Accelerated Approval for Oncology Drug Products: Regulatory Overview

Oncologic Drugs Advisory Committee Meeting
Atezolizumab Metastatic Triple Negative Breast Cancer
April 27, 2021

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Outline

- Regulatory Background
- Accelerated Approval Experience
- Oncologic Drugs Advisory Committee Agenda
- Conclusions

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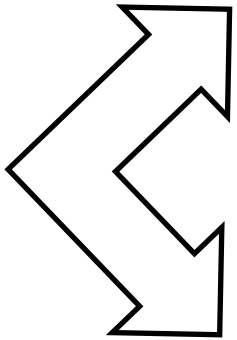
U.S. Approval of Drugs and Biologics



Accelerated approval pathway

Regular (or traditional) approval pathway

Accelerated Approval Requirements

- Serious and life-threatening disease
- Substantial evidence of Efficacy and Safety
- Endpoint reasonably likely to predict clinical benefit
- Meaningful therapeutic benefit over available therapy
- Confirmatory trial

21 CFR Part 314, Subpart H; 21 CFR Part 601, Subpart E

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Oncology Accelerated Approval Experience

- 151* Oncology Accelerated Approvals
  - 35* Accelerated Approvals for anti-PD-(L)1 antibodies
- 74 (49%)* converted to regular approval (median 3 years)
- 10 (6%)+ withdrawn indications

* to January 1, 2021
\+ to April 2021

PD-(L)1: programmed death-(ligand) 1

Accelerated Approval (AA) Withdrawal

- AA indications may be withdrawn by the FDA if:
  - Postmarketing trial(s) fails to confirm a benefit
  - Failure to perform postmarketing trial with due diligence
- Voluntary Withdrawal or FDA initiated withdrawal proceedings

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Accelerated Approvals

- 76* Total indications for anti-PD-(L)1 antibodies
  - 35* Accelerated Approvals
- Communication with companies
  - Withdrawal or advisory committee discussion

* to January 1, 2021
\+ to April 2021

PD-(L)1: programmed death-(ligand) 1

Voluntary Withdrawals

- 3rd line metastatic small cell lung cancer
  - Nivolumab
  - Pembrolizumab
- 2nd line advanced/metastatic urothelial carcinoma
  - Durvalumab
  - Atezolizumab

Oncologic Drugs Advisory Committee Meeting

Day 1: April 27, 2021	Day 2: April 28, 2021	Day 3: April 29, 2021
Metastatic Triple Negative Breast Cancer 1. Atezolizumab	**Metastatic Urothelial Carcinoma Cisplatin-ineligible** 2. Pembrolizumab 3. Atezolizumab	**Metastatic Gastric/ Gastroesophageal Junction Cancer** 4. Pembrolizumab **Hepatocellular Carcinoma** 5. Pembrolizumab 6. Nivolumab

Key Issues: Atezolizumab Metastatic Triple Negative Breast Cancer

- Treatment landscape has not changed
- Accelerated approval based on small PFS with non-significant OS
- Benefit not verified in confirmatory trial in same disease setting with concern of detriment in OS

PFS: Progression Free Survival
OS: Overall Survival

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Accelerated Approval Conclusions

- Tradeoff: earlier marketing of promising drugs with increased uncertainty
- Accelerated approval has successfully allowed for approval of transformative oncology drugs years earlier
- Re-evaluation necessary when results change the risk/benefit

Oncologic Drugs Advisory Committee Discussion

- Should the indication be maintained while additional trial(s) are conducted or completed


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Atezolizumab + Nab-Paclitaxel PDL-1+ Metastatic Triple Negative Breast Cancer (mTNBC)

April 27, 2021

Oncologic Drugs Advisory Committee Meeting

Laleh Amiri-Kordestani, MD
Division Director, Division of Oncology 1,
Office of Oncologic Diseases, FDA

Outline

- Key FDA review Issues
- Regulatory history
  - Initial Accelerated Approval
  - Confirmatory Study
- Treatment landscape
- Voting Question for ODAC
  - Should the indication for the atezolizumab in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors are PDL-1+ be maintained on the market while additional trial(s) are conducted or completed?
    - If your answer is “yes”, please discuss after the vote, what ongoing or alternative trials may serve to confirm clinical benefit.

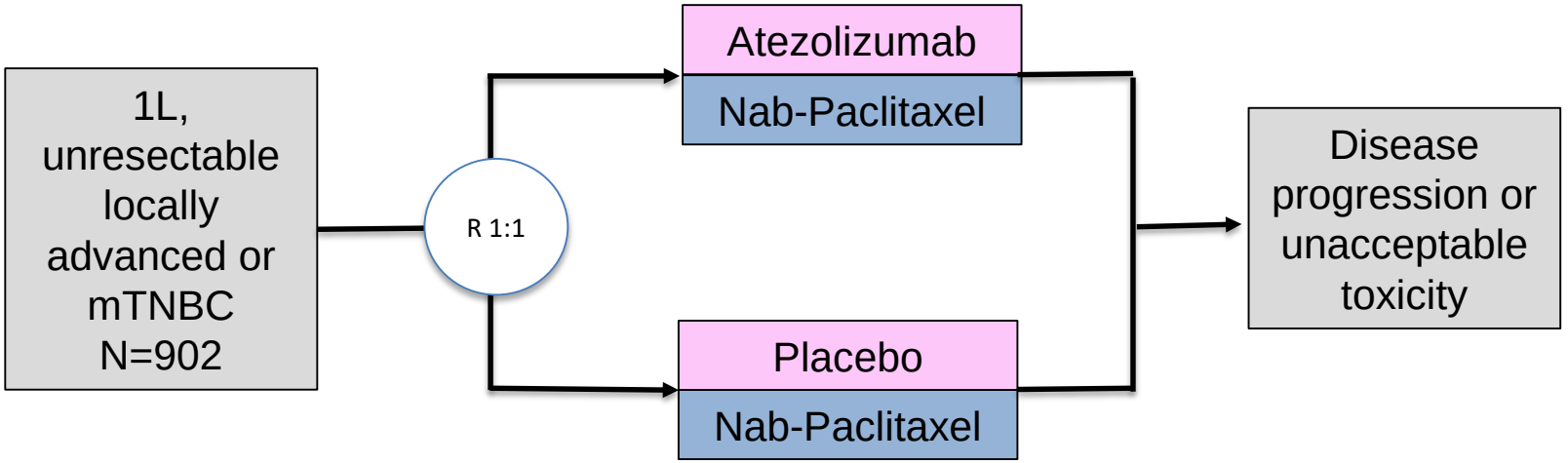
Key FDA Concerns

- Overall survival (OS) Results from IMpassion130 may be due to chance
- OS results from IMpassion131 are concerning
- The clinical benefit from AA has not been verified

Regulatory History

- March 2019 Accelerated approval IMpassion130
- July 2020 Confirmatory Trial IMpassion131 Result
- September 2020 Safety Alert
- December 2020 Label Updated

IMpassion130



Stratified:
- PD-L1 status
- Prior taxane
- Liver metastases

Co-Primary endpoints: INV-PFS in ITT and PD-L1+, OS (to be tested hierarchically in the ITT first, and then in the PD-L1+)

INV-PFS: Investigator-assessed progression free survival, ITT: Intention to treat, mTNBC: metastatic triple negative breast cancer, N: Number, OS: Overall survival

IMpassion130 Efficacy Results

		ITT		PD-L1+	
		Atezo+nP N=451	**Pl+nP N=451**	**Atezo+nP N=185**	**Pl+nP N=184**
PFS-INV	Median, months	7	5.5	7.4	4.8
	HR (95% CI)	0.79 (0.68–0.92)		0.60 (0.48–0.77)	
	p-value	0.0018		<0.0001	
IA2 OS	Median, months	18.7	21.0	18.0	25.0
	HR (95% CI)	0.86 (0.72-1.02)		0.71 (0.54–0.93)	
	p-value	Not significant		N/A	

Atezo: Atezolizumab, HR: Hazard ratio, IA: Interim analysis, ITT: Intention to Treat population, Pl: Placebo, nP : Nab-Paclitaxel, OS: overall survival, PFS-INV: Progression free survival by investigator

Benefit/Risk Assessment

Benefits

- PFS
- Response rate
- ? OS in PDL-1+

Risks/Uncertainties

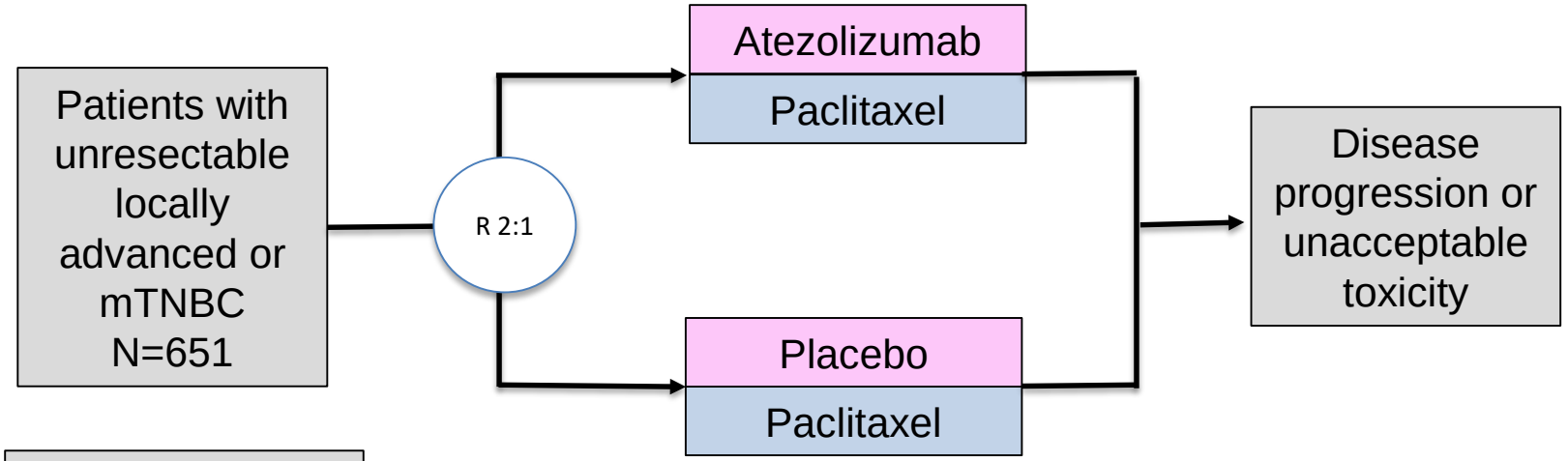
- Added toxicity
- Small magnitude of PFS

Accelerated Approval may Require Confirmation of Benefit

IMpassion130 Final OS Results

Final OS	ITT		PD-L1+	
	Atezo+nP N=451	Pl+nP N=451	Atezo+nP N=185	Pl+nP N=184
Median, months	21.0	18.7	25.0	18.0
HR (95% CI)	0.87 (0.75, 1.02)		0.71 (0.54–0.93)	
p-value	Not significant		N/A	

IMpassion131



Stratified:
- PD-L1 status
- Prior taxane
- Liver metastases
- region

Primary endpoints: INV-PFS in PD-L1+ and then ITT
Secondary endpoints: OS in PD-L1+ and ITT; ORR

FDA Actions Based on IMpassion 131 Results

- July 31, 2020 : IMpassion131 was reported
  - Interim analysis of OS HR of 1.55 (95% : 0.86, 2.80) in PDL-1+
- September 2020: Safety Alert
- December 2020: Label Updated
  - Limitation of use
  - Warning and Precaution

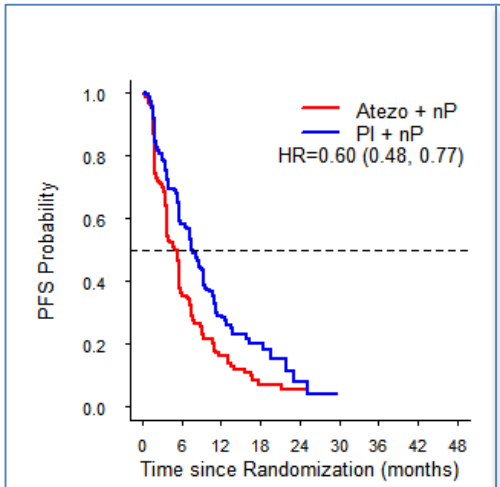
IMpassion131 Final Efficacy Results

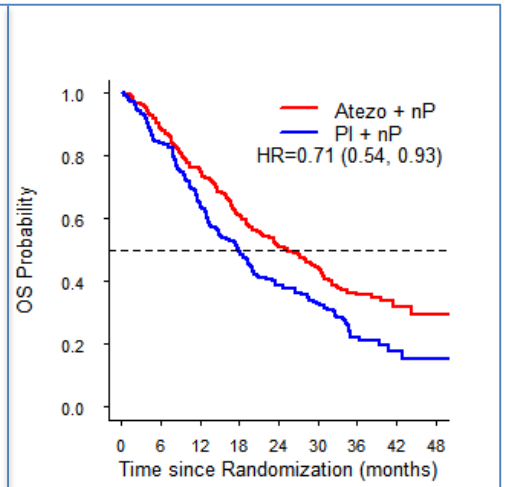
		PD-L1+		ITT	
		Atezo+P N=	Pl+P N=	Atezo+P N=431	Pl+P N=220
PFS-INV	Median, months	5.95	5.72	5.68	5.55
	HR (95% CI)	0.82 (0.60, 1.12)		0.86 (0.70, 1.05)	
		Not significant		N/A	
OS	Median, months	22.1	28.3	19.19	22.80
	HR (95% CI)	1.11 (0.76, 1.64)		1.12 (0.88, 1.43)	
		N/A		N/A	

Atezo = Atezolizumab, Pl = Placebo, nP = Nab-Paclitaxel, OS: Overall survival, P = Paclitaxel, PFS-INV: Progression free survival by investigator

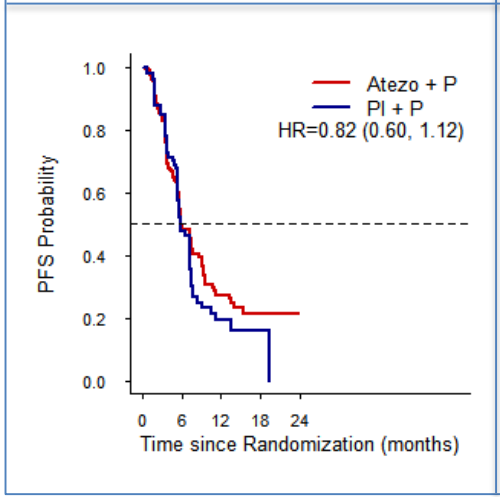
PFS | OS

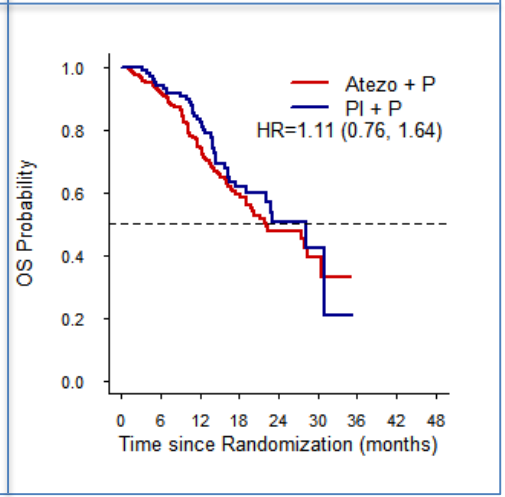
IMpassion130





IMpassion131





Atezo = Atezolizumab
Pl = Placebo
nP = Nab-Paclitaxel
P = Paclitaxel

Trial Designs IMpassion130 and IMpassion131

	IMpassion130	IMpassion131
Chemotherapy partner	Nab-paclitaxel 100 mg/m2	Paclitaxel 90 mg/m2
Mandatory steroids	No	Yes (Pre-medication)
Primary endpoint	Investigator-assessed PFS and OS (co-primary endpoints first tested in ITT followed by PD-L1+)	Investigator-assessed PFS only, first tested in PD-L1+ followed by ITT
Sample Size (ITT/PD-L1+)	902/369	651/292
Eligibility Criteria	1st line TNBC, Similar	1st line TNBC, Similar

Accelerated Approval Requirements

- Serious and life-threatening disease
- Substantial evidence of Efficacy and Safety
- Endpoint reasonable likely to predict clinical benefit
- Meaningful therapeutic benefit over available therapy
- Confirmatory trial

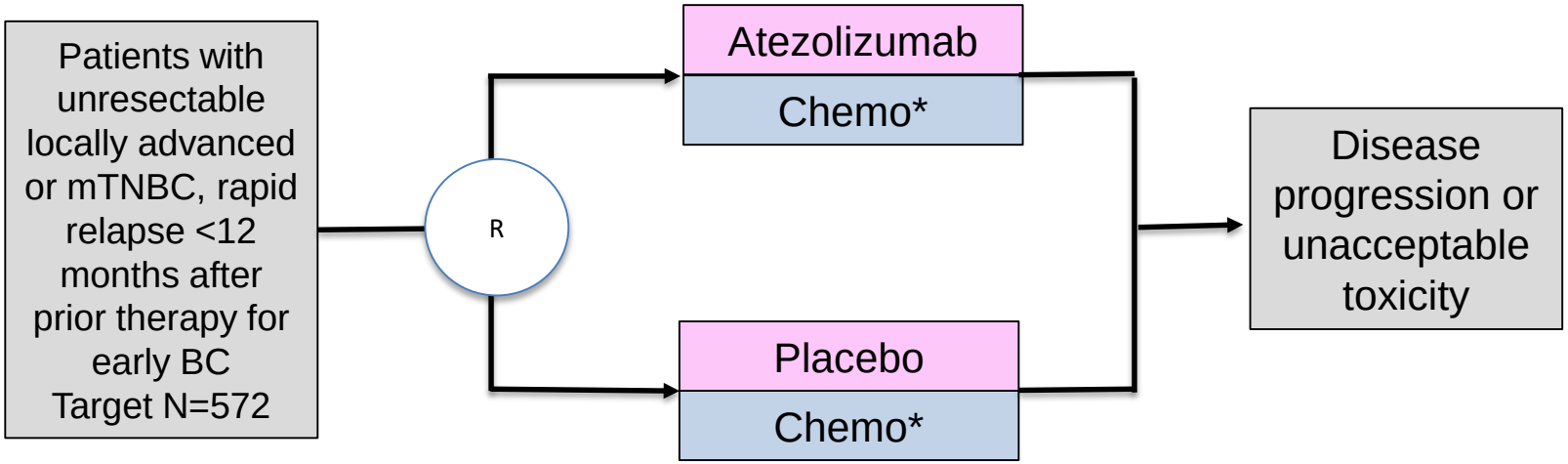
21 CFR Part 314, Subpart H; 21 CFR Part 601, Subpart E

Current Treatment Landscape of 1st line mTNBC

- Cytotoxic chemotherapies
- Under regular approval (considered available therapy)
  - olaparib and talazoparib for BRCAmut+ breast cancers
- Biomarker-targeted approaches (Under accelerated approval and NOT considered available therapy)
  - Pembrolizumab plus chemotherapy for PD-L1+ (CPS ≥10)
  - entrectinib and larotrectinib for NTRK fusion-positive tumors
  - Pembrolizumab monotherapy for TMB-high, MSI-high, dMMR tumors

CPS: Combined positive score, dMMR: Mismatch repair deficient, MSI: Microsatellite instability, NTRK: Neurotrophic Tyrosine Receptor Kinase gene, TMB: Tumor mutational burden

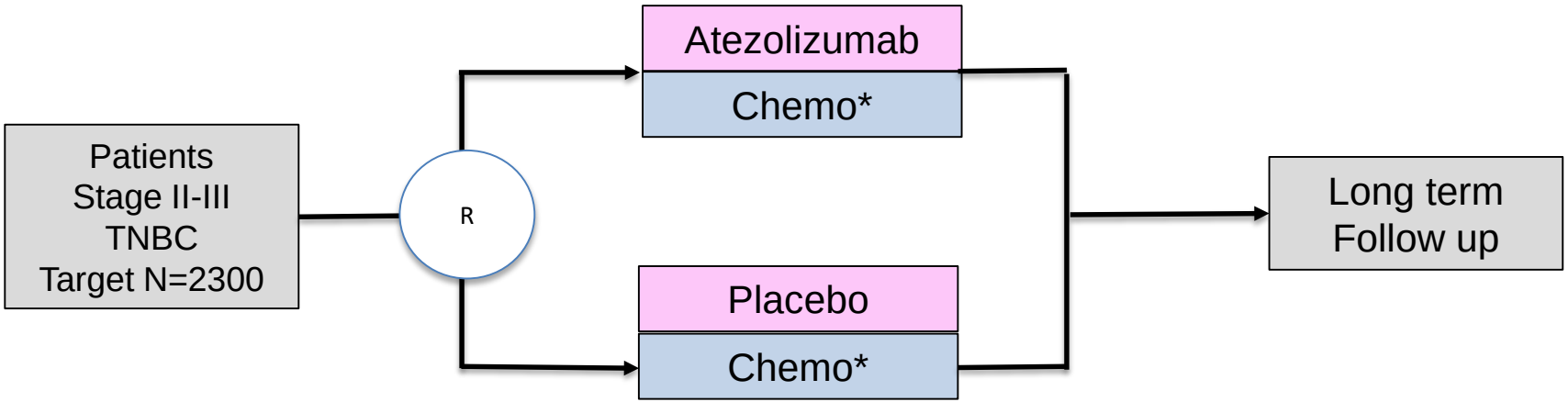
IMpassion132-Metastatic



Primary endpoints: OS (PD-L1+), expected Q1 2023
Secondary endpoints: 12-month and 18-month OS rates, PFS, ORR

*Chemo: Gemcitabine/carboplatin or capecitabine

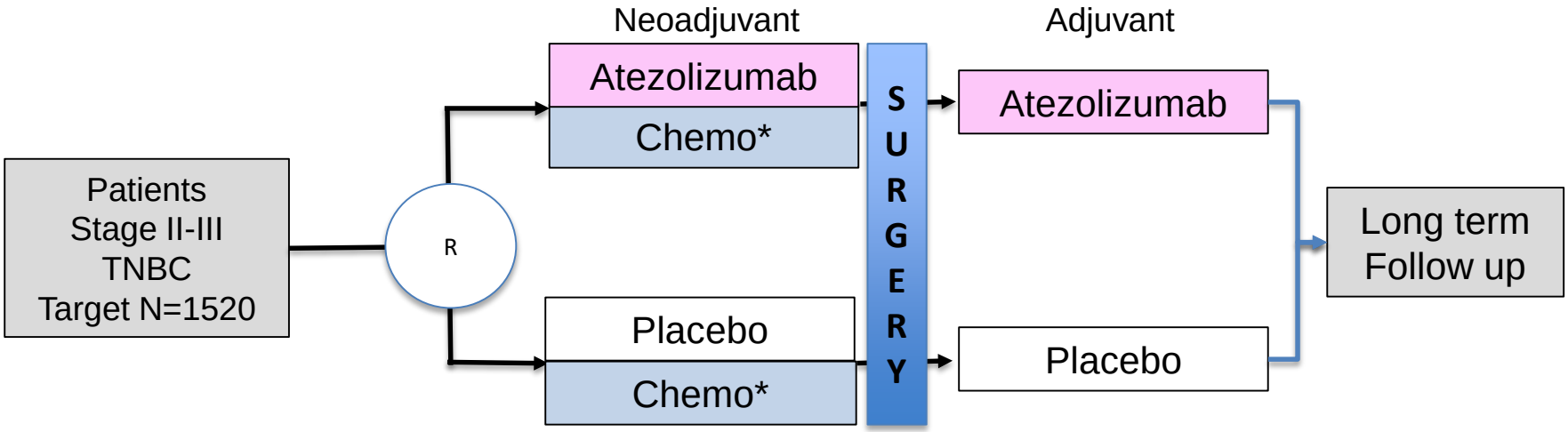
IMpassion030-Adjuvant



Primary endpoint: iDFS (IA at 50% maturity Q3 2022, Final Q4 2024)
Secondary endpoints: iDFS (PD-L1+), OS and …

*Chemo: **Paclitaxel**+ doxorubicin + cyclophosphamide

NSABP B-59/GBG 96-GeparDouze

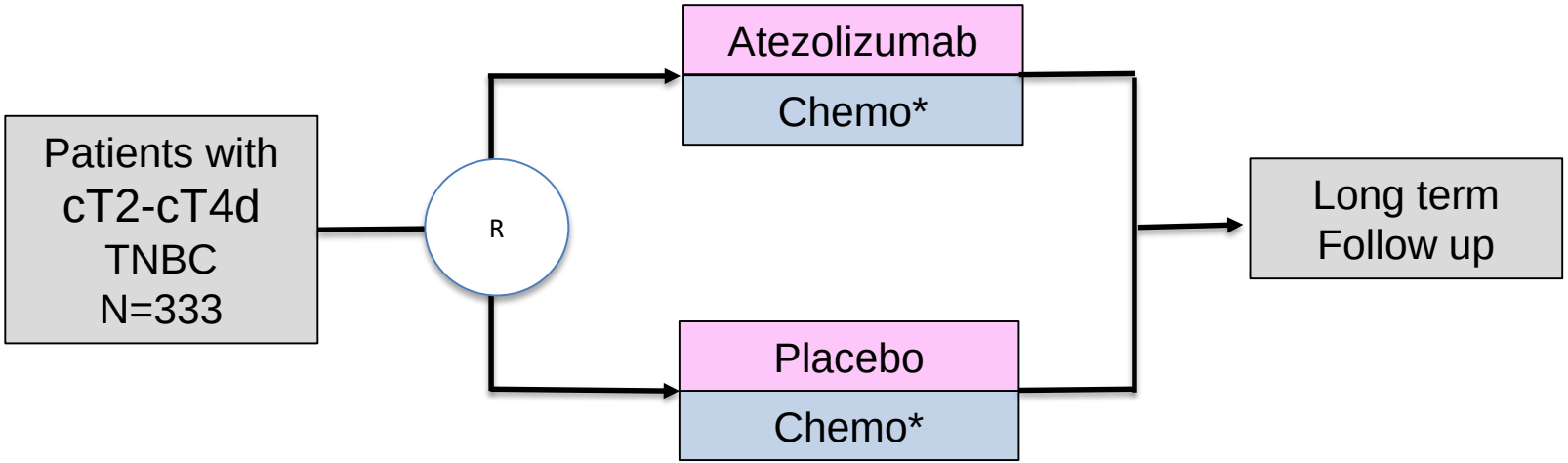


Co-Primary endpoints: pCR and EFS
(estimated primary completion date: Dec 2023)

*Chemo: Carboplatin+ **Paclitaxel**-> doxorubicin/epirubicin + cyclophosphamide

pCR: pathological complete response rate, EFS: event free survival

IMpassion031- Neoadjuvant



Primary endpoints: pCR (ITT & PD-L1+); occurred April 2020
Secondary endpoints: EFS, DFS, OS; expected Q3 2022

*Chemo: Nab-paclitaxel+ doxorubicin + cyclophosphamide

Conclusion

- **IMpassion 130** Atezolizumab received accelerated approval based on modest improvement in PFS and possible OS improvement in PDL1+
  - Final OS not significant
- **IMpassion 131** Confirmatory trial did not verify clinical benefit
  - Possible detriment in OS
- **IMpassion031** Neoadjuvant trial did not meet endpoint of pCR in PDL1+
- Available therapies unchanged – unmet medical need

Voting Question

Given the following:

1. Accelerated approval based on small PFS with non-significant OS
2. Benefit not verified in confirmatory trial in same disease setting
3. Possible detriment in OS in confirmatory trial
4. Alternative/ongoing trials are not in combination with nab-paclitaxel or in same disease setting

- **Should the indication for the atezolizumab in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors are PDL-1+ be maintained on the market while additional trial(s) are conducted or completed?**
  - **If your answer is "yes", please discuss after the vote, what ongoing or alternative trials may serve to confirm clinical benefit.**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