Supplementary tables

Ipatasertib plus paclitaxel for PIK3CA/AKT1/PTEN-altered hormone receptor-positive HER2-negative advanced breast cancer: primary results from cohort B of the IPATunity130 randomized, phase 3 trial

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**Supplementary Table S1.** Definition of PIK3CA/AKT1/PTEN-altered status

PIK3CA/AKT1/PTEN altered defined as the presence of one or more of the following:

**AKT1** missense mutations that result in amino acid substitution at the following residues: E17, L52 or Q79

**PIK3CA** missense mutations that result in amino acid substitution at the following residues:
- R88, G106, K111, G118, N345, C420, E453, E542, E545, Q546, M1043, H1047 or G1049

**PTEN** alterations that meet any of the following criteria:
- Homozygous deletion (copy number of 0)
- Dominant negative short variant (e.g., C124S, G129E, R130X)
- Loss of heterozygosity (LOH) with copy number of 1 without concomitant single-nucleotide variants
- One deleterious short variant (including insertions and deletions; classification criteria provided below) with a concomitant loss of the non-mutant PTEN allele defined by LOH with copy number of 1 or LOH with copy number ≥ 1:
  - Any protein-truncating mutations, including nonsense mutations and frameshift insertions and deletions
  - Any mutations in the consensus splice donor and acceptor sequence that disrupts the consensus, including insertions and deletions
  - Any missense or non-frameshift mutation that has been confirmed somatic as described in the COSMIC database
  - If there are two or more deleterious short variants under LOH, the patient will not be eligible for the study
**Supplementary Table S2. Summary of selected adverse events (safety population)**

| Adverse event, n (%)                  | Placebo + paclitaxel (n = 75) | Ipatasertib + paclitaxel (n = 145) |
|---------------------------------------|-------------------------------|-----------------------------------|
|                                       | Any grade (%)                 | Grade ≥ 3 (%)                     | Any grade (%) | Grade ≥ 3 (%) |
| Diarrhea                              | 28 (37)                       | 1 (1)                             | 123 (85)      | 17 (12)       |
| Peripheral neuropathy\(^a\)           | 48 (64)                       | 6 (8)                             | 93 (64)       | 15 (10)       |
| Neutropenia\(^b\)                     | 33 (44)                       | 11 (15)                           | 59 (41)       | 26 (18)       |
| Asthenia/fatigue                      | 30 (40)                       | 4 (5)                             | 53 (37)       | 2 (1)         |
| Nausea                                | 15 (20)                       | 0                                 | 60 (41)       | 2 (1)         |
| Erythropenia\(^c\)                    | 16 (21)                       | 0                                 | 44 (30)       | 1 (1)         |
| Rash\(^d\)                            | 15 (20)                       | 0                                 | 44 (30)       | 5 (3)         |
| Vomiting                              | 5 (7)                         | 0                                 | 42 (29)       | 3 (2)         |
| Hepatotoxicity\(^e\)                  | 21 (28)                       | 3 (4)                             | 22 (15)       | 9 (6)         |
| Oral mucositis\(^f\)                  | 9 (12)                        | 0                                 | 27 (19)       | 0             |
| Hyperglycemia\(^g\)                   | 9 (12)                        | 0                                 | 23 (16)       | 3 (2)         |
| Hyperlipidemia\(^h\)                  | 7 (9)                         | 1 (1)                             | 15 (10)       | 1 (1)         |
| Pneumonia                             | 3 (4)                         | 1 (1)                             | 5 (3)         | 1 (1)         |
| Pneumonitis                           | 0                             | 0                                 | 6 (4)         | 1 (1)         |
| Thrombocytopenia\(^i\)                | 1 (1)                         | 0                                 | 3 (2)         | 1 (1)         |
| Erythema multiforme                   | 0                             | 0                                 | 1 (1)         | 1 (1)         |
| Colitis\(^j\)                         | 0                             | 0                                 | 2 (1)         | 1 (1)         |

\(^a\)Includes neuropathy peripheral, peripheral sensory neuropathy, paresthesia, polyneuropathy, muscular weakness, neurotoxicity, hypoesthesia, peripheral motor neuropathy, dysesthesia, gait disturbance, hypotonia, neuritis;  
\(^b\)Includes neutropenia, neutrophil count decreased, febrile neutropenia;  
\(^c\)Includes anemia, hemoglobin decreased, hematocrit decreased;  
\(^d\)Includes rash, rash maculo-papular, erythema, dermatitis, drug eruption, folliculitis, dermatitis allergic, dermatitis bullous, rash erythematous, rash papular, rash pruritic;  
\(^e\)Includes alanine aminotransferase increased, aspartate aminotransferase
increased, blood alkaline phosphatase increased, hyperbilirubinemia, gamma-glutamyl transferase increased, blood bilirubin increased, cholestasis, hepatic function abnormal, hepatocellular injury, transaminases increased; \textsuperscript{\textregistered} Includes stomatitis, mucosal inflammation, mouth ulceration; \textsuperscript{\textregistered} Includes hyperglycemia, blood glucose increased, diabetes mellitus, glycosylated hemoglobin increased, type 2 diabetes mellitus; \textsuperscript{\textregistered} Includes blood cholesterol increased, hypertriglyceridemia, hypercholesterolemia, blood triglycerides increased, hyperlipidemia; \textsuperscript{\textregistered} Includes thrombocytopenia, platelet count decreased; \textsuperscript{\textregistered} Includes enterocolitis