Joint BWP / QWP workshop with stakeholders in relation to
prior knowledge and its use in regulatory applications

Atezolizumab:
A Case Study of Accelerated Development

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efpia
European Federation of Pharmaceutical Industries and Associations

ebe
european biopharmaceutical enterprises

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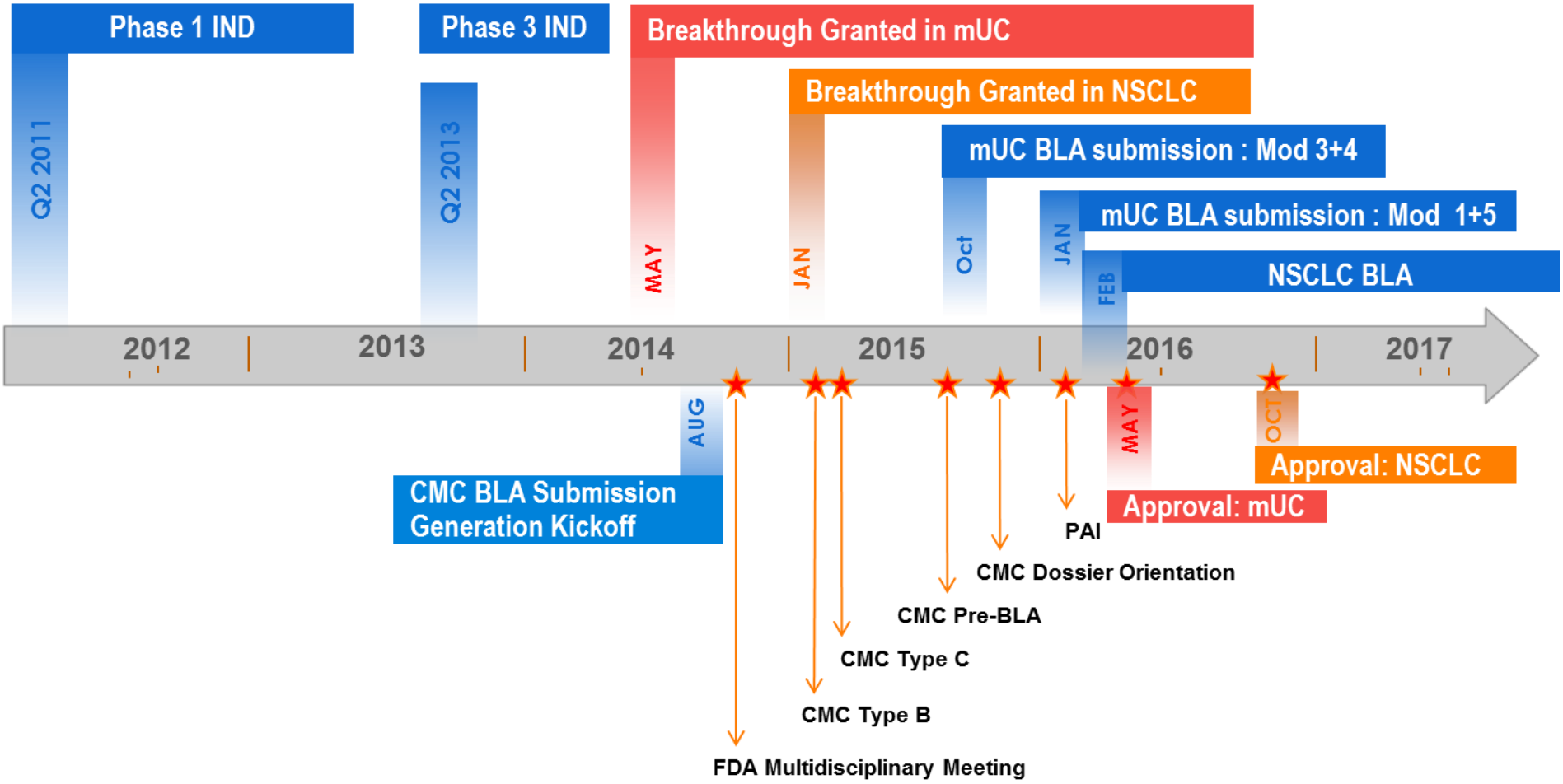
Project Background

Molecule Names:	Tecentriq™, Atezolizumab, MPDL3280A, Anti-PDL1
Molecule Type:	CHO derived aglycosylated full length Antibody (IgG1)
Target Indications:	Multiple tumor types: Non Small Cell Lung Cancer (NSCLC), Bladder (mUC), Triple Negative Breast (TNBC), Renal Cell Carcinoma (RCC), Colorectal Carcinoma (CRC)
Disease Type Area	Oncology
Mechanism of action:	Inhibition of ligation of PD-L1 to PD1 and B7.1, thereby inhibiting attenuation of T cell activation. Inhibition of PD-L1 ligation to PD1 and B7.1 restores T cell anti-tumor function.

- Breakthrough Therapy Designation granted by FDA:
  - for mUC on 22 May 2014
  - for NSCLC 29 Jan 2015
- Atezolizumab applied for the adaptive licensing pilot program in Europe but was not accepted as it was too advanced in development.

US Submission Milestones



Atezolizumab Acceleration

Atezolizumab Accelerated by a Total of 19 Months Compared to Standard Timeline

CMC Timeline (months)	
CMC Dev Stages	**Delta (gain for Atezo)**
DNA Received – IND Filing	0
Start Ph3 Dev activ. – Ph3 INDa Filing	9
Start Licensure Enabling activ. – BLA Filing	10
Total	19

US/ EU Submission Summary

US BLA Submission	EU MAA Submission
Rolling submission • Nonclinical and CMC Module submission on October 23rd, 2015 • Clinical Module and the label submitted on 12 January 12th, 2016	No rolling submission • Submission of all CTD modules on April 22nd, 2016
Five meetings with CMC topics	Two meetings with CMC topics
Nine Information Requests (IR's) with a total of 79 CMC questions; 1 PMC on clonal derivation	LoQ d120: No major objections; 30 "other concerns" issued; no d180 questions
Five meetings (TC's) during Q&A: • TC's requested by the Applicant were always granted • The Applicant reacted very quickly when FDA requested TC's	Written clarification requested for 4 questions: • Feedback was comprehensive and clear
FDA approval of first indication: May 2016	EC Approval of joint indications: Sept 2017
Time to approval: 8 months	Time to approval: 17 months

Standard CMC Development with Several Acceleration Opportunities

The following activities were done differently to save time:

- DP validation was performed using Phase III clinical DS batches
- Scale-down model qualified initially vs clinical manufacturing, then leveraged clinical-to-commercial comparability (same process & scale, different site)
- Filed with limited stability data package; Leveraged data from comparable clinical batches to support shelf-life request
- Method transfer was performed by co-validation; only two methods were changed and required analytical bridging for commercial testing
- Simplified process characterization studies compared to traditional program
  - Utilized Process Linkage Assessment instead of Worst-Case Linkage
- Method transfer was performed by co-validation. Only two methods were changed and required analytical bridging for commercial testing
- Application of prior knowledge (refer to next slide)

All strategies were vetted with Health Authorities in US, EU, and CA

Prior Knowlegde for CMC Development in the BLA/MAA

- Application of prior knowledge for the development and characterization of the manufacturing process
  - Application of risk-ranking and filtering (RRF) tools to design characterization and validation studies based on platform knowledge derived from 7 Mabs
  - A summary document of platform information was submitted (S.2.6_attachment)
  - RRF report for one unit operation in the cell culture and purification process was provided (S.2.5 attachment)
- Application of prior knowledge for the development of the control strategy
  - Application of a RFF tool for identification and classification of CQAs; criticality scoring matrix related to safety and immunogenicity based on knowledge gained from clinical experience derived from Atezolizumab or with other therapeutic proteins or literature (S.2.6_attachment; S.3.1_attachment)
  - Application of a RRF tool for the control system determination which was an iterative development of the tool used for two precedent programs (S.2.6_attachment)

Prior Knowlegde for CMC Development in the BLA/MAA

- PACMP usage
  - Roche/GNE uses CMP/ CP post-approval for manufacturing site transfers or NPI's
  - A PACMP for a DP manufacturing site transfer was submitted to EMA within two weeks of the EC approval of the MA
  - Inclusion of PACMP in an initial marketing application is challenging to achieve when the focus is on the generation of the BLA/MA, especially under an accelerated set-up
- PACMP content
  - CP: Close adherence in terms of content and structure to US FDA guidance: "Comparability Protocols for Human Drugs and Biologics: CMC Information" April 2016
  - CMP: Minor adaptation of regulatory reporting

Summary

- Standard CMC development with acceleration opportunities
- Acceleration: 19 months faster to BLA compared to standard time line; does not apply to MAA due to the clinical filing strategy
- Successful acceleration required significant resources
  - All activities conducted with significant overlap or done in parallel
  - Development and regulatory teams were well resourced
  - Establishment of “BT-mAb island” to allow team focus
- Successful acceleration required increased communication with FDA
  - Fast feedback on acceptability of approaches
  - Resource intense
- Successful application of prior knowledge leads to an increase in information in the BLA/MAA