, in a single randomised trial (approved by FDA and EMA).

Sunitinib for adjuvant treatment of RCC based on the results of one positive randomised trial showing an improvement in DFS, despite a second cooperative group trial failing to show a DFS benefit - *neither trial showed an improvement in overall survival* (approved by FDA and not by EMA).

**Pharmaceutical companies could, hypothetically, turn a profit by testing inert chemical compounds in phase III trials**

Prasad V, McCabe C and Mailankody S, Nature Reviews, Clinical Oncology, 2018; 15(7):399-400
A risky phase III trial in the absence of a strong rationale

The EVOLVE-1 study:

- Everolimus as a second-line treatment of hepatocellular carcinoma.
- A phase III trial with over 500 accrued patients that revealed no significant difference in the efficacy of everolimus versus best supportive care in this setting.

**Authors disclosure:** The rationale supporting the phase III trial was limited to phase I data, and biological plausibility derived through laboratory studies, but that no dedicated phase II trial had been conducted!

Prasad V, McCabe C and Mailankody S, Nature Reviews, Clinical Oncology, 2018; 15(7):399-400
The current situation could be remedied either

- By demanding a minimum of two independent randomised trials to support approval decisions (minimising false positive rates), as is the norm in areas of medicine outside of oncology
- and/or changing the financial incentives relating to the use of anticancer drugs, such that prices or reimbursement of drugs are based on their **clinical benefit**, according to robust value frameworks, and not mere statistical significance

Prasad V, McCabe C and Mailankody S, Nature Reviews, Clinical Oncology, 2018; 15(7):399-400
PROGRESS AGAINST CANCER

Depends on efficient drug approval system that brings safe, effective treatments to patients

The Accelerated Approval process may lead to delivery of exciting and promising new drugs earlier than waiting for the more extensive trial to be completed.

Rationale:
Biomarker-driven clinical cancer care is proven to work and have saved time, money, and lives.

Common cancers = rare cancers when divided into narrow subsets according to their genomics → smaller trials are often the only way forward.

Hayes K, ASCO Perspectives; 11 June 2018.
PROGRESS AGAINST CANCER

Depends on efficient drug approval system that brings safe, effective treatments to patients

EMA and FDA efforts to streamline continuously adapt the approval process for progress in drug development

Novel and pragmatic trial designs

Cleverly designed trials, with collection of biospecimens for (secondary) tumour biomarker test analyses

→

New therapeutic agents to the right patients at the right time,
More efficient use of novel drugs
EXPECTATIONS OF FUTURE DIRECTIONS OF DEVELOPMENTS AND CAVEATS

- Increased use with more nuanced assignment of patients to matched treatments
- Handling of ‘Exceptional responders’
- **Regulatory approvals based on single-arm trials with a small number of patients**\(^1\)
- High-stakes competition for the **combination of therapies** in registration studies\(^2\)

The accelerated approach has the potential to validate a novel combination faster

**BUT**

the potential for negative consequences is real

Evaluation of Clinical Benefit will become more and more important

- Harmonisation of HTA, pricing, and reimbursement decisions across all European countries to balance accessibility of new drugs for all European patients

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THANK YOU!
DISCLOSURES

- Urania Dafni has reported no conflict of interest
- Zoi Tsourti has reported no conflict of interest
- Panagiota Zygoura has reported no conflict of interest
- Alex A. Adjei has reported no conflict of interest
Ahmad Awada has reported advisory role, research grants to his institute. Speaker for Roche, Lilly, Amgen, EISAI, BMS, Pfizer, Novartis, MSD, Genomic Health, Ipsen, AstraZeneca, Bayer, Leo Pharma.

Christian Dittrich has reported honoraria for role as speaker/chair and advisory board/IDMC member as well as travel expenses – AstraZeneca Österreich, Bayer Austria, Bristol-Myers Squibb, Ellipses, Eli Lilly Austria, Ipsen Pharma, Merck Austria, Merck Serono, Novartis Pharma, Roche Austria, Sanofi-Aventis, Servier Pharma, Takeda. Research grants/educational grant – Amgen, AstraZeneca Österreich, Bayer Austria, EISAI, Boehringer Ingelheim, Merck Austria, Mundipharma, Novartis Pharma, Pfizer Corporation Austria, PharmaMar, Pierre-Fabre, Roche Austria, sanofi-Aventis, Janssen-Cilag Pharma. IDMC member-Institut Jules Bordet, Scientific Committee Member-Institut National du Cancer (INCa).

Denis Lacombe has reported no conflict of interest

Paul Morten Mau-Sørensen has reported advisory boards for Roche and Genmab. He has received research grant from Karyopharm. He has conducted sponsored trials with AstraZeneca, Bioclin, BMS, Cantargia, Genmab, Incyte, Loxo, Merck, Novartis, Pfizer, Puma biotechnology, Roche, Symphogen, Alligator Bioscience, Karyopharm, MSD, AbbVie, Sanofi-Aventis, Orion, Eli Lilly, (financial support paid directly to his institution).